CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-527

MEDICAL REVIEW(S)

CLINICAL REVIEW

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Division / Office	FDA/ODE1
Reviewer Name	Heather D. Fitter
Review Completion Date	August 26, 2010
Established Name	Fingolimod
(Proposed) Trade Name	Gilenya
Therapeutic Class	S1P receptor modulator
Applicant	Novartis
Formulation(s)	Oral tablets
Dosing Regimen	0.5 mg
Indication(s)	To reduce the frequency of relapses and delay the progression of disability in relapsing MS
Intended Population(s)	Relapsing Multiple Sclerosis

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Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The efficacy data presented in this submission demonstrates that a daily oral dose of 0.5 mg fingolimod (also referred to as FTY720 in this review) reduces the frequency of relapses in patients with relapsing remitting multiple sclerosis (RRMS).

The primary endpoint for both pivotal efficacy trials was the aggregate annualized relapse rate (ARR). D2301 was a 24 month multi-center randomized placebo controlled double blind trial in 1272 RRMS patients comparing FTY720 at two doses (1.25 mg and 0.5 mg) to placebo. Trial D2302 was a superiority 12 month study comparing two FTY720 doses (1.25 and 0.5 mg) to interferon ß- 1a in 1292 RRMS patients. Both trials had robust findings for the primary endpoint of aggregate annualized relapse rate, with p values < 0.001 for both doses compared to control. There was approximately a 54% reduction in the relapse rate of FTY 720 0.5 mg compared to placebo and approximately a 52% reduction compared to IFN ß- 1a. Although the intention to treat population included patients that remained in the study but were off study drug, the proportion of patients that were off study drug in each group was comparable, with the exception of the high dose FTY720 group in D2301. In addition, the supportive analysis in the per protocol population (on treatment with no major protocol violations) also provided consistent evidence that FTY720 is effective in reducing the aggregate ARR in patients with RRMS ($p<0.001$) as compared to control.

The two key secondary endpoints that were explored in these pivotal trials were 1) time to three month confirmed disability progression (using the EDSS scale), and 2) number of new or newly enlarged T2 lesions.

In trial D2301, disability progression as measured by the EDSS scale was significantly lower for FTY720 1.25 mg ($p=0.017$) and FTY720 0.5 mg ($p=0.024$), compared to placebo. In trial D2302, however, disability progression measured by the EDSS scale was not significantly lower for the FTY720 1.25 mg ($p=0.543$) or FTY720 0.5 mg ($p=0.209$) groups compared to IFN ß- 1a.

The next key secondary endpoint (pre-specified only in trial D2302) was the number of new or newly enlarged T2 lesions at month 12. While a statistically significant effect for that endpoint was clearly demonstrated for fingolimod 1.25 mg compared to placebo (mean of 2.51 vs. 4.86, $p=0.017$), the 0.5 mg group only trended in favor of fingolimod 0.5mg, compared to placebo (mean of 3.5 vs. 4.86, $p=0.053$), using the original analysis submitted by the sponsor. The sponsor submitted an alternative analysis for this endpoint with their justification for why a new analysis was warranted. This alternative analysis method yielded a statistically significant contrast ($p=0.002$). Although the FDA

analysis based on the updated T2 lesion datasets yielded different results, both the fingolimod 1.25 mg group (p =0.0017) and the fingolimod 0.5 mg group (p=0.0007) demonstrated a statistically significant effect compared to active control on this endpoint. Trial D2301 demonstrated a nominally significant contrast (p<0.001) for both fingolimod 1.25 mg (mean of 2.5 vs. 9.8) and 0.5 mg (mean of 2.5 vs. 9.8) as compared to placebo for new or newly enlarged T2 lesions up to month 24.

Although a 1.25 mg dose was also explored in the pivotal efficacy trials alongside the 0.5 mg dose, the sponsor is requesting marketing authorization for only the 0.5 mg dose due to the fact that the 0.5 mg dose has a more favorable safety profile than the 1.25 mg dose. Evidence was provided in this application to support the fact that the higher dose, while exposing patients to more risk, does not expose patients to significantly increased efficacy; therefore I agree with the sponsor's decision not to propose marketing of the 1.25 mg dose. The pivotal efficacy trials demonstrated a relatively flat dose response relationship for efficacy between 1.25 mg and 0.5 mg which suggests that a lower dose may also be efficacious. With consideration of the concerning safety profile of this product, further exploration is needed to determine the lowest effective dose.

1.2 Risk Benefit Assessment

Multiple safety signals that span multiple organ systems are present with chronic exposure to fingolimod and these signals are discussed in detail in the safety review by Dr. Lourdes Villalba. The fingolimod development program for RRMS has demonstrated efficacy in both decreasing the rate of relapses in both pivotal efficacy trials, and in delaying disability progression in the one pivotal placebo controlled trial. Therefore, benefit of this product has clearly been demonstrated for patients with RRMS. With adequate safety monitoring recommended in the product label and the accrual of additional post marketing safety information, this product will likely have an acceptable risk/benefit ratio.

2 Introduction and Regulatory Background

Multiple Sclerosis (MS) is a progressive neurologic illness with a distinctly variable phenotype and course in different individuals. The etiology remains unknown, although several factors, such as genetic susceptibility, autoimmune mechanisms, viral infection and sun exposure up to adolescence are thought to contribute to the development of MS in an individual. This illness is thought to trigger an autoimmune response that leads ultimately to demyelination in the central nervous system (CNS). More recently, data is accumulating to suggest that there also is a significant degree of gray matter involvement. Treatment for MS is generally directed in three areas 1) reduction of acute exacerbations, 2) reduction of relapses/disability progression or 3) symptomatic relief. The development program for fingolimod has explored this medication's utility to reduce relapses and disability progression. Currently there are several other first or

second line therapies with this target, but all require either intravenous, intra muscular or subcutaneous administration via injection. Fingolimod is distinct from these other agents, in that its mode of administration is oral and it is the first sphingosine 1 phosphate receptor modulator seeking marketing authorization in the United States.

2.1 Product Information

FTY720 is an orally active first in class, sphingosine 1 phosphate (S1P) receptor modulator. After oral dosing FTY720 is phosphorylated to create the active moiety FTY720-phosphate (in text below the active moiety will be referred to as FTY720 or fingolimod). This active moiety acts as an agonist at four of five G protein coupled S1P receptors, namely S1P1, S1P3, S1P4 and S1P5, but not S1P2. Different factors including FTY720 concentration, time following administration or cell type may determine whether FTY720 acts as an S1P receptor agonist or functional antagonist. The key pharmacodynamic effect of FTY720 is a dose-dependent reduction of the peripheral lymphocyte count mediated by down modulation of the S1P1 receptor on lymphocytes. This results in slowed egress of lymphocytes from the lymph nodes, thereby reducing the number of auto-aggressive T-cells re-circulating to tissue where they may cause inflammation and damage in the CNS.

This product was initially developed for the prevention of acute rejection after renal transplantation in adults at doses of 2.5 mg and 5.0 mg in combination with cyclosporine A and steroids. This development program was discontinued while in phase III.
The clinical program of MS was initiated due to the theoretical concept that restricting lymphocytes to peripheral lymphoid tissue could be of benefit. This was supported by data from experimental autoimmune encephalitis (EAE) models of MS in animals that showed potential efficacy.

2.2 Table of Currently Available Treatments for the Proposed Indication

Table 1: Table of Currently Available Treatment for Proposed Indications[1,2]

	Indication	Effect on exacerbation (exac) rate		Effect on disability progression	Safety issues (of concern)	1st or 2nd line	Approved dose
Avonex	Decrease clinical exac, slow physical disability	32% reduction (rn)		37% reduction	decreased blood counts, hepatic injury, flu like symptoms	1st	30 mcg IM q week
Betaseron	Decrease clinical exac	30% reduction		None described in label	injection site necrosis, flu like symptoms	1st	0.25 mg sq qod
Rebif	Decrease clinical exac, delay physical disability	22 mcg 29% rn	44 mcg 32 % rn vs. placebo and Avonex *	27% reduction	hepatic injury, flu like symptoms, injection site reaction	1st	22 mcg or 44 mcg tiw
Copaxone (glatimer acetate)	Reduce relapses including patients with CIS	75% reduction in first trial (n=48) 29% reduction in second trial (n=251)		None described in label	Post injection reaction, transient chest pain, skin necrosis	1st	20 mg sq q d
Mito-xantrone	Reduce neurologic disability and/or relapses in SPMS or worsening RRMS	60% reduction exacerbations; Primary outcome: 86% reduction in new enhancing lesions		64% reduction	Cumulative cardiotoxicity, AML[2]	2nd	12mg/m2 IV q 3 months
Tysabri (natalizumb)	To delay physical disability and reduce exac	61% reduction		33% reduction	PML[3], immunosuppression, hepatotoxicity	2nd	300 mg IV q 4 weeks

[1]annualized exacerbation rate
[2]acute myelogenous leukemia
[3] progressive multifocal leukoencephalopathy
*32% reduction in proportion of Rebif patients who experienced relapses compared to Avonex

1 Continuum, Multiple Sclerosis, Volume 10, Number 6, December, 2004, p. 120-163
2 Most recent approved labels for all products in table above

Two classes of agents are approved as first line treatment for the prevention of clinical relapses in relapsing forms of MS. The first class is recombinant interferon-b (IFN-b), which includes three formulations, specifically Avonex, Betaseron and Rebif. IFN-b is hypothesized to exert many effects at critical points in MS pathogenesis. It induces the expression of a number of genes and effects major histocompatability complex (MHC) gene expression, antiviral and antiproliferative actions and monocyte activation in vitro. The exact mechanism that leads to improvement in MS patients is not well understood. Some of the effects hypothesized to be important are the inhibition of leukocyte proliferation, the decrease of antigen presentation by microglia, a modulatory effect on the IgG synthesis of plasma cells, the reduction of T cell matrix metalloproteinase (MMPP) expression as well as the down regulation of adhesion molecules that allow T cell migration into the brain[3]. Another first line compound is glatiramer acetate (GA), which is a random polypeptide made up of four amino acids in a specific molar ratio that resembles myelin basic protein. This compound is thought to exert its immunomodulatory effect due to altered T cell activation and differentiation[4].

Mitoxantrone (Novantrone), an alkylating chemotherapeutic agent, is considered a second line treatment option because of its potential cumulative cardiotoxicity, which limits the individual maximum dose. Mitoxantrone intercalates into DNA, resulting in cross links and strand breaks[5]. In addition, this product interferes with the enzyme topoisomerase II that forms double strand breaks when DNA is altered during replication. Therefore, mitoxantrone is thought to affect replication predominantly in rapidly dividing cells. As a result of this effect, there are secondary effects on the immune system, including interference with antigen presentation, proinflammatory cytokines and attenuation of leukocyte migration[6].

Natalizumab (Tysabri) is another second line treatment option. Because of a risk for progressive multifocal leukoencephalopathy (PML), natalizumab is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate MS therapy. Natalizumab binds to the α4-subunit of α4β1 and α4β7 integrins expressed on the surface of all leukocytes except neutrophils, and inhibits the α4-mediated adhesion of leukocytes to their counter-receptors. Disruption of these molecular interactions prevents transmigration of leukocytes across the endothelium into inflamed parenchymal tissue. The specific mechanism by which Tysabri exerts its effects in multiple sclerosis has not been fully defined. Progressive multifocal leucoencephalopathy (PML) occurs in approximately 1/1000 patients treated

3 Markowitz, CE. Interferon-beta: mechanism of action and dosing issues. Neurology 2007;68:S8-11.
4 Menge T et al, Disease-Modifying agents for Multiple Sclerosis: Recent advances and future prospects. Drugs 2008; 68: 2445-2468.
5 Durr FE, Wallace RE, Citarella RV. Molecular and biochemical pharmacology of mitoxantrone. Cancer Treat Rev 1983; 10 Suppl. B 3-11.
6 Neuhaus O, et al. Multiple sclerosis: mitoxantrone promotes differential effects on immunocompetent cells in vitro. J Neuroimmunol 2005; 168: 128-137.

with Tysabri. This potentially deadly opportunistic infection caused by reactivation of a clinically latent JC polyomavirus infection has no available treatment.

Several other drugs are used off label in clinical practice, including cyclophosphamide, azothioprine, methotrexate and cyclosporine.

2.3 Availability of Proposed Active Ingredient in the United States

This is a new molecular entity, first in class, oral S1P receptor modulator, so there are no other marketed products with safety issues relevant to this product.

2.4 Important Safety Issues with Consideration to Related Drugs

See 2.3.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

IND 70139 for FTY720 was originally opened **May, 2005** with study CFTY720D2301. A decision was made at the 30 day SRD meeting to put the study on hold (**June 7, 2005**) and this was communicated to the sponsor. The main issue for this hold was the lack of sufficient monitoring in the proposed protocol for macular edema, pulmonary conditions, retroperitoneal fibrosis and pancreatitis. It was also noted that there was concern of increased infection rate and a lack of assessment of BK/ polyoma/ polioma virus activation, and PML risk. In addition, a suggestion was made by FDA to study lower doses in view of the emerging safety profile to identify "the minimum effective dose".

A request for an End of Phase 2 (EOP2) meeting came shortly after this IND was put on hold, so a meeting was granted to discuss the IND hold issues **June 16, 2005**. The sponsor submitted a response to the clinical hold, and was informed on **Dec 21, 2005** that they were still on full clinical hold. There continued to be insufficient monitoring for pulmonary, ophthalmologic, and cardiovascular toxicities so specific recommendations were made in the continue clinical hold letter sent **January 18, 2006**. After review of another complete response to clinical hold, a third clinical hold letter was sent **March 19, 2006** stating that the safety issues discussed in the **February 28, 2006** teleconference did not result in resolution of key hold issues and that the potential toxicities were not adequately characterized and monitored in the sponsor's proposed protocol.

After the third hold cycle regarding the safety monitoring for the proposed study D2301, the Agency received a package (**April 5, 2006**) for Dr. Temple's review specifically requesting input on three key areas of disagreement 1) overnight admission after initial dosing for holter monitoring, 2) Optical coherence tomography (OCT) frequency and stopping rules, and 3) the need to conduct high resolution computed tomography

(HRCT) of the chest in all patients at baseline and end of treatment. During the arbitration process, the company sent a submission (**April 25, 2006**) which contained two protocols. Protocol D2309 which contained all of the safety monitoring the division had requested and protocol D2301. After a discussion with FDA, the sponsor withdrew protocol D2301, as it did not include the FDA required safety monitoring. The arbitration resulted in an agreement between the FDA and the sponsor about the safety monitoring in the previously specified organs of concern. These changes would now apply to protocol D2309, as Study D2301 became a non-IND study. In addition, a recommendation was made to power the study to detect disability progression as a key secondary endpoint since this was an important endpoint to help with the assessment of the risk benefit profile of MS drugs. **On June 16, 2006** a teleconference was held with the sponsor to communicate the results of Dr. Temple's review. FDA told Novartis that the following revised monitoring plan would be acceptable in their protocol if it included the following:

Ophthalmology:

- Ophthalmic evaluation including eye history, careful assessment for changes in visual acuity (VA) and ophthalmoscopy at screening, month 1, 3, 6, 12, 18 and 24 and also at anytime if new visual symptoms or decrease in VA is detected.
- OCT in the event of any change in VA or findings on ophthalmoscopy; in addition OCT at screening and end of treatment in all patients.
- Fluoroscein angiography for any patient with suspicion of macular edema on ophthalmoscopy or decrease in VA and increased foveal thickness on OCT.
- Study drug will be discontinued in the event of a diagnosis of macular edema.
- A concurrent ophthalmologic substudy will be conducted based on serial OCT in 300 patients at selected sites.
- Stopping rules based on a diagnosis made by appropriately trained ophthalmologists conducting ophthalmic examinations rather than based on a predefined quantitative change in retinal thickness.

Pulmonary:

- HRCTs in 300 patients (100 patients per arm, 0.5 mg, 1.25 mg and placebo) at baseline and end of treatment.

Cardiac:

- 6-hours of monitoring in an outpatient setting post first dose, with discharge based on predefined criteria.
- 24-hour holter monitoring would be required in the first 300 patients (100 per arm; 0.5 mg, 1.25 mg and placebo).
- Holter results on the first 300 patients to be submitted to FDA for their review. If results are "OK" then holters could be discontinued for subsequent patients.

An EOP2 meeting was held on **March 26, 2007**. Important points made in this meeting were as follows: 1) Although 15% or less of the patients were to be from the U.S, the

division did not feel this would be unacceptable. 2) The sponsor said that safety data would be presented from studies D2301, D2302 and D2309 and FDA said that would be acceptable if similar patient populations were enrolled and monitoring was identical. 3) FDA also stated that in order to describe disability progression in labeling, there would have to be independent substantiation of this endpoint. FDA noted that study D2309 was not powered for this endpoint and 4) Discussion about possible filing for accelerated approval under Subpart H was addressed. FDA stated the conditions under which this could be acceptable.

On **June 6, 2007**, FDA sent a letter to the sponsor granting fast track designation to FTY720 oral capsules for the treatment of patients with relapsing forms of multiple sclerosis.

A pre-NDA meeting was planned and the sponsor's proposal was to submit a subpart H NDA. When FDA sent preliminary comments explaining why the proposed package would not be filable, a decision was made to reschedule the pre-NDA meeting to a later time. Instead the time scheduled for the pre-NDA meeting was used for a teleconference on **February 24, 2009** to discuss a rolling submission for this NDA. FDA agreed that FTY was a fast track drug and that a rolling submission was available although review of a rolling submission was resource dependent.

On **December 7, 2009** a pre-NDA teleconference was held. The sponsor briefly summarized information about the disability endpoint in their pivotal clinical trials of MS. FDA restated that this is a review issue and there should be no expectation that we can come to an agreement in this meeting. There was additional discussion about whether there would be insufficient data submitted from trial D2309 on the special safety issues. The sponsor stated that there should be approximately 180 echocardiograms, which includes 150 coming from study D2309. There should be approximately 30 echocardiograms per dose arm. FDA restated that this is less than what was originally requested, and that whether this would be a sufficient number was a review issue. The sponsor stated that they were considering transitioning study D2309 to an open label safety extension study from a placebo controlled trial. FDA expressed concerns that although it would not affect the filing of the NDA it may affect approval, as less controlled data on special safety issues would become available if this study was changed to an open label design.

On **September 8, 2009**, the DSMB sent a letter to Novartis recommending that the FTY720 1.25 mg dose be stopped in all MS trials unless review of the efficacy data from D2301 showed improved efficacy of the 1.25 mg dose over the 0.5 mg dose. The basis of their recommendation was largely based on six unexplained vascular events, all on treatment with FTY720 1.25 mg. Several serious adverse events all occurring in the FTY 1.25 mg dose group also contributed to this recommendation, although the DSMB felt these were not as concerning as the cluster of vascular events. The serious adverse events included one highly unusual MS relapse case (2301 409-8 Germany),

two viral infections (2302 212-21 Italy, 2302 821-07 Korea) and one 3rd degree heart block (2302E1 141-4 Belgium). On **December 1, 2009**, FDA was informed of this decision to discontinue the FTY720 1.25 mg dose in several of their ongoing studies due to the DSMB recommendation.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Overall the deficiencies that I will describe in this section slowed down the review process but do not affect approvability. In all cases, the sponsor was very receptive to FDA's requests for additional information, even though at times the information provided was not complete.

I will begin with the deficiency regarding the disability analysis. The original datasets provided for the disability progression analysis did not clearly identify all important aspects of particular variables. For example, visits were not clearly labeled; EDSS scores taken for disability progression vs. relapse occurrence were not clearly marked, nor was it always clear which patients were on study drug and which patients were off study drug at certain evaluation time points. When corrected datasets were requested, an explanation was sent, but updated datasets were not submitted. The FDA statistician continued to report that she did not have the necessary data to confirm the sponsor analysis of disability progression. A teleconference was held to discuss the deficiencies, and the sponsor reported that updated datasets would be sent as soon as possible. These datasets were provided and the FDA statistician was able to complete the analysis.

The pivotal efficacy trial's analysis plan included all patients (ITT) in the primary analysis for relapse rate and the key secondary analysis of disability progression. Patients that discontinued study drug were not censored, and continued in the ITT; therefore patients off study drug were analyzed as part of the primary evaluation of relapse rate and disability progression. With this analysis plan in mind, it becomes critical that there is consistency in the results for the prespecified primary and key secondary analyses on the ITT with the sensitivity analyses for the per protocol patients (on study drug without major protocol violations). Due to problems in the datasets, markings to determine which patients were on or off study drug were not always clear. In addition, another feature of this analysis plan that could affect interpretation of the primary analysis is the fact that patients who discontinued study treatment and continued in the ITT group, could and did in certain cases begin other labeled or off label medications for the treatment of RRMS. Therefore, differences in safety and effectiveness endpoints in various treatment groups could have been affected by differences in other disease modifying treatments taken during the trial.

The correct statistical analyses plans (SAPs) for the pivotal trials dated prior to the database lock were not provided with the original submission. The first time they were requested, the SAPs that came were dated after the database lock. The second time they were requested, the correct SAPs arrived.

An addendum was provided to the SAP, predominantly to present an alternate analysis for the variable new or newly enlarged T2 lesions at month 12 (trial D2302). A third addendum was provided with a re-analysis of the new and newly enlarged T2 lesion variable in trial D2302 after discussions between FDA and the sponsor about deficiencies in previous addendum.

A late major amendment was submitted to the this application on April 2, 2010 which resulted in a three month extension to the PDUFA date from June 21, 2010 to September 21, 2010.

Please refer to the Dr. Lourdes Villalba's safety review for any deficiencies affecting the quality and integrity of this submission in regards to the evaluation of safety.

3.2 Compliance with Good Clinical Practices

The efficacy trials were performed with good conduct, good clinical practices and with a sufficient number of patients evaluable for efficacy to allow for all the main objectives of the study to be adequately addressed. Please refer to Dr. Lourdes Villalba's safety review to determine whether adequate numbers for safety were provided in this application.

Division of Scientific Investigations (DSI) audits/inspections
Inspections from DSI of three clinical trial sites were requested for this NDA review. The sites, the rationale used for site selection and the audit results are as follows:

1) The Principal Investigator (PI) of Center 707 was Dr. Krzysztof Zelmaj at Oddzial Kliniczny Neurologii Uniwersytecki Szpital in Lodz, Poland. This site was selected because it enrolled the largest number of patients from a single site for protocol D2301. The audit revealed that 53 subjects were randomized and 50 subjects completed the study while 3 subjects withdrew their consent. The investigation found minor insignificant discrepancies between source documents and case report forms for four study subjects regarding calculation of pulmonary function tests. Two subjects had discrepancies in drug accountability records. Overall, the findings were unlikely to affect data integrity and appeared to be isolated occurrences and not systemic in nature. DSI concluded that the PI adhered to the applicable statutory requirements and FDA regulations and that no action was indicated.

2) The PI of Center 211 was Dr. Ruggero Capra at Presidio Ospedaliero di Montichiari in Montichiari, Italy. This site was selected because it enrolled the largest number of subjects from an individual site in protocol D2302, and because it was one of the two largest centers in Italy for this protocol. Twenty three subjects were randomized into this study. At this time the final inspection classification is pending, but the preliminary classification is "no action indicated" (NAI). Observations for Dr. Capra's site are based on email communication from the field. The establishment inspectional report (EIR) has not been received from the field and therefore the complete review of the EIR from DSI is pending.

3) The PI of center 303 was Dr. Karl Baum at Oberhavel Liniken in Heningsdorf, Germany. This site was selected because it had a relatively large proportion of unconfirmed relapses treated by rescue medication. The audit revealed that 20 subjects were randomized into the study and one subject withdrew from the study, leaving 19 patients from this site completing the study. A two item form FDA 483 was issued to Dr. Baum for the following two observations:

    - The drug storage temperature for the comparator drug Avonex syringes exceeded the storage temperatures set by the protocol during a 10.5 month period.
    - Three site personnel failed to document their yearly re-certification to perform the EDSS.

At the conclusion of the inspection, the form FDA 483 was discussed with the staff. Dr. Baum sent a written response to the inspectional findings on July 12, 2010 that stated that he plans to implement corrective actions to prevent the recurrence of the inspectional findings.

Reviewer's comment: The Avonex label states that this product can be stored up to temperatures of 25 degrees Celsius, so although the temperatures recorded were not within protocol specifications, they were within those described in labeling. In addition, since the design of the study was a superiority trial, any lack of activity of the active comparator would sway the results in that group towards results that would resemble those seen in placebo. The limitation would be in making any claim to superiority of fingolimod over Avonex, but not in identifying a treatment effect in the treatment group as compared to the comparator.

3.3 Financial Disclosures

The sponsor provided sufficient information about the processes used to collect financial disclosure information. Financial disclosure information for the MS program was obtained or requested for all Principal Investigators, Co-Investigators and Sub-Investigators. In addition, in the MS program, the sponsor also collected financial

disclosure information for physicians in the following categories since the information obtained from these clinicians were directly related to study outcomes: EDSS/EDSS rater (EDSSR); 1st dose administrator/independent first dose administrator (IFDA), Back up Treating Neurologist (BU TN), Examining Neurologist (EN); Back up Examining Neurologist (BU EN). There were twenty one investigators identified as receiving > $25,000, yet only three were investigators included in the pivotal efficacy trials. Details provided for these three Investigators are as follows:

1) [redacted] (b) (4) received > $25,000 for support of ½ position of research assistant and compensations for work as steering committee char.
2) [redacted] (b) (4) received > $50,000 for equity interest.
3) [redacted] (b) (4) did not disclose the exact amount provided, but stated that his father receives a pension from Novartis.

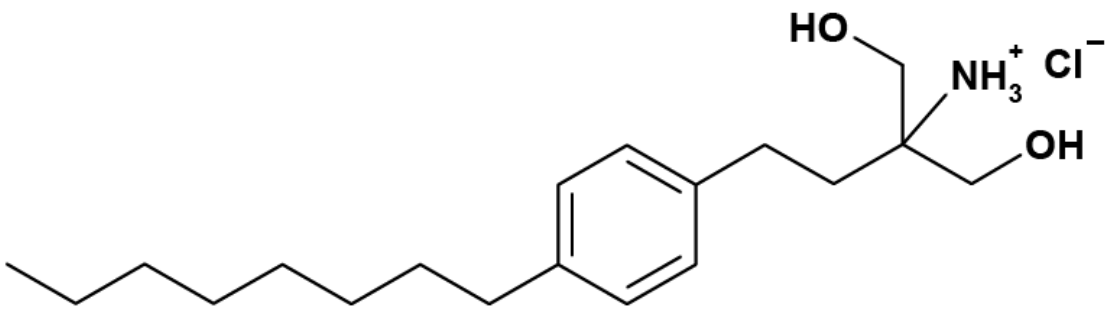
Information was obtained on 97-99% of the Investigators involved in the trials D2301 and D2302.

The FDA statistician, Dr. Yan, did an analysis of the efficacy data on the ARR in the pivotal efficacy trials excluding the data from the sites of the three Investigators above that received over $25,000 and found no significant differences in the efficacy results.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The chemical name for fingolimod is 2-amino-2-[2-(4octylphenyl)ethyl]propan-1,3-diol hydrochloride. The chemical structure of fingolimod is in the following figure:



The sponsor has proposed marketing immediate release capsules containing the equivalent of 0.5 mg fingolimod.

Please see the Agency Chemistry review for further details.

4.3 Preclinical Pharmacology/Toxicology

The following is based on information provided by the sponsor in the application. Please refer to the Agency Pharmacology/Toxicology review by Dr. Siarey for further details.

In safety pharmacology studies several potential safety signals were identified. A potential for bronchoconstriction and increased sensitivity induced by agents known to induce bronchoconstriction was found in experimental settings. In addition, FTY720 induced a transient decrease in heart rate and increase in blood pressure, both of which were not associated with relevant findings in long-term toxicology studies, although histopathological findings in the heart in dogs at high doses in chronic toxicity studies were seen. Effects on heart rate were characterized further and are related to an effect of FTY720-phosphate on GIRK channels at the level of the sinoatrial (SA) node. Although a slight inhibition of hERG channel activity at the solubility limit (0.5 μM) of FTY720 or FTY720-phosphate was seen, there was no indication of QT prolongation in a series of in vitro or in vivo studies up to high concentrations and/or doses. FTY720 treatment resulted in a decrease in motor coordination in mice and a mild depressive activity in the CNS in rats at high dose levels. A transient decrease in renal function was seen in rats and dogs at high oral doses, and kidney changes, consisting of basophilic tubuli or increased incidence of interstitial inflammation was found in toxicity studies with rats and mice. No effects on platelet activation or coagulation were found in preclinical in vitro or in vivo studies.

In repeated dose toxicity studies, oral doses up to 1 mg/kg for 26 weeks in dogs, or up to 10 mg/kg for 26 or 52 weeks in rats or monkeys, respectively, were well tolerated. There was generally no evidence of an increased infection rate in the animal toxicity studies, although effects on peripheral lymphocytes and lymphoid organs were noted in line with the pharmacological activity of the compound. Immunotoxicity studies did show a treatment-related decrease in immune response or T cell-dependent antibody production, although the immune memory function was not impaired.

Extra lymphatic organ toxicities were seen in some organ systems, the lungs being a sensitive and consistent target organ in all species tested. Lung weights were increased, and minimal to slight hypertrophy/hyperplasia of smooth muscle cells (SMH) in the broncho-alveolar junction was seen in rats and monkeys. Predominantly in dogs and mice, and at higher dose levels in rats and monkeys, alveolar macrophage infiltration and inflammatory lesions/ pneumonitis were present.

An increase in heart weight and myocardial changes in rats and dogs were observed. No treatment-related findings in the heart up to 10 mg/kg/day were noted in monkeys treated for 52 weeks. Generalized vasculopathy was observed in the chronic toxicity study and 2-year carcinogenicity study in Wistar rats, in which vascular lesions were dose and duration dependent.

At higher but sub lethal doses, pituitary and forestomach lesions were noted in rats; liver, adrenals and nervous system lesions were observed in dogs; and gastrointestinal tract and brain lesions were noted in monkeys. However, there were no effects on central or peripheral nervous system in a 52-week study in monkeys up to and including an oral dose of 10 mg/kg.

Effects on the liver were not consistently seen in animal toxicity studies and were mild and did only occur at high dose levels in some studies in combination with general clinical signs (i.e. body weight and food consumption), indicating that the MTD may have been exceeded.

FTY720 was not mutagenic, clastogenic or aneugenic in any of the in vitro or in vivo studies performed. The rat carcinogenicity study did not identify any carcinogenic potential up to the highest dose level tested (2.5 mg/kg). In mice, a statistically significant increase in the incidence of malignant lymphomas was observed at 0.25 and/or 2.5 mg/kg. Immuno-histochemical staining characterizing B and T-cell lymphocytes revealed no obvious difference in the type of malignant lymphoma between the spontaneous lymphomas of the control groups and that of the treated groups.

Reproductive toxicology studies showed that FTY720 had no effect on the fertility or early embryonic development in rats at doses up to 10 mg/kg. Available information does not suggest that FTY720 would be associated with an increased risk of reduced fertility in patients. FTY720 has to be considered as teratogenic in rats at doses of 0.1 mg/kg or higher. FTY720 treatment resulted in a significant increase in embryo-fetal mortality in rabbits at doses of 1.5 mg/kg or higher and a decrease in the number of viable fetuses, as well as, fetal growth retardation at 5 mg/kg in the absence of severe maternal toxicity. In rats, F1 generation pup survival was decreased in the early postpartum period. Treatment-related effects in neonatal/ juvenile animals were comparable to those seen in adult rats at that dose levels, with the exception of the absence of smooth muscle hypertrophy in the lungs of the juvenile rats.

4.4 Clinical Pharmacology

The following is based on information provided by the sponsor in the application. Please refer to the Agency Clinical Pharmacology review for further details.

4.4.1 Mechanism of Action

Fingolimod is phosphorylated by sphingosine kinase in vivo to form the active metabolite fingolimod phosphate (fingolimod-P). Fingolimod-P binds four of the five G protein-coupled sphingosine 1-phosphate (SIP) receptors, namely S1P1, S1P3, S1P4 and S1P5. With initial dosing there is agonism of S1P receptors, manifested as decreased heart rate, however with continued fingolimod dosing, functional antagonisms occurs with internalization of S1P receptors.

Lymphocytes exit from lymph nodes via S1P1 receptor signaling along a S1 phosphate gradient, so fingolimod-P blocks the capacity of lymphocytes to exit from lymph nodes causing a redistribution of lymphocytes. This redistribution is thought to reduce the infiltration of lymphocytes into the CNS where they may be involved in inflammation and nervous tissue damage. In addition, S1P receptors are expressed on neural cells. Since fingolimod crosses the blood brain barrier, it has been hypothesized that it may have a central effect on the CNS which involves modulating neurogenesis, glial cell function and migration. In the preclinical models of EAE, fingolimod administration (resulting in S1P1 deletion from neural cells) reduced astrogliosis, demyelination and axonal loss.

4.4.2 Pharmacodynamics

Initiation of fingolimod treatment results in dynamic effects which are observed within hours of the first dose administration. The principal dynamic effects are transient decreased heart rate, transient AV conduction blocks and a mean lymphocyte count reduced by approximately 70% from baseline that remains stable with chronic dosing. At supra-therapeutic dosing of fingolimod, greater than 10 fold the clinical dose, a dose dependent increase in airway resistance is also observed.

Lymphocytes
Treatment with fingolimod results in a dose-dependent reduction in circulating lymphocytes which is thought to be its core mechanism of action. A decrease in the lymphocytes occurs within 3-4 hours of the first oral dose. All main lymphocyte subsets appear to be affected; including B cells, CD4+ T cells and CD8+ T cells. The memory effector subset of T cells (which do not regulate traffic through lymph nodes) did not appear to be affected. These cells are important in immune surveillance and in restimulation by antigen and therefore may provide first line defense against recall infection. Although fingolimod may inhibit antibody response to localized antigen which require T/B cell trafficking to the local draining lymph nodes, the sponsor claims that the drug should not impair humeral immunity to systemic infection when the antigen is widely distributed to lymphoid organs.

Heart

Treatment with fingolimod results in a transient dose dependent decrease in heart rate and slowing of the atrioventricular conduction. S1P is a normal constituent of human blood which has heart rate lowering effects which is thought to act on S1P receptors in the atria of the heart.

Fingolimod at doses of 0.5 mg induces a mean negative chronotropic effect of 7-8 beats per minute and this effect is seen within 3 hours of the first doses, reaches its peak effect at 4-5 hours and attenuates over 24 hours post dose. After four weeks of chronic dosing the negative chronotropic effect is no longer observed. According to the sponsor, patients who stop chronic fingolimod treatment and then restart treatment within two weeks will have no recurrence of the negative chronotropic effect associated with treatment initiation. The acute combination of fingolimod with atenolol, but not diltiazem, results in an additional 15% reduction of heart rate when compared to fingolimod treatment alone. Fingolimod has no detectable effect acutely on ventricular function as measured by cardiac output or stroke volume.

In addition, clinical pharmacology studies revealed a link between FTY720 treatment and AV block. There was a dose dependent increase in AV block in the clinical trials. The sponsor says that after seven days of dosing, when a negative chronotropic effect of fingolimod was still present, fingolimod treatment resulted in a significant prolongation of QTcI, with the upper bound of the 90% CI being an increase of ≤13.0 ms. Yet, in the clinical trials with FTY720 there were no cases of Torsades de Pointe.

Unfortunately the QT study could not rule out an effect of prolongation of the QT interval in the presence of FTY720 due to deficiencies within the study. The thorough QT study in man revealed mild but significant prolongation of the QTcI, which the sponsor suggests was due to an indirect effect related to the negative chronotropic effect induced by FTY720 in the initial phase of treatment. Outlier analysis of QTcB and QTcF in the pivotal, phase III MS trials did not reveal a clear signal of QT prolongation with chronic dosing of FTY720.

Lung

Fingolimod treatment with single doses ≥ 5.0 mg is associated with a dose dependent increase in airway resistance. Multiple doses of 0.5 mg or 1.25 mg after varying periods of time may result in abnormal pulmonary function tests, but the exact relationship is not fully characterized and is still under exploration.

Overdose

An overdose is predicted by the sponsor to be associated with bradycardia, decreased lymphocyte count and increased airway resistance. There have not been any cases of overdose in the clinical trials to date, so limited data on overdose is available.

4.4.3 Pharmacokinetics

In pooled pharmacokinetic analyses of the two pivotal efficacy studies, D2301 and D2302, the average concentration of fingolimod at doses of 0.5 mg and 1.25 mg was 2-3 ng/ml and 5-6 ng/ml, respectively. Fingolimod-P average concentrations were approximately one-half the fingolimod concentrations.

Absorption
Fingolimod absorption is slow with a T_{max} of 12-16 hours, and a measured absolute oral bioavailability of 93%.

Dose linear pharmacokinetics is exhibited at single doses from 0.25-40 mg and at multiple once daily doses from 0.125-5 mg. A high fat meal has no significant effect on fingolimod pharmacokinetics. Steady state exposure is reached between 1-2 months during once daily dosing with an estimated 12 fold accumulation of blood levels from first dose to steady state. Both fingolimod and fingolimod-P are highly protein bound (>99.7%). Fingolimod and fingolimod-P protein binding is not altered by renal or hepatic impairment.

Metabolism
The biotransformation of fingolimod in humans occurs by three main pathways:

1) reversible stereoselective phosphorylation to fingolimod-P
2) oxidative biotransformation mainly via the cytochrome P450 4F2 isoenzyme and subsequent fatty acid-like degradation to inactive metabolites
3) formation of inactive nonpolar ceramide analogs of fingolimod

Fingolimod and fingolimod-P can be converted back and forth, therefore, it is assumed that these two analogs are in dynamic equilibrium at steady state. The steady state AUC ratio of these two analogs is dose independent and is approximately 0.4.

Excretion
Fingolimod has an average apparent terminal half life of 6-9 days. Fingolimod and fingolimod-P blood levels decline in a parallel fashion. After an oral administration, 81% of the dose is slowly excreted in the urine as inactive metabolites. Fingolimod and fingolimod–P are not excreted intact in the urine but are the major components in the feces with amounts representing less than 2.5% of the dose each. Due to high protein binding and a high volume of distribution, hemodialysis results in only a minor, 14% decrease in fingolimod blood concentration.

Pharmacokinetics in special patient populations
Ethnic origin, age, weight nor gender has a clinically relevant effect on the pharmacokinetics of fingolimod and fingolimod-P.

Mild, moderate and severe hepatic impairments have no influence on fingolimod C_{max} but fingolimod AUC is increased by 12%, 44% and 103% respectively. Fingolimod-P was measured in severe hepatic impairment only and C_{max} and AUC were increased by 22% and 29%. The sponsor suggests that no dose adjustment should be made in mild or moderate hepatic impaired patients and that fingolimod should be used with caution in severe hepatic impairment.

Severe renal impairment increases fingolimod C_{max} and AUC by 32% and 43% respectively, and fingolimod-P, C_{max} and AUC by 25% and 14% respectively. The sponsor does not recommend dose adjustments in renally impaired patients.

5 Sources of Clinical Data

5.1 Tables of Clinical Trials

Table 2: Summary of studies providing efficacy data

Study No.	Study Objective, Population	No. of patients Design	Treatment Duration	Medication dose/day	Primary Efficacy Endpoint
Phase III					
D2301	Efficacy and safety in RRMS	1272 randomized, double-blind	2 years	fingolimod 1.25mg/day fingolimod 0.5mg/day Placebo	Annualized relapse rate
D2302	Efficacy and safety in RRMS	1292 randomized, double-blind, double-dummy	1 year	fingolimod 1.25mg/day fingolimod 0.5mg/day IFN β-1a i.m. 30µg once weekly	Annualized relapse rate
Phase II					
D2201	Efficacy and safety in relapsing MS	281 randomized, double-blind	6 months	fingolimod 5.0mg/day fingolimod 1.25mg/day Placebo	Total number of Gd-enhancing lesions on 6 monthly post-baseline MRI scans
D2201E1	Long-term efficacy and safety, extension of study D2201	250 Initially double-blind, then open-label	Open (interim data up to Month 60 included)	fingolimod initially 1.25 mg or 5.0 mg orally o.d., between months 15 and 24, 5.0 mg patients switched to open label 1.25 mg orally o.d.	None. MRI and clinical endpoints evaluated

5.2 Review Strategy

Two large phase III trials contributed to the bulk of the efficacy data in this submission; a single two year placebo controlled trial and a single one year active controlled study using IFN β-1a as the active comparator. The sponsor presents data from the 6 month phase II placebo controlled study and its long term open label extension and requests that we consider some of this data to support efficacy of fingolimod in the target population.

The phase III studies used clinical endpoints of relapse and disability progression, supported by MRI measures of disease inflammatory activity. The early evaluation of efficacy in the phase II study was based on MRI measures of disease inflammatory activity, supported by relapse and other clinical endpoints.

This review will focus on efficacy issues, as the clinical safety review was done by a member of the clinical safety review team, Dr. Lourdes Villalba.

5.3 Discussion of Clinical Trials

5.3.1 Protocol CFTY720D2301

Study Title: A 24-month double-blind, randomized, multicenter, placebo-controlled, parallel-group study comparing the efficacy and safety of FTY720 1.25 mg and 0.5 mg administered orally once daily versus placebo in patients with relapsing-remitting multiple sclerosis

Objectives:

The primary objective was to compare two doses of FTY720 (1.25 mg and 0.5 mg) with placebo to demonstrate that at least 1.25 mg FTY720 is superior to placebo in terms of annualized relapse rate (ARR) in patients treated for up to 24 months.

The key secondary objective was to evaluate the effect of FTY720 (1.25 mg and 0.5 mg) relative to placebo on disability progression as measured by the time to 3 month confirmed disability progression (measured by the Expanded Disability Status Scale (EDSS)) in patients treated for up to 24 months.

Other secondary objectives were:

- To evaluate the safety and tolerability of FTY720 compared to placebo in patients with RRMS treated up to 24 months

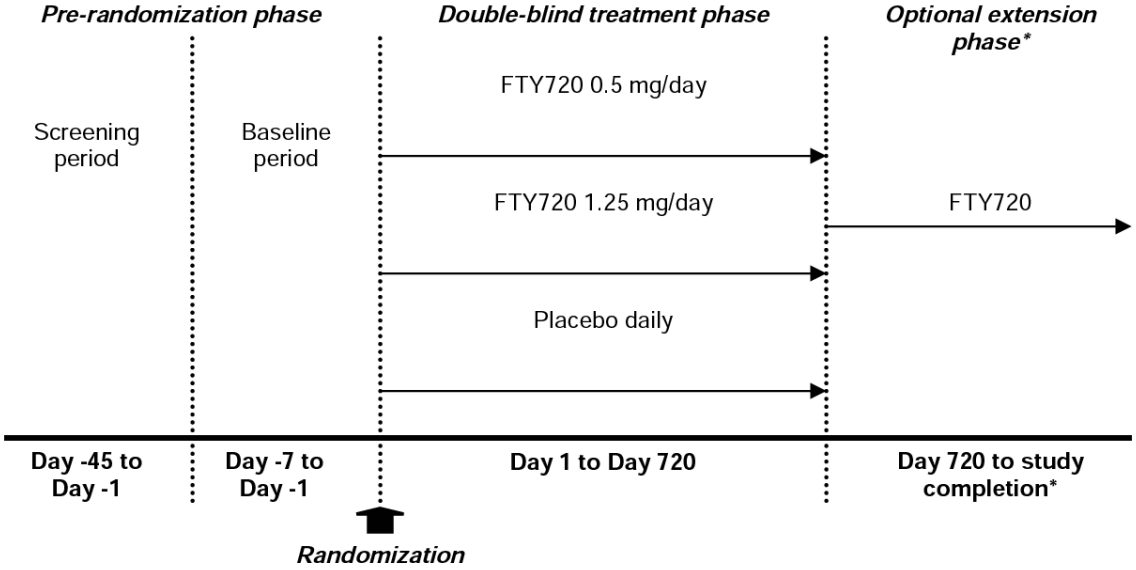
- To evaluate the effect of FTY720 1.25 mg and 0.5 mg compared to placebo in patients treated for up to 24 months with respect to MRI parameters of inflammatory disease activity, burden of disease, and brain volume (atrophy)
- To evaluate the effect of FTY720 1.25 mg and 0.5 mg compared to placebo in patients treated for up to 24 months with respect to relapse-related parameters:
  • time to the first relapse
  • proportion of relapse-free patients
- To evaluate the effect of FTY720 1.25 mg and 0.5 mg compared to placebo in patients treated for up to 24 months on disability progression with respect to:
  • time to 6-month confirmed disability progression as measured by EDSS
  • proportion of patients with confirmed disability progression
  • change from baseline to the end of the study on the Multiple Sclerosis Functional Composite (MSFC) z-score
- To evaluate the effect of FTY720 1.25 mg and 0.5 mg compared to placebo on multidimensional health status as measured by the Patient Utility Index derived from patients responses on the EuroQoL (EQ-5D)
- To evaluate the pharmacokinetics of FTY720
- To evaluate the pharmacokinetic/pharmacodynamic relationship of FTY720 1.25 mg and 0.5 mg for main efficacy and safety outcomes in patients with RRMS

Study Design: This was a 24-month double-blind, randomized, multicenter, placebo-controlled, parallel-group study in 1272 patients with RRMS. Patients were randomized to receive oral treatment with FTY720 1.25 mg, FTY720 0.5mg or placebo once daily for up to 24 months.

The study had two phases: pre-randomization and double-blind treatment (refer to Figure 1). The pre-randomization phase consisted of two periods, screening (day -30 to day -1, visit 1) and baseline (baseline visit, day 1, visit 2). Patients whose eligibility was confirmed, were randomized to one of three treatment groups. The first dose of the study drug was taken in the clinic at baseline visit and the patient was monitored for 6 hours after the first dose administration before discharge.

Patients who completed the 24-month double-blind treatment phase, could enter an optional long-term extension study under a separate protocol.

Figure 1: Study Outline for Protocol D2301



During the study, assessments were performed as indicated in the schedule of assessments (refer to Table 3). The interval between visit 2 (baseline) and visit 3 was 14 days and between visit 4 and 5 was one month. Subsequent visits were scheduled at 3-month intervals.

EDSS and MSFC assessments were performed by an independent evaluating physician, not involved in the treatment of patients. The MSFC evaluation was also performed by site personnel.

An independent nurse or physician, other than the study personnel, was assigned a role of the “First Dose Administrator” who monitored the intake of the 1st dose or re-start of the study medication in the clinic.

All MRI scans were evaluated by a blinded reader at the central MRI evaluation center.

An external data and safety monitoring board (DSMB) provided an independent assessment of safety and risk/benefit for the duration of the study.

Table 3: Assessment schedule: Protocol D2301

Phase	Pre-Randomization		Double-Blind Treatment										
Period	Screening	Baseline											
Visit No.	1	2	**3**	4	5	6	7	8	9	10	11	12	**13**
Study month	-1	0	½	1	2	3	6	9	12	15	18	21	24
Informed consent	X												
Background information, Demography	X												
Inclusion/exclusion criteria	X	X											
Medical history	X												
MS history/MS treatment	X												
Concomitant medications	X	X		X	X	X	X	X	X	X	X	X	X
Pregnancy test[1]	X	X											X
Physical exam	X					X			X				X
Dermatological Examination	X								X				X
Ophthalmologic Examination[2]	X						X		X		X		X
Chest X-ray	X								X				X
Pulmonary Function Tests[3]	X						X		X				X
Peak Flow Measurements[4]	X			X	X	X		X		X	X	X	
Vital signs[5]	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology[6]	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood chemistry[7]	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[8]	X	X	X	X	X	X	X	X	X	X	X	X	X
FTY720 dose administration[9]		X				X	X	X	X	X	X	X	
ECG (paper-based)	X	X[10]		X			X		X		X		X
MRI	X						X		X				X
QoL scales	X								X				X
EDSS[11]	X	X				X	X	X	X	X	X	X	X
MSFC		X					X		X		X		X
Two Training sessions for MSFC[12]	X												
MS relapse[13]	X	X		X	X	X	X	X	X	X	X	X	X
Adverse events/SAEs		X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetic sample FTY720/FTY720-P			X	X	X	X	X	X	X	X	X	X	X
Pharmacogenetic blood sample[14]	X												
Proteomics/metabonomics-plasma[14] sample	X					X	X		X		X		X
CSF sample (selected sites)	X								X				X
Phase Completion		X											X

Study centers: 138 centers in 22 countries (all non-U.S. centers): 5 centers in Australia, 7 centers in Belgium, 9 centers in Canada, 10 centers in Czech Republic, 1 center in Estonia, 5 centers in Finland, 11 centers in France, 17 centers in Germany, 4 centers in Greece, 3 centers in Hungary, 1 center in Ireland, 4 centers in Israel, 6

centers in Netherlands, 10 centers in Poland, 7 centers in Romania, 8 centers in Russia, 3 centers in Slovakia, 3 centers in South Africa, 3 centers in Sweden, 3 centers in Switzerland, 12 centers in Turkey, and 6 centers in the United Kingdom.

Study Population: The study population consisted of patients with RRMS. Treatment naïve patients and those previously treated with MS drugs were allowed to participate in the study.

Key Inclusion criteria:

1. Males or females aged 18-55 years
2. Diagnosis of MS as defined by 2005 revised McDonald criteria
3. A relapsing-remitting course with at least one documented relapse during the previous year or two documented relapses during the previous 2 years prior to randomization
4. EDSS score of 0-5.5 inclusive
5. Patients who declined initiation or continuation of treatment with available disease modifying drugs
6. No evidence of relapse or corticosteroid treatment within 30 days prior to randomization

Key Exclusion criteria

1. Manifestation of MS other than RRMS
2. History of chronic disease of the immune system other than MS or a known immunodeficiency syndrome
3. History of or presence of malignancy (except successfully treated basal or squamous cell carcinoma of the skin)
4. History or new diagnosis of diabetes mellitus
5. Diagnosis of macular edema during pre randomization phase (patients with a history of macular edema were allowed to enter the study provided that they did not have macular edema at the ophthalmic screening visit).
6. Active systemic infection
7. Received total lymphoid irradiation or bone marrow transplantation
8. Had been treated with systemic corticosteroids or adrenocorticotropic hormones (ACTH) within 1 month prior to randomization; immunosuppressive medications such as azathioprine or methotrexate within 6 months prior to randomization; immunoglobulins and/or monoclonal antibodies (including natalizumab) within 6 months prior to randomization; IFN-ß or GA within 3 months prior to randomization; or cladribine, cyclophosphamide, or mitoxantrone at any time
9. Any of the following cardiovascular conditions:

- Myocardial infarction within the 6 months prior to enrollment or current unstable ischemic heart disease
- History of angina pectoris due to coronary spasm or history of Raynaud's phenomenon

- Cardiac failure at time of screening or any severe cardiac disease as determined by the investigator
- History of cardiac arrest, symptomatic bradycardia, sick sinus syndrome or sino-atrial heart block, or positive tilt test from workup for vasovagal syncope
- Resting pulse rate < 55 bpm prior to randomization
- History or presence of a second degree AV block or a third degree AV block or an increased QTc interval > 440 ms on screening ECG
- Arrhythmia requiring current treatment with Class III anti-arrhythmic drugs (i.e. amiodarone, bretylium, sotalol, ibulitide, azimilide, dofelitide)
- Hypertension uncontrolled by medication

10. Any of the following pulmonary conditions:
- Severe respiratory disease or pulmonary fibrosis
- Tuberculosis, except for history of successfully treated tuberculosis or history of prophylactic treatment after positive PPD skin reaction
- Abnormal chest x-ray or HRCT (at selected sites) suggestive of active pulmonary disease
- Abnormal pulmonary function tests: FEV1, FVC values lower than 70% of value, diffusion capacity of carbon monoxide (DLCO) values lower than 60% of predicted value
- Asthma requiring daily (chronic) therapies

11. Any of the following hepatic conditions:
- Known history of alcohol abuse, chronic liver or biliary disease
- Total bilirubin greater than the upper limit of the normal (ULN) range, unless in context of Gilbert's syndrome
- Conjugated bilirubin greater than ULN range
- Alkaline phosphatase greater than 1.5 times ULN range
- Aspartate aminotransferase/ serum glutamic-oxaloacetic transaminase (AST/SGOT), alanine aminotransferase/ serum glutamic-pyruvic transaminase (ALT/SGPT) greater than 2 times ULN (Canada only: ALT/SGPT greater than 1.5 times ULN)
- Gamma-glutamyl-transferase (GGT) greater than 3 times ULN range

12. Any of the following abnormal laboratory values:
- Serum creatinine > 1.7 mg/dL (150 µmol/L)
- White blood cell (WBC) count < 3,500/mm^3 (< 3.5 x 10^9/ L)
- Lymphocyte count < 800/mm^3 (< 0.8 x 10^9/ L)

Removal of patients from therapy or assessments:

Patients who discontinued study drug were not considered withdrawn from the study unless one of the following reasons applied:

- Withdrawal of informed consent
- Lost to follow-up
- Death
- Withdrawal at the investigator's discretion

Protocol violations did not lead to patient withdrawal unless they indicated a significant risk to the patient's safety. Patients could have voluntarily withdrawn from the study for any reason at any time. Patients who were prematurely withdrawn from the study were not replaced.

Premature patient withdrawals and study drug discontinuations

Patients, who prematurely discontinued study drug for any reason, were to return for a follow-up safety visit 3 months after discontinuing study drug. Patients were then encouraged to continue in the study with an abbreviated schedule of assessments to provide additional safety and efficacy data (Table 4). Patients who prematurely discontinued study drug for any reason and did not wish to continue in the study as per protocol were considered to have prematurely withdrawn from the study.

Table 4: Abbreviated schedule of assessments for patients discontinuing study drug

Phase	Double-blind treatment						
Visit No.	7	8	9	10	11	12	13
Study month	6	9	12	15	18	21	24
MS relapses	X	X	X	X	X	X	X
MS treatment/ steroids	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X
EDSS	X	X	X	X	X	X	X
MSFC	X		X		X		X
MRI	X		X				X
EQ-5D			X				X
Physical exam	X		X		X		X
Dermatology exam (by a dermatologist)			X				X
Vital signs	X	X	X	X	X	X	X
Laboratory values	X		X		X		X
AEs	X	X	X	X	X	X	X
SAEs (if any)							

Patients were to complete the 3-month follow-up visit 3 months after discontinuing study drug and then follow the next scheduled visit outlined in this table.

Treatments administered

Investigational drug:
FTY720 0.5 mg capsules for oral administration once daily
FTY720 1.25 mg capsule for oral administration once daily

Reference therapy:
Matching FTY720 placebo in capsules for oral administration once daily

Patients were randomized 1:1:1. The first dose was taken in the clinic and the patient was monitored for 6 hours after this first dose intake. All other doses were taken at home. Dose adjustments were not allowed, but drug interruptions were allowed based on the judgment of the investigator. If treatment was restarted, then the first dose intake at re-start was to take place at the study site to ensure 6 hours of monitoring.

Concomitant therapy

A standard course of corticosteroids on an inpatient or outpatient basis was allowed for treatment of relapses as clinically warranted. Use of any oral tapering was not permitted. If the patient required an unscheduled MRI, steroids were not to be taken prior to conducting the MRI.

Prohibited medication

Use of the following treatments was not allowed during the course of the study:

- Immunosuppressive medications (i.e., azothioprine, methotrexate, cyclophosphamide, mitoxantrone, cladribine)
- Other concomitant medications: immunoglobulins, monoclonal antibodies (including natalizumab), INF-ß, glatiramer acetate, ACTH

The use of any live or live attenuated vaccines (including for measles) was not allowed concomitantly with the study drug during the course of the study and for 3 months after study drug discontinuation, after which they could be administered provided that lymphocyte counts were in the laboratory normal range.

It was recommended not to initiate treatment with beta-blockers, calcium channel blockers, or digoxin within one week before or after the first dose of the study drug or the day of re-initiation of study drug due to a possible additive effect on heart rate reduction.

Efficacy Outcome Measures

Primary efficacy outcome measure

The primary endpoint was the aggregate annualized relapse rate (ARR) at 24 months, which was defined as the number of relapses per year. For the primary analysis, the ARR of the treatment group was calculated by taking the total number of confirmed relapses for all the patients in the treatment group divided by the total number of days

on study for all patients in the group and multiplied by 365.25 to obtain the annual rate (ITT). Only confirmed relapses were considered for the primary analyses.

Key secondary efficacy outcome measure

The key secondary efficacy endpoint was time to 3-month confirmed disability progression up to month 24.

Analysis plan:

The primary endpoint (ARR) and the key secondary endpoint (time to 3-month confirmed disability progression) were tested in hierarchical order as follows:

1. FTY720 1.25 mg vs. placebo testing treatment difference for aggregate ARR (using negative binomial model with covariates treatment, country, number of relapses in previous 2 years, and baseline EDSS);

2. FTY720 0.5 mg vs. placebo testing treatment difference for aggregate ARR (using negative binomial model with covariates treatment, country, number of relapses in previous 2 years, and baseline EDSS);

3. FTY720 1.25 mg vs. placebo testing treatment difference for time to 3-month confirmed disability progression (using log-rank test);

4. FTY720 0.5 mg vs. placebo testing treatment difference for time to 3-month confirmed disability progression (using log-rank test).

Each testing was performed at a significance level of 0.05 for the four comparisons. However, the lower-rank testing was only performed when every higher-rank testing was statistically significant. The multiplicity adjustment was applied to control the type-I error rate for the study.

Primary endpoint analysis
For the negative binomial regression used to the primary endpoint analysis, the response variable was the number of relapses for each patient and quadratic variance estimate was used. Log (time on study in years) was used as the offset variable to account for the varying lengths of patients' time in the study, which allows the hypothesis testing and the estimates of the relapse rate. The ARR and its confidence interval for each treatment group were estimated from the model.

When calculating the number of days on study for each patient, the following was used. If a patient completed study and took extension medication, the number of days on study was calculated as (1st extension dose date – 1st core dose date). If a patient did

not take any extension medication, the number of days on study was calculated as the minimum of (max(Visit 778 date, last core dose date) – 1st core dose date +1) or 734 (720 days defined for 24 months + 14 days for visit window). In case study phase completion (Visit 778) date was not available, the latest date from VIS panel was used instead (i.e. max(latest date from VIS panel, last core dose date)). This was not the study drug discontinuation (SDD) date (Visit 777 date) because the protocol allowed the SDD patients to continue in the study until the end of the study. The confirmed relapses within this time period were counted for this patient that was used in the ARR computation.

Key secondary endpoint analysis

Log-rank test was the key secondary efficacy analysis for data up to 24 months for the ITT population. There were two treatment comparisons for the time to 3-month confirmed disability progression: FTY720 1.25 mg vs. placebo, and FTY720 0.5 mg vs. placebo.

Kaplan-Meier estimates at 12 and 24 months, together with their 95% confidence intervals, were calculated and presented. Two-sided 95% confidence intervals of the difference in Kaplan-Meier estimates at 12 and 24 months were also used to visually compare progression rates between the treatment groups. Corresponding Kaplan-Meier plots were provided.

Population definitions

- Randomized population (RND): All patients who were assigned randomization numbers. This population was used to summarize patient disposition, demographic and baseline characteristics, and protocol deviation information.

- Intention-to-treat population (ITT): All patients who were randomized and received at least one dose of study medication. Patients were grouped according to the assigned treatment. Efficacy analyses were performed on the ITT population.

- Per-protocol population (PP): All patients in the ITT population without any major protocol deviations. Major protocol deviations were determined before unblinding the treatment according to the pre-defined protocol deviation criteria, which have been specified prospectively. Any efficacy data after study drug withdrawal were excluded. This population was used for the supportive analyses of the primary efficacy endpoint and key secondary endpoints.

- Safety population (SAF): All patients who received at least one dose of study medication. Patients were analyzed according to the treatment received. Safety and tolerability analyses were performed on the safety population. Some of the safety assessment, such as chest HRCT (baseline and month 12 scheduled

assessments), OCT (month 1, 3 and 6 serial collection), and 24-hour holter were only done on a subgroup of patients. The analysis on these safety assessments was performed on the subgroup of the safety population.

- Follow-up population (FU): All patients who had at least one assessment after the study drug discontinuation and did not enter in the extension phase. Patients were analyzed according to the treatment received.

- Pharmacokinetic (PK) population: All patients with available PK samples. Patients were analyzed according to the treatment received.

Relapse and disability progression definitions

MS relapses
The appearance of a new neurological abnormality or worsening of a previously stable or improving pre-existing neurological abnormality, separated by at least 30 days from the onset of a preceding clinical demyelinating event. The abnormality must have been present for at least 24 hours and have occurred in the absence of fever (< 37.5°C) or infection.

Confirmed relapse
A relapse must have been confirmed by the independent evaluating Physician (examining neurologist). It was recommended that this occur within 7 days of the onset of symptoms. A relapse was confirmed when it was accompanied by an increase of at least half a step (0.5) on the EDSS or an increase of 1 point on two different functional systems (FS) of the EDSS or 2 points on one of the FS (excluding bowel/bladder or cerebral FS).

Disability progression
Disability progression required a one point (1) increase from baseline in patients with baseline EDSS score from 0 to 5.0; or half a point (0.5) increase in patients with baseline EDSS score of 5.5 or above.

Confirmed disability progression
A 3-month confirmed disability progression required onset EDSS, 3-month confirming EDSS, and all EDSS in between to meet the disability progression criteria. The confirmatory EDSS was required to occur in the absence of relapse, and to occur ≥ 76 days after the onset EDSS, and to be at a scheduled visit. However, unscheduled visits were not used as confirmation visits, whether or not in absence of a relapse.

Other secondary efficacy analyses

The following secondary analyses are exploratory, as there was no plan for correction for multiple comparisons for these endpoints. The ITT population was used for all other secondary efficacy analyses unless otherwise specified.

MRI inflammatory measures
MRI efficacy variables included the following:
Inflammatory activity up to 24 months:

- Number of new and newly enlarged T2 lesions
- Proportion of patients free of new/newly enlarged T2 lesions
- Proportion of patients free of Gd-enhancing T1 lesions
- Number of Gd-enhancing T1 lesions
- Volume of Gd-enhancing T1 lesions
- Proportion of patients free of new inflammatory activity (no Gd-enhancing T1 lesions and no new/ newly enlarged T2 lesions)

Burden of disease up to 24 months:

- Change and percent change from baseline in volume of T2 lesions
- Change and percent change from baseline in volume of T1 hypointense lesions

Brain volume up to 24 months:

- Percent change from baseline in brain volume (atrophy)

The proportions were analyzed using logistic regression model adjusted for treatment, country and corresponding MRI baseline measurement. The continuous and count variables were compared between treatment arms using rank ANCOVA adjusted for treatment, country and corresponding MRI baseline measurement. For change from baseline and percent changes from baseline for volume of T2 hyperintense lesions and volume of T1 hypointense lesions, rank ANCOVA with covariates of treatment, country, and baseline volume of T2 lesions (for volume of T2 lesions) or T1 hypointense lesions (for volume of T1 hypointense lesions) will be used for treatment comparisons, respectively.

In addition, for the number of new or newly-enlarged T2 lesions, treatment comparison was tested using a negative binomial model adjusted for treatment and country. This was the main analysis for this variable.

MRI analysis method
T1-weighted images before and after administration of contrast medium (gadolinium-DTPA at the single dose of 0.1 mmol/kg i.v.) as well as T2-weighted (T2 and proton density (PD)) images were performed at each scheduled visit. Investigators were requested to avoid performing MRIs within 30 days of the initiation of steroid treatment. MRI scans were evaluated centrally at the MS MRI Evaluation Center, University Hospital, Basel, Switzerland. The central reader checked the scans for completeness and quality. After completion of the quality check, all scans were analyzed by blinded readers. Numbers of new/newly enlarging T2 lesions, number and volume of Gd-

enhancing lesions, total volume of T2 lesions, total volume of T1 hypointense lesions, brain volume at baseline and change over time were obtained according to the protocol.

Lesions were identified as follows:

- Gd-enhancing lesions, hyper-intense areas after contrast administration by comparing the pre-contrast T1-weighted images with the post-contrast T1-weighted images. Lesions expanding throughout several slices were counted only on the first slice.
- T2 lesions, hyperintensity areas compared to the surrounding white matter and grey matter in PD-weighted images.
- New/newly enlarged T2 lesions were identified by comparing each T2 lesion in PD-weighted images with the T2 lesions already seen in previous examinations. New lesions were counted if they had a minimal major diameter of 5mm. Lesions were considered as newly enlarged if the size had increased by approximately 50%. All new/newly enlarged T2 lesions were counted independently whether it showed contrast enhancement or not in T1 weighted sequences. New/newly enlarged T2 lesions expanding throughout several slices were counted only on the first slice.
- T1-hypointense lesions (also called black holes) were identified as areas of hypointensity compared to surrounding white matter in T1-weighted images after contrast administration corresponding with a T2 lesion in PD-weighted images.

Calculations of brain volume change were performed using the structural image evaluation of normalized atrophy (SIENA).

To avoid potential interference caused by steroids used for the treatment of MS relapses, the following restrictions applied:

- In case of relapse, if an MRI was scheduled within 30 days of the initiation of steroid treatment, this MRI was to be performed before steroid treatment was initiated
- No MRI scan was to be performed while a patient was on intravenous steroid therapy and within 30 days after termination of steroid therapy

Health-related quality of life

The EuroQoL (EQ-5D) is an instrument designed for use as a measure of health outcome. The EQ-5D was offered at baseline (Visit 2), month 12 (Visit 9), and month 24 (Visit 13). This quality of life instrument has not undergone PRO validation at the FDA.

Relapse variables

The following confirmed relapse variables were analyzed to test for difference in efficacy of FTY720 (1.25 mg and 0.5 mg) vs. placebo in patients with RRMS treated for up to 24 months:

- Time to first relapse
- Time to second relapse
- Frequency of corticosteroid use to treat relapses
- Frequency of hospitalizations due to relapses

Additional endpoints were measured:

- Severity of relapses
- Impact on daily activities
- Recovery status
- Duration of relapse

For the time to first and second relapse (confirmed relapses only), a comparison of the survival curves among treatment groups was made with the log-rank test for the two FTY720 treatment groups (1.25 mg and 0.5 mg) versus placebo.

As supportive analyses, Cox's proportional hazards model was used to model time to event adjusted for treatment, country, number of relapses in previous 2 years, and baseline EDSS.

In addition, Kaplan-Meier estimates at 12 months and at 24 months, together with 95% confidence intervals, were presented. Two-sided 95% confidence intervals of the difference in Kaplan-Meier estimates were used to visually compare relapse rates between the treatment groups. Corresponding Kaplan-Meier survival curves were constructed (by treatment group).

The use of corticosteroid (to treat the relapse), hospitalizations due to relapse, severity of relapses, impact on daily activities, recovery status, and duration of relapse were summarized by treatment arm. The treatment arms were compared using fisher's exact test (for categorical variables) or Wilcoxon rank sum test (for continuous variables).

Disability progression-related variables

Other secondary disability progression endpoints included:

- Time to 6-month confirmed disability progression as measured by EDSS,
- Change from Baseline to the end of study on the EDSS, and
- Change from Baseline to the end of study on the MSFC z-score.

Change from baseline in EDSS and MSFC z-score and its components were analyzed using rank ANCOVA (adjusted for treatment, country, the corresponding baseline value, and age) to compare the scores between the treatment arms.

A 6-month disability progression based on MSFC for each patient was defined as a 20% or more deterioration from baseline that was confirmed 6 months later. Treatment differences were tested using fisher's exact test for proportions.

Interim analysis
No interim efficacy analyses were planned or performed for this study. Periodic efficacy analyses for ARR, T2 and Gd-enhancing lesion counts only were prepared for the DSMB to assess the benefit-risk of the drug.

Determination of sample size
The sample size calculation was performed for the primary efficacy endpoint (ARR) and the main secondary endpoint (the time to confirmed disability progression assessed up to 24 months).

The power calculations for the primary endpoint are based on the Wilcoxon/Mann-Whitney rank sum test to compare the 1.25 mg vs. placebo using the hierarchical method to adjust for multiplicity. Assuming that the annualized relapse rate at 24 months is 0.7 for placebo and 0.42 for FTY720 1.25 mg arm, the relative reduction is 40%. Based on data from the phase II study CFTY720D2201, its extension phase and other historical data for other MS treatment studies, the common standard deviation is assumed to be 1.06. With these assumptions, 416 patients per arm would provide 95% power at the two-sided significance level of 0.05. A simulation study confirmed that the sample size of 416 per arm would provide an adequate power for the primary efficacy analysis.

For the key secondary outcome, assuming an absolute difference of 12% in the proportion of progressing patients at 24 months (30% of patients progressing in the placebo arm and 18% in the FTY720 arms), the sample size required for each treatment group is 312 using a 0.05 level of two-sided log-rank test for equality of survival curves with a power of 93%. This estimate assumes no dropouts before month 24. It was planned to randomize a total of 1250 patients, i.e., approximately 416 patients per arm, to allow for a dropout rate of approximately 25% at 24 months. The expected placebo progression rate of 30% was based on the results of the meta-analysis of two large phase III studies. [7]

5.3.2 Protocol CFTY720D2302

Study Title: A 12-month double-blind, randomized, multicenter, active-controlled, parallel-group study comparing the efficacy and safety of 0.5 mg and 1.25 mg fingolimod (FTY720) administered orally once daily versus interferon ß-1a (Avonex) administered i.m. once weekly in patients with relapsing-remitting multiple sclerosis with optional extension phase

7 Liu C, et al. Disability outcome measures in therapeutic trials of relapsing-remitting multiple sclerosis: effects of heterogeneity of disease course in placebo cohorts. J Neurol Neurosurg Psychiatry 2000;68:450-457.

Major differences in study design between two pivotal trials D2301 and D2302

- Trial D2301 compared two doses of FTY720 to placebo over 24 months and was conducted in all non-US centers
- Trial D2302 compared two doses of FTY720 to an active comparator, Avonex, over 12 months and was conducted in US and non-US centers
- Trial D2302 had an additional key secondary endpoint to measure the effect of FTY720 on MRI inflammatory disease activity.
- Inclusion and exclusion criteria were the same except in trial D2302 patients on prior treatment with IFNβ-1a or glatiramer acetate could be randomized without a washout period
- Treatment naïve patients were defined differently in the two studies (in D2302 patients were still treatment naïve if they used only off label MS medication, but in D2301 patients that used labeled or off label MS medication were not treatment naive)

Objectives:

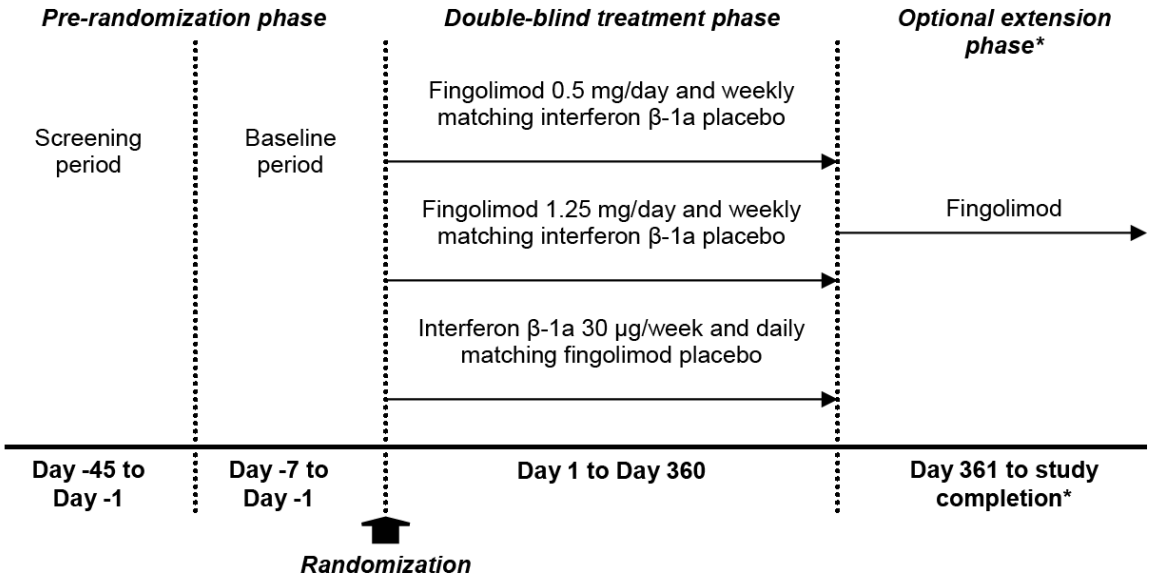
The primary objective was to compare two doses of FTY720 (1.25 mg and 0.5 mg) with IFNβ-1a i.m. to demonstrate that at least 1.25 mg FTY720 is superior to IFNβ-1a i.m. in terms of annualized relapse rate (ARR) in patients with relapsing-remitting multiple sclerosis (RRMS) treated for up to 12 months.

The key secondary objectives were to demonstrate superiority of FTY720 1.25 mg and 0.5 mg over interferon beta-1a i.m. in patients with RRMS treated for up to 12 months with respect to:

1. The effect on inflammatory disease activity as measured by number of new/ newly enlarged T2 lesions at 12 months of treatment.
2. The effect on disability progression as measured by the time to 3-month confirmed disability progression as measured by the EDSS.

Study Design: This was a 12-month, randomized, multicenter, double-blind, double-dummy active-controlled, parallel-group study in patients with RRMS. Patients were randomized to receive a fixed dose of FTY720 0.5 mg/day orally, FTY720 1.25 mg/day orally, or IFNβ-1a 30 µg/week i.m. in a double dummy design. The study consisted of three phases: a pre-randomization phase (lasting for up to 45 days), a double-blind treatment phase (lasting for up to 12 months), and an optional extension phase (see Figure 2).

Figure 2: Study design D2302



During the study, assessments were performed as indicated in the schedule of assessments (refer to Table 5).

Table 5: Assessment schedule: Protocol D2302

Phase	Pre-randomization		Double-blind treatment								
Period	Screening	Baseline									
Visit no.	1	2	3	4	5	6	7	8	9	10	FU[1]
Study month	-1	-1	Day 1	1/2	1	2	3	6	9	12	+3 mo
Informed consent	X										
Background, demography	X										
Inclusion/exclusion criteria	X	X									
Medical history	X										
MS history/MS treatment	X										
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test (serum)[13]	X	X					X	X	X	X	X
Physical exam (source docs only)[2]	X							X		X	X
Dermatology exam (dermatologist)	X									X	
Ophthalmologic examination	X[3]				X		X	X		X	
Chest X-ray/HRCT[4]	X									X	
PFTs	X				X		X	X		X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Hematology/blood chemistry[5]	X	X		X	X	X	X	X	X	X	X
Urinalysis	X	X						X		X	
FTY720 drug administration			X		X	X	X	X	X		
Interferon beta-1a i.m. drug administration			X		X	X	X	X	X		
ECG	X		X[6]		X			X		X	
24-hour Holter ECG[14]	X		X				X				
Echocardiography [15]	X						X			X	
MRI[7]	X									X	X
EQ-5D		X						X		X	
EDSS[8]	X	X					X	X	X	X	X
MSFC[9]	X	X						X		X	
MS relapse[8]	X	X	X	X	X	X	X	X	X	X	X
AEs/SAEs			X	X	X	X	X	X	X	X	X
Pharmacogenetic blood sample	X[10]	X[10]									
Biomarker-plasma sample[10]	X[10]	X[10]						X		X	
Study phase completion										X	
First dose administration			X								
PRIMUS–PRO (selected countries)[11]		X						X		X	
mFIS–PRO (selected countries)[11]		X						X		X	
Pharmacokinetics								X		X	
CSF sample (selected sites)[12]	X[12]	X[12]								X	

Study centers: 172 centers in 18 countries: 7 centers in Argentina, 7 in Australia, 6 in Austria, 4 in Belgium, 6 in Brazil, 9 in Canada, 2 in the Switzerland, 5 in Egypt, 6 in France, 28 in Germany, 6 in Greece, 6 in Hungary, 22 in Italy, 4 in Korea, 8 in Spain, 5 in Portugal, 4 in the United Kingdom, and 37 in the United States.

Study Population: The study population consisted of patients with RRMS.

Key inclusion and exclusion criteria are exactly the same as those for protocol D2301 with the exception that in trial D2302 patients on prior treatment with IFNβ-1a or GA could be randomized without a washout period.

Removal of patients from therapy or assessments was handled in the identical way as described for protocol D2301 in section 5.3.1. Patients that prematurely discontinued study drug were asked to return for a follow-up safety visit after 3 months and then were encouraged to continue in the study with an abbreviated schedule outlined in Table 6.

Table 6: Abbreviated schedule of assessments for patients discontinuing study drug: D2302

Phase	**Double-blind treatment**		
Visit no.[1]	**8**	**9**	**10**
Study month	**6**	**9**	**12**
MS relapses	X	X	X
MS treatment/steroids	X	X	X
Concomitant medications	X	X	X
EDSS	X	X	X
MSFC	X		X
MRI			X
EQ-5D	X		X
PRIMUS–PRO (selected countries)	X		X
mFIS–PRO (selected countries)	X		X
Physical exam	X		X
Dermatology exam (by dermatologist)			X
Vital signs	X	X	X
Laboratory values	X		X
AEs	X	X	X
SAE reporting (if any)	X	X	X

Treatments administered

Investigational drug
FTY720 1.25 mg capsules for oral administration once daily
FTY720 0.5 mg capsules for oral administration once daily

Control therapy
IFNβ-1a 30 µg in pre-filled syringes for i.m. injection once weekly

Reference therapy
Matching FTY720 placebo in capsules for oral administration once daily

Matching IFNβ-1a placebo in pre-filled syringes for i.m. injection once weekly

Patients were randomized 1:1:1
The first dose was taken in the clinic and the patient was monitored for 6 hours in a similar manner as in trial D2301.

Concomitant therapy and prohibited medication were identical to those specified in section 5.3.1 of this review for protocol D2301.

Efficacy Variables

Primary Outcome Measure

The primary endpoint was the ARR, which is defined as the number of relapses in a year. Only confirmed relapses were considered for the primary analyses.

Key Secondary Outcome Measure:

1. MRI key secondary efficacy endpoint: This endpoint determined the effect on inflammatory disease activity as measured by the number of new/newly enlarged T2 lesions at 12 months.

2. Disease progression key secondary efficacy endpoint: This endpoint determined the time to 3-month confirmed disability progression as measured by EDSS during 12 months.

Patient Reported Outcomes:

In trial D2301, the EuroQoL (ED-5D) was assessed to evaluate health related qualify of life. In trial D2302, in addition to the ED-5D, the patient reported indices in Multiple Sclerosis (PRISMUS) instrument was used to asses quality of life and the modified fatigue impact scale (mFIS) was used to assess fatigue.

Statistical Analysis Plan

There was one primary endpoint and two key secondary endpoints with two doses, which yields six FTY720 (1.25 mg and 0.5 mg) comparisons vs. IFNβ-1a i.m. The multiplicity adjustment was applied to control the type-I error rate for the study. The testing of FTY720 comparisons vs. IFNβ-1a i.m. was done in a hierarchical order as follows:

1. FTY720 1.25 mg, ARR
2. FTY720 0.5 mg, ARR
3. FTY720 1.25 mg, the number of new and newly enlarged T2 lesions at 12 months

4. FTY720 0.5 mg, the number of new and newly enlarged T2 lesions at 12 months
5. FTY720 1.25 mg, disability progression
6. FTY720 0.5 mg, disability progression.

Each testing was performed at a significant level of 0.05 for these six comparisons. However, the lower-rank testing was performed only when every high-rank testing was statistically significant.

Primary efficacy variable

The primary variable was the ARR, which is defined as the number of relapses in a year. The ARR of the treatment group was calculated by taking the total number of confirmed relapses for all the patients in the treatment group divided by the total number of days on study for all patients in the group and multiplied by 365.25 to obtain the annual rate. Only confirmed relapses were considered for the primary analyses.

The identical methods for primary analysis evaluations and handling of discontinuations were used as that in D2301.

Secondary efficacy variables

1. Number of new or newly enlarged T2 lesions at Month 12

Summary statistics of the variable were presented. Between-treatment comparisons of FTY720 with IFNβ-1a i.m. were performed using a negative binomial model adjusting for treatment group, country, baseline number of relapses in the previous 2 years, and baseline EDSS. There were two treatment comparisons: FTY720 1.25 mg vs. IFNβ-1a i.m. and FTY720 0.5 mg vs. IFNβ-1a i.m.

2. Time to 3-month confirmed disability progression at Month 12 (proportion of patients free of disability progression at Month 12)

Time-to-event curves for each treatment group were generated by the Kaplan–Meier method and compared by means of the log-rank test (primary analysis). In addition, Kaplan-Meier estimates at month 12, together with their 95% CIs, were calculated and presented. Two-sided 95% CIs of the difference in Kaplan-Meier estimates at 12 months were also used to compare progression rates between the treatment groups.

Cox proportional hazard model was used for the time to 3-month confirmed disability progression adjusting for treatment, country, baseline EDSS and age. Hazard ratios and p-values for the Cox proportional hazard model were provided.
There were two treatment comparisons for the time to 3-month confirmed disability progression: 1.25 mg FTY720 vs. IFNβ-1a i.m. and 0.5 mg FTY720 against IFNβ-1a i.m.

If disability progression did not occur by the 9 month visit, patients were censored for this endpoint since confirmation could not be obtained 3 months later within the planned 12 month study duration.

For patients classified to have confirmed progression, the time to disability progression was calculated from the date of randomization until the date on which a subsequently confirmed progression began. If a patient died due to MS after the start of tentative progression, then the time to disability progression was calculated using the onset date of progression. If a patient died due to MS before having progression, then the time to disability progression was to be censored using the date of death.

A patient was censored if follow-up ended before a confirmed progression occurred. This applied to both PPWs and patients who completed 12 months of study.

Determination of sample size

The sample size calculation used the Wilcoxon/Mann-Whitney rank sum test to compare the FTY720 1.25 mg group with the IFNβ-1a i.m. group. In study CFTY720D2201, a 54.5% relative reduction in the ARR was observed in the FTY720 1.25 mg group compared to the placebo group. Based on historical IFNβ-1a i.m. data and possible patient population difference, the ARRs for IFNβ-1a i.m. and FTY720 1.25 mg group were assumed to be 0.55 and 0.33, respectively (relative reduction 40%). Based on data from study CFTY720D2201, its extension, and limited historical data on other treatments for MS, the common standard deviation (SD) was assumed to be 0.9. With these assumptions, 368 patients per group would provide 90% power at the two-sided significance level of 0.05.

In study CFTY720D2201, the half-year drop-out rate was approximately 8%. Extrapolating this rate to this 12-month study and assuming that these patients contribute nothing to treatment comparison, 57 patients (15.5%) were added to each group. Therefore, a total sample size of 1275 was required (425 patients per group).

Based on the planned sample size of 425 per group, the power for analysis of key secondary variables was evaluated.

1) Treatment comparison for FTY720 1.25 mg vs. IFNβ-1a i.m. on the number of new or newly enlarged T2 lesions at month 12.

Based on historical data, it was assumed that the mean for the number of new or newly enlarged T2 lesions at month 12 for the IFNβ-1a i.m. group is 2.4.[8] It was assumed that the FTY720 1.25 mg group would have an effect size of 25% on the number of new or

8 Rudick, RA, et al. Natalizumab plus Interferon Beta-1a for Relapsing Multiple Sclerosis. N Engl J Med 2006;354:911-23.

newly enlarged T2 lesions at 12 month vs. IFNβ-1a i.m. (i.e. the mean is 1.375 or 25% of 2.4). With the sample size of 368 patients completing the 12-month study, the power to detect a treatment difference for the FTY720 1.25 mg group vs. the IFNβ-1a. group was 90% using a conservative Wilcoxon rank-sum test at a two-sided 0.05 significance level.

2) Treatment comparison for FTY720 1.25 mg vs. IFNβ-1a i.m. on the time to 3- month confirmed disability progression based on EDSS.

Based on historical data for IFNβ-1a i.m., it was assumed that 15% of patients in the IFNβ-1a i.m. group would have 3-month confirmed disability progression. With 425 randomized patients and 57 dropout patients in each group (exponentially distributed), assuming the 12-month progression rate for the FTY720 group was 12% (a relative reduction of 20% from interferon beta-1a i.m.), the power for detecting a treatment difference was 22% using a log-rank test at a two-sided 0.05 significance level.

Changes in the conduct of planned analyses

The following changes to the planned analyses were made through amendments of the statistical analysis plan prior to database lock:

1. The primary analysis method of the primary endpoint, ARR, was changed to negative binomial regression analysis method. Rank ANCOVA replaced Poisson regression with GEE as the supportive analysis method for the ARR.

2. The key secondary efficacy endpoints were changed to 1) the number of new and newly enlarged T2 lesions (MRI), and 2) 3-month confirmed disability progression. The original key secondary endpoint, proportion of relapse-free patients, was moved to a secondary efficacy endpoint.

3. Multiplicity adjustment was extended from primary endpoint only to one primary endpoint and two key secondary endpoints for two doses. For the hypothesis testing, the hierarchical approach was adjusted.

The sponsor sent an addendum to the clinical study report to correct (after data lock) the statistical analysis for key secondary endpoints and other related efficacy endpoints dated 11-22-2009. This addendum was sent in response to the identification by the sponsor that the variable new and newly enlarged T2 lesions was not counted and analyzed according to the methods described in protocol. The sponsor reports that the statistical analysis for the MRI-related key secondary endpoint presented in the clinical study report (CSR) did not count all new or newly enlarged T2 lesions on scans performed at month 12.

After finalization of the trial D2302 clinical study report, the sponsor states that they became aware of two issues that affected the analysis of MRI data for the number of new or newly enlarged T2 lesions.

Issue 1: The analysis plan included the results of all MRI scans that occurred at day 360 ± 14 days (Day 346 to Day 374) assuming that all scans performed within that window were compared to the screening scan to obtain the new or newly enlarged T2 lesions developing over 12 months. However, for patients prematurely discontinuing study drug, the central MRI reader compared the scans to the previous available post-baseline scan either performed at the time of study drug discontinuation or at the follow up visit, therefore not covering the 12 month interval from screening to Month 12. This effected data from eighteen patients who had MRI scans during day 346 to day 374 that was originally included in the analysis. The sponsor excluded data from these 18 patients from the reanalysis of new or newly enlarged T2 lesions at month 12.

Issue 2: The definition of the number of new or newly enlarged T2 lesions at 12 months as intended by the D2302 protocol includes all new or newly enlarged T2 lesions as counted on the month 12 MRI, irrespective of whether such lesions were also Gd-enhancing on T1 sequences. The presence of a corresponding Gd-enhanced T1 lesion at month 12 does not alter the classification of a T2 lesion as new or newly enlarged.

However, the central MRI reader followed the “combined unique active lesion” approach for the evaluation of new or newly enlarged T2 lesions. By using this analysis approach, new or newly enlarged T2 lesions observed at the month 12 MRI were counted as “new or newly enlarged T2 lesions” if they were not associated with Gd-enhancement or as “Gd-enhanced T1 lesions” if there was evidence of any Gd-enhancement for the lesion. This approach would underestimate the number of new or newly enlarged T2 lesions.

In addition, according to the central MRI reader, in order to be counted as a Gd-enhanced T1 lesion at month 12, the lesion had to have a corresponding new or newly enlarged T2 lesion at month 12. Thus, the true count of new and newly enlarged T2 lesions is the count provided by the central reader for T2 lesions plus the count for T1-Gd enhancing lesions at month 12.

Therefore, to obtain the total number of new or newly enlarged T2 lesions at month 12 as intended by the D2302 protocol, reflecting any new inflammatory activity detectable over the duration of a year of treatment, the sponsor provided a reanalysis which added the variable “new or newly enlarged T2 lesions” currently in the database to the variable “Gd-enhanced T1 lesions” to obtain the protocol intended “number of new or newly enlarged T2 lesions at month 12”.

After FDA review of the new analysis and discussions with the sponsor, it was agreed upon that the sponsor would submit another analysis of “new and newly enlarged T2

lesions" after correctly reading all previously incorrectly read MRIs. New datasets were submitted to FDA for confirmation of the sponsor analysis.

5.3.3 Protocol CFY720D2201

Study Title: Double-blind, randomized, placebo-controlled, parallel-group, multicenter study evaluating safety, tolerability and effect on MRI lesion parameters of FTY720 vs. placebo in patients with relapsing multiple sclerosis.

Study objectives:
The primary objective of this study was to evaluate the effect of two doses of FTY720 (5.0 mg and 1.25 mg) on inflammatory activity using MRI. Inflammatory activity was defined as the total number of Gd-enhancing lesions seen on monthly post-baseline MRI scans during 6 months of treatment.

Secondary objectives included evaluation of the effect of FTY720 on other parameters of MRI inflammatory activity and the exploration of the effect of FTY720 on clinical relapses.

Study design: D2201 was a 6 month, double-blind, randomized, placebo-controlled, parallel-group multicenter study evaluating the safety, tolerability and effect on MRI lesion parameters of FTY720 versus placebo in patients with relapsing MS. Monthly MRIs, quarterly EDSS and MSFC scores and MS relapses information was collected.

Study population: Patients had a diagnosis of RRMS or SPMS, were 18-60 years of age, and had at least two documented relapses during the 2 years prior to enrollment with EDSS scores between 0-6.

Outcome measures
Efficacy assessments included MRI scans at baseline and every month post baseline up to 6 months. The primary efficacy variable was the sum of Gd-enhancing lesions recorded on scans from month 1 to 6. Clinical efficacy assessments included MS relapses, EDSS and MSFC quarterly.

Method of Magnetic Resonance Imaging
MRI of the brain was performed using dual T2 weighted images (T2 weighted and proton density weighted) and T1 weighted images before and after double dose of contrast (in contrast to single doses used in D2301 and D2302).

Definition of MS relapse: The definition of a relapse was similar to the definition used in D2301 and D2302, but in D2201 only 14 days of stability or improvement were required between relapses. In addition, the definition of confirmed relapse allowed for a 0.5 point

change on the EDSS and/or 1 point in 1 or more functional systems of the EDSS (excluding bowel/bladder and mental FS).

Statistical Methods
The evaluable population included all randomized patients who had no major protocol deviation and did not discontinue the study drug prematurely and who had the baseline MRI and at least three valid post baseline MRI scans. The ITT included all randomized patients who received at least one dose of study drug and had at least one valid post baseline MRI scan. MRI related analyses used the evaluable population. Clinical endpoints were conducted on the ITT population. No adjustment for type I error was made.

5.3.4 Protocol FTY720D2201E1

Study Title: An extension of the double-blind, randomized, placebo-controlled, parallel-group, multicenter study evaluating safety, tolerability and effect on MRI lesion parameters of FTY720 vs. placebo in patients with relapsing multiple sclerosis.

Study objective
The objectives of this extension study were to evaluate long-term data of FTY720 on clinical and MRI outcomes and to collect long term safety and tolerability data in patients who completed the core study.

Study design
Trial D2201E1 was an open label extension to the 6 month multicenter, randomized double blind, parallel group placebo controlled phase II study D2201. All patients who completed the core study on study treatment were offered the option of continuing in the extension study. Patients randomized to the FTY720 1.25 mg or 5.0 mg dose in the core study were continued on the same dose of study medication in the extension and patients previously randomized to placebo in the core study were re-randomized in a 1:1 ratio to either FTY720 1.25 or 5.0 mg in the extension study. After review of the results of the study, a decision was made by the sponsor to only continue the 1.25 mg dose and transition all patients on the 5.0 mg dose to 1.25 mg. This decision was made because both doses had similar efficacy and the 1.25 mg dose had a more favorable safety profile, according to the sponsor.

Efficacy assessments
MS relapse, quarterly EDSS up to month 36 and every 6 months thereafter, EDSS during relapses, quarterly MSFC up to month 24 and MRI scans at month 12 and yearly thereafter were obtained. Efficacy assessments were performed following the same criteria and procedures as in the placebo controlled phase of the study.

Statistical Analysis

There was no primary efficacy endpoint for this open label extension so only descriptive statistics were provided. Month 60 analyses were conducted in the core ITT population for clinical measures and for MRI data for evaluable measures.

Patient Disposition
Of the 250 patients that entered the extension study 140 patients (49.8%) completed month 60.

5.3.5 Protocol FTY720D2309

A 24 month double blind, randomized, multicenter, placebo controlled, parallel-group study comparing the efficacy and safety of 0.5 mg and 1.25 mg fingolimod administered orally once daily versus placebo in patients with relapsing-remitting multiple sclerosis. This study is almost identical in design to D2301 except it also incorporates special safety studies, to address safety concerns identified during the development program. This trial includes in the study schedule ophthalmologic testing for the first 300 randomized patients, HRCT for the first 360 randomized patients and echocardiography between month 3 and 5. Pulmonary function tests were followed on all patients. 1089 patients have been enrolled into this study which is currently ongoing. Safety but not efficacy data has been provided in this new drug application.

6 Review of Efficacy

Efficacy Summary

Relapse rate

Substantial evidence of effectiveness for the reduction of relapses was provided in this application from the two pivotal efficacy trials, D2301 and D2302. Both trials had robust findings for the primary endpoint of aggregate annualized relapse rate, with p values < 0.001 for both doses compared to control. There was approximately a 54% reduction in the relapse rate of FTY 720 0.5 mg compared to placebo and approximately a 52% reduction compared to IFN ß- 1a. In addition, the supportive analysis looking at the per protocol population (on treatment with no major protocol violations) also provided consistent evidence that FTY720 is effective in reducing the aggregate ARR in patients with RRMS ($p<0.001$).

Disability progression

Disability progression, measured by the EDSS scale, was the only key secondary endpoint in trial D2301, and the second of two key secondary endpoints in trial D2302 (new or enlarging T2 lesion count was the first secondary endpoint of trial D2302).

In trial D2301, FTY720 1.25 mg (p=0.017) and FTY720 0.5 mg (p=0.024) both had a significantly reduced time to confirmed disability progression, compared to placebo. The proportion of patients free of progression was respectively 83%, 82% and 76% for FTY 1.25 mg, 0.5 mg and placebo. Compared to placebo, this represents respectively a 32% and a 30% reduction of the risk of confirmed disability progression for FTY720 1.25 mg and FTY720 0.5 mg.

Trial D2302 was unable to demonstrate a reduction in disability progression for the FTY720 1.25 mg (p=0.543) or FTY720 0.5 mg (p=0.209) group compared to IFN ß- 1a. It must be emphasized that the short duration of the study (12 months) and the comparison to an active control made that endpoint quite challenging in trial D2302. In general for MS patients, a longer study is necessary to demonstrate disability progression.

Exploratory secondary analyses (for which correction for multiple comparisons was not planned) included an alternate disability scale, the Multiple Sclerosis Functional Composite (MSFC). This scale has some important inherent limitations, such as a lack of clear clinical interpretability of the composite z score derived from three subscale scores. Therefore interpretation of the MSFC requires consideration of the changes in the three endpoints that are measured in the MSFC: the paced auditory serial addition test (PASAT-3), the 25 foot timed walk test (25'TWT), and the 9 hole peg test (9HPT). While the overall p values for the MSFC contrast were nominally under 0.05 (unadjusted for multiple comparisons) for both fingolimod groups compared to their control in both studies, data for the PASAT-3, 25'TWT and 9HPT were inconsistent.

Number of new or newly enlarged T2 lesions

The next key secondary endpoint pre-specified only in trial D2302 was the number of new or newly enlarged T2 lesions at month 12. The initial analysis provided by the sponsor with this application, was not supportive of efficacy of this endpoint for the low dose group (p=0.053), although there was evidence of efficacy at the high dose group (p=0.017) compared to placebo. An addendum to the statistical analysis was sent which included a reanalysis of this endpoint based on two issues identified by the sponsor. The sponsor reanalyzed the data without 18 patients that did not have a 12 month MRI to compare to the baseline and with revised data that resulted from recounting the new and newly enlarged T2 lesion variable. The sponsor claimed that the method pre-specified in the protocol for counting these lesions was not adhered to by the central MRI reader. Essentially, all new or newly enlarged T2 lesions were counted only if there was not Gd enhancement on T1 by the central MRI reader for the original analysis, but the lesions should have been counted as T2 lesions whether or not there was Gd enhancement. The sponsor proposed adding the T2 lesion variable with the Gd-enhanced variable to yield the new "T2 lesion variable". FDA requested that the sponsor go back to the MRIs and recount the lesions directly rather than adding the variables. In addition, FDA suggested including the 18 patients and if necessary using

the last observation carried forward method to obtain the missing variables for the MRI data. The sponsor submitted the new analysis and although there was a lack of concordance on many specific values for comparison groups between the sponsor and the FDA analysis for this endpoint, the FDA analysis demonstrated that there was a robust statistically significant treatment effect of fingolimod on the number of T2 lesions for both the high (p=0.0017) and the low dose (p=0.0007) fingolimod groups compared to control.

6.1 Indication

As disease modifying therapy for the treatment of patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.

Reviewer comment: The pivotal trials enrolled patients with the diagnosis of RRMS. The efficacy data submitted in this drug application included all patients with RRMS with the exception of the 31 patients with secondary progressive multiple sclerosis enrolled in the phase II trial. Data concerning efficacy cannot be generalized from this phase II trial since this trial used doses higher than that requested for marketing authorization by the sponsor. Therefore the development program for fingolimod in RRMS at relevant doses has only focused on patients with RRMS. For this reason, the approved indication statement should read " for the treatment of patients with relapsing remitting multiple sclerosis…..".

6.1.1 Method

Two pivotal studies were provided to support efficacy of fingolimod, protocol D2301 and D2302. Please see section 5.3 of this review for an in depth discussion of the trial protocols.

6.1.2 Demographics

The groups in both trials were balanced for age, sex and race overall. Patients were predominantly Caucasian, female and the mean age was 36.6 for all randomized patients in both trials.

There were slight differences in the populations studied in trial D2301 and D2302 in terms of demographic and baseline MS characteristics. The population in trial D2301 was, on average, one year older, had disease for one year longer, had a slightly higher mean EDSS and had slightly more MRI inflammatory activity at baseline compared with the population in study D2302. Overall, these minor differences do not represent significant baseline differences in the randomized patients in these two pivotal trials. Please see Table 7 and Table 8 below.

Table 7: Demographic characteristics-trials D2301 and D2302 (randomized population)

Study D2301	**FTY720 1.25mg N = 429**	**FTY720 0.5mg N = 425**	**Placebo N = 418**	**Total N = 1272**
Age (years)				
Mean (SD)	37.4 (8.91)	36.6 (8.77)	37.2 (8.60)	37.1 (8.76)
Median (range)	38.0 (17 – 55)	36.0 (18 – 55)	37.0 (18 – 55)	37.0 (17 – 55)
Gender n (%)				
Male	134 (31.2)	129 (30.4)	120 (28.7)	383 (30.1)
Female	295 (68.8)	296 (69.6)	298 (71.3)	889 (69.9)
Race - n (%)				
Caucasian	408 (95.1)	406 (95.5)	399 (95.5)	1213 (95.4)
Study D2302	**FTY720 1.25 mg (N = 426)**	**FTY720 0.5 mg (N = 431)**	**IFN β-1a i.m. (N = 435)**	**Total (N = 1292)**
Age (years)				
Mean (SD)	35.8 (8.39)	36.7 (8.81)	36.0 (8.29)	36.2 (8.50)
Median (range)	36.0 (18 – 54)	37.0 (18 – 55)	36.0 (18 – 55)	36.0 (18 – 55)
Gender- n (%)				
Male	133 (31.2)	149 (34.6)	140 (32.2)	422 (32.7)
Female	293 (68.8)	282 (65.4)	295 (67.8)	870 (67.3)
Race - n (%)				
Caucasian	404 (94.8)	404 (93.7)	408 (93.8)	1216 (94.1)

Table 8: MS disease baseline characteristics: trials D2301 and D2302 (randomized population)

Study D2301	FTY720 1.25 mg N = 429	FTY720 0.5 mg N = 425	Placebo N = 418	Total N = 1272
Duration of MS since first symptom (years)				
Mean (SD)	8.4 (6.86)	8.0 (6.60)	8.1 (6.35)	8.2 (6.60)
Median (range)	6.9 (0 – 37)	6.6 (0 – 35)	7.0 (0 – 32)	6.7 (0 – 37)
Number of relapses in the last 2 years				
Mean (SD)	2.1 (1.25)	2.1 (1.13)	2.2 (1.19)	2.1 (1.19)
Median (range)	2.0 (1 – 10)	2.0 (1 – 11)	2.0 (1 – 10)	2.0 (1 – 11)
EDSS				
Mean (SD)	2.4 (1.4)	2.3 (1.3)	2.5 (1.3)	2.4 (1.3)
Median (range)	2.0 (0.0 - 5.5)	2.0 (0.0 - 5.5)	2.0 (0.0 - 5.5)	2.0 (0.0 - 5.5)
Study D2302	**FTY720 1.25 mg N = 426**	**FTY720 0.5 mg N = 431**	**IFN β-1a i.m. N = 435**	**Total N = 1292**
Duration of MS since first symptom (years)				
n	420	429	431	1280
Mean (SD)	7.3 (6.0)	7.5 (6.2)	7.4 (6.3)	7.4 (6.2)
Median (range)	6.0 (0 – 33)	5.8 (0 – 34)	5.8 (0 – 40)	5.9 (0 – 40)
Number of relapses in the last 2 years				
n	425	431	434	1290
Mean (SD)	2.2 (1.2)	2.3 (2.2)	2.3 (1.2)	2.2 (1.6)
Median (range)	2.0 (1 – 8)	2.0 (1 – 40*)	2.0 (1 – 12)	2.0 (1 – 40)
EDSS				
n	420	429	431	1280
Mean (SD)	2.21 (1.31)	2.24 (1.33)	2.19 (1.26)	2.21 (1.30)

A higher proportion of treatment naïve patients were recruited in trial D2301 (59%) than D2302 (43%) (Refer to Table 9 below). Treatment naive patients were defined differently in trial D2301 and D2302. In trial D2301, patients who had previously not received any disease modifying agents (including off label use of drugs such as azathioprine, methotrexate, experimental drugs and one of the approved drugs for the treatment of MS) were classified as treatment naive. In trial D2302, patients who had previously been treated with any one of the five approved MS therapies were classified as previously treated; all others (including patients that received off label medication) were considered treatment naive. If study D2302 used the same definition as D2301, the proportion of treatment naïve patients in study D2302 would have been lower.

Table 9: MS medication history of previous disease-modifying agents- trials D2301 and D2302 (randomized population)

Study D2301	**FTY720 1.25 mg (N = 429)**	**FTY720 0.5 mg (N = 425)**	**Placebo (N = 418)**	**Total (N = 1272)**
Treatment-naïve patients[1], n (%)	259 (60.4)	244 (57.4)	249 (59.6)	752 (59.1)
Previously treated patients, n (%)	170 (39.6)	181 (42.6)	169 (40.4)	520 (40.9)
Study D2302	**FTY720 1.25 mg (N = 426)**	**FTY720 0.5 mg (N = 431)**	**IFN β-1a i.m. (N = 435)**	**Total (N = 1292)**
Treatment-naïve patients[2], n (%)	177 (41.5)	193 (44.8)	190 (43.7)	560 (43.3)
Previously treated patients, n (%)	249 (58.5)	238 (55.2)	245 (56.3)	732 (56.7)

Abbreviation: IFN = interferon

[1] Treatment-naïve patients were defined as those not receiving any of MS disease-modifying drugs, approved or not (excluding symptomatic therapies).
[2] Treatment-naïve patients were defined as those not receiving any of the approved 5 MS disease-modifying drugs (i.e., any interferon beta, glatiramer acetate or natalizumab).

MS MRI baseline characteristics

Baseline MRI characteristics were similar among treatment groups in D2301 and D2302 with the following exception. In study D2302 the mean number of Gd-enhancing lesions at baseline was slightly higher in the FTY720 1.25 mg group compared to the FTY720 0.5 mg and the active control. D2301 subjects had slightly more MRI activity than those of D2302. Fewer patients in D2301 were free of Gd-enhancing lesions, had higher numbers of Gd-enhancing lesions, Gd-enhancing volume and T2 lesion volume (see Table 10) as compared to D2302.

Table 10: Multiple Sclerosis MRI baseline parameters- Trial D2301 and D2302 (randomized population)

D2301	FTY720 1.25 mg N = 429	FTY720 0.5 mg N = 425	Placebo N = 418	Total N = 1272
Proportion of patients free of Gd-enhancing lesions – n (%)				
n	424	424	416	1264
n (%)	257 (60.6)	263 (62.0)	262 (63.0)	782 (61.9)
Number of Gd-enhancing lesions				
n	424	424	416	1264
Median (mean)	0.0 (1.8)	0.0 (1.6)	0.0 (1.3)	0.0 (1.6)
Total volume of T2 lesions (mm^3)				
n	425	424	416	1265
Median (mean)	3556.5 (6828.7)	3303.4 (6127.7)	3416.3 (6162.4)	3453.3 (6374.6)
Normalized brain volume (cc)				
n	423	424	414	1261
Median (mean)	1514.7 (1510.5)	1528.5 (1520.8)	1514.8 (1512.2)	1520.2 (1514.5)
D2302	**FTY720 1.25 mg N = 426**	**FTY720 0.5 mg N = 431**	**IFN β-1a i.m. N = 435**	**Total N = 1292**
Proportion of patients free of Gd-enhancing lesions – n (%)				
n	412	427	425	1264
n (%)	270 (65.5)	288 (67.4)	268 (63.1)	826 (65.3)
Number of Gd-enhancing lesions				
n	412	427	425	1264
Median (mean)	0.0 (1.5)	0.0 (1.0)	0.0 (1.1)	0.0 (1.2)
Total volume of T2 lesions (mm^3)				
n	413	428	425	1266
Median (mean)	3095.9 (5085.4)	2381.8 (5169.6)	2901.1 (4923.6)	2786.6 (5059.5)
Normalized brain volume (cc)				
n	409	421	420	1250
Median (mean)	1527.8 (1526.2)	1526.2 (1524.1)	1533.3 (1526.7)	1529.5 (1525.7)

Applicability of Foreign Data

The principal database provided to support efficacy for this NDA is derived from trials that include 144 U.S patients out of a total of 2564 randomized patients. The sponsor provided the following justification of why the data from predominantly non-U.S. patients can be generalized to a U.S. population: 1) MS is not a disease that has known geographical differences in terms of clinical phenotype or severity. The only exception, relating to disease severity and response to therapy is that of African Americans. African Americans represent only a small portion of MS patients in the US, and in the clinical trials described in this application. The majority of MS patients are Caucasian, likely the result of shared genetic background to European ancestry. In addition, emigration patterns to the U.S. suggest that a substantial portion of the US population share the genetic heritage with northern Europeans. 2) The demographics and disease patterns from the patients from the US who enrolled in D2302 are similar to that of the

overall study population. The US patients tended to be slightly older, with a lower proportion of Caucasians (85% vs. 95%) and had higher body mass indexes (BMIs). 3) Practice patterns in MS have become considerably more homogeneous than in the past, as more therapies have become available to treat this disorder. In addition, international attendance at major MS meetings has encouraged standardization of disease management. 4) Although the number of US patients included in the fingolimod trials were proportionately small compared to the overall program, many other marketed products for MS had equally small numbers of US patients at the time of marketing approval. These include Rebif (339 patients), Betaseron (207 patients), Copaxone (251 patients) and Mitoxanthrone (no US patients- 188 patients overall). 5) At a meeting with the sponsor, FDA agreed that on face, although it appeared that only 15% or less of patients would be from the US in this marketing application this would probably be acceptable.

An efficacy analysis for the ARR done by FDA statistician, Dr. Yan, is included in Table 11 below.

Table 11: Dr. Yan's Analysis of ARR by region- trial D2302

D2302	FTY720 1.25 mg N=420	FTY720 0.5 mg N=429	IFN β-1a N=430
Overall Adjusted ARR	0.20	0.16	0.33
By Region			
US, n	42	42	45
Adjusted ARR	0.16	0.28	0.28
95% CI	(0.075, 0.341)	(0.157, 0.499)	(0.163, 0.496)
Nominal p-value	0.2922	0.9043	
Non-US, n	378	387	386
Adjusted ARR	0.21	0.15	0.33
95% CI	(0.158, 0.271)	(0.110, 0.199)	(0.260, 0.424)
Nominal p-value	<.001	<.0001	
Non-US excluding Korea and Greece, n	360	370	372
Adjusted ARR	0.24	0.17	0.39
95% CI	(0.186, 0.307)	(0.132, 0.229)	(0.310, 0.478)
Nominal p-value	<.001	<.0001	

Reviewer's comments: The sponsor's justification of the applicability of foreign data is acceptable. The U.S. data represents approximately 5% of the efficacy data provided in this application. Due to the small numbers of U.S. patients and the large confidence intervals seen in the data generated from them, limited conclusions can be made about treatment effects in this subgroup of patients.

6.1.3 Subject Disposition

The number of patients randomized per treatment group in both trials was similar (Table 12). In trial D2301 a total of 1564 patients were screened, 1272 were randomized and 1033 completed the trial. Of the 326 patients that discontinued study drug, 88 patients remained in the study and completed the abbreviated schedule of assessments through month 24. In trial D2302 1573 patients were screened, 1292 were randomized and 1153 completed the study. Of the 157 patients that discontinued study drug, 30 patients remained in the study and completed the abbreviated schedule of assessments through month 12. There was a lower percentage of patients that completed the study in the 24 month trial, D2301 (81.2%) as compared to the 12 months trial, D2302 (89.2%), as would be expected with trials of different duration.

There was a slightly higher rate of discontinuations in the placebo and FTY720 1.25 mg treatment group than in the FTY720 0.5 mg treatment group in both studies. Discontinuations were higher in the FTY720 groups related to adverse events (AEs) and abnormal laboratory values, while discontinuations were higher in the control groups due to unsatisfactory therapeutic effect.

Table 12: Study participation and discontinuation- studies D2301 and D2302 (randomized population)

Study D2301 (24 months)	**FTY720 1.25 mg**	**FTY720 0.5 mg**	**Placebo**	**Total**
No. of patients randomized	**429**	**425**	**418**	**1272**
Number of patients who completed the study	**332 (77.4)**	**369 (86.8)**	**332 (79.4)**	**1033 (81.2)**
On study drug	297 (69.2)	345 (81.2)	303 (72.5)	945 (74.3)
Off study drug	35 (8.2)	24 (5.6)	29 (6.9)	88 (6.9)
Discontinued from the study – n (%)*	**97 (22.6)**	**56 (13.2)**	**86 (20.6)**	**239 (18.8)**
Subject withdrew consent	31 (7.2)	17 (4.0)	28 (6.7)	76 (6.0)
Adverse event(s)	22 (5.1)	13 (3.1)	18 (4.3)	53 (4.2)
Unsatisfactory therapeutic effect	13 (3.0)	6 (1.4)	25 (6.0)	44 (3.5)
Abnormal laboratory value(s)	20 (4.7)	9 (2.1)	1 (0.2)	30 (2.4)
Lost to follow-up	3 (0.7)	5 (1.2)	7 (1.7)	15 (1.2)
Protocol deviation	5 (1.2)	5 (1.2)	4 (1.0)	14 (1.1)
Abnormal test procedure result(s)	2 (0.5)	1 (0.2)	1 (0.2)	4 (0.3)
Death	1 (0.2)	0 (0.0)	2 (0.5)	3 (0.2)
Study D2302 (12 months)	**FTY720 1.25 mg**	**FTY720 0.5 mg**	**IFN β-1a i.m.**	**Total**
No. of patients randomized	**426**	**431**	**435**	**1292**
Number of patients who completed the study	**369 (86.6)**	**398 (92.3)**	**386 (88.7)**	**1153 (89.2)**
On study drug	358 (84.0)	385 (89.3)	380 (87.4)	1123 (86.9)
Off study drug	11 (2.6)	13 (3.0)	6 (1.4)	30 (2.3)
Discontinued from the study – n (%)*	**57 (13.4)**	**33 (7.7)**	**49 (11.3)**	**139 (10.8)**
Subject withdrew consent	11 (2.6)	9 (2.1)	16 (3.7)	36 (2.8)
Adverse event(s)	26 (6.1)	9 (2.1)	9 (2.1)	44 (3.4)
Unsatisfactory therapeutic effect	3 (0.7)	3 (0.7)	7 (1.6)	13 (1.0)
Abnormal laboratory value(s)	4 (0.9)	6 (1.4)	1 (0.2)	11 (0.9)
Lost to follow-up	1 (0.2)	1 (0.2)	4 (0.9)	6 (0.5)
Protocol deviation	0	0	2 (0.5)	2 (0.2)
Abnormal test procedure result(s)	4 (0.9)	3 (0.7)	3 (0.7)	10 (0.8)
Death	2 (0.5)	0	0	2 (0.2)
Administrative problems	6 (1.4)	2 (0.5)	7 (1.6)	15 (1.2)

6.1.4 Analysis of Primary Endpoint

Annualized relapse rate

The annualized relapse rate was the primary outcome measure in both pivotal studies and represents a widely used and accepted endpoint in patients with relapsing MS. All clinical efficacy measures were performed by two physicians (the treating physician and a second blinded EDSS rater). In an attempt to maintain blinding in trial D2302, enrolled patients were provided instructions to cover the injection site and not discuss

AEs associated with their study treatment injections with the blinded EDSS rater. All MS relapses were defined by the McDonald criteria. A prospective plan was in place for hierarchical testing of the primary endpoints in each study. The ITT group included patients that discontinued study drug but did not withdraw from the study. The percentage of patients that discontinued study drug is comparable for all treatments with the exception of FTY720 1.25 mg group in trial D2301, which had a higher discontinuation rate (refer to Table 12). Since patients that were "off drug" were included in this ITT analysis, the PP analysis becomes a very relevant supportive analysis

In trial D2301, treatment of both doses of FTY720 1.25 mg and 0.5 mg resulted in a significantly lower aggregate ARR compared to placebo, with ARR estimates of 0.16 and 0.18 vs. 0.40 respectively. This corresponds to a reduction of 60% and 54% in the ARR relative to placebo.

In trial D2302, treatment with both FTY720 doses 1.25 mg and 0.5 mg resulted in a significantly lower aggregate ARR compared with treatment with IFNβ-1a i.m. group. The estimated aggregate ARR was 0.20 in the 1.25 mg dose group and 0.16 in the 0.5 mg dose group, versus 0.33 in the IFNβ-1a group. This corresponds to reductions of 38% and 52% in the ARR estimates respectively. No significant dose difference was noted.

Table 13: Summary of clinical efficacy for the primary outcome measure, aggregate annualized relapse rate for protocol D2301 and D2302

	D2301			D2302		
Treatment group	FTY720 1.25 mg (n=429)	FTY720 0.5 mg (n=425)	Placebo (n=418)	FTY720 1.25 mg (n=420)	FTY720 0.5 mg (n=429)	IFNβ-1a, 30ug (n=431)
Number of relapses	86	101	206	105	89	179
ARR estimate	0.16	0.18	0.40	0.20	0.16	0.33
95% CI (ARR estimate)	(0.13,0.19)	(0.15,0.22)	(0.34,0.47)	(0.16,0.26)	(0.12,0.21)	(0.26,0.42)
ARR ratio	0.40	0.46		0.62	0.48	
P value	<0.001*	<0.001*		<0.001*	<0.001*	

*indicates two-sided statistical significance at 0.05 level

No statistically significant differences were observed in the ARR between FTY720 1.25 mg and 0.5 mg in both phase III studies D2301 and D2302.

Sensitivity analyses of the ARR
The sponsor performed three informative sensitivity analyses in the phase III studies D2301 and D2302. 1) aggregate ARR in the PP population for confirmed relapses (ARR in patients on study drug only with no major protocol violations) 2) aggregate ARR in the ITT for all relapses (confirmed and not confirmed) and 3) aggregate ARR in the PP for all relapses (confirmed and not confirmed). These analyses were performed up to month 24 for D2301 and up to month 12 for D2302 (refer to Table 14 and Table 15).

Table 14: Sensitivity analysis of the ARR up to 24 month- study D2301

Confirmed relapses	FTY720 1.25 mg	FTY720 0.5 mg	Placebo
Aggregate ARR estimate (95% CI) PP population	0.14 (0.11,0.18)	0.18 (0.15, 0.23)	0.41 (0.35, 0.48)
Rate ratio vs. placebo	0.34	0.45	
P value vs. placebo	<0.001	<0.001	
All relapses	FTY720 1.25 mg	FTY720 0.5 mg	Placebo
Aggregate ARR estimate (95% CI) ITT	0.24 (0.20, 0.29)	0.29 (0.25, 0.34)	0.62 (0.54, 0.71)
Rate ratio vs. placebo	0.40	0.47	
P value vs. placebo	<0.001	<0.001	
Aggregate ARR estimate (95% CI) PP	0.22 (0.18, 0.27)	0.29 (0.25, 0.35)	0.64 (0.55, 0.74)
Rate ratio vs. placebo	0.35	0.46	
P value vs. placebo	<0.001	<0.001	

Table 15: Sensitivity analyses of the ARR up to month 12- trial D2302

Confirmed relapses	FTY720 1.25 mg	FTY720 0.5 mg	Control
Aggregate ARR estimate (95% CI) PP population	0.21 (0.16,0.28)	0.17 (0.13, 0.22)	0.35 (0.28, 0.45)
Rate ratio vs. placebo	0.60	0.47	
P value vs. placebo	<0.001	<0.001	
All relapses	FTY720 1.25 mg	FTY720 0.5 mg	Control
Aggregate ARR estimate (95% CI) ITT	0.28 (0.23, 0.35)	0.24 (0.20, 0.30)	0.52 (0.44, 0.62)
Rate ratio vs. placebo	0.54	0.47	
P value vs. placebo	<0.001	<0.001	
Aggregate ARR estimate (95% CI) PP	0.29 (0.23, 0.36)	0.26 (0.20, 0.32)	0.64 (0.45, 0.64)
Rate ratio vs. placebo	0.54	0.48	
P value vs. placebo	<0.001	<0.001	

Reviewer's comments: The primary analyses for both pivotal trials suggest a robust treatment effect of FTY720 over control on the ARR in RRMS. Notable, is the fact that within both studies the relapse rates recorded for both treatment groups and placebo are lower than what has been documented with other approved therapies for RRMS. In addition, the relapse rate for the placebo group is within range for a typical previously approved therapy, rather than the annual relapse rate of an untreated patient. The sensitivity analyses described in Table 14 and Table 15 support the robust findings of the primary analyses. The per protocol analysis describes the ARR only in patients that remained on study treatment with no major protocol violations. In addition, evaluation of the ARR when "all relapses" are included provides consistent results as compared to that seen when only confirmed cases are evaluated. These sensitivity analyses provide further support that FTY720 is effective at lowering the relapse rate in RRMS patients.

6.1.5 Analysis of Key Secondary Endpoints

Disability Progression

In both phase III studies a key secondary objective was to compare the effect of FTY720 1.25 mg and 0.5 mg to control (placebo in D2301 and IFNβ-1a in D2302) on

disability progression as measured by the time to 3 month confirmed disability progression, measured by the EDSS in patients with RRMS. The EDSS is a widely accepted standardized test to evaluate disability in MS patients. A 3-month confirmed disability progression required onset EDSS, 3-month confirming EDSS, and all EDSS in between to meet the disability progression criteria. The EDSS rater used for confirmation of the disability progression was blinded to all information about the patient's treatment.

In Trial D2301, treatment with both doses of FTY720 1.25 mg (p=0.012) and 0.5 mg (p=0.024) resulted in a significantly reduced risk of disability progression compared to treatment with placebo in patients with RRMS. The kaplan- meier estimate of the proportion of patients free of 3-month confirmed disability progression at 24 months was 83.4% in the FTY 720 1.25 mg group and 82.3% in the FTY720 0.5 mg group versus 75.9% in the placebo group (refer to Table 16). Compared to placebo the reduction of the risk of 3 month disability progression was 32% for FTY720 1.25 mg and 30% for FTY720 0.5 mg.

Table 16: Time to 3 month confirmed disability progression up to month 24- trial D2301 (ITT population)

	FTY720 1.25mg n=429	FTY720 0.5 mg n=425	Placebo N=418
p value vs. placebo (log rank test)	0.012	0.026	
Kaplan-Meier estimate of proportion free of progression (95% CI)	83.4 (79.7, 87.1)	82.3 (78.6, 86.1)	75.9 (71.7, 80.2)

In trial D2302, there was no statistically significant difference in the proportion of patients with 3 month confirmed disability progression between the FTY720 and IFNβ-1a treatment groups (refer to Table 17). The sponsor reports that a low number of events occurred within this relatively short duration of observation resulting in wide confidence intervals that overlap with that of the active control. In order to identify disability progression in a 12 month study, a patient would have to progress by month 9 in order to have a 3 month confirmation by the end of the study.

Table 17: Time to 3 month confirmed disability progression up to month 12-trial D2302 (ITT population)

	FTY720 1.25 mg n=420	FTY720 0.5 mg n=429	IFN β -1a n=431
p value vs. IFN β -1a (log rank test)	0.498	0.247	
Kaplan-Meier estimate of proportion free of progression (95% CI)	93.3 (90.9, 95.8)	94.1 (91.8, 96.3)	92.1 (89.5, 94.7)

The second pivotal efficacy trial (D2302) did not provide independent substantiation of a delay in time to 3 month confirmed disability progression on FTY720 vs. control as was seen in trial D2301. Other secondary measures of disability progression were collected in these two phase III pivotal trials that did not have a pre-specified analysis plan and had no method in place to control the type I error rate.

Reviewer's comment: Trial D2301 demonstrated statistically significant results for three month confirmed disability progression. Data from trial D2302 showed that there was no statistically significant difference between both doses of fingolimod and active control on three month confirmed disability progression.

Disability Scales
Please note that in further discussion in this review, when referring to disability scales, an increase from baseline suggests a clinical deterioration for the EDSS, while an increase from baseline suggests an improvement with the MSFC z scores. In addition, all analyses described below for secondary endpoints not identified as key secondary endpoints are considered post hoc analyses with no pre-specified plan to correct for multiplicity and therefore no method in place to control the type I error rate. Interpretation of p values under 0.05 for such secondary endpoints should be made with that consideration.

EDSS
At month 24 in study D2301, there was a slight decrease from baseline in EDSS for the 1.25 mg dose; there was no change for the 0.5 mg dose while an increase was observed in the placebo group. The comparison of both doses of fingolimod to placebo (p=0.002) in the change from baseline in EDSS at month 24 was nominally significant at the 0.05 level.

Consistently, in study D2302 a slight decrease in EDSS was observed in FTY720 1.25 mg and FTY720 0.5 mg as compared to a slight increase in the IFN ß-1a group. In study D2302, the difference in mean EDSS change from baseline to Month 12 was nominally significant for FTY720 1.25 mg when compared to IFN ß-1a (p = 0.016) but not for FTY720 0.5 mg (p=0.059) Please refer to sponsor Table 18 for the full analysis.

Interestingly at month 12 in study D2301 (the 24 month study), the difference in mean EDSS change from baseline was nominally significant for FTY720 0.5 mg vs. placebo but not for FTY720 1.25 mg.

Table 18: Change from baseline in EDSS at month 12 and month 24- trials D2301 and D2302

Study D2301	**FTY720 1.25 mg N = 429**	**FTY720 0.5 mg N = 425**	**Placebo N = 418**
Month 24			
n	338	374	332
Median (mean)	0.00 (-0.03)	0.00 (0.00)	0.00 (0.13)
p-value vs. placebo	0.002*	0.002*	
Month 12			
n	382	400	364
Median (mean)	0.00 (0.02)	0.00 (0.00)	0.00 (0.08)
p-value vs. placebo	0.132	0.027*	
Study D2302	**FTY720 1.25 mg N = 420**	**FTY720 0.5 mg N = 429**	**IFN β-1a i.m. N = 431**
Month 12			
n	369	394	377
Median (mean)	0.00 (-0.11)	0.00 (-0.08)	0.00 (0.01)
p-value vs. placebo	0.016*	0.059	–

Abbreviation: IFN = interferon
Results are presented for ITT patients who had EDSS values at both baseline and Month 12 (or Month 24).
P-value was calculated using rank ANCOVA with covariates of treatment, country, the corresponding baseline value, and age.
*

Multiple Sclerosis Functional Composite
The Multiple Sclerosis Functional Composite (MSFC) is an alternate disability scale that was used in the pivotal trials as a secondary outcome measure. The MS community is exploring alternate disability scales to the EDSS and the MSFC is one of these scales. The MSFC has the advantage of being a more sensitive test that can detect change in a shorter time frame than the EDSS, but it remains unclear whether this change represents meaningful clinically relevant change in disability progression in the MS population. The MSFC produces a composite score by combining scores from the 25'TWT, the 9HPT and the PASAT-3. This composite score is converted to a z score based on the number of standard deviation units from the mean of an internal or external reference population. The PASAT-3 is considered the least specific test of the three subscales due to the effect of learning over time on the scale[9].

At month 24 in study D2301, there was slight decrease in the mean MSFC z-score values in the placebo group, while in the FTY720 1.25 mg and FTY720 0.5 mg groups a

9 Rudick, RA, et al. Assessing disability progression with the Multiple Sclerosis Functional Composite. Multiple Sclerosis 2009;15: 984-997.

slight increase was observed. The nominal p value (unadjusted for multiple comparisons) for the drug vs. placebo difference in MSFC z-score change from baseline was under 0.05 for both doses of fingolimod (see sponsor Table 19). Regarding MSFC subscales, nominal p values (unadjusted for multiple comparisons) were under 0.05 for the drug vs. placebo difference in 9HPT (both doses), and in 25'TWT change from baseline (0.5 mg dose), while p values were above 0.05 for the PASAT-3 contrasts.

At month12, in study D2302, the mean change from baseline in the MSFC z-score showed a slight increase for both FTY720 treatments (1.25 mg and 0.5 mg) versus a decrease for IFN ß- 1a. The nominal p value for the contrast of MSFC z-score changes between both doses of FTY720 and IFN ß-1a was under 0.05 (unadjusted for multiple comparisons). Regarding MSFC subscales, nominal p values (unadjusted for multiple comparisons) under 0.05 were observed between the FTY720 groups and IFN ß-1a only for the PASAT-3 (both doses) and the 9HPT (1.25 mg dose) contrasts. No significant differences were observed in 25'TWT.

Table 19: Change from baseline in MSFC z-score

Change from baseline in MSFC z-score at month 24- study D2301

	FTY720 1.25 mg N = 429	FTY720 0.5 mg N = 425	Placebo N = 418
MSFC z-score			
n	332	361	316
Median (mean)	0.05 (0.01)	0.07 (0.03)	-0.01 (-0.06)
P value vs. placebo	0.022*	0.010*	
MSFC subscale: 25-foot timed walking test (seconds)			
n	336	369	325
Median (mean)	0.10 (0.38)	0.05 (0.32)	0.20 (0.66)
p-value vs. placebo	0.062	0.005*	
MSFC subscale: 9-hole peg test (seconds)			
n	337	365	328
Median (mean)	-0.40 (-0.31)	-0.45 (0.36)	0.29 (0.61)
p-value vs. placebo	< 0.001*	< 0.001*	
MSFC subscale: PASAT 3 (number of correct answers)			
n	337	366	326
Median (mean)	2.0 (2.4)	1.0 (2.3)	1.0 (1.5)
p-value vs. placebo	0.085	0.252	

Change from baseline in MSFC z-score at month 12- study D2302

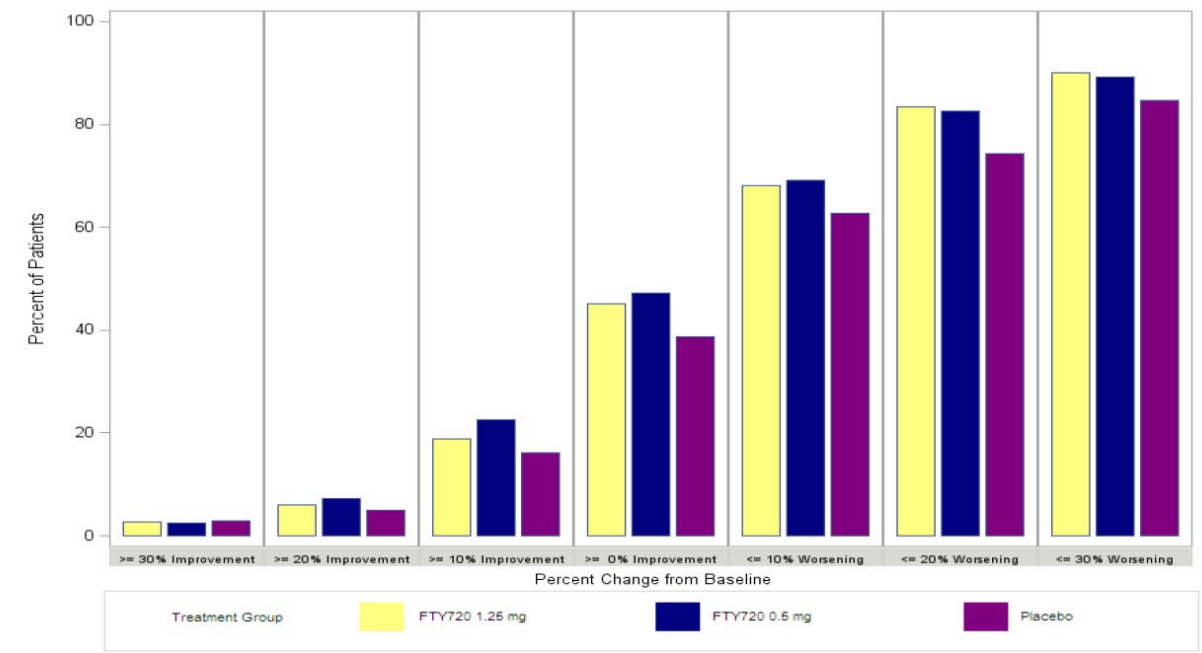
	FTY720 1.25 mg N = 420	FTY720 0.5 mg N = 429	IFN β-1a i.m. N = 431
MSFC z-score			
n	359	383	366
Median (mean)	0.06 (0.08)	0.02 (0.04)	-0.01 (-0.03)
p-value vs. IFN β-1a i.m.	< 0.001*	0.017*	--
MSFC subscale: 25-foot timed walking test (seconds)			
n	363	389	371
Median (mean)	0.0 (-0.71)	0.1 (-0.08)	0.0 (-0.05)
p-value vs. IFN β-1a i.m.	0.181	0.514	--
MSFC subscale: 9-hole peg test (seconds)			
n	366	389	371
Median (mean)	-0.3 (-1.53)	-0.2 (-0.79)	-0.2 (0.17)
p-value vs. IFN β-1a i.m	0.021*	0.327	--
MSFC subscale: PASAT-3 (no. correct answers)			
n	362	385	370
Median (mean)	1.0 (1.56)	1.0 (1.51)	0.0 (0.47)
p-value vs. IFN β-1a i.m.	0.020*	0.005*	--

Reviewer's comments: Although the overall composite z scores for the MSFC showed nominal significance (p values unadjusted for multiple comparisons under 0.05) in both trials D2301 and D2302, the subscale scores between trials lacked consistency. In particular, if one were to contemplate the use of the MSFC results for the 0.5 mg dose to support an effect on disability progression in study D2302, it is concerning that the entirety of the effect appears to originate from the PASAT-3 subscale, for which the only difference is on average one extra correct

response (out of a maximum of 60) compared to placebo. The clinical meaningfulness of that difference is certainly in question. If one were to consider using data from the MSFC as confirmatory evidence to support findings of disability progression, a minimum expectation is that there would be a very robust finding with consistent findings between trials on the most relevant subscales.

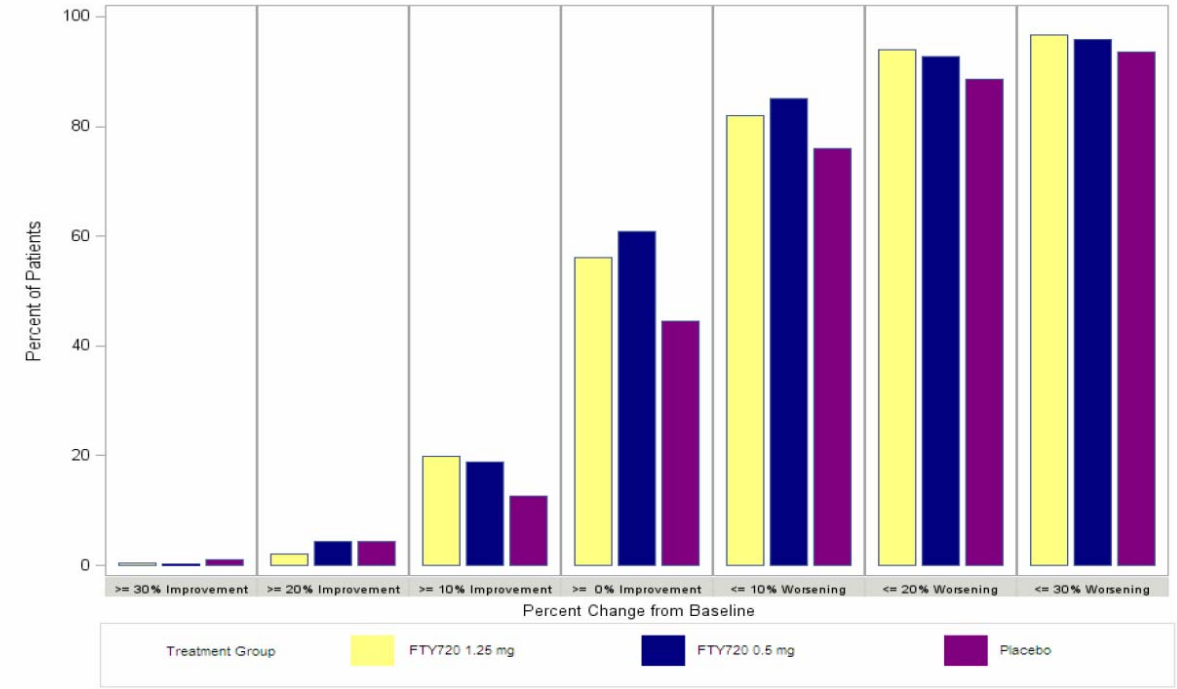
Additional analysis requested by FDA to evaluate MSFC subscale scores
To further evaluate the interpretability of the subscale raw scores for the three MSFC subscales, FDA asked the sponsor to provide graphs plotting (in the x axis) the percent change from baseline in score for each of the components of the MSFC score and each treatment arm against the proportion of patients who had the specified change (in the y axis). The sponsor provided 6 figures describing this relationship for the three subscales of the MSFC, for D2301 and D2302. Below are two figures, Figure 3 and Figure 4, which correspond with the 25'TWT and the 9HPT to demonstrate the two distributions with the most prominent effects in trial D2301. Table 20 provides statistical information on the comparisons described in the figures below. The other figures and tables corresponding to this subgroup analysis are provided in the appendix to this review for reference.

Figure 3: Percent change from baseline in 25-foot timed walking test (sec.) (Trial D2301)



Although a dose response effect was not consistently present, this data suggests that patients on both doses of FTY720 were less than 30% worse than placebo patients (another way to word this is -30% worse or better). This effect was maintained when looking at patients who were less than 20% worse through greater than 10% improvement. In all cases but the less than 30% and less than 20% worsening groups the low dose appeared to do better than the high dose. Those that were nominally significant for both doses (p values unadjusted for multiple comparisons under 0.05) compared to placebo were the categories “less than 20% worsening” and “less than 30% worsening”.

Figure 4: Percent change from baseline in 9-hole peg test (sec.) (Trial D2301)



Although for the 9HPT, there is more nominally significant categories for both dose groups when comparing FTY720 to placebo (in relation to the data from the 25’TWT), the same dose response relationship seen for the 25’TWT exists here. There is an expected dose response effect for less than 30% and less than 20% worsening (with the high dose doing better than the low dose), but the low dose does better than the high dose for the less than 10% worsening through greater than 10% improvement categories. Again, there is an inconsistent dose response relationship. Those comparisons that were nominally significant for both doses were “less than 20% worsening”, “less than 10% worsening”, “greater than 0% improvement” and “greater than 10% improvement” (refer to sponsor Table 20).

Table 20: Proportion of patients for categories based on percent change from baseline in MSFC (Trial D2301)

MSFC sub-scale	Percent change from baseline		FTY720 1.25 mg (N=429)	FTY720 0.5 mg (N=425)	Placebo (N=418)
25FTW (second)		Number of patients	415	418	410
	>=30% Improvement	n (%)	11 (2.7%)	10 (2.4%)	12 (2.9%)
		p-value	0.810	0.633	
	>=20% Improvement	n (%)	25 (6.0%)	30 (7.2%)	20 (4.9%)
		p-value	0.469	0.165	
	>=10% Improvement	n (%)	78 (18.8%)	94 (22.5%)	66 (16.1%)
		p-value	0.307	0.020*	
	>= 0% Improvement	n (%)	187 (45.1%)	197 (47.1%)	159 (38.8%)
		p-value	0.068	0.015*	
	<=10% worsening	n (%)	283 (68.2%)	289 (69.1%)	257 (62.7%)
		p-value	0.096	0.050*	
	<=20% worsening	n (%)	346 (83.4%)	345 (82.5%)	305 (74.4%)
		p-value	0.002*	0.004*	
	<=30% worsening	n (%)	374 (90.1%)	373 (89.2%)	347 (84.6%)
		p-value	0.018*	0.049*	
9-HPT (second)		Number of patients	414	418	411
	>=30% Improvement	n (%)	2 (0.5%)	1 (0.2%)	4 (1.0%)
		p-value	0.407 (0.450)†	0.172 (0.214)†	
	>=20% Improvement	n (%)	9 (2.2%)	18 (4.3%)	18 (4.4%)
		p-value	0.075	0.959	
	>=10% Improvement	n (%)	82 (19.8%)	79 (18.9%)	52 (12.7%)
		p-value	0.005*	0.014*	
	>= 0% Improvement	n (%)	232 (56.0%)	254 (60.8%)	183 (44.5%)
		p-value	<0.001*	<0.001*	
	<=10% worsening	n (%)	339 (81.9%)	356 (85.2%)	312 (75.9%)
		p-value	0.036*	<0.001*	
	<=20% worsening	n (%)	389 (94.0%)	388 (92.8%)	364 (88.6%)
		p-value	0.006*	0.035*	
	<=30% worsening	n (%)	400 (96.6%)	401 (95.9%)	385 (93.7%)
		p-value	0.049*	0.143	

The sponsor believes for trial D2301 the graphs of distribution by degree of improvement (or worsening) demonstrates that the proportion of patients at each level of change is higher for the active treatment groups than placebo, apart from the small numbers of patients with the greatest improvement, in which the proportions are comparable. These differences reach statistical significance for patients remaining stable (no worsening or worsening <20%) or with an improvement in the 25'TWT, or in the 9HPT. The treatment effect was of a lesser magnitude for the PASAT-3. For trial D2302, findings were less striking, potentially related to study duration and the active comparator, with differences on individual sub-scales infrequently being significantly better for fingolimod than interferon, with the most prominent effect on PASAT-3.

Reviewer's comment: Trial D2301 provides evidence to support fingolimod's ability to reduce time to 3 month disability progression. Trial D2302 was not able to independently substantiate these findings in the one year study against an active comparator. The MSFC data provides a post hoc analysis of an alternate disability measure that has uncertain clinical application. The ongoing trial D2309, although not powered to detect disability progression, may provide additional evidence concerning fingolimod's ability to delay disability progression.

New and newly enlarged T2 lesions

The first key secondary endpoint in trial D2302 was the number of new or newly enlarged T2 lesions at 12 months. Procedures were implemented to decrease bias when evaluating MRI variables as follows: 1) MRI efficacy measures followed standardized MRI scan technical procedures and 2) MRI images were centrally evaluated by blinded raters. In an addendum to the clinical study report, treatment with both FTY720 doses resulted in a statistically significant lower number of new or newly enlarged T2 lesions at month 12 compared to IFN ß-1a. In the original clinical study report for D2302, this key secondary endpoint was only statistically significant for the 1.25 mg dose (refer to Table 21 below).

Table 21: Number of new or newly enlarged T2 lesions at month 12 in D2302: Original analysis sent in clinical study report

	FTY720 1.25mg N=420	FTY720 0.5mg N=429	Interferon beta-1a i.m. N=431
n	356	380	365
Mean (SD)	1.4 (2.51)	1.5 (3.50)	2.1 (4.86)
Median	1.0	0.0	1.0
Range	0 - 22	0 - 32	0 - 60
P-value for treatment comparison of FTY720 vs. Interferon beta-1a i.m. (negative binomial regression with covariates)	0.017*	0.053	–

n=the number of patients with evaluable MRI at baseline and Month 12
P-value is calculated using a negative binomial model adjusting for treatment, country, baseline number of relapses in the previous 2 years, and baseline EDSS.
* Indicates two-sided statistical significance at 0.05 level.

The sponsor sent in an addendum to the clinical study report on 11-22-2009 to correct the statistical analysis for the key secondary endpoint “new and newly enlarged T2 lesions” and other related efficacy endpoints. This correction was described in this review (p. 48) refer to Table 22 below for the amended analysis. This new analysis now shows that there is a statistically significant difference between the numbers of new or newly enlarged T2 lesions at month 12 compared to IFN ß-1a in both FTY720 dose groups.

Table 22: Number of new or newly enlarged T2 lesions at month 12- trial D2302 (ITT population)

	FTY720 1.25mg N=420	FTY720 0.5mg N=429	Interferon beta-1a i.m. N=431
As Intended per Protocol			
n**	**350**	**372**	**361**
Mean (SD)#	**1.5 (2.73)**	**1.7 (3.92)**	**2.6 (5.81)**
Median	**1.0**	**0.0**	**1.0**
Range	**0 – 26**	**0 - 38**	**0 - 63**
P-value for treatment comparison of FTY720 vs. Interferon beta-1a i.m. (negative binomial regression with covariates)	**<0.001***	**0.004**	**–**
As analyzed by MRI Central reader			
n**	**350**	**372**	**361**
Mean (SD)	**1.4 (2.51)**	**1.5 (3.520)**	**2.1 (4.89)**
Median	**1.0**	**0.0**	**1.0**
Range	**0 - 22**	**0 - 32**	**0 - 60**
P-value for treatment comparison of FTY720 vs. Interferon beta-1a i.m. (negative binomial regression with covariates)	**0.017***	**0.041**	**–**
~~n**~~	~~356~~	~~380~~	~~365~~
~~Mean (SD)~~	~~1.4 (2.51)~~	~~1.5 (3.50)~~	~~2.1 (4.86)~~
~~Median~~	~~1.0~~	~~0.0~~	~~1.0~~
~~Range~~	~~0 – 22~~	~~0 – 32~~	~~0 – 60~~
~~P-value for treatment comparison of FTY720 vs. Interferon beta-1a i.m. (negative binomial regression with covariates)~~	~~0.017*~~	~~0.053~~	~~–~~

n=the number of patients with evaluable MRI at baseline and Month 12
P-value is calculated using a negative binomial model adjusting for treatment, country, baseline number of relapses in the previous 2 years, and baseline EDSS.
* Indicates two-sided statistical significance at 0.05 level.

**** Eighteen patients were excluded from analysis because the Month 12 T2 MRI was not compared to the Screening MRI.**

 # Calculated by adding the number of new or newly enlarged T2 lesions and the number of Gd-enhanced T1 lesions (both as recorded in the database) observed on the Month 12 MRI.

After FDA review of this second analysis and discussions with the sponsor, it was agreed upon that the sponsor would re-read the MRIs to correct the incorrect method used originally for counting new and newly enlarged T2 lesions and submit a third analysis of this variable. The new analysis provides evidence in support of fingolimod's ability to reduce the number of new and newly enlarged T2 lesions as compared to the active comparator in trial D2302 at 12 months.

The sponsor recounted the T2 lesions on all MRIs that were previously incorrectly counted and used the pre-specified method in the statistical analysis plan for D2302 to perform the new analysis. In addition, measures were implemented to maintain the blinding of the MRI central reader. The results provided in Table 23 show that both treatment groups of FTY1.25 mg and 0.5 mg had a lower mean number of new or newly enlarged T2 lesions at month 12 compared to IFN ß-1a, reaching statistical significance for both doses (p=0.002).

Table 23: Number of new or newly enlarged lesions at month 12 (ITT population)

	FTY720 1.25mg N=420	FTY720 0.5mg N=429	Interferon beta-1a i.m. N=431
n	356	380	365
Mean (SD)	1.6 (3.23)	1.6 (3.16)	2.6 (5.50)
Median	1.0	0.0	1.0
Range	0 - 42	0 - 23	0 - 56
P-value for treatment comparison of FTY720 vs. Interferon beta-1a i.m. (negative binomial regression with covariates)	0.002*	0.002*	–

n=the number of patients with evaluable MRI at baseline and Month 12
P-value is calculated using a negative binomial regression model adjusting for treatment, country, baseline number of relapses in the previous 2 years, and baseline EDSS.
* Indicates two-sided statistical significance at 0.05 level.

In addition, FDA requested that the sponsor include in the "new and newly enlarged T2 lesion "analysis all patients including the 18 that were eliminated because the appropriate 12 month comparison on MRI was not collected. The sponsor did an analysis for this endpoint in all patients whether the appropriate scans were present or not. In this case when patients completed the study and the month 12 MRI was present this month 12 scan was used, but for patients that did not complete the study, the MRI at the time of study drug end-point was carried forward. The statistical method used was pre-specified in the statistical analysis plan for D2302. Table 24 includes this sponsor analysis which shows again that a significantly lower number of new and newly enlarged T2 lesions occur in both treatment groups of FTY720 (p<0.001) as compared to IFN ß-1a.

Table 24: Number of new or newly enlarged T2 lesions at month 12 (study-drug endpoint carried forward, ITT population)

	FTY720 1.25mg N=420	FTY720 0.5mg N=429	Interferon beta-1a i.m. N=431
n	379	393	385
Mean (SD)	1.5 (3.20)	1.5 (3.09)	2.6 (5.48)
Median	1.0	0.0	1.0
Range	0 - 42	0 - 23	0 - 56
P-value for treatment comparison of FTY720 vs. Interferon beta-1a i.m. (negative binomial regression with covariates)	0.001*	<0.001*	–

n=the number of patients with evaluable MRI at baseline and Month 12 for patients who completed the study or at baseline and study drug end point for patients who did no complete the study.
P-value is calculated using a negative binomial regression model adjusting for treatment, country, baseline number of relapses in the previous 2 years, and baseline EDSS.
* Indicates two-sided statistical significance at 0.05 level.

The FDA statistical reviewer repeated the analysis for this variable and discovered several inconsistencies with the sponsor's analysis for new and newly enlarged T2 lesions. The submitted data included 1171 patients with MRI data on T2 lesion counts, yet the sponsor's analysis included 1101 subjects and the sponsor's study drug endpoint carry forward analysis included 1157 subjects. It is not clear why some subjects were not included in the sponsor's analysis.

The FDA statistical reviewer's analysis that follows includes 1170 subjects. Although the submitted data included 1171 subjects, one patient was excluded from the IFN ß-1a group because that patient had a missing value for the number of relapses in the prior 2 years. In this analysis, Dr. Yan, the FDA statistical reviewer, included all MRI data that was available for the 12 month comparison, and when MRI data was not available for this time period, the variable recorded at study drug discontinuation was carried forward. The FDA reviewer's Table 25 below shows that both treatment groups of FTY1.25 mg (p=0.0017) and 0.5 mg (p=0.0007) had a statistically significant lower number of new or newly enlarged T2 lesions at month 12 compared to IFN ß-1a.

Table 25: New or newly enlarged T2 lesions at month 12- study drug endpoint carried forward-(FDA statistical reviewer's analysis)

	FTY720 1.25 mg N=385	FTY720 0.5 mg N=399	IFN β-1a N=386
Mean (SD) new or enlarged T2			
Unadjusted (observed)	1.58 (3.26)	1.63 (3.30)	2.61 (5.48)
Adjusted	1.65	1.62	2.62
95% CI	(1.35, 2.01)	(1.33, 1.97)	(2.08, 3.07)
p-value	=0.0017	=0.0007	

In trial D2301, the 24 month pivotal trial of FTY720 1.25mg and 0.5 mg vs. placebo in patients with RRMS, the variable "number of new or newly enlarged T2 lesions" was not identified as a key secondary endpoint. Yet, there were robust nominal p values associated with strong differences in the number of T2 lesions in FTY720 treated patients compared to placebo (see sponsor Table 26).

Table 26: New or newly enlarged T2 lesions up to month 24- trial D2301

	FTY720 1.25 mg N** = 337	FTY720 0.5 mg N** = 370	Placebo N** = 339
Number of lesions[1]			
Median (mean)	0.0 (2.5)	0.0 (2.5)	5.0 (9.8)
p-value vs. placebo (negative binomial regression with covariates)	< 0.001*	< 0.001*	
Proportion (%) of patients free of lesions	51.9	50.5	21.2
p-value vs. placebo	< 0.001*	< 0.001*	

[1] Number of lesions at Month 24 were obtained by adding the Month 0 - 12 results to the Month 12 - 24.
p-value for number of lesions is calculated using a negative binomial model adjusted for treatment and country. p values for proportion of patients free of lesions was calculated using the logistic regression model adjusting for treatment and country
* Indicates two-sided statistical significance at the 0.05 level.
** Results are presented for ITT patients who had a T2-weighted scan at both baseline and Month 24.

Reviewer's comments: Although the original analysis submitted by the sponsor for D2302 did not find a statistically significant treatment effect for FTY720 0.5 mg over interferon for the reduction of the number of new or newly enlarged T2 lesions at 12 months, subsequent analyses clearly suggest a robust finding on this variable. In addition, although not specified as a key secondary endpoint in trial D2301, the findings from D2301 also support the robust finding found in D2302 for this variable.

6.1.6 Other Secondary Endpoints

All secondary endpoints described in this section are post hoc analyses with no pre-specified statistical plan to correct for multiplicity and control the type I error rate.

Gd-enhancing lesions

In study D2301, treatment with both FTY720 doses, 1.25 mg and 0.5 mg significantly reduced the number and volume of Gd-enhancing lesions at month 24 compared to placebo. In study D2302, treatment with FTY720 significantly reduced the number and volume of Gd-enhancing lesions at month 12 compared to placebo or IFN ß-1a. Please refer to Table 27.

Table 27: Gd-enhancing lesions-Trial D2301 and D2302

Gd-enhancing lesions at 2 years				
D2301		**FTY720 1.25 mg n = 343**	**FTY720 0.5 mg n = 369**	**Placebo n = 332**
Number of lesions	Median (mean)	0.0 (0.2)	0.0 (0.2)	0.0 (1.1)
	P-value vs. placebo	< 0.001*	< 0.001*	---
Total volume of lesions (mm^3)	Median (mean)	0.0 (28.9)	0.0 (39.5)	0.0 (149.1)
	P-value vs. placebo	< 0.001*	< 0.001*	---
Proportion of patients free of lesions	% lesion-free	89.8	89.7	65.1
	P-value vs. placebo	< 0.001*	< 0.001*	---
Gd-enhancing lesions at 1 year				
D2302		**FTY720 1.25 mg n = 352**	**FTY720 0.5 mg n = 374**	**IFN β-1a i.m. n = 354**
Number of lesions	Median (mean)	0.0 (0.1)	0.0 (0.2)	0.0 (0.5)
	P-value vs. IFN β-1a	< 0.001*	< 0.001*	---
Total volume of lesions (mm^3)	Median (mean)	0.0 (19.5)	0.0 (22.6)	0.0 (50.7)
	P-value vs. IFN β-1a	< 0.001*	< 0.001*	---
Proportion of patients free of lesions	% lesion-free	91.2	90.1	80.8
	P-value vs. IFN β-1a i.m.	< 0.001*	< 0.001*	---

Time to first relapse

In both phase III trials D2301 and D2302, there was a significant prolongation in the time to confirmed relapse with fingolimod 1.25 mg and 0.5 mg groups as compared to the control group. Refer to Table 28 below.

Table 28: Time to first confirmed relapse- trials D2301 and D2302

Time to first confirmed relapse			
Up to Month 24 – D2301	p-value vs. placebo (log rank test)	< 0.001*	< 0.001*
	Hazard ratio vs. placebo (95% CI)	0.38 (0.30, 0.48)	0.48 (0.39, 0.61)
	p-value[2] vs. placebo (Cox regression)	< 0.001*	< 0.001*
Up to Month 12 – D2302	p-value (log-rank test)	< 0.001*	< 0.001*
	Hazard ratio vs. IFN β-1a i.m. (95% CI)	0.63 (0.47, 0.83)	0.52 (0.39, 0.69)
	p-value[2] vs. IFN β-1a i.m. (Cox regression)	< 0.001*	< 0.001*

Brain Volume Change
In both pivotal efficacy trials, there was a nominally significant lower reduction in brain volume from baseline in both treatment groups as compared to placebo. In study D2301, there was a 30% reduction relative to placebo for both FTY720 doses, and in trial D2302, there was a 50% reduction compared to IFN ß-1a. The sponsor suggests that this reduction in brain volume represents less atrophy, although they acknowledge that there is no pathological confirmation that this represents true tissue loss. They also suggest that the greater effect size seen in trial D2302 (refer to Table 29) in brain volume change may reflect the "pseudo-atrophy" effect that has been observed with interferon within the first year.

Table 29: Percent Brain Volume Change from baseline: trials D2301 and D2302

Percent brain volume change from baseline to month 24- D2301			
	FTY720 1.25 mg	FTY720 0.5 mg	Placebo
n	334	357	331
Median (mean)	-0.7 (-0.9)	-0.7 (-0.8)	-1.0 (-1.3)
p-value vs. placebo	<0.001	<0.001	
Percent brain volume change from baseline to month 12- D2302			
	FTY720 1.25 mg	FTY720 0.5 mg	IFN b-1a
n	345	368	359
Median (mean)	-0.2 (-0.3)	-0.2 (-0.3)	-0.4 (-0.5)
p-value vs. control	<0.001	<0.001	

Reviewer's comments: Of interest, two other endpoints which are commonly used endpoints in MS trials, "time to first confirmed relapse" and "Gd enhanced lesions" provide supportive evidence of a positive effect of FTY720 on clinical as well as MRI inflammatory measures in RRMS patients in both trials. The sponsor also reports nominally significant changes in brain volume in patients on FTY720 vs. control in both pivotal trials. Although the sponsor suggests that this represents a reduced level of brain atrophy with FTY720, this cannot clearly be concluded. The mechanism leading to either brain volume reduction or expansion with immune modulating therapy remains hypothetical and not yet fully understood.

6.1.7 Subpopulations

ARR by age and gender
In a pooled analysis of trials D2301 and D2302, there were no clear differences in the effect of FTY720 on ARR by gender or age (refer to Table 30). A higher overall ARR was seen in the subgroup of patients that were younger, which is consistent with published data on the natural history of MS.

Table 30: Aggregated ARR (confirmed relapses) by age and gender and treatment (pooled ITT population)

		FTY720 1.25 mg N = 849	FTY720 0.5 mg N = 854	Placebo N = 418	Interferon N = 431
All patients	n	849	854	418	431
	Number of relapses	253	261	359	179
	Time on study (days)	435643	451054	279900	151844
	ARR	0.21	0.21	0.47	0.43
Age (years)					
≤ 40	n	537	547	262	297
	Number of relapses	156	147	252	133
	Time on study(days)	270511	293714	172024	104576
	ARR	0.21	0.18	0.54	0.46
	p-value				
	FTY720 1.25 mg vs. control			< 0.001	< 0.001
	FTY720 0.5 mg vs. control			< 0.001	< 0.001
> 40	n	312	307	156	134
	Number of relapses	97	114	107	46
	Time on study (days)	165132	157340	107876	47268
	ARR	0.21	0.26	0.36	0.36
	p-value				
	FTY720 1.25 mg vs. control			0.001	0.085
	FTY720 0.5 mg vs. control			0.024	0.330
Gender					
Male	n	266	277	120	139
	Number of relapses	86	73	117	46
	Time on study (days)	133193	139455	79782	49067
	ARR	0.24	0.19	0.54	0.34
	p-value				
	FTY720 1.25 mg vs. control			< 0.001	0.355
	FTY720 0.5 mg vs. control			< 0.001	0.063
Female	n	583	577	298	292
	Number of relapses	167	188	242	133
	Time on study (days)	302450	311599	200118	102777
	ARR	0.20	0.22	0.44	0.47
	p-value				
	FTY720 1.25 mg vs. control			< 0.001	< 0.001
	FTY720 0.5 mg vs. control			< 0.001	< 0.001

ARR by baseline EDSS
In a pooled analysis of trials D2301 and D2302, there were no clear differences in the effect of FTY720 on ARR by baseline EDSS. There is a higher ARR in both treatment groups and control patients that entered the study with higher baseline EDSS as would be expected. Please refer to Table 31 below.

Table 31: Aggregate ARR (confirmed relapses) by baseline EDSS and treatment (pooled ITT population)

	FTY720 1.25 mg n=849	*FTY720 0.5mg n=854*	*Placebo n=418*	*Interferon n=431*
EDSS 0.0-3.5				
n	*716*	*725*	*346*	*371*
ARR	*0.19*	*0.20*	*0.43*	*0.41*
P value 1.25 mg vs. control			*<0.001*	*<0.001*
P value 0.5 mg vs. control			*<0.001*	*<0.001*
EDSS > 4.0				
n	*133*	*129*	*72*	*60*
ARR	*0.34*	*0.27*	*0.67*	*0.58*
P value 1.25 mg vs. control			*<0.001*	*0.213*
P value 0.5 mg vs. control			*<0.001*	*0.032*

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

FTY720 was first tested in renal transplant patients at doses of 0.125-5.0 mg. Patients were given FTY720 once daily in combination with cyclosporine to prevent acute rejection. A one month study using this dose range showed a clear dose response according to the sponsor, demonstrated by a reduction of lymphocytes (the main proposed PD effect). The maximal effect on lymphocytes was seen with the 2.5 mg dose. Efficacy appeared to be dose dependent over this range, and the lowest incidence of rejection was seen with FTY720 in combination with conventional doses of cyclosporine at 2.5 mg and with 5.0 mg when combined with reduced doses of cyclosporine. The phase II studies were conducted in renal transplantation with the 2.5 mg and 5.0 mg doses.

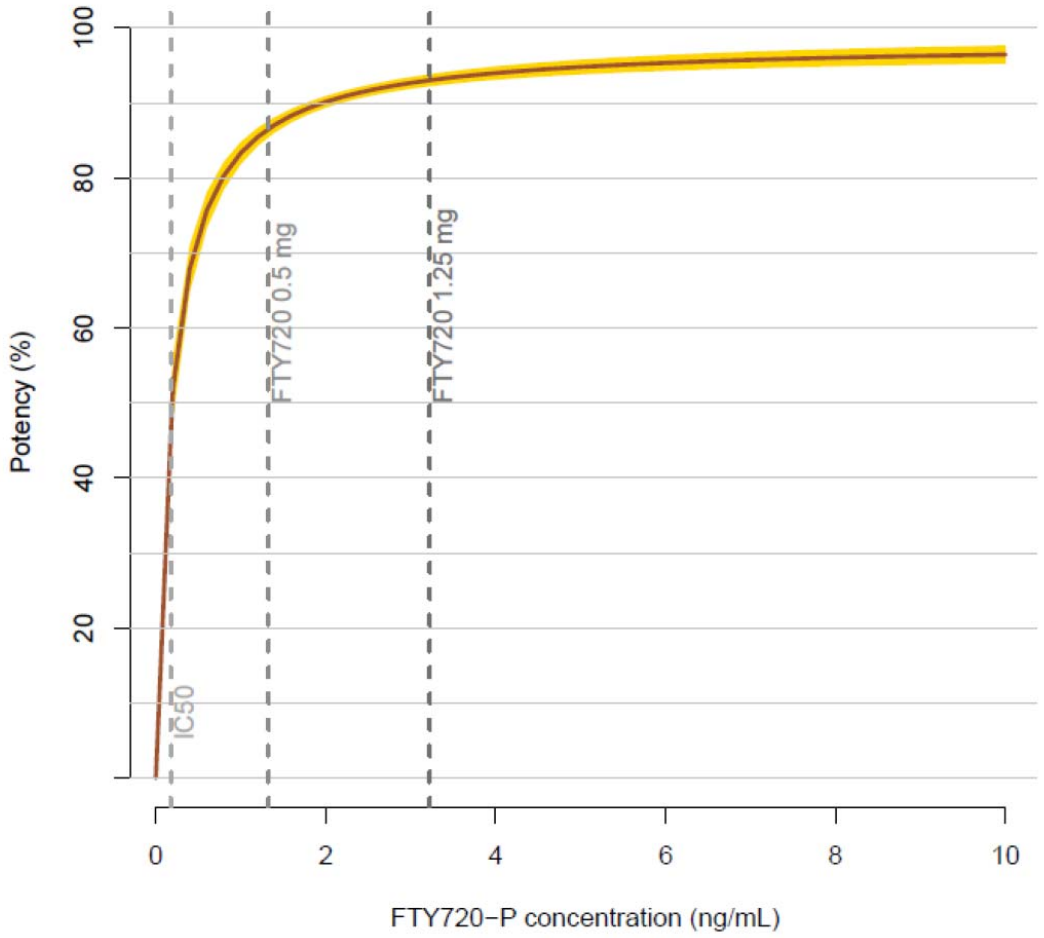
Within the MS studies a dose span of 0.5-5.0 mg FTY720 was studied.

Preclinical studies with FTY720 in rats demonstrated efficacy in the EAE model of MS when using doses yielding near maximal effects on lymphocyte counts. When the phase II MS study (D2201) was designed the sponsor selected two dose levels to compare to placebo, the 5.0 mg dose (the highest one studied in the transplant population) and a dose one quarter that level, 1.25 mg (expected to achieve a suboptimal effect on lymphocyte reduction).

The key PD effect of FTY720 is a dose-dependent reduction of the peripheral lymphocyte count mediated by down-modulation of the S1P1 receptor on lymphocytes. The effect of FTY720 on lymphocyte count has been assessed in several studies over a dose range from 0.25 mg to 40 mg in single dose studies and from 0.125 to 5 mg/day in multiple dose studies. A near maximal reduction from baseline in lymphocytes of 80% to 90% is achieved in the dose range from 2.5 mg to 40 mg. Treatment with FTY720 at lower doses exhibits a dose-dependent effect on lymphocyte counts as observed in doses between 0.125 mg and 2.5 mg. In the MS studies, a dose-dependent effect in the lymphocyte count reduction has been observed in each study (between 5.0 mg and 1.25 mg in the phase II D2201 study and between 1.25 mg and 0.5 mg in the phase III studies D2301 and D2302).

Modeling of the exposure-response relationship in patients from the phase III studies D2301 and D2302 showed that lymphocyte counts decrease with increasing FTY720-P concentration with an estimated maximum reduction of 85% in female and 80% in male patients. The 0.5 mg dose is on the shoulder of the response curve while the 1.25 mg dose is on the plateau (refer to sponsor Figure 5).

Figure 5: Predicted potency of FTY720-P to reduce the lymphocyte count at steady state



Study D2201 demonstrated efficacy compared to placebo on MRI endpoints at both doses (5.0 mg and 1.25mg) without a compelling difference between the two doses. It appeared that the 1.25 mg dose may have achieved maximal efficacy and that the 5.0 mg dose had a less favorable safety profile, so the 1.25 mg dose was selected for further evaluation in phase III.

Further modeling was done by the sponsor to predict potency of FTY720 in relation to reduction of new T2 lesions counts and annualized relapse rate and in both cases the 0.5 mg dose was at the shoulder of the curve with a steep exposure response predicted for lower FTY720 concentrations (see Figure 6 and Figure 7).

Figure 6: Predicted potency of FTY720-P to reduce the number of new T2 lesions at month 12

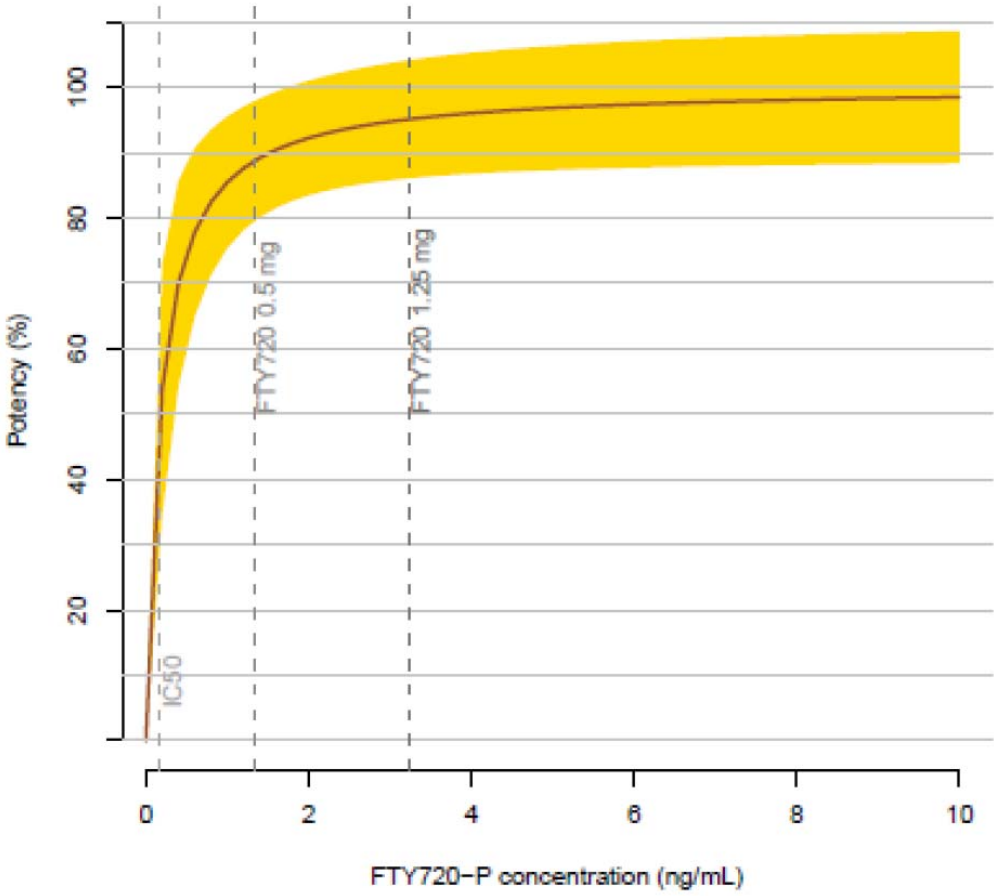
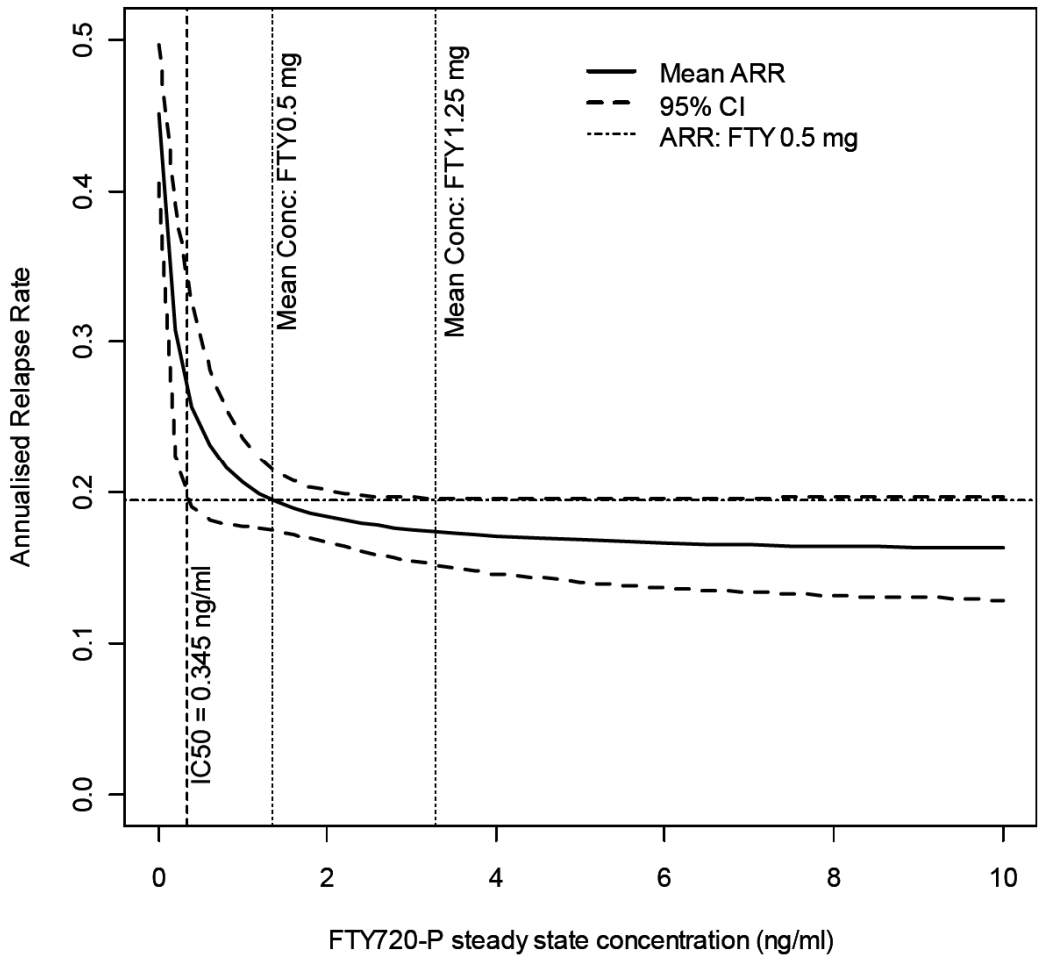


Figure 7: ARR versus predicted FTY720-P steady state concentration model with no covariates and approximate 95% confidence band



The 0.5 mg dose was selected to explore the presence of a lower efficacious dose with an improved safety profile. According to the sponsor, FTY720 was shown to exhibit dose proportional exposure (for C_{max} and area under the concentration time curve) at steady state over the dose range of 0.125-5.0 mg. The 0.5 mg dose represented the next lower dose offering adequate separation from the 1.25 mg dose in terms of PK exposure.

In study D2201, FTY720 1.25 mg and 0.5 mg reduced the number of circulating lymphocytes by 75% and 78% from baseline respectively. Phase I/II data from the renal transplantation studies, showed that 0.5 mg FTY720 reduced circulating lymphocytes approximately 70% relative to baseline. After completion of both pivotal efficacy trials the DSMB made a formal suggestion to the sponsor to discontinue the 1.25 mg dose in their MS development program due to an increased incidence of vascular events.

In contrast to the lack of significant difference of efficacy between doses, the lower dose of FTY720 (0.5 mg) was associated with a more favorable safety profile than the other two doses tested in MS clinical trials. Based on these clinical data, the sponsor is seeking marketing authorization for FTY720 at 0.5 mg administered orally once daily.

All FTY720 clinical studies have been conducted with once daily administration. The sponsor believes that once daily dosing is adequate since the half life of FTY720 is approximately 10 days. The sponsor was asked to justify the use of a daily schedule given the long half life of fingolimod. They stated that in order to reach the steady state fingolimod-P level seen with the daily dosing of 0.5 mg, a weekly dose of 3.5 mg would have to be administered. The sponsor thought that administering a dose this high would be associated with an increase in the degree of bradycardia seen with this product on initial dosing.

Reviewer's comment: The phase II trial, D2201, did not adequately evaluate a dose response for FTY720 on inflammatory MRI activity in the trial as conducted because it did not look at doses below 1.25 mg daily. A lower dose (0.5 mg) was explored in the phase III program. Although modeling is helpful in predicting drug effects, information from modeling alone cannot definitively predict clinical response. In this case, due to the multiple organ system toxicity seen with this product, exploration of the true clinical effect of a lower dose should be carried out.

6.1.9 Discussion of Persistence of Efficacy and/or Withdrawal/Rebound Effects

Persistence of efficacy
In trial D2301 the reduction of ARR which began in the first year was sustained throughout the course of the 24 month study. Additional information about the persistence of efficacy can be obtained from the extension study to the 6 month phase 2 trial: D2201E1. Generalizations are limited since this extension study used doses of 1.25 and 5.0 mg which are above those requested for marketing by the sponsor in this drug application. Other limitations of this study were that there was about a 33% dropout rate and no control group, so interpretation of the sustainability of efficacy must be made with this in mind. According to the sponsor, after 5 years of treatment 68% of patients in the FTY720 group were free of relapses, 70% of patients were free of MRI disease activity on every annual scan up to month 60 and there was no increase in MRI T2 lesion burden after 60 months of treatment in patients remaining on treatment. Two thirds of patients treated for 5 years were free of disability progression at study completion.

Withdrawal/Rebound effects on efficacy
Information on MS relapses and MRI scans were collected for at least 3 months after study drug discontinuation from all trials. The data from phase II and III trials were pooled for this analysis and only patients that were included in treatment for a minimum

of 3 months were included. If patients started another disease modifying therapy they were still included in this analysis. By 90 days after study drug discontinuation, ARRs of the placebo group were not different from those of the previous treatment group. There were no increases in the ARR in patients previously treated over patients on placebo to suggest a rebound effect. In the MRIs performed between 15 and 90 days after study drug discontinuation, an increase in Gd-enhancing lesions was observed in all groups including placebo. After 90 days of study drug discontinuation, there was no further increase in the number of Gd-enhancing lesions in the previously FTY720 treated patients, but there was a reduction in the number of Gd-enhancing lesions observed in the placebo group. This data is derived from more than 400 patients that discontinued FTY720 and more than 100 patients who discontinued placebo in FTY720 clinical trials. The mean follow up period was 104 days. It appears from this data that disease activity returned to baseline levels after 90 days off drug. It does not appear that there is a rebound effect after FTY720 discontinuation.

Reviewer's comment: Information about the persistence of efficacy over time and rebound effects are important to obtain with newly marketed drugs. Although limitations exist in the interpretation of this data due to the higher doses used in this extension study, it seemed relevant and reassuring to see persistence of an effect on study drug and no obvious rebound effect off study drug. When the data from the extension studies to D2301 and D2302 is reviewed more information about these important effects of fingolimod will be obtained at the dose the sponsor is proposing to market.

8 Postmarket Experience

No postmarketing experience exists as this product has not been marketed inside or outside the US.

9 Appendices

9.1 Literature Review/References

Literature references were incorporated in the review

9.2 Labeling Recommendations

Please refer to the proposed labeling document sent to the sponsor for fingolimod in RRMS.

9.3 Advisory Committee Meeting

Efficacy presentations were made by Dr. Eric Bastings from FDA and Dr. Gordon Francis from Novartis Pharmaceutical. Four questions were posed to the Advisory panel regarding efficacy. The panel answered unanimously "yes" to the first question which addressed whether the sponsor demonstrated substantial evidence of effectiveness for the treatment of patients with RRMS to reduce clinical exacerbations. The second question asked whether the sponsor demonstrated substantial evidence of effectiveness of fingolimod for patients with RRMS to delay the accumulation of physical disability. All members of the panel except one voted "yes". The member that voted "no" stated that longer studies are needed, and one of the members that voted "yes", commented that his answer referred to the evidence that was provided from the placebo controlled study. The third question asked whether studying lower doses than 0.5 mg should be a sponsor requirement. Twenty panel members voted "yes", while five panel members voted "no". The final efficacy question was whether lower doses should be studied prior to approval, and the answer from the panel was unanimously, "no". There was considerable discussion at the AC meeting about whether lower doses should be studied and how the dose of 0.25 mg was selected as the dose that the sponsor should study. In general the consensus was that the sponsor should attempt to identify the lowest effective dose in light of the safety profile of fingolimod. PK/PD modeling was limited because this information was based on data from very few patients at the lower end of the dose spectrum and modeling could not replace the more exact information that would be obtained from a clinical trial. In general, it was agreed upon that this study could be done post approval.

9.4 Pediatric Review Committee (PeRC) Meeting

June 30th, 2010, a PeRC meeting was held to discuss the pediatric studies required from the sponsor for fingolimod in MS. The committee agreed that pediatric studies for patients age 10 through 17 would be deferred because this product is ready for approval for use in adults and the pediatric studies have not been completed. In addition, the committee agreed that FDA would waive the pediatric study requirements for ages birth through nine years of age, because the necessary studies would be impossible or highly impracticable because there are too few children with this condition in this age category to study. The required deferred pediatric study for children age 10 through 17 should be a 24 month randomized, active controlled, parallel group study to evaluate the single and

multiple dose pharmacokinetics and the safety and efficacy of multiple doses of fingolimod compared to interferon beta 1-a intramuscular (Avonex) for the treatment of relapsing remitting multiple sclerosis. The study should be designed to demonstrate superiority of fingolimod over the active comparator. A final study report for this deferred study should be submitted by (b) (4) 2016.

9.5 Reference Material for sponsor MSFC evaluation

Figure 8: Percent change from baseline in paced auditory serial addition test (number of correct answers) (trial D2301 ITT population- 24 month LOCF)

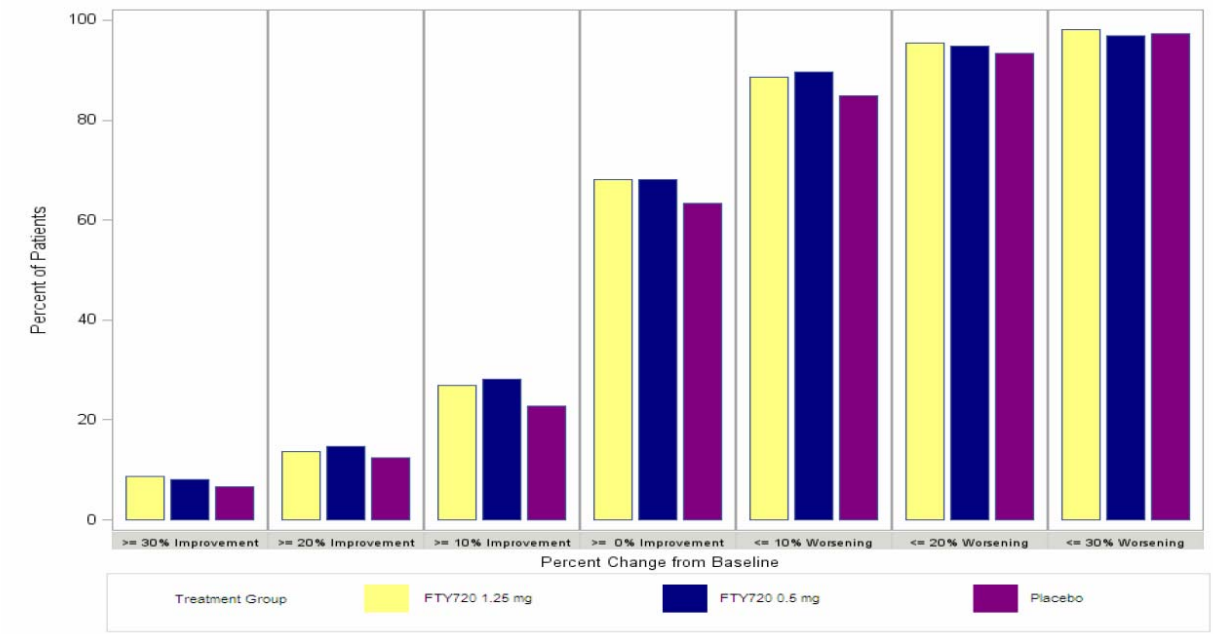


Figure 9: Percent change from baseline in 25-foot timed walking test (sec.) (trial D2302 ITT population- 12 month LOCF)

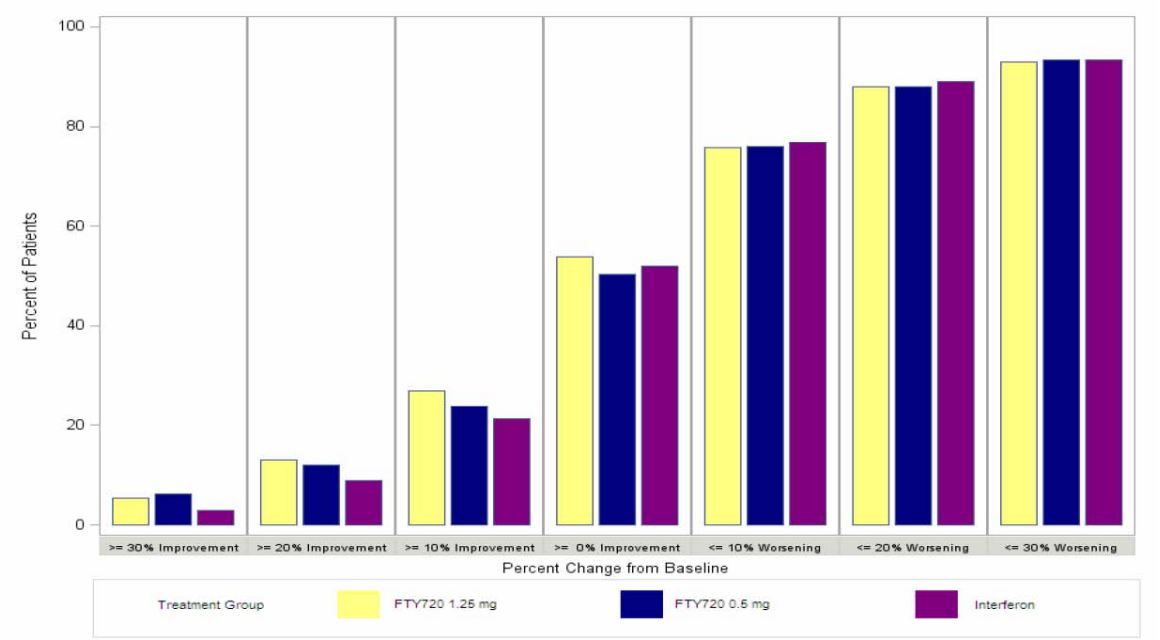


Figure 10: Percent change from baseline in 9-hole peg test (sec.) (triaD2302 ITT population- 12 month LOCF)

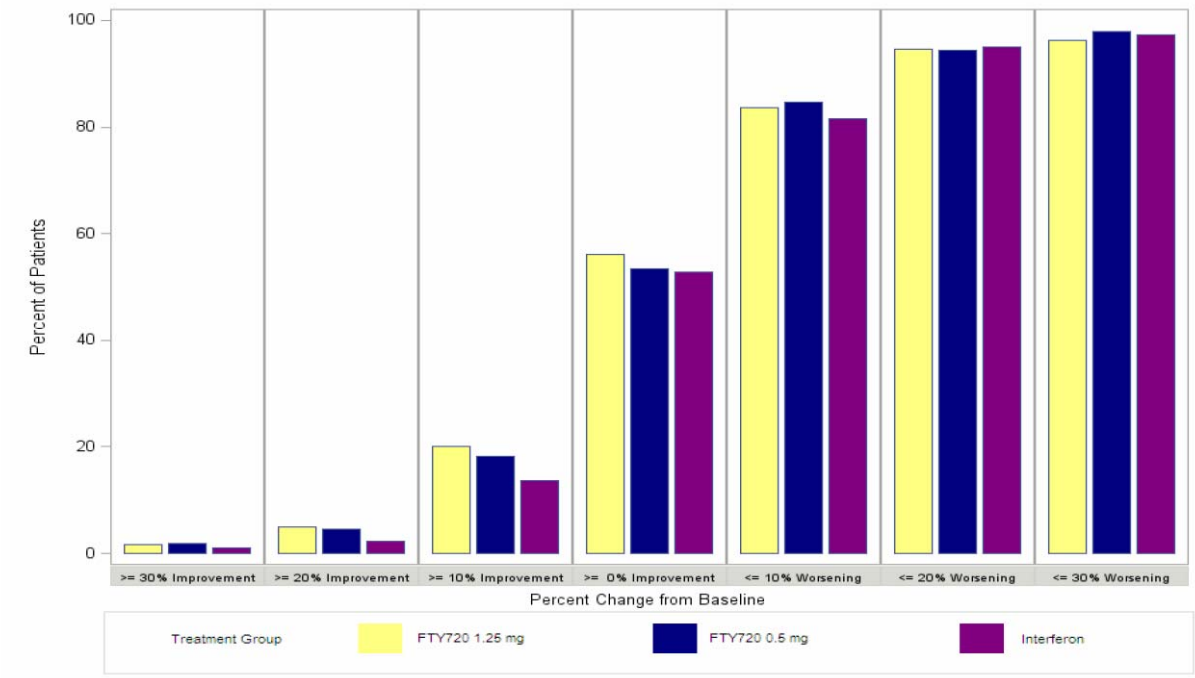


Figure 11: Percent change from baseline in paced auditory serial addition test (number of correct answers) (trial D2302 ITT population- 12 month LOCF)

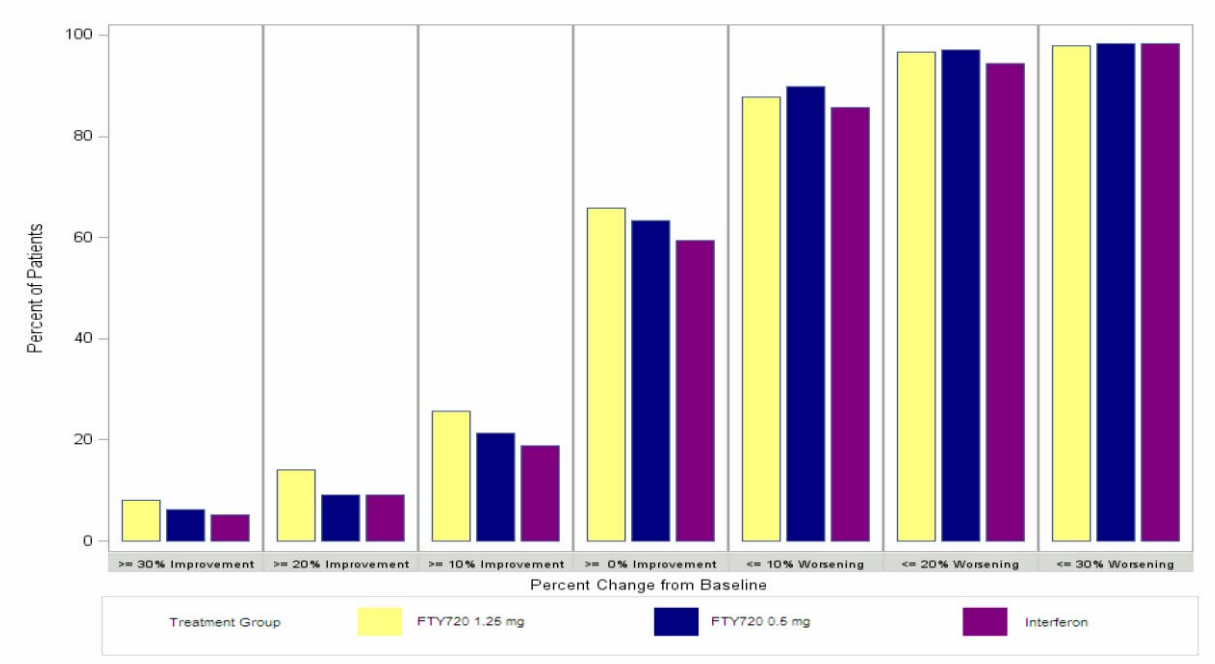


Table 32: Proportion of patients for categories based on % change from baseline in MSFC (trial D2302)

MSFC sub-scale	Percent change from baseline		FTY720 1.25 mg (N=420)	FTY720 0.5 mg (N=429)	Interferon beta-1a (N=431)
25FTW (second)		Number of patients	401	419	408
	>=30% Improvement	n (%)	22 (5.5%)	26 (6.2%)	12 (2.9%)
		p-value	0.071	0.025*	
	>=20% Improvement	n (%)	52 (13.0%)	50 (11.9%)	36 (8.8%)
		p-value	0.058	0.143	
	>=10% Improvement	n (%)	108 (26.9%)	100 (23.9%)	87 (21.3%)
		p-value	0.062	0.382	
	>= 0% Improvement	n (%)	216 (53.9%)	211 (50.4%)	212 (52.0%)
		p-value	0.587	0.645	
	<=10% worsening	n (%)	304 (75.8%)	318 (75.9%)	313 (76.7%)
		p-value	0.762	0.781	
	<=20% worsening	n (%)	353 (88.0%)	369 (88.1%)	363 (89.0%)
		p-value	0.675	0.684	
	<=30% worsening	n (%)	373 (93.0%)	391 (93.3%)	381 (93.4%)
		p-value	0.837	0.970	
9-HPT (second)		Number of patients	403	418	409
	>=30% Improvement	n (%)	7 (1.7%)	8 (1.9%)	4 (1.0%)
		p-value	0.350 (0.381)†	0.260 (0.385)†	
	>=20% Improvement	n (%)	20 (5.0%)	19 (4.5%)	9 (2.2%)
		p-value	0.034*	0.062	
	>=10% Improvement	n (%)	81 (20.1%)	76 (18.2%)	56 (13.7%)
		p-value	0.015*	0.078	
	>= 0% Improvement	n (%)	226 (56.1%)	223 (53.3%)	216 (52.8%)
		p-value	0.350	0.877	
	<=10% worsening	n (%)	337 (83.6%)	354 (84.7%)	334 (81.7%)
		p-value	0.461	0.245	
	<=20% worsening	n (%)	381 (94.5%)	395 (94.5%)	389 (95.1%)
		p-value	0.714	0.692	
	<=30% worsening	n (%)	388 (96.3%)	409 (97.8%)	398 (97.3%)
		p-value	0.403	0.616	

Table 33: Proportion of patients for categories based on percent change from baseline in MSFC- PASAT-3 (trial D2302)

PASAT (No. of correct answers)		Number of patients	398	413	404
	>=30% Improvement	n (%)	32 (8.0%)	26 (6.3%)	21 (5.2%)

MSFC sub-scale	Percent change from baseline		FTY720 1.25 mg (N=420)	FTY720 0.5 mg (N=429)	Interferon beta-1a (N=431)
		p-value	0.105	0.501	
	>=20% Improvement	n (%)	56 (14.1%)	38 (9.2%)	37 (9.2%)
		p-value	0.030*	0.983	
	>=10% Improvement	n (%)	102 (25.6%)	88 (21.3%)	76 (18.8%)
		p-value	0.020*	0.373	
	>= 0% Improvement	n (%)	262 (65.8%)	262 (63.4%)	240 (59.4%)
		p-value	0.060	0.236	
	<=10% worsening	n (%)	349 (87.7%)	371 (89.8%)	346 (85.6%)
		p-value	0.394	0.068	
	<=20% worsening	n (%)	385 (96.7%)	401 (97.1%)	381 (94.3%)
		p-value	0.097	0.049*	
	<=30% worsening	n (%)	390 (98.0%)	406 (98.3%)	397 (98.3%)
		p-value	0.772	0.967	

- p-value is from a chi-square test not adjusted for multiple comparisons.
- * indicates statistical significance at 0.05 level.
- † indicates p-value from an additional Fisher's exact test due to small number of events.

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/s/

HEATHER D FITTER
08/26/2010

ERIC P BASTINGS
09/20/2010

Review and Evaluation of Clinical Data
Safety Team Leader Memorandum

NDA:	22-527
Drug:	Fingolimod (Gilenya)
Route:	Oral (hard capsules)
Indication:	Treatment of patients with relapsing MS to reduce the frequency of relapses and to delay the progression of disability
Sponsor:	Novartis
Submission Date:	12/18/2009
Review Date:	8/25/2010
Reviewer:	Sally Usdin Yasuda, Safety Team Leader Division of Neurology Products, HFD-120

1. Background

Fingolimod (also referred to as FTY in this document) is a sphingosine -1-phosphate (S1P) receptor modulator that has been developed for the treatment of relapsing multiple sclerosis (MS). No other S1P modulator is currently approved for any indication. After oral dosing, fingolimod is phosphorylated, and fingolimod-phosphate induces internalization of the S1P receptor. There are 5 known S1P receptor subtypes, and fingolimod-P has effects at S1P 1, 3, 4, and 5. With initial dosing fingolimod acts as an agonist at S1P receptors, but with continued dosing it acts as a functional antagonist. The mechanism of action of fingolimod in MS is proposed to be a dose-dependent decrease in egress of lymphocytes from lymphoid tissue and reduction of auto-aggressive T-lymphocytes in the peripheral circulation, actions that are mediated by the S1P1 receptor subtype, and that are thought to prevent CNS penetration by pathogenic lymphocytes. All lymphocyte subsets (including B cells and CD4, CD8, and CD16 T cells) have been found to decrease. Other effects in nonclinical studies include transient activation of SIP receptors and GIRK/IKACh channels in atrial myocytes (associated with transient reduction of heart rate), and increased lung hyper-reactivity to bronchospasmogens and airway constriction, mediated by S1P1 and S1P3. Effects of actions on S1P4 and S1P5 are not currently known. The safety review notes that an increasing body of literature indicates that S1P has a role in the regulation of endothelial permeability and vascular tone.

In terms of the clinical pharmacology of fingolimod, at steady state fingolimod and fingolimod-P are in equilibrium. The median Tmax is approximately 12 hours. Fingolimod is extensively distributed with a Vd of approximately 17L/kg. It is metabolized primarily by CYP4F2 and that pathway can be inhibited by ketoconazole. The elimination half-life for fingolimod and for fingolimod-P is 6-9 days. In severe renal impairment, there is increased exposure to metabolites M2 and M3, for which the safety profiles are unknown.

The decrease in lymphocyte count occurs in a dose-dependent manner after single doses of 0.5 to 5.0 mg of FTY and multiple dose of 0.125 mg to 5 mg. This decrease results in lymphocyte counts from 60% of baseline count to as low as 10-15% of baseline count. In a multiple dose study in the renal transplant population, absolute lymphocyte counts returned to baseline within 3 months of discontinuation of study medication. In MS studies, follow-up in a small group of

patients showed that mean lymphocyte counts were still reduced by approximately 22% at 3 months compared with baseline, and information on recovery beyond 3 months is limited.

Fingolimod was initially developed for prevention of organ transplant rejection in the renal transplant population at doses of 2.5 and 5 mg/day. After evaluation of the risk and benefits, development in that population was stopped. During the development programs in renal transplant and in MS, several safety concerns emerged. These included adverse events of macular edema, first and second degree atrioventricular block, and dermatologic (skin malignancy) and pulmonary toxicity. The clinical development program in MS investigated the 1.25 and 0.5 mg/doses. Due to consideration of the finding of similar efficacy but greater toxicity with the higher dose, only the 0.5 mg once daily dose is being pursued for marketing.

This memorandum primarily summarizes the primary safety concerns from Dr. Lourdes Villalba's safety review. Dr. Heather Fitter has contributed to consideration of CNS adverse events. In addition the following FDA consultants have contributed to the consideration of safety: Dr. Marc Cavaille-Coll, FDA immunologist consultant from Division of Special Pathogens (DSPTP), Dr. Shari Targum, FDA cardiologist consultant, Dr. Wiley Chambers, ophthalmology consultant, and Dr. Brian Porter, pulmonologist consults from the Division of Pulmonary, Allergy, and Rheumatology products. Please refer to Dr. Villalba's review for detailed safety considerations.

2. Summary of Findings from the Safety Review

2.1 Sources of Data, Exposure, and Demographics

The integrated summary of safety (ISS) includes data from 3 completed double-blind randomized controlled clinical studies (2201, 2301, and 2302) and 2 ongoing open-label extension studies (2201E1 and 2302 E1) in patients with MS up to the cutoff date of 9/30/09, as shown below, extracted from Dr. Villalba's review.

Study ID	**Design/duration**	**Treatment/dose**	**Patients randomized per group**
FTY720D**2201** (Dose ranging)	DB, R, PC, MC (non-USA), 6 months	FTY 5 mg/d FTY 1.25 mg/d Placebo	92 92 92
FTY720D**2301** (FREEDOMS) (Pivotal efficacy and safety)	DB, R, PC, MC (non USA), 24 months	FTY 1.25 mg/d FTY 0.5 mg/d Placebo	429 425 418
FTY720 D**2302** (Pivotal efficacy and safety)	DB, R, Avonex-controlled, MC (with USA sites, 12 months)	FTY 1.25 mg/d FTY 0.5 mg/d Interferon beta-1a 30mcg i m. once a week	426 431 435
FTY720D2201E1	Open-ended, ongoing, interim data up to 60 months	FTY 1.25 mg/d Initially included FTY 5.0 mg/d	250
FTY720D2302E1	Open-ended, ongoing, interim data up to 24 months	FTY 0.5 mg/d FTY 1.25 mg/d	1030

DB = double blind, R= randomized, PC = placebo controlled, MC = multicenter

In addition, there are 5 ongoing studies in MS that were not pooled into the ISS, including Study 2309. Only blinded narratives of deaths and selected serious AEs from these studies were provided in the original application except for the special safety evaluations in study 2309. Study 2309 is a double blind, randomized, placebo controlled multicenter study (including U.S. sites) evaluating efficacy and safety of FTY 0.5 mg/d and 1.25 mg/day vs placebo (360 patients per group) in patients with RRMS, in which there were special safety evaluations including 24-hour Holter ECG, echocardiography, frequent optical coherence tomography (OCT), and chest HRCT as specifically requested by the FDA. Those data were reported separately in a Special Safety Interim (SSI) report, and some AE of interest were unblinded at the time of the update SSI report. Clinical pharmacology studies included a total of 1079 unique subjects, including 843 exposed to FTY at doses of 0.125 to 40 mg/day. Dr. Villalba also considered the ISS submitted separately for the renal transplant population for which she reviewed adverse event tables and selected narratives. Dr. Villalba has considered various safety pools, and generally shows results from Pool D (all double blind controlled studies, n=2833, includes studies 2301, 2302, and 2201) and Pool E (all FTY- treated population, n=2315, includes studies 2301, 2302, 2302E1 up to 6/1/09 and 2201E1 up to 60 month visit).

In the ISS 2103 MS patients received FTY for 6 months and 1720 for 1 year at doses at or above the proposed dose for marketing (0.5 mg). Approximately 300 have received the proposed marketed dose for 2 years, and 36 patients have received the 1.25 mg dose for 6 years. As of the cut-off date (1/10/10) for the Safety Update Report (SUR), 567 patients have been exposed to FTY 0.5 mg for at least 2 years, and 140 patients have been exposed to that dose for at least 900 days. As Dr. Villalba notes, exposure to fingolimod in the MS program exceeds minimum ICH guidance recommendations (minimum 1500 total, 300 subjects for 6 months and 100 for 1 year at a clinically relevant dose).

Study 2309 is a 2 year study with special safety evaluations. In that study, considering the SUR, 59 patients have been exposed to FTY 1.25 mg and 70 exposed to 0.5 mg for up to or more than 2 years. However, to date, only selected information from this study is available, and the number of patients with analyzed special safety data are few. Dr. Villalba recommends that when study 2309 is completed and analyzed, the sponsor should submit a pooled analysis of Safety Pool D + study 2309 for all AEs, serious AEs, discontinuations due to AE and frequent AEs. I agree.

Dr. Villalba notes that the demographics and disease characteristics of the MS population in the ISS are consistent with those in other applications for MS, and that the demographic characteristics of the different safety pools were similar. Approximately 70% of the patients were female with a mean age of 37 years; 95% were Caucasian and the mean weight was approximately 70kg. In the only completed study with U.S. patients (Study 2302) there were 144 U.S. patients including 16 African Americans. MS disease characteristics (mean duration and mean EDSS score at baseline) were similar among treatment groups. Fifty-nine percent of patients in 2301 and 43% in 2302 were treatment naïve with respect to the 5 approved MS disease modifying drugs. The most common prior immunomodulator or immunosuppressive treated was INF beta. Dr. Villalba notes the eligibility criteria that excluded patients with a known or new diagnosis of diabetes mellitus, a history of specific cardiovascular conditions including history of symptomatic bradycardia, resting pulse rate < 55 bpm, arrhythmia requiring current treatment with Class III antiarrhythmics drugs, and abnormal pulmonary function tests.

She also notes that there were no patients taking calcium channel blockers in the database and that approximately only 20 patients per treatment group in the controlled database were exposed to systemic beta-blockers.

2.2 Significant Safety Findings

2.2.1 Deaths

Dr. Villalba notes that there were 14 deaths in the MS program reported as of 4/26/10, of which 1 remains blinded and 9 occurred during or after fingolimod treatment (8 in the 1.25 mg group and 1 in the 0.5 mg group). Her interpretation of the relationship to study drug is summarized in the following table, extracted from her review.

Summary of deaths in the fingolimod MS program*

During or following FTY treatment
Likely Related - 2 herpes viral infections (Herpes simplex encephalitis and disseminated varicella zoster)
Can not rule out if related - 1 Multiple tumors (brain, lung, kidney, lymph nodes); possible T cell lymphoma/EBV related lymphoproliferative disease (symptoms started during treatment; died 1 year after drug dc) - 1 Rapidly deteriorating MS complicated with fatal respiratory infection - 1 MS progression/ADEM (can not r/o CNS infection) – complicated with aspiration pneumonia 6 months after drug dc - 2 metastatic tumors - Ovarian. Diagnosed 5 months after drug dc. Death 1 year after drug dc - Breast. Diagnosed 11 months into treatment. Death 3 years after drug dc
Unlikely related - 1 traffic accident - 1 suicide
Not on FTY
Placebo – 1 traffic accident - 1 pulmonary embolism
Blinded – 1 dissecting aortic aneurysm (relationship can not be ruled out)

*As of 4/26/10. Attribution of relationship to study drug as per FDA reviewer. Additionally, two deaths occurred during the screening period, before randomization (1 suicide and one sudden death).

Dr. Villalba notes that the two cases of herpes infections resulting in death occurred in young patients (23 and 29 y.o.) who were taking fingolimod 1.25 mg/day, were IgG negative indicating no prior exposure to these viruses, and had received a short course of high dose IV steroids for empiric treatment of MS relapse before they developed these fatal infections (2302-0212-000221 and 2302-0821-00007). The case of disseminated varicella zoster also had massive hepatic necrosis and multiorgan failure that could be due to disseminated varicella zoster. Lymphocyte levels were not available at the time of infection. I agree with Dr. Villalba that these cases are of particular concern in light of the immunosuppression that might be expected based on the mechanism of action of FTY. In addition, Dr. Villalba notes that a clinical pharmacology study has shown that subjects taking fingolimod 1.25 mg had decreased ability to mount an antibody response to a newly exposed antigen. Subsequent to these cases, protocols were modified to include IgG antibody testing for several viral infections and to include guidance to the investigators regarding procedures in case of a viral infection. Dr. Villalba notes that no infection-related deaths occurred in the FTY 0.5 mg, placebo or interferon groups.

One death occurred in a patient (2302-0254-00011) taking FTY 1.25 mg presenting with some features (disturbed consciousness level and convulsions) consistent with Acute Disseminated Encephalomyelitis (ADEM) according to the investigator. The initial deterioration was subsequent to "chest infection" that occurred approximately 11 months into FTY treatment. The patient died due to aspiration pneumonia (187 days after FTY discontinuation). Dr. Fitter reviewed the case and offered the following differential diagnoses: MS relapse in the setting of multiple infections, seizures, steroid induced encephalopathy; ADEM; and PML. JC virus testing done at a European laboratory was negative and no further samples remained for additional testing. There was a death in a patient (2306-362-00005) attributed to rapidly deteriorating MS complicated by a severe lower respiratory infection. There were no assessments (including autopsy, MRI, work up to rule out opportunistic infection) to rule out causes other than MS progression. Lymphocyte counts were not available for either case.

Patient 1201E-0005-00001 received FTY 0.5 mg/day for 7.5 months. He was treated with pulse steroids after finding new brain lesions consistent with MS relapse 1.5 months into the extension study, and discontinued FTY 2.5 months into the extension study. The patient died approximately 1 year after FTY discontinuation. Autopsy confirmed a diffuse B-cell lymphoma of the brain (Epstein Barr associated) accompanying "non-methotrexate-associated iatrogenic immunodeficiency associated lymphoproliferative disorder" of lung, kidney, thyroid, jejunum and T cell lymphoma of the skin.

Of note, in the renal transplant key safety population 8 patients (1.7%) died of cardiac causes in the FTY 5mg group, as compared with no patients in the FTY 2.5mg and active comparator groups. No cardiovascular deaths were reported in the MS trials.

2.2.2 Nonfatal Serious Adverse Events (SAEs)

Dr. Villalba notes that all AEs were collected up to 45 days after drug discontinuation and SAEs were collected up to 3 months after drug discontinuation. Given the elimination half-life and the length of time required for reversibility of lymphocyte counts, on average this should be adequate, but the collection period may not reflect the full scope of either SAEs or their reversibility.

SAEs in Safety Pool D (all controlled studies, data for 6 months to 2 years) occurred in 8.5%, 10.6%, 8.5%, 11.9% and 5.8% of patients in the FTY 5 mg, FTY 1.25 mg, FTY 0.5 mg, placebo, and interferon groups, respectively. The most common SAEs were in Cardiac disorders, infections and infestations, Nervous system disorders and Investigations (primarily related to liver enzymes) SOCs, with evidence of a dose response among fingolimod doses for these events, as shown in the table below, extracted from Dr. Villalba's review. For a complete discussion, please refer to Dr. Villalba's review.

Patients with SAE in at least 2 patients in any treatment group or fatal up to 90 days after last dose, safety pool D.

Primary system organ class Preferred term	FTY 1.25 (N=943) n (%)	FTY 0.5 (N=854) n (%)	Placebo (N=511) n (%)	INF (N=431) n (%)
Any primary system organ class	**100 (10.6)**	**73 (8.5)**	**61 (11.9)**	**25 (5.8)**

Primary system organ class Preferred term	FTY 1.25 (N=943) n (%)	FTY 0.5 (N=854) n (%)	Placebo (N=511) n (%)	INF (N=431) n (%)
Cardiac disorders	**23 (2.4)**	**10 (1.2)**	**4 (0.8)**	**1 (0.2)**
Bradycardia	11 (1.2)	5 (0.6)	1 (0.2)	0
Atrioventricular block first degree	4 (0.4)	1 (0.1)	0	0
Atrioventricular block second degree	4 (0.4)	1 (0.1)	1 (0.2)	0
Sinus bradycardia	2 (0.2)	1 (0.1)	0	0
Supraventricular extrasystoles	2 (0.2)	1 (0.1)	0	0
Nervous system disorders	**18 (1.9)**	**12 (1.4)**	**5 (1.0)**	**3 (0.7)**
Multiple sclerosis/ Multiple sclerosis relapse	3 (0.3)	5 (0.5)	2 (0.4)	1 (0.2)
Epilepsy	2 (0.2)	0	0	0
Grand mal convulsion	2 (0.2)	0	0	0
Headache	2 (0.2)	0	0	0
Infections and infestations	**18 (1.9)**	**8(0.9)**	**8 (1.6)**	**6 (1.4)**
Appendicitis	2 (0.2)	0	0	2 (0.5)
Herpes zoster disseminated*	1 (0.1)	0	0	0
Herpes simplex encephalitis*	1 (0.1)	0	0	0
Respiratory infection*	1 (0.1)	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**9 (1.0)**	**14 (1.6)**	**12 (2.3)**	**2 (0.5)**
Basal cell carcinoma	3 (0.3)	6 (0.7)	2 (0.4)	0
Breast cancer	3 (0.3)	1 (0.1)	3 (0.6)	0
Malignant melanoma	1 (0.1)	3 (0.3)	1 (0.2)	0
Uterine leiomyoma	0	2 (0.2)	0	0
Investigations	**9 (1.0)**	**6 (0.7)**	**1 (0.2)**	**1 (0.2)**
ALT increased	2 (0.2)	1 (0.1)	0	0
Hepatic enzyme increased	2 (0.2)	1 (0.1)	0	0
Liver function test abnormal	2 (02)	0	1 (0.2)	0
Gastrointestinal disorders	**8 (0.8)**	**4 (0.5)**	**4 (0.8)**	**3 (0.7)**
Constipation	2 (0.2)	0	1 (0.2)	0
Eye disorders	**7 (0.7)**	**2 (0.2)**	**1 (0.2)**	**0**
Macular oedema	4 (0.4)	1 (0.1)	0	0
Musculoskeletal and connective tissue disorders	**6 (0.6)**	**3 (0.4)**	**4 (0.8)**	**1 (0.2)**
Back pain	0	2 (0.2)	1 (0.2)	0
Intervertebral disc protrusion	0	0	2 (0.4)	0
Respiratory, thoracic and mediastinal disorders	**6(0.6)**	**3(0.4)**	**3 (0.6)**	**1 (0.2)**
Dyspnoea	2 (0.2)	0	0	0
Pleurisy	2 (0.2)	0	0	0
Pulmonary embolism	0	0	1 (0.2)	0
General disorders and administration site conditions	**5 (0.5)**	**5 (0.5)**	**2 (0.4)**	**2 (0.5)**
Chest pain	1 (0.1)	2 (0.2)	0	0
Psychiatric disorders	**4 (0.4)**	**1 (0.1)**	**4 (0.8)**	**0**
Depression	2 (0.2)	0	0	0
Suicide*	1 (0.1)	0	0	0
Vascular disorders	**3 (0.3)**	**1 (0.1)**	**2 (0.4)**	**0**
Arterial occlusive disease	2 (0.2)	0	0	0
Blood and lymphatic system disorders	**3 (0.3)**	**1 (0.1)**	**0**	**0**

Primary system organ class Preferred term	FTY 1.25 (N=943) n (%)	FTY 0.5 (N=854) n (%)	Placebo (N=511) n (%)	INF (N=431) n (%)
Lymphopenia	3 (03)	0	0	0
Renal and urinary disorders	**1 (0.1)**	**2 (0.2)**	**1 (0.2)**	**1 (0.2)**
Nephrolithiasis	1 (0.1)	2 (0.2)	0	1 (0.2)
Hepatobiliary disorders	**2 (0.2)**	**4 (0.5)**	**1 (0.2)**	**1 (0.2)**
Injury, poisoning and procedural complications	**1 (0.1)**	**5 (0.6)**	**5 (1.2)**	**5 (1.2)**
Pregnancy, puerperium and perinatal conditions	**0**	**0**	**4 (0.8)**	**1 (0.2)**
Abortion	0	0	3 (0.6)	1 (0.2)
Traffic accident*	0	0	1 (0.2)	0

Source: Post text Table 4.4-9 of ISS. Safety Pool D includes all placebo-controlled studies in ISS (2201, 2301 and 2302). Cut-off: 90 days after drug discontinuation. A patient with multiple SAEs within a primary SOC is counted only once in the total row. A patient with multiple occurrences of an AE under one treatment group is counted only once in the AE preferred term for that treatment group. *Fatal SAE.

Cardiac - As Dr. Villalba notes, evaluations of SAEs in the cardiac SOC in the controlled studies showed a clear dose response for bradycardia and first and second degree atrioventricular block (AVB) in the fingolimod treatment group, and there was 1 case of complete AVB upon first dose of FTY 1.25 mg in the extension studies. These events all occurred within the first 6 hours after first dosing and resolved within 24 hours. In some cases, treatment was required (atropine in at least 4 cases [3 on FTY 1.25 and 1 on FTY 0.5 mg] and isoproterenol in 1 case on FTY 0.5 mg). In addition to the SAEs in cardiac disorders, there were SAEs of ischemic heart disease in controlled studies. Dr. Villalba reports no imbalance in the number of cases of serious MI or angina in the controlled studies, but she notes that most of these events on FTY occurred in young people without prior cardiovascular risk. Among the 6 serious events of ischemic heart disease (2 MI on placebo, 1 unstable angina on interferon, 1 angina pectoris on FTY 1.25 and 2 on FTY on 0.5 mg), the cases in FTY were female, and ages of 27, 34, and 44 y.o. , while the cases on placebo and interferon were male, ages 42-55 y.o.

Nervous System - The most common SAEs in the Nervous system SOC in Safety pool D were seizure-related events and MS relapse, and the profile in the safety pool E was similar. In the controlled studies, 5 subjects presented seizure-related SAEs - 4 on FTY 1.25 mg, 1 on FTY 0.5 mg, and none on interferon or placebo. None of these patients had a previous history of epilepsy. The case on FTY 0.5 mg appears related to a new MS lesion identified within 2 months of the seizure and did not lead to discontinuation. One of the SAEs on 1.25 mg was in the patient who died of herpes encephalitis. Two of the cases were thought to be due to MS relapse, and the reason for the seizure was considered unknown in the 4th case but was not considered to be due to MS relapse. There were 4 seizure-related AEs in the extension studies, 2 on FTY 5 mg, one on 1.25 mg, and one on 0.5 mg. In the latter case, antibody testing, DNA testing, and cultures for bacteria, viruses (including herpes), mycobacteria, and fungus were negative, and the investigator did not suspect a relationship with study drug but due to progression of underlying disease. Study medication was interrupted but restarted and the patient was discharged from the hospital, with the outcome of the progression of MS reported as still present and unchanged. Dr. Villalba notes that there is no mention that JC virus testing was performed (although the investigator concluded that this was not PML), and I agree with her that it is unlikely PML because if PML were present, a progression of disease would be expected.

Two SAEs of status epilepticus and one of grand mal convulsion were reported in study 2309. The grand mal case was unblinded on FDA request and was a patient on placebo. The status epilepticus cases were unblinded on FDA request. One was receiving FTY 0.5 mg and was considered to be due to disease progression, although the role of FTY cannot be ruled out. The other case (on FTY 1.25 mg) was found to have herpes encephalitis (nonfatal). Two additional SAEs of seizures occurred in ongoing blinded study 1201 extension in patients receiving FTY, but the dose remains blinded. Of these, 1 patient with a history of MS for approximately 18 years without a seizure had an epileptic seizure with loss of consciousness 10 months into treatment, and MRI showed no new lesions in the brain. I agree with Dr. Villalba that a causal relationship cannot be ruled out. The other patient had a diagnosis of MS for 9 years prior to study entry; he had no history of seizures; 8 months into treatment he fell out of bed and had "limb rigidity" and convulsions in left arm and face for about 40 minutes, and did not respond when spoken to. He was treated with diazepam and phenytoin. Study drug was discontinued but restarted when consciousness improved. MRI showed no new lesion. He had a fever of 38.7 ºC and was given antibiotics because of the possibility of aspiration pneumonia, although 1 week after the episode he remained febrile and urinalysis was consistent with a urinary tract infection. Study drug was not discontinued and the reason for the seizure remains unexplained.

Dr. Villalba reviewed SAEs of MS relapse and found the reported risk to be low and similar in all treatment groups in the controlled studies (0.2% on FTY 1.25 mg, 0.5% on FTY 0.5 mg, 0.4% on placebo, and 0.2% on interferon). Dr. Fitter has provided input on several of these cases. There were unusual cases and some uncommon neurological diagnoses in the fingolimod treatment groups, such as posterior reversible encephalopathy syndrome (PRES) vs embolic stroke; MS relapse vs ADEM, opportunistic infection malignancy and reported in a publication as a case of hemorrhagic focal encephalitis in a patient treated with IV acyclovir, antibiotics, antifungals, and heparin; neurologic manifestations consistent with Sjogren's syndrome; rapid progression of MS in a patient with MS for 14 years and 3 relapses in the 2 years prior to FTY and 2 relapses within a month of starting FTY; and multifocal diffuse leukoencephalopathy vs Neuromyelitis optica (NMO) vs PML vs atypical MS relapse, stroke, or infection. I agree with Dr. Villalba that the numbers of cases of each are too small to draw definitive conclusions regarding a potential role for fingolimod.

Serious vascular events were also reported with FTY 1.25 mg within the Nervous system disorders SOC. These included 3 cases of stroke (1 in controlled studies and 2 during extensions of which 1 may have been consistent with complicated migraine and stroke work up was negative) and 1 reported in Study 2309. An additional case in 2309 was reported as stroke initially but later changed to transient ischemic attack (TIA). Dr. Villalba reports that no thrombus or source of emboli was found in these cases, but that the workup was not complete. I agree with Dr. Villalba's concern regarding the possibility of increased risk of ischemic/thrombotic cerebrovascular events observed with FTY 1.25 mg, given also the finding of SAEs of ischemic cardiac events in the healthy young women previously discussed.

Infections and Infestations – There does not appear to be a major difference in the risk of these events between fingolimod groups and placebo or interferon in the controlled studies. Dr. Villalba shows a dose response in Safety pool E (3.6% for FTY 1.25-5mg, 2.6% in FTY 1.25

mg, and 1.3% in FTY 0.5 mg). Dr. Villalba notes that in the renal transplant population, 35% of patients had serious infections with FTY as compared to 42% with mycofenolate mofetil, and that these included opportunistic infections in patients taking fingolimod with cyclosporine A and corticosteroids. Opportunistic infections have not been identified in the MS population. Dr. Villalba also notes that there did not appear to be an increase in risk with longer exposure in the MS population. There appears to be an increase risk of serious viral herpetic infections, particularly in the FTY 1.25 mg group. Leukocyte counts, lymphocyte counts, and immunoglobulin levels were not available at the time of the serious infections. SAEs of infections are summarized below.

Herpetic infections – In addition to the 2 fatal herpes cases previously discussed, there were 5 SAEs of herpetic infections in the controlled studies (1 in the interferon group, 2 additional in FTY 1.25 mg both treated with IV acyclovir, and 2 in the FTY 0.5 mg group (an ocular herpes zoster treated with valacyclovir and a herpes simplex virus infection treated with acyclovir). There were 6 SAEs of herpes infections in the extension studies (1 on FTY 5-1.25 mg, 4 on FTY 1.25 mg, and 1 on FTY 0.5 mg). In addition, Dr. Villalba notes that 2 subjects who presented with atypical MS relapses were treated with IV acyclovir because of the possibility of viral infection. There were also SAEs of disseminated herpes zoster, herpes simplex encephalitis and ocular herpes zoster treated with IV antiviral therapy in ongoing study 2309; the cases of encephalitis and disseminated herpes were unblinded and both patients were on or had been on FTY 1.25 mg. The case of the patient with encephalitis had this presentation 6 months after FTY was discontinued. However, as Dr. Villalba notes, his lymphocyte count at the time of the event was 5.5% (normal 15-49%). Although the applicant states that mean levels usually return to baseline within 2 months, I have noted earlier in this memo that even at 3 months in one study, mean levels had not completely returned to baseline, and Dr. Villalba notes that the time to full recovery has not been evaluated in all patients. Thus, it is not inconceivable that this event could be related to fingolimod treatment.

Lower respiratory tract infections – In controlled studies these SAEs were reported only in the FTY 1.25 and 0.5 mg groups. These SAEs were reported in 4 patients in the controlled studies and 1 in the extension study. In addition, Dr. Villalba has identified 3 respiratory tract infections in other SOCs in extension studies, including 1 case of acinetobacter pneumonia.

Other SAEs of Infection – There was one patient on FTY 1.25 mg in Study 2301 with acute right bullous otitis media, atypical mastoiditis and acute right catarrhal sinusitis on day 205 for which she underwent arthromastoidotomy. No microbiology tests were performed. There was a case of pericarditis, pleuritis, and possible pneumonic infiltrate (reported under cardiac SAEs) on Day 65 of FTY 1.25 mg that may have been due to a viral infection.

Neoplasms – Dr. Villalba has summarized the serious neoplasms in the MS database and I agree with her that there does not appear to be definitive evidence of increased risk in the fingolimod treatment group in the present database. She notes 3 lymphomas in the ongoing non-ISS studies in patients receiving fingolimod (EBV related lymphoproliferative disorder, malignant B cell lymphoma and T cell lymphoma, described in deaths; malignant B cell lymphoma 1 year after beginning treatment; skin T cell lymphoma that was a pre-existing skin lesion for which Dr. Villalba believes the role of FTY in worsening cannot be ruled out). Dr. Villalba reports that the

rate of lymphoma in the entire fingolimod-treated MS population is 0.53 per 1000 PYRs, and that the Sponsor finds in an epidemiologic study in the MS population that the rate of non-Hodgkin's lymphoma is 0.17 per 1000 PYRs. However, Dr. Villalba notes that the numerator in the fingolimod database is uncertain as 2 of the 3 cases may have preceded treatment and therefore, definitive conclusions regarding the rate of lymphoma cannot be made. Dr. Villalba also notes an increased risk of basal cell carcinoma for FTY 0.5 mg (that includes a case presenting at 3 different locations), but not for FTY 1.25 mg compared to placebo. I agree that because the long-term exposure in this database is limited, given the known effect of fingolimod on circulating lymphocytes and the potential effect on immunosurveillance, an increased risk with longer exposure cannot be ruled out, and should be addressed with long-term data.

Eye disorders – A dose dependent increase in SAEs of macular edema (ME) was observed in Safety Pools D and E between the 1.25 mg and 0.5 mg doses of FTY (12 patients, 5 in the controlled studies, all on FTY). In the controlled studies, 4 of the subjects had no prior history of MS ocular symptoms and 1 had a history of optic neuritis. Three subjects had decreased or loss of vision in 1 eye at the time of the event, whereas the other 2 were asymptomatic and diagnosed by dilated ophthalmoscopy/ OCT during protocol-scheduled evaluations. Onset was 11-932 days into treatment (mean 207 days, median 99 days), and most were earlier than 3-4 months. SAEs led to discontinuation. In all cases, ME resolved 2-4.5 months after drug discontinuation and 3/4 cases on FTY 1.25 mg and 1 on FTY 0.5 mg recovered with decreased vision at the time of the last available evaluation. There were additional cases of ME coded as nonserious that led to study discontinuation (8 in FTY 1.25 mg and 1 in FTY 0.5 mg).

There were 3 additional ocular SAEs highlighted by Dr. Villalba. Papilloedema (non-inflammatory swelling of the optic disc) was reported on Day 11 in a patient with previous history of optic neuritis and blurred vision; drug DCd on Day 40; papilloedema still present, but improved 188 days after drug DCd; the DSMB ophthalmologist thought it was due to oral contraceptive use. Retinal micro thrombosis was reported on Day 29 in 1 patient with MTHFR mutation+ hyperhomocysteinemia, resulting in drug discontinuation in a patient; Dr. Villalba notes that although the patient may have a predisposition to develop thromboses, as S1P is involved in the regulation of thrombogenesis, the role of FTY cannot be ruled out. I agree. There was 1 case of retinal detachment with the 0.5 mg dose.

Respiratory - In Safety Pool D, the most common respiratory SAE was dyspnea and in most cases, the work-up was incomplete to adequately characterize and to determine the possible etiology. There were no reports of asthma/worsening asthma bronchoconstriction in the fingolimod treated groups in the controlled studies, although Dr. Villalba shows 4 subjects presenting with asthma in the extension studies (2 new onset), and points out that this finding is consistent with known effects of S1P increasing bronchoconstriction.

Vascular disorders – There were 2 SAEs of peripheral arterial occlusion with FTY 1.25 mg in the controlled studies. In subject 2302-0330-00005, a 41 y.o. female with mild hyperhomocysteinemia and heterozygote polymorphism of the MTHFR 677T gene, the event (pain in left hand, blue fingertips, but not cold, splinter hemorrhages in fingernails of left hand) began on Day 7 of FTY. This resolved within 2 days, but recurred on Day 13; drug was DCd on Day 14. Symptoms worsened up to 15 days after drug discontinuation, with angiography

showing a thrombus in the radial artery that was treated with rTPA. By 28 days after discontinuation, her hand appeared warm with good color in most fingers, but there was evidence of necrosis in fingertips, and radial and ulnar pulses were absent. By 2 months after discontinuation there was improvement, and she recovered with sequelae (left hand cooler than right). Subject 2302-0306-00011, a smoker until 1 year prior to event, had a nonserious migraine-like headache on Day 130, treated with naratriptan. On Day 140 she presented with peripheral arterial occlusion in both feet with "necrosis and hemorrhages" under the nails in several digits of both feet, with coldness and discoloration of toes. Study Drug was discontinued on Day 145. Doppler sonography showed a patent but narrow pedal dorsal artery with spastic flow profile. The patient was started on acetylsalicylic acid and clopidogrel. The event resolved 37 days after the last dose of study medication. The patient had no other vascular risk factors such as diabetes and was not taking hormones. I agree with Dr. Villalba that the number of events is too small to draw definitive conclusions, but given the role for S1P in vascular homeostasis vascular tone and permeability, angiogenesis, and thrombogenesis suggested in the literature, the role of FTY in the observed events must be considered.

Hepatobiliary disorders – Dr. Villalba notes that the most common SAEs in this SOC were cholelithiasis (1 each in FTY 0.5 and 1.25 mg, placebo, and interferon in Safety Pool D and 2 cases each in FTY 0.5 and 1.25 mg in Safety pool E), and biliary colic (1 case each in FTY 0.5 mg and 1.25 mg in Safety pool D and 2 in each of those doses in Safety pool E). She did not believe that those events were drug related.

Liver-related SAEs were identified in this SOC and in Investigations and suggest an increased risk of liver related SAEs in the FTY-treated groups. In Safety pool D Dr. Villalba notes that in the FTY groups with elevations in LFTs, except for 1 case, bilirubin (BR) and alkaline phosphatase (ALK Phos) were within normal limits. In that case, in a patient with pre-existing elevated liver enzymes and suspected alcohol abuse, there was an abrupt >10x increase in ALT and AST, increase in GGT and increase in ALK Phos that occurred subsequent to a 3 day treatment with IV paracetamol. The case is complicated by alcohol abuse and paracetamol administration, but I agree with Dr. Villalba that the role of FTY in any underlying liver enzyme elevations cannot be ruled out. There was a case of hepatitis in the extension study 2201E (elevated transaminases with normal BR and ALK Phos) for which a role for FTY cannot be ruled out. A case of jaundice was reported on 4/29/10 in a patient on study 2302 E1. The case was reviewed by Dr. John Senior and details of the case and his considerations are in Dr. Villalba's review. That case appears to have been likely due to Hepatitis E infection.

Blood and Lymphatic system disorders – Dr. Villalba notes that there were few serious events in this SOC (4 total in Safety pool D). The most common event was lymphopenia (n=3, in FTY 1.25 mg only). A case of thrombocytopenia in FTY 0.5 mg on Day 122 led to discontinuation but the patient had not fully recovered 9 months after discontinuation; the patient was also taking gabapentin and pregabalin that have been associated with thrombocytopenia. There was a case of thrombocytopenia in an extension study that resolved after discontinuation, and FTY was restarted 2 months later. There was a case of autoimmune idiopathic thrombocytopenia purpura (ITP) in the extension studies that occurred on day 181 of FTY treatment and had recovered completely by 5 months after drug discontinuation. There was another case of ITP in study 2309 that remains blinded. Dr. Villalba also notes that in the renal transplant database, there were 2

events of autoimmune hemolytic anemia, 7 of hemolytic uremic syndrome, and 3 of thrombotic microangiopathy, all in the FTY treatment group. She points out that these events raise concerns about additional hematologic effects other than redistribution of lymphocytes.

2.2.3 Dropouts and Other Significant Adverse Events

In Safety Pool D, 235 subjects discontinued drug because of AEs (10.6% of subjects on FTY 5mg, 11.9% on FTY 1.25mg, 7% on FTY 0.5mg, 7% on placebo, and 2.9% of interferon-treated patients). The differences were driven by AEs in Investigations (primarily liver enzyme related with 39 discontinuations for liver-related investigations in FTY 1.25 (4.1%) and 29 in FTY 0.5 mg (3.4%) , 3 on placebo (0.6%), and 7 on interferon (1.6%)), Eye disorders (primarily macular edema with 1.1% on FTY 1.25 mg, 0.1% on FTY 0.5 mg, none on placebo and 0.2% on interferon), and Cardiac disorders that occurred in 1.3% of FTY 1.25 mg and 0.1% of FTY 0.5mg (primarily bradycardia and 1st and 2nd degree AV block that only occurred in FTY 1.25 mg) SOCs. Patterns of discontinuations in Safety Pool E were consistent with those in the controlled studies.

For the *liver enzyme* events, most were categorized as "non-serious", were associated with increases in ALT or GGT of 3-5x ULN without associated increase in BR or Alk Phos, and resolved two weeks to several months after drug discontinuation, although some had not fully resolved at the time of last testing. For those cases with an increase in BR, I agree with Dr. Villalba that there was an alternate explanation (e.g. paracetamol, Gilbert's disease).

In addition to the cases of macular edema in *Eye disorder* events, Dr. Villalba notes a case of bilateral ischemic retinopathy/vasculitis and a case of small intra-retinal hemorrhage in patients treated with FTY, suggesting that there could be some deleterious vascular effect in the retina besides macular edema.

In the *Cardiac* SOC, in addition to cases of bradycardia and AV block that were consistent with those described in SAEs, there was a case of "nonserious angina pectoris" with inverted T waves on Day 62 of FTY 1.25 mg in a 30 y.o. male with no other risk factors. (There was also 1 case of angina resulting in discontinuation in a patient on interferon). There was also 1 case of pulmonary hypertension in a patient on FTY 1.25 mg in Study 2309 that had improved by 68 days after study drug discontinuation.

Fourteen subjects discontinued because of events in the *Infections and infestations* SOC in the controlled database: 2 (2.1%) on FTY 5 mg, 7 (0.7%) on FTY 1.25 mg, 2 (0.2%) on FTY 0.5 mg, 2 (0.4%) on placebo), and 1 (0.2%) on interferon. Serious and fatal infections have been discussed earlier in this memo and in Dr. Villalba's review.

Fifteen subjects discontinued because of AE in the *Nervous system disorders* SOC in the controlled database. There did not appear to be an increased risk for FTY compared to placebo in the controlled database. Nonserious events on FTY included headache (1 on FTY 1.25 mg, 1 on 0.5 mg, and 1 on placebo) and 1 case of cognitive dysfunction (in a patient with SAE of MS relapse with symptoms consistent with Sjogren's syndrome).

Thirteen subjects in the controlled database discontinued because of events in the *General disorders and administration site conditions* SOC. Serious AEs were previously considered. Dr. Villalba notes 3 cases of fluid retention/edema in the ISS database (with FTY 1.25 in 2 cases and FTY 0.5 mg in 1 case) with onset on Day 1, 3, and 36, respectively leading to discontinuation, and an additional case that discontinued from 2309 but still remains blinded. I agree with Dr. Villalba that there is limited information and few cases with which to draw conclusions but the finding requires further evaluation.

In the *Respiratory, thoracic and mediastinal disorders* and *Investigations* (respiratory related) SOCs, 21 subjects discontinued because of an AE in the controlled trials. Overall, in those 2 categories, there was no excess of subjects discontinuing between FTY 1.25 and placebo, although there appeared to be a dose response between FTY 1.25 and 0.5 mg. Preferred terms for the events included dyspnea, obstructive airway disorder, diffusing capacity for carbon monoxide (DLCO) decreased, and PFT abnormal. Dr. Villalba provides the narratives in her review. Time course of onset and recovery in several cases supported the role for FTY in the AE, although some cases had not resolved at the time of the last follow-up, and many lacked adequate follow-up at the time of the event or after drug discontinuation. There were 14 additional discontinuations due to respiratory related events in the extension studies in the ISS. In the FTY 0.5 mg group these included 2 cases of DLCO decreased, 3 cases of dyspnea, and 1 case of respiratory distress, none reported as serious. One case of DLCO decreased occurred in a 19 y.o. healthy female non-smoker taking no concomitant meds (2302E1-0219-00002), who had baseline DLCO of 75.4% of predicted at screening and had progressive decrease in DLCO to 50% of predicted at 2 years into FTY 0.5 mg treatment. HRCT 3 weeks after discontinuation was normal and pulmonologist evaluation showed no progressive, active disorders 1 month after discontinuation. I agree with Dr. Villalba that the role of FTY in this event cannot be ruled out.

In addition to those cases, there have been discontinuations from ongoing study 2309 for respiratory-related adverse events related and unblinding of these cases was requested. Dr. Villalba shows, from information as of 6/9/10, that there is a dose response in discontinuations for these events between FTY 1.25 mg (1.9%) and FTY 0.5 mg (0.9%). Discontinuations due to these events were 0.3% in placebo.

Six subjects discontinued because of adverse events in the *Vascular disorders* SOC. In the FTY group there were 3 discontinuations for hypertension (1 in each dose group), and 2 for arterial occlusive disease (previously discussed in SAEs). There was 1 discontinuation for hypotension on placebo. There were no additional discontinuations due to vascular events in the extension studies.

Dr. Villalba did not find an increased risk of discontinuation from FTY in the *Psychiatric disorders* SOC. In the *Musculoskeletal system disorders* SOC there were no discontinuations for serious events. The events resulting in discontinuation were 2 back pain (one on interferon, one on FTY), and 1 muscle spasm, 1 pain in extremity, and 2 myalgia all on FTY.

Six subjects discontinued because of AEs in the *Skin and subcutaneous disorders* SOC: 1 pruritic rash on placebo and 5 rashes in the fingolimod controlled database (2 on FTY 1.25 mg and 3 on FTY 0.5 mg). One of the latter included a blister-like rash approximately 7 hours after

the first dose in which FTY was discontinued on Day 2, and rash continued on 26 days after study drug discontinuation; the other was an "allergic skin rash" of moderate intensity, drug was discontinued on day 30 and rash resolved 47 days later. Dr. Villalba notes 2 anaphylactic reactions and 1 case of serum sickness in the renal transplant population, but no signal for hypersensitivity reactions in the MS database.

Nonserious AE leading to discontinuations in the controlled studies in the *Blood and lymphatic* SOC and blood-related *Investigations* SOC were 1 case of platelet count decreased on Day 90 of FTY 5 mg (thus 4 cases of thrombocytopenia in the ISS of SAE or discontinuation), 1 case of lymphadenopathy on Day 101 with FTY 1.25 and 1 case of lymphopenia on Day 548 with FTY 0.5 mg. Nine subjects discontinued in extension studies due to non-serious AE of lymphopenia.

In summary, the risk of AEs leading to discontinuation was higher in FTY 1.25 mg vs 0.5 mg FTY, placebo, or interferon, and there was a dose-response for 1.25 mg and 0.5 mg. The differences were driven by liver enzyme-related AEs, macular edema, and cardiac events (bradycardia and AV block). This is consistent with the findings of SAEs. In addition, AEs leading to discontinuation or SAEs of vascular events and infections (primarily serious herpetic infections) are of concern.

2.2.4 Significant Adverse Events (Nonserious)

AE in the *Eye disorders SOC* – Dr. Villalba notes 4 cases of retinal detachment in Safety Pool D coded as non-serious, (3 on FTY 1.25 and 1 on FTY 0.5), of which 1 led to discontinuation. There were 7 (non-serious) retinal hemorrhages in the FTY-treated group, (3 in FTY 1.25 and 4 in FTY 0.5). Dr. Villalba notes that none of those patients had a history of hypertension or diabetes or developed an AE of hypertension in the study, and all were asymptomatic with no changes in visual acuity. In addition there was 1 case of bilateral ischemia/vasculitis and 2 retinal microaneurysm cases in the FTY 1.25 group, and 1 retinal vascular spasm and 1 splinter hemorrhage in the FTY 0.5 group.

In the controlled studies, macular edema (serious and nonserious) occurred in 1.3% of patients with FTY 1.25, and 0.2% with FTY 0.5. Dr. Villalba lists the 23 cases of macular edema in the ISS (serious and nonserious). In the controlled period there were 12 on FTY 1.25 mg, 2 on FTY 0.5 mg, 1 on interferon, and none on placebo. There were 9 additional FTY cases in the extension studies, with more on FTY 1.25 mg than 0.5 mg. Mean time to onset in the FTY treatment group was 202 days (6.5 months) with a median of 99 days (range 15-932 days), consistent with the findings for SAEs of macular edema. In Study 2309, there were 6 cases on FTY 1.25, 5 on FTY 0.5 and 2 on placebo (0.9% for confirmed events with FTY 0.5 mg). In Study 2309, the onset was 2-3 months into the treatment (34-168 days).

Cardiac – In addition to the 6 events of ischemic heart disease coded as serious, there were 6 events on FTY (myocardial ischemia, myocardial infarction, and angina pectoris) coded as nonserious. Serious and nonserious events consistent with ischemic heart disease in the controlled trials did not show an imbalance, but Dr. Villalba notes that there was limited cardiac workup. Most patients continued without specific treatment and without subsequent episodes.

There were 4 additional cases of angina and 1 MI in the extension studies and 2 additional cases of MI in ongoing studies.

There was 1 serious AE of hypertension and 3 nonserious cases leading to discontinuation in the controlled population. Overall, there were 102 serious and nonserious hypertension related events on FTY in pool D: 59 (6.3%) on FTY 1.25, 43 (5.0%) on FTY 0.5 mg, 17 (3.3%) on placebo and 9 (2.1%) on interferon. Dr. Villalba notes that this is consistent with a dose related increase in systolic and diastolic blood pressure over time for FTY treated groups (discussed in Section 2.2.8 of this memo). In addition, Dr. Villalba notes that evaluation of medications after start of study drug suggests greater use of antihypertensive medication in FTY groups.

Respiratory – Risk of developing serious or nonserious AEs in this SOC was similar among treatment groups overall, although risk of dyspnea was higher in the FTY groups (5.3% for FTY 1.25 mg and 4.4% for FTY 0.5mg) than in placebo (3.9%) or interferon (1.6%). Productive cough, respiratory disorder, and wheezing occurred in less than 1% for FTY 1.25 mg or 0.5mg but were not observed on placebo. The number of patients on FTY with AEs of asthma, restrictive respiratory disease, and obstructive pulmonary disease was no higher than placebo.

Lung neoplasm/benign lung neoplasm - These cases were distributed among groups in controlled studies as follows: 1 case on placebo, 1 on interferon, 2 on FTY 1.25, and 3 on FTY 0.5 ,and there were 3 cases in the extension studies). One case was serious and led to study drug discontinuation (necrotizing granulomatous pneumonitis seen in a transbronchoscopic biopsy).

FDA requested that the sponsor submit cases coded as pulmonary fibrosis. One case in a 35 y.o. male non smoker (2301 0754 00004), with HRCT showing "local pneumofibrosis" and DLCO that declined > 30% from baseline) led to discontinuation. The other case, in an asymptomatic patient with normal PFTs and no change in DLCO, but with High Resolution Computed Tomography (HRCT, tests for interstitial lung disease) done per protocol and read as abnormal, not clinically significant, was coded as nonserious and did not lead to discontinuation.

Nervous System SOC – Except for seizure-related events (discussed under SAEs), the only AE with a higher incidence in FTY compared to placebo was migraine (3.2% FTY 5, 3% FTY 1.25, 3.4% FTY 0.5, 1.8% placebo, and 1.5% interferon). Syncope was reported in 3 subjects (one on placebo Day 163, one on FTY 1.25 Day 724, one on FTY 0.5 Day 203). Evaluation of all cases of syncope and loss of consciousness (serious and nonserious) had similar incidence across all treatment groups (FTY, placebo, and interferon), and generally were spread throughout the duration of the studies, but most common within the first year.

Metabolic Disorders – There were 2 cases of nonserious abnormal weight gain in controlled studies, one on FTY and one on interferon, 2 cases of fluid retention on FTY 1.25 (1 already described), and 1 subject was reported to have "overweight" on FTY 1.25 mg.

Neoplasms – The risk of any neoplasm (serious and nonserious) was similar among treatment groups when evaluated as "n patients with event/N patients randomized". However, the rates per 100 patient years of exposure were higher in the FTY groups as compared to placebo, and similar to interferon (10.3 in FTY 1.25, 9.8 in FTY 0.5, 4.9 in placebo, and 10.9 in IFN). The

difference appears to be driven by nonmalignant lesions of melanocytic nevus and fibrous histiocytoma that according to Dr. Villalba are reported to be associated with immunosuppression. However, she notes that Study 2201 did not have pre-specified dermatologic examinations and in 2301 and 2302, these exams were implemented when the studies were already ongoing. Most of the diagnoses of skin lesions were done at the first dermatologic exam after patients had been on treatment for several months. There was one case in which the role of fingolimod on development or acceleration of a malignant neoplasm could not be ruled out in a patient who had a pre-existing mole at that site.

Infections and Infestations – Dr. Villalba does not report a greater incidence of AE for this category (serious and nonserious) in Safety Pool D for FTY vs placebo. She does not find an excess for any specific organism for FTY vs placebo (including herpes viral infections or viral infections NEC, except for Candida infections that had a slight excess (1.2% in FTY 1.25, 1.1% in FTY 0.5 mg, 0.6% in placebo, and 1.9% on interferon). None of the cases was serious.

The percentage of patients with infections for the group of patients with the lowest lymphocyte counts ($\leq 0.4 \times 10^9$ /L) was increased relative to those patients with higher lymphocyte counts, but similar to placebo. The risk of infections with nadir $> 0.4 \times 10^9$ /L was lower than placebo (except for UTI that was more frequent in placebo). An analysis at time of "nadir" did not reflect the lymphocyte counts at the time of infection and is not useful.

2.2.5 Submission Specific Primary Safety Concerns

Increased Risk of Infections – This was anticipated due to decreased peripheral lymphocytes. Dr. Villalba's' review did not find an excess of overall infections, serious, infections, or opportunistic infections in the fingolimod groups in the MS population. There does appear to be an increased risk of serious herpetic infection with fingolimod 1.25 mg. Dr. Villalba notes an increased use of systemic and topic antiviral agents for FTY (1.8% for 1.25 mg and 1.1% for 0.5 mg) compared to 0.2% for placebo, supporting an increased risk of viral infections compared to placebo.

The potential for development of progressive multifocal leukoencephalopathy (PML) is a concern, given the experience with immunosuppressors such as natalizumab. No cases of PML were identified in this database, although I agree with Dr. Villalba that the database is relatively small and with relatively short exposure to be able to rule out the possibility of PML.

Dr. Villalba summarizes the results of a clinical pharmacology study evaluating immunologic response to vaccination, in which the data suggests that this response may be decreased.

Dr. Cavaille-Coll, FDA immunologist consult from Division of Special Pathogens (DSPTP) recommends:

- Vaccination prior to initiation of long-term fingolimod therapy should be considered
- Consideration should be given as to whether live vaccines should be avoided.
- While peripheral lymphocyte counts may serve as a pharmacodynamic marker of fingolimod, they reflect redistribution and not lymphocyte depletion and should not be interpreted as a reflection of infectious risk.

- Due to fingolimod's effect on lymphocyte circulation and distribution, FTY has the potential to modify signs and symptoms of infection, and one should maintain a higher degree of suspicion for infection and atypical presentations.
- The question as to whether to recommend cessation of FTY in the event of a new infection or for what type of infection remains unresolved.

Neoplasias – The basis for this concern was nonclinical carcinogenicity studies in mouse showing increased risk of lymphoma, and lymphoid tumors observed in the renal transplant population (at a dose of 2.5 mg in patients receiving cyclosporine A).

There was no evidence of increased risk of neoplasia in FTY-treated groups in the MS database, except for an increase in non-malignant melanocytic nevous and fibrous histiocytoma, with a rate higher than placebo but similar to interferon. There were 3 cases of lymphoma in non-ISS studies, and 1 case of skin sarcoma in an ongoing study. I agree with Dr. Villalba that the database is too small and too short to adequately assess the risk for malignancy, and that it should be addressed in a larger, long-term database.

Eye toxicity – In the renal transplant database, serious macular edema was reported in approximately 4% of patients receiving FTY 5 or 2.5 mg (1.5% for MMF). In patients with diabetes mellitus, the risk of macular edema was 30% for FTY doses and 15% for MMF.

Significant events of ME in the MS database are summarized in Section 2.2.4 of this memo. Dr. Villalba has summarized the findings regarding diagnosis and outcomes of macular edema in the MS population for Safety pool D + Study 2309 in the table below.

	FTY 1.25 N=1302 n (%)	**FTY 0.5 N=1204 n (%)**	**Pbo N=861 n (%)**	**IFN N=431 n(%)**
Any ME	19 (1.5)	7 (0.6)	2 (0.2)	1 (0.2)
Presence of ME confirmed by DSMB ophthalmologist	14 (1.0)	5 (0.4)	1 (0.1)	-
Serious ME	6 (0.5)	2 (0.2)	1 (0.1)	-
Eye symptom at time of dx of ME	9 (0.7)	1 (0.1)	1 (0.1)	-
AE of ME reported as not resolved at last FU[1]	5 (0.4)	1 (0.1)	1 (0.1)	-
Clinically significant decrease in VA reported at last FU	4 (0.3)	3 (0.1)	1 (0.1)	

[1] Most reports of "not resolved" at last follow up were based on Fluorescein Angiography (FA). Not every patient with ME had FA.

Dr. Wiley Chambers reviewed all of the cases of macular edema and recommended that an ophthalmologic evaluation with dilated ophthalmoscopy should be obtained at baseline or near baseline and with subsequent follow-up. As Dr. Villalba notes, the members of the AC in June 2010 agreed that all patients should have a baseline ophthalmologic exam before starting to use the drug, with regular assessments of visual acuity at routine neurologic visit and referral to an

ophthalmologist if clinically indicated. Dr. Villalba recommends baseline ophthalmic exam, but follow-up at 3-4 months as that is when most events occurred, and follow-up as clinically indicated for symptoms or changes in visual acuity assessments. I agree with her recommendation.

Pulmonary toxicity - Nonclinical studies showed lung toxicity. Increased bronchoconstriction was seen in a clinical pharmacology study at doses ≥ 5 mg/day, and in the renal transplant population there was an excess of dyspnea and pulmonary edema in fingolimod-treated patients.

In the MS population, respiratory tract associated serious AEs and discontinuations were not frequent, and there were no major differences between treatment groups in the controlled studies. However, Dr. Villalba notes that evaluation was not as complete as desirable giving the example of patients with dyspnea or chest pain that were discontinued without chest X-Ray, HRCT, PFT, ECG or echocardiogram at the time of the event or possibly having those performed several weeks or months after the event.

PFTs

Across all trials, PFT measures (changes in predicted FEV1, FVC, and DLCO) decreased from baseline to a greater degree in FTY-treated patients compared to placebo, and in a dose-related pattern. PFT changes were not always associated with clinical symptoms, and I agree with Dr. Villalba's hypothesis that this may be due to the high level of baseline pulmonary function in the Phase 3 trial population. Dr. Villalba discusses PFTs and HRCT in Section 7.4.5 of her review (Special Safety Studies). In Study 2201 PFTs were assessed at screening and month 6, and indicate that more FTY-treated patients had decreased FEV1 and DLCO ≥ 15% from baseline compared to placebo (23.1% for FTY 1.25 mg vs 8% for placebo). A greater change in FTY-treated patients vs placebo in FEV1 and in DLCO is also seen in pooled studies 2301 and 2302 with a sharp decline seen at 1 month followed by a progressive decrease over time. Results for DLCO are shown, as an example, in the table below from Dr. Villalba's review.

Table 1. Change from baseline in Percentage of predicted DLCO, studies 2301 and 2302

Visit	n	Baseline Mean (SD)	Δ from baseline Mean (SD)
Month 1			
FTY 1.25 (N=849)	743	86.1 (15.7)	- 2.0 (12.1)
FTY 0.5 (N=854)	781	84.7 (15.7)	- 1.0 (12.0)
Placebo (N=418)	386	87.8 (17.8)	0.0 (15.0)
Month 12			
FTY 1.25 (N=849)	683	86.1 (15.7)	-3.3 (13.7)
FTY 0.5 (N=854)	736	84.7 (15.7)	-1.5 (12.8)
Placebo (N=418)	351	87.8 (17.8)	1.3 (17.1)
Month 24			
FTY 1.25 (N=849)	292	88.8 (14.9)	- 7.3 (12.2)
FTY 0.5 (N=854)	342	86.3 (15.0)	- 3.8 (13.4)
Placebo (N=418)	303	88.0 (17.8)	- 2.7 (15.8)

Source: FDA response for information submitted 3 31 10

For both FEV1 and DLCO there is substantial overlap in the data points. However, the point estimates show a dose-dependent decrease. Dr. Porter, the FDA pulmonologist consultant, noted

that the change in FEV1 for FTY 0.5 was > 100 ml at 6 months, and that is greater than the annual decline in FEV1 seen in healthy patients, patients with COPD, or MS patients in general. There was no difference in FVC for any dose. For Study 2309, consistent with the findings from the Phase 3 studies, there were decreases from baseline in FEV1 and DLCO, although in FEV1 the change observed at 1 month appeared to be maintained at the 24 month evaluation. Outlier analysis of PFTs supported these findings, although for the analysis for 2301 and 2302 core studies, the risk was observed for FTY 1.25mg but not for 0.5 mg.

Tyere is no evidence for a permanent structural change in the lung due to fibrosis, for example. Dr. Villalba suggests that the decrease in FEV1 could be in part explained by the known pharmacologic bronchoconstrictive effects of fingolimod, but that the reason for decreased diffusion capacity is not clear. She notes that prolonged S1P antagonist exposure increases damage in mice with bleomycin-induced lung injury, and that in the literature it has been proposed that this could be explained by perturbations in lung endothelial barrier function, although that has not been evaluated.

Per protocol, patients in study 2309 with FEV1, FVC, or DLCO < 80% of baseline were to have HRCT. Dr. Villalba finds that a higher percentage of patients fulfilled PFT abnormal criteria for FTY 1.25 (18.2%) or FTY 0.5 (14.4%) than for placebo (9.2%), but many who fulfilled abnormal PFT criteria did not get follow-up HRCT and at least 50% of patients with abnormal PFTs are missing a follow-up HRCT.

A subset of patients in Safety pool E (288 patients on FTY 1.25 mg and 211 on FTY 0.5 mg), was followed up after discontinuation (mean of 4 months). Dr. Villalba shows in Table 100 and Table 101 of her review that the changes in FEV1, but not DLCO, appeared to be reversible at 3 months after discontinuation, although it appears that they had not completely returned to baseline. Reversibility requires further follow-up.

HRCT

In 2301, HRCT at 2 years suggested a slightly higher risk for pulmonary toxicity for FTY vs placebo (approximately 14% in either FTY 1.25 mg or 0.5 mg groups have new or worsened abnormality vs 9.5% on placebo), but no particular pattern of toxicity was observed and no evidence of pulmonary fibrosis. In 2302 at 1 year the proportion of patients with HRCT showing new or worsening abnormalities was similar across FTY doses and interferon, and there were no changes consistent with pulmonary fibrosis. In 2309, the % of new or worsened findings was also similar across both doses of FTY and placebo, although the proportion of new or worsened abnormalities compared to baseline abnormal HRCT among unscheduled tests was higher in the FTY 1.25 group (38.5%) vs FFTY 0.5 (13.3%) or placebo (16.7%). As Dr. Villalba notes, the numbers are small (11-12 patients in each group with unscheduled HRCT).

Pulmonary Recommendation – Dr. Brian Porter is the FDA pulmonologist consultant from the Division of Pulmonary, Allergy and Rheumatology Products (DPARP). Based on his review, DPARP recommended that information about the decline in pulmonary function and higher incidence of new or worsened HRCT abnormalities be included in the fingolimod labeling, and in the REMS. DPARP thought there was insufficient data to support a specific monitoring schedule. As Dr. Villalba notes in her review, Dr. Carrie Redlich, the pulmonologist at the

FDA AC meeting of 6/2010 noted that patients with impaired lung function at baseline would not tolerate a drop in PFTs as well as patients included in the clinical studies. The majority of the panel agreed with her, that baseline spirometry and DLCO should be obtained in all patients receiving fingolimod and that it would be desirable to obtain more information from patients with underlying lung problems. DPARP recommended that a prospective, controlled study be conducted to evaluate reversibility of pulmonary function reduction.

Cardiovascular Toxicity – The basis for this concern was known effect of S1P modulation on heart rate in vitro and in vivo; more cardiovascular deaths, MI and pulmonary edema in renal patients at the 5 mg dose of FTY than in the MMF group; and literature reports of the role of S1P in regulation of vascular permeability, vascular tone, and angiogenesis.

As discussed earlier in this memo, there is a dose related effect on heart conduction on first fingolimod treatment resulting in SAEs, with onset of bradycardia or 1st or 2nd degree AV block within 6 hours of the first dose that in some cases required treatment with either atropine or isoproterenol.

LV function and ischemic heart disease – There was no excess of congestive heart failure or ischemic heart disease in the FTY treated groups in the controlled studies, although Dr. Villalba notes that not all patients who presented with dyspnea, chest pain, or angina underwent a complete cardiovascular evaluation and follow-up. The only event of serious pulmonary edema was associated with transient LV dysfunction that was confounded by use of alternative medicine and varnish preceding the event. No evidence of effect on LV function was observed in the echocardiogram database, although the number of paired echoes is limited and long-term data are not available (a total of 183 subjects were included in the echocardiogram population, but at the time of the original submission, only 17 had paired echocardiograms for up to 2 years). There was a case of pulmonary hypertension in Study 2309, mentioned under discontinuations, above.

Ischemic/thrombotic events (CV death, non fatal MI, and nonfatal stroke) – There were no cardiovascular deaths in the application, and few MI (2 in placebo, 1 in interferon, none in FTY in controlled studies) and strokes (1 at the 1.25 mg dose in controlled studies, 2 in extension studies, and 1 in 2309 and 1 on placebo in 2309). There were several cases of "angina pectoris" and noncardiac chest pain": although the workup was incomplete.

Other (noncardiac) vascular events –2 cases of peripheral vascular disease were described under SAEs in controlled studies, both on FTY 1.25 mg. There was 1 case of retinal artery microthrombosis, one of bilateral retinal ischemia/vasculitis in the FTY 1.25 mg group in the controlled studies, and several non-serious vascular related AEs (retinal hemorrhage in the Eye disorders SOC).

Special studies included 24-hour Holter monitoring at screening, Day 1 and Month 3 in all patients in Study 2309 and at selected sites including all US sites in Study 2032, as well as in 2201 in some subjects. All three studies showed a dose-related decrease in heart rate. For FTY 0.5 mg, the maximum change from baseline was approximately 20-22 bpm and occurred at 6 hours post-dose in 2302 and 2309, and had returned to values similar to pre-dose values by 24

hours post-dose. In 2309 average heart rate ≤ 40 bpm for any hour was observed in 1.4% and 0.3% of patients in the FTY 1.25 and 0.5 mg groups, respectively, during the first 24 hour Holter, but not at 3 months, and was not observed in any patients on placebo. Risk of second degree AV block on Day 1 (Wenckeback and 2:1 block) was higher in FTY groups than in placebo, with evidence of dose-response during the Day 1 24 hour Holter.

Echocardiography assessments were performed in studies 2302 and 2309 at selected US sites at Screening, Month 3, and Month 12, and in 2309 also at Month 24. This included assessment of myocardial function and estimation of pulmonary arterial pressure by echocardiography-doppler. Dr. Villalba points out that there were very few patients available for echocardiogram evaluation at 1 year (n=101) and 2 years (n=31), and that many patients discontinued from 2309 because of respiratory related events (that could reflect a cardiac finding). A small increase in mean systolic pulmonary artery pressure was observed in the last post-baseline analysis for both doses of FTY compared to a small decrease on placebo, the clinical significance of which is unclear (and Dr. Villalba notes that echocardiography only provides and estimate of the pulmonary pressure value). Pulmonary artery pressure could not be estimated in 2/3 of the patients in the database. As previously noted, 1 patient on FTY discontinued from study 2309 due to pulmonary hypertension. Two other patients had an increase from baseline in systolic pulmonary artery pressure of > 10 mm Hg; both were asymptomatic. Two additional patients, 1 on FTY 1.25 mg and 1 on placebo, had a pulmonary artery pressure nonmeasurable at screening but > 35 mm Hg at a follow up. Dr. Shari Targum was the FDA consultant cardiologist who reviewed the echocardiogram data and concluded that the data do not reveal a large safety signal. Dr. Targum noted that she could not comment on the image quality or methods of calculation, or intra- or inter-reader variability. Dr. Targum said that if there were a large signal, one would have expected consequences of chronic volume overload such as left ventricular and left atrial dilation that were not observed here, but she says that a smaller signal or a signal appearing over a longer time period could not be excluded, and one could not exclude safety signals that might surface in a more vulnerable population. Dr. Targum reviewed a retrospective evaluation of the morphology of the valves (mitral, aortic, and tricuspid). Valves were evaluated with respect to mobility, thickness, calcification, and reduction in excursion; with extent of changes assessed as trace, mild, moderate, or severe, or diffuse/focal. The mitral and tricuspid valves were evaluated for presence of stenosis or regurgitation. Dr. Targum commented that while there may be a numerical imbalance in "trace" tricuspid regurgitation on FTY 1.25 vs placebo, this is not generally considered clinically significant and may be a function of the high sensitivity of Doppler testing. She found no clinically meaningful signal for valvular abnormalities.

Liver toxicity -
The risk of ALT elevation > 3X ULN in the renal transplant population was approximately 20% and slightly higher with FTY 5mg and 2.5 mg compared to MMF. In MS, the liver adverse events and laboratory evaluations showed dose-related toxicity. In Safety pool D, 72 (8.5%) of patients on FTY 0.5 had ALT ≥ 3X ULN (9.7% on FTY 1.25 mg and 1.6% on placebo) and 14 patients (1.6%) on FTY 0.5 mg had ATL ≥ 5X ULN (vs 2.2% on FTY 1.25 mg and 0.8% on placebo), and 29 patients (3.4%) had discontinuations due to liver-related investigations. In most cases transaminase elevation occurred without increase in bilirubin and alkaline phosphatase, as discussed under SAEs in this memo, and when there was an increase in BR or Alk Phos there was another reasonable explanation.

Neurologic Toxicity –
In dog studies, perivasuclar mononuclear infiltration was observed in brain. In the renal transplant population, the risk of seizures was slightly higher in the fingolimod 2.5 and 5 mg groups vs MMF. In the MS population, seizures, and unusual MS relapse have been observed, including those reported as SAEs (Section 2.2.2 of this memo). There is a dose-related increase in seizure related events in safety pool D (1.1% in FTY 5 mg, 0.6% in FTY 1.25 mg, 0.2% in FTY 0.5 mg, and 0.2% on placebo (none on interferon). As Dr. Villalba notes, the applicant references a publication in which seizures reportedly occur in about 2-3% of patients with MS, and the baseline history of epilepsy or seizures in the MS population in this application was about 1%.

Cases of unusual MS relapse were discussed in section 2.2.2 of this memo. I note Dr. Villalba's concern that unusual or atypical MS relapses might be related to an unidentified CNS infection, and agree that additional data on unusual/atypical cases of MS relapse should be collected in the planned postmarketing studies.

Edema/renal toxicity – Fluid retention resulted in drug discontinuation in 4 patients on FTY, none of whom had urine protein measurement available at the time of the event. Dr. Villalba notes that there were no adverse events of renal failure and no increase in creatinine or decrease in estimated creatinine clearance. However, she notes that if S1P modulation interfered with glomerular function, proteinuria would be observed before renal failure.

Hematologic Toxicity (Other than Lymphocytes) –Cases of thrombocytopenia were reported as SAEs or leading to discontinuation in the ISS, as described above. Analysis of mean change from baseline in hematologic parameters in safety pool A (12 month treatments in controlled studies 2301 and 2302) suggests a small (mean up to approximately 5%) dose - related decrease in platelet count most notable at 1 month, the clinical significance of which is unknown. Outlier analysis in safety pool D does not suggest an increased risk of thrombocytopenia or thrombocytosis compared to placebo. Dr. Villalba also notes, in analysis of mean changes from baseline in pool A, a slight dose-related decrease in neutrophil count (mean decrease from baseline of up to 1. 5x 10^9/L for FTY 1.25, 0.73 for FTY 0.5, .14 for placebo and 0.05 for interferon at 12 months). Outlier analysis from Safety Pool D showed a dose related risk of patients with neutrophil count < 1000/mm^3 (3.2% for FTY 1.25 mg, 2% for FTY 0.5 mg, 1.2% for placebo and 1.2% for interferon). In the 2 year study 2301, 15% of patients in the FTY 1.25 and FTY 0.5 mg groups had a neutrophil count ≤ 1.5x 10^9/L vs 4% in the placebo group. One case of absolute neutropenia was observed in the FTY 1.25 mg group.

Teratogenicity – Dr. Villalba notes that fingolimod was teratogenic in the rat where it was associated with cardiovascular malformations. There is limited information in pregnant women. As of 1/29/10 there had been 30 pregnancies reported in FTY –treated patients: 13 resulted in successful delivery, 5 in spontaneous abortion, 8 in elective abortions, and 4 still ongoing. The 13 term deliveries included 12 normal newborns and 1 congenital abnormality (congenital shortening of the right leg). One case of Tetralogy of Fallot was reported in a recently submitted IND report a fetus whose mother was taking fingolimod. The sponsor plans to implement a pregnancy registry. Azoospermia was reported in 2 patients in non ISS studies. MHT has been

consulted. As of 7/30/10 there had been 60 pregnancies in the MS program. This was despite recommendations for adequate contraception in the studies. Of note, approximately 35-42% of women taking FTY in safety group D received hormonal treatment and this was to a large extent for contraception.

2.2.6 Common Adverse Events

The percent of patients with common adverse events (≥ 5%) was similar across all groups including placebo and interferon in Safety pool D , approximately 91% (although it was slightly higher, 96%, in FTY 5 mg). Among the FTY 1.25 and 0.5 mg groups, the most common (>10% and > placebo) were headache and fatigue. Events that were > 1% and at least 1% > placebo were diarrhea, ALT increased (at least 2x > placebo), back pain, influenza/influenza-like illness, nausea, bronchitis (2X > placebo), hypertension, melanocytic nevus (2X > placebo), GGT increased (at least 5x> placebo), dyspnea, sinusitis, pyrexia, gastroenteritis, leukopenia. Pyrexia and influenza like illness were, however, higher in the interferon group than in the fingolimod groups. As Dr. Villalba notes, these findings are consistent with analyses of SAEs and AEs leading to discontinuations.

2.2.7 Laboratory findings

Hematologic and *liver enzyme* findings have been discussed elsewhere in this memo.

Chemistry – Electrolytes (sodium, potassium, bicarbonate, calcium, magnesium) were not collected in phase 2 and 3 MS studies, and are missing from narratives and patient profiles of patients who developed AEs that could be associated with electrolyte disturbances. I agree with Dr. Villalba that this is of concern. In the clinical pharmacology study, outlier analyses and shift analyses for electrolytes were unremarkable. A retrospective analysis of electrolytes was available from a subset of patients in study 2301 (10-15 subjects per treatment group at 12 months and 25-30 per group at 24 months), and suggests a higher risk of sodium > 155 mEq/L in FTY 1.25 and 0.5 mg vs placebo. There is no data from this analysis on bicarbonate levels. Dr. Villalba notes that ongoing protocols have been amended to include electrolyte measurements.

Metabolic parameters - Dr. Villalba reports no clinically relevant changes in mean change from baseline for total cholesterol, HDL, LDL, or Triglycerides, creatinine, estimated CrCl, glucose, or albumin in safety pool D. In outlier analysis in Safety pool D, more patients had markedly elevated triglycerides in the FTY groups (12.1% and 11.2%) than in placebo (7.7%) and slightly more had elevated glucose (0.5% vs 0.2%). The clinical significance of these changes is unclear.

Urinalysis – The only urinalysis results in the ISS were analyses of proteinuria. In the controlled studies, there were more cases of 2+, 3+, and 4+ proteinuria in the FTY 1.25 mg and 0.5 mg groups vs placebo or IFN, but Dr. Villalba notes that the numbers were too small to draw definitive conclusions (e.g. < 5 in each group had 3+ proteinuria) and only 1 (in a patient on FTY 1.25 mg) had 4+ proteinuria. None of the subjects had 24 hour protein collection. Dr. Villalba looked at shift analysis in Studies 2301, 2302, and 2201, and finds that in all studies, shifts from normal baseline to abnormal findings on treatment were rare but slightly more frequent in FTY 1.25 compared to FTY 0.5 or the control group, and there was no notable difference between 0.5 mg FTY and interferon in Study 2302. Dr. Villalba notes that there were cases of unexplained edema in the database (previously discussed), and is concerned that this might be due in part to

the role of S1P in regulation of vascular permeability and vascular tone, a potential target organ being the glomerulus. She is especially concerned that a risk for renal toxicity would be increased in patients with underlying vascular problems, such as diabetics, who were excluded from the Phase 3 studies. I agree that this risk should be further evaluated, and that any postmarketing study should include 24 hour urine protein measurement in patients who develop edema during the study.

Coagulation parameters – Dr. Villalba notes that S1P accumulates in platelets and induces platelet aggregation. She reports that PT and PTT were unremarkable in clinical pharmacology study 2113 (a 28 day study), and that PT and PTT were not collected in phase 2 and 3 studies.

2.2.8 Vital Signs

Although a decrease in blood pressure and pulse is observed upon first dose of FTY, chronic use increases systolic and diastolic blood pressure in a dose-dependent manner. This increase is evident at the 1 month evaluation, plateaus at 6 months, and was maintained throughout the end of the evaluations. On FTY 0.5 mg, the mean change from baseline to the last nonmissing value on treatment was a 2 mm Hg increase in Systolic blood pressure and a 1 mm Hg in diastolic blood pressure. A slightly higher percentage of patients on either FTY group had an increase from baseline of ≥ 10 mm Hg in systolic and in diastolic blood pressure compared to placebo, and there is evidence of a dose response. In outlier analysis, more patients fulfilled "notable" criteria in the FTY groups than in the placebo group in Safety pool D.

2.2.9 ECGs

The thorough QT study (2101) failed to exclude a 10 ms prolongation of the QT interval for both doses of FTY (1.25 and 2.5 mg). At 6 hours post-dose on Day 7, the maximum mean QTCI was 10 ms with an upper one sided 95% CI of 14 ms. The study was reviewed by the QT IRT, who did not have confidence in the accuracy of the estimated effect because the positive control, moxifloxacin, failed to have the expected effect, and because there was no dose-response relationship for FTY for QT prolongation. I agree with Dr. Villalba's comment that review of the available data (adverse events, ECG, and Holter evaluations) from the clinical program does not suggest an increased risk of QT prolongation, although the population at risk (heart failure, hypokalemia, drugs that prolong QT) was not included in these studies.

On first dose evaluation in 2301 and 2302 (as well as 2201E1 and 2302E1), patients were monitored in the clinic for at least the first 6 hours after taking the first dose. After 6 hours of observation, patients could be discharged if the maximal lowering of heart rate had already been observed, if the patient was asymptomatic, and the 6 hour ECG did not show any new relevant abnormality. More patients in the FTY 1.25 (18%) and 0.5 mg (12.3%) groups required extended monitoring compared to placebo (3.3%) and more required hospitalization (2.7% for FTY 1.25 mg, 1.8% for FTY 0.5 mg, and 0.7% for placebo) in safety pool A. The most frequently observed ECG findings at 6 hours post first dose were related to conduction and rhythm disturbances and were primarily AV block and sinus bradycardia. QTcF values at 6 hours post-dose showed increases of 8.8 msec, 7.6 msec, and 2.5 msec in the FTY 1.25 mg, FTY 0.5 mg, and placebo groups, respectively. At > 6 hours increases in QTcF were also seen, with bigger changes seen in FTY 1.25 mg compared to FTY 0.5 mg and Placebo. There was a prolongation in mean PR and RR intervals for FTY 6 hours post-dose consistent with effects on

first and second degree AV block. On chronic use the increases from baseline in QTc were less than 4 msec.

2.2.10 Advisory Committee Meeting

The Peripheral and Central Nervous System Drugs Advisory Committee met on June 1, 2010 to discuss NDA 22-257. Dr. Villalba has summarized their findings and I have listed them briefly below:

- Evaluate effects of doses lower than 0.5 mg daily to see if efficacy would be maintained while reduced adverse events (a postmarketing study).
- Receive the first dose in a monitored setting due to risk of bradycardia and heart conduction abnormalities. The majority of members agreed that all patients should receive the first dose in a monitored setting. ECG before starting therapy was recommended.
- Baseline ophthalmologic evaluation by an ophthalmologist; neurologists should monitor visual acuity.
- Perform baseline pulmonary function tests.
- Postmarketing safety studies with an interest on use in patients excluded from trials (diabetes and cardiovascular disease). Establish optimal screening and surveillance practices, especially in high risk populations. Routine pharmacovigilance is not sufficient to mitigate the risks associated with pulmonary toxicity.

2.2.11 Postmarketing Risk Management Plan

The sponsor has submitted a proposed REMS that has a goal of educating prescribers and patients about the potential serious risks that include bradycardia/bradyarrhythmia, infections, macular edema, and teratogenicity. It does not include pulmonary function or liver toxicity**.** The proposed REMS consists of a Medication Guide, Communication Plan (Dear HCP letter and Safety Information Brochure) that will be distributed after approval and annually, and a Timetable for Submission of Assessments.

The maternal health team (MHT) was consulted and recommends a pregnancy registry to be required as a PMR as follows:

> Develop and maintain a prospective, observational pregnancy exposure registry study conducted in the United States that compares the maternal, fetal, and infant outcomes of women exposed to fingolimod during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, adverse effects on immune system development, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes will be assessed through at least the first year of life.

The MHT suggests that for guidance on how to establish a pregnancy exposure registry, the sponsor should review the Guidance for Industry on Establishing Pregnancy Exposure Registries available at

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071639.pdf.

The applicant also proposes to conduct a 6,000 patient (4,000 newly treated with fingolimod and 2,000 already treated with other MS disease-modifying therapies), 5-year postmarketing registry to investigate the incidence of selected safety-related outcomes in patients with MS receiving fingolimod under conditions of routine clinical practice. This is being reviewed by James Williams, Division of Epidemiology.

2.2.12 Conclusions

Fingolimod causes dose-related toxicity, including bradycardia and AV block on the first dose, macular edema, liver enzyme increases, and pulmonary toxicity. Because of the mechanism of action on egress of lymphocytes, there is a potential for increased risk of serious infections, and neoplasms, although these have not been well characterized. The application excluded pre-existent conditions such as diabetes mellitus, heart conduction disorders, or pulmonary disease in which patients would not tolerate adverse events as well as the relatively healthy subjects in the clinical trials. To address the known adverse events and to further evaluate several serious adverse events I agree with recommendations for the following:

Labeling and REMS recommendations:

- Cardiovascular – I agree with Dr. Villalba that all patients should be given the first dose of fingolimod in a monitored setting because of the risk of bradycardia and AV block.
- Dr. Villalba recommends that, if approved, fingolimod should be contraindicated in patients with diabetes and arrhythmias requiring antiarrhythmics treatment as these patients have not been studied in clinical trials and are likely to have an increased risk for serious cardiovascular adverse event. If not contraindicated, Dr. Villalba recommends a prominent warning. I believe that contraindicating these populations and restricting to those in the clinical trials could too severely restrict the population who can use the drug. I recommend a prominent warning.
- Eye toxicity – macular edema – Dr. Wiley Chambers recommend an ophthalmologic evaluation with dilated ophthalmoscopy should be obtained at baseline or near baseline wit subsequent follow-up (every 6 months). The AC recommended baseline exam with regular assessments of visual acuity at routine neurologic visit and referral to an ophthalmologist if clinically indicated. Dr. Villalba recommends that the follow-up occur at 3-4 months as that is when most events occur and as clinically indicated for symptoms or changes in visual acuity assessments. I agree with these recommendations for baseline exam, initial follow-up at 3-4 months, then regular assessments every 6 months, and as clinically indicated.
- Pulmonary Toxicity – I agree with Dr. Villalba that pulmonary function testing should be recommend at baseline, prior to initiating therapy. Pulmonary function should also be addressed in the REMS.
- Hepatic toxicity – Labeling should recommend obtaining transaminases and bilirubin prior to beginning therapy to have a baseline to compare in cases of hepatotoxicity. This should also be addressed in the REMS.
- Dermatologic – I agree with Dr. Villalba's recommendation that a baseline dermatologic exam should be recommended for all patients who start fingolimod treatment. The signal

for skin malignancies is weak. However, I agree with Dr. Villalba that this should be studied in the post-marketing setting.

- Infections – The risk of serious infection should be addressed in the labeling and the REMS. I agree with Dr. Villalba that labeling should recommend that baseline WBC should be obtained prior to starting therapy. I also agree with Dr. Cavaille-Coll's recommendations as follows:
    - FTY can modify signs and symptoms of infection, and physicians should be cautioned to maintain a higher degree of suspicion for infection and atypical presentations
    - Immunologic response to vaccination may be decreased, and physicians should
        - Consider vaccination prior to initiation of fingolimod therapy
        - Consider whether live vaccine should be avoided

Dr. Cavaille-Coll noted that coadministration of immunosuppressants with FTY may result in additive immune system effects. Given the long pharmacokinetic and pharmacodynamic half-life, I agree with Dr. Villalba that since there are no data about concomitant use with immunosuppressants – patients should undergo washout before being treated with other immunosuppressants other than corticosteroids.

Additional Studies

- Low Dose Trial –

I agree with the recommendation for a lower dose clinical trial, and I agree with Dr. Villalba's recommendation that the study should include patients who had been excluded from the original trials, as they may be at greater risk for toxicity. Potential for renal toxicity should be evaluated as part of this trial, and 24 hour urine should be collected in patients who develop edema in the trial. I agree with Dr. Villalba's recommendation that electrolyte measurements at baseline and at fixed timepoints should be included in the trial. Lymphocyte values and all lab values taken outside pre-scheduled evaluations should be included in the narratives and datasets in the study report for that study. I agree with Dr. Villalba's recommendation to evaluate pulmonary function in low dose trial, and that patients with respiratory related events should have an echocardiogram if pulmonary hypertension is a consideration.

- Pregnancy Registry to be conducted as a PMR, according to the recommendations of the MHT.
- Pooled analysis of Safety pool D + 2309 for all AE, serious AE, discontinuations due to AE, and frequent AEs should be submitted when Study 2309 is completed and analyzed, as Dr. Villalba has recommended. This should be submitted as a PMR.
- PMR for oral contraceptive – fingolimod interaction study – Dr. Villalba notes that the application was to include a drug interaction study in patients taking fingolimod and oral contraceptives, although it was not submitted in the current application. It will be a PMR. This study will not only evaluate the PK interaction, but should also include measures of hypercoagulability as recommended by Dr. Villalba. As Dr. Villalba has stated, this is a very important consideration due to the potential for teratogenicity, the potential for vascular events with oral contraceptives, and the potential for vascular events in patients taking fingolimod.

- Post-marketing Registry Study to be conducted as a PMR
    - *Cardiovascular and thrombotic events* – I agree with the proposal to explore the potential for increased risk of myocardial infarction in the postmarketing registry study. The Sponsor has also proposed to evaluate hypertension, as well as symptomatic bradyarrhythmias on treatment initiation or on re-starting after an interruption, and I agree that those events should be evaluated. I also agree with Dr. Villalba's concern about the possibility of increased risk of ischemic/thrombotic cerebrovascular events and peripheral vascular disease, and the Sponsor proposes to address this in the registry.
    - *Risk for malignancy* - The Sponsor proposes that this should be addressed in the postmarketing registry. I agree.
    - *Serious Infections* – The Sponsor should attempt to identify through the postmarketing study or other mechanism additional information to help consider whether FTY should be stopped in the event of some sorts of new infections. In addition, I agree with Dr. Villalba that atypical cases of MS relapse be evaluated in the postmarketing setting.
    - *Pulmonary toxicity* - I agree with Dr. Villalba that pulmonary function should be evaluated as part of this registry. The Sponsor proposes to collect data regarding new onset or worsening of dyspnea and asthma.
    - *Hepatotoxicity* – I agree with the sponsor's proposal to include evaluation of liver injury.
- Testing for PML - Potential for development of PML is a concern, although PML was not observed in this database. I recommend that a protocol put in place for appropriate follow-up for any case in which PML is suspected. This includes having samples for JC virus sent to a laboratory that is recognized internationally as having the expertise to quantitatively analyze these samples.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22527	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	FINGOLIMOD HCL ORAL CAPSULES

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/s/

SALLY U YASUDA
08/25/2010

CLINICAL REVIEW - SAFETY

Application Type	NDA
Submission Number(s)	22-527
Priority or Standard	P
Submit Date	December 18, 2009
Received Date	December 21, 2009
Major Amendment	April 2, 2010
PDUFA Goal Date	September 21, 2010
Reviewer Name(s)	Lourdes Villalba, M.D.
Team Leader	Sally Yasuda, Pharm D.
Review Completion Date	August 8, 2010
Established Name	Fingolimod
(Proposed) Trade Name	Gilenya™
Therapeutic Class	Sphingosine-1 Phosphate modulator
Applicant	Novartis
Formulation	Oral capsules
Dosing Regimen	0.5 mg daily
Indication(s)	Treatment of patients with relapsing MS to reduce the frequency of relapses and to delay the progression of disability
Intended Population(s)	Adults

TABLE OF CONTENTS

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Analysis

This is the safety review of NDA 22-527 (fingolimod) as of August 8, 2010. The efficacy of fingolimod in multiple sclerosis (MS) is being reviewed by Dr. Heather Fitter. Final recommendations on approval of this application will be provided by Drs. Fitter (primary reviewer) and Bastings (CDTL).

Several safety issues have been identified in this application with evidence of a dose response between fingolimod 1.25 and 0.5 mg daily. Given the need for additional efficacious therpies for this devastating disease, the safety of fingolimod 0.5 mg orally once daily appears to be acceptable in view of its efficacy.

An important consideration in the evaluation of this drug is that it is a first in class molecule that targets a novel family of receptors (sphingosine 1 phosphate receptors) that in addition to immunomodulation are involved in the regulation of numerous biological activities such as vascular permeability and tone, angiogenesis, atherogenesis and thrombogenesis, among other yet unknown functions. No serious cardiovascular toxicity was observed at the 0.5 mg dose in the available database. However, it is anticipated that toxicities that have not been observed in the premarketing database might be identified once the drug is used in the postmarketing setting, particularly in patients who are not as healthy as those included in the clinical trials. One of the populations that have been specifically excluded from these trials is patients with diabetes mellitus, who are at increased risk of cardiovascular complications and of macular edema.

This application was discussed at the Peripheral and Central Nervous System Advisory Committee Meeting on June 10, 2010. The panel recommended approval of fingolimod 0.5 mg, provided that adequate monitoring is carried out for events of bradycardia and atrioventricular block upon first dose and of macular edema; that postmarketing data are collected to further evaluate the long term safety of the 0.5 mg dose, including patients with clinical conditions that were excluded from the premarketing trials, such as diabetes, and that the efficacy of a lower fingolimod dose is evaluated in a controlled study.

If approved, this drug should have a Risk Evaluation and Mitigation Strategy (REMS) that addresses

- Bradycardia and atrioventricular block upon first dose
- Macular edema
- Potential for increased risk of serious infections
- Potential for pulmonary toxicity
- Potential for liver toxicity
- Teratogenecity

- Recommendations for Postmarket Studies/Clinical Trials.
  - Postmarketing registry of patients receiving fingolimod 0.5 mg under routine clinical care.
  - Pregnancy registry

- Prospective, randomized, controlled study to evaluate the efficacy of fingolimod 0.25 mg as compared to fingolimod 0.5 mg and placebo or an active comparator.
- A clinical pharmacology study to evaluate drug drug interaction between fingolimod and oral contraceptives, as well as the effect on fingolimod on coagulability parameters.
- Additional analysis of clinical trials: Ongoing study 2309 is expected to be completed by 4Q2011. In addition to the complete study report, the applicant should submit safety analyses for pooled studies 2301, 2302 and 2309.

2 Introduction and Regulatory Background

Multiple sclerosis (MS) is a chronic, autoimmune and neurodegenerative disorder of the central nervous system (CNS), characterized by inflammation, demyelination, and oligodendrocyte and neuronal loss. MS affects an estimated 2.5 million individuals worldwide. Treatment strategies in MS usually involve symptom management and use of disease modifying therapies to reduce the frequency of relapses and to slow the accumulation of disability. Fingolimod has been developed for the treatment of MS, particularly relapsing remitting (RR) MS, the most frequent clinical presentation of the disease.

2.1 Product Information

Fingolimod (also referred to as FTY720 or FTY in this application) is a sphingosine- 1-phosphate (S1P) receptor modulator. After oral dosing, fingolimod is phosphorylated *in vivo* by sphingosine kinase to form the active metabolite fingolimod-phosphate (fingolimod-P), which induces internalization of the S1P receptor (s). There are five distinct high-affinity G protein-coupled sphingosine 1-phosphate receptors subtypes (GPCR $S1P_{1-5}$), namely S1P1, S1P2, S1P3, S1P4 and S1P5. Depending on the cell type, the concentration, and the time following administration, fingolimod-P may act as an "agonist" or "functional antagonist" at S1P receptors. Fingolimod-P has effects at S1P 1, 3, 4 and 5.

The key mechanism of action of fingolimod in multiple sclerosis (MS) is proposed to be the decrease in egress of lymphocytes from lymphoid tissue and the reduction of auto-aggressive T-lymphocytes in the peripheral circulation, mediated by S1P1. Fingolimod might also have some down-modulation effect of S1P receptors in the CNS.

Fingolimod was initially developed for prevention of organ transplant rejection in the renal transplant population at the doses of 2.5 and 5 mg/day. After evaluation of the risk and benefits, development in renal transplant was stopped. The clinical development program of fingolimod in MS investigated the 1.25 and 0.5 mg/day doses. After evaluation of the available data, based on the finding of similar efficacy but greater toxicity, only the 0.5 mg/day dose is being pursued for marketing at this time.

2.2 Available Treatments for Proposed Indications

Currently available first-line therapies are interferon β and glatiramer acetate. These products reduced the relapse rate of MS compared to placebo over 2 years. Interferon (IFN) β-1a also reduced disability accumulation in patients with RRMS. These agents are administered by

injections (daily s.c. to once weekly i.m.) and have known side effects such as flu-like symptoms and injection site reactions which are frequent and affect tolerability and compliance.

Second line therapies include natalizumab and mitoxantrone. Natalizumab, administered via monthly i.v. infusions, reduced relapse rate and the risk of sustained progression of disability as compared to placebo in a 2-year study of patients with RRMS. Natalizumab has been associated with hypersensitivity reactions, and a rare, often fatal demyelinating disease of the brain - progressive multifocal leukoencephalopathy (PML). Mitoxantrone, a chemotherapeutic agent, is approved for use in relapsing forms of MS. However, cumulative dose-related cardiac toxicity and risk for secondary leukemia limit the total amount that can be administered.

Most recently, dalfampridine (Ampyra®) has been approved for improvement of walking in patients with MS.

2.3 Availability of Proposed Active Ingredient in the United States

None.

2.4 Important Safety Issues With Consideration to Related Drugs

Several S1P modulators are in either pre-clinical or clinical development in various therapeutic areas (e.g. KRP-203, SEW2871, JTE-013, VPC23019, W123, BML-241).[1] No S1P modulator is currently approved for any indication.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The first IND for fingolimod opened in November of 1998 (IND 57,293) for prophylactic adjuvant treatment (add on therapy to Cyclosporine A and corticosteroids) at the doses of 5 and 2.5 mg/day in renal transplant patients. This IND was placed on a partial clinical hold in August, 2005 secondary to macular edema. Fingolimod did not confer an efficacy advantage over the comparator, mycophenolate mofetil (MMF). The applicant stopped drug development in this population.

The initial IND for use in MS (IND 70,139) was submitted in May of 2005. The proposed IND study (study 2301) was placed on a full clinical hold because of several safety concerns, beginning in June 6 2005 (first hold letter), until the FDA and the applicant reached agreement about the safety monitoring in MS studies. The main concerns were adverse events of macular edema, first and second degree atrioventricular block and pulmonary toxicity observed in the transplant program and in a phase 2 clinical study in MS (Study 2201).

The FDA recommended that study 2301 should include special follow up for potential lung toxicity (High Resolution Computerized Tomography [HRCT] every 6 months in at least a subgroup of subjects; real time Pulmonary Function Tests [PFT]); cardiac toxicity (keeping patients in-house for 24 hours post dose with Holter or telemetry for bradycardia in at least 600

[1] Huwiler and Pfeilschifter. New players on the center stage: sphingosine 1 phosphate and its receptors as drug targets. Biochemical Pharmacology 2008, 75(10) 1893-1900.

patients; cardiac echo every 6 months in at least a subgroup of patients; conduction of a QTc study; a Data Safety Monitoring Board [DSMB] should monitor CV adverse events and decide if longer follow up was needed), and eye toxicity (optical coherence tomography [OCT] monitoring at baseline, close follow up for up to 3 months and then periodically thereafter in the first 300 patients enrolled in the study).

After extensive discussions that included two additional clinical hold letters (1/18/06 and 3/19/06) and arbitration by Dr. Robert Temple, the clinical hold was lifted in May, 2006. Of note, while the IND was on hold in the US, the applicant proceeded with study 2301 outside the US. The agreed upon protocol which included US centers was protocol 2309 (a 2-year placebo-controlled study, similar to 2301 but with additional safety monitoring). Around this time, the applicant also started study 2302 (a 1-year interferon-controlled study which incorporated additional safety monitoring) that also included US centers.

The current submission includes data from completed studies 2201, 2301 and 2302, and an interim report of special safety results from study 2309, which is ongoing and still blinded.

2.6 Other Relevant Background Information

- The IND was granted fast track designation in June 7, 2007.
- The NDA application was submitted as a rolling NDA, with the first piece submitted on June 5, 2009. The clinical piece for MS was submitted on December 18, 2009.
- The application was granted priority review on February 18, 2010.
- The PDUFA goal date for the review of this application was June 21, 2010.
- A Major amendment was submitted on April 2, 2010
- The new PDUFA goal date is September 21, 2010
- The 4-month Safety Update Report (SUR) was submitted on April 21, 2010.
- A FDA Advisory Committee was held on June 10, 2010.
- Updated labeling, REMS and proposal for postmarketing studies, July 9, 2010
- This safety review of fingolimod was completed on August 8, 2010.

3 Ethics and Good Clinical Practices

Clinical studies included in the ISS were conducted in compliance with Good Clinical Practice.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.3 Preclinical Pharmacology/Toxicology

The following information has been excerpted from the applicant's overview of non-clinical safety. For a detailed review of the full program the reader is referred to Dr Siarey's review.

Fingolimod is phosphorylated *in vivo* by sphingosine kinase to form the active metabolite fingolimod phosphate (fingolimod-P). Fingolimod-P binds four of the five G protein-coupled

sphingosine 1-phosphate (S1P) receptors (S1P1, S1P3, S1P4 and S1P5) and induces receptor internalization. With initial dosing of fingolimod, there is agonism of S1P receptors and transient signaling. However, with continued fingolimod dosing, functional antagonism occurs with internalization of S1P receptors.

By acting as a functional antagonist of the $S1P_1$ receptor on lymphocytes, fingolimod-P blocks the capacity of lymphocytes to exit from lymph nodes, causing a redistribution of lymphocytes and preventing CNS infiltration by pathogenic lymphocytes. Other effects in non-clinical studies are the transient activation of S1P receptors and GIRK/IKACh channels in atrial myocytes (which is associated with transient reduction of heart rate), and the increase of lung hyper-reactivity to bronchospasmogens and airway constriction effects, mediated by S1P1 and S1P3. Fingolimod might display additional activities relevant to MS through functional antagonism of S1P1 receptors on astrocytes or neural cells in the CNS. The *in vivo* dynamic effects of agonism or functional antagonism of S1P4 (expressed in lymphoid tissue) and S1P5 (present in spleen and white matter tracts of the CNS -primarily on oligodendrocytes -) are not currently known. An increasing body of literature indicates that S1P also has an important role in the regulation of endothelial permeability and vascular tone.[2,3]

The following is selected information from some of the toxicology studies in the applicant's overview of non-clinical safety.

- Lymphoid-related effects

Non-clinical toxicity studies with fingolimod showed effects related to its pharmacologic effect on lymphoid organs. Atrophy of the cortical part of the thymus, splenic white pulp and lymph nodes were observed in multiple dose studies at doses of ≥ 0.1 mg/kg/day in the rat, ≥0.01 mg/kg/day in dog and ≥1 mg/kg/day in monkey. Doses of ≥ 0.5 mg/kg/day in monkey (39 week study) resulted in decreases in white blood cell (WBC) due to decreases in absolute lymphocyte, monocyte and neutrophil counts. Microscopic examination showed decreased cellularity of the lymphoid tissues at all dose levels. In this study, there was also increased plasmacytosis, sinus histiocytosis and lymphadenitis, and increased myeloid hyperplasia in the sternal bone marrow.

- Non-lymphoid toxicities

- In a 26-week oral toxicity in Wistar rats, reversible increases in lung weight were seen for males at 1.5 or 7.5 mg/kg/day and all treated female groups. Isolated incidences of foamy bronchial outflow or reddish foci in the lungs of treated animals were observed at necropsy on completion of the treatment or recovery periods. Smooth muscle cell hypertrophy in the alveolar ducts was observed microscopically in all treated groups and was still present after recovery but showed a tendency to be reversible. Additionally, there was increased serum urea and creatinine concentrations in all treatment groups, some of which presented basophilic hyaline casts. Systemic vascular lesions were observed in multiple organs. These changes were reversible.

[2] L.Want & S Dudek. Regulation of vascular permeability by Sphingosine 1-Phosphate. Microvascular Reaearch, 2009, January; 77 (1) 39-45.
[3] J. Igarashi and T. Michel. Sphingosine-1-phosphate and modulation of vascular tone. Cardiovascular Research 2009, 82 (2): 212-220

- In 4-week oral toxicity studies in dogs, macroscopic examination showed enlarged and dark red lungs and intratracheal foamy contents at ≥ 0.1 mg/kg/day. At the end of the recovery period, pleural adhesions and white areas on the lungs were observed in both males at 10 mg/kg/day and in one female at 30 mg/kg/day. Vascular wall thickening and perivascular and focal perimysial fibrosis of the left ventricular papilla in the heart at ≥ 3 mg/kg/day were observed. Microscopic examination showed pulmonary alveolar infiltrates and pneumonia at ≥ 0.1 mg/kg/day. In addition, at 30 mg/kg/day, there was perivascular mononuclear cell infiltration in the gray matter of the brain and peripheral nerve degeneration in the heart. At the end of the recovery period, subpleural fibrosis and focal bronchiolar alterations of the lung were found in females at 0.01 mg/kg/day. Similar findings in the lung, heart and brain were observed at doses of 1 to 10 mg/kg/day, in a 26-week oral toxicity study in the dog.

- In a 13-week oral toxicity study in monkey, there was smooth muscle hypertrophy of the lung and increased pulmonary weight was observed with doses ≥ 1 mg/kg/day.

- In a 39-week oral toxicity study in monkey at doses of 0.5 and 3 mg/kg/day, a trend towards increased mean lung weights in females (high dose) and males (low and high dose) was noted, which was partially reversible following a 13 and 26-week recovery period and correlated with microscopic compound-related lung changes. Gross changes consisted of decreased pulmonary collapse, which correlated, in most animals with hypertrophy of pulmonary smooth muscle fibers and/or increased collagen. The principal test article-related findings consisted of pulmonary smooth muscle hypertrophy and/or increased collagen occasionally accompanied by distended alveoli. Smooth muscular hypertrophy and/or increased collagen, was most commonly seen in walls of alveolar ducts and respiratory bronchioles. The lung alterations aforementioned were occasionally observed in control animals; however, the incidence and/or severity of these lesions increased in compound-treated groups.

- In a 52-week oral toxicity study in monkeys, a dosage-related increase in group mean lung weights was noted in both sexes, at doses as low as 1 mg/kg/day. The lungs did not collapse on opening the thoracic cavity in 7/8 animals receiving 10 mg/kg/day, 5/8 animals treated with 3 mg/kg/day and one receiving 1 mg/kg/day. These findings correlated with treatment-related pathology including hypertrophy of the smooth muscle component of the walls of the respiratory bronchioles, alveolar ducts or the entrances to the alveolar sacs and/or to hyperdistension of the alveoli. A single control animal showed non-collapse of the lungs, however this monkey showed only minimal pneumonitis, considered to be a spontaneous change. Areas of collapse were subsequently noted upon removal of the lungs in three animals receiving 10 mg/kg/day and two receiving 3 mg/kg/day. These findings generally correlated with focal inflammatory lesions. Two animals receiving 10 mg/kg/day had a concave ventral aspect to the ribcage, considered indicative of prolonged respiratory distress.

- Lung toxicity was also observed in the mice carcinogenicity studies

> *In summary, in several non-clinical studies (rat, dog, monkey, mice) of different doses and durations, there was evidence of pulmonary congestion, smooth muscular hypertrophy and increased collagen in walls of alveolar ducts and respiratory bronchioles, and subpleural fibrosis at doses as low as 0.01 mg/k/day in the dog. There was also evidence of vascular wall thickening and perivascular and focal*

perimysial fibrosis of the left ventricular papilla in the heart in the dog at doses ≥ 1 mg/kg/day.[4] *All these areas will be extensively evaluated in this clinical review.*

4.4 Clinical Pharmacology

For details on the Clinical Pharmacology of fingolimod the reader is referred to the review by the Clinical Pharmacology/Biopharmaceutics review team.

The following is an excerpt from the executive summary of that review:

- Fingolimod is phosphorylated to the active moiety, *S*-enantiomer fingolimod-P and fingolimod-P is dephosphorylated back to the inactive form fingolimod. At steady state, fingolimod and fingolimod-P are in dynamic equilibrium.

- The median of Tmax is ~12 hours. Fingolimod is extensively distributed to body tissues with volume of distribution (Vz,b) ~1200±260 L. Fingolimod is believed to be metabolized mainly via the cytochrome P450 4F2 isoenzyme. The average apparent terminal half-life for both fingolimod and fingolimod-P is 6-9 days.

- Steady-state exposure is reached between 1 to 2 months during once-daily dosing with an estimated 11-fold accumulation of blood levels from first dose to steady state. The fingolimod blood concentration profile at steady-state shows a peak to trough fluctuation of approximately 20% while the peak to trough fluctuation for fingolimod-P is approximately 45%.

  - Moderate and severe hepatic impairment increased fingolimod AUC by 44% and 103%, respectively. The apparent elimination half-life is prolonged by 49-50% in moderate and severe hepatic impairment. Fingolimod-P Cmax and AUC(0-96) were increased by 22% and 29% in severe hepatic impairment. The fingolimod dose does not need to be adjusted in mild or moderate hepatic impaired patients. The Office of Clinical Pharmacology recommends decreasing the dose by 50% in severe hepatic impaired patient. However, as there is no lower strength (0.25 mg) formulation available, use of fingolimod is not recommended in severe hepatic impairment.

- Severe renal impairment increases fingolimod Cmax and AUC by 32% and 43%, respectively, and fingolimod-P Cmax and AUC by 25% and 14%, respectively. The apparent elimination half-life is unchanged for both analytes.
  Exposure to the inactive metabolites is also increased with severe renal impairment, by at least 300% for M2 and by 805% for Cmax and 1356% for AUC for M3. The clinical impact of such an increase is unknown. The use of fingolimod should be contraindicated in renally impaired patients due to uncertainty of the safety profiles of M2 and M3.

- A 50% reduction in dosing is recommended if fingolimod is used with ketoconazole. However, as there is no lower strength (0.25 mg) formulation available, it is recommended that fingolimod not be coadminstered with ketoconazole.

No dose-adjustments are recommended based on age, gender, weight, or race, or fasting/fed status.

[4] The human equivalent doses are 0.324 mg (0.0054 mg/kg) for 0.01 mg/kg in dog and 32.43 mg (0.54 mg/kg) for 1 mg/kg in dog. Therefore, fingolimod 0.5 mg/day would be 0.008 mg/kg/day for a 60 kg person

Isoproterenol and atropine reversed the negative chronotropic effects of fingolimod. Diltiazem did not appear to have additive negative chronotropic effects *(nevertheless, patients taking calcium channel blockers were not included in the phase 2 and 3 studies).* Atenolol had a 15% additional negative chronotropic effect than fingolimod alone *(very few subjects taking beta blockers were included in the phase 2 & 3 studies).*

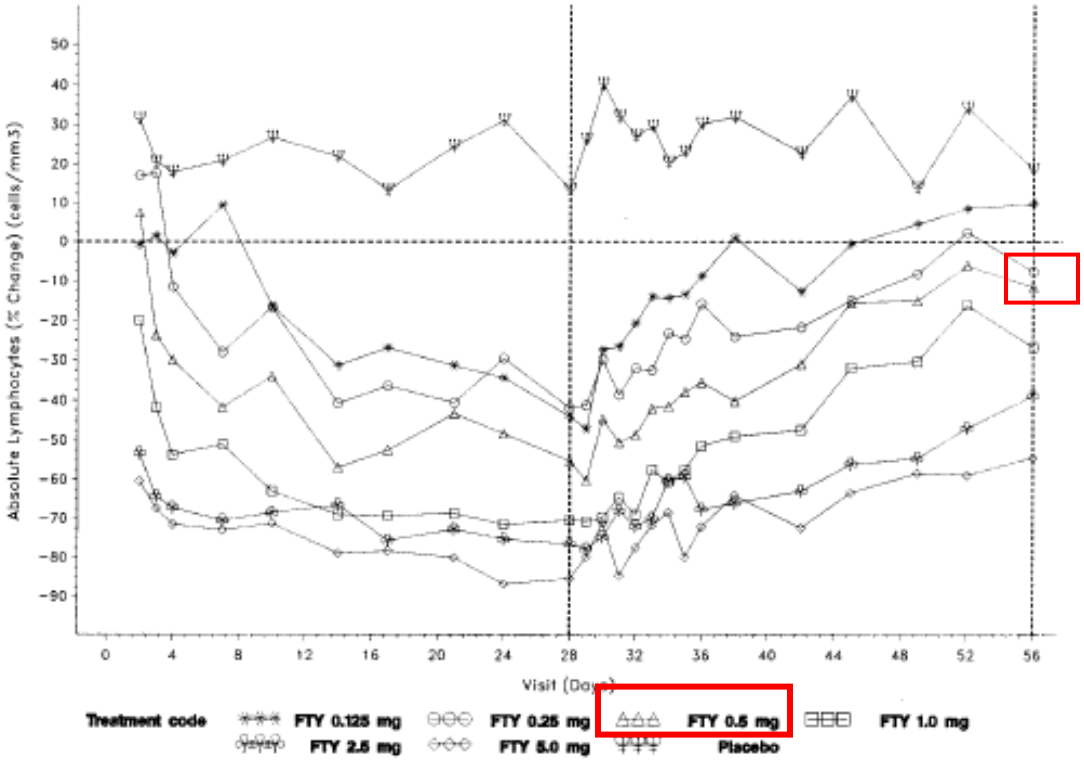
The main pharmacodynamic effects identified by the applicant in clinical pharmacology studies were decreased lymphocyte count, transient bradycardia and increased airway resistance and they are discussed in the clinical pharmacology review. I will discuss the effect on lymphocyte counts as well as the results of a clinical pharmacology study that evaluated cerebrovascular flow and a study that evaluated the effects of fingolimod on antibody response following immunizations in healthy volunteers.

- Decreased lymphocyte count

Single doses of fingolimod from 0.5 to 5.0 mg result in a dose dependent decrease in lymphocyte count (all, B and T [helper, suppressor, memory and naïve T]). This decrease occurs rapidly, within 3-4 hours of the first oral dose. With single doses from 5 to 40 mg, there is minimal additional effect on the lymphocyte count. With multiple dosing of fingolimod from 0.125 mg to 5 mg there is a dose-dependent decrease in lymphocyte count, resulting in counts from 60% of baseline count to as low as 10- 15% of baseline count, respectively. In a multiple dose study (FTY720AB102) in renal transplant patients all lymphocyte subsets (CD20 [B cell], CD3 [T cell], CD4 [T helper], CD8 [T suppressor], CD16 [Natural killer], CD45RO [T memory], CD45RA [T naïve] were found to decrease in a dose dependent manner in the setting of multiple doses of fingolimod. The monocyte count was not affected by multiple dose fingolimod treatment. The figure below shows changes in absolute lymphocyte count in study FTY720AB102.

Figure 1. Effects of fingolimod on percentage absolute lymphocyte counts in Study FTY720AB102 (renal transplant population).

Figure 10-2. Mean percent change from baseline for absolute lymphocytes by visit (safety population)



This was a 28-day treatment study, with 28 additional days of follow up. This figure suggests that 28 days after last dose of study drug (day 56 of the study), absolute lymphocyte counts were not fully recovered for doses ≥ 0.5 mg (they were about 10% below baseline).

Three-month follow-up data on lymphocyte recovery are available from the renal transplant study B201 which evaluated the safety, tolerability and efficacy of four doses of FTY720 (0.25, 0.5, 1.0 and 2.5 mg/day) given for 12 weeks in combination with a full dose of Neoral and corticosteroids. In all four FTY720 dose groups, absolute lymphocyte counts returned to baseline values within 3 months after the discontinuation of study medication [FTY720 B201CSR].

In the MS studies, follow-up data are available only for a small subset of FTY720-treated patients (Group E follow-up population) who were followed for different periods of time so that comparisons between different time points do not allow clear conclusions. In these patients, mean lymphocyte counts were returning to within the normal range in the first 45 days after discontinuation. Three months after study drug discontinuation, mean values were reduced by approximately 22% compared with baseline. Only few patients were followed for longer periods so that the information on the recovery beyond 3 months is very limited.

Of note, the FDA Clinical pharmacology reviewers conducted an exposure-response modeling analysis in terms of lymphocyte counts. Based this modeling analysis, there is a suggestion that the 0.25 mg dose may be as effective as the 0.5 mg dose. For details the reader is referred to the Clinical Pharmacology review.

- Evaluation of cerebrovascular flow, platelet function, and macular thickness

Study D2113 was an exploratory, randomized, blinded, placebo-controlled, parallel group, multiple-dose study to assess the effect of FTY720 0.5 and 1.25 mg on mean flow velocity in cerebral vessels, platelet function, and macular thickness following once daily dosing for 4 weeks in 88 healthy subjects 18 to 50 years of age. This study was conducted because of the potential signal for increased ischemic/thrombotic cerebrovascular events observed in the phase 2-3 studies. Pharmacodynamic endpoints included:

Primary
- Cerebral blood flow rate: Mean blood flow velocity (Vm) in the MCA
- Platelet function: Platelet adhesion time in response to epinephrine (PFA100® assay)
- Macular thickness: Central foveal thickness by OCT

Secondary
- Cerebral blood flow rate: Vm in the posterior cerebral artery (PCA),basilar cerebral artery (BA) and MCA in response to hypercapnia
- Platelet function: Platelet aggregation percentage (%) in response to collagen, epinephrine, ADP, ristocetin; plasma factors that can affect platelet function including von Willebrand factor (vWF), fibrinogen and d-dimers.

Results: This study did not find alterations in cerebrovascular blood flow or platelet function, and did not find increased foveal thickness by OCT.

> *Comment: this negative study does not rule out an effect on these parameters with longer term exposure or in subjects with underlying cardiovascular or metabolic diseases such as hypertension or diabetes. The study did not find an increase in foveal thickness, while several subjects developed macular edema with the 1.25 and 0.5 mg doses in the phase 2 and 3 studies. The study did not evaluate all factors that may be involved in hypercoagulability (e.g. homocysteine).*
>
> *Of note, a clinical pharmacology study to evaluate PK drug interaction with oral contraceptives was planned in the pre-NDA package, but was not completed at the time of the NDA submission. This study might be conducted as a postmarketing requirement, and in addition to PK information, could include markers of platelet function and hypercoagulability.*

- Evaluation of antibody response to immunization (Submitted with SUR)

Study D2109 was an exploratory, randomized, double-blind, placebo controlled, parallel group, multiple dose study to assess the pharmacodynamic effect of fingolimod given for 4 weeks, on antibody response following multiple immunizations in healthy volunteers. The study included 72 healthy subjects (24 on FTY 1.25mg, 24 on FTY 0.5 mg and 24 on placebo).

Primary pharmacodynamic endpoints included assessment of Keyhole limpet hemocyanin (KLH) specific IgG and IgM following administration of KLH via intramuscular injection. Secondary endpoints included measurement of levels of Pneumococcal Polysaccharides Vaccine (PPV)-23-specific IgG and IgM, and Tetanus toxoid-specific IgG following administration of PPV-23 and TT via intramuscular injection. Immediate and delayed type hypersensitivity was assessed by investigator site staff by the measurement of wheal and erythema present on the arm of each subject following intradermal administration of antigens KLH, TT and Candida albicans.

Fingolimod showed a decreased capacity to mount an immune response to neoantigen, recall antigen and delayed hypersensitivity mediated response as compared to placebo, with evidence of a dose response between fingolimod 1.25 and 0.5 mg. More details about this study are provided in section 7.4.6 of this review (Immunogenicity) (See Table 112 of the review).

5 Sources of Clinical Data

This application evaluates the efficacy and safety of fingolimod (FTY720) for the treatment of multiple sclerosis in patients 18 years of age and older. NDA 22-527 was submitted as a rolling NDA. The Clinical sections related to MS were submitted on 12/18/09 (SN 003 and 004).

The integrated summary of safety (ISS) of fingolimod in relapsing multiple sclerosis (MS) includes data from three completed double-blind, randomized, controlled clinical studies and two ongoing open-label extension studies up to the cut-off date September 30, 2009. The controlled studies include two placebo-controlled (one 6-month and one 24-month) studies, and one Interferon beta-1a (12-month) controlled study in patients with relapsing remitting MS at the doses of 0.5 and 1.25 mg/day. These studies are summarized in Table 1 of this review.

In the original ISS, approximately 2700 MS patients received FTY720, of whom more than 2000 have exposure for over 1 year, approximately 1000 patients for over 2 years and some patients (~150) are into their sixth year of therapy. Additionally, safety data were available from 843 subjects exposed to at least one dose of FTY720 in 29 clinical pharmacology studies.

Five additional clinical studies in MS patients were ongoing at the time of the original NDA submission. Safety from these studies was not pooled for analysis into the ISS.

A separate ISS for the renal transplant population was submitted as part of the rolling NDA on 10/5/09 (SN 002).

The 4-month Safety Update Report (SUR) was submitted on April 21, 2010 and contained safety data through January 29, 2010. It includes updated analyses of safety pool E; serious AEs in ongoing studies; an updated Special safety Interim Report (SSIR) from 2309; two clinical study reports (Study FTY720D2109 (antibody response study) and Study FTY720D2302E1-24 month report); updated analyses of ECG data for all populations and a revised package insert. During the review cycle, the applicant responded diligently to multiple FDA informational requests. The applicant's responses up to August 6, 2010 have been reviewed.

There is no available postmarketing data for this NME.

5.1 Tables of Clinical Studies

A summary table of phase 2 and 3 studies included in the integrated summary of safety are presented in the following table.

Table 1. Fingolimod in multiple sclerosis. Studies included in the ISS.

Double blind controlled studies (completed; all data are included)				
Placebo-controlled				
Study ID	Design/ duration	Treatment/dose	Patients randomized Per group	Comment
FTY720D2201 Dose-ranging efficacy and safety in patients with relapsing MS[1]	DB, R, PC, MC (non-USA) **6 months**	FTY720 5 mg/d FTY720 1.25 mg/d Placebo	92 92 92	281 total (81 M, 196 F, age 18-60 y) Primary Endpoint: MRI total number of monthly lesions on post-baseline scans. Safety evaluation included Holter and PFTs. Dates: May 2003- October 2004
FTY720D2301 Pivotal efficacy & safety in patients with RRMS [FREEDOMS]	DB, R, PC, MC (non USA) **24 months**	FTY720 1.25 mg/d FTY720 0.5 mg/d Placebo	429 425 418	1272 (383 M, 889 F; age 17-55 y) Primary endpoint: MS relapses Safety evaluation included HRCT, PFTs, opththamologic and dermatologic examination and OCT Dates: Jan 2006 - Jul 2009
Active-controlled				
FTY720D2302 Pivotal efficacy & safety in patients with RRMS [TRANSFORM]	DB, R, Avonex-controlled MC (with USA sites) **12 months**	FTY720 1.25 mg/d FTY720 0.5 mg/d Interferon beta-1a 30mcg i.m. once a week	426 431 435	1292 (422M, 870 F; age 18-55) Primary endpoint: annualized relapse rate. Safety includes derm and opthalm exam, echocardiography at selected sites, HRCT and PFTs. Dates: May 2006 - Nov 2008
Long Term extension studies (interim data)				
FTY720D2201E1 Extension to FTY720D2201 core study (which was a 6 month study)	Open ended (ongoing) Interim data up to 60 months	FTY720 1.25 mg/day. Initially included the FTY720 5.0 mg dose.	250	Open-label. Initially dose-blinded (FTY720 patients continued on their original dose; placebo patients were re-rando mized to 1.25 mg or 5.0.mg). When patients were 15-24 months in study the FTY720 5.0 mg dose was discontinued and patients switched to 1.25 mg. Extension started: May 2003
FTY720D2302E1 Extension to FTY720D2302 core study (which was a 12 week study)	Open ended (ongoing) Interim data up to 24 months	FTY720 0.5 mg/day FTY720 1.25 mg/day	1030	Dose-blinded (FTY720 patients continued on their original dose; interferon patients were rerandomi zed to FTY720 either 0.5 mg or 1.25) Extension started April 2007

Source: NDA 22-257. Tables 1-1, 1-2 and 1-3 of Summary clin safety. [1] The majority of patients had Relapsing Remitting Multiple Sclerosis (RRMS) (89.0%); the remaining 11.0% of patients had secondary-progressive MS.

In addition to the extension studies 23021E1 and 2201E1 which were included in the ISS, five ongoing clinical studies in MS were not pooled into the ISS. These studies are summarized in the following table.

Table 2. Ongoing clinical studies of Fingolimod in MS[1]

Study ID	Treatment duration	Treatment/dose	Number of patients randomized (planned) Per group	Comment
Placebo-controlled				
FTY720D2309 Efficacy and safety of FTY720 in patients with RRMS	DB, R, PC MC (includes US centers) **24 months**	FTY720 0.5 mg/d FTY720 1.25 mg/d Placebo	360 360 360	1080 planned (1084 entered as of 9/30/09). Age 18-55 Safety eval. Includes derm and ophth exam, HRCT, PFTs Started May 2006. Report anticipated 4Q2011. **Only special safety data, provided separately**
FTY720D1201 Efficacy & safety FTY in relapsing MS in Japan	DB, R, PC (Japan) **6 months**	FTY720 0.5 mg/d FTY720 1.25 mg/d Placebo	55 55 55	165 planned. Age 18-60 planned Started: October 2007. Report anticipated 3Q2010
FTY720D 2306 Efficacy and safety of 1.25 mg daily in patients with PPMS	DB, R, PC MC (includes US centers) **36 months**	FTY720 1.25 mg/d Placebo	327 327	654 planned/281 entered as of 9/30/09; age 25-65 Started: July 2008. Report anticipated 4Q2013
Long Term extension studies				
FTY720D2301E1 Extension to FTY720D2301 (which was a 24 month study)	Open ended	FTY720 0.5 mg/d FTY720 1.25 mg/d	467 per group planned	FTY720 patients continued on their original dose; placebo patients were re-randomized to FTY720 either 0.5 mg or 1.25 mg. End of DB extension all patients offered open label FTY720.
FTY720D2309E1 Long-term efficacy and safety in patients with RRMS, extension to 2309 (which was a 24 month study)	Open ended USA only	FTY720 0.5 mg/d FTY720 1.25 mg/d		Planned total 762. Dose-blinded until last patient completes core study (FTY720 patients continued on their original dose; placebo patients re-randomized to FTY720 either 0.5 mg or 1.25 mg), then open label FTY. Extension started September 2008.

Source: NDA 22-257. In addition to these four studies, studies FTY720D2302E1 and FTY720D2201E1 for which 24-month and 60-month data were included in the ISS, respectively, are also ongoing. DB= double blind, R= randomized, PC= placebo controlled, MC= multicenter. [1] NOT INCLUDED IN ISS POOLED ANALYSES.

For the ongoing studies listed above, only blinded narratives of deaths and selected serious AEs were provided in the original application, except for special safety evaluations in Study 2309 (24-hour Holter ECG, echocardiography, frequent OCT and chest HRCT) which were specifically requested by the FDA to better characterize the safety of fingolimod. These data were not part of the integrated analysis but were reported separately in a Special Safety Interim

report. Some AE of interest were unblinded at the time of the updated special safety interim report (e.g. macular edema).

The clinical pharmacology studies included a total of 1079 unique subjects, including 843 exposed to FTY at doses of 0.125 to 40 mg/day, 611 to placebo and 174 to non-FTY treatments (some subjects received more than one treatment in crossover studies). These were 60% male/40% female; mean age was 35 years (range 18-70, including 7 subjects <18 years). (Source: post text table 13.2-1.a and 13.1-2, ISS). Clinical Pharmacology studies included in this application are presented in Table 3.

Table 3. Fingolimod. Listing of Clinical pharmacology studies in this application.

Study	Description
B0101	Pharmacokinetic study – Transplant patients with co-administration of immunosuppressive drug – SD
B0102	Pharmacokinetic study – Transplant patients with co-administration of immunosuppressive drug – MD (28 days)
A0106	Pharmacokinetic food effect study – NVs – SD
A0107	Pharmacokinetic DDI study – Interacting drug: Cyclosporine – Psoriasis patients – SD (FTY)
A0108	Pharmacokinetic Absolute BA study – NVs – SD
A0112	Pharmacokinetic Hepatic Impairment study – NVs + Impaired patients – SD
A0114	Pharmacokinetic DDI study – Interacting drug: Atenolol and Diltiazem – NVs – SD (FTY)
A0115	Pharmacokinetic Pediatric study – Stable renal Tx patients – SD
A0116	Pharmacokinetic Relative BA study – NVs – SD
A0118	Pharmacokinetic DDI study – Interacting drug: Atropine – NVs – SD
A0119	Pharmacokinetic DDI study – Interacting drug: Isoproterenol – NVs – SD
A2204	Pharmacokinetic Severe Hepatic Impairment study – NVs + Impaired patients – SD
A2213	Pharmacological study – Heart Rate – NVs – MD (8 days)
A2213E1	Pharmacological study – Heart Rate – NVs – SD
A 2215	Pharmacokinetic SAD study – NVs – SD
A 2217	ADME study – NVs – SD
A 2304	Pharmacokinetic Ethnic Sensitivity study – NVs – SD and MD (7 days)
A 2305	Pharmacological study – Heart Rate + Rechallenge – NVs – MD (7 days) then SD
A 2306	Pharmacokinetic AMD study – NVs – MD (14 days)
A 2309	Pharmacokinetic BE study – NVs – SD
A 2311	Pharmacokinetic DDI study – Interacting drug: Ketoconazole – NVs – SD(FTY)
D2101	Pharmacological study – QT – NVs – MD (7 days)
D2102	Pharmacological study – FEV1 – Asthma patients – MD (10 days)
D2105	Pharmacological study – pulmo/cardia – NV – MD (14 days)
D2106	Pharmacological study – DDI – SD
D2107	Pharmacokinetic food effect study – NVs – SD
D2108	Pharmacokinetic Renal Impairment study – NVs + Impaired patients – SD
D2110	Pharmacological study – Heart Rate – NVs – MD (10 days)
D2113	Pharmacological study – flow velocity in cerebral vessels + platelet function + macular thickness – NVs – MD (4 weeks)

Source: NDA 22-257 SN 003. SD= single drug; MD= multiple drug; NV= normal volunteers

Studies included in the renal transplant population are presented in Appendix 9.4 of this review.

5.2 Review Strategy

This review focuses on the safety of fingolimod in the MS population and in Clinical Pharmacology studies. All narratives were reviewed for deaths, serious AEs and discontinuations due to AEs. Selected CRFs and patient profiles were reviewed when narratives provided insufficient or unclear information. Adverse event tables and selected narratives were reviewed for the transplant studies. The efficacy of fingolimod in patients with multiple sclerosis is being reviewed by Dr. Heather Fitter.

5.3 Discussion of Individual Studies

Characteristics of the studies have been described in Table 1 of this review. The study design and population for the phase 2 & 3 controlled studies were similar. Studies 2201 (the phase 2, 6-month study) and 2301 (phase 3, 2-year study) were placebo-controlled, while 2302 (phase 3, 1-year study) used interferon beta-1a (Avonex®) as a control. Study 2201 included FTY 5 and 1.25mg. Studies 2301 and 2302 included FTY 1.25 and 0.5 mg. All subjects in studies 2301 and 2302 and most subjects in 2201 had relapsing remitting MS (RRMS) (11% of subjects in 2201 [n=31] had progressive remitting MS).

Studies 2201 and 2301 were conducted outside the US, while studies 2302 and 2309 included US centers (study 2302, one of the pivotal studies, included 144 subjects from the US). The clinical monitoring in study 2201 (the phase 2 study which was completed before the IND submission in the US) was not as comprehensive as the monitoring agreed upon with the FDA for study 2309. Monitoring and special safety evaluations in 2309 were also included in study 2302. Study 2301 did not include 24 hour Holter or echocardiograms, but included PFTs and OCT in all patients and HRCT in some patients.

6 Review of Efficacy

Please refer to Dr. Heather Fitter's review.

7 Review of Safety

Safety Summary

In the original NDA submission (cut-off date of September 30, 2009), a total of 2315 subjects had been exposed to fingolimod (FTY) (any dose or duration) in phase 2 and 3 MS studies and 843 subjects had been exposed to fingolimod in phase 1 clinical pharmacology studies (any dose or duration). Additional data were available from renal transplant patients who had received doses of FTY 2.5 mg and FTY 5 mg a day. The 4-month Safety Update Report (SUR) contained additional information up to January 10, 2010, with a total of 2615 patients in the ISS, including 567 patients at the dose of 0.5 mg/day (the dose proposed for marketing in MS) for 2 years. Additional studies are being conducted with fingolimod that are still blinded and partial information is available from those studies.

Two deaths occurred during the controlled period of the studies (one disseminated varicella zoster infection and one herpes simplex encephalitis) in young subjects taking FTY 1.25 mg (<0.1% of all FTY patients included in the ISS). No infection-related deaths occurred in the FTY 0.5 mg, placebo or interferon groups. As of July, 2010, a total of 14 deaths occurred in the fingolimod MS program, including 10 during or after FTY treatment. No particular pattern was observed among these deaths. Of note, in the renal transplant key safety population 8 patients (1.7%) died of cardiac causes in the FTY 5mg group, as compared with no patients in the FTY 2.5mg and active comparator groups. No cardiovascular deaths were reported in the MS trials.

The rate of serious adverse events (SAE) during the controlled portion of the studies (safety pool D) was similar among FTY and placebo (10.6%, for FTY 1.25, 8.5% for FTY 0.5, 11.9% for placebo) and higher than that of interferon (5.8%). The most frequent SAE were in the Cardiac SOC (2.4% for FTY 1.25, 1.2% for FTY 0.5, 0.8% for placebo and 0.2% for IFN). Most common events in this SOC were bradycardia and atrio-ventricular (AV) block (first and second degree) upon first treatment dose, with evidence of a dose response. One case of third degree AV block upon first fingolimod dose occurred in the extension studies. Most cases of bradycardia and AV block resolved without specific treatment but some required treatment with atropine or isoproterenol, and/or led to study drug discontinuation. There was no imbalance in the number of major cardiovascular ischemic/thrombotic events but there were two cases of peripheral arterial ischemic disease and one stroke in the FTY 1.25 mg group in the controlled studies. Serious events of macular edema occurred in 0.4% of FTY 1.25 and 0.1% of FTY 0.5 treated patients (no cases on placebo or INF) in the ISS and in 0.6%, 0.3% and 0.3% of patients on FTY 1.25, FTY 0.5 and placebo, respectively in study 2309. Most events of macular edema resolved after drug discontinuation but some did not, or did resolve with remaining loss of visual acuity at the time of last available follow up (approximately one third of patients). SAE in the Infections SOC occurred in 1.9% of patients in the FTY 1.25 group, 0.9% in the FTY 0.5%, 1.6% of placebo and 1.4% of INF-treated patients. There was no evidence of increased overall risk of serious infections or opportunistic infections in the fingolimod groups, and no evidence of increased risk of infections over time in the available database. There were few serious herpetic infections and lower respiratory infections, but they occurred only in FTY-treated patients (including 2 deaths in patients receiving FTY 1.25 mg, mentioned earlier). No cases of tuberculosis, fungal infections or other opportunistic infections were identified in this database. No cases of PML were identified, but not all subjects with unusual MS relapse had the full work-up for PML. There was no imbalance in the risk or rate of malignancies in the controlled studies, however, the database is relatively small and short for assessment of long-term effects of fingolimod. The most common malignancy was basal cell carcinoma (0.3% on FTY 1.25, 0.7% on FTY 0.5 and 0.4% on placebo).

The overall risk of discontinuations due to AE in the controlled studies was higher in the FTY 1.25 group (11.9%) as compared to 7%, 7%, and 3.9% in the FTY 0.5, placebo and INF groups, respectively. The most common AEs leading to drug discontinuation were liver enzyme related abnormalities (4.6% of patients in the FTY 1.25 group and 3.6% of patients in the FTY 0.5 mg group) as compared to 0.8% on placebo and 1.6% on IFN. The next most common events leading to drug discontinuation were eye disorders (mostly macular edema; there was also one case of bilateral retinal ischemia/vasculitis in the FTY 1.25 mg group) and cardiac disorders (bradycardia and AV block).

Evaluation of vital signs showed a clear dose-related increase in systolic and diastolic blood pressure. The mean change from baseline to the last non missing value on treatment in the controlled studies for the FTY 0.5 mg group at one year was 2 mmHg increase in SBP and 1 mmHg increase in DBP. The clinical significance of this change is unclear.

Chemistry evaluations were notable for the lack of electrolyte data in the phase 2 and 3 studies. Available chemistry evaluations other than liver enzyme elevation were unremarkable. In the controlled safety pool D, the risk of ALT elevation 3 x ULN was 9.7% in the FTY 1.25 group, 8.5% in the FTY 0.5 mg group, 1.6% on placebo and 2.5% in the IFN group. The great majority of these events occurred without increase in bilirubin and alkaline phosphatase. At the time of the original ISS, four patients were identified as having increased ALT>3xULN and increased BR >2 mg/dL (two had prior history of Gilbert's disease and recovered soon after drug discontinuation; one had received iv paracetamol prior to the event; one occurred in a subject receiving placebo), and one case of hepatic failure was reported in a subject who died of disseminated varicella zoster infection. No additional cases were identified in the SUR. After submission of the SUR, one patient was identified as having ALT >20x ULN and jaundice. This patient was found to have acute Hepatitis E. Hematology evaluations in the pooled phase 3 studies showed a decrease in mean absolute WBC and lymphocyte counts, but also a slight decrease in mean neutrophil and platelet counts from baseline in the fingolimod groups, as compared to placebo or interferon. The clinical significance of these small changes is unclear. Outlier analyses of hematologic parameters in all controlled and extensions studies were unremarkable. In a 1-month multiple dose study, one month after discontinuation of FTY 0.5 mg lymphocyte counts recovered up to 90% of baseline. No formal evaluation has been done until full lymphocyte recovery after longer-term treatment.

A "Thorough QT" study failed to exclude a 10 ms prolongation of the QT interval for both doses of FTY included in the study (1.25 and 2.5 mg), although there are difficulties in the interpretation of this study including lack of the expected effect of the positive control. Extensive ECG evaluations were conducted for 6 hours following the first dose of fingolimod, and regularly throughout the clinical studies. Upon initiation of FTY treatment in the pooled phase 3 studies (2301 and 2302), there was a decrease in mean heart rate from baseline on ECGs at the 6 hours evaluation for FTY groups and placebo (-12 bpm for FTY 1.25, -9 bpm for FTY 0.5, -1.1 bpm for placebo) and an increase of 9.6 bpm for the IFN group; there was a dose-related mean PR prolongation (11.3 msec for FTY 1.25, 4.5 mg sec for FTY 0.5) as compared to placebo (-0.8 msec) and IFN (-3.2 msec) and a small increase in QTcF (8.8 msec for FTY 1.25, 7.6 msec for FTY 0.5, 2.5 msec for placebo and -4.6 msec for IFN). With chronic use, there were no relevant changes from baseline in PR,QRS or QT interval duration for FTY 0.5 mg.

Special safety evaluations were incorporated into the MS trials submitted in the original application and in the ongoing study 2309. Information was updated with the 4-month Safety update report (SUR) and updated Special safety interim report (SSIR) submitted 4/21/10. Findings are summarized as follows:

- 24 hour Holter evaluations showed a decrease in HR of approximately 28 bpm for FTY 1.25 and 22 bpm for FTY 0.5 mg, at around 6 hours post first FTY dose. This was not observed at the 3 month Holter evaluation.
- PFT evaluation found a decrease in PFTs, particularly FEV1 and DLCO for FTY 1.25 mg, and to a lesser extent for FTY 0.5 mg. These changes are observed at the one month

and 3 month visit. The observed change in FEV1 of >100 mL for FTY 0.5 mg appears to be clinically meaningful, as it exceeds the changes observed with patients with COPD and MS in general. Evaluation of PFTs in a subset of patients who were followed after drug discontinuation (safety pool E follow up) suggests that the changes in FEV1 were reversible, but the changes in DLCO were not reversible within the 3 month evaluation period.

- HRCT showed that slightly more patients had new abnormal HRCT findings in the FTY 1.25 mg group as compared to placebo, but the numbers are small and there is no particular pattern.
- Echocardiogram was done in a subset of patients who participated in studies in the US. No clinically significant changes were identified in the small available database. One case of pulmonary hypertension was diagnosed in a patient who reported dyspnea and developed systemic hypertension while on FTY 1.25 mg during study 2309.
- Ophthalmologic evaluations were conducted at screening and regularly throughout the studies. 23 cases of macular edema were identified in the controlled and extension studies in the original ISS (one on IFN, all the others on FTY; not all cases were confirmed by the DSMB ophthalmologist). Most cases were diagnosed by dilated ophthalmoscopy or optic coherence tomography (OCT), within the first 3-4 months of treatment, but some cases were found after 2 years. Central foveal thickness (CFT) by OCT showed a mild increase in mean values over time for FTY 1.25 and FTY 0.5 mg and a higher number of outliers with CFT change from baseline >40 microns in FTY treated patients at 1 and 3 months, as compared to placebo.
- Dermatologic evaluations were implemented in some studies when they were ongoing. The risk of basal cell carcinoma appears to be slightly higher in FTY treated patients as compared to placebo, however, some of these diagnoses were made at the first dermatologic assessment and it is not clear whether the lesion was there at baseline. That information is being prospectively collected in study 2309.

Several areas of safety concerns have been identified in this review. Main limitations of this application are the lack of data in patients with pre-existent conditions who would be at increased risk for developing eye and cardiovascular complications (such as diabetics and patients taking concomitant medications that were excluded from the studies), and the lack of adequate electrolyte information.

The risk of macular edema has been extensively studied. However, the long-term effects of fingolimod on immunosurveillance (risk of infections and malignancy), lung, liver and vascular toxicity are not fully characterized. It is also unclear whether fingolimod may be associated with increased risk of seizures. Given the benefits of the 0.5 mg dose, it appears that the benefits overweight the risks associated with the drug, however, if approved the drug will need a Risk Evaluation and Mitigation Strategy (REMS) and postmarketing safety studies to address long-term safety. Additionally, there are several ongoing studies from which the FDA has received only selected information. Full study reports are expected when the studies are completed.

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

Studies in the MS ISS are included in Table 2 of this review. Clinical pharmacology studies are described in the Clinical Pharmacology review and summarized in Table 3 of this review. A listing of clinical studies and main findings in the renal transplant population are presented in Appendix 9.4 of this review.

7.1.2 Categorization of Adverse Events

The MedDRA dictionary (Version 12.1) was used to code adverse events. An AE was defined as any untoward medical occurrence in a clinical study subject administered a pharmaceutical product. [5] For all safety data except serious AE, the cut-off date for analysis was up to 45 days after the last dose of study medication for the MS population or up to 7 days for the renal transplant population. Across the studies, SAE and deaths were reported from the time the patient provided informed consent until up to 3 months after the patient stopped participating in the study. SAEs after this period were reported to Novartis at the discretion of the investigator.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

Safety data in the MS population were pooled in 5 different groups, to better assess and compare risk/rate of events. Pooled safety groups in phase 2 and 3 studies in MS are presented in the following table.

[5] A serious AE (SAE) is defined as any event that was fatal or immediately life-threatening, resulted in or prolonged an existing hospitalization, was permanently or significantly disabling, was a congenital anomaly, or required medical or surgical intervention to prevent permanent sequelae or any of the previously mentioned outcomes. SAEs included other important medical events that were judged by the investigator as jeopardizing the subject or potentially requiring intervention to prevent one of the previously listed outcomes.

Table 4. Table of Safety Analysis Pools in MS ISS

Analysis datasets, number of patients	Studies (cut-off)	Treatment regimens	Pooled treatment groups	N (PYRS)
Pool A (12-month treatment) N = 2552	D2301 (up to Month 12 visit)	FTY 1.25 mg FTY 0.5 mg Placebo	FTY720 1.25 mg FTY720 0.5 mg Placebo	849 (764.8) 854 (793.2) 418 (376.7)
	D2302	FTY 1.25 mg FTY 0.5 mg IFNβ-1a i m.	 IFNβ-1a i m.	 431 (401.9)
Pool B (24-month treatment) N = 1272	D2301	FTY 1.25 mg FTY 0.5 mg Placebo	FTY720 1.25 mg FTY720 0.5 mg Placebo	429 (682.2) 425 (750.2) 418 (703.2)
Pool C (6-month treatment) N = 2833	D2301 (up to Month 6 visit)	FTY 1.25 mg FTY 0.5 mg Placebo	FTY720 5 mg FTY720 1.25 mg	94 (43.2) 943 (429.2)
	D2302 (up to Month 6 visit)	FTY 1.25 mg FTY 0.5 mg IFNβ-1a i m.	 FTY720 0.5 mg Placebo	 854 (405.1) 511 (239.4)
	D2201	FTY 5 mg FTY 1.25 mg Placebo	 IFNβ-1a i m.	 431 (205.3)
Pool D (all DB controlled studies regardless of differences in treatment duration or comparators) N = 2833	D2301	FTY 1.25 mg FTY 0.5 mg Placebo	FTY720 5 mg FTY720 1.25 mg	94 (43.2) 943 (1111.2)
	D2302	FTY 1.25 mg FTY 0.5 mg IFNβ-1a i m.	 FTY720 0.5 mg Placebo	 854 (1153.2) 511 (746.9)
	D2201	FTY 5 mg FTY 1.25 mg Placebo	 IFNβ-1a i m.	 431 (401.9)
Pool E (all FTY720-treated population) N = 2315	D2301	FTY 1.25 mg FTY 0.5 mg Placebo	FTY 5 mg–1.25 mg*	
	D2302, D2302E1 (up to 1-Jun-09)	FTY 1.25 mg FTY 0.5 mg IFNβ-FTY 0.5 mg IFNβ–FTY 1.25 mg	 FTY 1.25 mg	 1157 (1919.9)
	D2201, D2201E1 (up to the Month 60 visit)	FTY 5 mg–1.25 mg FTY 1.25 mg Placebo–FTY 1.25mg Placebo–FTY 5–1.25mg	 FTY 0.5 mg	 1021 (1583.3)

Source: Table 1-5 Integrated Summary of Safety; Tables 1-5, 2-5, 2-8, 2-12, 2-17. Cut-off date: June 1, 2009.
Note: FTY 0 5 mg–1.25 mg indicates the treatment regimen of FTY720 5 mg switched to FTY 1.25 mg during D2201E1. Interferon–FTY indicates the interferon treatment group switched after completing core D2302 to either FTY 0.5 mg or 1.25 mg in D2302E1. Likewise, Placebo–FTY indicates the placebo treatment group switched to FTY 1.25 mg or 5 mg in D2201E1; the Placebo–FTY 5 mg–1.25 mg indicates the treatment regimen of placebo in D2201 initially switched to FTY 5 mg in D2201E1 and then switched to FTY 1.25 mg during D2201E1.

There is an additional population called safety pool E follow up, with 538 subjects followed from Group E, to evaluate reversibility of AEs after drug discontinuation.

The pooling strategy was discussed with the Agency prior to the NDA submission. Given the difference in the duration of these studies, using several pools to evaluate safety was considered appropriate. All five safety pools are relevant.

I find safety pool D to be the most informative because it includes all controlled studies for up to 2 years. Interpretation of results from FTY 5 mg in any of the safety pools (C, D and E) is limited by the fact that there were only 94 patients randomized in a 6-month study. Time adjusted exposure in safety pool D for FTY 1.25 mg (1111.2 PYRs) and 0.5 mg (1153.2 PYRs) is almost twice of that of placebo (746.9 PYRs), but so it is in safety pools A and C.

Most summary tables in this review include results from safety pools D and E.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The exposure to fingolimod in the MS program exceeds minimum ICH guidance recommendations (minimum 1500 total, 300 subjects for 6 months and 100 for one year at clinically relevant doses). However, ICH E1A specifically states that "there are a number of circumstances where the harmonized general standards for the clinical safety evaluation may not be applicable," such as in instances where there is concern that the drug will cause late developing adverse drug effects or cause ADEs that increase in severity or frequency over time.

In the case of fingolimod, an excess of cardiovascular and lung toxicity and macular edema was observed in the renal transplant population as compared to mycophenolate mofetil (MMF). The unfavorable benefit risk profile of FTY 2.5 mg and 5 mg in the renal transplant population led to stopping development of fingolimod for this indication. (For a summary of the safety profile of fingolimod in the renal transplant population the reader is referred to Appendix 9.4 of this review.)

The safety issues identified in the renal transplant population can not be directly extrapolated to the MS population, as patients in renal transplant studies had end stage renal disease, were mostly diabetic and/or hypertensive, with underlying cardiovascular disease, were taking concomitant Cyclosporin A and corticosteroids, and were taking fingolimod at higher doses than the doses used in the MS program. However, safety issues identified in that population need to be adequately evaluated in the MS population. Additionally, because of the immunosuppressive effects of fingolimod, the possibility of increased risk of serious and opportunistic infections and the possibility of an increased risk of malignancies also needs to be adequately explored. Therefore, the fingolimod program in MS required a larger and longer exposure than minimum ICH recommendations.

As seen in the following table, at the time of the cut-off date of the original application, there were close to 2000 subjects and 1700 subjects exposed for at least 6 months and 1 year respectively, at doses at or above the proposed dose for marketing (0.5 mg), in the ISS MS

population, including approximately 300 subjects exposed for 2 years at this dose. The 1.25 mg dose has longer exposure, including 36 subjects exposed for 6 years.

Table 5. Duration of exposure to study in safety pool E (all FTY-treated patients, safety population)

	FTY720 5 mg–1.25 mg (N=137)	**FTY720 1.25 mg (N=1157)**	**FTY720 0.5 mg (N=1021)**	**Total (N=2315)**
Exposure (days)	n (%)	n (%)	n (%)	n (%)
≥ 1 day	137 (100)	1157 (100)	1021 (100)	2315 (100)
≥ 90 days	126 (92.0)	1074 (92.8)	986 (96.6)	2186 (94.4)
≥ 180 days	118 (86.1)	1027 (88.8)	958 (93.8)	2103 (90.8)
≥ 270 days	111 (81.0)	969 (83.8)	907 (88.8)	1987 (85.8)
≥ 360 days	108 (78.8)	831 (71.8)	781 (76.5)	1720 (74.3)
≥ 540 days	101 (73.7)	715 (61.8)	691 (67.7)	1507 (65.1)
≥ 720 days	96 (70.1)	354 (30.6)	289 (28.3)	739 (31.9)
≥ 1080 days	85 (62.0)	85 (7.3)	0 (0.0)	170 (7.3)
≥ 1440 days	70 (51.1)	79 (6.8)	0 (0.0)	149 (6.4)
≥ 1620 days	58 (42.3)	70 (6.1)	0 (0.0)	128 (5.5)
≥ 1710 days	42 (30.7)	48 (4.1)	0 (0.0)	90 (3.9)
≥ 1800 days	33 (24.1)	36 (3.1)	0 (0.0)	69 (3.0)
Patient-years	439.5	1919.9	1583.3	3942.7

Source: Table 5-3 Applicant's Clinical Overview original application. The duration of exposure is the total actual days patients took the study medication until cut-off date of September 30, 2009. Patients are cumulatively counted by each level of the duration of exposure intervals. The FTY720 5 mg–1.25 mg group includes patients who received either FTY720 5 mg alone or FTY720 5 mg switched to 1.25 mg. Includes data from 2201E1 up to 60 months into extension study and 2302 up to 24 months into the extension. Cut-off date September 30 2009.

In addition to these subjects, approximately 1800 subjects are participating in 3 clinical studies that are currently ongoing and blinded (See Table 4 of this review). Subjects included in the original ISS are also participating in extension study 2301E1 (the ISS only included the core study data) and extension studies 2201E1 and 2302E1, beyond the exposure submitted in the original NDA. Only narratives of deaths and selected serious AEs of particular interest (some blinded, some unblinded) were submitted from the non- ISS studies in the original application and in the 4-month update reports (SUR and SSIR).

NOTE: This review includes all responses to FDA requests for clarification submitted up to August 6,2010, the SUR and the updated SSIR. Tables for safety pool E (controlled and open label studies) and the SSIR from study 2309 refer to the information submitted with the original application, unless noted otherwise.

- Updated exposure in Safety pool E in the 4-month Safety Update Report

The cut-off date for the SUR was January 10, 2010. The updated ISS includes 2615 patients (4582.6 PYRs of exposure), including 1176 patients (1878 PYRs) at the FTY 0.5 mg dose. Of the five pools presented in the original ISS, only safety pool E has been updated because no new

data became available from the core studies. Standard ECG data has also been updated for the other pools due to an incorrect exclusion of some ECG abnormal findings at baseline.

As of the cut-off date of the SUR, 567 patients have been exposed to FTY 0.5 mg for at least 2 years, and 140 patients have been exposed to this dose for at least 900 days. The original application included 123 patients who received fingolimod in the US. The updated SUR contains the same number of patients but the total exposure (all doses combined) increased from 147.5 to 161.4 PYRs. (Table 6).

Table 6. Updated exposure in safety pool E (Safety Update Report)

Duration of Exposure (days)	FTY720 5 mg-1.25 mg (N=137)	FTY720 1.25 mg (N=1302)	FTY720 0.5 mg (N=1176)	Total (N=2615)
≥ 1	137 (100)	1302 (100)	1176 (100)	2615 (100)
≥ 7	135 (98.5)	1285 (98.7)	1173 (99.7)	2593 (99.2)
≥ 14	134 (97.8)	1279 (98.2)	1168 (99.3)	2581 (98.7)
≥ 30	131 (95.6)	1259 (96.7)	1163 (98.9)	2553 (97.6)
≥ 60	128 (93.4)	1222 (93.9)	1141 (97.0)	2491 (95.3)
≥ 90	126 (92.0)	1170 (89.9)	1100 (93.5)	2396 (91.6)
≥ 180	118 (86.1)	1087 (83.5)	1025 (87.2)	2230 (85.3)
≥ 360	108 (78.8)	884 (67.9)	851 (72.4)	1843 (70.5)
≥ 540	101 (73.7)	724 (55.6)	697 (59.3)	1522 (58.2)
≥ 720	96 (70.1)	561 (43.1)	567 (48.2)	1224 (46.8)
≥ 900*	91 (66.4)	204 (15.7)	141 (12.0)	436 (16.7)
≥ 1080	85 (62.0)	114 (8.8)	29 (2.5)	228 (8.7)
≥ 1260	77 (56.2)	79 (6.1)	1 (0.1)	157 (6.0)
≥ 1440	70 (51.1)	79 (6.1)	0 (0.0)	149 (5.7)
≥ 1620	66 (48.2)	76 (5.8)	0 (0.0)	142 (5.4)
≥ 1800	62 (45.3)	73 (5.6)	0 (0.0)	135 (5.2)
≥ 1980	45 (32.8)	47 (3.6)	0 (0.0)	92 (3.5)
≥ 2160	5 (3.6)	9 (0.7)	0 (0.0)	14 (0.5)
n	137	1302	1176	2615
Mean	1296.7	622.3	583.3	640.1
SD	780.45	459.01	295.43	447.20
Median	1542.0	675.0	715.5	711.0
Minimum	1	1	2	1
Maximum	2240	2246	1266	2246
Patient years	486.4	2218.3	1878.0	4582.6

The duration of exposure is the total actual days patients took the study medication until cut-off date. - Patients are counted by each level of the duration of exposure cumulatively. - Patient years is defined as the sum of the number of days on study drug for all patients in each dose group divided by 365.25. - FTY720 5 mg-1.25 mg group includes patients who received either FTY720 5 mg alone or FTY720 5 mg switched to 1.25 mg.

On July 16 2010, at the FDA request, the applicant provided the total exposure to fingolimod in MS studies, including the ISS and non-ISS studies as of the cut-off date of the SUR, as follows:

Exposure to FTY 5 to 1.25mg= 486.4 PYRs; to FTY 1.25 mg= 2777.4 PYRs and to FTY 0.5 mg= 2388.7 PYRs. **Total exposure (any dose, any duration) was N= 3706 patients or 5652.5 PYRs**.

- Exposure in study 2309

Study 2309, the 2-year study with the most comprehensive safety evaluations is ongoing and still blinded. Special safety evaluations from this study were made available through a firewall and submitted to the NDA application as part of a Special Safety Interim Report.

Table 7. Exposure in study 2309, original submission

Table 1-3 Duration of exposure to study drug (Safety population in study D2309)

	FTY720 1.25 mg N=370	FTY720 0.5 mg N=358	Placebo N=355	Total N=1083
Descriptive statistics (days)				
Mean (SD)	371.9 (242.54)	377.1 (245.10)	371.2 (237.23)	373.4 (241.46)
Median	356.0	344.0	335.0	343.0
Range	1 - 778	2 - 776	3 - 772	1 - 778
Duration of exposure in days - n (%)				
≥1	370 (100.0)	358 (100.0)	355 (100.0)	1083 (100.0)
≥7	363 (98.1)	357 (99.7)	354 (99.7)	1074 (99.2)
≥14	361 (97.6)	353 (98.6)	351 (98.9)	1065 (98.3)
≥30	358 (96.8)	345 (96.4)	349 (98.3)	1052 (97.1)
≥60	339 (91.6)	332 (92.7)	344 (96.9)	1015 (93.7)
≥90	309 (83.5)	300 (83.8)	309 (87.0)	918 (84.8)
≥180	261 (70.5)	248 (69.3)	252 (71.0)	761 (70.3)
≥270	218 (58.9)	211 (58.9)	204 (57.5)	633 (58.4)
≥360	183 (49.5)	173 (48.3)	165 (46.5)	521 (48.1)
≥450	146 (39.5)	149 (41.6)	137 (38.6)	432 (39.9)
≥540	119 (32.2)	120 (33.5)	111 (31.3)	350 (32.3)
≥630	80 (21.6)	91 (25.4)	81 (22.8)	252 (23.3)
≥720	39 (10.5)	34 (9.5)	33 (9.3)	106 (9.8)
Patient-years	377	370	362	1108

Source: Table 1-3. Special safety interim report, original submission.

The updated information from 2309 in the SUR includes 59 patients exposed to FTY 1.25, 70 exposed to FTY 0.5 mg and 70 exposed to placebo, for up ≥ 2 years (table not shown).

The number of patients who underwent special safety evaluations in study 2309 at the time of the original application is summarized in the following table. Of note, some echocardiograms done in study 2302 were pooled with some of those done in 2309 into a "pooled echo analysis set".

Table 8. Number of patients undergoing special safety evaluations in study 2309

	FTY720 1.25 mg n (%)	FTY720 0.5 mg n (%)	Placebo n (%)	Interferon beta-1a i.m. n	Total n (%)
Study D2309					
Randomized population	370 (100.0)	358 (100.0)	355 (100.0)	0	1083 (100.0)
Safety population	370 (100.0)	358 (100.0)	355 (100.0)	0	1083 (100.0)
Holter ECG analysis set	366 (98.9)	356 (99.4)	353 (99.4)	0	1075 (99.3)
Chest HRCT analysis set	88 (23.8)	88 (24.6)	90 (25.4)	0	266 (24.6)
OPH analysis set for OCT	357 (96.5)	348 (97.2)	348 (98.0)	0	1053 (97.2)
Study D2309 and study D2302					
Pooled echo analysis set	64	60	48	11	183

ECG = electrocardiogram, HRCT = high resolution computed tomography, OPH = ophthalmology, OCT = optical coherence tomography, echo = echocardiography. Source Table 1-2. Fingolimod Safety Interim Report, original application.

As per the Special Safety Interim Report update, the following number of patients were exposed for ≥720 days (tables not shown):

- For the echo analysis set: 10 to FTY 1.25 mg, 12 to FTY 0.5 mg and 9 to placebo (total of 31 patients)
- For the HRCT analysis set: 54 to FTY 1.25mg, 67 to FTY 0.5 mg and 68 to placebo (total 189 patients)

There are several ongoing studies from which we only have "selected" information. Therefore, the fingolimod program exceeds minimum ICH guidance recommendations and includes special safety evaluations to address specific safety concerns; however, the data are still insufficient to fully address the long term safety of fingolimod.

The applicant has provided demographics and clinical characteristics of the population in study 2309, concomitant diseases and medications, blinded narratives for AE that were submitted as IND safety reports, unblinded narratives of selected cases of interest and results of analyses of special safety studies. Analyses of serious AEs and discontinuations due to AE from this study have not been provided.

When study 2309 is completed and analyzed, the applicant should submit a pooled analysis of Safety pool D + study 2309 for all AE, serious AE, discontinuations due to AE and frequent AEs.

- Baseline characteristics of the population in MS studies

The demographics and disease characteristics of the MS population in the ISS are consistent with those in other applications for MS. Demographic characteristics of the different safety pools were similar. Differences between treatment groups were not clinically meaningful. Approximately 70% of patients were female, with a mean age of 37 years; 95% were Caucasian, and the mean weight was approximately 70 kg. Of note, study 2201 and 2301 were conducted

entirely outside the US. The only completed study that has participating sites in the US was 2302, with a total of 144 U.S. patients including 16 African American.

> *The applicant states that MS is not a disease that has known geographical differences in terms of clinical phenotype or severity and that the demographics and disease characteristics of patients from the US who enrolled into 2302 are similar to the overall study population. US patients tend to be slightly older and to have a higher BMI, but as per PK data, adjustment is not needed based on body weight. Moreover, the applicant states that MS practice patterns are homogeneous around the world.*

MS disease characteristics were similar among treatment groups, within each of the studies. The mean duration of MS since first symptoms was approximately 7 to 8 years and the mean EDSS score was around 2.5 at baseline. Of note, 2201 included 31 patients with Secondary progressive MS (SPMS). For details about the disease characteristics the reader is referred to Dr. Fitter's review of efficacy.

With regard to previous MS treatment, 59% of patients in D2301 and 43% of patients in D2302 were treatment-naïve (defined as not receiving any of the five approved MS disease modifying drugs). The most common prior immunomodulator or immunosuppressive treatment received was INF beta (approx. 30% of patients in study D2301 and 50% of patients in D2302). The most common prior treatment in study D2201 was corticosteroids (78 to 83% of patients in different treatment groups), followed by IFN beta 1a (approx. 20% of patients) and IFN beta 1b (7.5% on placebo, 4.3% on FTY 1.25, 6.5% on FTY 5mg).

- Prior and concomitant diseases and medications at baseline

I would like to emphasize the eligibility criteria for the phase 3 MS studies, particularly the exclusion criteria:

Exclusion criteria:
Patients who meet any of the following exclusion criteria during the Pre-Randomization Phase will not be eligible for enrollment in the study:
1. A manifestation of MS other than RRMS
2. A history of chronic disease of the immune system other than MS or a known immunodeficiency syndrome
3. A history of epileptic seizures within 3 months of randomization
4. A history or presence of malignancy (except for successfully treated basal or squamous cell carcinoma of skin)
5. A known or 'new' diagnosis of diabetes mellitus (if screening blood glucose is suspicious for diabetes [≥126 mg/dL or ≥7 mmol/L if fasting; ≥200 mg/dL or 11.1 mmol/L if random testing] a patient should be further evaluated for diabetes mellitus)
6. A diagnosis of macular edema during Pre-randomization Phase
7. Active systemic bacterial, viral or fungal infections, or diagnosis of AIDS
8. Have received total lymphoid irradiation or bone marrow transplantation
9. Have been treated with:
   • corticosteroids or adrenocorticotropic hormones (ACTH) within 1 month prior to randomization

- immunosuppressive medications such as azathioprine or methotrexate within 6 months prior to randomization
- immunoglobulins and/or monoclonal antibodies (including natalizumab) within 6 months prior to randomization
- cladribine, cyclophosphamide or mitoxantrone at any time

10. Any medically unstable condition, as assessed by the primary treating physician
11. Any of the following cardiovascular conditions:
    - myocardial infarction within the past 6 months prior to enrollment or current unstable ischemic heart disease
    - history of angina pectoris due to coronary spasm or history of Raynaud's phenomenon
    - cardiac failure at time of Screening (Class III, according to NYHA Classification; or any severe cardiac disease as determined by the investigator
    - history of cardiac arrest
    - history of symptomatic bradycardia
    - resting pulse rate <55 bpm prior to randomization
    - history of sick sinus syndrome or sino-atrial heart block
    - History or presence of a second degree AV block or a third degree AV block or an increased QTc interval >440 ms on Screening ECG
    - arrhythmia requiring current treatment with Class III antiarrhythmic drugs (e.g., amiodarone, bretylium, sotalol, ibulitide, azimilide, dofelitide)
    - history of a positive tilt test from workup for vasovagal syncope
    - hypertension, uncontrolled by medication
12. Any of the following pulmonary conditions:
    - severe respiratory disease or pulmonary fibrosis
    - tuberculosis, except for history of successfully treated tuberculosis or history of prophylactic treatment after positive PPD skin reaction
    - abnormal chest High Resolution Computer Tomography (HRCT) [or chest x-ray in case HRCT is not permitted by local regulations] suggestive of active pulmonary disease
    - abnormal Pulmonary Function Tests: FEV1;, FVC values lower than 70% of predicted value, DLCO values lower than 60% of predicted value
    - patients receiving daily therapies for asthma
13. Any of the following hepatic conditions:
    - known history of alcohol abuse, chronic liver or biliary disease, with the exception of Gilbert's syndrome
    - total or conjugated bilirubin greater than the upper limit of the normal range
    - alkaline phosphatase (AP) greater than 1.5 times the upper limit of the normal range
    - AST (SGOT), ALT (SGPT) greater than 2 times the upper limit of the normal range
    - gamma-glutamyl-transferase (GGT) greater than 3 times the upper limit of the normal range
14. Any of the following abnormal laboratory values:
    - serum creatinine greater than 1.7 mg/dL (150 μmol/L)
    - white blood cell (WBC) count <3,500/mm3 (<3.5 X 109 / L)
    - lymphocyte count <800/mm3 (<0.8 X 109 / L)
15. Any of the following neurologic/psychiatric disorders:
    - severe depression within three months of randomization

• relevant history of suicide attempt or who are at risk of suicide attempt
• history of substance abuse (drug or alcohol) or any other factor that may interfere with the subject's ability to cooperate and comply with the study procedures;
• progressive neurological disorder, other than MS, which may affect participation in the study or require the use of medications not allowed by the protocol.
16. unable to undergo MRI scans
17. history of hypersensitivity to natural or recombinant interferon beta, human albumin, or any other component of the formulation
18. participation in any clinical research study evaluating another investigational drug or therapy within 6 months prior to randomization, or history of fingolimod therapy.

In April 2010, the FDA requested information about the number of patients who failed screening due to unacceptable lab values, unacceptable test procedure results, unacceptable past medical history/concomitant diagnosis and/or unacceptable use of excluded medications/therapies, in each study, and also the number of patients with diabetes or elevated glucose levels who were excluded from study entry in each study. The applicant responded that they do not have that detailed information.

Comment: These exclusion criteria are reasonable for the development program of a drug suspected to be associated with multiple toxicities, including cardiac, lung and ocular toxicity. However, once the drug is approved, it will be used in a much wider population than the population included in these studies. Most NDA clinical trials exclude subjects with recent cardiac ischemic events, complete AV block, uncontrolled diabetes, and active infections. However, the fingolimod trials excluded patients with diabetes (even those with new diagnosis by laboratory evaluation at screening), as well as patients treated with antiarrhythmic drugs (although only Class III were supposed to be excluded by protocol, there were no patients taking calcium channel blockers in this database). Therefore, in my opinion, if approved, fingolimod should be contraindicated in patients with diabetes and arrhythmias requiring antiarrhythmic treatment, because these patients have not been studied in clinical trials and are likely to have an increased risk for serious cardiovascular adverse events. If not, there should be a prominent WARNING for these patients.

Upon discussion at the FDA AC meeting, the panel recommended approval of fingolimod 0.5 mg, however, they recommended baseline ECG and 6 hour in-office monitoring for all patients who received the first dose of fingolimod. Additionally, they recommended that a study evaluating lower doses than 0.5 mg be conducted, including patient populations that had been excluded from the original trials (such as diabetics, patients taking beta blockers, patients with less than perfect PFT evaluations, etc.).

- Medical history at baseline

As per Post table 3.7-1 of the ISS (Relevant medical history and continuing medical condition in the randomized population, pool D – all controlled studies-) 90 % of patients in this group had at least one past or ongoing continuing medical condition, the most common being nervous system disorders (55% overall). Some events of interest are discussed as follows for pool D

(percentages for the FTY 5 mg group are not in included because they were usually different from the other groups).

The most frequently reported medical history/continuing medical condition in pool D, was optic neuritis (approximately 40% of subjects in each treatment group). Epilepsy was reported by 0.5%, 0.7%, 1.2% and 0.2% of patients randomized to FTY 1.25, FTY 0.5, placebo and IFN, respectively, although subjects with seizures within 3 months prior to entry were excluded from the studies.

Prior and continuing medical conditions in the cardiac SOC were reported for 3.4 to 4.2% of patients depending on treatment group. The overall frequency of first degree AV block was 0.4%. One patient (in the FTY720 0.5 mg group) had a reported history of bradycardia. *(ECGs done at baseline indicated that approximately 3% of patients had undiagnosed first degree AV block).*

Of note, patients with diabetes were excluded per protocol. However, as per Post table 3.7-1 of the ISS, a few patients (<10) reported a history of diabetes mellitus. Review of these cases indicates that only two had active diabetes requiring concomitant medications. The lack of data on the use of fingolimod in patients with diabetes is of concern, because diabetes is a prevalent disease. Patients with diabetes may be at in increased risk of developing vascular complications with fingolimod.

History of uveitis was reported by 1.3% of FTY720 1.25 mg patients, 0.8% of FTY720 0.5 mg patients, 0.7% of placebo patients, and 1.6% of interferon patients. One patient (0.1%) in the FTY720 0.5 mg group had a history of macular edema. No patient had active macular edema or uveitis at the time of randomization.

Respiratory, thoracic and mediastinal disorders were reported in approximately 11% of patients. Asthma was reported in 3.7%, 3.3%, 2.5% and 2.3% of patients randomized to FTY 1.25 mg, FTY 0.5 mg, placebo and IFN, respectively. Active tobacco use was reported in 1.2%, 1.8%, 0.2% and 2.3% of patients randomized to FTY 1.25 mg, FTY 0.5 mg, placebo and IFN, respectively.

Hypertension was reported in 7.1%, 5.3%, 6.1% and 6% of patients randomized to FTY 1.25 mg, FTY 0.5 mg, placebo and IFN, respectively. A history of congestive heart failure or ischemic heart disease was reported in ≤0.1% of patients.

There were no clinically relevant differences in medical history between the treatment groups.

- Prior and concomitant medications at baseline

As per Table 3.1.1 of the response to an FDA request for information submitted in March 23, 2010, (Concomitant medications and significant non-drug therapies at baseline in all controlled studies – Pool D-) approximately 66% of patients were taking at least one concomitant medication at baseline in the FTY 1.25mg, 0.5mg, IFN and placebo groups. In the FTY 5 mg group 73% were taking concomitant medications (data not shown).

The most common medications at baseline were Progesterone and estrogens fixed combinations, which were taken by 15.5%, 16.7%, 18.2% and 11.8% of subjects in the FTY 1.25, FTY 0.5, IFN and placebo groups, respectively, followed by selective serotonin reuptake inhibitors (mean 9% in each treatment group) and benzodiazepine derivatives (mean 7.5% in each treatment group). The most common drug used at baseline was paracetamol (used by approximately 7% of patients). Approximately 20 patients were exposed to systemic beta-blockers per treatment group in the controlled database. No patient was taking calcium channel blockers.

7.2.2 Explorations for Dose Response

There does not seem to be substantial difference in efficacy for the 1.25 and 0.5 mg/day doses, however, there is a dose clear response in terms of safety between these two doses in the MS population. While the safety profile of the 0.5 mg day dose is more favorable than the 1.25 mg dose, it is unclear whether a lower dose would still be effective and would be associated with less toxicity.

The applicant was asked to explain why the once daily schedule, given the long half life or fingolimod. Of the several reasons provided by the applicant the most relevant is the impact of the dose on the negative chronotropic effect of fingolimod. To achieve a daily, mean systemic concentration of fingolimod-P equal to that measured for 0.5 mg daily would require a weekly fingolimod dose of 3.5 mg. Treatment initiation of this 3.5 mg dose would be associated with a significantly increased negative chronotropic effect compared to treatment initiation with 0.5 mg daily.

Upon discussions at the FDA AC meeting of June 10, 2010, the expert panel recommended evaluation of the 0.25 mg dose to see whether a dose lower than 0.5 mg is still effective and could potentially be associated with less toxicity. This could be done as a postmarketing study.

7.2.3 Special Animal and/or In Vitro Testing

Please refer to the pharmacology toxicology review.

7.2.4 Routine Clinical Testing

- Routine clinical and laboratory evaluations in MS studies

Hematology and chemistry were done at screening, baseline, 2 weeks, monthly for 3 months, and then every 3 months and evaluated at a central lab.

Chemistry evaluation included: random glucose, albumin, alkaline phosphatase, creatinine, ALT, AST, GGT, amylase, total bilirubin, conjugated bilirubin, total cholesterol, triglycerides, HDL, LDL. Urinalysis was collected as screening, baseline, month 6 and month 12. Of note, electrolytes were not analyzed in the MS Phase 2 and Phase 3 studies in MS. Analyses of electrolytes were submitted for study D2113, a clinical pharmacology study (28 day study of FTY 1.25 mg, FTY720 0.5 mg and placebo). A retrospective analysis of a subset of patients in study 2301 was submitted with the SUR.

Comment: It is unusual that routine testing such as sodium, potassium and bicarbonate were not analyzed in the phase 2 and 3 studies of a new molecular entity. I find this troublesome. The fact that data on electrolytes at the time of ECG changes during first dose monitoring are not available is disturbing. Electrolytes should be included in the clinical study that will evaluate the lower dose of fingolimod. Ongoing studies have been amended to include electrolyte testing.

Hematology evaluations included: red blood cell (RBC) count, total and differential WBC count (basophils, eosinophils, lymphocytes, monocytes, neutrophils, WBC segments), platelet count, hemoglobin, hematocrit, MCV, MCH, MCHC, RBC morphology. The absolute total WBC, neutrophil and lymphocyte counts were blinded from the sponsor and the investigator and were only communicated to the site in case of a notable abnormality.

Additional serology testing was performed in all patients in all studies (as per a protocol amendment after the occurrence of the fatal disseminated herpes infection) on the last available serum sample in the central lab and/or at study phase completion visit to determine the patient's immune status with respect to the following viruses (in all cases immunoglobulin G (IgG) antibodies were measured): Varicella-zoster virus, Herpes simplex virus (1 and 2) and Rubeola (measles). The following is an excerpt from the Guidance to investigators on monitoring infections:

> "Patients who were varicella-zoster virus IgG negative were informed of their status and of the increased risk for serious and potentially fatal primary infection, should the patient be exposed to varicella zoster virus in a setting of potential immunosuppression related to study drug and/or the use of corticosteroids. These patients were instructed that they must promptly report any possible exposure to a person with chicken-pox or shingles to the investigator. In the event of such exposure, the investigator was to promptly initiate the appropriate antiviral therapy and passive immunization with varicella-zoster immunoglobulin in consultation with a local infectious diseases expert. Varicella-zoster IgG negative patients in the study were allowed to continue on study drug provided the above risk and actions needed to mitigate risk were clearly explained and accepted by the patient.
>
> Patients who were negative for HSV-1 IgG, HSV-2 IgG or rubeola IgG antibodies were informed of their status and were instructed to promptly report any exposure to these viruses, e.g. to a person with cold sores, herpes genitalis, or measles, respectively. In case of exposure, early treatment with appropriate antiviral drugs and/or immunoglobulin was considered in consultation with a local infectious disease expert.
>
> Patients with prior infection may be at risk of viral reactivation (e.g. cold sores, genital ulcers or shingles) and should be instructed to inform the investigator of any signs or symptoms suggestive of these conditions, so that prompt treatment may be initiated."

A complete physical examination was performed at Screening (Visit 1), Month 6 (Visit 8), and Month 12 (Visit 10). Neurological examination was part of the physical examination.

- Vital signs

In Study 2201 vital signs were recorded at each visit, once a day, except from the day of first dose administration, when vital signs were recorded pre-dose and every hour for at least 4 hours post-dose. Vital signs included sitting pulse rate, sitting systolic and diastolic BP, body weight and oral temperature. In Studies 2301 and 2302 vital signs on the Randomization visit day were recorded pre-dose and every hour for at least 6 hours post-dose. Given the known effects of first-dose fingolimod, investigators were given guidelines for management of bradycardia. Orthostatic blood pressure was not measure in phase 2 & 3 studies.

- ECGs

In study 2201, ECGs were done at screening, on the day of first dose administration (prior to dosing and 4 hours post-dose), Week 1, Month 1, Month 3, Month 6. For the extension D2201E1, first dose assessments were repeated and performed at Month 12 and as needed for re-initiation of study drug following temporary study drug interruption. ECGs were paper based.

In studies 2301 and 2302, ECGs were done at screening, on the day of first dose administration (prior to dosing and 6 hours post-dose), Month 1, Month 6, every subsequent 6 months up to Month 12, and as needed for re-initiation of study drug following temporary study drug interruption. In study 2301, ECGs continued every 6 months up to Month 24. The initial protocol 2301 included paper based ECGs but was amended to digital ECG (protocol amendment 1).

The ECG data were collected and analyzed by a central reader.

- Special safety assessments

Because of the concerns raised in the renal population, special safety assessments for evaluation of lung toxicity (PFT's, HRCT), ophthalmologic toxicity (ophthalmologic evaluations including OCT), cardiac toxicity (Holter, echocardiography) and dermatologic toxicity were evaluated in MS studies. These are described under the Special Safety studies section.

- Reasons for removal from study treatment

In addition to the usual reasons for study termination (e.g serious AE, withdrawal of consent, use of prohibited medications), the following conditions were to result in study drug discontinuation:
• Abnormal pulmonary function tests: FEV1, FVC, or DLCO < 60% of baseline at any visit
• Abnormal liver function tests: increase in AST or ALT > 5 x ULN
• Bilirubin > 2.0mg/dl (34.2 micromol/L)
• Lymphocyte count < 0.1x109/L or 100 cells/mm3 confirmed on repeat test would result in study drug interruption; following Amendment 8 of the study protocol (25-Aug-2008), lymphocyte count was increased to 0.2x109/L or 200 cells/mm3 (confirmed on repeat test)
• New neurological symptoms accompanied by MRI findings unexpected for MS
• Diagnosis of macular edema
• Uveitis requiring systemic immunosuppressive treatment (other than corticosteroids)

The criteria for removal from the study are reasonable.

Routine and special safety assessments in study 2302 are presented as follows.

Table 9. Assessments in study 2302

Phase	Pre-randomization		Double-blind treatment								
Period	Screening	Baseline									
Visit no.	1	2	3	4	5	6	7	8	9	10	FU[1]
Study month	-1	-1	Day 1	1/2	1	2	3	6	9	12	+3 mo
Informed consent	X										
Background, demography	X										
Inclusion/exclusion criteria	X	X									
Medical history	X										
MS history/MS treatment	X										
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test (serum)[13]	X	X					X	X	X	X	X
Physical exam (source docs only)[2]	X							X		X	X
Dermatology exam (dermatologist)	X									X	
Ophthalmologic examination	X[3]				X		X	X		X	
Chest X-ray/HRCT[4]	X									X	
PFTs	X				X		X	X		X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Hematology/blood chemistry[5]	X	X		X	X	X	X	X	X	X	X
Urinalysis	X	X						X		X	
FTY720 drug administration			X		X	X	X	X	X		
Interferon beta-1a i.m. drug administration			X		X	X	X	X	X		
ECG	X		X[6]		X			X		X	
24-hour Holter ECG[14]	X		X				X				
Echocardiography [15]	X						X			X	
MRI[7]	X									X	X
EQ-5D		X						X		X	
EDSS[8]	X	X					X	X	X	X	X
MSFC[9]	X	X						X		X	
MS relapse[8]	X	X	X	X	X	X	X	X	X	X	X
AEs/SAEs			X	X	X	X	X	X	X	X	X
Pharmacogenetic blood sample	X[10]	X[10]									
Biomarker-plasma sample[10]	X[10]	X[10]						X		X	
Study phase completion										X	
First dose administration			X								
PRIMUS–PRO (selected countries)[11]		X						X		X	
mFIS–PRO (selected countries)[11]		X						X		X	
Pharmacokinetics								X		X	
CSF sample (selected sites)[12]	X[12]	X[12]								X	

Source: Table 9-2, Study D2302 Complete Study Report. [1]Patients that completed the double-blind treatment phase but did not enter the extension phase or discontinued drug completed a 3-month follow-up visit. [2]P exam included a dermatological exam. [3]An OCT test was conducted at screening and at Visit 10 for all patients to determine central foveal thickness. [4] Chest HRCT scans were performed instead of chest X-ray at all US sites and at sites outside the US where feasible. [5]Lab results needed to determine eligibility. Hematology results were partially blinded to maintain the study blind. [6]ECG was to be obtained on Day 1 before dose administration and 6 hours post-first dose. [7]MRI scan was to be performed within 30 days prior to randomization. 8Unscheduled visits were required to confirm MS relapse. [9]Three to four MSFC training sessions were to be performed during screening prior to the baseline MSFC.[10]Blood draw(s) were done under separate informed consent. [11] Patient reported outcomes. Countries included Australia, Canada, France, Germany, Italy, Spain, United Kingdom, and the United States. [12]CSF collection was only done after the separate informed consent was signed only once (either screening or baseline visit). [13]Additional pregnancy tests at the discretion of the investigator. [14]Twenty-four hour Holter ECG was conducted at US sites and at selected sites outside the US (where feasible). The 24-hour Holter ECG for the Month 3 visit could have been performed between Month 3 and Month 5 for scheduling convenience. [15]Echocardiography was performed at selected sites.

Comment: Comprehensive special safety evaluations in the MS program to address safety concerns of first dose conduction disorders, macular edema, potential cardiac and lung toxicity, and assessment of skin malignancies were implemented as part of protocol 2302 (completed) and study 2309 (ongoing), after extensive discussions with the FDA. Study 2301 also included some of the special assessments (it did not include echocardiogram and 24 hour Holter). Routine monitoring in the MS program is notable for the lack of evaluation of electrolytes and coagulation parameters in the phase 2 and 3 studies.

- Criteria for notable laboratory abnormalities in fingolimod NDA

Table 10. Criteria for notable abnormalities for laboratories in fingolimod NDA

Laboratory variable	**Notably abnormal**
Liver function and related variables	
AST (U/L)	>82
ALT (U/L)	>90
GGT	>130 U/L
Alkaline phosphatase (U/L)	>280
Total bilirubin	≥ 34.2 µmol/L
Renal function, metabolic and electrolyte variables	
Glucose	≥ 11.11 mmol/L
Creatinine	≥ 176 µmol/L
Amylase	≥ 300 U/L
Cholesterol (mg/dL)	≥ 6.21 mmol/L
Triglycerides	≥ 3.39 mmol/L
Urea (BUN)	≤ 0.71 mmol/L or ≥ 10.71 mmol/L
Hematology variables	
Hemoglobin	≤ 100 g/L
Platelets (thrombocytes)	≤ 100 or ≥ 600 × 10^9/L
Leukocytes (WBCs)	≤ 2.0 or ≥ 15 × 10^9/L
Hematology variables: differential	
Granulocytes (poly, neutrophils)	≤ 1 or ≥ 12 × 10^9/L
Lymphocytes	<0.2 or ≥ 8 × 10^9/L
Monocytes	Not defined
Red blood cells (RBCs)	<3.3 or >6.8 × 10^{12}/L

Source: Table 3-1, Summary of Clinical Safety (Criteria for notable lab abnormalities) and normal range for central lab values provided with patient profiles.

Tables with reference ranges used by the applicant for studies 2301/2302 and 2201 were provided by applicant at FDA request, on 3/4/10 (data not shown). Based on the normal laboratory ranges, the values chosen to identify markedly abnormal labs are acceptable.

7.2.5 Metabolic, Clearance, and Interaction Workup

Please see clinical pharmacology review by Clinical pharmacology team.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

No drugs in this class are currently available for clinical use.

7.3 Major Safety Results and Discussion

7.3.1 Deaths

As of September 30, 2009 (cut-off date of the original application) 12 deaths had occurred in the Fingolimod MS program. Two additional deaths were reported after the original submission as 15-day IND reports, and later included in the SUR.

Of the 14 deaths reported as of 4/26/10, nine occurred during or after fingolimod treatment (8 in the FTY1.25 mg/day dose group, one in FTY the 0.5mg group); two occurred during treatment with placebo; 2 occurred during the screening period and one remains blinded. There were no deaths in subjects enrolled in the clinical pharmacology studies. Deaths in the renal transplant program are presented in Appendix 9.4 of this review.

Deaths in the Fingolimod MS program with this reviewer's interpretation of the relationship to study drug, are summarized in the following table (as of 8/6/10).

Table 11. Summary of deaths in the fingolimod MS program*

During or following FTY treatment
Likely Related - 2 herpes viral infections (Herpes simplex encephalitis and disseminated varicella zoster)
Can not rule out if related - 1 Multiple tumors (brain, lung, kidney, lymph nodes); possible T cell lymphoma/EBV related lymphoproliferative disease (symptoms started during treatment; died 1 year after drug dc) - 1 Rapidly deteriorating MS complicated with fatal respiratory infection - 1 MS progression/ADEM (can not r/o CNS infection) – complicated with aspiration pneumonia 6 months after drug dc - 2 metastatic tumors - Ovarian. Diagnosed 5 months after drug dc. Death 1 year after drug dc - Breast. Diagnosed 11 months into treatment. Death 3 years after drug dc
Unlikely related - 1 traffic accident - 1 suicide
Not on FTY
Placebo – 1 traffic accident - 1 pulmonary embolism
Blinded – 1 dissecting aortic aneurysm (relationship can not be ruled out)

*As of 8/6/10. Attribution of relationship to study drug as per FDA reviewer. Additionally, two deaths occurred during the screening period, before randomization (1 suicide and one sudden death). Brief narratives of the deaths that occurred in the fingolimod MS program are summarized in the following table.

Narratives for these cases are summarized in the following table.

Table 12. Brief narratives of deaths in the Fingolimod MS program

SubjID	Age Sex	Treat. group (mg/day)	AE Rel day	AE term	Comment
Original submission (12 18 09, cut-off September 30 2009)					
Study 2301 (2-year study)					
708-00011	53 M	FTY 1.25	359	Suicide	Approximately 6 months prior to his death, the patient had experienced depression for which he was hospitalized and received treatment. The patient was reported to have recovered from depression within 3 months. Unlikely to be drug related.
304-00045	52 M	Placebo	657	Pulm. Embolism	Patient presented with acute periodontitis with pyrexia and died approximately 1 week later due to pulmonary embolism 6 days after last dose of placebo. Not drug related.
702-00005	37 F	Placebo	365	Road traffic accident	Patient was hit by a car while walking, receiving multiple injuries 58 days after last dose of placebo. Not drug related.
Study 2302 (1-year study)					
0212-00021	29 F	FTY 1.25	320	Hepatic failure. Herpes zoster disseminated.	MS symptoms for 3 years. Prior history of treatment with IFNβ1a. EDSS=1. Patient had started high dose steroid therapy for an MS relapse approximately 8 days prior to the onset of the event. She continued to work in a child care/nursery center where recent cases of chickenpox had been reported. She was varicella-zoster virus IgG negative at study entry. She died approx. 11 months into fingolimod treatment. Autopsy showed hepatic necrosis and multiorgan failure. For details, see Appendix 9.4.1.
0821-00007	23 M	FTY 1.25	407	Herpes simplex encephalitis HSV 1	MS symptoms for 2 ½ months. Prior history of treatment with IFNβ1b. EDSS=3. He developed fever and headache approx. 11 months into fingolimod treatment, followed by intermittent high fever and seizures despite antiepileptic therapy. He was treated with high dose steroid therapy for suspected MS relapse. Seven days later, he was diagnosed with viral encephalitis and treated with acyclovir. His brain function did not improve and he died 67 days after last fingolimod dose. For details, see Appendix 9.4.1.
0254-00011	42 M	FTY 1.25	187 days after last	Acute disseminated Encephalomyelitis-like symptoms, aspiration pneumonia	MS diagnosed 2 ½ years prior to entry. Prior history of treatment with IFNβ1a. Baseline EDSS of 5. He developed fever, cough and mild hemoptisis approx. 11 months into fingolimod treatment. Study drug was discontinued. Three days later he developed generalized seizures and confusion. An MRI showed a new T2 lesion that did not explain the extent of neurologic changes. JC virus testing done at a laboratory in Europe was negative (no samples remain for additional testing.). A diagnosis of acute disseminated encephalomyelitis (ADEM) was made. The

					patient's neurological condition continued to decline and he died of aspiration pneumonia approx. 6 months after drug discontinuation. He did not have an autopsy. This case was evaluated by Dr. Heather Fitter, DNP neurologist, who offered the following differential diagnoses: MS relapse in the setting of multiple infections, seizures and steroid induced encephalopathy, and PML. For details, see Appendix 9.4.1.
331-00011	53 F	FTY 1.25	-	Breast cancer metastatic	Patient was diagnosed with invasive breast cancer approximately 11 months after commencing FTY720 1.25 mg. She died due to metastatic breast cancer 305 days after last fingolimod dose. Unlikely to be drug related but the role of fingolimod can not be ruled out.
Study 2306 (ongoing study)					
362-00005	46 M	FTY 1.25	103	Rapidly deteriorating MS Severe respiratory infection	2 and ½ years history of MS. No prior immunomodulators for MS. EDSS at entry =6. Nine days into fingolimod treatment developed muscle spasm and deterioration of neurologic status that was thought to be related to a urinary infection. Two months into fingolimod treatment he died of a severe respiratory infection. There was no autopsy, no following MRI, no information on level of immuno suppression, no adequate work up to rule out opportunistic infections. For details, se Appendix 9.4.1.
2201E1 (OL extension, ongoing)					
029-00007* 003-00016	55 F 35 F	FTY 5 FTY 1.25	- E638	Ovarian adenocarcinoma Road traffic accident	Cancer diagnosed 5 months after stopping drug. Died 3 years after stopping drug. Unlikely to be drug related but the role of fingolimod can not be ruled out. Not drug related.
Deaths reported after original submission.					
1201E-0005-00001	42 M	FTY 0.5	Died 1 year after last dose but brain mass dx during therapy	Malignant B-cell lymphoma of brain Lymphoproliferative disorder in multiple organs Skin T cell lymphoma	MS diagnosed 4 ½ years prior to entry. He received fingolimod 0.5 mg/day for 7 ½ months. At the 6-month core study evaluation he was found to have new brain lesions consistent with MS relapse. He was treated with pulse steroids without improvement. He discontinued drug 2 ½ months into the study extension and received a total of 7 IV steroid pulses over 2 ½ months followed by oral steroids. He was admitted to the hospital with aspiration pneumonia. CT scans showed multiple lung and kidney tumors along with enlarged lymph nodes and hepatosplenomegaly. Brain MRI showed multiple ring enhancing lesions, consistent with metastatic disease of unknown primary or a malignant lymphoma. A kidney biopsy was consistent with renal cell cancer or EBV-related lymphoproliferative disease. The biopsy of a skin rash showed T cell lymphoma. He died approximately one year after study drug discontinuation. The autopsy

					confirmed Epstein Barr virus related Diffuse B cell non Hodgkin lymphoma of the brain and lymphoproliferative disease of other organs. For details, see Appendix 9.4.1.
2309 0507 00028	55 F	blinded	2 months after drug dc	Dissecting aortic aneurism	As per IND safety report, 7 months into study treatment, a routine mammogram showed 10 nodules in her left breast. A sonogram showed they were benign. No surgery was done. She stopped blinded treatment. Two months after drug dc she went to the ER after using methamphetamines and having a seizure. She had back and abdominal pain and hypotension. A CT scan showed thoracic and abdominal dissecting aneurysm. She was DNR. Concomitant conditions included hyperlipide mia, HTN, LVH, mitral, aortic and tricuspid valve incompetence (recorded as ongoing and trivial), tobacco and drug abuse. Treatment is blinded.

Source: Narratives and CRFs. Additionally, two deaths occurred during the screening period before receiving study drug (sudden death [ID# 1201 106 00005], and suicide [2306 461-00006]). EDSS= Expanded Disability Status Scale. For details about these cases see Appendix 9.4.1.

Reviewer's comment:

Given fingolimod's pharmacologic effects (decrease circulation of peripheral lymphocyes), some degree of immunosuppression is not unexpected. However, the fact that two patients died due to herpes infections in this database is of concern (subject 2302-0212-00021, disseminated varicella zoster infection and subject 2302-0821-00007, herpes simplex encephalitis). Both patients were young (23 and 29 years), were taking fingolimod 1.25 mg/day and had received a short course of high dose iv steroids for empiric treatment of MS relapses before they developed these fatal herpes infections. Both were IgG negative, indicating that they had no prior exposure to these viruses. Of note, a clinical pharmacology study that evaluated the antibody response to neoantigen immunogenicity showed that patients taking fingolimod 1.25 had decreased ability to mount an antibody response to newly exposed antigens. Lymphocyte levels are not available at the time of the fatal infection. Subsequently to these cases, the applicant appropriately modified the protocols to include IgG antibody testing for several viral infections and included specific guidance to investigators regarding procedures in case of a viral infection. Physicians and patients need to be aware of the risk of serious viral infections associated with fingolimod use. The applicant has proposed to address this issue with a Risk Evaluation and Mitigation Strategy (REMS).

Differential diagnoses for the cases of ADEM (2302-0254-00011) and rapidly deteriorating MS (2306-362-00005) include CNS opportunistic infections. In one case, extensive work up was done and an infection was not identified (however, PML is not completely ruled out). In the second case, there was worsening of the neurologic condition

without any assessments to rule out causes other than MS progression. Both cases were complicated by fatal respiratory infections. No data on lymphocyte counts are available at the time of the deaths.

Patient 1201E-0005-00001 originally presented with a brain mass. It is unclear if at that time of identification of the initial brain lesion a complete work up to identify lymphoma (or other malignancy) in other parts of the body was conducted. A follow up report for this case was submitted to the FDA on June 9, 2010. The autopsy confirmed a Diffuse B-cell lymphoma of the brain (Epstein-Barr virus associated), accompanying "non Methotrexate-associated iatrogenic immunodeficiency associated lymphoproliferative disorder" of lung, kidney, thyroid and jejunum and T cell lymphoma of the skin. This case is of concern, because fingolimod was discontinued, but the lymphoproliferative process did not revert. Methotrexate associated immunodeficiency is usually reversible. The applicant proposes to evaluate the possibility of an increased risk of malignancies with fingolimod in the postmarketing setting. This approach is acceptable.

7.3.2 Nonfatal Serious Adverse Events (SAE)

SAE in Safety pool D, which includes all controlled studies (6 months to 2 years data) occurred in 8.5%, 10.6 %, 8.5%, 11.9 % and 5.8% of patients in the FTY 5, FTY 1.25, FTY 0.5 mg, placebo and interferon groups, respectively. The most common SAEs were in Cardiac disorders, Infections and infestations and Nervous system disorders SOCs, with evidence of a dose response among fingolimod doses for these events.

The number of patients with SAEs in at least 2 patients in any treatment group or fatal, in the controlled studies are presented in the following table.

Table 13. Patients with SAE in at least 2 patients in any treatment group or fatal up to 90 days after last dose, safety pool D.

Primary system organ class Preferred term	FTY 1.25 (N=943) n (%)	FTY 0.5 (N=854) n (%)	Placebo (N=511) n (%)	INF (N=431) n (%)
Any primary system organ class	**100 (10.6)**	**73 (8.5)**	**61 (11.9)**	**25 (5.8)**
Cardiac disorders	**23 (2.4)**	**10 (1.2)**	**4 (0.8)**	**1 (0.2)**
Bradycardia	11 (1.2)	5 (0.6)	1 (0.2)	0
Atrioventricular block first degree	4 (0.4)	1 (0.1)	0	0
Atrioventricular block second degree	4 (0.4)	1 (0.1)	1 (0.2)	0
Sinus bradycardia	2 (0.2)	1 (0.1)	0	0
Supraventricular extrasystoles	2 (0.2)	1 (0.1)	0	0
Nervous system disorders	**18 (1.9)**	**12 (1.4)**	**5 (1.0)**	**3 (0.7)**
Multiple sclerosis/ Multiple sclerosis relapse	3 (0.3)	5 (0.5)	2 (0.4)	1 (0.2)
Epilepsy	2 (0.2)	0	0	0
Grand mal convulsion	2 (0.2)	0	0	0
Headache	2 (0.2)	0	0	0
Infections and infestations	**18 (1.9)**	**8(0.9)**	**8 (1.6)**	**6 (1.4)**

Primary system organ class Preferred term	FTY 1.25 (N=943) n (%)	FTY 0.5 (N=854) n (%)	Placebo (N=511) n (%)	INF (N=431) n (%)
Appendicitis	2 (0.2)	0	0	2 (0.5)
Herpes zoster disseminated*	1 (0.1)	0	0	0
Herpes simplex encephalitis*	1 (0.1)	0	0	0
Respiratory infection*	1 (0.1)	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**9 (1.0)**	**14 (1.6)**	**12 (2.3)**	**2 (0.5)**
Basal cell carcinoma	3 (0.3)	6 (0.7)	2 (0.4)	0
Breast cancer	3 (0.3)	1 (0.1)	3 (0.6)	0
Malignant melanoma	1 (0.1)	3 (0.3)	1 (0.2)	0
Uterine leiomyoma	0	2 (0.2)	0	0
Investigations	**9 (1.0)**	**6 (0.7)**	**1 (0.2)**	**1 (0.2)**
ALT increased	2 (0.2)	1 (0.1)	0	0
Hepatic enzyme increased	2 (0.2)	1 (0.1)	0	0
Liver function test abnormal	2 (02)	0	1 (0.2)	0
Gastrointestinal disorders	**8 (0.8)**	**4 (0.5)**	**4 (0.8)**	**3 (0.7)**
Constipation	2 (0.2)	0	1 (0.2)	0
Eye disorders	**7 (0.7)**	**2 (0.2)**	**1 (0.2)**	**0**
Macular oedema	4 (0.4)	1 (0.1)	0	0
Musculoskeletal and connective tissue disorders	**6 (0.6)**	**3 (0.4)**	**4 (0.8)**	**1 (0.2)**
Back pain	0	2 (0.2)	1 (0.2)	0
Intervertebral disc protrusion	0	0	2 (0.4)	0
Respiratory, thoracic and mediastinal disorders	**6(0.6)**	**3(0.4)**	**3 (0.6)**	**1 (0.2)**
Dyspnoea	2 (0.2)	0	0	0
Pleurisy	2 (0.2)	0	0	0
Pulmonary embolism	0	0	1 (0.2)	0
General disorders and administration site conditions	**5 (0.5)**	**5 (0.5)**	**2 (0.4)**	**2 (0.5)**
Chest pain	1 (0.1)	2 (0.2)	0	0
Psychiatric disorders	**4 (0.4)**	**1 (0.1)**	**4 (0.8)**	**0**
Depression	2 (0.2)	0	0	0
Suicide*	1 (0.1)	0	0	0
Vascular disorders	**3 (0.3)**	**1 (0.1)**	**2 (0.4)**	**0**
Arterial occlusive disease	2 (0.2)	0	0	0
Blood and lymphatic system disorders	**3 (0.3)**	**1 (0.1)**	**0**	**0**
Lymphopenia	3 (03)	0	0	0
Renal and urinary disorders	**1 (0.1)**	**2 (0.2)**	**1 (0.2)**	**1 (0.2)**
Nephrolithiasis	1 (0.1)	2 (0.2)	0	1 (0.2)
Hepatobiliary disorders	**2 (0.2)**	**4 (0.5)**	**1 (0.2)**	**1 (0.2)**
Injury, poisoning and procedural complications	**1 (0.1)**	**5 (0.6)**	**5 (1.2)**	**5 (1.2)**
Pregnancy, puerperium and perinatal conditions	**0**	**0**	**4 (0.8)**	**1 (0.2)**
Abortion	0	0	3 (0.6)	1 (0.2)
Traffic accident*	0	0	1 (0.2)	0

Source: Post text Table 4.4-9 of ISS. Safety Pool D includes all placebo-controlled studies in ISS (2201, 2301 and 2302). Cut-off: 90 days after drug discontinuation. A patient with multiple SAEs within a primary SOC is counted only once in the total row. A patient with multiple occurrences of an AE under one treatment group is counted only once in the AE preferred term for that treatment group. *Fatal SAE.

In general, evaluation of SAE in Safety Pool E, which includes the open label extensions for studies 2201 and 2301, were consistent with those in the controlled studies.

> *Fingolimod has a prolonged half life of 6-9 days. All AE were collected up to 45 days after drug discontinuation and SAE were collected by protocol up to 3 months after drug discontinuation. At the FDA request the applicant submitted analyses of all SAEs for the entire observation period beyond 3 months after drug discontinuation. However there were very few additional SAEs because reporting was not mandatory.*

The following tables present patients with SAE in safety pools D and E for selected MedDRA System Organ Classes (SOCs) (those in which the rate of SAE was higher in any fingolimod group than placebo, or for events of special interest, e.g. malignancies). In these tables, a patient with multiple occurrences of the same AE under one treatment is counted only once in the AE preferred term for that treatment. A patient with different adverse events within a primary system organ class is counted only once in the total row. For some events (e.g. infections & malignancies), the rate of events (n events/patient years) are also presented.

- Cardiac related SAEs

The most common SAEs in the Cardiac disorders SOC were bradycardia and AV block. There was evidence of a dose response for the three fingolimod doses and higher risk of bradycardia and AV block on fingolimod as compared to placebo and IFN.

Table 14. Serious AE, Cardiac SOC, pool D

Primary system organ class Preferred term	FTY720 5 mg (N=94) n (%)	FTY720 1.25 mg (N=943) n (%)	FTY720 0.5 mg (N=854) n (%)	Placebo (N=511) n (%)	Interferon (N=431) n (%)
Cardiac disorders					
-Total	3 (3.2)	23 (2.4)	10 (1.2)	4 (0.8)	1 (0.2)
Bradycardia	3 (3.2)	11 (1.2)	5 (0.6)	1 (0.2)	0 (0.0)
Atrioventricular block first degree	0 (0.0)	4 (0.4)	1 (0.1)	0 (0.0)	0 (0.0)
Atrioventricular block second degree	0 (0.0)	4 (0.4)	1 (0.1)	1 (0.2)	0 (0.0)
Sinus bradycardia	0 (0.0)	2 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)
Supraventricular extrasystoles	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Angina pectoris	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)
Arrhythmia	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Palpitations	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)
Pericarditis	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Sinus tachycardia	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Ventricular extrasystoles	1 (1.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Angina unstable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Extrasystoles	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Left ventricular dysfunction	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Tachycardia paroxysmal	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Ventricular tachycardia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

Source: Post Table 4.4-9, ISS. All three placebo controlled studies. N= randomized. n= patients with events. A patient with multiple occurrences of the same AE under one treatment is counted only once in the AE preferred term

for that treatment. A patient with different adverse events within a primary system organ class is counted only once in the total row.

The most common SAE in the Cardiac SOC was bradycardia and atrioventricular block.

Table 15. Patients with SAEs, Cardiac disorder SOC, safety pool E

Primary system organ class Preferred term	FTY720 5 mg - 1.25 mg (N=137) n (%)	FTY720 1.25 mg (N=1157) n (%)	FTY720 0.5 mg (N=1021) n (%)
Cardiac disorders			
-Total	4 (2.9)	29 (2.5)	11 (1.1)
Bradycardia	3 (2.2)	15 (1.3)	6 (0.6)
Atrioventricular block second degree	0 (0.0)	6 (0.5)	1 (0.1)
Atrioventricular block first degree	0 (0.0)	4 (0.3)	1 (0.1)
Palpitations	1 (0.7)	2 (0.2)	0 (0.0)
Sinus bradycardia	0 (0.0)	2 (0.2)	1 (0.1)
Supraventricular extrasystoles	0 (0.0)	2 (0.2)	0 (0.0)
Angina pectoris	0 (0.0)	1 (0.1)	1 (0.1)
Arrhythmia	0 (0.0)	1 (0.1)	0 (0.0)
Atrioventricular block complete	0 (0.0)	1 (0.1)	0 (0.0)
Extrasystoles	1 (0.7)	1 (0.1)	0 (0.0)
Hypertensive heart disease	0 (0.0)	1 (0.1)	0 (0.0)
Pericarditis	0 (0.0)	1 (0.1)	0 (0.0)
Sinus tachycardia	0 (0.0)	1 (0.1)	0 (0.0)
Ventricular extrasystoles	1 (0.7)	1 (0.1)	0 (0.0)

Source: Post Table 4.5-12 original ISS. Controlled and open label studies. N= randomized. n=patients with event. A patient with multiple occurrences of the same AE under one treatment is counted only once in the AE preferred term for that treatment. A patient with different adverse events within a primary system organ class is counted only once in the total row.

Of note, pool E includes subjects who received FTY in pool D plus those who received FTY during extensions, after receiving placebo or IFN during the core studies. Several subjects developed bradycardia and AVB upon first fingolimod dose in the extension studies. Findings in pool E in the SUR were consistent with the original application.

- SAE of Bradycardia and Atrio-ventricular block (AV B) events

A summary table of the risk of bradycardia and AV block in safety pool D is presented in the following table:

Table 16. Patients who developed SAE of bradycardia or AV Block, safety pool D

	FTY 5 mg N=94 n (%)	FTY 1.25 mg N=943 n (%)	FTY 0.5 mg N=854 n (%)	IFN N=431 n (%)	Placebo[1] N= 511 n (%)
Any event	3 (3.0)	22 (2.3)	7 (0.8)	0	2 (0.4)
Led to drug dc	2 (2.0)[2]	9 (1.0)[3]	1 (0.1)[4]		1 (0.2)
Bradycardia	3 (3.0)	15 (1.6)	6 (0.7)	-	1 (0.2)
dc	2	5	-		1
AV B 1st degree	-	4 (0.4)	1 (0.1)	-	-
dc		2	-		
AV B 2nd degree	-	4 (0.4)	1 (0.1)	-	1 (0.2)
dc		3	1		-

Source: FDA analysis of AE datasets and narratives. dc= drug discontinuation. [1] Events on placebo were not upon first dose; bradycardia occurred on Day 121;AV B occurred on Day 684 (patient had prior episodes of first and second AVB and had sick sinus syndrome). All cases of AV Block in FTY occurred upon first dose. [2] One with bigiminism; one with chest pain. [3] One recurrent brady+ dyspnea on re-dosing; 3 associated with chest pain/pressure/discomfort. [4] Recurrent event upon re-dosing 70 days after the first dose; not listed as leading to drug discontinuation, but patient withdrew consent after second event. For details see Appendix 9.1.2.

Of note, bradycardia and AV block upon first dose was observed only in the fingolimod treated groups. The cases on placebo occurred several months into the study.

In addition to these cases, one subject presented a SAE of supraventricular extrasystoles on Day 1 (2301 0707 00049) and one presented sinus tachycardia, supraventricular extrasystoles and extrasystoles on Day 344, associated with hyperventilation (2302 0307 00001) in the FTY 1.25 mg group; and one presented tachycardia paroxysmal (2301 0707 00001) in the FTY 0.5 mg group on Day 1. None of them led to study drug discontinuation.

Brief narratives of patients with SAEs in the Cardiac disorders SOC, related to rhythm and conduction disorders in the original ISS for FTY 0.5 mg are summarized as follows.

Brief narratives of SAE in Cardiac SOC, rhythm and conduction disorders, for FTY 0.5 mg group.

Controlled studies					
Patient ID	**Age /sex**	**Preferred term**	**Rel Study day**		**Comment**
2302 0207_00001	49 F	Sinus bradycardia AVB 1st degree AVB 2nd degree AVB 2nd degree	1 1 1 (re dosing)	- - dc	No CV history. Smoker. PR at screening was 209 msec. Sitting pulse 76 bpm. On Day 1, monitor showed sinus bradycardia 3 hours post dose. Lowest HR= 46 bpm. She was hospitalized. ECG showed sinus bradycardia and 2nd degree AVB (Mobitz 1) and 1st degree AVB with occasional supraventricular premature complexes. PR ranged from 188 to 237 msec. She was treated with isoproterenol. Study drug was temporarily interrupted The AE resolved on Day 2 (lasted 21 hours). A Holter ECG on Day 11 showed increased PR interval, supraventricular arrhythmias and 2nd degree AVB. When restarted on Day 71, HR 4 hrs post dose was 36 bpm and 6 hrs post dose was 52. The patient was monitored again on Day 73 and also showed drop in pulse as low as 38 bpm 4 hrs post dose. The patient withdrew her informed consent on Day 76. *(As per patient profile re-dosing was on day 70, pre dose she had first degree AVB [PR 230 msec]. After the second re-dose, ECG 6 hours post dose showed 2nd degree AVB (Mobitz I)*
2302 0252_00009	28 F	AVB first degree	1	-	No CV history. Non smoker. On day 1, pt experienced dizziness, nausea and palpitations 6 hrs after first dosing. ECG showed 1st degree AVB. HR was 42 bpm and BP was 130/90. She was hospitalized but no treatment was given. Maximum PR interval measured was approx. 260 msec. Event resolved the following day. No action taken with study drug.
2301 0109_00002	41 F	Bradycardia	1	-	No CV history or risk factors, but active smoker 1pack/day x 27 years. On day 1, HR noted to be below 80% of baseline. The lowest HR was 66 bpm 6 hours after the first dose. Asymptomatic. ECG showed no other changes.
2301 0404_00004	20 F	Bradycardia	1	-	No CV MHx. On day one: 3 hrs & 5 hrs after first dose HR 60 pm. Asymptomatic. ECG no other changes. No further events with second dose. No action taken with drug.
2301 0707_00002	40 M	Bradycardia	1	-	No history of heart disease. Non-smoker. Baseline HR= 76 bpm; 5 hours after first dose HR= 56-60 bpm. Lowest HR =55 bpm. Asymptomatic. At 10pm HR= 80 bpm. Event resolved without intervention.
2301 0903_00005	45 M	Bradycardia	1	-	No history of heart disease. Non-smoker. Baseline HR= 57 bpm. Six hours after first dose HR= 43 bpm, associated with non-specific chest pain. ECG HR 45 bpm, no other changes; chest xray and cardiac enzymes normal. BP= 132/77. He recovered without specific treatment the following day.

2302 0904_00006	52 M	Bradycardia	1	-	No CV history. On Day 1, 4 hrs after first dose, developed severe bradycardia and was hospitalized. No action taken with study drug. No other meds were given. Pt recovered completely the same day. Drug not discontinued.
2301 0707_00001	52 F	Tachycardia paroxysmal	1	-	No significant medical history other than MS. On Day 1 ECG post dose showed changes in V2 (intraventricular conduction disturbances). She was hospitalized. Echocardiography was normal. At 6 hours, ECG showed a "different" QRS morphology in V2. She was asymptomatic. The following day, morphology was normal. She was discharged and continued in the trial.
Extension studies					
2302E_ 0252_00002	42 F	Bradycardia	1	dc	Received IFN during core. HR down to 36 bpm 4 hours after 1st dose. Received atropine. Discharged the following day. Discontinued from study on Day 118 due to lack of efficacy.

Source: original AE datasets submitted 12/18/09. Narratives (12/18/09) & patient profiles (2/16/10). Rel study day: relative day of study at onset of study day. Rel day FTY: relative day on fingolimod treatment during extension study. DC: drug discontinuation Y= yes; N= no.

Narratives of SAE related to rhythm and conduction disorders for placebo (1 bradycardia, one 2nd degree AV block) and FTY 1.25 (15 bradycardia, four 1st degree and four 2nd degree AV block) are presented in Appendix 9.4.2.

Five additional cases of bradycardia and/or atrioventricular block (AVB) upon first fingolimod dosing were reported in the extension studies in the original ISS with FTY 1.25, including a case of 3rd degree AVB.

The case of 3rd degree AV block upon first FTY 1.25 dose in the extension studies is as follows

- **2302E 0141_00004**. 39 F. AVB 3rd degree with loss of consciousness on Day 1 of FTY 1.25 therapy. She received IFN during core study. No cardiovascular history. Non smoker. Concomitant meds included oral contraceptive, magnesium-vitamin B. On Day 372, extension day 1, 2 hrs after first dose the patient had no complaints but her pulse went from 74 at baseline to 50 bpm, irregular. An ECG showed 1st degree AVB, 59 bmp. One minute later, an ECG showed 2nd degree AVB type I (Wenckebach) with a heart rate of 55 bpm. No meds were given. Approx. 3 hours after the first dose the patient complained that she was not feeling well and reported having strange dreams. She lost consciousness. A heart monitor showed 3rd degree AVB which lasted 30 seconds, followed by an escape rhythm for 19 seconds. She recovered spontaneously and hear rate returned to the 40's. Heart monitoring showed irregular rhythm with 2nd degree AV B type II. BP was low. Atropine 0.125 mg was given because of low heart rate. She was transferred to ICU. 11 hours post dose, monitor showed 2nd degree AVB type I. Few minutes later she was in sinus rhythm. Drug was discontinued. An echo showed mild mitral valve insufficiency that was not considered to be significant. The drug was discontinued (she only received one dose). The patient recovered completely and was discharged home one day after the event.

Review of the available narratives of bradycardia and AVB during core and extension studies indicates that all adverse events of bradycardia or AV block in the fingolimod groups had an onset within the first 6 hours after first dosing and resolved within 24 hours. Most cases were not medically severe and required overnight hospitalization by protocol. However, not all events were benign.

- In the controlled studies, almost half of patients with bradycardia or AV B discontinued after the event in the FTY 1.25 mg dose group. No patient discontinued upon first dose from the FTY 0.5 mg group.

- Several patients had recurrent bradycardia/AV B upon first re-dosing, leading to study drug discontinuation. One patient had recurrent bradycardia and dyspnea upon first re-dosing on Day 11 (2301_0176_00001; another patient developed bradycardia upon first dose, and recurrent bradycardia with chest pain and pressure on Day 4 (2201_0025_00016). One event led to study drug discontinuation from the FTY 0.5 mg dose group (patient 2302 0207_00001 withdraw her consent when the event recurred upon first re-dosing).

- One subject developed AVB upon first dose, and chest pain/pressure on Day 16, apparently without having stopped medication after the first event (2301 0651 00016 on FTY 1.25). This second event led to drug discontinuation.

- Some events required specific treatment (at least four patients received atropine (3 on FTY 1.25 mg, one on FTY0.5) and one received isoproterenol (2301 0101 00003 on FTY 0.5mg).

- One subject on FTY 5 mg (a dose 10-fold the proposed dose for marketing) (2201 0066 00006) woke up with chest pain/pressure 10 hours after first FTY dose. 4 hours post dose she had a pulse of 54 bpm with no change in BP. She went home after 6 hour observation, with a Holter monitor. The Holter recording showed a HR of 34 bpm, right before the episode of chest pain. Some subjects on FTY 1.25 who were hospitalized for observation, presented the lowest heart rate 10 hours after the first dose (2301 0612_00002, 2302 0361_00013) and 13 hours after the first dose (2301 0101_00003).

- One case of 3rd degree AV B occurred in a 39 year old female receiving FTY 1.25 mg during the extension period (she received IFN in the core study [2302 0141_00004]) and one case of AVB 2nd degree with competing junctional rhythm (which technically could not be interpreted as 3rd degree AV B) occurred in a 26 year old female upon first FTY 1.5 mg in the extension (she had received placebo during core study [2301E 0707 00055]).

> *The applicant proposes some labeling to address the risk of bradycardia and proposes 6 hours observation for those on beta blockers and low baseline HR. Of note, these events were pretty well tolerated but the population in this NDA is very selected and excluded patients with diabetes and prior history of arrhythmias. Very few patients in the NDA were taking beta blockers. No patient*

was taking calcium channel blockers or other antiarrhythmics. Very few had a history of CHF or coronary artery disease. Some had underlying first degree AV block (by ECG) at screening, but no patient had second decree AV block or higher. Subjects with pre-existing cardiovascular disease will not tolerate bradycardia and AV block as well as these patients with healthy hearts.

These data were discussed at the FDA Peripheral and Central nervous system Advisory Committee meeting of June 10, 2010. The committee recommended that rather than monitoring only patients who fulfilled exclusion criteria for CV disease, all patients should be monitored in the office for at least 6 hours, for symptomatic bradycardia. Also some members supported obtaining an ECG before starting therapy with fingolimod in all patients.

- SAE of Ischemic heart disease in controlled studies

Six serious events of ischemic heart disease (2 MI on placebo, 1 angina unstable on IFN, 1 angina pectoris on FTY 1.25, and two on FTY 0.5mg) were identified in the controlled population during treatment and up to 90 days after study drug dc. Of note, all cases in FTY were female, while the cases on placebo and IFN were male.

One additional non serious AE of myocardial ischemia occurred in the FTY 0.5 mg dose 15 days after discontinuation of FTY1.25 mg due to "lung disorder" and two subjects receiving FTY had angina pectoris that was not coded as serious but nonetheless led to drug discontinuation in the controlled studies (described under AE leading to drug discontinuation). Additionally, several subjects presented events of angina pectoris that were not considered serious (from the regulatory point of view) and did not lead to study discontinuation. These cases are discussed under "Other significant AEs"

Brief narratives of SAE of ischemic heart disease in controlled studies are summarized in Appendix 9.4.3.

The applicant proposes to explore the potential for increased risk of myocardial infarction (among other safety issues) in a post-authorization safety study (PASS) in patients with MS under conditions of routine clinical care.

In addition to these cases, there was a serious AE of unexplained lung edema in which the possibility of myocardial ischemia was considered, but the case was confounded by exposure to alternative medicine (snake venom) and to varnish prior to the event. The narrative of the case of lung edema is as follows:

- **2301 0408_00009** – Left ventricular dysfunction and pulmonary edema, myocardial ischemia?

  This 21 year old female with MS was randomized to fingolimod 0.5 mg/day. She had no history of CV disease and did not smoke. She was taking oral contraceptive. Two days prior to hospital admission she had received an intramuscular injection of an alternative medicine therapy (Horvi-Crotalus-Reintoxin forte –containing snake venom) for MS. On **Day 8** of study she felt unwell. She had dyspnea and abundant secretions of upper respiratory tract. Oxigen saturation was 88%. Initial

suspicion was pulmonary edeman or pneumonia. Admitted to hospital: HR 100 bpm, BP 85/45, O2 saturation 74%. Chest X-ray: bilateral infiltrates compatible with pulmonary edema. Empirical treatment with ceftriaxone and erythromycin for possible pneumonia. Labs showed CK-MB elevation (17 U/L, normal 0-6 U/L). troponin positive. WBC: 22,000 per mm^3. ECG: ST elevation in anterior leads. Echocardiography in ICU: akinesia in septum and apical areas. Initial diagnosis anterior MI and pulmonary edema. Patient intubated and received IV dobutamine. Coronary angiograpy showed normal coronary arteries. LVEF 48%. Unclear abnormalities of the LV wall movement. Pressure values:
Pulmonary artery: Systolic=40/Diastolic=14/median=29 (after contrast media)
Aortic arch: Systolic=118/Diastolic=73/median=91(after contrast media)
LV: Systolic=131/End diastolic=37 (at rest)
LV: Systolic=132/End diastolic=35 (after contrast media)
Repeat ECG showed no abnormalities.
Day 9: febrile, stable vital signs on dobutamine and mechanical ventilation. WBC 16,800 mm^3, lymphocytes 200 mm^3. CK 1819/ MB 20 UI/L. Imipenem added. Study drug discontinued. On Day 10 patient was extubated and hemodynamically stable. Chest x-ray showed bilateral consolidation and possible pleural effusion. Culture of bronchial secretions obtained by bronchoscopy showed β-hemolytic Streptococcus type C with evidence of inflammatory cells. Cultures from the patient's mouth, central catheter and vaginal smear revealed a yeast-like fungi. On Day 16 she was improved and ambulatory, and was transferred to the Dept. of Neurology at the investigator's site. On Day 19 chest and abdominal CT were normal. Echocardiogram was normal. Physical exam was normal. MRI of brain showed new T2 enhancing lesion in the brainstem. The patient completely recovered for pulmonary edema, temporary ventricular dysfunction on Day 21. The etiology of the pulmonary edema remains unclear. Further diagnostic work-up, including evaluation by a pulmonologist and a cardiologist at the investigational site were done. Investigator suspected relationship with study drug.

In response to an FDA request for clarification, the sponsor submitted the following follow up information on 3/4/10:

The consultant cardiologist reviewed the original angiography and confirmed that the patient had had temporarily reduced left ventricular function but "could not find any evidence for Takotsubo cardiomyopathy." Myocardial infarction was also excluded. He reported that although left ventricular function was reduced, that reduction did not appear enough to have induced the pulmonary edema. In his opinion, the pulmonary edema may possibly have been stress induced temporary myocardial ischemia. The final etiology of the pulmonary edema was considered to be either toxic due to exposure to varnish (the day before the event the patient had been varnishing the whole day with a product containing 2-Butanonxin, a toxin known to have the potential to initiate pulmonary edema) or neurogenic due to a new brain stem lesion seen on the brain MRI. Follow up information received confirmed that the patient had completely recovered from the events.

> *This patient presented a complex picture of pulmonary edema and pneumonia 8 days into treatment, with LV dysfunction and elevated CK MB and troponin suggestive of myocardial ischemia. She was lymphopenic (200 mm^3) but had total WBC of 16,800. She required intravenous antibiotics and antifungals, vasopressors and mechanical ventilation. She improved after 2 weeks. A following CT scan and echocardiogram were normal. The patient may have been septic. Relationship to study drug is possible but given the long half life of fingolimod such a rapid recovery would be unexpected. The case is confounded by the use of alternative medicine (snake venom injected during the study 2 days prior to hospitalization) and exposure to varnish.*

- Serious cardiac-related SAE in the Investigations SOC in controlled studies

Cardiac related serious AE in the Investigations SOC in the controlled studies included 4 cases of ECG change on Day 1 (one case on FTY 1.25 mg (PR prolongation) and 3 on FTY 0.5 mg (including one ECG change (unspecified); one QT prolongation; and one ECG ST segment elevation). None of the cases led to study drug discontinuation. The case of ST segment elevation is as follows.

- **2302_0535_00002.** 39 M – ECG ST segment elevation Day 1. As per pt profile, the patient had hypertension but no other cardiac history. ST elevation was noted 6 hours post FTY 0.5 mg dose and lasted 3 days. Pre-dose pulse 90 bpm. Post dose there was bradycardia with mild dizziness. 24 hour Holter showed bradycardia with lowest HR 43 bmp 19 hours post dose. No cardiac enzymes provided. Drug interrupted. Patient started on low dose aspirin (for MI prophylaxis) and lisinopril (for hypertension). Drug re-started 13 days later. No report of AE with second dose. Subject discontinued study due to administrative problems on Day 191 (patient moved out of state). *This appears to be an episode of ischemia upon first dose fingolimod, although no further symptoms were reported.*

- SAE of Chest pain in controlled studies

In addition to the cases coded as angina or ischemic heart disease in the Cardiac disorders SOC, several events of "chest pain" and "non-cardiac chest pain" are described under the General disorders and administration site conditions SOC. Some of these cases appear to have had insufficient work-up to rule out a cardiac cause.

- Additional SAEs of interest in the Cardiac disorders SOC

The following case occurred in the controlled studies:

- **2301 0601_00012.** Pericarditis, pleuritis, pneumonitis and liver enzyme elevation

  24 year old female with MS randomized to FTY 1.25 mg in study 2301. No CV history. OCD treated with paroxetine. Non-smoker. On Day 65: chest pain, dyspnea, nausea/vomiting. Echocardiogram showed pericarditis. CT scan showed pleuritis and mild pneumonic infiltration. Drug was stopped on Day 69.

  On Day 71, WBC was 2.8 (nl 3.5 – 10.9 E9/L), absolute lymphocyte count was 0.28 (nl 0.8 to 2.8 E9/L); neutrophil count was 2.1 (nl 2.1 – 7.8 E9/L); ALT= 122 U/L (nl up to 40), Alk Phosphatase 446 U/L (nl up to 125), BR was 24 umol/L (nl 2-21). She was treated with clindamycin and improved. AutoAB panel was negative; Viral panel negative except for EBV-VCA IgG and Parvovirus IgG. This was considered by the investigator to be a likely a viral infection but the agent could not be identified. A per the patient profile, viral titers done 1 ½ years after the event, showed high IGG for HSV, Arbovirus and VZV, which indicate past infection. Relationship to study drug was suspected. By Day 77, liver enzymes had decreased and were close to normal. First available normal lymphocyte count was on Day 150, approximately 80 days after drug discontinuation. Liver enzymes were normal. There were no major changes on Hgb, hematocrit, platelet counts, neutrophil and monocyte counts. Two follow up HRCTs (Date not provided) showed mild-moderate pericardial fluid and left posterobasal pleural thickening

respectively. There were no changes in PFT's. A subsequent HRCT, done approximately 1 month later, was normal.

This is a case of pericarditis, pleuritis and possible pneumonic infiltrate on Day 65 of FTY 1.25 treatment, associated with transient increase in liver enzymes. Hepatitis serology was negative. Potential viral agent causing the event was not identified. I agree that this was likely a viral infection. A differential diagnosis could be some form of vasculitis, however, an autoantibody panel is said to have been negative.

- The following SAE occurred in extension studies:

  - **2201E1_0049_00001** Hypertensive heart disease

44 F. No CV history. Received 1.25 mg during core. She developed epigastric pain and worsening anemia on Day 182. Developed leg swelling on Day 1329 (1508 of FTY treatment); HTN diagnosed on Day 1471. Drug discontinued because of HTN heart disease.

- The following occurred in the ongoing blinded studies not included in the ISS.

- **1201-0019-00005 -** Transient inverted T wave and LV dysfunction ("Suspicious Takotsubo [stress] cardiomyopathy)

51 year old, Japanese female, receiving blinded treatment in study 1201. Event suspected to be related to study drug and led to study discontinuation. She was diagnosed with MS approximately 1 year prior to study entry, and received INF treatment up to 5 months before entering this study. Medical history included anxiety. The patient was receiving concomitant medications for constipation and allergic rhinitis.

Three months into the study she was hospitalized with eye pain and double vision, and was diagnosed with MS relapse. At that time an ECG showed negative T-waves in all precordial leads. Echocardiography revealed apex hypomotility from the papillary muscle level to apex area. The patient had no associated clinical symptoms. Creatine phosphokinase (CPK) and creatine kinase myocardial band (CPK-MB) was normal. Takotsubo cardiomyopathy, ischemic heart disease, myocarditis and drug-induced myocardial disorder were suspected, the study medication was permanently discontinued. The patient was transferred to another hospital to receive a detailed check-up by a cardiovascular specialist.

Four days later, the cardiologist did not detect any abnormality on ECG and did not find significant constriction on cardiac catheter test. The cardiologist suspected that there had been Tako-tsubo cardiomyopathy, although he did not diagnose the cardiomyopathy definitely. The patient completely recovered. The investigator did not exclude the possibility of a causal relationship between this event and this investigational drug, since ECG before starting the study medication was normal.

51 yo woman with no cardiovascular history, admitted for MS relapse, incidentally found to have inverted T waves in all ECG leads, associated with apex hypomotility on echocardiogram. The patient was asymptomatic. Drug was discontinued. Four days later, repeated tests were normal. The cause of the transient LV dysfunction remains unclear but the role of FTY in the development of transient ischemia and cardiac dysfunction can not be ruled out.

- 2309-0585-00008 – Papillary muscle disorder

A 53 year old, male (0585/00008) diagnosed with MS 8 years prior to entry. The patient's medical history included bladder spasm hypercholesterolaemia, and he was an active smoker for 27 years. Concomitant medication taken prior to randomization included modafinil sildenafil, and pregabalin. The patient had no cardiac co-morbidities or history, and was not receiving any cardiovascular comedications.

On Day 113 of blinded treatment an abnormal Holter revealed non-sustained ventricular tachycardia (3-10 beats, 1 episode) which was a change from the baseline Holter. An echocardiogram was abnormal and the conclusion was: lesion in left ventricle hyperechoic and close to septum (can't rule out possible left ventricular lymphoma, possible prominent papillary muscle). The investigator described this event as 'tumor on heart'. The investigator assessed this event as life threatening and medically significant, and the study medication was temporarily interrupted pending outcome of the event.

On Day 122, the patient underwent a non-scheduled Transoesophaeal echocardiogram (TEE) which revealed a prominent papillary muscle in the left ventricle, mild mitral valve prolapse with mild mitral regurgitation and mild aortic atherosclerosis. The patient was subsequently 'cleared to resume study drug' and an unscheduled visit was to be arranged with the patient to resume study drug.

The investigator confirmed that there was no tumor but a prominent papillary muscle in the left ventricle and this was considered a 'variant of normal'. LV myxoma was ruled out. The investigator considered that non-sustained ventricular tachycardia, mixomatous mitral valve prolapse (mild) with mild regurgitation, and mild aortic atherosclerosis were all non-serious events. The study medication was re-started Day 141. The patient did not receive any treatment for this event and was reported to have completely recovered on Day 122.

According to the investigator, the event (papillary muscle disorder) was considered medically significant, and life-threatening. However, the investigator indicated that this event was due to progression of underlying illness and did not suspect a relationship between the event and the study medication. The patient completed the study in January 2010. He discontinued study drug in April 2009 following a diagnosis of asthma and remained in treatment-free follow-up. The patient has not had any signs or symptoms of cardiac disease. No cardiac examinations (echocardiograms, Holter ECG, etc.) were performed outside the study protocol. The site has re-assessed this event as not serious. The final diagnosis was "a prominent papillary muscle in the left ventricle."

It would be interesting to know what the bases for the diagnosis of asthma were, and whether the echocardiogram continued to show prominent papillary muscle but no follow up data are available.

In summary, evaluations of SAE in the cardiac SOC in the controlled studies showed a clear dose response in terms of rhythm and conduction disorders (bradycardia and AVB) in the fingolimod treatment group.

In the controlled studies, the risk of developing SAE of first or second AVB upon first dose with FTY 1.25 was 0.4% and 0.4%, respectively; the risk for FTY 0.5 mg was 0.1% and 0.1%, respectively.

Approximately half of the patients with these events discontinued from the FTY 1.25 mg group, and one discontinued due to 2nd degree AVB from the FTY 0.5 mg group.

There was one case of Complete AVB upon first dose of FTY 1.25 mg in this database (in the extension studies).

There was no imbalance in the number of cases of serious MI or angina in the controlled studies but the numbers are small. Additionally, several cases of angina were coded as non-serious, and it is unclear how the diagnosis of angina was made. Most of these events occurred in young people without prior cardiovascular risks.

Three cases of SAE of LV hypokinesia were reported in this application. Two were thought to be related to transient myocardial ischemia (one during the controlled studies on FTY 0.5 mg, and one in the ongoing blinded studies); and one was confounded by the use of alternative medicine and varnish previous to the event.

One case of pericarditis, pleuritis and increased transaminases (probably viral) occurred in the FTY 0.5 mg group in the controlled studies. Additionally a SAE of prominent papillary muscle occurred in the ongoing study 2309 (he eventually discontinued because of asthma).

- SAEs in the Nervous system disorders SOC

SAES in the Nervous system disorders SOC in Safety pool D are summarized in the following table.

Table 17. SAES in Nervous system disorders SOC, safety pool D.

Primary system organ class Preferred term	FTY720 5 mg (N=94) n (%)	FTY720 1.25 mg (N=943) n (%)	FTY720 0.5 mg (N=854) n (%)	Placebo (N=511) n (%)	Interferon (N=431) n (%)
Nervous system disorders					
-Total	1 (1.1)	18 (1.9)	12 (1.4)	5 (1.0)	3 (0.7)
Multiple sclerosis relapse	0 (0.0)	3 (0.3)	3 (0.4)	2 (0.4)	1 (0.2)
Epilepsy	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Grand mal convulsion	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Central nervous system lesion	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Cerebrovascular accident	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Cervicobrachial syndrome	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Coma	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Dural fistula	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Ischaemic stroke	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Monoparesis	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Neuropathy peripheral	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Paraparesis	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Presyncope	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)
Radicular syndrome	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Spinal cord ischaemia	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Status epilepticus	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Syncope	0 (0.0)	1 (0.1)	1 (0.1)	1 (0.2)	0 (0.0)
Amnesia	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Migraine with aura	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Monoplegia	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Multiple sclerosis	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)
Nerve root lesion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Optic neuritis	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Partial seizures with secondary generalisation	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Reversible posterior leukoencephalopathy syndrome	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sciatica	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)
Somnolence	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

Source: Post Table 4.4-9, ISS. All three placebo controlled studies. A patient with multiple occurrences of the same AE under one treatment is counted only once in the AE preferred term for that treatment. A patient with different adverse events within a primary system organ class is counted only once in the total row.

The most common SAES in this SOC were MS relapse and seizure-related events, followed by terms consistent with MS manifestations. The SAE profile in safety pool E was similar to that in the controlled population (data not shown).

- Seizures

SAE of Seizures in controlled studies

Five subjects presented seizure-related SAE (grand mal convulsion, epilepsy, status epilepticus, partial onset seizure) in the controlled studies (4 on FTY 1.25mg and 1 on FTY 0.5 mg). No SAE of seizures occurred on IFN or placebo. None of these five patients had a previous history of epilepsy.

The SAE of seizure with FTY 0.5 mg in the controlled studies is as follows:

- 2301_0453_00003. 19 M. Recurrent partial seizures with secondary generalization.

The patient had no prior history of seizures. Had 1 relapse in 2 yrs prior and one relapse in the year prior to randomization. Most recent relapse was 6 mo. prior to randomization. Treated with IFN and glatiramer up to 6 months prior to randomization. Hx of optic neuritis. Smoker. On Day 308 of FTY 0.5 mg he had partial seizure with secondary generalization. CT scan showed subarachnoidal bleeding thought to be due to head trauma during seizure. He recovered from the event. On Day 365 MRI showed an active MS lesion very close to the cortex. It was suggested that this lesion could be the cause of the seizure. This was considered an MS relapse and was treated with methylprednisolone. The event did not lead to drug dc. The clinical course was favorable with recurrent partial seizures but no new neurological symptoms.

This case seems to be related to a new MS lesion.

Of the four SAE of seizures on FTY 1.25, one occurred in the patient who died of herpes encephalitis (described under Deaths) and two were thought to be related to MS relapse (2301 0657 00019 and 2302 0253 00003). In the fourth case (2301 0707 00007), the EEG showed "sharp waves of general nature, mostly in posterior regions bilaterally." The latter two cases (2302 0253 00003 and 2301 0707 00007) continued having seizures in the extension studies.

Narratives of the non-fatal cases are as follows.

Brief narratives of patients with serious AE of Seizure

FTY 1.25 mg						
2301_0657_00019	34 F	Epilepsy Epilepsy Epilepsy	45 176 177	Y Y Y	. dc dc	MS dx 10 year prior. No hx of seizures. Most recent relapse 2 months prior to entry, treated with steroids. On day 45 had decreased consciousness and motor abnormalities c/w seizure. EEG showed varying epileptic activity. NO MRI or CT scan done during hospitalization. On Day 176 she had 2 epileptic attacks and developed a fever treated with paracetamol. She was treated with IV methylprednisolone x3 and drug was discontinued. MRI showed active MS lesions. Investigator stated that epileptic attack could be drug related but was probably 2nd to active MS. No additional work up provided for this patient.
2301_0707_00007	43 F	Grand mal convulsion Epilepsy Epilepsy Epilepsy	678 789 789 789	Y N N Y	. . . .	MS dx 8 years prior to entry. No hx of epilepsy. Most recent relapse was 3 months prior to randomiz, treated with steroids. Hx of optic neuritis and HTN. On Day 678 had grand mal Sz with nystagmus, ataxia and left sided hemiparesis. EEG showed "sharp waves of general nature, mostly in posterior regions bilaterally." She was found to have leukocytes & bacteria in urine, and she was treated for UTI. On Day 760 during extension phase she had 3 grand mal seizures. A CT scan showed cortical-subcortical brain and cerebellum atrophy and lesions with symmetric dilatation of the ventricular system and extracerebral fluid space. Also regions of reduced density around lateral ventricles associated with "chronic ischaemic processes" She was started on valproic acid. Final diagnosis was epilepsy and MS. The investigator stated that the reason for the seizure was not known and that there was no evidence to suggest an MS relapse.
2302_0253_00003	34 M	Grand mal convulsion Status epilepticus	33 358	N Y	. .	MS dx 13 years prior. Last relapse prior to random. Was 7months prior, treated with steroids. Patient also received IFN beta 1a in the past. No history of seizures. No concomitant meds. He had two relapses during the study, the second one on Day 118 was associated with generalized tonic clonic seizure and was treated with steroids and carbamazepine. On Day 369 he was hospitalized with status epilepticus. MRI was not done. The cause of status was thought to be non-compliance with his antiepileptic medication. The patient remains in the study.

SAE of Seizures in the extension studies

Four seizure–related AEs were reported in the extension studies. Two in the FTY 5mg-1.25 mg dose group, one in FTY 1.25 and one in FTY 0.5 mg. The narrative case on FTY 0.5 is as follows

- 2301E_0951_00001. 22 M. Epilepsy.

Diagnosed with MS 2 years prior to randomization. Not treated with nay MS disease modifiying drug before randomization. EDSS score was 3. Medical history included optic neuritis, encephalitis, chronic obstructive pulmonary disease (prior to study entry) and amblyopia. Concomitant medications included atorvastatin, bupropion, trazodone and sildenafil. No history of seizures. On Day 765 of FTY 0.5 mg treatment he was hospitalized because four generalized epileptic seizures. Blood tests were reportedly normal. CSF was also normal (lymphocytes 6 (reference range 0-5), glucose 3.7 and total protein 0.63 g/L). No organisms were identified. MRI showed diffuse atrophy and ring enhancing lesions (described as 3 large 2.0-2.5cm sub-cortical plaques in the white matter. In response to an FDA request for information on July 1, 2010 the applicant clarified that CSF results were as follows: Herpes Virus Type 1 DNA not detected; Herpes Virus Type 2 DNA not detected; M. tuberculosis DNA not detected; CMV IgG CSF negative; CMV IgM CSF negative; Gram stain bacteria and fungal elements both not observed; Bacterial antigens H. influenza type b, N menig/ E.coli, S pneumoniae, Streptococcus group all negative; Cryprococcis indian ink negative; cryptococcal antigen negative; bacterial culture: no growth after 24-48 hours. The investigator concluded that the lesions were probably MS cavitation lesions and were not PML (Progressive Multifocal Leuko-encephalitis) or herpes encephalitis. A tuberculous abscess or another abscess was also considered but ruled out. No details are available regarding treatment received in the hospital. The investigator considered the event to be due to disease progression of underlying disease. Study medication was interrupted but re-started, and the patient was discharged from the hospital. The investigator did not suspect a relationship with study drug. The outcome of the progression of MS was reported as still present and unchanged.

> *Antibody testing, DNA testing and cultures for bacteria, viruses, mycobacteria and fungus were negative. The nvestigator concluded that the ring enhancing lesion was probably MS and it was not PML. There is no mention that JC virus testing was performed. However, PML is a progressive and often fatal condition and it is unlikely that a patient with PML would survive without stopping immunosuppressive treatment.*

SAE of Seizure in the ongoing studies

Two SAE of status epilepticus and one of grand mal convulsion were reported in study 2309. Blinded narratives were submitted with the SUR. Unblinding of the cases of status epilepticus was submitted upon FDA request on June 9, 2010. One case was receiving FTY 0.5 mg (ID USA/2309 0586/00019, 40 F) and was considered to be due to disease progression. The other was found to have herpes encephalitis (ID USA/2309 0587/00010, 54 M) on FTY 1.25 (this case was non-fatal). The case on FTY 0.5 is as follows (the other case is in Appendix 9.4.15c.)

- 2309 0586/00019. Status epilepticus. 40 F, history of bipolar disorder on bupropion. 27-year history of MS. History of optic neuritis. No history of seizures. During study received dextromethorphan for cough, and an oral contraceptive. On day 209 of therapy she had loss of consciousness and status epilepticus. She was intubated for airway

protection and treated with levitiracetan. Study drug was interrupted. MRI of the brain revealed diffusion restriction in the left temporal pole including the medulla and hippocampus which was "possibly related to seizure activity." She recovered. A follow up MRI showed no evidence of infarction or hemorrhage. She was discharged on clonazepam and levitiracetam. At some point she also started phenytoin. Study drug was re-started. One and ½ month into FTY 0.5, she developed status epilepticus again. She was intubated and treated with lorazepam and propofol. She recovered the following day. She was lethargic but arousable. Study drug was discontinued. She was found to have E Coli urinary tract infection that was treated with antibiotics. During this hospitalization she had a lumbar pucture for CSF analysis. The CSF ws clear, colorless and negative for Cryptococcal antigen, CMV (PCR) HSV (PCR) and JC virus (PCR, performed at Mayo Clinic). CSF lab results were: protein 39 mg/dL, glucose 64 mg/dL, RBC 4/mm^3, lymphocyte 56/mm^3 (as per info submitted 7/1/20). On an unspecified date during hospitalization electroencephalogram (EEG) monitoring showed bilateral independent temporal epileptiform waves with background slowing, diffuse frontal predominant slowing in the delta range bilaterally. The diffuse slowing in this EEG recording suggested an encephalopathy. The hospital course was significant for a decline in memory and confusion. The patient was discharged from hospital. At the time of reporting, the patient's medical regimen for seizures was ongoing.

This case was considered by the investigator to be due to "disease progression", although the investigator suspected a relationship between the events of status epilepticus and the study drug. The role of fingolimod in this case can not be ruled out.

- Patient 2309 558 00011 was a 37 M with no prior history of seizures who developed grand mal convulsion on day 293 of blinded treatment. He was treated with acyclovir. A CT scan showed no acute change. An EEG and MRI of brain were done but no results were available in the narrative. As per FU information submitted 7/1/10, he had a frontal ring enhancing lesion that was consistent with multiple sclerosis. Atrophy was out of proportion to the patient's age and extensive T2 abnormality was found consistent with the clinical hx of MS. There was also a periventricular ring of increased T2 signal noted. There was no evidence of viral encephalitis. On Day 294, an EEG was normal. Lab results from lumbar puncture were: glucose 81 mg/dL, protein 38 mg/dL, RBC 0, WBC 12/mm^3 (lymphocytes 93%, monocytes 7%), HSV PCR-negative, bacterial/fungal/AFB cultures negative; other labs included normal CBC and urinalysis, ESR of 30 mm/hour, and normal ECG. Concomitant medications included levetiracetam, later changed to oxcarbazepine. The patient recovered from the event and is still taking oxcarbazepine with no further seizures.

Two additional SAE of seizures occurred in ongoing blinded study 1201 extension study (one epileptic seizure with loss of consciousness (1201E1-0019-00001) and one status epilepticus (1201E1-0024-00002). Blinded narratives were submitted with the SUR. The patients are receiving FTY, but the dose is unknown. Narratives are included in Appendix 9.4.15c. The cases are still blinded.

Additional cases of non-serious seizures occurred in the fingolimod program in the ISS. Seizures are discussed in section 7.3.4 of this review (Other significant AEs).

-MS relapse

The primary outcome measure in this application was the annualized rate of relapse. MS relapse was defined in Phase III studies as the appearance of a new neurological abnormality or worsening of previously stable or improving pre-existing neurological abnormality, separated by at least 30 days from onset of a preceding clinical demyelinating event (McDonald et al, 2001). The abnormality must have been present for at least 24 hours and occurred in the absence of fever (< 37.5°C) or known infection. If relapse was suspected, a neurological examination was performed by a blinded EDSS rater. Some of these neurological abnormalities were reported as an adverse event of relapse, at the investigator's discretion. In this case, the investigator was to follow the following guidance:

Appendix 9 reads as follows:

> **Guidance on monitoring of patients with symptoms of neurological deterioration, inconsistent with MS course**
> Should a patient develop any unexpected neurological or psychiatric symptom (e.g. cognitive symptoms, cortical visual disturbances, seizures, psychiatric symptoms) or accelerated neurological deterioration, the investigator should schedule an MRI before beginning any steroid treatment. Conventional MRI as well as Fluid-attenuated Inversion Recovery (FLAIR) and Diffusion-weighted imaging (DWI) sequences should be performed. The MRI will be evaluated by the local radiologist. The investigator will contact the Medical Advisor at Novartis to discuss findings and diagnostic possibilities as soon as possible. A copy of the unscheduled MRI should be sent to the MS MRI Evaluation Center as soon as possible.
> AE/SAEs need to be filed as appropriate. If the MRI show new MS lesions, diagnosis and treatment of the relapse will be performed as described in the protocol. In case of new findings in the MRI images not compatible with MS lesions, other evaluations, such as further MRI sequences, cerebrospinal fluid analysis, screening of bacterial, viral or parasitic evaluations, etc, will be performed at discretion of the investigator in consultation with the Medical Advisor at Novartis. The study drug will be discontinued until a definitive diagnosis is made.

In the original ISS, 16 SAE of MS/MS relapse were reported in 15 subjects. Of those, 9 occurred during the controlled phase, 2 during the extension and 4 after study drug discontinuation. The listing of patients with serious AEs of MS and MS relapse is presented in Appendix 9.1.4.

Notwithstanding the limitations of subjective reporting of MS relapse as an adverse event, the reported risk of serious AE of MS relapse was low and similar in all treatment groups in the controlled studies (0.2% on FTY 1.25, 0.5% on FTY 0.5 mg, 04% on placebo and 0.2 % on IFN).

Narratives of selected cases of AE of MS relapse and other neurologic diagnoses of interest in the MS program are summarized as follows.

Brief narratives of patients with unusual MS relapse or uncommon neurologic diagnosis in the fingolimod program

CONTROLLED STUDIES

FTY 5 mg

2201-0004-00014 – Posterior Reversible Encephalopathy Syndrome (PRES) – FTY 5mg. 52 F, Day 73
MS dx 8 yrs prior. EDSS= 2.5. She had 2 relapses in the 2 years prior to randomization, 2 relapses in the year prior to randomization and her most recent relapse was 9 months prior to randomization. Active smoker. She was taking conjugated estrogens and medroxyprogest. On Day 73 she was hospitalized with vomiting, rapid onset of blindness and slurred speech. Study drug was discontinued. Four days later, the patient's condition improved.She had left hemianopsia, left hyperreflexia and bilateral Babinski. An MRI done 10 days later showed improvement of previously noted T2 and Flair hyperintensity in all areas but the left occipital lobe, which had changes that could be pre-ischemic in nature. There was progressive improvement, although there were residual symptoms of R homonymous hemianopsia, mild paraparesis, mild ataxia and mild bilateral dysmetria. A diagnosis of **PRES** (Posterior reversible encephalopathy syndrome) was made. The investigator suspected a relationship to study medication. *This case was reviewed by Dr. Heather Fitter, DNP neurologist, who suggested an alternative diagnosis of embolic stroke. Of note, a case of PRES was diagnosed in the renal transplant population and the possibility of PRES is being entertained in a patient in an ongoing study (1201E1-0112-00004).*

FTY 1.25 mg

2301_0409_00008 - Unusual MS relapse. 6 months into study
27 F. MS dx 2 years prior. EDSS at baseline= 0. No prior immunosuppressants. One relapse in the 2 years prior to random. 2 relapse in the year prior to randomiz, last relapse 3 months prior to random. MS had manifested by optic neuritis with multiple subcortical T2 hyperintense MRI lesions & CSF oligoclonal bands. Most recent relapse prior to entry: gait ataxia, fatigue and numbness of both hands which improved after steroid Rx. The patient's medical history included headache and optic neuritis. Approximately 6 months into FTY 1.25 treatment she presented to the ER with headache and vomiting, without fever. CSF showed 88 WBCs, mostly activated lymphocytes and no granulocyes, with normal protein. An MRI showed a new left parieto-occipital mass (2x3 cm). CSF cultures; PCR for JC virus, herpes and TB and autoantibodies were negative. She developed neurologic symptoms, partial complex and generalized seizures and cognitive impairment. The investigator provided a differential diagnosis of autoimmune encephalitic disease (ADEM) versus opportunistic infection versus hematologic malignancy. At some point the possibility of sinus vein thrombosis was considered, but later thought to be unlikely. She was treated with IV acyclovir, antibiotics and antifungals, as well as with heparin. The patient recovered from the event (MS relapse) with sequelae on an unspecified date. The investigator did suspect a relationship between the events 'overall weak', brain mass, new MS lesions and the complex partial seizures and the study medication. The final diagnosis was unusual MS relapse. Differential diagnoses discussed by the investigator included CNS infection, ADEM and malignancy. At the FDA request, on 2/12/10 the sponsor provided additional follow up on this patient as follows: "Follow-up: Patient has intermittent symptoms of vertigo and tingling which are discussed as minor seizures. She is now on lamotrigine (125mg) for seizures. Her neurological condition is otherwise stable under Copaxone. MRI in April-09 showed residual lesion but no new disease activity. There have been no relapses."

Patient is stable on current treatment. Although final diagnosis was MS relapse, she was treated as if she had a viral infection and also treated with heparin, therefore, the role of fingolimod in this event can not be ruled out. It is somewhat surprising that she did not have a biopsy for the "brain mass", which is still present.

This case was reported in the journal Neurology as a case of hemorrhagic focal encephalitis (Neurology, 2009; 72;1022-1024). Upon FDA

request for clarification of the discrepancy in the diagnosis, Novartis provided comments from the central MRI reader (Prof. Radue, Basel), who stated that although atypical, the imaging was consistent with a large MS lesion and that "encephalitis" was "from the MRI point of view only one very unlikely differential diagnosis"
2302 0254-00011. Acute Disseminated Encephalomyielitis (ADEM) 11 months into treatment presented with fever, cough and seizures (described under Deaths).
FTY 0.5 mg
2301-0453-00003 – MS relapse, subarachnoid hemorrhage, seizure *Comment: New onset seizure in a patient with 4 ½year history of MS but MRI suggested active MS lesion that could explain the seizure. Narative described under SAE of seizure in controlled studies.*
2302-0822-00003 – Atypical MS. Sjögren's syndrome. 46 Asian male. MS dx 2 ½ yrs prior. Prior hx of optic neuritis 5 years earlier. He had 4 relapses in the 2 yrs prior to randomization and 1 relapse in the year prior to randomiz. Most recent relapse was 3 months prior to first dose (optic neuritis treated with iv MP). On Day 16 of FTY treatment, he experienced impaired memory, dysarthria, emotional lability, generalized weakness, abnormal behavior, abulia, left hemiparesis with increased deep tendon reflexes on the left side and generalized paresthesia. Study medication was permanently discontinued on Day 18. Differential diagnoses included MS relapse, strategic infarct and drug-related side effect. MRI showed increased lesion extent of high signal intensity. The subcortical white matter was involved extensively in both frontal lobes, both thalami and in both parieto-occipital regions. The diffusion-weighted image showed a pattern consistent with vasogenic and cytotoxic edema. Salivary gland and lower lip biopsies revealed lymphocytic adenitis consistent with Sjögren's syndrome. Laboratory data included a positive anti-RoAb test and a positive Schrimer test. CSF and frozen serum were sent to NIH for JC virus testing and the Mayo Laboratories for NMO IgG testing. PCR assay for JCV DNA indicated that the virus was undetectable in CSF but detectable in serum (which does not mean an infection since 3% of the population is viremic). On 1-Nov-2007, the investigator concluded that the laboratory results were consistent with Sjögren's syndrome. The investigator did suspect a relationship between this event and the study drug. *Comment: Neurologic manifestations of Sjogren's syndrome include MS-like symptoms. Still, Sjogren's syndrome is characterized by lymphocytic infiltration. The role of fingolimod in this event can not be ruled out.*
EXTENSION STUDIES
2302_0202_00010. **FTY 0.5 mg.** Unusually Severe MS relapse. 33 F, MS dx 5 yrs prior. EDSS=3.5. Five relapses in the 2 yrs prior to randomization; 2 relapses in the year prior to randomization. Most recent relapse was 5 months prior to randomization. She had received azathioprine in the past, and glatiramer acetate for 4 years, until one month prior to starting FTY. Medical history included optic neuritis, hypothyroidism, urinary urgency and fatigue. On Day 590 of FTY 0.5 mg treatment she presented hyposthenia of R leg and pain on legs. An MRI showed increased lesion load and active lesions. She discontinued drug due to the event on Day 616. There is no description of the symptoms associated with this "unusually severe relapse." After 3 months she started treatment with natalizumab and she is neurologically stable.
2301E_0951_00001. **FTY 0.5 mg.** 22 M. Epilepsy. Not treated with MS disease modifiying drug before randomization. Medical history of optic neuritis, encephalitis, COPD. Concomitant medications included bupropion. No history of seizures. On Day 765 of FTY 0.5 mg treatment he was hospitalized because four generalized epileptic seizures. MRI showed diffuse atrophy and ring enhancing lesions. Blood tests and CSF were normal. Serology, DNA testing and cultures were negative for viruses, bacteria, AFB and fungus. JC virus was not tested. Case was described under seizures.

2302E1 0253 00003 – **FTY 1.25 mg.** MS relapse. Atypical MS with "burst of MS lesions" vs. another inflammatory process, such as vasculitis.
34 M. MS dx 14 years prior and 7 relapses since diagnosis, all treated with steroids. He had 3 relapses in the 2 years prior to randomization. He did not receive immunosuppressives for MS. Baseline EDSS score was 3. Medical history of optic neuritis. No concomitant medications. During the core phase he had 2 relapses teated with iv CS. During the first relapse he had grand mal convulsions (on Day 33) and was started on carbamazepine. On Day 358 he had seizure requiring hospitalization. On Day 362 and EEG showed status epilepticus which was attributed to non-compliance with his antiepileptic meds. Drug was interrupted but re-started. He entered the extension phase. On Day 401 of FTY 1.25 he developed cognitive impairment with inattention, disorientation and decreased memory, as well as language impairment, with disarthria, bilateral pyramidal signs, and ataxia, urine an stool incontinence. Apparently a generalized seizure had occurred a few days before the onset of these symptoms. From Day 401 to 410, the patient's condition worsened, requiring hospitalization. On Day 412 EEG showed multiple artifacts and revealed diffuse slowing, indicating encephalopathy. The EEG could not confirm nor exclude status epilepticus. On Day 414 the patient had an MRI of the brain. According to the central reader, who compared the MRI to previus images, the scans at screening and 12 months showed many large subcortical lesions. The unscheduled scan shows an "EXPLOSION" of lesions in the subcortical and periventricular whitematter and cerebellar peduncle bilaterally. Differential dx incluced PML, an atypical burst of MS lesions or another inflammatory process, such as vasculitis. Patient was discharged with some improvement in neurologic status on Day 422. CSF obtained on Day 431 showed normal glucose, protein, chloride and LDH. Cytology was negative for cells. JC virus testing done at a reference lab in Spain was negative. The final diagnosis for the events was progression of MS with unusually severe MS. *This case is of concern. He had MS for 14 years, with 3 relapses in the last 2 years; he had 2 relapses within a month of starting therapy, and rapid progression of MS with "burst of MS lesions".*

ONGOING STUDIES

1201E1-0112-00004 (Blinded Japanese study) – Multifocal diffuse leukoencephalopathy. 48 F, MS dx 2 ½ yrs prior. EDSS=2.5. She had 2 relapses in the 2 years prior to randomization, 1 relapse in the year prior to randomization and her last relapse prior to randomization was 3 months prior, treated with steroids. MS manifested as difficulty moving R hand, decreased sensation and dyslalia. She had received treatment with IFN and immunoabsorption in the past. History of venous thrombosis and hypothyroidism. She had positive anti-AQP4 antibodies. On Day 9 of treatment she experienced headache and disturbed level of consciousness. A new lesion was observed on both sides of the cerebellum and around the cerebral ventricle., consistent with MS relapse. She developed aphasia, right hemisensory neglect and paresis of the right upper limb. CSF was within normal and did not identify any bacteria or opportunistic infections, but did not test for viruses. She received iv immunoglobulin and iv corticosteroids. A head CT was performed, which showed noticeable 'map-like low absorption areas' in the white matter in the cerebellum and in both sides of the cerebrum. She was diagnosed with multifocal diffuse leukoencephalopathy. She was treated with immunoabsorption plasmapheresis. PCR of the spinal fluid tested from a sample obtained before IV IG and plasmapheresis was negative for JC virus. The DSMB felt that although atypical, this patient may have MS or Neuromyelitis optica (NMO). Regarding the episode of encephalopathy (disturbed level of consciusness), the MRI was suggestive of PRES (posterior reversible leukoencephalopathy) either due to NMO or drug toxicity. *There is limited information from this case to draw definitive conclusions, but it is certainly an odd case.*

2306 0406 00007. 43 M with PPMS. Blinded (IND report PHHO2010ES02722). During treatment an MRI done by protocol showed new atypical left frontal hyperintense T2 lesion. Differential dx were PML, brain lymphoma, posterior reversible leukoencephalopathy and diffuse inflammatory demyelinating lesion but the subject had no new symptoms. CSF PCR for JCV was negative at NIH, although JCV was present in urine. Biopsy of the brain lesion did not indicate evidence of viral infection (he had been treated with mefloquine). Histology was normal with minimal infiltration of lymphocytes. There were no genetic markers for lymphoma. The local pathologist was not sure about the diagnosis but thought it could have an

inflammatory lesion.
CASES AFTER FINGOLIMOD DISCONTINUATION
2301_0407_00021 – 34 M. Unusually severe MS relapse. Received FTY 1.25 during controlled study. Discontinued on Day 141 of core study because of lack of efficacy. Treated with Rebif for 5 months. After Rebif presented severe relapse with tetraparesis, ataxia, required PEG and tracheostomy. Treated with plasmapheresis, now on natalizumab. Tracheostomy closed. Pt improved but remains bedridden.
2301E1_0412_00004 – Impairment of MS symptoms. Received placebo during core and FTY 1.25 in Extension. On day 1638 (1449 of FTY treatment) the patient withdrew consent and discontinued from the study for unclear reason. 57 days after the last dose of the study drug, she had vertigo and tiredness, progressive hemiparesis and decline in cognition. Hospitalized. An MRI showed large demyelinating lesions, and new enlarging lesions with edema. She was treated with solumedrol & antibiotics. LP: JCV negative. EEG: intermittent slow waves discharges with epileptiform features. Possibility of viral encephalitis was considered. Treated with acyclovir infusions and MP infusions. Patient improved. She recovered with sequelae.

Therefore, there are some unusual cases of severe MS relapse and uncommon neurological diagnoses in this database in the fingolimod treatment groups, but the numbers are too small to draw definitive conclusions.

- Serious vascular events within the Nervous system disorders SOC

Three cases of cerebral ischemia/stroke were reported with FTY 1.25 mg in the fingolimod original ISS (one during the controlled studies and two during the extensions). One additional stroke was reported in a patient receiving FTY 1.25 in study 2309. An additional case in 2309 was initially reported as stroke was later changed to a transient ischemic attack. This patient was on placebo. Brief narratives of serious vascular events in the nervous system disorders SOC are as follows. More details are presented in Appendix 9.4.5. The following cases occurred in patients receiving FTY 1.25 mg.

- **2301 0108 00010** was a 40 year old that collapsed and was found to have a large Middle Cerebral artery stroke. She had mildly elevated homocysteine. Based on the CT angiography there was a suspicion that she may have had arteriopathy, consistent with a possible vasculitic process.

- **2302E1 0142 00005** was a 25 year old with left sided headache and photophobia and tingling and heaviness on the right. Stroke work up was negative, and it was suspected that she had a complicated migraine. Although this could have been a TIA, it doesn't sound consistent with that due to the photophobia that was present on presentation.

- **2302E1 0365 00002** was a 40 yo smoker and had herpes zoster opthalmicus, then developed left cerebral ischemia due to an arterial occlusion. This patient had several risk factors that may have been in play (he was a smoker which can contribute to a hypercoagulable state and then had herpes zoster which may have contributed to the development of vascultitis).

- **2309 0567 00008** was a 41 yo with a bilateral occipital ischemic stroke with hemorrhagic complication. No source of an embolis was found, and a hypercoagulable risk factor work up was negative. Embolic stroke was suspected.

No thrombus or a source of emboli was found in the fingolimod cases. No coagulation abnormalities were found, however, the workup was not complete in all cases. Although these are few cases, they raise concern about the possibility of increased risk of ischemic/thrombotic cerebrovascular events with FTY 1.25.

The applicant conducted a 28-day clinical pharmacology study evaluating cerebrovascular flow and platelet function in normal volunteers. The study did not show abnormalities at the doses of 1.25 and 0.5 mg a day for 28 days, but it does not rule out an effect with longer duration of treatment.

The applicant proposes to address the possibility of an increased risk for ischemic/thrombotic cerebrovascular events in the PASS registry, a 5-year postmarketing registry in patients receiving FTY 0.5mg under routine clinical care. This approach is acceptable.

Of note, the preNDA package proposed (b) (4) *For administrative reasons,*

the study has not been completed at the time of the NDA submission. This study can be conducted as a postmarketing requirement.

- Syncope

3 subjects presented SAE of syncope in the controlled studies. One occurred on placebo, on Day 163; one on FTY 1.25 on Day 724 and one on FTY 0.5, on Day 203.

One subject presented a SAE of syncope in the extension studies (2201_0003_00014). She was a 39 year old female in the 5mg-1.25 mg group who fainted on Day 505 of treatment. The event did not lead to study drug discontinuation.

- SAE in the Infections and Infestations SOC

SAE in the Infections and Infestations SOC in Safety Pool D is presented in the following table.

Table 18. Serious AE, Infections and Infestations SOC, safety pool D

Primary system organ class Preferred term	FTY720 5 mg (N=94) n (%)	FTY720 1.25 mg (N=943) n (%)	FTY720 0.5 mg (N=854) n (%)	Placebo (N=511) n (%)	Interferon (N=431) n (%)
-Total	0 (0.0)	18 (1.9)	8 (0.9)	8 (1.6)	6 (1.4)
Appendicitis	0 (0.0)	2 (0.2)	0 (0.0)	1 (0.2)	2 (0.5)
Abscess	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Abscess jaw	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Acute sinusitis	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Anal abscess	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Dermo-hypodermitis	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Encephalitis herpes	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Encephalitis viral	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Genital herpes	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Helicobacter gastritis	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Herpes zoster	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Herpes zoster disseminated	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Lower respiratory tract infection	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Mastoiditis	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Otitis media acute	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)
Pyelonephritis acute	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Pyelonephritis chronic	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory tract infection	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Streptococcal abscess	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Tonsillitis	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Tooth abscess	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Urosepsis	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Administration site infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Bartholin's abscess	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)

Clostridial infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Cystitis	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Gastroenteritis	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.2)	0 (0.0)
Herpes virus infection	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)
Herpes zoster ophthalmic	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Incision site abscess	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Peritoneal abscess	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Peritonsillitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Pharyngitis	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.2)	0 (0.0)
Pharyngotonsillitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Pyelonephritis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Sinusitis	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Upper respiratory tract infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Urinary tract infection	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	1 (0.2)

Source: Post Table 4.4-9, ISS. All three placebo controlled studies. N= patients randomized. n= patients with events. A patient with multiple occurrences of the same AE under one treatment is counted only once in the AE preferred term for that treatment. A patient with different adverse events within a primary system organ class is counted only once in the total row.

Evaluation of overall serious infections and infestations does not indicate a major difference in the risk of these events between fingolimod groups and placebo or interferon in the controlled studies. The percentage of SAEs in this SOC suggests a dose response between fingolimod doses in safety pool E. The analysis of event rates (events per 100 PYRs) in safety pool E also suggests a higher rate in fingolimod 5 and 1.25 as compared to 0.5, but the numbers are small.

Patients with serious events in the Infections and Infestations SOC in safety Pool E are presented as follows:

Table 19. SAES in Infections and Infestations SOC, safety pool E

Primary system organ class Preferred term	FTY720 5 mg - 1.25 mg (N=137) n (%)	FTY720 1.25 mg (N=1157) n (%)	FTY720 0.5 mg (N=1021) n (%)
[illegible]			
-Total	5 (3.6)	30 (2.6)	13 (1.3)
Appendicitis	1 (0.7)	3 (0.3)	0 (0.0)
Herpes zoster	1 (0.7)	3 (0.3)	0 (0.0)
Herpes zoster ophthalmic	0 (0.0)	2 (0.2)	1 (0.1)
Pneumonia	0 (0.0)	2 (0.2)	1 (0.1)
Abscess	0 (0.0)	1 (0.1)	0 (0.0)
Abscess jaw	0 (0.0)	1 (0.1)	0 (0.0)
Acute sinusitis	0 (0.0)	1 (0.1)	0 (0.0)
Anal abscess	0 (0.0)	1 (0.1)	1 (0.1)
Cholecystitis infective	0 (0.0)	1 (0.1)	0 (0.0)
Dengue fever	0 (0.0)	1 (0.1)	0 (0.0)

Dermo-hypodermitis	0 (0.0)	1 (0.1)	0 (0.0)
Encephalitis herpes	0 (0.0)	1 (0.1)	0 (0.0)
Encephalitis viral	0 (0.0)	1 (0.1)	0 (0.0)
Gastroenteritis	0 (0.0)	1 (0.1)	1 (0.1)
Genital herpes	0 (0.0)	1 (0.1)	0 (0.0)
Helicobacter gastritis	0 (0.0)	1 (0.1)	0 (0.0)
Herpes zoster disseminated	0 (0.0)	1 (0.1)	1 (0.1)
Lower respiratory tract infection	0 (0.0)	1 (0.1)	0 (0.0)
Mastoiditis	0 (0.0)	1 (0.1)	0 (0.0)
Otitis media acute	0 (0.0)	1 (0.1)	0 (0.0)
Papilloma viral infection	0 (0.0)	1 (0.1)	0 (0.0)
Pyelonephritis	0 (0.0)	1 (0.1)	0 (0.0)
Pyelonephritis acute	1 (0.7)	1 (0.1)	0 (0.0)
Pyelonephritis chronic	0 (0.0)	1 (0.1)	0 (0.0)
Respiratory tract infection	0 (0.0)	1 (0.1)	0 (0.0)
Streptococcal abscess	0 (0.0)	1 (0.1)	0 (0.0)

Primary system organ class Preferred term	FTY720 5 mg - 1.25 mg (N=137) n (%)	FTY720 1.25 mg (N=1157) n (%)	FTY720 0.5 mg (N=1021) n (%)
Tonsillitis	0 (0.0)	1 (0.1)	0 (0.0)
Tooth abscess	0 (0.0)	1 (0.1)	0 (0.0)
Urinary tract infection	1 (0.7)	1 (0.1)	2 (0.2)
Urosepsis	0 (0.0)	1 (0.1)	0 (0.0)
Bartholin's abscess	0 (0.0)	0 (0.0)	1 (0.1)
Cystitis	0 (0.0)	0 (0.0)	1 (0.1)
Herpes virus infection	0 (0.0)	0 (0.0)	1 (0.1)
Infection	0 (0.0)	0 (0.0)	1 (0.1)
Otitis externa	1 (0.7)	0 (0.0)	0 (0.0)
Pharyngitis	0 (0.0)	0 (0.0)	1 (0.1)
Salpingitis	1 (0.7)	0 (0.0)	0 (0.0)
Sinusitis	0 (0.0)	0 (0.0)	1 (0.1)
Viral infection	0 (0.0)	0 (0.0)	1 (0.1)

Source: Post table 4.5-12. ISS

Rate of serious Infections and infestations (in PYRs of exposure), safety Pool E

Primary system organ class Preferred term	FTY720 5 mg - 1.25 mg (Ny=439.5) n (PR)	FTY720 1.25 mg (Ny=1919.9) n (PR)	FTY720 0.5 mg (Ny=1583.3) n (PR)
Infections and infestations -Total	6 (1.4)	35 (1.8)	15 (0.9)

Source: Table 4.2-5a. Response to request for information submitted 2/24/10, refers to original ISS.

In the renal transplant population, the overall risk of infections was similar or lower than with MMF (average 35% of patients had serious infections with FTY as

compared to 42% with MMF in the primary population). Of note, there were two cases of aspergillosis, one cryptococcal meningitis, and one pneumocistis jaroveci pneumonia among fingolimod treated patients in the renal transplant population. However, these patients were taking concomitant Cyclosporin A and corticosteroids. No opportunistic infections have been identified in the MS population.

Evaluation of serious infections and infestations over time did not suggest an increased risk of infections with longer exposure (data not shown).

- Analyses of serious Infections and infestations by High level term group

As per the AE datasets, there were 46 serious AES in 37 subjects in the Infections and Infestations SOC, in all controlled studies (pool D). Analysis of serious infections and infestations by High level term (HLT) group in the controlled database is shown as follows:

Table 20. SAE in Infections SOC, by MedDRA HLT group, pool D

HLT	FTY 1.25 **N= 943**	FTY 0.5 **N= 854**	Placebo **N= 511**	IFN **N= 431**
	n (%)	**n (%)**	**n (%)**	**n %**
Total	**18 (1.9)**	**8 (0.8)**	**8 (1.6)**	**6 (1.4)**
Herpes viral infections	4(0.4)[1]	2 (0.2)	-	1 (0.2)
Urinary tract infections	1(0.1)	3 (0.3)	1 (0.2)	1 (0.2)
Lower respiratory tract and lung infections	3 (0.3)[2]	1 (0.1)	-	-
Upper respiratory tract infections	2 (0.2)	2 (0.1)	4 (0.9)	-
Abdominal and gastrointestinal infections	2 (0.2)	2 (0.2)	2 (0.4)	2 (0.4)
Ear infections	1 (0.1)	-	-	-
Infections NEC	1 (0.1)	-	-	2 (0.4)
Bone and joint infections	1 (0.1)	-	-	-
Dental and oral soft tissue infections	1 (0.1)	-	-	-
Helicobacter infections	1 (0.1)	-	-	-
Skin structures and soft tissue infections	1 (0.1)	-	-	-
Streptococcal infections	1 (0.1)	-	-	-
Clostridia infections	-	-	1 (0.2)	-
Female reproductive tract infections	-	-	-	1 (0.2)

Source: FDA MO analysis of SUR AE datasets and narratives. HLT: MedDRA High Level Term group. One patient may have had events in various HLT. [1]Includes one death due to disseminated zoster infection and one death due to herpes simplex encephalitis infection coded under the Viral infections NEC HLT. [2] Includes one case of respiratory tract infection coded under the Infections NEC.

The rate of SAE of all infections and infestations and of herpetic infections in pool D is as follows.

Rate (per 100 PYRs) of SAE in Infections & Infestations SOC and herpetic infections in pool D

	FTY 1.25 mg	**FTY 0.5 mg**	**Placebo**	**Interferon**
Patient years of exposure	1111.2 PYRs	1153.2 PYRs	746.9 PYRs	401.9 PYRs
Patients with any event in Infections in SOC	18	8	8	6
Rate per 100 PYRs	**1.6**	**0.7**	**1.1**	**1.5**

The numbers are not very different if one looks at risk (% of patients with events among randomized patients) or rate (per patient time).

The listing of patients with SAE of infections in safety pool D are presented in Appendix 9.4.6.

- SAE of herpetic infections

In the controlled studies, serious herpes viral infections requiring hospitalization occurred only in the active treatment groups. In the FTY 1.25 mg group there were 2 fatal cases (disseminated varicella zoster and herpes simplex encephalitis), one polysegmental herpes zoster and one herpes zoster genitalis that required intravenous acyclovir. In the FTY 0.5 mg group there were one herpes zoster ophthalmic and one severe herpes simplex facial associated with pneumococcal pneumonia.

Brief narratives of SAE of herpetic infections in the controlled studies are presented as follows.

CONTROLLED studies
IFN
2302_0202_00016 - Herpes virus infection. 34 F. MS diagnosed 9 years earlier. Treated with Rebif until one month prior to study entry. On Day 187, herpes infection of mild intensity in the sacral area with a cutaneous lesion, treated with acyclovir. It resolved on Day 202. The patient reported the event at the 1 year visit. *It is unclear to me why this AE was coded as serious.*
FTY 1.25
2301_0303_00018 – herpes zoster genitalis 33 F. MS diagnosed 6 months prior to entry. She received corticosteroids before entering the study. On Day 106 she had eruption of herpes zoster genitalis. Hospitalized and treated with intravenous acyclovir. She recovered on Day 114.
2302_0318_00005 - Herpes zoster (polysegmental) 25 M. MS diagnosed approx 1 year earlier, treated with Rebif. On Day 230 he presented skin abnormalities that became painful. Patient was hospitalized with polysegmental herpes zoster (T12 & L1), treated with intravenous acyclovir. Drug was interrupted. Event resolved on Day 264. Drug re-started. Patient entered the extension.
2302_0212_00021 – Herpes zoster disseminated. 29 F. Day 319 *Case described under Deaths.*
2302 0821 0007 – Encephalitis viral (HSV type 1). 23 M, Day 339. *Described under Deaths.*
FTY720 0.5 mg

2302_ 0442_00005 Herpes zoster ophthalmic 46 M, MS diagnosed 12 years earlier. Prior MS medications included Betaseron and Rebif. On Day 186 he had mild headache above L eye, followed by puffiness around both eyes. On Day 188 he presented vesicles above the left eye. Hospitalized with diagnosis of ocular herpes zoster. Treated with valacyclovir. He recovered on Day 212 and re-started drug.
2301_0652_00013 - Herpes simplex virus infection 48 F, Day 622. See narrative below, under Pneumonia and pneumococcal sepsis.

Six SAE of herpes infections were reported in the extension studies in the original ISS (one on FTY 5-1.25 mg; four on FTY 1.25 mg –including 2 herpes zoster ophthalmic and one varicella zoster with lung involvement thought to be viral reactivation- and one on FTY 0.5 mg). Two cases required iv acyclovir (one on FTY 1.25 and one on FTY 0.5 mg). No additional cases were reported with the SUR. Brief narratives are presented in Appendix 9.4.7.

In addition to these cases, two subjects presented with atypical MS relapses (with decreased cognitive function and seizure activity) and their treatment included intravenous acyclovir because of the possibility of viral encephalitis (2301_0409_0008, during the controlled studies, with FTY 1.25, who also had a differential diagnosis of brain tumor; and E12301_0412_00004 two months after last dose of FTY 1.25). These cases were described in the Nervous system disorders section.

- SAE of herpetic infections in ongoing studies

SAEs of disseminated herpes zoster, herpes simplex encephalitis and herpes zoster ophthalmic (treated with intravenous antiviral therapy) occurred patients in ongoing study 2309, which is blinded. The applicant was asked to unblind the case of herpes encephalitis and disseminated herpes zoster. Both were on or had been on FTY 1.25 mg. The narrative of the case of non-fatal herpes encephalitis follows:

- **2309 0587 00010.** Ependimoma. Status epilepticus. Herpes simplex encephalitis. 56 M. He was randomized to FTY 1.25 mg. Nine months into treatment he was diagnosed with a low grade ependimoma (that was already present in the screening MRI, but seemed to have grown); he had surgery and the study drug was discontinued. Six months after drug discontinuation he presented status epilepticus. He was treated with anitconvulsants and worked up to rule out viral infections such as herpes. At the time of the SUR, the etiology of the status epilepticus was unknown. As per a follow up report (June 16, 2010) the diagnosis for this patient was herpes simplex type I virus infection. Of note, the lymphocyte count at the time of hospital admission for status epilepticus was 5.5% (normal 15 to 40%). He was slightly anemic; the granulocyte count was normal. *In my opinion, this event of herpes simplex encephalitis could be related to prior fingolimod treatment because the patient was lymphopenic at the time of the event. The applicant has stated that lymphocyte levels usually return to normal within 2 months, but time to full recovery has not been formally evaluated in all patients. HSV antibody status previous to the infection ws not provided in the narrative. It is not known if this was a primary infection or a viral reactivation.*

- SAE of lower respiratory infections

In the controlled studies, SAE of lower respiratory tract infections were reported only in the FTY 1.25 and 0.5 mg treatment groups (3 on 1.25 mg and one on 0.5mg). Brief narratives of these cases are presented below, however, there is very limited information in these cases.

Brief narratives of serious lower respiratory tract infections in the fingolimod trials.

CONTROLLED STUDIES
FTY 1.25 mg
2302_0254_00011. - Lower respiratory tract infection 42 M. This patient developed ADEM complicated with lower respiratory tract infection. He died approximately 6 months after last dose of FTY. No information about possible agent or treatment. Narrative of ADEM is under Deaths.
2301_0601_00012 - Pneumonic infiltrate, pleurisy 24 F. This patient developed pneumonic infiltration, atelectasies, pleurisy, pericarditis and elevated liver enzymes on Day 65. The case was described under serious cardiac disorders (pericarditis). It was thought to be viral.
2301_0501_00003 - Respiratory infection, leucopenia, leucopenia, herpes simplex infection. 50 F, on FTY 1.25. No significant medical history other than MS. On Day 628 she had decreased leucocyte count at $2.0x10^{9/}L$ and lymphocyte at $0.15x10^{9}/L$. Drug was interrupted and then discontinued on Day 642. On the same day the present presented exanthema of the lumbar region and was diagnosed with herpes simplex infection based on clinical presentation. No microbiological testing was performed to confirm HSV. She was treated with valacycloivr. The next day she experienced fever and fatigue. 17 days after drug dc she was diagnosed with respiratory tract infection. Clinical examination revealed "cracks" at the lower lung zones bilaterally. A chest x-ray showed bronchiectasies, bilaterally. She was treated with moxifloxacin. She was discharged ten days later and completely recovered from upper respiratory infection and HSV infection. She was then readmitted to the hospital and received immunoglobulin. One and ½ months after drug dc the lymphocyte count was $1.2x\ 10^{9}/L$. The event of herpes simplex was initially assessed as serious but later assessed by non-serious by the investigator.
FTY 0.5 mg
• 2301_0652_00013 – Pneumonia Pneumococcal sepsis 49 F. Diagnosed with MS 5 years prior. She received corticosteroids for MS relapses until 2 months prior to randomization. Prior history of cystitis and pyelonephritis. Non smoker. On Day 566 she had fever and dyspnea, Xray showed basal infiltrate, WBC was 14.500. She was treated with amoxicillin for pneumonia and discharged without sequelae. On Day 622 she again developed dyspnea and fever, with sores on the lip and nose. She was hospitalized with pneumococcal sepsis and herpes simplex virus type 1. Blood culture showed pneumococcus. She was treated with penicillin and acyclovir (unclear if oral or intravenous). She recovered.
EXTENSION studies
FTY 1.25 mg
• 2302E1_0445_00006. 43 M. Pneumonia. The patient presented several episodes of nasopharyngitis during core. On Day 517 again mild upper respiratory tract infection. On Day 533 he had MS relapse and band like tightness, treated with steroids. On Day 551 he had persistent relapse and was to the ER. Work up showed in infection with increased LFTs and decreased sodium. A chest x-ray showed pneumonia. He underwent bronchoscopy. He was treated with ceftriaxone, azithromycin and

acyclovir and discharged on Day 570. Drug was interrupted but re-started. Last lab evaluation prior to infection showed absolute lymphocyte count of 190.

As per the original AE database, only five patients developed serious lower respiratory tract infections in the fingolimod MS studies, while receiving fingolimod treatment. However, some events coded under other MedDRA SOCs from the extension studies, could potentially be infectious-related:

- **ID # 2201E1-0004-00004** was reported to have a "benign solid mass lesion of the left lower lung lobe" (Neoplasms SOC).
  52 y.o female, randomized to FTY 5 mg during the core study and switched to FTY 1.25 mg during the extension study. No history of asthma. Three years into FTY treatment she presented "asthma exacerbation". On Day 1347 a CT scan showed a mass/tumor (3.25cm x 4.64 cm) located in the lower left lung (tumor or infection). Study medication was discontinued. On Day 1399 the patient underwent lung lobectomy. Biopsy showed necrotizing granulomatous pneumonitis with no evidence of malignancy, metastases or lymph node reactive changes, and mid centrilobular emphysema. Cultures were negative. Although no organisms were identified the possibility of tuberculosis was considered. Laboratory results 82 days after study drug discontinuation showed absolute lymphocyte counts of 0.1 x109/L and 0.3 x109/L. The patient discontinued from the study on Day 1454. No further laboratory results are available.

- **2302E1-0124-00001** Lung disorder, Benign mediastinal neoplasm. (Respiratory SOC and Neoplasm SOCs)

  43 year old female. On Day 205 of FTY 1.25 mg treatment had acute chest pain, dyspnea and hypoxia. Hospitalized. CT scan showed pneumopathy with basal infiltrates in inferior lobe, a benign mediastinal lesion/mass, parenchymatous opacities left side and mild pleural disorder. A BAL showed "hypercellularity" and discrete eosinophilia (4%). Treatment included paracetamol and dextropropoxyphene (no mention of antibiotics). The events of chest pain and dyspnea resolved the same day. The patient was discharged from the hospital 5 days after the last dose of the study medication. A follow-up CT scan performed 8 days after the last dose of the study medication showed complete recovery from parenchymatous and pleural lesions. The CT scan also showed a "supracentrimetric nodule" located in the left cardiophrenic angle. The functional respiratory tests were normal on the same day. The event of mediastinal mass is said to have resolved 89 days after the last dose of study drug.

  This event appears to be an infection, perhaps viral, that resolved within a few days without antibiotic treatment, although, given the half life of fingolimod, relationship to study drug is unlikely.

- **Patient** D2302E1-0525-00002, Pneumothorax (acinetobacter pneumonia) (Respiratory SOC)

  At the one-year visit after treatment with FTY 1.25 mg he was found to have "scattered benign pulm nodules" and bronchiectasis. The baseline HRCT showed interlobular septal thickening, ground glass opacities and traction bronchiectasis. A month after the one-year visit, while in the extension study, the subject had a bronchoscopy with biopsy. The procedure was complicated by pneumothorax. Cultures taken at the time of the bronchoscopy grew acinetobacter and he was diagnosed with acinetobacter pneumonia. Drug was discontinued. He was reported to improve with intravenous antibiotic treatment (tobramycin and pepercillin).

Acinetobacter infection is usually seen after prolonged hospitalization and is most associated with ventilated patients or those with repeated procedures (such as bronchoscopies). This patient apparently had no previous procedures.

- Other SAE of Infection

Other SAE occurred in only one patient in the FTY treatment groups. The following case appears of interest because it required surgery (arthormastoidotomy), but she re-started treatment and remained in the study.

- 2301_0757_00016 on FTY 1.25 mg. Ear infection with mastoiditis; acute and chronic pyelonephritis. 45 F, with MS for 15 years. She had been treated with corticosteroids for MS relapses until 3 months prior to study entry. History of chronic tonsillitis, bronchopneumonia and pyelonephritis chronic. On day 205 of FTY 1.25 mg treatment she woke up with acute right acute ear pain. She was hospitalized with acute right bullous otitis media, atypical mastoiditis and acute right catarrhal sinusitis. Six days later she underwent arthromastoidotomy on the right. No microbiology tests were performed. Study drug was stopped on Day 211 and re-started on day 218. She was treated with cefazolin and completely recovered on Day 224. On Day 344 she was hospitalized and treated for an exacerbation of her chronic pyelonephritis. Study was treated with antibiotics and recovered on Day 353. On Day 683 she was hospitalized again with exacerbation of chronic pyelonephritis. Study drug was interrupted for 10 days and she was treated with norfloxacin, ceftriaxone and metronidazole. Study medication was restarted. The event resolved on Day 694 of study treatment.

No other serious infections of note occurred in the extension studies.

The FDA requested the applicant to provide WBC, neutrophil and lymphocyte counts for patient who had serious infections, at the time of the infection. This information was not available for most patients. A table providing the last available value prior to the SAE of infection showed that, as expected, that lymphocyte counts were lower than baseline in FTY-treated subjects, as compared to INF and placebo-treated subjects (data not shown). Only 2 subjects had a lymphocyte count <200 (at the time of last measurement before the infection) in the controlled studies (a subject with helicobacter pylori infection and a subject with non-fatal disseminated herpes zoster infection) both with FTY 1.25 mg. Three additional subjects had a lymphocyte count <200 in the extension studies (one subject with pneumonia, one with gastroenteritis and one with respiratory tract infection).

In summary, a review of serious infections in the MS program suggests an increased risk or serious viral herpetic infections, particularly for the FTY 1.25 mg dose. There does not appear to be an increased risk of bacterial, mycobacterial, opportunistic or fungal infections. No leukocyte counts, lymphocyte counts or immunoglobulin levels were available at the time of the serious infections. An analysis of the most recent laboratory evaluations before the diagnosis of the serious infection showed that five subjects had lymphocyte

counts<200 in the FTY 1.25 mg treatment group in the ISS database. No patient was neutropenic at the time of last available WBC.

- SAEs in Neoplams benign, malignant and unspecified (including cyst and polyps) SOC

There did not seem to be an increased risk of serious neoplasms in the analysis of Safety Pool D or E. In safety pool D, the overall risk of neoplasms was lower in the fingolimod treatment groups. In Safety Pool E, there was no dose response between fingolimod doses. The most common SAE in the Neoplasms SOC was basal cell carcinoma. There seems to be a suggestion of a greater risk/rate of basal cell carcinoma in the FTY 0.5 mg and placebo, but the numbers are small.

Table 21. SAE in the Neoplasm disorders SOC, safety pool D

Primary system organ class Preferred term	FTY720 5 mg (N=94) n (%)	FTY720 1.25 mg (N=943) n (%)	FTY720 0.5 mg (N=854) n (%)	Placebo (N=511) n (%)	Interferon (N=431) n (%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
-Total	1 (1.1)	9 (1.0)	14 (1.6)	12 (2.3)	2 (0.5)
Basal cell carcinoma	0 (0.0)	3 (0.3)	6 (0.7)	2 (0.4)	0 (0.0)
Breast cancer	0 (0.0)	3 (0.3)	1 (0.1)	3 (0.6)	0 (0.0)
Bowen's disease	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Brain neoplasm benign	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Malignant melanoma	0 (0.0)	1 (0.1)	2 (0.2)	1 (0.2)	0 (0.0)
Benign breast neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Benign ovarian tumour	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Breast cancer in situ	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Cervix carcinoma stage 0	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Endometrial cancer	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Malignant melanoma in situ	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Ovarian adenoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Ovarian neoplasm	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Prostate cancer	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Squamous cell carcinoma	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Uterine leiomyoma	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	1 (0.2)

Source: Post Table 4.4-9, ISS. All three placebo controlled studies. A patient with multiple occurrences of the same AE under one treatment is counted only once in the AE preferred term for that treatment. A patient with different adverse events within a primary system organ class is counted only once in the total row.

The most common SAE in this SOC was basal cell carcinoma. The percentage of patients with basal cell carcinoma was similar for FTY 1.25 and placebo (0.3 - 0.4%) and slightly higher for FTY 0.5 mg (0.7%). The difference is small and the diagnosis whether the skin lesion was there before treatment could not always be made because some subjects underwent their first dermatologic examination several months into treatment. However, one case of basal cell carcinoma on FTY 0.5 is notable for presenting at multiple sites. This case is as follows.

- **2301_0412_00004**. 45 F. On day 104 of FTY 0.5 mg she presented a "macular rash." She noted red macular lesions on her skin in three different locations, two on the back and one in the R arm, of about 0.5 cm. The lesions were not present at the time of screening. Biopsies showed basal cell

carcinoma at all 3 sites. Subsequently she was also found to have a new dysplastic nevus on the thigh. Drug was discontinued. The lesions were thought to be related to study drug.

Table 22. SAE in the Neoplasm disorders SOC, safety pool E Updated

Primary system organ class Preferred term	FTY720 5 mg - 1.25 mg (N=137) n (%)	FTY720 1.25 mg (N=1302) n (%)	FTY720 0.5 mg (N=1176) n (%)
-Total	8 (5.8)	17 (1.3)	22 (1.9)
Basal cell carcinoma	1 (0.7)	5 (0.4)	7 (0.6)
Malignant melanoma	0 (0.0)	4 (0.3)	2 (0.2)
Breast cancer	1 (0.7)	3 (0.2)	2 (0.2)
Benign mediastinal neoplasm	0 (0.0)	1 (0.1)	0 (0.0)
Bowen's disease	1 (0.7)	1 (0.1)	0 (0.0)
Brain neoplasm benign	0 (0.0)	1 (0.1)	0 (0.0)
Malignant melanoma in situ	0 (0.0)	1 (0.1)	1 (0.1)
Squamous cell carcinoma of skin	0 (0.0)	1 (0.1)	1 (0.1)
Benign lung neoplasm	1 (0.7)	0 (0.0)	0 (0.0)
Benign uterine neoplasm	0 (0.0)	0 (0.0)	1 (0.1)
Breast cancer in situ	0 (0.0)	0 (0.0)	1 (0.1)
Cervix carcinoma	1 (0.7)	0 (0.0)	0 (0.0)
Ovarian cancer metastatic	1 (0.7)	0 (0.0)	0 (0.0)
Ovarian epithelial cancer	0 (0.0)	0 (0.0)	1 (0.1)
Ovarian neoplasm	0 (0.0)	0 (0.0)	1 (0.1)
Squamous cell carcinoma	1 (0.7)	0 (0.0)	0 (0.0)
Thyroid cancer	1 (0.7)	0 (0.0)	0 (0.0)
Uterine leiomyoma	0 (0.0)	0 (0.0)	5 (0.4)

Source: Post text Table 4.5-12 SUR ISS.

The analyses of rates (n/PYRS of exposure) were consistent with the analysis of risk (n/pts randomized) (see table below).

Table 23. Incidence rate of serious neoplasms (events/100 PYRs), safety pools D and E.

	FTY 5	**FTY 1.25**	**FTY 0.5**	**Placebo**	**IFN**
All controlled studies (Pool D)	43.2 PYRs	1111.2 PYRs	1153.2 PYRs	746.9 PYRs	401.9 PYRs
All SAE neoplasm	1 (2.3)	15 (1.3)	14 (1.2)	12 (1.6)	2 (0.5)
Basal cell carcinoma	0	3 (0.3)	6 (0.7)	2 (0.4)	0
Controlled and extensions (Pool E)	**FTY 5 to 1.25** 486.4 PYRs	**FTY 1.25** 2218.3 PYRs	**FTY 0.5** 1878.0 PYRs	-	-
All SAE neoplasms	8 (1.6)	17 (0.8)	22 (1.2)	-	-
Basal cell carcinoma	1 (0.2)	5 (0.2)	7 (0.4)		

Source: Tables 4.2-4b and 4.2-5a. Response to FDA request for information submitted 2/22/10. SUR submitted 4/21/10. Patient year defined as sum of no. days on study drug for all patients in each treatment group divided by 365.25. - n = Number of adverse events that occurred to a patient. PR = 100 Patient year rate calculated as n/Ny*100. - If a patient had multiple AEs (or different occurrences of AEs) with different preferred terms on the same date then the AEs will be counted differently. - If a patient had multiple AEs (or different occurrences of AEs) on the same date and with the same preferred term but different levels of severity, then the AE will be counted only once using the maximum severity.

The rate of neoplasms (rate/100PYRs) did not increase in the long term follow up group of the ISS (pool E).

- Additional cases of lymphoma from ongoing studies

A fatal case of B-cell lymphoma of the brain with disseminated EB Virus related lymphoproliferative disorder and skin T cell lymphoma has been described under deaths from a non ISS study *(Subject 1201E1-0005-00001).* Two additional lymphomas were described in the ongoing studies not included in the ISS:

- **2306 0262 00002** – 66 yo M from Germany (IND 15-day report). Medical history of psoriasis and osteoarthritis. One year into treatment with **FTY 1.25 mg** he reported swelling of R inguinal lymph node, 4x4 cm. Ultrasound showed multiple enlarged lymph nodes along the vessels. He was hospitalized and the lymph nodes were removed. Histology showed B cell non-Hodgkin lymphoma (**Diffuse large B-cell lymphoma** – DLBCL-). Lymphocyte count was 0.14 x 10^9 /L. Two months later, lymphocyte count was 0.80 x 10^9 /L. He denied pain, fever or night sweats, but he noted weight loss of 2 kg over one month and 5 kg total during the past year. Study drug was discontinued. Serology was negative for hepatitis A, B, and C. Serology showed HS virus, VZ virus, EBV and CMV IgG positive, IgM negative. EBV EBNA AK was positive. A bone marrow biopsy did not show lymphoid cell infiltrates.

  The temporal association is not inconsistent with a drug induced lymphoproliferative disorder, although the weight loss preceded the initiation of fingolimod treatment..

- **2309 0547/00004** cutaneous T cell lymphoma. FTY 1.25 mg.
  54 year old male patient with a 10 year history of a pruritic lesion (scaly plaque) on the right upper thigh which had been growing over the time and was not responsive to topicals. One year into treatment, a biopsy of the skin lesion was performed. The histopathology evaluation showed cutaneous T cell lymphoma (mycosis fungoides). Drug was permanently discontinued due to this event.

  This patient had a pre-existing skin lesion, however, the role of fingolimod in worsening the pre-existent lesion can not be ruled out.

In the renal transplant population, the risk of neoplasms (all) seemed to be higher with FTY 5 mg as compared to FTY 2.5 and MMF (5.3%, 3.4% and 2.8%, respectively). The tumors that seem to be contributing to the difference in overall risk were squamous cell carcinoma (0.6% and 0.4% in FTY 5 and 2.5, respectively, as compared to 0.2% on MMF) and Kaposi sarcoma (also 0.6% and 0.4% in FTY 5 and 2.5, respectively, as compared to 0.2% on MMF). Of note, there were two T-cell lymphoma (one in each FTY group- 5 and 2.5 mg-), and one lymphoproliferative disorder, one B-cell lymphoma and one myelodisplastic syndrome in the FYT 2.5 mg group. There was one brain lymphoma in the MMF group. All patients were taking concomitant Cyclosporin A.

Non-clinical carcinogenicity studies showed an increase incidence of lymphoma. For details the reader is referred to the Pharm tox review by Dr. Siarey. In the MS population, there were no reported lymphoproliferative disorders or lymphoma in the studies included in the ISS. However, three subjects presented lymphoma in the MS program in non ISS studies.

In summary, the analysis of serious neoplasms in the present MS database does not indicate a definitive increase in risk of malignancies in the fingolimod treatment group. In the ISS there was an apparent increase in risk of basal cell carcinoma for FTY 0.5 mg, but not for FTY 1.25 mg as compared to placebo. One patient presented skin basal cell carcinoma at three different sites within 3 months of FTY 0.5 mg treatment. There were three lymphomas in the ongoing non-ISS studies (one case of an EBV related lymphoproliferative disorder, malignant B cell lymphoma and T cell lymphoma; one malignant B-cell lymphoma and one skin T cell lymphoma) in patients receiving fingolimod. In two of the cases the lymphoma may have preceded initiation of fingolimod treatment. The long term exposure in this database is limited, and data are uncontrolled. Given the known effect of fingolimod on circulating lymphocytes and the potential effect on immunosurveillance, an increased risk of malignancy with longer exposure can not be ruled out. This issue should be addressed with longer term data.

The applicant proposes to explore the possibility of increased risk of malignancies in a post-marketing registry (PASS). This approach is acceptable.

- SAES in Investigations SOC

Individual AE in the Investigation disorders SOC have been incorporated into the respective SOCs (e.g ECG under Cardiac SOC, etc.).

- SAEs in GI dosorders SOC

Serious AE in the GI disorders SOC in the controlled database are presented in the following table.

Table 24. SAEs in GI disorders SOC, safety pool D

Primary system organ class Preferred term	FTY720 5 mg (N=94) n (%)	FTY720 1.25 mg (N=943) n (%)	FTY720 0.5 mg (N=854) n (%)	Placebo (N=511) n (%)	Interferon (N=431) n (%)
Gastrointestinal disorders					
-Total	0 (0.0)	8 (0.8)	4 (0.5)	4 (0.8)	3 (0.7)
Constipation	0 (0.0)	2 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
Abdominal pain upper	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)
Anal skin tags	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Dyspepsia	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)
Ileus paralytic	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Pancreatitis acute	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Pancreatitis chronic	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal pain	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.2)	1 (0.2)
Diarrhoea	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Gastritis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Haemorrhoids	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Inguinal hernia	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Oesophagitis	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Rectal haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Vomiting	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.2)	1 (0.2)

Source: Post Table 4.4-9, ISS. All three controlled studies. A patient with multiple occurrences of the same AE under one treatment is counted only once in the AE preferred term for that treatment. A patient with different adverse events within a primary system organ class is counted only once in the total row.

Within the GI disorders SOC in the controlled studies, the only SAE that occurred in at least 2 patients in one treatment group was constipation, but occurred in similar percentage as placebo (0.2%). Other SAEs occurred in one patient only (e.g. abdominal pain, dyspepsia, anal skin tags, gastritis). Of note, there was one case of acute and one case of chronic pancreatitis, both in the FTY 1.25 mg group. *Review of the narratives of these two cases of pancreatitis shows that they occurred 265 and 350 days after drug discontinuation, therefore they were misclassified as occurring in the controlled period in the ISS table.*

Serious AE in the GI disorders SOC in Safety Pool E were consistent with those observed in the controlled studies (data not shown).

- SAEs in the Eye disorders SOC

Analyses of SAE in the Eye disorders SOC in Safety pool D is presented in the following table.

Table 25. Serious AE, Eye Disorders SOC, safety pool D

Primary system organ class Preferred term	FTY720 5 mg (N=94) n (%)	FTY720 1.25 mg (N=943) n (%)	FTY720 0.5 mg (N=854) n (%)	Placebo (N=511) n (%)	Interferon (N=431) n (%)
Eye disorders					
-Total	0 (0.0)	7 (0.7)	2 (0.2)	1 (0.2)	0 (0.0)
Macular oedema	0 (0.0)	4 (0.4)	1 (0.1)	0 (0.0)	0 (0.0)
Eye pain	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Papilloedema	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Photopsia	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Retinal disorder	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Retinitis	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Iridocyclitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Keratitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Retinal detachment	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)

Source: Post Table 4.4-9, ISS. All three placebo controlled studies. A patient with multiple occurrences of the same AE under one treatment is counted only once in the AE preferred term for that treatment. A patient with different adverse events within a primary system organ class is counted only once in the total row.

Eye disorders are common in patients with MS, and it is sometimes difficult to distinguish if the reported AEs are truly AEs or part of the disease. Reports of SAE in this SOC were higher in the FTY 1.25, as compared to FTY 0.5, placebo or IFN.

There were four cases of serious ME in the FTY 1.25 mg group, and 1 in the FTY 0.5 mg group. There were no cases on INF or placebo. Four of the subjects had no prior history of MS ocular symptoms, one subject had a history of optic neuritis. Diagnoses of ME were made 1 to 4 months into treatment. Three subjects had decreased or loss of vision in one eye at the time of the event. The other two were asymptomatic and diagnosed by dilated ophthalmoscopy/OCT during protocol scheduled ophthalmic evaluations. In all cases macular edema resolved 2 to 4 ½ months after drug discontinuation. Three out of 4 cases on FTY 1.25 and 1/1 on FTY 0.5

recovered from the ME with decreased vision at the time of the last available evaluation. In addition to these cases, there were cases of macular edema coded as non-serious that led to study drug discontinuation (8 in the FTY 1.25 mg group and 1 in the FTY 0.5 mg group). They are described in the Discontinuation section of this review.
As seen in the following table, in Safety pool E there was evidence of a dose response between the 1.25 and 0.5 mg doses for macular edema.

Table 26. SAE in the Eye Disorders SOC, safety pool E (updated)

Primary system organ class Preferred term	FTY720 5 mg - 1.25 mg (N=137) n (%)	FTY720 1.25 mg (N=1302) n (%)	FTY720 0.5 mg (N=1176) n (%)
Eye disorders			
-Total	1 (0.7)	12 (0.9)	3 (0.3)
Macular oedema	1 (0.7)	9 (0.7)	2 (0.2)
Eye pain	0 (0.0)	1 (0.1)	0 (0.0)
Papilloedema	0 (0.0)	1 (0.1)	0 (0.0)
Photopsia	0 (0.0)	1 (0.1)	0 (0.0)
Retinal disorder	0 (0.0)	1 (0.1)	0 (0.0)
Retinitis	0 (0.0)	1 (0.1)	0 (0.0)
Retinal detachment	0 (0.0)	0 (0.0)	1 (0.1)

Source: SUR. Post text table 4.5-12.

Seven SAE of macular edema (ME) were reported in the extension studies original ISS (1 on FTY 5 mg, 5 on FTY 1.25 and 1 on FTY 0.5). No additional case was reported from the extension studies at the time of the SUR.

Brief narratives of SAE of macular edema in the Eye disorders SOC with FTY 0.5 mg are described as follows. Cases for other doses are presented in Appendix 9.4.7.

- **2302_0424_00010 (controlled study).** 41 M, randomized to FTY 0.5 mg. MS diagnosed 2 ½ years earlier. Had received IFN in the past. History of epilepsy. No prior history of eye problems. Non smoker but started to smoke during first month of study. Concomitant meds at entry: carbamazepine. Screening visual acuity: 20/20. OCT CFT: 169/170 L/R. On 1-month visit: dilated ophthalmoscopy showed unspecific maculopathy bilaterally. On Day 94, there was a suspicion of classical macular edema in the left eye (severe intensity) which was confirmed by FA. The patient denied any visual symptoms. Drug was discontinued on Day 95. (Patient profile states that on Day 94 there was a macular hole on L eye that was not confirmed by the DSMB ophthalmologist.) OCT FT at 4 ½ months: 250/171 L/R. He was treated with ketorolac eye drops. 61 days after receiving the last dose of the study medication, an ophthalmoscopy with three mirrored lens revealed fovea brightness loss in the right eye with no other changes. In the left eye, there was fovea brightness loss with macular pigment epithelium recovery without edema. The patient's visual acuity was 20/25 in the right eye and 20/50 in the left eye.

- **2302E1_0211_00008 (extension study).** 36 M. Randomized to IFN in core study. Received FTY 0.5 mg during the extension. Diagnosed with MS 2 years prior to randomization. EDSS score at entry= 1. Prior history of IFN treatment. No history of optic neuritis or eye symptoms. On Day 189 of FTY 0.5 mg during regular ophthalmic assessment, OTC revealed thickening of the macula in the left eye (CFT= 203 microns compared to 152 at the end of the core study). He was asymptomatic. Visual acuity was 20/20. FA was not done. No treatment was given. Drug was discontinued. The event of macular edema was resolved 18 days after drug dc. At this time a repeat OCT showed CFT= 164 microns and FA showed no macular edema.

- Serious AE of macular edema in study 2309

At the time of the original application, one SAE of ME was reported from study 2306, and 4 from study 2309 (all blinded). At the time of the Special safety interim report update, the SAE of ME from study 2309 were unblinded (2 on FTY 1.25, 1 on FTY 0.5 and one on placebo). The case on FTY 0.5mg is described below. It required surgery for repair of a macular hole thought to be related to the development of an epiretinal membrane.

- **2309-0547-00007. 37 F. Macular edema on Day 114, requiring surgery (FTY 0.5)**

  20 year history of MS. Hx optic neuritis of L eye 4 years prior to entry and depression. No evidence of retinopathy at study entry. Concomitant meds bupropion, lorazepam, floxetine, levothyroxine. Screening VA 20/30+1 R, 20/25-2 L. CFT 186 microns in L and 220 in R. She complained of blurred vision in L eye. On day 36 she complained of stabbing pain in R eye. Fundoscopic exam showed epiretinal membrate (ERM) in R eye. OCT showed CFT 209 in L and 253 in R. Foveal contour was irregular in R eye but the overall assessment was negative for ME. **On Day 114** she c/o 1 week hx of decreased vision in R eye. VA was 20/30-2 in L and 20/50+ in R. Cystoid macular edema was dx in R eye. CFT was 198 in L and 471 microns in R eye. Drug was dc. For the ensuing 3 months she reported having a line across her field of vision but did not see an ophthalmologist. 3 months after drug dc VA was 20/200 at R and unchanged at L. Fundus exam showed a stage 4 macular hole in R eye. CFT was 504 microns in R eye and 208 in L eye. One image showed full thickness macular hole. She underwent ocular surgery to repair macular hole in R and ERM in L. Six months after surgery VA was 20/30 in L and 20/40 in R.

- Summary of review of cases of SAE of macular edema in fingolimod MS studies

Five patients presented serious macular edema with FTY in the controlled studies in the ISS (four in the FTY 1.25 group (0.4%) and one in the FTY 0.5 mg group (0.1%)). There were no such cases in the placebo and IFN treatment groups. Seven SAE of macular edema were reported from extension studies included in the ISS (1 on FTY 5mg, 5 on FTY 1.25mg and 1 on FTY 0.5 mg). Four SAE of macular edema were reported in study 2309 (2 on FTY 1.25, 1 on FTY 0.5 and 1 on placebo).

Of the 12 patients who developed SAE of macular edema in the ISS, 4 had a past history of optic neuritis or uveitis before entering the study. None of the patients was diabetic. Except for one subject who retrospectively may have had active uveitis at the time of randomization, no patients had active uveitis or macular edema at screening (because that would be an exclusion criterion).

Few patients had symptoms at the time of the diagnosis of macular edema (decreased vision, blurred vision, feeling of pressure in one eye or visual acuity testing decreased) but most were asymptomatic. Most cases were diagnosed by dilated ophthalmologic evaluation or OCT at protocol scheduled timepoints. In some cases CFT measured by OCT was obviously increased; in others it was mildly increased, but fluorescein angiography (FA) confirmed capillary leaking consistent with macular edema. Some cases were bilateral but most cases involved only one eye.

Onset of SAE of macular edema in the ISS was reported as early as 11 days and as late as 932 days into study treatment, however the two cases with the longer time to onset were actually not

confirmed by OCT. Most cases occurred earlier than 3-4 months into treatment (mean= 207 days; median 99 days).

SAEs of ME led to drug discontinuation. Few patients received additional treatment (NSAIDs, topical steroids). Most patients recovered completely within a few weeks or months after drug discontinuation, with or without additional treatment but some recovered with sequelae of decreased vision.

It appears clear that fingolimod causes macular edema, including at the dose recommended for marketing (0.5 mg/day).

- SAE in the Eye disorders SOC, other than macular edema

There were three SAE of note other than macular edema, in the controlled studies. Two were in the FTY 1.25 mg group (one papilledema and one retinal micro-thrombosis), and one in the FTY 0.5 mg group (retinal detachment).

SAE in the Eye disorders SOC other than macular edema with FTY 1.25 in Pool D are as follows:

- **2301_0701_00036**. 18 F. Papilloedema on Day 11. Drug dc.
  Optic neuritis and blurred vision 15 months prior to study entry. OCT CFT at screening; 186/175 L/R. On Day 7, pain of L side of head without visual symptoms. On Day 11, left papilloedema. Day 40, OCT CFT: 192/183 L/R. Drug discontinued. Later treated with IFN on Day 116. FU on Day 100, OCT CFT: 194/199; FU Day 198, OCT CFT: 192/195. Ophthalmologic evaluation 30 days after drug dc still showed papilledema. Pt withdrew consent. On a f/u visit, 188 days after drug discontinued, an ophthalmologist said that papilloedema was still present but improved from prior visit.
  The DSMB ophthalmologist thought it was most likely related to papillophlebitis due to oral contraceptive use and not related to drug.

- **2301_0458_00002**. 30 M. Retinal disorder (retinal micro-thrombosis) on Day 29.
  No history of eye problems. On Day 29 presented retinal microthrombosis (MTHFR mutation +hyperhomocysteinemia). Drug permanently discontinued. Relationship to study drug was suspected. Treated with folic acid. CFT at screening: 150/153 L/R; CFT at End of study (D29) 165/156 L/R.
  The patient may have a predisposition to develop thromboses, however, S1P is involved in the regulationof thrombogenesis and the role of FTY in this event can not be ruled out.

The narrative of the SAE of retinal detachment on FTY 0.5 mg is as follows

- **2301_ 0851_00019.** 51 M. Retinal detachment on days 136, 189 and 261. MS diagnosed 4 years prior. No history of eye problems. Concomitant meds: oxcarbazepine. On Day 136 he suffered a loss of vision in one eye. He was diagnosed with retinal detachment. Treated with surgery x 3 (because of recurrent detachment). Investigator thought it was not related to drug.
  It is difficult to attribute this to study drug when there is no previous suspicion and there were no cases at the higher dose. There were no SAE of retinal detachment with the 1.25 mg dose, however, there were 2 "non-serious" retinal detachments with the 1.25 mg dose. Whether retinal detachment is related to fingolimod use will require a larger database and can be evaluated in the applicant's proposed postmarketing registry.

In addition to the serious AE in the Eye disorders SOC there were some cases that led to drug discontinuation and were coded as non-serious, including one case of "bilateral retinal ischemia/retinal occlusive disease/vasculitis", in the fingolimod 1.25 mg treatment group. These cases are described among cases leading to discontinuation in the Eye disorders SOC.

- SAE in the Respiratory, Thoracic and mediastinal disorders SOC and Investigations (respiratory related) SOC.

The number of patients with SAE in the Respiratory SOC in safety pool D and E are presented in the following tables.

Table 27. **Serious AE, Respiratory, thoracic & mediastinal disorders SOC, safety pool D.**

Primary system organ class Preferred term	FTY720 5 mg (N=94) n (%)	FTY720 1.25 mg (N=943) n (%)	FTY720 0.5 mg (N=854) n (%)	Placebo (N=511) n (%)	Interferon (N=431) n (%)
Respiratory, thoracic and mediastinal disorders					
-Total	1 (1.1)	6 (0.6)	3 (0.4)	3 (0.6)	1 (0.2)
Dyspnoea	1 (1.1)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Pleurisy	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperventilation	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia aspiration	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Productive cough	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Asthma	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Chronic obstructive pulmonary disease	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Dyspnoea exertional	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Pneumothorax	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)
Pulmonary embolism	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Pulmonary oedema	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)

Source: Post Table 4.4-9, ISS. All three placebo controlled studies. A patient with multiple occurrences of the same AE under one treatment is counted only once in the AE preferred term for that treatment. A patient with different adverse events within a primary system organ class is counted only once in the total row.

> *Most episodes of dyspnea in the controlled studies appear to be cardiac-related, but the work-up was incomplete to adequately characterize them. Of note, one subject on placebo developed worsening asthma. There were no reports of asthma/worsening asthma/bronchoconstriction in the fingolimod treatment groups in the controlled studies. Brief narratives of SAE in this SOC in the controlled studies are presented in Appendix 9.4.8.a.*

SAE in the Respiratory SOC in safety pool E are presented in the following table.

Table 28. Serious AE, Respiratory, thoracic & mediastinal disorders SOC, safety pool E (updated).

Primary system organ class Preferred term	FTY720 5 mg - 1.25 mg (N=137) n (%)	FTY720 1.25 mg (N=1302) n (%)	FTY720 0.5 mg (N=1176) n (%)
-Total	4 (2.9)	10 (0.8)	5 (0.4)
Dyspnoea	1 (0.7)	4 (0.3)	0 (0.0)
Pleurisy	0 (0.0)	2 (0.2)	0 (0.0)
Asthma	2 (1.5)	1 (0.1)	0 (0.0)
Hyperventilation	0 (0.0)	1 (0.1)	0 (0.0)
Hypoxia	0 (0.0)	1 (0.1)	0 (0.0)
Lung disorder	0 (0.0)	1 (0.1)	0 (0.0)
Pneumonia aspiration	0 (0.0)	1 (0.1)	0 (0.0)
Pneumothorax	0 (0.0)	1 (0.1)	1 (0.1)
Productive cough	0 (0.0)	1 (0.1)	0 (0.0)
Bronchospasm	1 (0.7)	0 (0.0)	0 (0.0)
Dyspnoea exertional	0 (0.0)	0 (0.0)	1 (0.1)
Pulmonary embolism	0 (0.0)	0 (0.0)	1 (0.1)
Pulmonary oedema	0 (0.0)	0 (0.0)	1 (0.1)
Snoring	0 (0.0)	0 (0.0)	1 (0.1)

Source Table 4.5-12 ISS SUR.

SAE in the Respiratory, thoracic and mediastinal disorders in the fingolimod extension studies included 3 cases of asthma/bronchospasm in the FTY 5 – 1.25 mg group; one of exacerbation of asthma, one lung disorder, one hypoxia and one pneumothorax/ acinetobacter pneumonia in the FTY 1.25 mg group (the latter was described under SAE of Infections); and one pulmonary embolism in the FTY 0.5 mg group. One SAE of hypoxia was reported in the FTY 1.25 mg group and one of pneumothorax was reported in the FTY 0.5 mg group in the SUR. Brief narratives of these cases are presented in Appendix 9.1.8.b

> *Four subjects presented asthma/bronchospasm during the extension studies: three in the 5 to 1.25 mg/day treatment group (two of them were new onset and one was exacerbation in subject with a history of asthma) and one in the FTY 1.25 mg group (in a subject with a prior history of mild asthma). Although they occurred in the uncontrolled portion of the studies, the finding is consistent with known effects of SP1 (increasing bronchoconstriction). No episodes of asthma occurred in the 0.5 mg group.*

- SAES in Vascular disorders SOC

Two serious AE of peripheral artery disease occurred in the FTY 1.25 mg group in the controlled studies. SAE in the vascular disorders SOC are presented in the following tables, for safety pools D and E.

Table 29. Serious AE, Vascular disorders SOC, safety pool D

Primary system organ class Preferred term	FTY720 5 mg (N=94) n (%)	FTY720 1.25 mg (N=943) n (%)	FTY720 0.5 mg (N=854) n (%)	Placebo (N=511) n (%)	Interferon (N=431) n (%)
Vascular disorders					
-Total	1 (1.1)	3 (0.3)	1 (0.1)	2 (0.4)	0 (0.0)
Arterial occlusive disease	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Hypertensive crisis	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Peripheral arterial occlusive disease	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Circulatory collapse	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Hypertension	1 (1.1)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Varicose vein	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)

Source: Post Table 4.4-9, ISS. All three placebo controlled studies. A patient with multiple occurrences of the same AE under one treatment is counted only once in the AE preferred term for that treatment. A patient with different adverse events within a primary system organ class is counted only once in the total row.

The two cases of peripheral arterial occlusion are described in detail below.

- **2302_0330_00005 - Peripheral arterial occlusive disease**

  41 y.o. female. MS diagnosed 24 years prior to study entry. No treatment with other immuno suppressors prior to entry. Concomitant meds included carbamazepine (started 38 days prior to entry for brainstem paroxisms). She was not taking other concomitant medications. On **Day 7** of FTY 1.25 mg she had pain in the left hand. Fingertips were blue but not cold. The following morning there were splinter hemorrhages in all fingernails of L hand. This resolved within 2 days and patient remained asymptomatic. She was treated with ibuprofen for Raynaud's phenomenom. On Day 13 she awoke with a similar episode. On physical exam she had normal appearing left hand with symmetrical radial pulse and splinter hemorrhages. Drug was discontinued on Day 14. Laboratory findings on Day 15 showed no evidence of vasculitis, thrombosis or Thrombotic Thrombocytopenic Purpura (D dimer, fibrinogen, platelet count, ANA, ANCA, cardiolipin IgG, cardiolipin IgM, rheumatoid factor, C3c-complement, C4- complement, cryoglobulins, immunofixation and C reactive protein normal). The consulting rheumatologist suggested the diagnosis of a "non-specific collagenosis." Blood pressure was normal. No values for CBC including lymphocyte and platelet count were provided in the narrative or in the patient profile.

  Two days after the last dose of the study medication, duplex ultrasound of the arteries of the left arm was normal. There was increased blood pressure to 165/85 mmHg (HR 80 bpm) for 30-60 minutes in relationship to emotional stress. Complete normalization was seen within 1 hour.

  Eleven days after study drug discontinuation, the patient experienced worsening of the symptoms (increase in left hand pain and fingers getting blue and cold) and tramadol was added as treatment.

  Two days later (13 days after drug dc) she presented to the emergency room with increasing pain. She had a livid and cold left hand and fingers with a decreased left radial pulse. An emergency Doppler-duplex scan showed evidence of left hand hypoperfusion clearly asymmetric compared with the right hand. Additionally, an emergency angiography (performed via the femoral artery) revealed the absence of distal perfusion of all lower arm and hand arteries in the left upper extremity. Ulnar and radial arteries were visible but with somewhat delayed outflow. There was no Doppler signal in the

arterial arch of left hand. Arteries in the R hand appeared normal. The right radial pulse was detectable. The patient was hospitalized in the intensive care unit. An intra-arterial angiography catheter was placed and left in the brachial artery for monitoring and treatment. She was given fibrinolytic therapy (intraarterial urokinase) and infusions of alprostadil (PG E1) and heparin. The following morning (14 days after drug dc), the distal pulse in her left upper extremity was absent and further empirical therapy was administered.

Fifteen days after drug dc, angiography showed a thrombus in the radial artery which was treated with intra-arterial fibrinolysis (rtPA bolus). Concomitant medication was given. Between 23-Mar-2007 and 30-Mar-2007, progressive clinical improvement was seen. The patient's left hand was warm but with livid and blue fingertips (especially 2nd finger) and blisters on her fingertips. Her radial pulse was absent. A follow up angiography showed the absence of representation of radial and ulnar artery with distal perfusion of the hand via the interosseus artery. The patient was discharged from the intensive care unit to the vascular surgery department.

24 days after drug dc, due to persistent pain and in order to improve distal perfusion, it was decided to implant a catheter for continuous anesthetic treatment in the left brachial plexus. Symptoms of MS relapse were reported to be resolved. 28 days after drug dc her hand appeared warm, with good color in most fingers but evidence of necrosis in 2nd and 5th left fingertips. The radial and ulnar pulses were absent.
The patient was discharged home with continuous analgesic and anesthetic therapy via catheter in the region of the left brachial plexus. Surgical sympathetic block of the left brachial plexus planned for beginning of May as analgesic therapy and in order to permanently improve distal perfusion in left upper extremity.

Two months after drug dc the patient experienced an MS relapse that improved after steroid treatment. Finger necrosis was reported to have decreased and the functionality of her hand had improved. The sympathetic blockade that was planned initially was not carried out.

Hypercoagulability workup showed mild hyperhomocysteinemia: 14.8 μmol/l (nl <12) but otherwise was unremarkable. She had heterozygote polymorphism of the MTHFR 677T gene. Serum testing for antibody to β-2-glycoprotein 1 was negative. Specific platelet function/activation tests were not performed. Transesophageal echocardiography revealed no evidence for a cardiac embolism source. There was moderate reduced systolic function of the left ventricle and the cardiologist believed this to be of no clinical relevance and not related to the left forearm event.

She recovered with sequelae (left hand still felt cooler than right). No further occurrences of hypoperfusion or Raynaud symptoms have been observed since the SAE. After changing the therapy to interferon-beta, no further clinical relapses of MS were reported. The patient discontinued from the core phase of the study.

Comment: This case was published as a case report in the journal Neurology.[6] It was reported as a case of vasospasm.

- **2302_0306_00011 - Peripheral artery disease**

MS diagnosed 17 years prior. History of optic neuritis, sinus tachycardia, migraines. Smoker until 1 year prior. Family history of cardiac disorders. She had no other vascular risk factors such as HTN or

[6] Schwarz et al. Critical vasospasm during fingolimod (FTY720) treatment in a patient with multiple sclerosis. Neurology. June 15 2010, 74(24):2022-4.

diabetes and was not taking hormones. Received IFN in the past. Concomitant meds: bisoprolol for sinus tachycardia for several years. On Day 130 she had nonserious migraine-like headache and was treated with naritriptan. On Day 140, she presented with peripheral arterial occlusion in both feet, with "necrosis and hemorrhages" under the nails in digit 3 and 4 of R foot and digit 5 of L foot. She had coldness of the skin and discoloration of toes. On Day 144 the 5 toe of L foot had a dark red discoloration. Study drug was discontinued due to arterial occlusive disease on Day 145. Lesions looked like those seen with skin embolism.

A color coded Doppler sonography of the arteries of the right distal lower leg was performed and revealed a patent but narrow pedal dorsal artery with a spastic flow profile, a patent posterior tibial artery that could be traced down to the tarsal bones and a fibular artery that faded away on the distal lower leg. The popliteal artery was noted to be of normal caliber with a pronounced collateral in the first posterior branch (P1), the cause of which was not apparent. The patient was started on acetylsalicylic acid and clopidogrel.

Nine days after the discontinuation of the study medication, the blood flow disorders in the forefoot had markedly regressed and the investigator was able to palpate the dorsal pedal artery well on both sides again. The feet were less cold and the livid alterations and bleeding in the toes were noted to be regressing. There was no hypercoagulable state. The patient's condition was further improved at this visit, but was not completely resolved. The patient still had livid coloring (though better than the previous week) on digit I and V of the right foot and digit V on the left foot. The patient had no motor impairment and the arteries were palpable.

On (b) (6), a magnetic resonance angiography (MRA) of the arteries of both legs was performed and revealed no pathological findings. The event (arterial occlusive disease) resolved on (b) (6), 37 days after the last dose of the study medication.

In addition to these cases, a patient in study 2309 developed right leg vasospasm (2309 0510-0006) and another developed transient cyanotic bilateral hands and bilateral tight blotchiness (2309 0606 00002)(the latter was unblinded and was on placebo).

> *Because of these events of arterial occlusive disease, the applicant was asked to submit brief narratives of cases suggestive of arterial ischemia/thrombosis in the renal transplant population. Review of these cases identified two cases of finger or toe necrosis, one in a patient receiving FTY 2.5 mg and one in a patient receiving MMF. Both were diabetic. The first patient had inadequate glycemic control during the study. On Day 197 post transplant/FTY treatment she presented necrosis of the right big toe requiring amputation. The second patient approximately 2 months into MMF treatment, developed ulceration and necrosis of the fingertips of both hands. Review of these cases did not provide any clue as to the potential mechanism of toe/finger ischemia in the MS population.*

Vascular disorders in safety pool E are presented in the following table:

Table 30. SAES in Vascular disorders SOC, safety pool E

Primary system organ class Preferred term	FTY720 5 mg - 1.25 mg (N=137) n (%)	FTY720 1.25 mg (N=1157) n (%)	FTY720 0.5 mg (N=1021) n (%)
Vascular disorders			
-Total	3 (2.2)	5 (0.4)	1 (0.1)
Arterial occlusive disease	0 (0.0)	1 (0.1)	0 (0.0)
Deep vein thrombosis	0 (0.0)	1 (0.1)	0 (0.0)
Flushing	0 (0.0)	1 (0.1)	0 (0.0)
Hypertensive crisis	0 (0.0)	1 (0.1)	0 (0.0)
Peripheral arterial occlusive disease	0 (0.0)	1 (0.1)	0 (0.0)
Hypertension	1 (0.7)	0 (0.0)	0 (0.0)
Varicose ulceration	1 (0.7)	0 (0.0)	0 (0.0)
Varicose vein	1 (0.7)	0 (0.0)	1 (0.1)

Table 4.5-12 original ISS.

As seen in these tables, the number of vascular disorders was small and there did not seem to be a difference in risk among groups in the controlled studies. Overall, there seemed to be a dose response in terms of vascular events among fingolimod 1.25 and 0.5 mg in safety Pool E. No cases of peripheral artery occlusion occurred at the 0.5 mg dose in the ISS studies.

> *An increasing body of literature indicates that S1P has a role in the regulation of vascular homeostasis, vascular tone and vascular permeability, angiogenesis and thrombogenesis, raising the possibility that S1P receptor modulation by fingolimod might have some effects (favorable or deleterious) in the CV system. The number of serious ischemic/thrombotic events is too small to draw definitive conclusions. However, it suggests an increased risk of ischemic/thrombotic events with FTY 1.25 mg. The applicant proposes to explore the possibility of increased risk of cerebrovascular disease in a post-marketing registry (PASS). The potential increase of peripheral vascular disease should also be explored in such a study.*

- SAES in the General disorders and administration site conditions

SAES in the General disorders and administration site conditions SOC are presented in the following table for Safety Pool D.

Table 31. Serious AE, General disorders and administration site conditions, safety pool D

Primary system organ class Preferred term	FTY720 5 mg (N=94) n (%)	FTY720 1.25 mg (N=943) n (%)	FTY720 0.5 mg (N=854) n (%)	Placebo (N=511) n (%)	Interferon (N=431) n (%)
General disorders and administration site conditions					
-Total	2 (2.1)	5 (0.5)	5 (0.6)	2 (0.4)	2 (0.5)
Chest pain	2 (2.1)	1 (0.1)	2 (0.2)	0 (0.0)	0 (0.0)
Fatigue	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Haemorrhagic cyst	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Multi-organ failure	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Pyrexia	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.2)
Inflammation	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Influenza like illness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Non-cardiac chest pain	0 (0.0)	0 (0.0)	2 (0.2)	2 (0.4)	0 (0.0)

Source: ISS Table 4.4-9. A patient with multiple occurences of the same AE under one treatment is counted only once in the AE preferred term for that treatment. - A patient with different adverse events within a primary system organ class is counted only once in the total row.

Within the General disorders and administration site conditions, the only events that occurred in more than one patient were chest pain and non-cardiac chest pain.

There was no imbalance in the distribution of these cases and all were thought to be non-cardiac, and only one required drug discontinuation. However, some appear to have had incomplete work up to determine the etiology of the chest pain. Three cases occurred within the first few days of FTY treatment, in association with bradycardia, dizziness or increased blood pressure. Narratives of the cases in safety pool D are presented in Appendix 9.4.9.

Other events occurred in one patient only and were similarly distributed among groups. Of note, the patient listed as having multi-organ failure was the patient who died of disseminated herpes infection.

The analysis in Pool E was consistent with the analysis in pool D (data not shown).

- SAEs reported in the Hepatobiliary disorders SOC

SAES in the Hepatobiliary disorders SOC are shown in the following tables for Safety Pool D and E.

Table 32. Serious AE, Hepatobiliary disorders SOC, safety pool D.

Primary system organ class Preferred term	FTY720 5 mg (N=94) n (%)	FTY720 1.25 mg (N=943) n (%)	FTY720 0.5 mg (N=854) n (%)	Placebo (N=511) n (%)	Interferon (N=431) n (%)
Hepatobiliary disorders					
-Total	0 (0.0)	2 (0.2)	4 (0.5)	1 (0.2)	1 (0.2)
Biliary colic	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)
Cholelithiasis	0 (0.0)	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.2)
Jaundice	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Cholecystitis acute	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Cytolytic hepatitis	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Hepatic steatosis	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Hepatomegaly	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)

Source: Post Table 4.4-9, ISS. All three placebo controlled studies. A patient with multiple occurrences of the same AE under one treatment is counted only once in the AE preferred term for that treatment. A patient with different adverse events within a primary system organ class is counted only once in the total row.

Table 33. Serious AE, Hepatobiliary disorders SOC, safety pool E.

Primary system organ class Preferred term	FTY720 5 mg - 1.25 mg (N=137) n (%)	FTY720 1.25 mg (N=1157) n (%)	FTY720 0.5 mg (N=1021) n (%)
Hepatobiliary disorders			
-Total	0 (0.0)	5 (0.4)	5 (0.5)
Biliary colic	0 (0.0)	2 (0.2)	2 (0.2)
Cholelithiasis	0 (0.0)	2 (0.2)	2 (0.2)
Hepatitis	0 (0.0)	1 (0.1)	0 (0.0)
Jaundice	0 (0.0)	1 (0.1)	0 (0.0)
Cholecystitis acute	0 (0.0)	0 (0.0)	1 (0.1)
Cytolytic hepatitis	0 (0.0)	0 (0.0)	1 (0.1)
Hepatic steatosis	0 (0.0)	0 (0.0)	1 (0.1)
Hepatomegaly	0 (0.0)	0 (0.0)	1 (0.1)

Source Table 4.5-12 original ISS.

The most common serious events in this SOC were cholelithiasis and biliary colic in the FTY treatment groups. One episode of cholelithiasis was accompanied by jaundice (2201_0023_00003, 52 year old male). None of the cases led to drug discontinuation. Review of these cases does not suggest that the events are drug related. Other than cholelithiasis and biliary colic, there was one case of cytolitic hepatitis/esteatosis/ hepatosplenomegaly (ID# 2301.0109-00002) and one "hepatitis toxic" (2201 0002_0001) in subjects receiving fingolimod in the controlled studies, and one case coded as "hepatitis" in the extension studies (E12201_0061_00011).

Additionally, 8 subjects presented liver-related SAEs in the Investigations SOC (5 on FTY 1.25, 2 on FTY 0.5 and one on placebo). Most SAE of liver-related investigations led to study drug discontinuation. On the other hand, there were many liver-related events that led to study discontinuation but were not coded as serious (these are discussed in the Discontinuation due to AE section).

The number of patients with SAE in the Hepatobiliary disorders SOC and Investigations SOC in the controlled studies is presented as follows.

Table 34. Patients with SAE in Hepatobiliary and Investigations (liver-related) SOCs, safety pool D

MedDRA SOC	FTY 5 mg **N=94**	FTY 1.25 **N= 943**	FTY 0.5 **N= 854**	Placebo **N= 511**	IFN **N= 431**
	n (%)	n (%)	n (%)	n (%)	n (%)
Total	0	7 (0.7)	5 (0.6)	1 (0.2)	1 (0.2)
Hepatobiliary	-	2	4	-	1
Investigations[1]	-	5	2	1	-

Source: AE datasets. [1]Investigations include: liver function test abnormal, ALT increased, GGT increased, AST increased and hepatic enzyme increased.

This analysis suggests an increased risk of liver-related SAES in the FTY treatment groups as compared to placebo, but the numbers are small.

Review of the available narratives indicated that except for 1 case, bilirubin (BR) and alkaline phosphatase (ALK P) were within normal values. This case is presented as follows. Additional narratives are presented in Appendix 9.4.10.

- **2301_0109_00002. 41 F.** Cytolytic hepatitis on Day 301. Led to dc. On FTY 0.5 mg. Concomitant use of iv paracetamol.
  Medical hx of depression, elevated GGT for one year, taking multiple concomitant meds. On Day 203 of FTY 0.5 mg she was admitted to hospital for a few days with vomiting, syncope and elevated liver enzymes (GGT was 4x ULN and AST 2x ULN). She was diagnosed with anorexia, depression, exacerbation of consumption of alcoholic drinks and stable MS. On Day 298 of FTY 0.5 mg treatment, she was hospitalized with MS relapse and pain on L hip. On admission AST was 121 U/L (nl <37), and ALT was 101 U/L (nl <40). BR was 0.57 mg/dl (nl 0.2-1.0). Patient was treated with IV paracetamol for 3 days. On Day 301 the patient had an abrupt elevation in liver enzymes with AST was 9580 U/L ALT was 4332 U/L, GGT was 160 U/L (reference range: 5 – 36), and AP (alkaline phosphatase) 123 U/L (reference range: 5 – 36). Total bilirubin was not reported. Study medication was permanently discontinued on Day 304 due to the event. Hepatitis serology was negative. Negative HSV and EVB IgM serology. An abdominal US on Day 304 showed moderate hepatomegaly and steatosis. Discharge diagnosis was hepatomegaly and steatosis and episode of "acute hepatic cytolysis of undetermined origin". This patient had pre-existent elevated liver enzymes (AST>ALT), and suspected alcohol abuse. She received intravenous and oral paracetamol (up to 4 g i.v. on the second day of admission).
  Two factors (alcohol abuse and paracetamol use) may explain the dramatic increase in liver enzymes and hepatic steatosis, although the role of FTY in the underlying liver enzyme elevation can not be ruled out.

In the extension studies in the original ISS, one case of hepatitis, one biliary cholic and two cases of cholelithiasis were reported as SAEs in the Hepatobiliary system disorders SOC. Only one subject reported a serious liver-related event in the Investigations SOC in the extension studies in

the original ISS (hepatic enzyme increased, that did not lead to drug dc). The case of hepatitis is as follows.

- **2201E_0061_00011**. 23 F. Hepatitis on Day 179.

  Concomitant medication taken prior to randomization included alprazolam, gabapentin and omeprazole for 2 months prior to study entry. On Day 153 started oxybutinin for urinary incontinence. On Day 179 of FTY treatment (day 1 of extension study) she had elevated transaminases with normal BR and ALK Phos (ALT 250 U/L, AST 147 U/L, bilirubin 3.4 µmol/L (normal up to 20.5) and Alkaline Phosphatase 41 U/L. She was subsequently diagnosed with hepatitis. Oxybutinin was stopped on Day 189. No treatment was reported to be given for this event. On Day 207, there was further increase of liver enzymes with ALT of 644 U/L, AST 288 U/L, bilirubin 5.1 µmol/L and alkaline phosphatase 45 U/L. The study medication was permanently discontinued due to the event (hepatitis) and the patient received the last dose of the study medication on Day 213, extension Day 35. The last available laboratory showed ALT 45 and AST 35 U/L, respectively.

On 4/29/10, an IND report of a patient who developed ALT >20x ULN and jaundice while receiving fingolimod in extension study 2302E1 was submitted to the FDA. This case is as follows.

- **2302E1-0303-00021.** 41 M. Jaundice (with FTY 1.25 mg and with FTY 0.5 mg)

  41 year old male, received IFN during core study and FTY 1.25 mg during the extension. No history of liver disease or alcohol abuse. He had normal liver enzymes at baseline and throughout the core study. He started FTY 1.25 mg on Day 366 of the study. On Day 429 (Day 51 on FTY 1.25 mg) he had increase in ALT= 246 U/L (nl 0-45), AST 83 U/L (nl 0-41). Drug was interrupted until full normalization and re-started on study day 635, at the dose of 1.25 mg day. As per a protocol amendment, the dose was decreased to 0.5 mg on study day 925 (approximately 9 months after being on FTY 1.25 for the second time). That day (approximately 3 weeks before the event of jaundice was reported) he had normal liver enzymes.

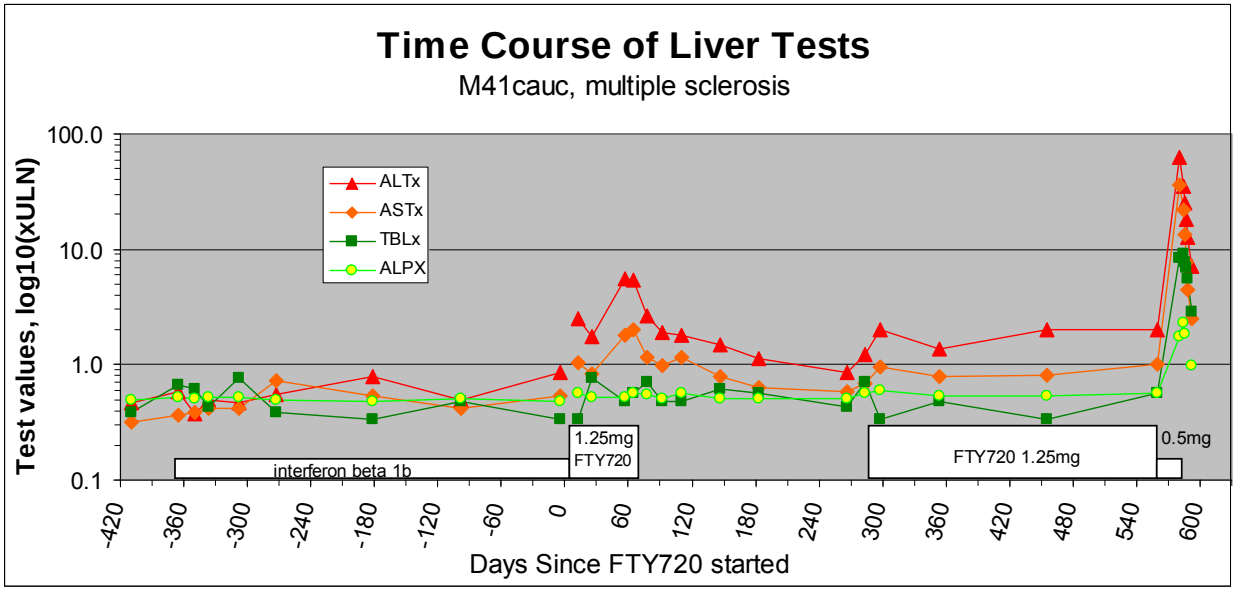
  On study day 945 (21 days into taking the 0.5 mg dose), he informed the investigator by telephone that he had been noted to be yellow for 2 days. He stopped study drug. The following day the patient was found to have jaundice with scleral involvement, fatigue, exhaustion, feeling pressure under the right costal arch, dark stools and urine. His ALT was 2787 U/L, AST was 1466 U/L, GGT was 292 U/L, total BR 177 µmol/L, direct bilirubin was 139 µmol/L and alkaline phosphatase was 218 U/L. The patient was hospitalized with icteric syndrome. An abdominal ultrasound showed moderate splenomegaly. The liver and gall bladder looked normal. Additional laboratory analysis showed leukocyte count 3.9x10^9/L, platelet count 208x10^9/L and haemoglobin 163g/L. HBsAg, anti-HBs Ab, anti HBc/IgM and IgG Ab and anti HAV/IgM and IgG Ab were all negative. Anti HCV Ab was also negative and Heptatitis C virus RNA in blood was negative. Epstein-Barr EBV-VCA-gp125-IgG antibody test was negative. EBV-EBNA-IgG antibody test was positive. EBV-EA-IgG antibody test was negative. EBV-VCA-p18-IgG antibody test was positive. EBV-VCA-IgM antibody test was lesser than 4 U/mL (reference range lesser than 5). Cytomegalovirus IgG antibody in serum was 0.8 AU/mL (reference range lesser than 15). Cytomegalovirus IgM antibodies in serum was negative. Herpes simplex 1/2 IgG antibodies in serum was 114.3 U/mL (reference range lesser than 20). Herpes simplex 1/2 IgM antibodies in serum was 18.0 U/mL (reference range lesser than 20).

On study day 953, liver enzymes had decreased as follows: ALT 802 U/L, total BR 115.69 µmol/L. He was found to have mild decreased albumin of 34 g/L (NR 35-50 g/L) and increased ferritin at 775 ng/mL (NR 22-322 ng/mL). Serum creatinine, electrolytes, PT and PTT were normal. C-reactive protein was elevated at 14.5 mg/L (NR 0.1-5 mg/L). Serum amylase and lipase and blood glucose were all normal.

Further history revealed that the patient's female partner was discovered "by chance" to have a hepatitis C infection five years prior. This was reported to be a chronic form with liver damage. However, no treatment had been instituted because of low viral load. Reportedly, she had not so far taken any virus inhibiting medications.

Prior to the event of jaundice he had been taking sodium bicarbonate and a combination of magnesium and aluminium salts. He did not take paracetamol. On the day after he called the investigator to report jaundice, he started taking holy thistle, a herbal medicine. He also reported that prior to the event he developed pain in the lower legs after cutting down a tree and he applied Chinese oil to the lower limbs.

The patient was discharged from the hospital 9 days after drug discontinuation. A repeat abdominal ultrasound showed no changes from the first one. He was seen as an outpatient 3 days and 1 week after discharge. He still had slight scleral jaundice and liver biochemistry continued to improve. At the last available laboratory evaluation 11 days after drug discontinuation showed ALT 318, ALT 103, GGT 97, total BR 60, direct BR 40, Alkaline phosphatase 122. The course of liver enzymes is presented as follows (graphic provided by Dr. John Senior):



Dr. John Senior, FDA hepatologist consultant, reviewed this case on May 25, 2010. He recommended that retesting of hepatitis antibodies be done to absolutely rule out an infection. Failing discovery of any alternative cause, the case would have to be considered serious and very likely fingolimod-induced. Additional information on this case was received on 5/25/10. At the time of the jaundice, the patient had positive serology testing for Hepatitis E (IgG and IgM), consistent with a recent Hepatitis E infection. Hepatitis E RNA PCR in the blood sample from 3

weeks previous to the event and at the time of the initial report of jaundice was positive. A follow up laboratory test indicated negative Hepatitis E RNA PCR and a drop in IgM levels.

Review of liver related SAE indicates a relationship between the use of fingolimod and liver enzyme elevation, mostly transaminase and GGT elevation, with normal BR and alkaline phosphatase. Patients were asymptomatic and the diagnosis was made during protocol scheduled laboratory examinations, as early as 2-3 weeks into the study (mean 162 days, range 19 to 301 days in the FTY group; the case on placebo was diagnosed on day 540). Several cases were confounded by the use of concomitant medications that may have caused hepatotoxicity, such as paracetamol or other analgesics. However, all cases improved and most fully resolved after fingolimod discontinuation (10 days to 3 months after dc). One patient who was on FTY received intravenous paracetamol and developed ALT> 4000. There was at least one clean case with FTY 0.5 mg where there was no use of concomitant medications (2302_0330_00004).

Dr. Senior's recommendation regarding liver enzyme monitoring ar as follows:

"It is not clear that systematic monitoring of serum ALTs should be attempted. It has not been found to be effective in preventing serious problems for other drugs and generally is not well done. Warning physicians alert for early symptoms of liver dysfunction, and interrupting treatment promptly to investigate liver injury further, may be sufficient."

Given Dr. Senior's experience, I would agree with not monitoring transaminases with a pre-determined schedule. However, I would recommend that baseline transaminases and bilirubin be obtained, to have a baseline to compare in case of development of liver toxicity during fingolimod treatment.

- SAE in Blood and lymphatic system disorders SOC in Safety pools D and E

There were few serious events in the Blood and lymphatic system disorders SOC. The most common event was lymphopenia, although there were two serious cases of thrombocytopenia with fingolimod (one thrombocytopenia at the 0.5 mg dose during the controlled studies and one autoimmune thrombocytopenia at the 1.25 mg dose during the extension studies). SAES in this SOC are shown in the following tables.

Table 35. Serious AE, Blood and Lymphatic system disorders SOC, safety pool D

Primary system organ class Preferred term	FTY720 5 mg (N=94) n (%)	FTY720 1.25 mg (N=943) n (%)	FTY720 0.5 mg (N=854) n (%)	Placebo (N=511) n (%)	Interferon (N=431) n (%)
Blood and lymphatic system disorders					
-Total	0 (0.0)	3 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)
Lymphopenia	0 (0.0)	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Leukopenia	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Thrombocytopenia	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)

Source: Post Table 4.4-9, ISS. All three placebo controlled studies. A patient with multiple occurrences of the same AE under one treatment is counted only once in the AE preferred term for that treatment. A patient with different adverse events within a primary system organ class is counted only once in the total row.

Three cases of Lymphopenia on FTY 1.25 and one thrombocytopenia on FTY 0.5 were reported in the controlled studies. The narrative of the case of thrombocytopenia is as follows. Listing of the cases of lymphopenia are in Appendix 9.1.11.

- **2301_0501_00005.** 45 M. Thrombocytopenia on Day 122. Led to dc. (On FTY 0.5 mg in pool D) On Day 97 of FTY 0.5 mg, laboratory showed platelet count = 85,000/ul. Baseline platelet value is not available. He was receiving gabapentin and pregabalin for neuropathic pain. Patient advised to discontinue these antiepileptic drugs and retest in 3 weeks. Repeat testing on Day 122 confirmed platelet count= 64,000/ ul. Pt hospitalized. Bone marrow biopsy on Day 122 showed slight reduction of cellularity and normal levels of megakaryocytes with hypolobulated nuclei. Antiplatelet antibodies were negative. Serum protein electrophoresis was within normal. US of spleen was normal. Fingolimod was discontinued on Day 122 due to this event. Repeat test 18 days after the last dose, platelet = 56,000/ul, without evidence of bleeding. He was treated with i.v. immunoglobulin therapy x 5 days. Platelet count was follow regularly at the local lab, the lowest count was 53,000 (48 days after drug discontinuation). The latest platelet count was 160,000 2 months after drug discontinuation. Follow up 9 ½ months after drug discont: platelet count remained 88-105,000, without bleeding. The patient continues to get iv immunoglobulin. Bone marrow biopsy showed "bone marrow with a low degree of cellularity reduction" with "megakaryocytes at the upper limit of normal" Spleen was normal. No autoantibodies detected.

  This AE was temporarily related to initiation of FTY therapy but the patient did not fully recover 9 months after drug discontinuation. This case is consistent with ITP because of the response to IVIG. The role of FTY in development of thrombocytopenia can not be ruled out. Gabapentin and pregabalin may have also played some role in this case.

Table 36. Serious AEs, Blood and Lymphatic disorders SOC, safety pool E

Primary system organ class Preferred term	FTY720 5 mg - 1.25 mg (N=137) n (%)	FTY720 1.25 mg (N=1157) n (%)	FTY720 0.5 mg (N=1021) n (%)
-Any primary system organ class -Total	36 (26.3)	146 (12.6)	99 (9.7)
Blood and lymphatic system disorders -Total	1 (0.7)	5 (0.4)	3 (0.3)
Lymphopenia	0 (0.0)	4 (0.3)	0 (0.0)
Autoimmune thrombocytopenia	0 (0.0)	1 (0.1)	0 (0.0)
Leukopenia	0 (0.0)	1 (0.1)	1 (0.1)
Lymphadenopathy	0 (0.0)	0 (0.0)	1 (0.1)
Neutropenia	1 (0.7)	0 (0.0)	0 (0.0)
Thrombocytopenia	0 (0.0)	0 (0.0)	1 (0.1)

Source Table 4.5-12 original ISS.

The case of SAE of autoimmune thrombocytopenic purpura in the extension studies is as follows.

- **2302E1-0316-00010.** FTY 1.25 mg . 44 F Idiopathic thrombocytopenic purpura on Day 181 of FTY treatment. Received IFN during core study. MS dx 10 years prior to randomization. Hx of hyperthyroidism and menopause, taking levothyroxine and estrogens. During screeing platelet count was 236 $x10^9$/L. On day 487 it was 209 $x10^9$/L. On day 181 of FTY treatment platelet count was 4 $x10^9$/L. A hematologist diagnosed ITP. Drug was discontinued and patient was treated with steroids. At the time of last reporting, 5 months after drug dc the patient was considered completely recovered from ITP.

One SAE of thrombocytopenia was reported in study extension phase, on day 174 of FTY 1.25 mg, with a platelet count down to 20.000/L. Event resolved and study medication was restarted 2 months later.

In addition to these cases, there was a case of idiopathic thrombocytopenic purpura in study 2309 (non-ISS study) that is blinded. USA/0591/00001, a 48/F discontinued because of ITP on Day 421. Unblinding of this case has been requested.

> *Of note, in the renal transplant database, there were two events of autoimmune hemolytic anemia, seven of hemolytic uremic syndrome and 3 of thrombotic microangiopathy in the FTY treatment group, with no such cases in the MMF treated group. Findings in the renal program can not be extrapolated to the MS program, but raise concerns about additional hematologic fingolimod effects other than redistribution of lymphocytes. No hematologic concerning events such as those observed in the renal transplant program were observed in the MS program. However, two SAE of thrombocytopenia were reported with FTY (one in the controlled period with FTY 0.5 and one in the extension studies with FTY 1.25).*

7.3.3 Adverse Events leading to study drug discontinuation

235 subjects discontinued drug because of AEs in safety pool D (10.6% of subjects on FTY 5; 11.9% of FTY 1.25; 7% of FTY 0.5; 7% of placebo and 2.9% of IFN treated subjects). Overall, the risk of AE leading to study drug discontinuation was higher in the FTY 1.25 group as compared to placebo, FTY 0.5 and interferon. The difference was driven by AE in the Investigations (mostly liver-related investigations), Cardiac, and Eye disorders SOCs, which were the most common events leading to drug discontinuation. There was a dose response between FTY 1.25 and FTY 0.5 in these three SOCs.

The number of patients with adverse events that led to study drug discontinuation in pool D are presented in the following table, by SOC, for those events that occurred in at least 2 patients in at least one treatment group.

Table 37. Patients with AE leading to drug discontinuation in fingolimod MS studies, safety pool D*

System organ class Preferred term	FTY 1.25 **(N=943)** **n (%)**	FTY **0.5** **(N=854)** **n (%)**	**Placebo** **(N=511)** **n (%)**	**Interferon** **(N=431)** **n (%)**
Any AE leading to study drug discontinuation	**112 (11.9)**	**60 (7.0)**	**36 (7.0)**	**17 (3.9)**
Investigations	**47 (5.0)**	**30 (3.5)**	**7 (1.4)**	**9 (2.1)**
ALT increased	21 (2.2)	16 (1.9)	3 (0.6)	3 (0.7)
Hepatic enzyme increased	8 (0.8)	7 (0.8)	0 (0.0)	2 (0.5)
AST increased	5 (0.5)	6 (0.7)	1 (0.2)	1 (0.2)
GGT increased	5 (0.5)	9 (1.1)	1 (0.2)	0 (0.0)
Transaminases increased	5 (0.5)	1 (0.1)	0 (0.0)	0 (0.0)
DLCO decreased	4 (0.4)	0 (0.0)	2 (0.4)	2 (0.5)
Liver function test abnormal	4 (0.4)	0 (0.0)	0 (0.0)	2 (0.5)
Blood ALK P increased	1 (0.1)	2 (0.2)	0 (0.0)	0 (0.0)
Eye Disorders	**15 (1.6)**	**2 (0.2)**	**2 (0.4)**	**1 (0.2)**
Macular edema	10 (1.1)	1 (0.1)	0 (0.0)	1 (0.2)
Cardiac disorders	**12 (1.3)**	**1 (0.1)**	**2 (0.4)**	**1 (0.2)**
Bradycardia	5 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
AV block 2nd degree	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
AV 1st degree	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**9 (1.0)**	**8 (0.9)**	**9 (1.8)**	**1 (0.2)**
Basal cell carcinoma	3 (0.3)	3 (0.4)	2 (0.4)	0 (0.0)
Breast cancer	3 (0.3)	1 (0.1)	3 (0.6)	0 (0.0)
Malignant melanoma	1 (0.1)	2 (0.2)	1 (0.2)	0 (0.0)
Infections and infestations	**7 (0.7)**	**2 (0.2)**	**2 (0.4)**	**1 (0.2)**
General disorders and administration site conditions	**6 (0.6)**	**1 (0.1)**	**5 (1.0)**	**0 (0.0)**
Fatigue	2 (0.2)	0 (0.0)	2 (0.4)	0 (0.0)

System organ class Preferred term	FTY 1.25 **(N=943)** **n (%)**	FTY **0.5** **(N=854)** **n (%)**	**Placebo** **(N=511)** **n (%)**	**Interferon** **(N=431)** **n (%)**
Respiratory, thoracic and mediastinal disorders	**5 (0.5)**	**2 (0.2)**	**2 (0.4)**	**0 (0.0)**
Dyspnea	3 (0.3)	1 (0.1)	2 (0.4)	0 (0.0)
Nervous system disorders	**4 (0.4)**	**3 (0.4)**	**6 (1.2)**	**1 (0.2)**
Dizziness	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Multiple sclerosis relapse	0 (0.0)	1 (0.1)	2 (0.4)	0 (0.0)
Psychiatric disorders	**3 (0.3)**	**1 (0.1)**	**2 (0.4)**	**2 (0.5)**
Depression	2 (0.2)	1 (0.1)	0 (0.0)	1 (0.2)
Vascular disorders	**3 (0.3)**	**1 (0.1)**	**1 (0.2)**	**0 (0.0)**
Gastrointestinal disorders	**3 (0.3)**	**3 (0.4)**	**3 (0.6)**	**0 (0.0)**
Dyspepsia	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	1 (0.1)	1 (0.1)	2 (0.4)	0 (0.0)
Skin and subcutaneous tissue disorders	**2 (0.2)**	**3 (0.4)**	**1 (0.2)**	**0 (0.0)**
Dermatitis allergic	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	**2 (0.2)**	**3 (0.4)**	**0 (0.0)**	**1 (0.2)**
Myalgia	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)
Blood and lymphatic system disorders	**2 (0.2)**	**3 (0.4)**	**0 (0.0)**	**0 (0.0)**
Thrombocytopenia	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)
Metabolism and nutrition	**2 (0.2)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**

Source: ISS Post table 4.4-10 (*only those in two or more subjects in any group) -Primary SOCs are sorted descending frequency for the FTY720 1.25 mg group. A patient with multiple AEs within a primary SOC may be counted under more than one preferred term but is counted only once in the Total row. A patient with multiple occurrences of an AE under one treatment group is counted only once in the AE preferred term for that treatment group.

The safety profile of fingolimod in safety pool E (which included the double blind and open label extensions, which included some exposure up to 5 ½ years in study 2201E1 and up to 4 years in study 2302E1) was consistent with that of the core studies. There was a mild increase in the overall risk of discontinuations with longer exposure.

Patients with AE leading to discontinuation in safety pool E (original ISS) are presented as follows, for those events that occurred in at least 2 patients in at least one treatment group in descending order of frequency.

Table 38. Patients with AE leading to study drug discontinuation in fingolimod by SOC, safety pool E*

System organ class Preferred term	FTY 1.25 N=1157 n(%)	FTY 0.5 N=1021 n (%)
Any AE leading to drug discontinuation	**169 (14.6)**	**84 (8.2)**
Investigations	61 (5.3)	42 (4.1)
Eye disorders	21 (1.8)	3 (0.3)
Cardiac disorders	19 (1.6)	1 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	12 (1.0)	10 (1.0)
Infections and infestations	11 (1.0)	4 (0.4)
Nervous system disorders	7 (0.6)	4 (0.4)
Gastrointestinal disorders	5 (0.4)	4 (0.4)
Hepatobiliary disorders	5 (0.4)	2 (0.2)
Metabolism and nutrition disorders	4 (0.3)	0
Vascular disorders	4 (0.3)	2 (0.2)
Psychiatric disorders	3 (0.3)	1 (0.1)
Skin and subcutaneous tissue disorders	3 (0.3)	3 (0.3)
Musculoskeletal and connective tissue disorders	2 (0.2)	3 (0.3)

Source: Post text Table 4.5-13, original ISS. * At least 2 patients in any treatment group). Primary SOCs are sorted descending frequency for the FTY720 1.25 mg group. A patient with multiple AEs within a primary SOC is counted only once in the total row. A patient with multiple occurrences of an AE under one treatment group is counted only once in the AE preferred term for that treatment group.

Evaluation of events leading to drug discontinuation in the updated safety pool E is consistent with that in the original submission (data not shown).

Analyses patients with AE events leading to drug discontinuation for selected SOCs are discussed as follows, in descending order of frequency in the controlled population.

- AE leading to drug discontinuation in the Investigations SOC

The SOC that led to most study drug discontinuations was the Investigations SOC (5.0% of subjects receiving FTY 1.25 mg group, 3.5% of those receiving FTY 0.5 mg, 1.4% of those on placebo and 2.1% of those on IFN). Discontinuations in this SOC were mostly due to liver related tests, lymphopenia, respiratory-related investigations and cardiac related investigations. These events will be discussed under their organ-related SOC.

- AE leading to drug dc in the Hepatobiliary system disorders SOC and Investigations (liver related terms)

Eighty five subjects discontinued drug treatment because of either hepatobiliary disorders (n= 7) or liver related Investigations (n=78). Altogether, 43 pts in FTY 1.25; 31 in FTY 0.5; 4 on

placebo; 7 on IFN discontinue drug because of hepatobiliary or liver related investigations AEs. This analysis is shown in the following table:

Table 39. Patients who discontinued due to hepatobiliary SOC and liver related investigations in fingolimod controlled studies, safety pool D

	FTY 1.25 N= 943	**FTY 0.5 N=854**	**Placebo N=511**	**IFN N=431**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Total number of patients	43 (4.6%)	31 (3.6)	4 (0.8)	7 (1.6)
Hepatobiliary disorders SOC	4 (0.4)	2 (0.2)	1 (0.2)	0
Liver-related investigations[1]	39 (4.1)	29 (3.4)	3 (0.6)	7 (1.6)

Source: AE datasets submitted 12 18 09. n= patients with events. [1] Liver-related investigations include the following preferred terms (PT): ALT increased, AST increased, GGT increased, transaminases increased, blood Alkaline phosphatase increased, blood bilirubin increased, hepatic enzymes increased, hepatic enzyme abnormal.

There is a clear signal for liver toxicity, with a dose response between FTY 1.25 and FTY 0.5 mg.

Liver related AEs that were serious and led to drug discontinuation were described earlier in this review. Seventy four subjects had liver-related AE leading to drug dc that were coded as non serious in the controlled database. In addition to these subjects, some subjects who presented liver enzyme elevation at the end of the core study evaluation, did not appear in the dataset as leading to drug discontinuation, however, they did not enter the extension studies.

Selected cases of non-serious AE of elevated liver enzymes leading to drug dc in the controlled studies are summarized as follows:

Brief narratives of selected non-serious AE leading to drug discontinuations in the Hepatobiliary SOC and Investigations SOC (hepatobiliary HLGT), in the controlled studies (Pool D).

FTY 1.25 mg
2301 0606 00014. 53 F. ALT increased on Day 83. History of hyperlipidemia and anemia, treated with rosuvastatin and pyridoxine. ALT up to 248 U/L (nl up to 45 U/L), AST 227 (nl up to 41 U/L) and GGT 164 (nl up to 66 U/L), with normal BR and ALK Phosphatase. Resolved 50 days after drug dc.
2301 0657 00012. 39 M. GGT increased on Day 13. During study received paracetamol for headaches. On Day 13 GGT was 75 U/L; on Day 27 ALT was 103 U/L (nl up to 45) and GGT was 160 (nl up to 66). Drug was discontinued. Seven days after drug DC ALT was 100; ALT 43; GGT ws 298 U/L (almost 5xULN) and BR was 42 μmol/L (nl up to 21), with normal ALK P. Liver enzymes and BR were still elevated 35 days after drug dc. Liver enzymes resolved on Day 118, although GGT persisted elevated <2xULN.
2301 0701 00007. 27 M. ALT increased on Day 81. On day 15, mild increase in GGT. Progressive increase in liver enzymes up to Day 278, when ALT was 230 U/L (>5xULN), AST 90 U/L and GGT 208 U/L (nl up to 65). He received amoxicillin during the study. Liver enzymes decreased 6 days after study drug dc. At last evaluation still mild ALT elevation (61 U/L). BR and ALK phosphatase remained normal.
2301 0752 00001. 31 M. ALT increased day 29. He had mild ALT elevation at screening (ALT=61, nl up to 45 U/L); On day 29 ALT was 434 (9xULN); AST 192 (nl up to 41 U/L). BR and ALK phosp were normal. Liver enzyme elevation resolved 60 days after drug dc.
2301 0758 00001. 40 M. Transaminase increased on day 24: ALT 222 U/L (>5xULN) with AST 2x ULN and GGT 3x ULN. Enzymes continued to increase up to ALT 293; AST 121 & GGT 296 on day 26, with normal BR and ALK P. Resolved 3 months after drug dc.
2302_ 0215_00001. 35 M. Transaminase increased on day 15. Normal liver enzymes at screening. On Day 15 ALT 251 U/L, AST 96 U/L GGT 178 U/L. BR and ALK normal. Drug discontinued. At last follow up 10 days after last dose, ALT was still 158 U/L and GGT was 193 U/L.
2302_0426_00005. 40 M. Transaminases and BR increased on Day 74. Medical hx of Gilbert's syndrome, optic neuritis, abnormal CT scan. During study he received paracetamol for myalgia and back pain. Screening ALT was normal, but there was mild increase in GGT (76 U/L), and BR was 36 μmol/L (nl 2-21). On Day 17 ALT was 96 U/L, GGT was 356 U/L (>5xULN) and BR was 45. Drug dc on Day 131. BR and ALK P were normal. ALT normalized while GGT was still mildly elevated 46 days after last dose of study drug.
FTY 0.5 mg
2302_0322_00006. 28 F. Isolated Hyper BR on Day 92. History of tension headache treated with paracetamol. At screening total BR was 17 (nl up to 21 μmol/L). On Day 92 total BR was 33. ALT, AST and ALK P were normal. Drug was discontinued. Last dose of study drug was Day 111. Five days later, BR was 21. She discontinued from the study.
2301_0701_00031. 18 M. Hyper BR on day 458. History of acne treated with nicotinamide, clindamycin and isotretinion. ALT a screening was 68 U/L (nl up to 41), but at month 2 it was 28 U/L. Other medications prior to randomization included "phospholipids and protective diet for prophylaxis of liver parameters dysfunction." During the study he also received amoxicillin clavulanate for eczema. On Day 458 he had hyperbilirubinemia (BR 35 U/L). On the same day ALT was 67 U/L. Drug was discontinued due to the event (last dose Day 461). On day 472, BR had decreased to 21 and the event was considered resolved.
2301 0701 00039. 39 F. ALT increased 11x ULN on Day 360 Concomitant meds prior to randomization included betahistine, pentoxyfilline and oral contraceptive. During the study she also received acetylcysteine, amoxicillin for bronchitis, paracetamol for pain. Patient reported arthralgia on Day 354. On day 360 she was noted to have increased ALT (11x ULN and AST >5x ULN (*before paracetamol*). She received paracetamol (1x 0.5g) on Day 361. Drug was discontinued because of

elevated liver enzymes on Day 362. Eleven days after drug discontinuation liver enzymes were down to normal. BR was normal at all times.

Selected Laboratory Values (Blood Chemistry)

Visit, Visit Date (Days since first dose)	ALT (NR 0-45 U/L)	AST (NR 0-41 U/L)	GGT (NR 2-65 U/L)	Total Bilirubin (NR 2-21 µmol/L)	Alkaline Phos (NR 30-125 U/L)	Creatinine (NR 44-80 µmol/L)
Screening 29-Jun-2007	18	20	10	8	48	76
Month 12 18-Jul-2008 Day (360)	**522**	**225**	**87**	12	128	74
Selected Laboratory Values (Blood Chemistry) after the study drug discontinuation						
22-Jul-2008 (2 days since study drug discontinuation)	**249**	85	86	7	119	75
Follow-up 24-Oct-2008 (97 days since study drug discontinuation)	19	23	10	11	47	85

Apparently only one dose of paracetamol 500mg was given, and the increased ALT preceded the single dose of paracetamol.

2301 0702 000011. 35 F. ALT increased on Day 541. During the study she received ranitidine and omeprazole, thiamine, cyanocobalamin, magnesium aspartic acid, and betahistidine, asparigines, hydroxyzine, zolpidem . On Day 541 she was noted to have increased ALT >7xULN. The study medication was discontinued due to this event. Last dose was on Day 543. On follow up 88 days after drug discontinuation ALT was almost normal. ALT normalized 181 days after last dose. BR remained normal throughout the study.

Selected Laboratory Values (Blood Chemistry)

Visit, Visit Date (Days since first dose)	ALT (NR 0-45 U/L)	AST (NR 0-41 U/L)	GGT (NR 2-65 U/L)	Total Bilirubin (NR 2-21 µmol/L)	Alkaline Phos (NR 30-125 U/L)	Creatinine (NR 44-80 µmol/L)
Screening 07-Dec-2006	17	19	14	11	48	54
11-Mar-2008 (Day 450)	81	35	29	9	35	56
Month 18	**326**	**174**	27	12	32	55
Selected Laboratory Values (Blood Chemistry) after the study drug discontinuation						
Unscheduled 17-Jun-2008 (5 days since study drug discontinuation)	**282**	**94**	27	12	37	49
10-Dec-2008 (97 days since study drug discontinuation	26	21	20	11	38	55

2301-0852 00007. 40 M. Hepatic enzymes increased on Day 261.
History of headache and insomnia. Concomitant meds included codeine phosphate guaifenesin. During the study, the patient received carnitine, magnesium, vitamins and mineral supplement for nutrition supplement, levocarnitine and magnesium for diet supplement, ciclopirox for sealing

redness of face and scalp and acetanilide-ascorbic acid-pheniramine maleate-phenylephrine hydrochloride (Neocitran) and paracetamol for common cold. On Day 261 was noted to have increased hepatic enzyme with ALT >6x ULN, AST >2 ULN. Drug was discontinued on Day 264 due to this event. Liver enzymes were back to normal 36 days after drug dc. BR and Alk phosp remained normal.
2302_0202_00006. 37 F. ALT, AST and GGT elevation on Day 195 Medical hx of headaches, urinary tract infections, esophagitis, insomnia. Smoker. During thestudy she received lorazepam, zolpidem and amitriptylin and nimesulide. On Day 93 ALT was 63 U/L. On Day 195 ALT was 382 (>8xULN) AST was 178 (>4xULN) and GGT was >4 ULN. BR was 7 µmol/L and ALK P was <2xULN. Drug was dc. Liver enzymes were normal 64 days after drug dc.
2302_0308_00003, 21 M. Hepatic enzyme increase days 14 and 72 No significant hx. Normal enzymes at entry. On Day 14, ALT was 88 U/L, AST was 54 U/L. On Day 71 ALT was 269 U/L (>5xULN) and AST was 161 U/L, GGT was 5xULN. Drug was dc. The event resolved 127 days after drug dc. Total BR remained below 10 during the study.
2302_0327_00001. 34M. Hepatic enzymes increased on Day 36 Liver enzymes at baseline were normal. On Day 36 ALT was 65 U/L (nl up to 45). On Day 84 ALT was 172 U/L, GGT was 164 (nl up to 65). BR remained <8µmol/L. Drug was discontinued. ALT and GGT normalized 59 days after drug dc.

- Discontinuations due to hepatobiliary disorders and Investigations (liver-related) SOC in the extension studies

The number of patients with AE leading to study drug discontinuation in safety pool E (UPDATED) is presented as follows.

Table 40. Patients with liver-related investigations AE leading to drug discontinuation, safety pool E (SUR)

	FTY 1.25	FTY 0.5
	N= 1302 n%	N= 1176 n%
Total unique patients	54 (4.2)	40 (3.4)
ALT increased	25 (1.9)	20 (1.7)
Hepatic enzyme increased	15 (1.2)	13 (1.1)
AST increased	6 (0.5)	6 (0.5)
GGT increased	7 (0.5)	10 (0.9)
Transaminases increased	7 (0.5)	2 (0.2)
Liver function test abnormal	4 (0.3)	0 (0.0)
Blood alkaline phosphatase increased	1 (0.1)	2 (0.2)
Blood bilirubin increased	0 (0.0)	2 (0.2)

n= number of patients with event. Source: n for individual preferred terms is from SUR Table 4.5-13. Total number of unique patients is from the SUR AE dataset. Include events in the Investigations SOC, Hepatobiliary investigations HLGT.

Review of the narratives of all events that led to study discontinuation in the controlled and extension studies indicates that most of these were categorized as "non-serious" adverse events. They were associated with increases in ALT or GGT elevation 3 to 5x ULN, without associated increase in BR or alkaline phosphatase and resolved two weeks to several months after drug discontinuation. However, some cases were associated with markedly abnormal ALT elevation (>5x ULN) and some cases had not fully resolved at the time of last testing after drug dc.

Many events were confounded by concomitant use of other medications that are known to induce liver toxicity such as paracetamol or other analgesics, or had a baseline ALT or GGT that was already above normal. However, even in those cases, there was improvement in transaminase values after fingolimod discontinuation (positive de-challenge). In several cases liver enzyme elevation led to drug interruption but recurred when the drug was re-started (positive re-challenge). Therefore, there is a clear relationship between fingolimod and transaminase elevation, without increases in BR and alkaline phosphatase. In cases in which there was increase in BR there was another explanation (e.g. paracetamol use, Gilbert's disease). SAE leading to discontinuation have been described in the SAE section of this review.

- AE leading to drug dc in the Eye disorders SOC

A total of 20 subjects had AE that led to drug dc in the Eye disorders SOC in the fingolimod controlled studies. Some of them were coded as serious and already described in the SAE section of this review, but some events of interest such as a case of bilateral retinal ischemia/vasculitis were coded as non serious.

Table 41. AE leading to drug discontinuation, Eye disorders SOC, safety pool D

PT	FTY 1.25 N= 943	FTY 0.5 N=854	Placebo N=511	IFN N=431
	n (%)	n (%)	n (%)	n (%)
Total	15 (1.6)	2 (0.2)	2 (0.4)	1 (0.2)
Ischemic retinopathy	1	-	-	-
Macular edema	10	1	0	1
Retinitis	1	-	-	-
Detachment of retinal pigment	-	1	-	-
Papilledema	1	-	-	-
Retinal disorder	1	-	-	-
Eyelide edema	1	-	-	-
Iridocyclitis	-	-	1	-
Keratitis	-	-	1	-
Conjuntivitis	-	-	1	-

Source: Post text Table 4.4-10. ISS.. n= number of patients with events

Non-serious cases leading to discontinuation in this SOC in the controlled studies included eight cases of macular edema in the FTY 1.25 mg group, one in the FTY 0.5 mg group and one in a subject receiving IFN therapy.

The subject with non-serious macular edema in the IFN group was a 22 year old female diagnosed by dilated ophthalmoscopy on day 37 of study treatment. The case was not confirmed by OCT and by the DSMB ophthalmologist.

The case of non-serious macular edema in the FTY 0.5 mg treatment group in the controlled studies is as follows.

- **2302 0408 00005**, 53 F, Macular edema. Day 367. Did not recover. *(in dataset coded as non-serious, not leading to discontinuation, as per narrative, led to drug dc)*
  No history of eye problems. MS diagnosed 5 yrs prior. 2 relapse during previous 2 years. Previous treatment: glatiramer, IFN beta 1b and beta 1a. History of HTN. On Day 367 of FTY 0.5 mg, OTC showed macular edema. She did not have any symptoms but on examination had mild visual acuity loss in the right eye. The ophthalmologist reported bleeding surrounding the upper temporal vein and venous thrombosis of upper temp. vein in R eye, with macular edema. On Day 374, FA showed moderated macular edema in R eye. The patient discontinued drug due to macular edema on Day 375. Three months after drug dc digital angiography showed that macular edema was still present. Eight months after drug dc angiography still showed mild macular edema. Nine months after drug dc macular edema was still present although it was improving. As per the DSMB ophthalmologist, pt had a superotemporal retinal branch vein occlusion in the R eye, most likely secondary to HTN.

  This patient had no prior history of uveitis or ME. The ME was diagnosed at the 1-year visit. ME improved after drug discontinuation but was still present 9 months after drug dc.

In the FTY 1.25 mg group in the controlled studies eight patients had non-serious ME leading to drug discontinuation. Four of the 8 cases had not fully recovered from ME at the time of the last available evaluation in the original ISS. These cases are listed in Appendix 9.1.12.a.

- Macular edema leading to drug discontinuation in extension studies

Nine cases of ME led to drug discontinuation in the extension studies (one from the FTY 5-1.25 mg group, 6 from the FTY 1.25 mg group and two from the FTY 0.5 mg group). SAE were described in the SAE section. The case of non- serious ME with FTY 0.5 mg leading to drug discontinuation in the extension studies is as follows:

- **2301E1 0657 00005**. 50 F. FTY 0.5 mg. Hx of HTN, amblyopia, migraine, palpitations, insomnia, prior treatment for suspected Lyme disease. No diabetes or CV disease. During the core phase while on placebo she developed non-serious eye hemorrhage. On **Day 106** of FTY 0.5 mg she was noted with moderate macular edema confirmed by OCT (CFT of 339 microns L, and 283 microns R) and FA (retinal capillary leakage both eyes). Visual acuity was not done, as patient refused. Drug was discontinued. Two months after drug dc a follow OCT and FA showed persistent cystoid macular edema L>R.

  As per the DSMB ophthalmologist the case could represent persistent Cystoid ME due to study drug despite discontinuation of therapy or a case of MS associated uveitis, or other cause of uveitis (such as Lyme disease, for which the patient had been treated previously). I agree with his assessment.

One non-serious ME led to study drug discontinuation in the FTY 1.25 mg group in the extension studies (Appendix 9.1.12.b).

- Macular edema leading to study drug discontinuation in study 2309

At the time of the Special safety interim report update submitted 4/21/10, 14 cases of macular edema were reported and unblinded from study 2309. Of the 14 cases, five (1.4%), five (1.4%) and one (0.3%) led to study drug discontinuation in the FTY 1.25, FTY 0.5 and placebo groups, respectively. A summary of AE of ME in the FTY 0.5 mg dose group in study 2309 is as follows.

Macular edema leading to drug discontinuation, FTY 0.5, study 2309.

Patient ID	Age/ sex/ race †	History of ME, uveitis	Treat-ment	Baseline CFT µm OS, OD	Post-baseline CFT, study day & OS, OD values		ME SAE/AE start day (date) (action taken)	ME confirme by DSMB	Comment
0524-00004	51/F/ Ca	none	FTY720 0.5 mg	OS 189 OD 180	day 99	OS 196 OD 191	AE: ME OD Day 99 (23Jul07) (discont.)	No	1
					day 135#	OS 186 OD 236			
0547-00007	37/F/ Ca	none	FTY720 0.5 mg	OS 186 OD 220	day 114	OS 198 OD 471	SAE: ME OD day 114 (6Nov07) (discont.)	Yes	2
0548-00003	49/F/ Ca	none	FTY720 0.5 mg	OS 164 OD 166 (OCT2)	day 98	OS 164 OD 151	AE: ME OS day 98 (21Nov07) (discont. on day 196)	No	3
					day 196	OS 154 OD 147			
0601-00009	49/F/ Ca	none	FTY720 0.5 mg	OS 263 OD 199	day 52	OS 425 OD 195	AE: ME OS day 52 (8Nov07) (discont.)	Yes	4
					day 87#	OS 268 OD 290			
					day 101#	OS 251 OD 236			
0616-00002	41/F/ Ca	ME, uveitis	FTY720 0.5 mg	OS 180 OD 205	day 34	OS 327 OD 462	AE: ME OD day 34 (5Jun07) (discont.)	Yes	5
					day 93#	OS 185 OD 198			

Source: Table 5-4 Special safety interim report update (4/21/10). OS = left eye, OD = right eye, BL = baseline, discont. = discontinued study drug, # Off-study drug. Comments:

1. 0524-00004. Hx of HTN, mitral valve incompetence. Unclear how the diagnosis of ME was made, as visual acuity and dilated ophthalmoscopy were normal. Drug was dc and event resolved 6 months later. DSMB ophthalmologist did not find evidence of ME, although FA showed evidence of mild bilateral papillitis and vasculitis in the temporal parafoveal region of R eye.
2. 0547 00007. Described in SAE section.
3. 0548 00003. Unclear how diagnosis was made. Event resolved DSMB ophthalmologist stated OCT and FA did not confirm diagnosis. Medication was re-started.
4. 0601 00009. Hx of HTN, prior optic neuritis, hypothyroidism and osteoarthritis. Diagnosis confirmed by OCT and FA. VA was normal; 2 weeks after drug dc VA decreased to 0.4 on L and was normal on R; 35 days after drug dc VA was 0.5 on L and 0.7 on R; 5 weeks after drug dc VA was normal.
5. 0616 00002. Hx of uveitis and macular edema 1 year prior to randomization (no data on which eye). Dx by ophthalmic exam and OCT. Day 34 VA decreased to 0.5 on R; bilateral ME by ophthalmoscopy. VA restored within 2 months of study discontinuation. 5 months after drug dc, ophthalmoscopy showed ME on R eye. One year after drug dc, VA R eye decreased to 0.3125.

Of the 5 cases of ME on FTY 0.5 in study 2309 reported so far, three were confirmed and 2 were not. One case was serious and has been described under SAEs (this case required surgery and recovered with loss of some visual acuity). One case resolved and recurred with decreased vision one year after drug dc. This patient had a history of uveitis and ME prior to study entry. The episode of ME one year after drug dc is probably related to the underlying MS and unlikely related to FTY; however, the role of FTY in the episode of ME that occurred while she was on FTY treatment can not be ruled out. One of the not confirmed cases showed papillitis and vasculitis of R eye.

The findings in 2309 are consistent with those in the ISS. FTY is associated with dose-related macular edema, including the 0.5 mg dose. The question is whether FTY is associated with other eye toxicities and what kind of monitoring would be recommended.

A case of bilateral ischemic retinopathy/vasculitis with FTY 1.25 is described as follows

- **2301 0456_0008** bilateral ischemic retinopathy, intravitreal hemorrhage, vasculitis
  32 yo F, no history of eye problems. History of migraines. Approximately one year into treatment, she complained of phosphenes. On day 358 (12 mo visit) she was noted to have severe ischemic retinopathy. Fundoscopic exam showed vaso-occlusive retinopathy with very thin, thread-like vessels and adjacent retinal ischemia with multiple retinal hemorrhages in the peripheral area, R>L eye. There was no evidence of ME. Visual acuity remained unchanged. FA showed very thin arteries with evidence of ischemic retinopathy in both eyes. Drug was discontinued on Day 395. She was treated with trimetazidine and laser photocoagulation x 3 within the ensuing 3 months. 3 months after drug dc, there were no changes. Visual acuity 10/10 for both eyes. Eye fundus: both eyes, multiple peripheral zones with vascular microinvasion. FA: no new ischemic zone but vascular rearrangement increased. Ophthalmologist indicated that there was a vascular progression nearby the ischemic zones despite the lasers. 8 months after drug dc, OCT showed normal CFT at L; dense macula, retinal detachment associated to vitreoretinal tension syndrome at R. 320 days since study medication discontinuation, an increase in central foveal thickness of 15 and 73 microns was observed for the left and right eye, respectively, compared to screening values. Visual acuity assessments were normal in both eyes. Fluorescein angiography showed retinal capillary leakage in both eyes that was not consistent with macular edema; "ischemic retinopathy" was observed in the right eye. One year after drug dc ischemic retinopathy was present and the patient still required laser treatments. 383 days since study medication discontinuation retinopathy was ongoing. The investigator did suspect a relationship between the event (retinopathy) and the study medication. Approximately 15 months after discontinuing study medication, the patient experienced an intravitreal hemorrhage. The DSMB ophthalmologist stated that the fluorescein angiogram showed definite evidence of peripheral vasculitis. There was mild peripheral intraretinal hemorrhage and a suggestion of peripheral capillary dropout on the fluorescein angiogram. There was no evidence of retinal neovascularizа-tion but the patient should be followed in this respect. "In addition to the possibility that study medication is the cause of the peripheral retinal vascular changes, other possible causes should be considered and ruled out including: blood dyscrasia (CBC, serum viscosity, hemoglobin electrophoresis (e.g., thalassemia, sickle cell disease)), aortic arch syndrome (e.g., Takayasu disease; Doppler imaging), multiple emboli (e.g., intravenous drug abuse, atrial myxoma; transesophageal echocardiography); idiopathic uveitis (e.g., Eale's disease; audiology, chest x-ray, PPD); drug use (e.g., birth control pills), and metabolic abnormalities (e.g., diabetes mellitus)."

A case of small intra-retinal hemorrhage led to study drug discontinuation in study 2309 (as per the listing of discontinuations submitted with the SUR). The narrative and unblinding of this case has been requested. The patient was on FTY 0.5 mg.

There was one single case of bilateral retinal ischemia/vasculitis and one can not draw conclusions from one case. However, there was also one case of retinal artery microthrombosis (described in the SAE section of this review), and few non-serious retinal hemorrhage and retinal aneurysms (that did not lead to drug discontinuation)in this database), all in the FTY treatment groups (discussed in the Other Significant AEs section), suggesting that there could be some deleterious vascular effect in the retina besides macular edema.

- AE leading to discontinuation in Cardiac disorders SOC and Investigations (cardiac related) SOC.

Patients with events leading to drug discontinuation in the Cardiac SOC for safety pool D are presented in the following table:

Table 42. AE leading to drug discontinuation, Cardiac SOC, pool D

	FTY720 5 mg	FTY720 1.25 mg	FTY720 0.5 mg	Placebo	Interferon
Preferred term	(N=94) n (%)	(N=943) n (%)	(N=854) n (%)	(N=511) n (%)	(N=431) n (%)
-Total	**2 (2.1)**	**12 (1.3)**	**1 (0.1)**	**2 (0.4)**	**1 (0.2)**
Bradycardia	2 (2.1)	5 (0.5)	-	1 (0.2)	-
AVB block 2nd degree	-	3 (0.3)	-	-	-
AVB block 1st degree	-	2 (0.2)	-	-	-
Angina pectoris	-	1 (0.1)	-	-	1 (0.2)
Arrhythmia	-	1 (0.1)	-	-	-
Pericarditis	-	1 (0.1)	-	-	-
Tachycardia	-	1 (0.1)	-	-	-
Ventricular extrasystoles	1 (1.1)	1 (0.1)	-	-	-
Diastolic dysfunction	-	-	-	1 (0.2)	-
Extrasystoles	1 (1.1)	-	-	-	-
LV dysfunction	–	-	1 (0.1)	-	-
Palpitations	-	-	-	1 (0.2)	-

Source: Post text Table 4.4-10, original ISS.

There was a dose response in the number of patients who discontinued drug due to events in the Cardiac events SOC (1.3% in FTY 1.25 as compared to FTY 0.5 mg). The most common cause of discontinuation was bradycardia, followed by second and first degree AV Block.

Most cases of discontinuations in the Cardiac SOC were serious and were described earlier in this review. The following cases were not coded as serious but led to study drug discontinuation in the controlled studies.

Subjects who discontinued due to non-serious AE in the Cardiac SOC, safety pool D

Placebo	2301_0610_00003	49 F	Diastolic dysfunction on day 596. No date of recovery was provided.
Interferon	2302_0407_00003	48 M	Angina pectoris on day 383. Resolved after 5 days.
FTY720 1.25 mg	2301_0180_00007	53 M	Bradycardia on day 1. Resolved on the same day.
FTY720 1.25 mg	2301_0757_00011	52 F	Tachycardia on day 20. resolved after 10 days.
FTY720 1.25 mg	2301_0176_00001	45 F	Bradycardia on day 11, resolved in 2 days.
FTY720 1.25 mg	2301_0413_00003	41 F	Ventricular extrasystoles on day 1. Resolved on the same day.

The cases on placebo and IFN occurred late in the study (days 596 and 383, respectively), while the events on FTY 1.25 occurred within the first 3 weeks of study

treatment, including two cases bradycardia upon the first dose, which is consistent with the analysis of SAEs.

The following case in the Investigations SOC led to study drug dc but was coded as non-serious in the controlled studies

- 2302_0216_00013: Electrocardiogram T wave inversion 30 M, Day 62 on 1.25.
  MS was diagnosed five years prior to study entry. He had been previously treated with IFN beta-1a, IFN beta 1-b in the past. MS relapses had been treated with corticosteroids. He had no history of diabetes and did not smoke. He was not taking concomitant medications. This subject had an AE of intermittent chest pain coded as "non-serious angina pectoris" on Day 56. On Day 62 an ECG showed inverted T waves. The event of chest pain resolved on Day 64. The inverted T wave resolved on Day 69. Drug was discontinued on Day 69. The investigator did not suspect a relationship to study drug. No further work up is available from this patient.

  This young subject with no risk factors presented intermittent chest pain described as non-serious angina, associated with inverted T waves. The drug was discontinued and there is no further workup available.

- Case of discontinuation due to AE in the Cardiac SOC in ongoing study 2309

- **2309-0528-00003 –** Pulmonary artery hypertension (on FTY 1.25 mg).

  This narrative was submitted by the applicant in response to the FDA request of results of unscheduled echocardiograms in study 2309.

  A 48 year old black female had MS for 11 years. Medical history included chest discomfort, dizziness and anxiety. No cardiovascular history.

  On Day 253 of blinded study therapy, the patient was seen by a cardiologist and was diagnosed with labile hypertension. It is unclear for how long she had seen a cardiologist. Blood pressure measurements taken during the office visit ranged from 136-152 mmHg/80-88 mmHg. No anti-hypertensive medications were started. The patient was instructed to continue home blood pressure monitoring.
  On Day 283, the patient was seen at an unscheduled study visit for complaints of shortness of breath when speaking for a long period time. The patient was evaluated by her pulmonologist on the same day and no new acute pulmonary pathology was detected. Follow-up pulmonary function tests were performed on Day 288, as shown below.

Rel Day	FEV1	Change from baseline	FVC	Change from baseline	DLCO	Change from baseline
288	2.77	4.53%	3.47	6.77%	20.8	6.67%

  Study medication was temporarily interrupted for these symptoms from Day 284 to Day 289.
  On Day 349 the patient had her Month 12 visit and the regularly scheduled echocardiogram was performed. (The results of which became available at a later date.)

On Day 406, the patient had a routine follow-up visit with her cardiologist. At the time of the visit, the patient denied having any shortness of breath or any chest discomfort. The cardiologist noted a gradual increase in her pulmonary artery pressure estimate since her baseline visit. Her pulmonary artery pressure estimates were 32 mmHg at baseline, 37 mmHg at Month 3 and 49 mm Hg at Month 12, Day 349. The cardiologist also noted a worsening of her baseline tricuspid regurgitation. Her tricuspid regurgitation was mild to moderate at baseline and month 3 but worsened to moderate to severe at Month (Day 349) on the echocardiogram. In light of the increasing pulmonary artery pressure estimate and worsening tricuspid regurgitation, the investigator and cardiologist decided to permanently discontinue study medication on Day 407.

A follow up (unscheduled) echocardiogram was performed Day 475. According to the local echocardiogram report, pulmonary artery pressure estimate had improved to 35.2 mmHg and the tricuspid regurgitation improved to moderate in severity. The patient subsequently saw her cardiologist on Day 503. He reports that she remains clinically stable from a cardiac standpoint with no cardiac symptoms. All her other parameters, including pulmonary artery pressure, tricuspid regurgitation as well as blood pressure are improved. The case was reviewed by the DSMB cardiologist and he concurs with the interpretations of the Echocardiograms.

Date	Pulmonary artery pressure-local echocardiogram report (mmHg)	Pulmonary artery pressure estimate (RV-RA systolic gradient + 10 mmHg) – central reader	Tricuspid valve regurgitation – local echocardiogram report
Screening	32	27.2	Mild to moderate
3 months (scheduled)	37	34.3	Mild to moderate
12 months (scheduled)	49	47.3	Moderate to severe
Day 475 (unscheduled)	35.2	33.7	Moderate

According to the investigator this event (pulmonary arterial hypertension) was non-serious. The investigator did suspect a relationship between the event (pulmonary arterial hypertension) and the study medication.

> *Patient seems to have developed pulmonary hypertension during fingolimod treatment. She did not have a known history of pulmonary hypertension at entry. It is unclear why she saw a cardiologist on Day 253. Of note, a Holter monitoring done at month 3 as part of study 2309 scheduled assessments had shown intermittent ectopic atrial rhythm. No AE were reported at that time. On Day 283 she developed increasing shortness of breath. Study drug was interrupted and then re-started after a few days with no apparent complaints. On Day 407 the cardiologist noted increased pulmonary artery pressure in an echocardiogram done as part of study 2309 scheduled 12-month assessments. I believe that this case could be related to study drug use because it improved after drug discontinuation.*

- AE leading to drug dc in the Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC

A total of 27 subjects discontinued study drug because of an AE of neoplasm in the controlled database. The number, percentage and rate per 100 PYRs was similar among treatment groups (0.8%, 0.7%, 1.2% and 0.2% in the FTY 1.25 mg, 0.5 mg, placebo and IFN groups, respectively). Twenty six of the 27 were serious. The only non-serious case that led to discontinuation occurred in a 39 year old subject who was diagnosed with uterine leiomyoma Day 42 of FTY 1.25 mg treatment.

Additionally, nine subjects discontinued from the extension studies up to the cut-off date of the original submission. All of them were serious and described earlier in this review. Of note, one patient with a "benign lung neoplasm" showed to be a necrotizing granulomatous pneumonitis. This case was described in the Serious infections and infestations section of this review.

- AE leading to drug discontinuation in the Infectious & infestations disorders SOC

Fourteen subjects discontinued study drug because of events in the infections and infestations SOC in the controlled database: 2 on FTY5, 7 on FTY 1.25, 3 on FTY 0.5 and 2 placebo, 1 IFN.

Table 43. AE leading to drug discontinuation in the Infections and Infestation SOC, safety pool D, by high level group term (HLGT)

PT	FTY 5 mg N=94	FTY 1.25 N= 943	FTY 0.5 N=854	Placebo N=511	IFN N=431
	n (%)	n (%)	n (%)	n (%)	n (%)
Total	2 (2.1)	7 (0.7)	2 (0.2)	2 (0.4)	1 (0.2)
Bacterial infectious disorders					
Cellulitis	1	-	-	-	-
Staphylococcal infection	-	1	-	-	-
Infections- pathogen unspecified					
Appendicitis	-	-	-	-	1
Genital infection female	1	-	-	-	-
Pneumonia	-	1	1[3]	-	-
Lower resp. tract infection	-	1	-	-	-
Viral infectious disorders					
Oral herpes	-	-	-	1	-
Genital herpes	-	-	-	1	-
Anogenital warts	-	1	-	-	-
Herpes zoster disseminated[1]	-	1	-	-	-
Viral pharyngitis	-	1	-	-	-
Encephalitis viral[2]	-	1	-	--	-
Bronchiolitis	-	-	1	-	-
Herpes virus infection	-	-	1	-	-

Source: AE datasets. [1,2] Fatal infections. [3] One subject had pneumonia and herpes virus infection.

The numbers are small but suggest an increased risk of discontinuation due to infections in the FTY 1.25 mg group (but not in the FTY 0.5 mg group) as compared to placebo and INF.

Serious and fatal infections have been described earlier in this review. Non-serious infections that led to study drug discontinuation in the controlled database are listed as follows:

Listing of non-serious infections leading to drug discontinuation in the controlled studies.

ID	Age sex	PT	Rel day	Duration (days)
Placebo				
2301_0609_00003	40 F	Oral herpes	539	18
2301_0703_00005	45 M	Genital herpes	59	139
FTY 5 mg				
2201_0005_00005	42 F	Cellulitis	116	11
2201_0052_00005	32 F	Genital infection female	143	46
FTY 1.25 mg				
2301_0153_00002	35 F	Anogenital warts	389	250
2302_0447_00004	33 M	Viral pharyngitis	10	110
2302_0505_00010	41 F	Staphylococcal infection	101	NA
FTY 0.5 mg				
2301_0601_00007	46 F	Bronchiolitis	338	125

AE leading to drug discontinuation in the Infections and Infestations SOC in pool E are presented as follows.

Table 44. AE leading to drug discontinuation in Infections SOC, pool E (SUR)

Primary system organ class Preferred term	FTY720 5 mg - 1.25 mg (N=137) n (%)	FTY720 1.25 mg (N=1302) n (%)	FTY720 0.5 mg (N=1176) n (%)
Infections and infestations			
-Total	5 (3.6)	11 (0.8)	5 (0.4)
Herpes zoster	2 (1.5)	2 (0.2)	0 (0.0)
Anogenital warts	0 (0.0)	1 (0.1)	0 (0.0)
Encephalitis viral	0 (0.0)	1 (0.1)	0 (0.0)
Herpes zoster disseminated	0 (0.0)	1 (0.1)	1 (0.1)
Herpes zoster ophthalmic	0 (0.0)	1 (0.1)	0 (0.0)
Lower respiratory tract infection	0 (0.0)	1 (0.1)	0 (0.0)
Pneumonia	0 (0.0)	1 (0.1)	1 (0.1)
Staphylococcal infection	0 (0.0)	1 (0.1)	0 (0.0)
Upper respiratory tract infection	0 (0.0)	1 (0.1)	0 (0.0)
Viral pharyngitis	0 (0.0)	1 (0.1)	0 (0.0)
Bronchiolitis	0 (0.0)	0 (0.0)	1 (0.1)
Cellulitis	1 (0.7)	0 (0.0)	0 (0.0)
Genital infection female	1 (0.7)	0 (0.0)	0 (0.0)
Herpes virus infection	0 (0.0)	0 (0.0)	1 (0.1)
Influenza	1 (0.7)	0 (0.0)	0 (0.0)
Nasopharyngitis	1 (0.7)	0 (0.0)	0 (0.0)
Otitis externa	1 (0.7)	0 (0.0)	0 (0.0)
Papilloma viral infection	0 (0.0)	0 (0.0)	1 (0.1)
Perirectal abscess	0 (0.0)	0 (0.0)	1 (0.1)
Urinary tract infection	1 (0.7)	0 (0.0)	0 (0.0)

Source: Post text table 4.5-13. SUR.

Few additional events in the Infections and Infestations SOC led to discontinuation from the extensions studies. The events were consistent with those in the core phase. There is a suggestion of a dose response between FTY 1.25 and 0.5 mg for discontinuation for overall infections, but the numbers are small.

- AE leading to drug dc in the Nervous system disorders SOC

Fifteen subjects discontinued study drug because of AE in this SOC. These events are summarized in the following table.

Table 45. AE leading to drug discontinuation, Nervous system disorders SOC, safety pool D

PT	FTY 5 mg N=94	FTY 1.25 N= 943	FTY 0.5 N=854	Placebo N=511	IFN N=431
	n (%)	n (%)	n (%)	n (%)	n (%)
Total	1(1.0)	4 (0.4)	3 (0.4)	6 (1.2)	1 (0.2)
Cerebrovascular accident	-	1	-	-	-
Cognitive disorder	-	-	1	-	-
Grand mal seizure, coma	-	1	-	-	-
Dizziness	-	-	-	2	-
Epilepsy	-	1	-	-	-
Headache	-	1	1	1	-
Multiple sclerosis relapse	-	-	1	2	-
Nerve root lesion	-	-	-	-	1
Presyncope	-	-	-	1	-
Posterior Reversible Leukoencephalopahy (PRES)	1	-	-	-	-

Source: AE dataset. Original ISS. n= number of patients with event.

There is no increased risk of discontinuations due to nervous system disorders AEs in the controlled database. Serious events were described in the SAE section of this review. Non serious events that led to discontinuation included two episodes of dizziness (both on placebo), three of headache (one in on placebo, one on FTY 1.25 and one on FTY 0.5mg) one case of cognitive dysfunction in a patient taking FTY 0.5 mg/day. This last case was the subject who was eventually diagnosed with Sjogren's syndrome and his narrative is under the serious AE section.

Events leading to discontinuation from the Nervous system SOC in the extension studies were consistent with those in the core studies (data not shown).

- AE leading to drug dc in the General disorders and administration site conditions SOC

A total of 13 subjects discontinued because of AE in this SOC in the controlled database.

Table 46. AE leading to drug discontinuation, General disorders SOC, safety pool D

PT	FTY 5 mg N=94	FTY 1.25 N= 943	FTY 0.5 N=854	Placebo N=511	IFN N=431
	n (%)	n (%)	n (%)	n (%)	n (%)
Total	1 (1.0)	6 (0.6)	1 (0.1)	5 (1.0)	0
Asthenia	-	1	-	1	-
Chest pain	1	-	1	1	-
Fatigue	-	2	-	2	-
Generalized edema	-	1	-	-	-
Malaise	-	1	-	-	-
Non-cardiac chest pain	-	-	-	1	-
Pyrexia	-	1	-	-	-

Source: ISS table.

Serious AEs leading to drug discontinuation were described in the SAE section of this review. Non-serious AEs that led to discontinuation in the controlled studies were two cases of chest pain (one on FTY 5, one on FTY 0.5 mg); two cases of fatigue, one asthenia, one malaise, one generalized edema and one pyrexia in the FTY 1.25 group and two cases of fatigue, of one asthenia and one of chest pain (on Day 12 of the study) in the placebo group. The case of generalized edema is described as follows.

- **2301_0102_00001.** Generalized edema, Day 3 (FTY 1.25 mg)

  53 year old female. No significant history of cardiac, respiratory, liver disease, hypertension or diabetes. On Day 3 of FTY treatment she developed generalized edema and eyelid edema. On Day 15 she was found to have elevated ALT and GGT (2x ULN). The study drug was discontinued. The generalized edema was treated with indapamide for 2 days. According to the investigator, the generalized edema resolved 15 days after drug discontinuation while the eyelid edema and elevated liver enzymes resolved 133 days after drug discontinuation. The investigator suspected that these events were related to study medication. Additional information regarding the generalized edema was provided on 4/22/10 at the FDA request.

  On Day 3 of study therapy the patient developed generalized edema with symptoms of feeling bad, dyspnea, orthopnea and increase in bilateral pitting edema (edema in the face, eyelids, hands and feet). By Day 15 of the study, the patient had gained 8 kg from baseline. Biochemistry results taken at that time were normal (including the albumin and creatinine), except for ALT and GGT (which were 2-3 x ULN). Urinalysis results were indicative of urinary tract infection. PFT results showed normal lung function. A chest X-ray showed no signs of structural abnormality. ECG and Echo were both normal. An evaluation by a cardiologist concluded that there was no sign of cardiac failure and the complaints of the patient were not of cardiac origin. The drug was discontinued on Day 15, she was treated with indapamide for two days and events resolved 8 days after drug discontinuation.

  This is a case of generalized edema with 8 kg weight gain from baseline over a 2-week period. Apparently all laboratory evaluations on Day 15 were within normal, except modest liver enzyme elevation. No electrolytes were mentioned in the narrative. It is unclear if she had proteinuria. She responded to diuretic treatment. The events appear to be drug related, because it started 3 days into

treatment and improved after drug discontinuation, however, the cause of the edema remains unknown. It is unclear when the chest X-ray, PFTs and echocardiogram were done.

A case of drug discontinuation due to fluid retention during the controlled studies on FTY 1.25 mg was coded under the Metabolic disorders SOC. The case is included here, as follows.

- **2301_0206_00017**. 53 F, Fluid retention on day 36 of FTY 1.25. Medical Hx of asthma, hypersensitivity, epilepsy, among others; no history of diabetes or hypertension. Concomitant meds included hydroxychloroquine, pregabalin, minocyclin and baclofen. On Day 10 she complained of fatigue. On Day 36 presented water retention in lower body and extremities and abdominal distension with weight gain. Drug was discontinued on Day 121. Treated with furosemide. Weight, electrolytes and urinalysis not available in narrative or patient profile. Additional information has been requested.

  There is limited information about this case. The relationship to study drug can not be ruled out.

One additional subject discontinued due to edema during the extension study, upon the first dose of FTY 0.5 mg, as follows.

- **2302E1-0145-00001.** Edema. Day 1 of extension study (FTY 0.5 mg)

  42 F, diagnosed with MS 10 years earlier. Medical history included syncope, optic neuritis, hypercholesterolemia, hypertension and hypothyroidism. No history of diabetes or cardiovascular disease. She received INF during the core study for 1 year. On extension Day 1, upon first FTY 0.5 mg dose, she developed mild diffuse edema that led to drug discontinuation on extension Day 78. She was treated with furosemide. The event of edema resolved completely one day after the last dose of study medication. The investigator suspected a relationship to study drug. There is weight measurement at first dose in the extension phase, but no post-baseline measurements at the time the patient complained of edema.

  An additional case discontinued from study 2309 because of lower extremity and upper extremity swelling (2309 0510 00003) on Day 10 of blinded treatment.

  Three cases of fluid retention/edema with onset on Day 1, 3 and 36 led to study drug discontinuation in the original ISS database. One additional case (blinded) discontinue drug on day 10 of treatment. No conclusions can be drawn based on a few cases, particularly with very limited information, however, the finding requires further evaluation.

- AE leading to drug dc in the Respiratory, thoracic and mediastinal disorders SOC and Investigation (respiratory related) SOC

- Discontinuations in the controlled studies

Twenty one subjects discontinued because of AE in the Respiratory, thoracic and mediastinal disorders SOC and or the Investigation (respiratory related) SOC in the controlled database.

Table 47. Respiratory related AE leading to drug discontinuation, safety pool D.

SOC / PT	FTY 5 mg N=94	FTY 1.25 N= 943	FTY 0.5 N=854	Placebo N=511	IFN N=431
	n (%)	n (%)	n (%)	n (%)	n (%)
total	**2 (2.1)**	**9 (1.1)**	**3 (0.4)**	**5 (1.0)**	**2 (0.4)**
Respiratory, thoracic and mediastinal disorders SOC	2 (2.1)	5	2	2	-
Dyspnea	2	3	1	2	-
Obstructive airway disorder	-	1	-	-	-
Pleurisy	-	1	-	-	-
Pulmonary edema	-	-	1	-	-
Investigations - Respiratory and pulmonary investigations (excl blood gases)	-	4	1	3	*2*
Spirometry	-	-	-	1	-
DLCO decreased	-	4	-	2	*2*
PFT abnormal	-	-	1	-	-

Source: AE datasets and narratives submitted with original application. Infection-related events in the respiratory system are not included in this table.

Some events in the Respiratory SOC were coded as serious and were described in the SAE section of this review. None of the events in the Investigation SOC were coded as serious.

> *Overall, there was no excess of subjects discontinuing from the studies because of dyspnea or respiratory related events between FTY 1.25 and placebo. However, there seemed to be a dose response between FTY 1.25 and 0.5 in the risk of developing these events.*

The narrative of the case of PFT abnormal leading to drug dc from FTY 0.5 is as follows:

- **2302_0608_00007**, 49 M. Pulmonary function test abnormal on day 154; duration 2 days. FTY 0.5. Dx of MS 2 years prior. Treated with IFN in the past. Hx of headache. Concomitant meds: mirtazapine. On Day 154 she had abnormal PFTs and drug was dc, but it is unclear what the PFT abnormality was. She recovered the following day.

Selected narratives of non-serious events leading to drug discontinuation in the controlled studies with FTY 1.25 mg are presented as follows.

- **2302_0307_00007**, 38 F. Dyspnea on Day 20.; duration 86 days .FTY 1.25 mg.
  Non smoker. Concomitant meds: oral contraceptive. On Day 20 experienced dyspnea of mod intensity. Drug was discontinued on Day 103. No treatment reported. The event of dyspnea resolved 2 days after receiving last dose of study drug. *Time course suggests a drug-related event. No data on PFT, chest Xray or HRCT are available for this patient.*

- **2301_0754_00004,** 35 M. DLCO decreased on day 195. FTY 1.25 mg.
  MS was Dx 4 months prior to study entry, treated with CS. No concomitant meds. Non-smoker. Screening PFTs showed FEV1 3.87 L; FVC 5.02 L, DLCO 11.86 mmol/min/kPa. On Day 368 14 months into FTY 1.25 mg treatment he developed acute bronchitis with DLCO reduction (69% from

baseline). A pulmonologist diagnosed acute bronchitis with hyperactivity and bronchial asthma onset. A HRCT done one month later showed "local pneumofibrosis S5 from the R side and CT signs of abnormalities in the distal parts of the broncus", however, no PFTs were done at that time. Follow up PFT on Day 466 showed that FEV1, FVC and DLCO continued to decline (DLCO decline >20% from baseline). No HRCT was done at that time. Drug was discontinued on Day 468 because this AE. No further PFT or HRCT are available for this patient. *Patient is said to have developed asthma but also has restrictive disease with decreased DLCO>30% from baseline that had not recovered at the time of last available PFT. No further evaluations are available for this patient.*

- **2301_0758_00012,** 35 F. DLCO decreased on day 547; duration 264 days. FTY 1.25
  Smoker (1 pack per day per 16 years). At screening DLCO was 8.15 mmol/min/Kpa; FEV1 3.22 L; FVC 3.61 L. On Day 547 he was noted to have decreased DLCO of severe intensity. DLCO was 4.31 mmol/min/KPa, FEV1 2.82 L and FVC 2.99 L. Study drug was discontinued. DLCO decreased further but showed some increase 43 days after drug discontinuation. The event resolved 250 days after drug dc. *No HRCT was done for this patient.*

- **2301_0601_00007**, 46 F. Dyspnea. On Day 293, duration 56 days. FTY 0.5 mg
  MS diagnosed 10 years prior. No immunomodulators. EDSS=2. Medical history, depression. Active smoker 1 pack x 20 years. Concomitant meds: oxacarbazepine and escitalopram. Dyspnea started 10 months into study "even without making any effort". On day 336, a pulmonologist found normal physical exam and PFT but X-rays showed interstitial nodular increased shadowing at several places of the R lung. HRCT on Day 338 showed diffuse parenchymal changes consistent with panbronchiolitis. Repeated PFTs remained normal. At screening visit the HRCT had showed multiple findings but none were considered clinically significant. Drug was dc on Day 343. Dyspnea resolved on Day 348, five days after last dose. A follow up CT 4 months later showed improvement of radiological findings. A HRCT scan 9 months later was normal. *The time course suggests a drug-related event, as dyspnea started 10 months into the study and resolved 5 days after drug discontinuation. Radiologic findings resolved several months after drug discontinuation.*

> *Review of the narratives indicates that many of these patients had inadequate follow up and that they lacked a HRCT at the time of the decreased PFTs or after drug discontinuation. Moreover, some cases had not resolved at the time of last follow up (2301_0754_00004, 2302_0220_00013, 2302_0333_00008). The cause of the decrease in DLCO in these patients remains unexplained.*

Additional narratives of respiratory related events leading to drug discontinuation from the controlled studies are presented in Appendix 9.4.13.a.

- Discontinuations in the extension studies in the ISS

As per the SUR, there were 14 discontinuations due to respiratory related events in the extension studies in the ISS (3 in the FTY 5-1.25 mg group, five in the FTY 1.25 mg group and six in the FTY 0.5 mg group).

Listing of cases that led to discontinuation from FTY 0.5 mg in the extension studies are as follows:

2302E1_0219_00002, 19F DLCO decreased, Day 582
2301E1_0711_00002, 36M DLCO decreased, Day 180
2302E1_0307_00002, 42F Dyspnea, hypertension, asthenia, Day 109

2302E1_0609_00006, 41F Dyspnea, non cardiac chest pain Day 35
2301E1_0176_00003, 48M Dyspnea, Day 2
2301E1_0407_00015, 41F Respiratory distress, Day 757

Narratives of selected cases are as follows (none of them was reported as serious):

- **2302E1-0219-00002** – Carbon monoxide diffusing capacity decreased. FTY 0.5 mg core & extension. A 19 year old, Caucasian female with no reported relevant medical history. Non smoker. No concomitant medications were reported. At screening, the patient's DLCO, FEV1 and FVC values were 22.12 mL/min/mmHg (75.4% predicted), 3.52 L (102.3% predicted), and 4.01 L (102.2% predicted), respectively. On Day 464 of FTY 0.5 mg treatment the patient was noted with a decreased DLCO value of 16.4 mL/min/mmHg (56.4% predicted), which slightly improved to 17.48 (60.1% predicted), on Day 504. Study medication was not interrupted due to the event.
  On Day 582 the patient's DLCO value was 14.41 mL/min/mmHg (49.6% predicted). The patients FEV1 and FVC values were 3.31 L (97.6% predicted), and 3.46 L (89.3% predicted), respectively. No symptoms were associated with the DLCO reduction. Study drug was discontinued. No treatment was given for the event.

  The patient was evaluated by a pneumologist as required by the protocol safety monitoring guidance. The pneumologists notes indicate that the patient had a DLCO value of 75.8% of theoretical normal at baseline which decreased during the course of the study to a "low theoretical normal." The clinical examination was always negative. A HRCT was conducted 3 weeks after drug discontinuation did not indicate interstitial lung abnormalities. The pneumologist evaluation took place one month after study drug discontinuation. He stated that at that time there was no evidence of active diseases in progress.

  144 days after discontinuing study drug the patient had a study completion visit. At this visit the patient had a DLCO value of 15.63 mL/min/mmHg (53.8% of predicted) with FEV1 of 3.17 (93.4% predicted) and FVC of 3.34 (93.2% of predicted). She does no have any further follow up.

  The investigator suspected a relationship between the event (carbon monoxide diffusing capacity decreased) and the study medication.

Pulmonary Function Tests in patient 2302E1-0219-00002

Visit, Visit Date (Days since first dose)	**FEV1 (L)**	**FVC (L)**	**Diffusion capacity for carbon monoxide (mmol/min/KPa)**	**PImax (kPa)**	**PEmax (kPa)**	**HRCT**
Screening,	3.52	4.01	22.12	103	156	
Visit 5 (Day 30)	3.54	3.83	21.5	113	158	
Visit 7, (Day 90)	3.46	3.61	19.15	93	126	
Visit 8, (Day 182)	3.46	3.67	20.57	95	156	
Visit 777, (Day 370)	3.36	3.44	19.67	82.29	163	
Visit 13, (Day 408)	3.19	3.24	19.5	101	126	
Visit 15, (Day 464)	3.32	3.4	16.4	107	151	

Unscheduled (Day 504)	3.46	3.67	17.48	110	142	
Visit 16, (Day 441)	3.24	3.44	16.21	96	147	
PFTs after drug discontinuation						
(1 day since drug dc)	3.31	3.46	14.41	94	134	
3 weeks after drug dc						No abnormality
(145 days since drug dc)	3.17	3.34	15.63	93	139	

This case is of concern. This is a healthy 19 year old female non smoker, taking no concomitant meds, who had slight decrease of predicted DLCO (75.4% of predicted) at screening and developed progressive decrease in DLCO, down to 50% of predicted around 2 years into FTY 0.5 mg treatment. HRCT (done 3 weeks after drug dc) was normal. A pulmonologist evaluation (done one month after drug dc) showed "no progressive, active disorders". However, at the time of last follow up, the patient had not recovered from decreased DLCO. The cause of the substantial decrease in DLCO remains unknown. The role of fingolimod in worsening the diffusing capacity of carbon monoxide in this patient can not be ruled out.

- **2302E1-0307-00002 –** Dyspnea. 42 F. Medical history included psoriasis, headache, intercostal neuralgia and migraine. No history of diabetes mellitus, HTN or cardiovascular disease. She received IFN during the core study. On Day 109 of the extension study (on FTY 0.5 mg) she experienced mild dyspnea, asthenia, hypertension and diarrhea. She received last dose of study drug on extension Day 122. The event of dyspnea resolved 5 days after the last dose of study drug. The narrative does not provide any information about work-up conducted in this patient. *Additional information provided on May 21, 2010:* the dyspnea symptoms were mild and stopped a few days after onset and did not require any additional follow-up. A retest of the original PFT assessments with a pulmonologist was also not performed, as the patient's condition improved and the AE (dyspnea) was only of mild intensity. Fourteen days after study drug discontinuation, the patient came back to the clinic to have the end of study visit which included PFT, lab and ECG assessments. No chest x-ray or HRCT was performed. At this visit the patients DLCO was 79.7% of the baseline value. However, review of PFTs done at the end of the core study (Day 366 shows that the decrease in DLCO preceded the first dose of FTY. 105 days after drug discontinuation at the 3-month follow-up visit the patients DLCO was still 78% of the screening value.

- **2302E1-0609-00006** –Fatigue, dyspnea, non-cardiac chest pain
  41 F, MS diagnosed 14 years earlier. Medical history headaches, seasonal allergy, optic neuritis, bronchitis. No diabetes, HTN, CV or respiratory disease. Smoker. She received IFN during core. On E Day 4 of FTY 0.5 mg, she experienced mild fatigue and dizziness. On E Day 14 increased fatigue and headache. On E Day 35 mild dyspnea and non-cardiac chest pain. Drug was discontinued on E Day 38. No treatment was given. The narrative has no information about work-up done in this patient. *Additional information provided on May 21, 2010:* Physical exam, PFT and ECG were normal. The investigator concluded that the patient had intolerance to FTY and decided to stop study medication and switch to IFN. The patient did not see a pulmonologist or cardiologist as it was not

deemed necessary by the investigator. Evaluation of PFTs indicate that the patient had a decrease in DLCO during the core phase (from 24.23 ml/min/mmHg to 21.92), with normal Xray. PFTs done on E day 38 showed DLCO of 24.72 ml/min/mmHg. No Xray was done at that time.

- **2301E1-0176-00003.** Dyspnea associated with bradycardia that led to study drug dc on Day 3 of the extension study (on FTy 0.5). This was a cardiac-related event.

- Discontinuations due to respiratory related AEs in the ongoing studies

In addition to these cases, the blinded listing of discontinuations due to AE in study 2309 submitted with the SUR indicates that several patients discontinued from the study because of respiratory related events. Unblinding of these cases was requested and showed the following: 7 patients discontinued because or respiratory related events from FTY 1.25 mg; 3 discontinued from FTY 0.5 mg and one discontinued from placebo. These events are summarized in the following table.

Table 48. Discontinuations due to respiratory related adverse events in study 2309

	FTY720 1.25 N=359 n(%)	**FTY720 0.5 N=350 n(%)**	**Placebo N=350 n(%)**
Total	**7 (1.9)**	**3 (0.9)**	**1 (0.3)**
Dyspnea	**3**	**2**	**1**
Cough	**1**	**-**	**-**
Asthma/bronchospastic airway	**2**	**1**	**1**
Interstitial lung disease	**1**	**-**	**-**

Source: response to FDA request for information submitted June 9, 2010.

The listing of patients is as follows:

FTY 1.25 mg
USA/0503/00006 45/F/Bl BREATHING DIFFICULTY
USA/0514/00016 52/F/Ca COUGH
USA/0545/00014 42/M/Ca SHORTNESS OF BREATH
USA/0580/00003 38/F/Ca INCREASED SHORTNESS OF BREATH, ASTHMA.
USA/0585/00005 32/M/Bl ASTHMA
USA/0585/00008 52/M/Bl OBSTRUCTIVE AIRWAY DISEASE
USA/0602/00018 55/F/Ca WORSENING LUNG INTERSTITIAL CHANGES
USA/0605/00002 47/F/Ca SHORTNESS OF BREATH OR EXERTION

FTY 0.5 mg
USA/0581/00005 54/F/Ca SHORTNESS OF BREATH
USA/0585/00002 50/F/Ca BRONCHOSPASTIC AIRWAY DISEASE
USA/0586/00001 32/M/Ca TRANSIENT DYSPNEA

Placebo
USA/0580/00003 38/F/Ca Dyspnea, asthma

Results of study 2309 indicate a clear dose response in discontinuations due to respiratory related adverse events between FTY 1.25 (1.9%) and 0.5mg (0.9%). The numbers are small to draw conclusions regarding the safety of FTY 0.5 mg as compared to placebo (discontinuations due to respiratory related events were 0.9% and 0.3%, respectively). The applicant proposes to conduct a postmarketing registry to explore potential safety issues with FTY. The evaluation of lung toxicity is currently not included, but should be included in such a study. Additionally, the AC panel that met on June 10, 2010 recommended that a lower dose of fingolimod be studied. Pulmonary function should be evaluated in such a study. Patients who discontinue because of respiratory related events should also have an echocardiogram, if the possibility of pulmonary hypertension is a consideration.

- AE leading to drug dc in the Vascular disorders SOC

Six subjects discontinued because of AE in the Vascular disorders SOC in the controlled database.

Table 49. AE that led to study drug discontinuation in Vascular SOC, safety pool D.

PT	FTY 5 mg N=94	FTY 1.25 N= 943	FTY 0.5 N=854	Placebo N=511	IFN N=431
	n (%)	n (%)	n (%)	n (%)	n (%)
total	**1 (1.0)**	**3 (0.3)**	**1 (0.1)**	**1 (0.2)**	**-**
Hypotension	-	-	-	1	-
Hypertension	1	1	1	-	-
Arterial occlusive disease	-	2[1]	-	-	-

[1] One event described as vasospastic occlusion and one as occlusion.

The serious cases have been described in the SAE section (the two arterial occlusions). The 3 cases of hypertension leading to discontinuation that were coded as non-serious events are summarized as follows (all new onset HTN).

- **2201_0025_00009**, 49 M. Hypertension on day 127 of FTY 5 mg treatment; duration of event 87 days. Patient had total cholesterol level of 5.96 mmol/L (upper normal value 5.69 mmol/L) and sitting blood pressure of 126/82 mmHg at baseline. No hx of HTN. On Day 95 total cholesterol was 6.76 mmol/L. Treatment with simvastatin was initiated on day 113. The investigator suspected a relationship with the study medication. On day 127 the patient presented with mild hypertension showing a sitting blood pressure of 140/100 mmHg. No treatment for hypertension was initiated. No relationship to the study medication was suspected. On day 154 mild hypercholesterolaemia still persisted. A relationship with the study medication was suspected. The patient discontinued study medication on day 164.

- **2301_0757_00011,** 52 F. No Hx of HTN or diabetes. Non smoker. Baseline BP 131/75 mmHg. She developed moderate tachycardia and arterial HTN on day 20 of FTY 1.25 mg treatment (exact value not provided); drug was discontinued and patient was treated with metoprolol. The event resolved 7 days after drug dc.

- **2302_0316_00013**, 39 F. Hypertension on day 2 of FTY 0.5 mg treatment; No history of HTN, diabetes or smoking. Prior to randomization sitting BP was 136.6/ 93.3 mmHg. On Day 2 of treatment she was noted with high BP. On Day 30. BP was 157/98 mmHg. Drug was discontinued. She was treated with amlodipine for HTN. Event was present at the time of last available report.

One subject was reported to have an AE of high blood pressure leading to drug dc in the extension studies (2302E_0307_00002, a 42 F on FTY 0.5mg).

Although the number is small, all cases of HTN leading to drug dc occurred in FTY treated patients. No additional discontinuations due to vascular events occurred in the extension studies.

- AE leading to drug dc in the Psychiatric disorders SOC

Seven subjects discontinued because of AE in the Psychiatric disorders SOC: one acute psychosis on placebo, on day 240 (described under SAES); four cases of depression (one IFN, 2 on FTY 1.25 and 1 on FTY 0.5mg) and one suicide attempt in the FTY 1.25 mg group (described under SAEs). Depression is not uncommon among subjects with MS, and there was no increased risk with fingolimod.

- AE leading to drug dc in the Skin and subcutaneous disorders SOC

Six subjects discontinued because of AE in this SOC: one pruritic rash (on placebo), and five rashes in fingolimod in the controlled database (Two on FTY 1.25 – one eczema, one erythema, and 3 on FTY 0.5). Two cases on FTY 0.5 mg are as follows.

- **2301_0205_00002**. 49 M. Dermatitis allergic on day 1. Patient developed blister-like rash approximately 7 hours past first dose. The study medication was dc due to the event (dermatitis allergic) on Day 2. On day 3 there was slight blistering on the skin located on the arms and less apparent on the chest and back. She was treated with Benadryl. Rash 26 days after study drug discontinuation. The patient was then lost to follow-up.

- **2301_0302_00007.** 35 F. Dermatitis allergic on day 29. She presented allergic skin rash (moderate intensity, located on extrimities). Drug was dc on day 30. No details were given about treatment. Rash resolved 47 days after drug discontinuation.

The third case was coded as macular rash but was actually basal cell carcinoma at 3 sites (described under Neoplasms).

In the renal transplant population there were two anaphylactic reactions and one case of serum sickness. A signal for hypersensitivity reactions was not observed in the MS database.

- AE leading to drug dc in the Musculoskeletal system disorders SOC

Six events in this SOC led to drug discontinuation: two back pain (one on IFN, one on FTY 1.25), one muscle spasm (on FTY 1.25), one pain in extremity (on FTY 0.5) and two myalgia (one on FTY 1.25 and one on FTY 0.5). None of these events were serious.

- AE leading to drug dc in the Metabolic disorders SOC

Three subjects discontinued due to AE in the metabolic disorders SOC in the controlled database: one case of abnormal loss of weight (on FTY 1.25), one case of hypercholesterolemia (on FTY 5 mg), one weight decreased (on FTY 1.25) and one fluid retention (also on FTY 1.25 mg). The case of fluid retention was described under AE leading to drug discontinuation in the General disorders section.

- AE leading to drug dc in the Blood and lymphatic SOC and blood-related Investigations SOC

Non-serious blood related AE that led to study drug discontinuation in the controlled studies were one case of platelet count decreased (Investigations SOC) on Day 90 of FTY 5 g, one case of lymphadenopathy on Day 101 with FTY 1.25 and one case of lymphopenia on Day 548 with FTY 0.5 mg. The case of platelet decreased is as follows.

- **2201_0031_00007**, on FTY 5 mg. 37 M. Platelet count decreased (investigations) on Day 90. Decreased platelet count of $28x10^9$/L on day 90. No known risk factors for the development of thrombocytopenia could be identified. The investigator suspected a relationship with the study medication. Treatment with study medication was discontinued on day 99. During a follow-up visit on day 120 a platelet count of $80x10^9$/L was measured. The patient discontinued the study on day 120 after withdrawal of consent.

  Therefore, altogether, there were 3 cases of thrombocytopenia in the original ISS, two serious and one leading to discontinuation.

Additionally, 9 subjects discontinued from the extension studies due to non-serious AE of lymphopenia in the original ISS (2 from the FTY 5mg to 1.25 mg group, five from the FTY 1.25 mg group and two from the FTY 0.5 mg group).

In summary, AE leading to study drug discontinuation was higher in the FTY 1.25 group as compared to placebo, FTY 0.5 and interferon. The SOCs with the highest incidence of AE leading to drug discontinuation were Investigations (mostly liver-related investigations), Cardiac, and Eye disorders SOCs, There was a dose-response between FTY 1.25 and FTY 0.5 for these SOCs.

In the controlled studies, hepatobiliary disorders and liver-related Investigations led to drug discontinuation in 4.6%, 3.6% and 0,8% of patient on FTY 1.25 mg, FTY 0.5 mg and placebo groups, respectively.

In the Eye disorders SOC, AE led to drug discontinuation in 1.6%, 0.2% and 0,4% of patients in the FTY 1.25 mg, FTY 0.5 mg and placebo groups, respectively, including 10 (1.1%), 1 (0.1%) and 1 (0.2%) cases of macular edema (ME) in the

FTY 1.25, FTY 0.5 and IFN groups, respectively. At the time of the SUR, 9 cases of ME had led to study drug discontinuation from the extension studies in the ISS, including 2 on FTY 0.5 mg. The special safety interim report update included 11 cases of ME that led to drug dc from study 2309, including 5 on FTY 1.25 (1.4%), 5 on FTY 0.5 (1.4%) and one on placebo (0.3%).

The risk of AE leading to drug discontinuation in the Cardiac SOC in the controlled studies was 1.3%, 0.1% and 0.4% for FTY 1.25 mg, FTY 0.5 mg and placebo, respectively. One patient discontinued drug because of pulmonary hypertension diagnosed during a scheduled echocardiogram in study 2309.

Several patients discontinued drug because of respiratory related events of dyspnea or abnormal PFTs in the controlled and extension studies in the ISS. There was no excess AE leading to discontinuation due to AE in the FTY treatment groups (1.1% and 0.4%) as compared to placebo (1.0%). However, most have a less than optimum work-up and discontinued without having PFT's, chest X-ray or HRCT. The cause of dyspnea and decreased DLCO remains unclear in these patients. Of note, there was a dose related increase in risk of discontinuations due to respiratory-related events in study 2309 (1.9%, 0.5% and 0.3% in the FTY 1.25, FTY 0.5 mg and placebo groups, respectively).

AEs leading to drug discontinuation in the Infections and infestations SOC in the controlled studies suggested an increased risk in the FTY 1.25 mg group (but not in the FTY 0.5 mg group) as compared to placebo (0.7%, 0.1% and 0.4%, respectively).

7.3.4 Significant Adverse Events

This section discusses AE that were non-serious or did not lead to discontinuation but are potentially relevant.

- AE in the Eye disorders SOC

There were four cases of retinal detachment coded as non-serious in the controlled database (3 on FTY 1.25 and 1 on FTY 0.5 mg). Except for one case that led to drug discontinuation and had three surgical procedures to repair detachment), no narratives are available for the other cases.

There were several non-serious AE related to the retinal artery: one bilateral ischemia/vasculitis, and 2 retinal microaneurysm in the FTY 1.25 group; one retinal vascular spasm and one splinter hemorrhage in the FTY 0.5 mg, and 7 retinal hemorrhages (3 in FTY 1.25 and 4 in the FTY 0.5 mg group). Cases that led to study drug discontinuation have been described. Narratives of those non-serious that did not lead to study discontinuation were submitted at the FDA request and did not provide additional significant clinical information.

Selected serious and non-serious AE in the Eye disorders SOC in the controlled studies are presented as follows.

Table 50. Selected serious and non-serious AE in the Eye disorders SOC, safety pool D

	FTY 1.25 N= 943	FTY 0.5 N= 854	placebo N= 511	IFN N= 431
	n(%)	n(%)	n(%)	n(%)
Any AE in SOC	136 (14.4)	137 (16.0)	74 (14.5)	52 (12.1)
Macular edema	12 (1.3)	2 (0.2)	0	1 (0.2)
Retinal detachment	3 (0.3)	1 (0.1)	0	0
Vascular	7 (0.7)	6 (0.6)	-	-
Bilat ret ischem	1 (0.1)	-	-	-
Ret art microthr.	1 (0.1)	-	-	-
Ret vasc. spasm	-	1 (0.1)	-	-
Splinter hemorr.	-	1 (0.1)	-	-
Ret microaneurysm	2 (0.2)	-	-	-
Retinal hemorr.	3 (0.3)	4 (0.4)*	-	-
Arteriosclerotic retinopathy	-	1 (0.1)	-	-

Source: AE dataset, ISS. * includes one case who had a retinal hemorrhage and retinal vein thrombosis.

Narratives of cases of non-serious retinal hemorrhage and retinal detachment were submitted at the FDA request on 5/3/10. None of the patients had a history of hypertension or diabetes and no patient developed an AE of hypertension during the study. All cases were asymptomatic and there were no changes in visual acuity.

The listing of patients with macular edema in the ISS (serious and nonserious) is as follows:

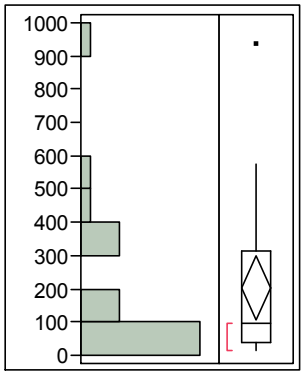
Controlled period		ID	Age	Sex	Rel day on FTY	S	dc	Country	Duration (days)
	Interferon	CFTY720D2302_0255_00003	22	F	.	0	dc	EGY	No data
	FTY 0.5	CFTY720D2302_0408_00005	53	F	367	0	.	ARG	No data
	FTY 0.5	CFTY720D2302_0424_00010	41	M	94	Y	dc	BRA	63
	FTY 1.25	CFTY720D2301_0651_00024	38	M	15	0	dc	NLD	420
	FTY 1.25	CFTY720D2301_0904_00003	41	M	36	Y	dc	GBR	77
	FTY 1.25	CFTY720D2301_0952_00006	42	F	37	0	dc	ZAF	147
	FTY 1.25	CFTY720D2301_0953_00007	27	M	183	0	dc	ZAF	No data
	FTY 1.25	CFTY720D2302_0106_00005	37	F	99	0	dc	ESP	No data
	FTY 1.25	CFTY720D2302_0251_00002	32	M	145	0	dc	EGY	No data
	FTY 1.25	CFTY720D2302_0524_00005	36	M	98	0	dc	USA	33
	FTY 1.25	CFTY720D2302_0602_00005	44	F	99	0	dc	CAN	85
	FTY 1.25	CFTY720D2302_0915_00006	46	F	54	Y	dc	PRT	117
	FTY 1.25	CFTY720D2301_0151_00003	50	F	26	0	dc	ISR	65
	FTY 1.25	CFTY720D2301_0701_00033	39	F	99	Y	.	POL	52

	FTY 1.25	CFTY720D2301_0708_00020	21	M	15	Y	.	POL	61
Extension studies									
	Rx during core								
FTY 0.5	Interferon	CFTY720D2302_0211_00008	36	M	189	Y	dc	ITA	24
FTY 1.25	FTY 1.25	CFTY720D2201_0023_00003	52	M	932	Y	dc	DNK	43
FTY 1.25	FTY 1.25	CFTY720D2201_0043_00001	40	F	575	y	dc	DEU	17
FTY 1.25	Placebo	CFTY720D2201_0072_00001	48	F	302	0	dc	CHE	No data
FTY 1.25	Interferon	CFTY720D2302_0145_00004	53	F	40	Y	dc	BEL	71
FTY 1.25	Interferon	CFTY720D2302_0324_00008	50	F	312	Y	dc	DEU	No data
FTY 1.25	FTY 1.25	CFTY720D2302_0610_00001	37	M	359	Y	dc	CAN	60
FTY 5 - 1.25	FTY 5	CFTY720D2201_0052_00001	38	F	476	Y	.	ITA	64
FTY 0.5	Placebo	CFTY720D2301_0657_00005	50	F	106	0	dc	NLD	No data

Source: SUR datasets.

Analysis of time to onset for events of ME in the FTY treatment group (total of 23 subjects) shows a mean of 202 days (6.5 months), with a median of 99 days. Of note, only one case was from USA.

Distributions – Onset of ME in 23 patients taking FTY in ISS



Quantiles

100.0%	maximum	932.00
99.5%		932.00
97.5%		932.00
90.0%		535.40
75.0%	quartile	312.00
50.0%	median	99.00
25.0%	quartile	40.00
10.0%		19.40
2.5%		15.00
0.5%		15.00
0.0%	minimum	15.00

Moments

Mean	202.52174
Std Dev	222.81441
Std Err Mean	46.460016
upper 95% Mean	298.87391
lower 95% Mean	106.16956
N	23

The following are serious and non-serious AE of macular edema in study 2309 (cut-off September 2009), from Table 54 of Special safety interim report Update (SN0051)

Table 51. Patients with macular edema Adverse Events (OPH analysis set in study 2309)

Patient ID	Age/ sex/ race †	History of ME, uveitis	Treat-ment	Baseline CFT µm OS, OD	Post-baseline CFT, study day & OS, OD values	ME SAE/AE start day (date) (action taken)	ME confirmed by DSMB
0507-00027	53/M/ Ca	ME	FTY720 1.25 mg	OS 220 OD 211	day 38 OS 361 OD 220 day 54# OS 331 OD 217	AE: bilateral ME day 38 (6May09) (discont.)	Yes (confirmed Feb 2010)
0513-00023	40/F/ Ca	none	FTY720 1.25 mg	OS 168 OD 184	day 288# OS 388 OD 174	SAE: ME OS day 287 (3Jun09) (discont.)	Yes
0524-00007	39/F/ Ca	none	FTY720 1.25 mg	OS 187 OD 184	day 38 OS 209 OD 207	AE: bilateral ME day 38 (9Nov07) (discont.)	No
Patient ID	**Age/ sex/ race †**	**History of ME, uveitis**	**Treat-ment**	**Baseline CFT µm OS, OD**	**Post-baseline CFT, study day & OS, OD values**	**ME SAE/AE start day (date) (action taken)**	**ME confirmed by DSMB**
0531-00002	52/F/ Ca	not known	FTY720 1.25 mg	OS 100 OD 195	day 168 OS 221 OD 188 day 203# OS 198 OD 199	SAE: ME OS day 168 (15Apr08) (discont.)	Yes
0545-00014	42/M/ Ca	none	FTY720 1.25 mg	OS 190 OD 186	day 55# OS 184 OD 160	AE: ME OS day 55 (8Jul08)	No
0557-00006	49/F/ Ca	none	FTY720 1.25 mg	OS 167 OD 166	day 45 OS 205 OD 179 day 60# OS 262 OD no data	AE: ME OS day 47 (26Oct07) (discont. day 58)	No
0588-00013	48/M/ BI	none	FTY720 1.25 mg	OS 201 OD none	day 57# OS 157 OD 524	AE: bilateral ME day 31 (17Sep08)	Yes

Cases on FTY 0.5 mg:

Patient ID	Age/ sex/ race †	History of ME, uveitis	Treat-ment	Baseline CFT µm OS, OD	Post-baseline CFT, study day & OS, OD values	ME SAE/AE start day (date) (action taken)	ME confirmed by DSMB
0524-00004	51/F/ Ca	none	FTY720 0.5 mg	OS 189 OD 180	day 99 OS 196 OD 191 day 135# OS 186 OD 236	AE: ME OD Day 99 (23Jul07) (discont.)	No
0547-00007	37/F/ Ca	none	FTY720 0.5 mg	OS 186 OD 220	day 114 OS 198 OD 471	SAE: ME OD day 114 (6Nov07) (discont.)	Yes
0548-00003	49/F/ Ca	none	FTY720 0.5 mg	OS 164 OD 166 (OCT2)	day 98 OS 164 OD 151 day 196 OS 154 OD 147	AE: ME OS day 98 (21Nov07) (discont. on day 196)	No
0601-00009	49/F/ Ca	none	FTY720 0.5 mg	OS 263 OD 199	day 52 OS 425 OD 195 day 87# OS 268 OD 290 day 101# OS 251 OD 236	AE: ME OS day 52 (8Nov07) (discont.)	Yes
0616-00002	41/F/ Ca	ME, uveitis	FTY720 0.5 mg	OS 180 OD 205	day 34 OS 327 OD 462 day 93# OS 185 OD 198	AE: ME OD day 34 (5Jun07) (discont.)	Yes

Cases on Placebo:

Patient ID	Age/ sex/ race †	History of ME, uveitis	Treat-ment	Baseline CFT µm OS, OD	Post-baseline CFT, study day & OS, OD values		ME SAE/AE start day (date) (action taken)	ME confirmed by DSMB
0545-00007	47/M/ Ca	none	Placebo	OS 181 OD 167	day 34	OS 182 OD 157	AE: bilateral ME day 90 (20Nov07) (discont. day 42 due to GGT & ALP raised)	No
					day 90#	OS 159 OD 153		
0561-00028	33/M/ Ca	none	Placebo	OS 212 OD 184	day 34	OS 234 OD 196	SAE: bilateral ME day 61 (28Jul08) (discont.)	Yes
					day 64#	OS 258 OD 214		

OS = left eye, OD = right eye, BL = baseline, discont. = discontinued study drug, GGT = gamma glutamyltransferase, ALP = alkaline phosphatase. † Demography taken from PT-Listing 16.2.4-1.1 (may be different from demography data in the patient narrative). # Off-study drug

As per this table, in most cases the onset of ME was detected at 2 to 3 months into fingolimod treatment. One case was detected as early as 34 days, and one as late as 168 days. The cases on placebo were detected on day 34, at the one-month visit.

It is unclear why the risk of ME with 0.5 mg appears to be greater in study 2309 (0.9% for confirmed events) as compared to the risk in the ISS studies.

- Non serious events of ischemic heart disease

In addition to the cases of serious ischemic heart disease in the Cardiac SOC and the cases that led to study drug discontinuation in the Cardiac and Investigations (ECG SOC), some events of myocardial ischemia, myocardial infarction and angina pectoris were coded as non-serious.

Serious and non-serious AE reports with preferred terms consistent with coronary artery ischemia in the Cardiac SOC and Investigations SOC (ECG related) are summarized as follows.

Table 52. Serious and non-serious ischemic heart disease in safety pool **D**

FTY 5 mg **N=94**	FTY 1.25 **N= 943**	FTY 0.5 **N= 854**	Placebo **N= 511**	IFN **N= 431**
n (%)	n (%)	n (%)	n (%)	n (%)
-	5 (0.5)	7(0.7)	4 (0.8)	3 (0.6)

Source: AE datasets and narratives for Cardiac SOC and Investigations (ECG) SOC. Patients included in this analysis are presented in Appendix 9.4.14.

Review of serious and non-serious events consistent with ischemic disease does not show an imbalance of events in the controlled studies. However, most diagnoses were made based on limited or no additional cardiac work-up. Most patients continued in the trials without receiving specific treatment but without subsequent episodes.

Additionally, there were 4 cases of angina and one MI in the extension studies included in the original ISS, and two MI were recently reported from the ongoing studies as IND safety reports.

- Hypertension

There was only one serious AE of hypertension and three non-serious cases of HTN leading to drug discontinuation in the controlled population. However, there were several non-serious cases, as shown in the following table.

Table 53. Serious and non-serious hypertension- related events, safety pool D

	1.25 mg	**0.5 mg**	**Placebo**	**Interferon**
	(N = 943) n (%)	**(N = 854) n (%)**	**(N = 511) n (%)**	**(N = 431) n (%)**
Any vascular event	**80 (8.5)**	**76 (8.9)**	**43 (8.4)**	**23 (5.3)**
Total number of patients with HTN related AEs	59 (6.3)	43 (5.0)	17 (3.3)	9 (2.1)
Hypertension	55 (5.8)	42 (4.9)	17 (3.3)	9 (2.1)
Hypertensive crisis	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Secondary hypertension	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Systolic hypertension	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Diastolic hypertension	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)

Source: SUR AE dataset. n= number of patients with events.

This finding is consistent with the analyses of vital sign evaluations have shown a dose-related increase in systolic and diastolic BP over time for FTY treatment groups.

Evaluation of medications after start of study drug suggests greater use of anti hypertensive medications in FTY groups (data not shown).

- Respiratory-related disorders, including serious and non-serious events

Overall, the risk of developing AEs in this SOC was similar among treatment groups. The AE with higher incidence for both FTY 1.25 and FTY 0.5 mg as compared to placebo and at least >1% difference was dyspnea. Dyspnea exertional was observed only in the active treatment groups. Other events that presented in the FTY groups but not on placebo were productive cough, respiratory disorder and wheezing. Of note, the number of patients with asthma, restrictive respiratory disease and obstructive pulmonary disease was no higher than placebo.

Table 54. Serious and non-serious AE, Respiratory thoracic and mediastinal disorders, safety pool D (selected AEs)

	5 mg (N = 94) n (%)	1.25 mg (N = 943) n (%)	0.5 mg (N = 854) n (%)	Placebo (N = 511) n (%)	Interferon (N = 431) n (%)
Any preferred term	31 (33.0)	198 (21.0)	168 (19.7)	109 (21.3)	63 (14.6)
Cough	5 (5.3)	69 (7.3)	63 (7.4)	37 (7.2)	16 (3.7)
Dyspnoea	12 (12.8)	50 (5.3)	38 (4.4)	20 (3.9)	7 (1.6)
Dyspnoea exertional	3 (3.2)	7 (0.7)	8 (0.9)	0 (0.0)	1 (0.2)
Productive cough	1 (1.1)	6 (0.6)	3 (0.4)	0 (0.0)	0 (0.0)
Respiratory disorder	0 (0.0)	1 (0.1)	2 (0.2)	0 (0.0)	1 (0.2)
Wheezing	3 (3.2)	1 (0.1)	3 (0.4)	0 (0.0)	0 (0.0)
Asthma	0 (0.0)	5 (0.5)	3 (0.4)	4 (0.8)	4 (0.9)
Lung disorder	0 (0.0)	4 (0.4)	1 (0.1)	1 (0.2)	1 (0.2)
Obstructive airways disorder	0 (0.0)	4 (0.4)	3 (0.4)	2 (0.4)	0 (0.0)
Bronchitis chronic	0 (0.0)	1 (0.1)	2 (0.2)	0 (0.0)	0 (0.0)
Emphysema	0 (0.0)	1 (0.1)	1 (0.1)	2 (0.4)	1 (0.2)
Increased upper airway secretion	0 (0.0)	1 (0.1)	0 (0.0)	3 (0.6)	0 (0.0)
Chronic obstructive pulm disease	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)

Source: ISS addendum 1 (Post text Table 4.4-1).

The rate and risk of dyspnea/dyspnea exertional in pool D is as follows:

Table 55. Rate and risk of dyspnea/dyspnea exertional, safety pool D.

	5 mg	1.25 mg	0.5 mg	Placebo	Interferon
Dyspnea or dyspnea exertional	13	57	46	20	8
N randomized	**N = 94)**	**(N = 943**	**(N = 854**	**N = 511**	**N = 431**
%	**15**	**6.0**	**5.4**	**3.9**	**1.9**
Patient years of exposure	43.2 PYRs	1111.2 PYRs	1153.2 PYRs	746.9 PYRs	401.9 PYRs
Rate per 100 PYRs	**30.0**	**5.1**	**4.0**	**2.9**	**2.0**

Source: FDA analysis. SUR AE datasets.

- Lung neoplasm and benign lung neoplasm in the fingolimod database

Eight subjects were reported to have a lung neoplasm or a benign lung neoplasm in the controlled studies. Additionally 3 subjects were reported to have a benign lung neoplasm in the extension studies in the original application. Only one case was serious and led to study drug discontinuation (necrotizing granulomatous pneumonitis in a transbronchoscopic biopsy). The other diagnoses were based on imaging, not on tissue pathology. The listing of cases is below:

Listing of subjects with lung neoplasm

CONTROLLED		PT	Verbatim	Rel day
Placebo				
2301_0206_00025	46 M	Benign lung neoplasm.	Subpbleura / left nodules along oblique tissues, lung	709
Interferon				
2302_0601_00015	35 M	Benign lung neoplasm	Nodule on left lower lung non malignant	184
FTY720 1.25 mg				
2301_0206_00028	46 F	Benign lung neoplasm	Lt posterior apical ground glass nodule - lung,benign	711
2302_0525_00002	41 F	Lung neoplasm	Scattered pulmonary nodules right middle lobe non specific benign	360
FTY720 0.5 mg				
2301_0211_00002	27 F	Benign lung neoplasm	Pulmonary node (benign)	370
2302_0141_00001	43 M	Lung neoplasm	Several nodular pulmonaire with nature unknown	359
2302_0535_00005	45 F	Lung neoplasm	Small nodule in lingual	351
EXTENSION				
2201_0004_00004 (FTY720 5 - 1.25)	52 F	Benign lung neoplasm	Benign solid mass lesion left lower lung lobe (Biopsy showed necrotizing granulomatous pneumonitis)	1356
2301_0109_00002 (FTY720 0.5 mg)	41 F	Benign lung neoplasm	Micro nodules bilateral sub-pleuraly (benign) (still observed but not treated)	367
2301_0703_00007 (FTY720 0.5 mg)	25 M	Benign lung neoplasm	Benign lung nodule (still observed but not treated in extension)	329

The percentage of these "lung neoplasms" appear to be similarly distributed among groups in the controlled studies.

- Pulmonary fibrosis

The FDA requested the sponsor to submit cases coded as pulmonary fibrosis. One of the cases was discussed under AE leading to discontinuation in the respiratory disorders SOC. The other case was coded as non-serious and did not lead to drug discontinuation, is as follows:

- **Patient 2301-0703-00016.** Coded as having "pulmonary fibrosis".

  44 F enrolled in 2301, received first dose in core phase on Jun 30 07 (FTY 1.25). Previously participated on monoclonal ab study (CNTO 1275) anti IL12 and IL23 from Mar 2005 to Mar 2006. EDSS score: 3. Non smoker, no asthma or respiratory disorders.

  End of study, Jun 9 09 (DAY 711) patient had a chest HRCT scan per protocol. HCRT reported abnormal findings of "fibrosis lingual of the left lung after inflammatory". AE reported as fibrosis of the left lung inflammatory and left lung after inflammatory, which were coded as "Pulmonary fibrosis" and "pneumonia".

  During the study, the patient's pulmonary function test DLCO had been 76% of baseline on visit 1 (Day 35) and 3 months (Day 117). An unscheduled PFT and HRCT were done on Dec 13, 2007 (day 167), which were normal. The patient continued treatment.

On Day 711, she had the abnormal HRCT finding at the end of study visit. Further details on the HRCT report was provided by the investigator as the following; "*No focal lesions in the lungs, except for minor post-inflammatory fibrosis in the medial segment of the lingula of the left lung. No signs of diffuse fibrosis. Reduced lung aeration in the expiratory phase, proportional*". The finding was considered by the local radiologist to be abnormal compared to baseline but not of clinical significance. Patient was examined by the pulmonologist on 19-Jun-2009 (Month 24, EOS visit). The patient's pulmonary function test was normal, no findings were reported, and the examination results were normal.

PFT evaluations in this patient are as follows.

Visit, Visit Date (Days since first dose)	**FEV1 (L)**	**FVC (L)**	**Diffusion capacity for carbon monoxide (mmol/min/K Pa)**	**PImax (cm H2O)**	**PEmax (cm H2O)**	**HRCT**
(Screening)	2.88	3.82	6.93	103	125	Normal
(Day 35)	2.83	3.82	5.30	107	142	-
(Day 117)	2.78	3.7	5.31	130	133	-
(Unscheduled	2.63	4.11	7.56	105	84	Normal
(Day 188)	2.76	4.31	6.93	119	103	-
(Day 363)	2.65	4.62	7.72	127	109	-
(Day 549)	2.91	4.35	7.76	116	103	-
(Day 549)	2.91	4.35	7.76	116	103	-
(Day 711, EOS)	2.75	4.2	6.58	111	82	Fibrosis lingula of the left lung after inflammatory. Abnormal compared to baseline. Not clinically significant.
(Day 788, Ext Day 35)	2.7	3.87	7.36	121	101 -	-

Blank field = Not done

The patient completed the core phase of the study and entered the extension phase. The patient is still ongoing in the extension phase, and her last pulmonary function tests performed as per protocol on Month 1 of extension (Month 25 of study) were normal with no decrease in DLCO.

Comment: Asymptomatic, HRCT done per protocol. Normal PFTs. The clinical significance of the HRCT finding is unclear. Patient continued in study.

- Nervous system disorders SOC – Serious and non-serious events

Other than seizure-related events, most AE in the Nervous system disorders SOC were actually slightly more common in the placebo arm than in the fingolimod groups, suggesting that they were related to MS. The only AE with a higher incidence in the fingolimod groups (both FTY 1.25 and FTY 0.5 mg) with >1% difference was migraine (3.2% on FTY 5mg, 3% on FTY 1.25, 3.4% on FTY 0.5mg, 1.8% on placebo and 1.5% on IFN.

3 subjects presented SAE of syncope in the controlled studies. One occurred on placebo, on Day 163; one on FTY 1.25 on Day 724 and one on FTY 0.5, on Day 203. Evaluation of all cases (serious and non-serious) of syncope and loss of consciousness showed similar incidence in all

treatment groups: 7 on FTY 1.25 (0.7%), 6 on FTY 0.5 (0.6%), 4 on placebo (0.8%) and 4 on IFN (0.8%). Except for one case of syncope on Day 1 with IFN, events were spread throughout the whole duration of studies but they were most common within the first year.

- Metabolic disorders SOC

Non-serious abnormal weight gain were reported in two subjects in the controlled studies (one on FTY 0.5 mg [2302_0424_00004, a 36 yo M on day 199]; and one on IFN [2302_0543_00003, a 44 F on day 280]. Fluid retention was reported in two subjects on FTY 1.25 (one already described under discontinuations, a 53 F] and another one in a 42 F who developed fluid retention on day 356 [2302_0506_00006]). Additionally, one subject was reported to have overweight on Day 155 of FTY 1.25 mg treatment (2302_0101_00006). No narratives are available for these patients.

- Neoplasms benign, malignant and unspecified (including cysts and polyps) SOC

Given the potential long-term immunosuppressive effects of fingolimod, the possibility of an increased risk of neoplasms was evaluated in this database. The risk (n patients with event/N patients randomized) of any neoplasm (serious and non-serious) was similar among groups. However, the rate (number of patients with events/number of patient years of exposure) was higher in the FTY groups as compared to placebo, and similar to IFN.

Looking at the table of serious and non-serious cases in the controlled studies, there does not appear to be an increased risk of any particular neoplasm, except perhaps for melanocytic nevus, basal cell carcinoma and fibrous histiocytoma. These tumors have been reported to be associated with immunosuppression. However, 2201 did not have pre-specified dermatologic examinations and dermatologic examinations by a dermatologist were implemented in studies 2301 and 2302 when the studies were already ongoing. Most of the diagnoses of skin lesions were done at the first dermatologic examination, after the patients had been on treatment for several months, therefore there is a suggestion for an increase of skin tumors in FTY treated patients but prospective evaluation is needed. Study 2309 (the ongoing study) had dermatologic examinations from the start.

The risk of selected Neoplams (serious and non-serious) in safety pool D is presented in the following table.

Table 56. Selected serious and non-serious events in the Neoplams SOC, safety pool D

	FTY 1.25	FTY 0.5	Placebo	IFN
	N=943 n(%)	N=845 n(%)	N=511 n(%)	N=431 n(%)
All neoplasm	**114 (12.1)**	**113 (13.2)**	**56 (11.0)**	**44 (10.2)**
Melanocytic nevus	55 (5.8)	47 (5.5)	15 (2.9)	26 (6.0)
Fibrous histiocytoma	6 (0.6)	5 (0.6)	1 (0.2)	5 (1.2)
Basal cell carcinoma	3 (0.3)	7 (0.8)	3 (0.6)	1 (0.2)
Melanoma	1 (0.1)	3 (0.3)	1 (0.2)	0
Bening breast neoplasm	5 (0.5)	2 (0.2)	4 (0.8)	0
Breast cancer	3 (0.3)	1 (0.1)	3 (0.6)	0
	FTY 1.25 PYRs=1111.2	FTY 0.5 PYRs=1153.2	Placebo PYRs=746.9	IFN PYRs=401.9
All neoplasms Rate per 100 PYRS	10.3	9.8	4.9	10.9

Source: Original ISS tables.

The rate per 100 PYRs suggest a higher rate of overall neoplasias in the FTY treatment groups and interferon, as compared to placebo. The difference is driven by non malignant lesions of melanocytic nevus and fibrous histiocytoma.

Evaluation of cases in the controlled and OL database (safety group E) was consistent with findings in the controlled database (data not shown).

Evaluation of blinded SAE and discontinuations due to AE in study 2309 do not suggest the presence of tumors related to immunosuppression. Of note, a case of skin sarcoma was reported in a patient taking FTY 0.5 mg. The narrative of this patient is as follows.

- **D2309-0545-00011 – Sarcoma of skin**

46 F, diagnosed with MD 8 years prior to entry. She had 2 relapses in the 2 years prior to randomization and one relapse in the year prior to randomization. She had received interferon beta 1a and beta 1b in the past. No additional immunomodulatory drugs for MS were administered. She had a history of optic neuritis, lumpectomy, hysterectomy. She was fair skinned and did not have a family history of cancer. Skin sun exposure type III. At screening she had a normal sized, colored mole on her right arm. On day 135 of FTY 0.5 mg treatment, she reported a possible growing of the mole on her right arm, with associated irritation. A skin biopsy was performed. The biopsy was initially read as "unclassified spindle cell and epitheliod malignant neoplasm". A second opinion was obtained from another expert in soft tissue pathology. The second pathologist reported that the lesion was best classified as "primary dermal sarcoma with features of a variant of atypical fibroxanthoma" and described the presence of peripheral collagen trapping in a pattern typical of fibrous histiocytomas. The final diagnosis was dermal sarcoma consistent with variant of atypical fibroxanthoma. A whole body PET (positron emission tomography) and CT scans of chest, pelvis and abdomen indicated that there were no metastasis. The event was considered by the investigator to be medically significant and related to study medication.

The risk/rate of fibrous histiocytoma was higher in the FTY treatment groups and interferon, as compared to placebo in safety pool D. One patient in study 2309 developed a malignant sarcoma, with other features typical of fibrous histiocytoma. This case suggests that some of the cases of fibrous histiocytoma could become malignant. The patient already had a mole at the site of the skin lesion. No conclusions can be drawn from one case, however, the role of fingolimod on the development or acceleration of a malignant lesion can not be ruled out.

As discussed for SAE in this SOC, the lack of findings of increased malignancies in this database does not rule out an effect after long-term use. Additional information on long term effects of immunosuppression need to be collected with this drug. The applicant proposes to address this safety concern in a postmarketing registry (PASS).

- Serious and non-serious Infections and infestations

The analysis of all infections and infestations by HLT in pool D, as submitted by the applicant is as follows.

All AE in the Infections and Infestations SOC were presented by 59.5% of patients on FTY 1.25, 61.6 % of those on FTY 0.5, 65.2 % of patients on placebo, and 51 % of patients on IFN (from ISS post text Table 4.4.1). The analysis of serious and non-serious AEs in this SOC by microorganism related HLT is as follows:

Table 57. Infections and Infestations SOC by microorganism-related HLT, safety pool D

Microorganism-related high-level term	FTY720 5 mg (N=94) n (%)	FTY720 1.25 mg (N=943) n (%)	FTY720 0.5 mg (N=854) n (%)	Placebo (N=511) n (%)	Interferon (N=431) n (%)
Influenza viral infections	7 (7.4)	74 (7.8)	84 (9.8)	44 (8.6)	32 (7.4)
Herpes viral infections	6 (6.4)	49 (5.2)	46 (5.4)	35 (6.8)	12 (2.8)
Viral infections NEC	2 (2.1)	37 (3.9)	34 (4.0)	28 (5.5)	7 (1.6)
Fungal infections NEC	2 (2.1)	33 (3.5)	30 (3.5)	21 (4.1)	16 (3.7)
Infections NEC	0 (0.0)	33 (3.5)	32 (3.7)	19 (3.7)	12 (2.8)
Bacterial infections NEC	1 (1.1)	20 (2.1)	7 (0.8)	9 (1.8)	3 (0.7)
Tinea infections	1 (1.1)	14 (1.5)	27 (3.2)	7 (1.4)	11 (2.6)

Microorganism-related high-level term	FTY720 5 mg (N=94) n (%)	FTY720 1.25 mg (N=943) n (%)	FTY720 0.5 mg (N=854) n (%)	Placebo (N=511) n (%)	Interferon (N=431) n (%)
Candida infections	1 (1.1)	11 (1.2)	9 (1.1)	3 (0.6)	8 (1.9)
Papilloma viral infections	0 (0.0)	6 (0.6)	3 (0.4)	2 (0.4)	1 (0.2)
Borrelial infections	0 (0.0)	2 (0.2)	1 (0.1)	3 (0.6)	0 (0.0)
Molluscum contagiosum viral infections	0 (0.0)	2 (0.2)	2 (0.2)	1 (0.2)	0 (0.0)
Sepsis, bacteraemia, viraemia and fungaemia NEC	0 (0.0)	2 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
Streptococcal infections	0 (0.0)	2 (0.2)	2 (0.2)	1 (0.2)	1 (0.2)
Bordetella infections	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)
Campylobacter infections	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Coxsackie viral infections	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Enteroviral infections	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Flaviviral infections	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)
Helicobacter infections	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Staphylococcal infections	0 (0.0)	1 (0.1)	2 (0.2)	0 (0.0)	0 (0.0)
Adenoviral infections	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Clostridia infections	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Corynebacteria infections	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Ectoparasitic infestations	0 (0.0)	0 (0.0)	3 (0.4)	1 (0.2)	1 (0.2)
Helminthic infections NEC	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Mycoplasma infections	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Nematode infections	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Trichomonas infections	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

-High level terms are sorted in descending frequency as reported in the FTY720 1.25 mg column.
-A patient with multiple AEs within a High level term is counted only once in the total row. Source: ISS addendum 1. [ISS PT-Table 4.4-12]

There does not seem to be an excess for any specific organism in this analysis, except perhaps a higher percentage of candida infections in the fingolimod groups. Of note, some of the events coded under Viral infections NEC HLT, could have been herpetic or any other kind of viral infection but were not specified.

32 unique subjects presented events in the Candida infections HLT. Of those, one was in the FTY 5 mg dose, 11 on FTY 1.25, 9 on FTY 0.5, 3 on placebo and 8 on IFN. Events on placebo included candidiasis and vulvovaginal candidiasis. Events on IFN included these terms and oral candidiasis. Events on FTY included these terms plus one case of oropharyngeal candidiasis (one year into FTY 1.25). None of the cases was serious.

- Analyses of infections by lymphocyte count

As per an analysis included in Table 6-16 of the applicant's AC background document, analyses of the relationship of nadir blood lymphocyte counts and occurrence of infections in study 2301 showed that the percentage of patients with infections for the group with nadir lymphocyte counts $\leq 0.4 \times 10^9$ /L was increased relatively to those with a

lymphocyte count >0.4 x $10^{9/}$L (the risk of infection in patients treated with fingolimod was 75.7% for the group with lymphocyte count <0.2 x 10^9/L; 72.4% for the 0.2 -0.4 x 10^9/L group and 57.7% for the >0.4 x $10^{9/}$L group). However, the overall risk in the lowest nadir lymphocyte count groups was similar to that of placebo (72%). The risk of infections among patients with a nadir lymphocyte count >0.4 x $10^{9/}$L was lower than placebo for all infections, except urinary tract infections and female reproductive tract infections (data not shown).

The lack of relationship between nadir lymphocyte count and infections is not unexpected, since the "nadir" analysis refers to counts at protocol scheduled visits, not at the timed when the infections were diagnosed. Lymphocyte values at the time of infections, even at the time of serious infections that led to hospitalization are not available for most patients.

When the applicant conducts the study to evaluate the efficacy and safety of fingolimod 0.25 mg, the lymphocyte values (and laboratory values in general) taken outside the pre-scheduled evaluations should be included in the narratives and datasets.

7.3.5 Submission Specific Primary Safety Concerns

1) Increased risk of Infections

- Background
    - Anticipated possibility of an increased risk of infections because decreased peripheral lymphocytes.
- Findings in MS

There was no excess of overall infections, serious infections or opportunistic infections in the fingolimod groups. However, all serious herpetic infections occurred in fingolimod treated subjects, including two cases of fatal herpes virus infections (herpes encephalitis and disseminated zoster) in young people not taking concomitant MS immunomodulators but receiving IV methylprednisolone for empiric treatment of MS relapse and four other herpetic infections that required hospitalization and intravenous acyclovir. An additional case of non-fatal herpes encephalitis was reported from ongoing study 2309 in a patient who had received fingolimod 1.25. He had stopped FTY treatment 6 months prior, but he was still lymphopenic at the time of the diagnosis. The HSV antibody status before receiving fingolimod is unknown. Therefore it appears that the risk of serious herpetic infections in increased with fingolimod 1.25 mg. No other serious viral or opportunistic infections were observed in this database.

Evaluation of concomitant medications used after start of study drug in safety pool D (Post text Table 3.11-1 of ISS, data not shown) supports an increased risk of viral infections in the fingolimod treated groups as compared to placebo. The use of antiviral agents (systemic and topical) was 1.8%, 1.1%, 0.2% and 1.6%, for FTY 1.25mg, FTY 0.5 mg, placebo and IFN, respectively.

Given the experience with natalizumab and other immunosuppressors (e.g rituximab), a potential concern with immunosuppresors is the development of progressive multifocal leukoencephalopathy (PML). Fingolimod has a different mechanism of action than natalizumab and rituximab and it is not supposed to be severely immunosuppresive. No cases of cases of PML were identified in this database, however, this is a relatively small and short database to rule out the possibility of PML.

Immunologic evaluation in response to neoantigen, recall antigen and cellular immunity in a clinical pharmacology study submitted with the SUR indicated a dose-related decrease in immune responses for fingolimod 1.25 as compared to 0.5mg. IgM antibody response to KLH neoantigen was 0% for FTY 1.25, 23% for FTY 0.5 and >90% for placebo. IgG antibody response was 57% for FTY 1.25 and >90% for FTY 0.5 and placebo. Tetanus booster response rate was 5% for FTY 1.25 and 0.5 mg, and 15% for placebo. These results suggest that the immunologic response to vaccination may be decresed during treatment with fingolimod even at the dose of 0.5 mg. It is recommended that subjects be immunized against varicella zoster before starting fingolimod. Whether fingolimod 0.5 affects acquired immunity to viral infections is unclear at this point.

The applicant states that the pharmacologic effect on lymphocytes lasts 1-2 months after drug discontinuation. However, in a 28-day clinical pharmacology study, 2 months after 0.5 mg discontinuation the lymphocyte count was approximately 10% below baseline. Time to full recovery was not formally evaluated when fingolimod is given for one or two years.

The following are comments from Dr. Cavaille Coll, FDA immunologist consultant from the Division of Special Pathogens (DSPTP):

> The risk of opportunistic infections in MS patients treated with fingolimod is not expected to be as great as that in solid organ transplantation patients or HIV-infected patients. Therefore, it is difficult to recommend that guidelines for monitoring, early treatment and prevention of opportunistic infections developed in solid organ transplant recipients or HIV-infected patients, should be systematically applied for MS patients treated with fingolimod. However, vaccination prior to initiation of long-term fingolimod therapy should be considered, as well as wording to the effect that immunosuppressants may affect vaccination, and therefore, vaccination may be less effective during treatment with fingolimod. (Note: this is class labeling for immunosuppressants in solid organ transplantation.)
>
> Class labeling for immunosuppressants for the prevention of rejection in solid organ transplantation recommends that the use of live vaccines should be avoided; live vaccines may include, but are not limited to measles, mumps, rubella, oral polio, BCG, yellow fever, and TY 21a typhoid . A similar recommendation should be considered for fingolimod.
>
> Peripheral blood lymphocyte counts and subsets cannot be used to reliably gauge the net state of immunsuppression in MS patients, treated with the proposed recommended dose of fingolimod, as these counts are used in HIV-infection. While peripheral blood lymphocyte counts may serve as a potential pharmacodynamic marker of fingolimod, to the extent that decreased lymphocyte counts may signify the presence of active drug on board, these counts appear to reflect redistribution and not lymphocyte depletion, and should not be interpreted as a reflection of infectious risk in the way they may be in HIV-infection.
>
> Due to fingolimod's effect on lymphocyte circulation and distribution, fingolimod has the potential to modify the signs and symptoms of infection. Thus, one should maintain a higher degree of suspicion for infection and atypical presentations in patients treated with fingolimod, as one would with other immunosuppressants or modulators of inflammation.
>
> The question as whether to recommend cessation of fingolimod administration in the event of a new infection and for what type of infection, remains unresolved; however, the prolonged pharmacokinetic and pharmacodynamic half-life of fingolimod implies that the immunosuppressive effect may persist for several days after cessation of the drug.

Although Dr. Cavaille-Coll did not recommend specific monitoring, in my opinion, at a minimum, a baseline WBC count should be obtained before initiating fingolimod therapy, so if a serious infection were to develop, one would know what the baseline was.
Fingolimod should not be initiated in patients with serious active acute or chronic infections.

2) Neoplasias

- Background

Non-clinical carcinogenicity studies in mouse showed an increased risk of lymphoma.
Some lymphoid tumors were observed in the renal transplant population, at the 2.5 mg dose (however, patients were also receiving Cyclosporin A).

- Findings in MS

Overall, there was no evidence of an increased risk of neoplasia in the FTY treated groups, except for an increase in non-malingnant melanocytic nevus and fibrous histiocytoma, with a risk/rate higher than placebo but similar to that of patients receiving interferon.

No cases of lymphoma were reported in the MS ISS population. However, three lymphomas were reported in the non-ISS studies: One was a case of brain mass and multiple tumors in lung, kidney, thyroid, yeyunum, and skin T cell lymphoma, in a patient receiving FTY 0.5 mg who died and the autopsy showed that the brain mass was a diffuse large B-cell lymphoma, and the other tumors were Epstein Barr virus-associated lymphoproliferative disorder. Another was in a patient receiving FTY 1.25 mg, who one year into treatment was diagnosed with diffuse large B-cell lymphoma, but reported a weight loss of 5 kg over the previous year. The third was a patient who had a preexisting skin lesion and one-year into FTY 1.25 mg treatment was biopsied and the pathology was T cell lymphoma.

B cell lymphoma is a relatively common tumor, but T cell lymphoma is a rare tumor. All three lymphomas occurred in ongoing studies. The overall rate of lymphoma in the MS program (all ISS and non-ISS trials) was 0.53 per 1000 PYRs.

One case of skin sarcoma was also reported in one of the ongoing studies.

> *It is unclear whether the cases of lymphoma are related to study drug. It appears that one year is too short for an immunosuppressive agent to induce a neoplasia. The database is relatively small and short to adequately assess the risk of malignancy. The question whether fingolimod is associated with increased risk of malignancy needs to be addressed in a larger database, such as postmarketing registry, as proposed by the applicant.*

3) **Eye toxicity**

- Background
  - In the controlled renal transplant database, serious macular edema (ME)was reported in 4.1%, 3.9% and 1.5% of patients receiving FTY 5, FTY 2.5 mg and MMF, respectively. In patients with diabetes mellitus, the risk of ME was 30% for FTY doses and 15% for MMF.

- Findings in MS population

There was a clear dose response for serious and non-serious macular edema in the controlled studies (1.3% on FTY and 0.2% % on FTY 0.5). There was one case of ME in the IFN group (0.2%) and none in the placebo group. Serious and non-serious AE of macular edema were reported in twenty three subjects on FTY in the ISS database (13 in the controlled period, 9 during the extensions, including 4 cases on FTY 0.5 mg). As per the Special safety interim report update, 14 cases of ME were reported in study 2309, including 5 on FTY 0.5 mg (one was serious and all 5 led to study drug discontinuation).

Table 58. Reported AE of macular edema in MS ISS and in study 2309

	FTY 1.25 n/N	**FTY 0.5 n/N**	**Placebo n/N**	**IFN n/N**
Safety Pool D	12/943 (1.2%)	2/854 (0.2%)	0/511 -	1/431 (0.2%)
Safety Pool E[1]	18/1302 (1.4%)	4/1176 (0.3%)		
Study 2309[2]	7/359 (2.0%)	5/350 (1.5%)	2/350 (0.6%)	

[1] Additionally, one patient on FTY 5mg-1.25 mg had an AE of macular edema in Pool E. n= patients with events. N= patients in safety population. [2] For study 2309 N refers to Ophthalmology analysis set.

The denominators for safety pool D and E are patients who took at least one dose of study drug. The denominator for study 2309 is the number patients who took drug and underwent OCT ("ophthalmology set population"). The risk of macular edema in study 2309 appears to be higher for all treatment groups, including placebo, probably because more OCTs were performed in study 2309.

Of note, some patients were found to have decreased visual acuity (VA) at the time of the diagnosis of ME, however, most patients recovered on follow up after drug discontinuation. On July 7, 2010, at the FDA request, the applicant submitted VA evaluations in all patients who had a diagnosis of ME in safety pool E and in study 2309, using LogMAR units. As per discussion with Dr. Wiley Chambers, an increase in VA of ≥0.3 LogMAR units is considered to be a clinically significant decrease in vision.

Review of the listings indicates that 6 out of 22 (27%) patients with ME in safety pool E and 4 out of 12 (30%) in study 2309 had significant decrease in visual acuity at the time of diagnosis of ME. At the time of last available follow up, 4 patients in safety pool E (3 on FTY 1.25 and one on FTY 0.5) and 4 in study 2309 (one on FTY 1.25, two on FTY 0.5 and one on placebo) had clinically significant lost of vision.

The listing of visual acuity assessments in safety pool E and study 2309 are presented in the following tables.

Table 59. Listing of visual acuity assessments in patients with macular edema, pool E

Patient ID	Treatment	VA [LogMAR] At Screening L/R	VA [LogMAR] At Time of ME Diagnosis L/R (Relative Day on FTY or MMF)	VA [LogMAR] At Last Follow-Up L/R (Relative Day After Drug Discontinuation)	Comments
Multiple Sclerosis ISS Pool E					
Study D2201					
ITA/0052/00001	FTY720 5 mg		0.22 / 0.00 (476)	0.00 / 0.00 (63)	Not confirmed by DSMB
CHE/0072/00001	FTY720 1.25 mg		---- / 0.22 (302)	---- / 0.15 (83)	Not confirmed by DSMB
DEU/0043/00001	FTY720 1.25 mg		0.00 / 0.10 (575)	0.00 / 0.00 (16)	Not confirmed by DSMB
DNK/0023/00003	FTY720 1.25 mg		0.00 / 0.17 (932)	0.00 / 0.17 (27)	Not confirmed by DSMB
Study D2301					
GBR/0904/00003	FTY720 1.25 mg	0.00 / 0.00	0.00 / 0.00 (36)	0.00 / 0.18 (27)	Confirmed by DSMB Last follow-up VA (not in database): 0.00 / 0.00 (76)
ISR/0151/00003	FTY720 1.25 mg	0.00 / 0.00	0.30 / 0.00 (26)	0.00 / 0.00 (23)	Confirmed by DSMB
NLD/0651/00024	FTY720 1.25 mg	0.00 / 0.00	0.10 / 0.00 (15)	0.30 / 0.40 (28)	Confirmed by DSMB Last follow-up VA (not in database): 0.10 / 0.00 (416)
POL/0701/00033	FTY720 1.25 mg	0.10 / 0.05	0.22 / 0.15 (99)	0.22 / 0.15 (32)	Confirmed by DSMB Last follow-up VA (not in database): 0.10 / 0.22 (577)
POL/0708/00020	FTY720 1.25 mg	0.05 / 0.00	1.00 / 0.00 (15)	0.10 / 0.00 (32)	Confirmed by DSMB Last follow-up VA (not in database): 0.15 / 0.05 (92)
ZAF/0952/00006	FTY720 1.25 mg	0.00 / 0.00	0.00 / 0.00 (37)	0.00 / 0.00 (15)	Confirmed by DSMB
ZAF/0953/00007	FTY720 1.25 mg	1.30 / 1.30	1.30 / 1.30 (183)	No Further Data	Confirmed by DSMB VA "unchanged" 15 months after drug discontinuation
NLD/0657/00005	FTY720 0.5 mg	0.49 / 0.00	0.49 / 0.10 (90)	No Further Data	Confirmed by DSMB No VA assessment at time of ME diagnosis Closest assessment 16 days before
Study D2302					
BEL/0145/00004	FTY720 1.25 mg	---- / 0.22	---- / 0.30 (40)	---- / 0.30 (25)	Confirmed by DSMB Last follow-up VA (not in database): ---- / 0.22 (68)
CAN/0602/00005	FTY720 1.25 mg	0.00 / 0.00	0.40 / 0.00 (99)	0.48 / 0.10 (28)	Confirmed by DSMB
CAN/0610/00001	FTY720 1.25 mg	0.00 / 0.00	0.00 / 0.00 (362)	0.00 / 0.00 (3)	Confirmed by DSMB No VA assessment at time of ME diagnosis Closest assessment 3 days after
DEU/0324/00008	FTY720 1.25 mg	0.10 / 1.30	0.30 / 1.30 (361)	0.30 / 1.30 (44)	Confirmed by DSMB Last follow-up VA (not in database): 0.17 / 1.30 (241)
EGY/0251/00002	FTY720 1.25 mg	0.18 / ----	0.17 / ---- (106)	No Further Data	No VA assessment at time of ME diagnosis Closest assessment 49 days after Not confirmed by DSMB
	FTY720 1.25 mg	0.18 / ----	---- / 1.00 (41)	No Further Data	No VA assessment at time of ME diagnosis Closest assessment 39 days before Not confirmed by DSMB No VA assessment at time of ME diagnosis Closest assessment 103 days before
ESP/0106/00005	FTY720 1.25 mg	0.18 / 0.00	0.52 / 0.10 (99)	No Further Data	Confirmed by DSMB Last follow-up VA (not in database): 0.30 / 0.10 (34)
PRT/0915/00006	FTY720 1.25 mg	0.30 / 0.00	0.22 / 0.00 (35)	No Further Data	Confirmed by DSMB No VA assessment at time of ME diagnosis Closest assessment 19 days before
USA/0524/00005	FTY720 1.25 mg	-0.10 / 0.00	-0.10 / -0.10 (98)	-0.10 / -0.10 (32)	Confirmed by DSMB
ARG/0408/00005	FTY720 0.5 mg	0.15 / 0.15	0.18 / 0.30 (367)	No Further Data	Confirmed by DSMB
BRA/0424/00010	FTY720 0.5 mg	0.00 / 0.10	0.48 / 0.10 (94)	No Further Data	Confirmed by DSMB
ITA/0211/00008	FTY720 0.5 mg	0.00 / 0.00	0.00 / 0.00 (189)	0.00 / 0.00 (17)	Not confirmed by DSMB

Response to request for information submitted July 7, 2010. Patients with clinically significant visual acuity loss are marked with a box.

Table 60. Listing of visual acuity assessments in patients with macular edema in study 2309

Patient ID	Treatment		VA [LogMAR] At Screening L/R	VA [LogMAR] At Time of ME Diagnosis L/R (Relative Day on FTY or MMF)	VA [LogMAR] At Last Follow-Up L/R (Relative Day After Drug Discontinuation)
Multiple Sclerosis ISS Pool E					
Study D2309					
~~USA/0507/00027~~	~~FTY720~~	~~1.25 mg~~	~~-0.223/-0.223~~	~~-0.223/-0.223 (38)~~	~~0.00 / 0.00 (93)~~
USA/0513/00023	FTY720	1.25 mg	0.000 / 0.000	0.693/0.000(288)	0.693/0.000(54)
USA/0524/00007	FTY720	1.25 mg	0.000 / 0.000	0.000 / 0.223 (38)	0.00 / 0.00 (71)
USA/0531/00002	FTY720	1.25 mg	0.000 / 0.000	0.000 / 0.000 (168)	0.000 / 0.000 (270)
USA/0588/00013	FTY720	1.25 mg	-0.223 / NA	-0.223 / NA (31)	-0.223 / NA (211)
~~USA/0524/00004~~	~~FTY720~~	~~0.5 mg~~	~~0.000 / 0.000~~	~~0.000 / 0.223 (99)~~	~~0.000 / 0.223 (134)~~
USA/0547/00007	FTY720	0.5 mg	0.223 / 0.405	0.405 / 1.253 (114)	0.405/ 1.253 (0)
USA/0548/00003	FTY720	0.5 mg	0.223 / 0.223	0.223 /0.223 (98)	0.223 /0.223 (40)
USA/0601/00009	FTY720	0.5 mg	0.000 / 0.000	0.405 / 0.000 (52)	0.223 /0.223 (93)
~~USA/0616/00002~~	~~FTY720~~	~~0.5 mg~~	~~-0.223/-0.223~~	~~-0.223 / 0.693 (34)~~	~~-0.223 / 1.163 (365)~~
USA/0545/00007		Placebo	0.000 / 0.000	Date not known	-0.288 / 0.000 (132)
USA/0561/00028		Placebo	0.000 / 0.000	0.000 / 0.000 (40)	.405 / 0.000 (113)

Source: Response to FDA request for information submitted July 7, 2010.

The following table summarizes the cases of ME in controlled studies (safety pool D + study 2309).

Table 61. Summary of cases of macular edema in controlled studies (safety pool D + study 2309)

	FTY 1.25 N=1302 n (%)	**FTY 0.5 N=1204 n (%)**	**Pbo N=861 n (%)**	**IFN N=431 n(%)**
Any ME	19 (1.5)	7 (0.6)	2 (0.2)	1 (0.2)
Presence of ME confirmed by DSMB ophthalmologist	14 (1.0)	5 (0.4)	1 (0.1)	-
Serious ME	6 (0.5)	2 (0.2)	1 (0.1)	-
Eye symptom at time of dx of ME	9 (0.7)	1 (0.1)	1 (0.1)	-
AE of ME reported as not resolved at last FU[1]	5 (0.4)	1 (0.1)	1 (0.1)	-
Clinically significant decrease in VA[2] reported at last FU	4 (0.3)	3 (0.1)	1 (0.1)	-

ME= macular edema. [1] Most reports of "not resolved" at last follow up were based on Fluorescein Angiography (FA). Not every patient with ME had FA. [2]VA= visual acuity at last follow up, based on an increase in 0.3 LogMAR units as compared to baseline. The AE of ME could be resolved but with loss of vision.

Therefore, approximately 30% of patients had decreased vision at the time of the diagnosis of ME, and approximately one third of patients with diagnosis of ME had clinically significant loss of vision at the time of the last available ophthalmologic evaluation. (The last follow up may have been shortly after drug discontinuation or may not be available after drug discontinuation.)

The cases of ME on FTY 0.5 mg are summarized as follows (these are the same patients that were described in other sections of this review):

Controlled studies:

1. Patient # 2302_0424_00010. 41 M. No eye history. At screening, Visual acuity (VA) was 20/20 Bilaterally. OCT Central Foveal Thickness (CFT): 169 L & 170 R; At Month 1 dilated ophthalmoscopy (DO) showed unspecific maculopathy bilaterally. **On Day 94** DO was suspicious of classical macular edema (ME). Reported as SAE. Drug discontinued. CFT at 12 mo: 250 L, 171 R. Treated with ketorolac eye drops, ME resolved 61 days after drug dc. At last assessment VA was 20/50 L, 20/25 R. FU CFT not available.

2. Patient # 2302 0408 00005.53 F. History of HTN. **On Day 367** dx with ME. At the time of dx of ME she had no eye symptoms but had mild decreased VA in R eye. DO showed bleeding surrounding upper temporal vein and venous thrombosis of upper temp vein in R eye, with macular edema. FA confirmed ME in R eye. Reported as non-serious AE. Drug discontinued. Three months after drug discontinuation digital angiography showed that ME was still present but improving. ME thought to be secondary to retinal branch vein occlusion, which was thought to be secondary to HTN.

Extension studies:

3. Patient # 2302E1 0211 00008. 36 M. No eye history. Screening VA 20/20. CFT on L eye at the end of core study was 152 microns. On **Day 189** of FTY treatment OCT showed CFT 203 microns. Reported as SAE. ME was not confirmed with FA. Pt was asymptomatic. Drug dc. No treatment. ME resolved 18 days after drug dc (VA 20/20; CFT 164 in L).

4. Patient # 2301E1 0657 00005. 50 F. Hx of HTN, amblyopia, prior treatment for suspected Lyme disease. Received placebo on core study. On **Day 106** CFT was 339 microns L, and 283 microns R; FA: retinal capillary leakage both eyes. VA not done. Reported as non serious AE. Drug was discontinued. Two months after drug dc a follow OCT and FA showed persistent cystoid macular edema L>R.

Study 2309:

5. Patient # 2309-0547-00007. 37 F. Hx of optic neuritis L eye since 4 years prior to entry. Screening VA 20/30+1 R, 20/25-2 L. CFC 186 microns in L and 220 in R. She complained of blurred vision in L eye. On day 36 she complained of stabbing pain in R eye. Fundoscopic exam showed epiretinal membrate (ERM) in R eye. OCT showed CFT

209 in L and 253 in R. Foveal contour was irregular in R eye but the overall assessment was negative for ME. **On Day 114** she c/o 1 week hx of decreased vision in R eye. VA was 20/30-2 in L and 20/50+ in R. Cystoid macular edema was dx in R eye. CFT was 198 in L and 471 microns in R eye. Reported as SAE. Led drug dc. For the ensuing 3 months she reported having a line across her field of vision but did not see an ophthalmologist. 3 months after drug dc VA was 20/200 at R and unchanged at L. Fundus exam showed a stage 4 macular hole in R eye. CFT was 504 microns in R eye and 208 in L eye. One image showed full thickness macular hole. She underwent ocular surgery to repair macular hole in R and ERM in L. Six months after surgery VA was 20/30 in L and 20/40 in R.

Four additional cases with FTY 0.5 mg (non-serious, leading to drug discontinuation) were submitted from study 2309 at the time of the safety update report (described in AE leading to drug discontinuation).
In addition to the cases of macular edema, there were 6 non-serious retinal hemorrhages in the controlled studies, all on FTY (3 on FTY 1.25 and 4 on FTY 0.5), and 4 cases of retinal detachment (3 on FTY 1.25 and 1 on FTY 0.5)(the one on FTY 0.5 led to drug discontinuation). No particular characteristics were observed in patients who developed retinal hemorrhages.

Dr. Wiley Chambers was the FDA consultant for ophthalmologic issues. He reviewed all cases of macular edema. He was asked to specifically assess whether the cases noted as "not resolved" were indeed cases of ME. He stated that these patients fell into the following categories:
1. Never had macular edema
2. Had macular edema which resolved after discontinuation of fingolimod.
3. Had macular edema which was resolving, but was not followed long enough to see complete resolution
4. Had an additional ophthalmic condition which led to visual loss or retinal thickening. It is not possible to tell what role fingolimod played, but the natural history of the additional ophthalmic condition is typical for that condition.

Dr. Chambers recommended (via email, on June 5, 2010) that ophthalmologic evaluation with dilated ophthalmoscopy shoud be obtained at baseline or near baseline and then every 6 months.

The ophthalmologic findings led to extensive discussion at the FDA AC meeting of June 2010. Experts in the panel initially had a different approach as to what kind of monitoring should be required for fingolimod, with some suggesting that OCT be requested for all patients. At the end there was agreement that all patients should have an ophthalmologic examination before starting to use the drug, with regular assessments of visual acuity at the routine neurologic visits and referral to an ophthalmologist if clinically indicated.

I agree with the panel with baseline ophthalmologic examination for all, and with Dr. Chambers in that ophthalmologic examination should include dilated ophthalmoscopy. Given that most events of ME occurred before 3-4 months, I would obtain a follow up examination at 3-4 months and then as clinically indicated if there are any symptoms or changes in visual acuity assessments.

4) Pulmonary toxicity

- Background
  - Non-clinical studies showed extensive lung toxicity
  - Increased bronchoconstriction in clinical pharmacology study at doses ≥5 mg day
  - In the renal transplant population, there was an excess of dyspnea and pulmonary edema in fingolimod treated subjects. It was unclear whether the cause was cardiac, pulmonary or infectious.

- Findings in MS population

Respiratory tract associated serious AE and discontinuations due to respiratory related AE (Respiratory, thoracic and mediastinal disorders SOC, and Investigations SOC –Pulmonary investigations HGLT) were not frequent, and there were no major differences between treatment groups in the controlled studies. However, evaluation in these subjects was not as complete as desirable. For instance, several subjects with dyspnea or chest pain were discontinued from the studies without having a chest XRay, HRCT, PFT, ECG or echocardiogram at the time of the event. Or if they did, it was several weeks or months after the event. In study 2309, there was a dose-related increase in the risk of discontinuations due to respiratory related events (1.9%, 0.9% and 0.3% in FTY 1.25, FTY 0.5 and placebo groups, respectively).

With regard to asthma, subjects with asthma were allowed in the study if they did not require active treatment for it. Only one patient had asthma exacerbation in the controlled database, and that occurred in a subject taking placebo. Three events of asthma (two exacerbation, one new onset) and one new onset broncho-constriction occurred in fingolimod treated patients during the extension studies (three in the FTY 5mg/1.25 mg; one on FTY 1.25 mg), suggesting that FTY may increase the risk of asthma exacerbation at least at the 5 and 1.25 doses. No events of asthma occurred at the 0.5 mg dose.

Across all trials, PFT measures (changes in percent predicted FEV1, FVC, and DLCO) consistently decreased from baseline to a greater degree in fingolimod-treated subjects versus placebo in a dose-dependent fashion. The changes in percent predicted PFT parameters correlated with changes in absolute values. The 0.5 mg dose group demonstrated declines in absolute FEV1 of ≥100 mL as early as 6 months after starting study drug, which is a greater annual decline in pulmonary function than is typically seen in healthy patients, patients with COPD, or MS patients in general. PFT decreases were not always associated with clinical symptoms, which may have been related to the high level of baseline pulmonary function in the Phase 3 trial population, as FEV1 and FVC were consistently greater than 100% of predicted values. Evaluation of PFT outliers also suggested a dose response. This was observed in the controlled database (safety pool D) as well as in PFT analyses from study 2309 as discussed in section 7.4.5 (Special studies) below.

With regard to HRCT scan data, there appear to be more events of HRCT abnormal in the FTY treated groups but the incidence did not appear to be dose-dependent. The HRCT scans were

read by local radiologists; no central adjudication of scans was performed in the phase 2 & 3 studies, which limits the interpretation of the results.

The following are the recommendations from Dr. Brian Porter, FDA pulmonologist consultant from the Division of Pulmonary, Allergy and Rheumatology Products (DPARP).

> Based on these findings, DPARP recommends that DNP consider including information about the fingolimod-associated decline in pulmonary lung function and the higher incidence of new or worsened HRCT abnormalities in the fingolimod product label. At the current time, there are insufficient data to support a specific PFT monitoring schedule or to recommend routine HRCT screening of fingolimod recipients. However, providing information on the observed fingolimod-associated PFT and HRCT changes will facilitate the development of individualized monitoring plans by healthcare providers for MS patients on fingolimod. In turn, DPARP recommends that DNP consider inclusion of similar information about pulmonary toxicities in the REMS. Finally, DPARP recommends further study of pulmonary safety to determine the stability and reversibility of pulmonary function deficits with long-term use of fingolimod.
>
> *Dr. Carrie Redlich, pulmonologist at the FDA AC meeting of June 10, 2010 was very concerned about the observed effect on PFTs (FEV1 and DLCO). She noted that mean values do not allow identification of changes in individual patients, and that PFTs are usually adjusted by gender and other parameters. By getting average PFTs some of the information may be missing. She also noted that patients with impaired lung function at baseline would not tolerate a drop in PFTs as well as the patients included in these clinical studies. She recommended, and the majority of the panel agreed, that baseline spirometry and DLCO should be obtained in all patients receiving fingolimod, and that it would be desirable to obtain more information from patients with underlying lung problems such as patients with asthma and some degree of lung impairment.*
>
> *On further discussion, DPARP recommends that a prospective, controlled study be conducted to evaluate reversibility of pulmonary function reduction. This evaluation could be included in the postmarketing study that will evaluate a lower dose of fingolimod.*

5) CV toxicity – Heart and rhythm disorders; LV function; ischemia/thrombosis

- Background
  - Known effect of S1P modulation on heart rate in vitro and in vivo
  - Renal patients had more cardiovascular deaths, MI and pulmonary edema at the 5 mg dose than the MMF group
  - Increased reports of S1P role in regulation of vascular permeability, vascular tone and angiogenesis
- Findings in MS

- Heart conduction disorders

There is a clear dose related effect in the heart conduction system upon first fingolimod treatment. 2.3% and 0.8 % of subjects in the FTY 1.25 mg and FTY 0.5 mg groups developed serious AE of bradycardia or 1st or 2nd degree AVB in the controlled studies. All had onset within 6 hours of first dose fingolimod treatment. One case of bradycardia and one of AVB occurred in the placebo group, but the bradycardia was on day 121 and the AVB occurred on Day 684 (in a subject who had prior episodes of first and second AVB consistent with sick sinus syndrome).

Most cases of bradycardia/AVB recovered without intervention and continued treatment, however, one fifth of patients who developed bradycardia and half of the patients who developed AV block with FTY 1.25 mg discontinued the trial because of the AE. The cases that led to discontinuation were associated with chest pain/pressure/discomfort or dyspnea, and one was associated with bigeminism. Three subjects who interrupted treatment presented a similar episode of bradycardia or AVB when the drug was re-started. One subject who presented 2nd degree AVB on day one in the FTY 0.5 mg dose, presented chest pain/pressure leading to study discontinuation on Day 4.

Four subjects received atropine (3 on FTY 1.25 and 1 on FTY 0.5). One subject who developed 3rd degree AVB required isoproterenol, upon first dose of FTY 0.5 in the extension study.

The applicant proposes monitoring for six hours with the first fingolimod dose in subjects with sitting heart rate less than 55 bpm or receiving beta-blockers. However, patients who developed AE of bradycardia and AV block in fingolimod studies had normal HR and were not taking beta-blockers. Moreover, the studies included in the application excluded subjects with pre-existent diseases such as diabetes mellitus, heart conduction disorders taking antiarrhythmic medications or having pulmonary disease. It is anticipated that subjects with any of these disorders will not tolerate the events of bradycardia or AV block as well as these relatively healthy subjects. This population may need to be studied, at some point, before or after approval. Additionally, the labeling is imprecise as to where the monitoring needs to take place. That would likely be in a medical unit capable of immediate treatment for severe cases of bradycardia and heart block.

- LV function and ischemic heart disease

There was no excess of congestive heart failure or ischemic heart disease in the fingolimod treated groups in the controlled studies. However, not all patients who presented dyspnea, chest pain or angina underwent a complete cardiovascular evaluation and follow up (or if they were, they were not documented in the application).

There was only one event of serious pulmonary edema associated with transient LV dysfunction confounded by the use of alternative medicine and use of "varnish" preceding the event. There were no cases of congestive heart failure.

No evidence of effect on LV function was observed in the echocardiogram database but number of paired echoes is limited and long-term data are not available. Analysis of mean changes in LV function and wall thickness were unremarkable in the relatively small number of studies done in

studies 2309/2302 (see review by Dr. Targum). A total of 183 subjects were included in the echocardiogram population. However, at the time of the original submission, only 17 pts had paired echocardiograms for up to 2 years.

One patient developed pulmonary hypertension during fingolimod treatment in study 2309. She was diagnosed during scheduled echocardiogram ongoing studies (the narrative is presented in the AE leading to drug discontinuation section in the Cardiac SOC in study 2309). The possibility of fingolimod associated pulmonary hypertension needs further evaluation.

Additional echocardiographic evaluation of heart valves is pending from echocardiograms conducted in studies 2302 and 2309 is pending.

- Major ischemic/thrombotic events (CV death, non fatal MI and non fatal stroke)

There were no cardiovascular deaths in this application, and the number of myocardial infarction and stroke was small. Two MI were reported in the placebo group, one in the IFN group and none in the FTY groups in the controlled studies. There was one stroke at the 1.25 mg dose and no stroke in other treatment groups in the controlled studies.

Several cases of "angina pectoris" and "non-cardiac chest pain" were reported in this application, however, the reasons for the diagnosis and the work up done in these patients appears to be incomplete in most cases. These events have a similar distribution among treatment groups in the controlled studies.

Three additional strokes occurred in this application at the 1.25 mg dose (2 in the extension studies, one in study 2309). Additionally a TIA occurred on placebo in study 2309.

- Other vascular events

Two cases of peripheral vascular disease occurred in the controlled studies, both in the FTY 1.25 mg group, in association with nail splinter hemorrhages in both cases, and toe necrosis in one case.

There was one case of retinal artery microthrombosis, and one of bilateral retinal ischemia/ vasculitis in the FTY 1.25 mg group in the controlled studies. Additionally, several non-serious vascular-related AE (retinal hemorrhage) occurred in the Eye disorders SOC.

One patient in study 2309 was diagnosed with pulmonary hypertension during fingolimod 1.25 mg treatment. Pulmonary artery pressure improved after drug discontinuation (the narrative is presented in the AE leading to drug discontinuation in the cardiac SOC, in ongoing studies). The possibility of fingolimod associated pulmonary hypertension needs further evaluation. Information on pulmonary artery pressure from the available echocardiograms from studies 2302 and 2309 is limited. Echocardiographic evaluation of heart valves from echocardiograms did not reveal any significant findings but the number of patients with available echoes at 1 and 2 years is limited.

The applicant proposes to explore the possibility of increased cardiovascular toxicity (MI, cerebrovascular events) in a post-marketing registry (PASS).

The June 10, 2010 FDA AC panel recommended baseline ECG and 6-hour in office monitoring of patients receiving fingolimod. They also recommended that patients at risk of developing heart conduction abnormalities (patients taking beta blockers and calcium channel blockers) and patients with diabetes should be studied in a future study evaluating lower doses of fingolimod.

6) Liver toxicity

- Background

The risk of ALT elevation >3xULN in the renal transplant population was around 20%, and slightly higher with FTY 5 and 2.5 mg as compared to MMF (19%, 20% and 15%, respectively).

- Findings in MS

Review of liver-related adverse events and laboratory evaluations showed clear dose-related liver toxicity. The risk of ALT elevation ≥3 and ≥5 x ULN in the controlled studies and of drug discontinuation due to increase in liver-related enzymes in the controlled population are summarized in the following table.

Table 62. Liver-related analyses in pool D

	FTY 1.25 N= 943	**FTY 0.5 N=854**	**Placebo N=511**	**IFN N=431**
	n (%)	**n (%)**	**n (%)**	**n (%)**
ALT ≥ 3x ULN	91 (9.7)	72 (8.5)	8 (1.6)	10 (2.3)
ALT ≥ 5x ULN	21 (2.2)	14 (1.6)	4 (0.8)	2 (0.5)
Discontinuation due to Liver-related investigations[1]	39 (4.1)	29 (3.4)	3 (0.6)	7 (1.6)

[1] Hepatobiliary investigations HGLT

Review of SAE and discontinuations due to liver related events in the controlled and extension studies indicates that transaminase elevation occurred without increase in bilirubin and alkaline phosphatase in the great majority of cases. A total of 5 subjects presented ALT ≥3x ULN and total BR≥ 2 mg/dL in the original ISS. These cases are as follows

2301-0109-00002. Patient had been treated with FTY 0.5 mg for 10 months. She was hospitalized for pain on her hip and received IV paracetamol for 2 or 3 days. Before paracetamol ALT and AST were moderately elevated, but right after IV paracetamol, ALT was 4332 U/L and BR was 2.07 mg/dL. Liver enzymes started to decrease while the patient was still on FTY and resolved within 17 days after FTY discontinuation.

2301- 0307-00030 had liver transaminase elevations 5 days after dc placebo treatment.

2302E1-0724-00006 had history of Gilbert's disease. He had ALT <3 x ULN and BR elevation up to >2x ULN intermittently during core study; during extension (FTY 0.5 mg) ALT >3 xULN and BR >2x ULN on Day 14 and 66; drug was interrupted and restarted. ALT increased to 4x ULN leading to drug discontinuation on Day 214 of FTY treatment. Patient was asymptomatic. Liver enzyme elevation improved after drug discontinuation.

2201E1-0019-00004 also had a history of Gilbert's disease and showed intermittent BR elevation during the core phase of the study.

2302-0212-00021. 39 F. Herpes zoster disseminated, acute hepatic failure, multiorgan failure (narrative provided under Deaths.)

A case of ALT elevation and jaundice was reported as an IND safety report on 4/29/10. This case was described under serious AEs and was a case of Hepatitis E.

7) Other potential safety concerns

- Potential for Neurologic toxicity

- Background
    - Perivascular mononuclear infiltration was observed in the brain in 4-week and 26 week dog studies.
    - In the renal transplant population, the risk of seizures was slightly higher in the fingolimod 2.5 and 5 mg groups as compared to MMF.

- Findings in MS: seizures and unusual MS relapse

    - Seizures

Evaluation of tables of serious AE in the renal transplant population found 15 individual patients with seizure-related terms (e.g. epilepsy, convulsion, grand mal convulsion, partial seizures). The analysis of serious seizure related events suggested a higher risk of seizures with fingolimod 5 mg (8/461 = 1.7%) and 2.5 mg (6/456= 1.3%) as compared to MMF (1/461= 0.2%) in the renal transplant population. These patients had renal failure, were taking concomitant Cyclosporin A and most had other acute problems at the time of the seizure.

Ten patients had seizure related events in the controlled studies in the ISS (epilepsy, convulsion, grand mal convulsion, partial seizures and petit mal). Of those 9 were on fingolimod and one on placebo. No cases were reported on iFN. Three patients had a previous history of epilepsy and others presented in the setting of an unusual MS relapse. Although the numbers are small (0.5% with FTY 1.25, 0.2% with FTY 0.5 mg), the analysis suggests an increased risk with FTY 1.25 mg as compared to placebo (it is unclear if the case on placebo was a real seizure), which is consistent with the signal in the renal transplant database.

Table 63. Seizure related events, safety pool D

	FTY720 5 mg N= 94 (Ny=43.2)	FTY720 1.25 mg N=943 (Ny=1111.2)	FTY720 0.5 mg N= 845 (Ny=1153.2)	Placebo N= 511 (Ny=746.9)	Interferon N= 431 (Ny=401.9)
Number of patients with event (%)	1 (1.1)	6 (0.6)	2 (0.2)	1 (0.2)	0
Number of events (rate per 100 PYRs)	1 (2.3)	13 (0.54)	4 (0.17)	1 (0.13)	0

Source: Response to request for information submitted 2/23/10.

Brief narratives of the cases of seizure-related events in fingolimod controlled studies are included in Appendix 9.1.15. The narrative of the case of "convulsion" on placebo is as follows.

- **2201_0017_00004**. 45 F. No history of epilepsy. On Day 108 of placebo, the patient experienced "moderate convulsion which included dysesthesia in lower limbs and Lhermitte's sign."

In the extension studies in the original ISS, 4 additional patients were reported to have seizures (2 in the FTY 5mg-1.25 mg, 1 in the FTY 1.25 mg group and 1 in the FTY 0.5 m group).

In addition to the cases of seizures in the ISS, two SAE of status epilepticus and one grand mal seizure were reported from study 2309. Unblinding of the cases of status epilepticus was requested. One was on FTY 1.25 in a patient who was found to have non-fatal herpes simplex encephalitis; the other was on FTY 0.5 mg. In addition to these cases, two SAE of seizures occurred in ongoing study 1201E1 (0019-00001 and 002-00002) which are blinded.

> *Description in the narrative for the case on placebo does not suggest that it was a seizure. Therefore, all cases of seizures were on FTY treated patients. These included Two cases of herpes simplex encephalitis, three cases in which seizures were thought to be due to MS relapse, and 3 cases in whom there was a previous history of seizures (2 on FTY720 1.25 mg and 1 on FTY720 0.5 mg).*

The applicant references a publication in which seizures have been reported to occur in about 2–3% of all patients with MS (Koch et al 2008, Kelley and Rodriguez 2009) suggesting that the rate of convulsions observed in the 0.5 mg FTY720 group in MS clinical studies would be within the epidemiological experience. A baseline history of epilepsy or seizures in the MS population was around 1%.

> *The applicant proposes to explore the possibility of a higher risk of seizures with a postmarketing registry (PASS).*

- Unusual MS relapse

Some uncommon neurologic conditions were diagnosed in subjects receiving FTY or after having received FTY (e.g ADEM) (see page 67 of this review). In addition to the cases in the ISS, one case of PRES and one case of diffuse multifocal leukoencephalopathy were diagnosed in blinded ongoing studies. One case of PRES was also diagnosed in the renal transplant population at the 5 mg dose.

Three patients presented with a brain mass atypical for MS in this database. One in the controlled studies (subject #2301_0409_0008 with unusual MS relapse, reported in the journal Neurology as a case of Focal hemorrhagic encephalitis) and two in ongoing studies (subject #1201E_0005_00001 with tumors of the brain, liver, lung, etc, possible disseminated T cell lymphoma), and one in a study that is still blinded (submitted as IND safety report). This latter subject had a brain biopsy that did not show lymphoma but showed lymphocytic infiltration (he had been treated with mefloquine, for possible PML). Additionally, patient #2302E1 0253 00003 who had a 14-year history of MS, with a total of 7 relapses since diagnosis, had a MS relapse within a month of starting FTY 1.25 mg followed by a "burst of MS lesions" that looked like vasculitis. No organism was identified in this patient.

> *I am concerned that some of the unusual or atypical MS relapses might actually be related to an unidentified central nervous system infection. However, the fingolimod studies were successful in demonstrating a decrease in the rate of MS relapse. Additional data on unusual/atypical cases of MS relapse should be collected in the planned postmarketing studies.*

- Edema: renal toxicity?

Four patients presented fluid retention/edema leading to study drug discontinuation during fingolimod treatment. None of them had urine protein measurement available at the time of the event.

There were no adverse events of renal failure, and there was no increase in creatinine or decrease in estimated creatinine clearance. However, if S1P modulation were to interfere with glomerular function, it would show proteinuria before it shows failure. There was no measurement of 24 hour protein in any of these studies. Weight should be measured and 24 hour protein should be collected in patients who develop edema in future and ongoing studies.

- Hematologic toxicity other than effect on lymphcytes?

- Thrombocytopenia

Thrombocytopenia as a serious AE or leading to discontinuation due to AE was reported in four patients in the ISS. One of them was diagnosed with ITP; another was not diagnosed with it, but the narrative was consistent with ITP. One additional case of ITP was reported from the ongoing, blinded studies. The analysis of mean changes from baseline in hematologic parameters in safety pool A (Table 62 of this review) suggests a small dose-related decrease in platelet count that was most notable at month 1. The outlier analysis in safety pool D (Table 66 of this review) does not suggest an increased risk of either thrombocytopenia or thrombocytosis as compared to placebo.

- Neutropenia

Analyses of mean changes from baseline in pool A (Table 62) suggests a very slight decrease in mean neutrophil count. The outlier analysis from study 2301 (Table 66) shows that the incidence of patients with neutrophil count <1000/mm^3 was 3.2% for FTY 1.25mg, 2% for FTY 0.5mg, 1.2% for placebo and 1.2% for IFN. The frequency distribution of neutrophil count by dose in study 2301 (the 2-year study, Table 67 of this review) indicates that 15% of patients in FTY 1.25 and 0.5 mg had a neutrophil count $\leq 1.5 \times 10^9$L as compared to 4% of patients in the placebo group. One case of absolute neutropenia was recorded in the FTY 1.25 mg group.

- QTc prolongation

The TQTc study did not exclude possibility of QTc prolongation. The guidance recommends evaluating AE in population at risk such as those with electrolyte abnormalities (no electrolytes were measured in this program); congestive heart failure (patients with CHF NY Class III classification were excluded); and patients taking certain antiarrhythmics. No patients at risk of QTc prolongation were included in the fingolimod studies.

- Teratogenecity

Fingolimod was clearly teratogenic in the rat, where it was associated with cardiovascular malformations. There is limited information in pregnant women. One case of Fallot tetralogy was reported in a fetus whose mother was taking fingolimod.

The applicant's proposed REMS includes teratogenecity. A pregnancy registry will be implemented.

7.4 Supportive Safety Results and Discussion

7.4.1 Common Adverse Events

A similar percentage of patients presented AE in the treatment groups in pool D (approximately 91%). The % in FTY 5 mg was slightly higher.

Number of patients with AE in =>5% of patients in pool D is presented in the following table.

Table 64. Number of patients with AE in =>5% of patients, safety pool D

	FTY720 5 mg (N=94) n (%)	FTY720 1.25 mg (N=943) n (%)	FTY720 0.5 mg (N=854) n (%)	Placebo (N=511) n (%)	Interferon (N=431) n (%)
Any preferred term	90 (95.7)	864 (91.6)	771 (90.3)	464 (90.8)	396 (91.9)
Headache	18 (19.1)	233 (24.7)	207 (24.2)	109 (21.3)	88 (20.4)
Nasopharyngitis	26 (27.7)	221 (23.4)	203 (23.8)	128 (25.0)	88 (20.4)
Fatigue	8 (8.5)	114 (12.1)	92 (10.8)	54 (10.6)	45 (10.4)
Upper respiratory tract infection	2 (2.1)	102 (10.8)	104 (12.2)	76 (14.9)	27 (6.3)
Diarrhoea	12 (12.8)	84 (8.9)	82 (9.6)	33 (6.5)	21 (4.9)
Alanine aminotransferase increased	7 (7.4)	82 (8.7)	71 (8.3)	18 (3.5)	8 (1.9)
Back pain	8 (8.5)	76 (8.1)	76 (8.9)	32 (6.3)	23 (5.3)
Influenza	7 (7.4)	74 (7.8)	84 (9.8)	44 (8.6)	32 (7.4)
Nausea	10 (10.6)	74 (7.8)	78 (9.1)	38 (7.4)	29 (6.7)
Cough	5 (5.3)	69 (7.3)	63 (7.4)	37 (7.2)	16 (3.7)
Bronchitis	3 (3.2)	61 (6.5)	54 (6.3)	16 (3.1)	11 (2.6)
Dizziness	7 (7.4)	55 (5.8)	55 (6.4)	28 (5.5)	21 (4.9)
Hypertension	6 (6.4)	55 (5.8)	42 (4.9)	17 (3.3)	9 (2.1)
Melanocytic naevus	0 (0.0)	55 (5.8)	47 (5.5)	15 (2.9)	26 (6.0)
Gamma-glutamyltransferase increased	0 (0.0)	51 (5.4)	36 (4.2)	4 (0.8)	1 (0.2)
Pharyngitis	3 (3.2)	51 (5.4)	40 (4.7)	26 (5.1)	13 (3.0)
Dyspnoea	12 (12.8)	50 (5.3)	38 (4.4)	20 (3.9)	7 (1.6)
Sinusitis	2 (2.1)	49 (5.2)	38 (4.4)	21 (4.1)	11 (2.6)
Arthralgia	3 (3.2)	48 (5.1)	42 (4.9)	38 (7.4)	24 (5.6)
Pain in extremity	5 (5.3)	48 (5.1)	50 (5.9)	32 (6.3)	28 (6.5)
Urinary tract infection	3 (3.2)	48 (5.1)	60 (7.0)	50 (9.8)	22 (5.1)
Depression	4 (4.3)	47 (5.0)	54 (6.3)	34 (6.7)	33 (7.7)
Insomnia	2 (2.1)	42 (4.5)	39 (4.6)	28 (5.5)	13 (3.0)
Oropharyngeal pain	2 (2.1)	40 (4.2)	46 (5.4)	32 (6.3)	15 (3.5)
Abdominal pain upper	5 (5.3)	37 (3.9)	29 (3.4)	19 (3.7)	13 (3.0)
Hypercholesterolaemia	1 (1.1)	37 (3.9)	34 (4.0)	26 (5.1)	3 (0.7)
Pyrexia	7 (7.4)	35 (3.7)	26 (3.0)	9 (1.8)	77 (17.9)
Gastroenteritis	5 (5.3)	33 (3.5)	29 (3.4)	13 (2.5)	12 (2.8)
Rash	5 (5.3)	31 (3.3)	19 (2.2)	22 (4.3)	8 (1.9)
Rhinitis	2 (2.1)	30 (3.2)	38 (4.4)	27 (5.3)	11 (2.6)
Leukopenia	5 (5.3)	25 (2.7)	17 (2.0)	1 (0.2)	1 (0.2)
Myalgia	1 (1.1)	24 (2.5)	26 (3.0)	14 (2.7)	44 (10.2)
Constipation	6 (6.4)	22 (2.3)	28 (3.3)	23 (4.5)	10 (2.3)
Influenza like illness	1 (1.1)	19 (2.0)	24 (2.8)	6 (1.2)	159 (36.9)
Somnolence	6 (6.4)	11 (1.2)	9 (1.1)	11 (2.2)	4 (0.9)
Chest pain	5 (5.3)	9 (1.0)	7 (0.8)	7 (1.4)	2 (0.5)

Source: Table 4-2. ISS addendum, submitted in February 2010.

The following discussion will not involve FTY 5 because the number of patients is small and they were only exposed for ≤6 months. The most common events were headache, nasopharyngitis, fatigue and upper respiratory infection (with at ≥10% of patients presenting the AE in any treatment group).

Events that occurred most frequently in the fingolimod treatment groups (FTY 1.25 and/or FTY 0.5 mg) with at least 1% higher risk as compared to placebo were: headache, fatigue, diarrhea,

ALT increased, back pain, influenza, nausea, bronchitis, hypertension, melanocytic nevus, GGT increased, dyspnea, sinusitis, pyrexia, gastroenteritis, leukopenia and influenza like illness. Not unexpectedly, pyrexia and influenza like illness were much higher in the INF group (17.9% and 36.9%, respectively) as compared to fingolimod (2-4%) and placebo (1.8 for pyrexia, 1.2% for influenza-like illness).

The events with the greater difference in risk were ALT increased (at least twice as compared to placebo), GGT increase (at least 5 fold the risk on placebo), bronchitis (twice the risk as compared to placebo) and melanocytic nevus (almost twice as compared to placebo, but similar to IFN).

Evaluation of common AE is consistent with the analyses of serious AEs and AEs leading to discontinuations, with a signal for increased liver enzymes. There is no signal for increased infections, except for bronchitis. It is unclear if the increased risk of melanocytic nevus is related to immunosuppression.

7.4.2 Laboratory Findings

Hematology mean changes from baseline in WBC, absolute lymphocyte, neutrophil and platelet counts at month 1 and month 12, by treatment in Pool A, are presented as follows:

Table 65. Change in selected hematologic parameters over time, Safety pool A

Parameter	FTY 1.25 N=849	FTY 0.5 N=854	Placebo N=418	Interferon N=431
WBC (total) (10^9/L)				
n	793	801	401	402
Baseline Mean (SD)	6.57 (1.93)	6.46 (1.81)	6.69 (1.90)	6.47 (1.76)
Month 1 Mean (SD)	4.33 (1.73)	4.43 (1.50)	6.54 (1.82)	6.19 (1.78)
Change from baseline Mean (SD)	-2.24 (1.77)	-2.03 (1.48)	-0.15 (1.70)	-0.28 (1.58)
n	733	784	384	382
Baseline Mean (SD)	6.56 (1.91)	6.46 (1.80)	6.70 (1.86)	6.49 (1.79)
Month 6 Mean (SD)	3.98 (1.50)	4.30 (1.47)	6.54 (2.03)	6.33 (1.89)
Change from baseline to Month 6 Mean (SD)	-2.59 (1.69)	-2.16 (1.54)	-0.16 (1.74)	-0.16 (1.84)
n	696	748	354	365
Baseline Mean (SD)	6.60 (1.93)	6.46 (1.80)	6.68 (1.86)	6.44 (1.76)
Month 12 Mean (SD)	3.99 (1.53)	4.26 (1.65)	6.44 (1.77)	6.30 (1.99)
Change from baseline to Month 12 Mean (SD)	-2.61 (1.75)	-2.20 (1.71)	-0.24 (1.47)	-0.14 (1.83)
Absolute lymphocytes (10^9/L)				
n	780	785	399	398
Baseline Mean (SD)	1.81 (0.54)	1.82 (0.59)	1.82 (0.57)	1.77 (0.54)
Month 1 Mean (SD)	0.42 (0.24)	0.49 (0.24)	1.76 (0.52)	1.69 (0.56)
Change from baseline to Month 1 Mean (SD)	-1.39 (0.52)	-1.33 (0.56)	-0.06 (0.41)	-0.07 (0.50)
n	714	772	378	380
Baseline Mean (SD)	1.81 (0.54)	1.81 (0.58)	1.83 (0.58)	1.77 (0.53)
Month 6 Mean (SD)	0.39 (0.23)	0.49 (0.29)	1.77 (0.59)	1.71 (0.57)
Change from baseline to Month 6 Mean (SD)	-1.41 (0.53)	-1.33 (0.56)	-0.06 (0.47)	-0.06 (0.53)
n	685	736	353	359
Baseline Mean (SD)	1.81 (0.54)	1.82 (0.58)	1.82 (0.59)	1.74 (0.52)
Month 12 Mean (SD)	0.41 (0.26)	0.49 (0.32)	1.76 (0.57)	1.69 (0.57)
Change from baseline to Month 12 Mean (SD)	-1.40 (0.53)	-1.33 (0.55)	-0.06 (0.44)	-0.05 (0.49)

Absolute neutrophils (10^9/L)				
n	780	786	399	400
Baseline Mean (SD)	4.09 (1.57)	4.00 (1.45)	4.21 (1.57)	4.04 (1.45)
Month 1 Mean (SD)	3.36 (1.60)	3.39 (1.36)	4.13 (1.51)	3.84 (1.50)
Change from baseline to Month 1 Mean (SD)	-0.73 (1.57)	-0.61 (1.30)	-0.09 (1.55)	-0.20 (1.40)
n	686	739	353	360
Baseline Mean (SD)	4.12 (1.54)	3.99 (1.44)	4.20 (1.53)	4.02 (1.45)
Month 12 Mean (SD)	3.07 (1.36)	3.26 (1.45)	4.06 (1.46)	3.96 (1.69)
Change from baseline to Month 12 Mean (SD)	-1.05 (1.50)	-0.73 (1.49)	-0.14 (1.34)	-0.05 (1.67)
Platelet count (10^9/L)				
n	792	799	401	400
Baseline Mean (SD)	269.97 (65.56)	268.68 (64.76)	270.16 (63.16)	268.48 (61.78)
Month 1 Mean (SD)	256.72 (62.00)	259.95 (57.36)	268.08 (59.94)	267.55 (65.56)
Change from baseline to Month 1 Mean (SD)	-13.26 (38.89)	-8.73 (37.18)	-2.08 (38.26)	-0.93 (47.38)
n	694	746	354	364
Baseline Mean (SD)	270.58 (66.03)	269.91 (65.11)	269.26 (63.74)	267.28 (61.06)
Month 12 Mean (SD)	263.86 (65.11)	266.35 (64.07)	269.97 (65.08)	268.89 (66.54)
Change from baseline to Month 12 Mean (SD)	-6.71 (42.70)	-3.56 (44.10)	0.71 (45.69)	1.61 (46.81)

Source: Modified from Post text Table 5.1-2, ISS.

As seen in this table, there was a clear decrease in mean absolute WBC and lymphocyte counts, but also a slight decrease in mean neutrophil and platelet counts from baseline in the fingolimod groups, as compared to placebo or interferon. The clinical significance of these small changes is unclear. Evaluation of median changes from baseline in hematologic parameters showed results similar to the evaluation of mean changes.

Percentage change in lymphocytes in Study 2301 (the 2 year study, also the only study in Safety pool B) presented in the following table:

Table 66. Percentage Change in absolute lymphocyte count in study 2301

		Baseline			Post-baseline			Percent of Baseline				
Treatment	n	Mean	SD	Med	Mean	SD	Med	Mean	SD	Min	Med	Max
Week 2												
FTY720 1.25mg(N=429)	391	1.8225	0.54262	1.7500	0.4701	0.29886	0.4000	26.42	14.123	0.0	23.33	104.9
FTY720 0.5mg (N=425)	403	1.8610	0.63279	1.7900	0.5492	0.23261	0.5200	30.86	12.401	10.1	28.57	92.6
Placebo (N=418)	389	1.8170	0.57581	1.7600	1.7496	0.54376	1.6800	98.74	23.285	22.4	96.01	178.5
Month 1												
FTY720 1.25mg(N=429)	394	1.8394	0.55265	1.7700	0.4452	0.26019	0.3900	25.15	14.351	4.2	21.65	106.8
FTY720 0.5mg (N=425)	392	1.8702	0.63205	1.8000	0.5134	0.26984	0.4600	28.84	13.922	7.3	26.05	105.2
Placebo (N=418)	399	1.8196	0.57269	1.7600	1.7631	0.52407	1.7000	99.38	22.067	31.4	98.34	202.4
Month 2												
FTY720 1.25mg(N=429)	379	1.8473	0.55548	1.7700	0.4678	0.30584	0.3900	26.18	15.955	4.7	22.70	126.4
FTY720 0.5mg (N=425)	391	1.8692	0.63338	1.7900	0.5014	0.26554	0.4300	28.21	14.151	6.5	25.19	96.2
Placebo (N=418)	383	1.8270	0.58173	1.7800	1.7622	0.57525	1.6800	98.44	22.357	49.6	96.10	193.4
Month 3												
FTY720 1.25mg(N=429)	383	1.8423	0.55144	1.7700	0.4537	0.32737	0.3700	25.33	16.484	5.1	21.05	181.5
FTY720 0.5mg (N=425)	399	1.8690	0.63467	1.7900	0.4904	0.25452	0.4400	27.72	14.515	4.8	25.00	107.0
Placebo (N=418)	390	1.8155	0.57550	1.7550	1.7422	0.51179	1.6800	98.77	22.247	21.5	96.16	181.9
Month 6												
FTY720 1.25mg(N=429)	364	1.8433	0.55084	1.7700	0.4228	0.26132	0.3600	23.92	14.664	4.5	20.57	113.9
FTY720 0.5mg (N=425)	396	1.8419	0.61568	1.7800	0.4830	0.27546	0.4200	27.54	15.063	5.1	24.09	93.8
Placebo (N=418)	378	1.8288	0.58327	1.7650	1.7733	0.58608	1.7000	99.33	24.086	12.5	98.06	193.3
Month 9												
FTY720 1.25mg(N=429)	356	1.8500	0.54847	1.7750	0.4343	0.26895	0.3600	24.11	13.356	4.2	20.40	75.5
FTY720 0.5mg (N=425)	385	1.8456	0.61759	1.7900	0.4982	0.33823	0.4200	28.01	16.736	6.1	23.98	142.0
Placebo (N=418)	368	1.8271	0.58341	1.7600	1.7682	0.58812	1.7300	99.51	26.755	19.8	96.64	221.2
Month 12												
FTY720 1.25mg(N=429)	348	1.8370	0.54281	1.7650	0.4224	0.26068	0.3600	23.82	13.916	3.1	20.47	120.4
FTY720 0.5mg (N=425)	380	1.8524	0.62069	1.7850	0.4985	0.33341	0.4100	27.72	15.687	5.0	23.72	107.7
Placebo (N=418)	356	1.8228	0.58296	1.7550	1.7649	0.56413	1.7200	99.34	23.753	44.3	96.96	229.8
Month 15												
FTY720 1.25mg(N=429)	335	1.8462	0.54429	1.7800	0.4385	0.26002	0.3700	24.79	14.343	5.1	21.05	122.8
FTY720 0.5mg (N=425)	365	1.8340	0.61751	1.7700	0.5013	0.33380	0.4200	28.30	15.701	6.9	25.00	138.7
Placebo (N=418)	343	1.8054	0.55237	1.7500	1.7699	0.59826	1.6700	100.43	29.263	36.9	96.75	411.9
Month 18												
FTY720 1.25mg(N=429)	313	1.8441	0.52948	1.7900	0.4550	0.32688	0.3700	25.33	15.656	3.8	20.71	97.2
FTY720 0.5mg (N=425)	357	1.8403	0.62244	1.7700	0.4970	0.32750	0.4200	27.91	15.156	5.5	24.55	126.0
Placebo (N=418)	323	1.8147	0.55702	1.7600	1.7662	0.55842	1.7200	100.22	27.342	29.7	98.32	277.2
Month 21												
FTY720 1.25mg(N=429)	304	1.8450	0.54365	1.7900	0.4495	0.31444	0.3700	25.34	16.795	4.9	21.05	117.3
FTY720 0.5mg (N=425)	349	1.8296	0.61942	1.7600	0.5134	0.35579	0.4200	29.19	17.882	7.0	24.84	182.7
Placebo (N=418)	319	1.8124	0.55609	1.7500	1.7532	0.56086	1.7000	99.53	26.007	18.7	98.08	205.7
Month 24												
FTY720 1.25mg(N=429)	292	1.8487	0.54129	1.7850	0.4208	0.26175	0.3575	23.39	12.823	3.2	20.15	109.0
FTY720 0.5mg (N=425)	339	1.8412	0.61544	1.7600	0.4855	0.34226	0.4100	27.23	15.549	6.4	23.53	135.4
Placebo (N=418)	304	1.8154	0.56276	1.7500	1.7605	0.56800	1.6750	99.55	24.365	41.3	97.79	191.3
Last assessment on study drug *												
FTY720 1.25mg(N=429)	415	1.8384	0.54581	1.7700	0.4324	0.28931	0.3600	24.47	15.680	3.2	20.67	110.1
FTY720 0.5mg (N=425)	421	1.8559	0.62470	1.7900	0.4933	0.34283	0.4100	27.31	15.274	5.5	23.86	103.9
Placebo (N=418)	413	1.8188	0.56878	1.7600	1.7846	0.62259	1.6900	100.53	26.083	18.7	98.55	210.4

Source: Table 14.3-2.2d (pg 6) of CSR Lymphocyte % change over time in study 2301. - If a patient has more than one value in a visit window, the mean of the values is used. - n = patients with non-missing baseline and post-baseline values. - * The last laboratory value taken at or before last day of study drug is summarized in row 'Last assessment on study drug'.

As seen in these analyses, the absolute lymphocyte count went down by approximately 75%, and was as low as 23% and 28% of baseline at month 6, for fingolimod 1.25 and 0.5 mg, respectively. The decrease in lymphocyte count was observed at 2 weeks and was maintained

through the 2 year period among the patients who stayed in the study. There was some suggestion of a dose response, with slightly greater effect with fingolimod 1.25 mg.

There was no decrease in neutrophil, eosinophil, monocytes and RBC percentages over time, but there appear to be a tiny effect on platelet count (decrease by 3-5 % in mean counts, with wide standard deviation), that does not seem to be clinically relevant (data not shown) . There was also a decrease from baseline on basophil count as compared to placebo (approximately 80% for FTY and 35% for placebo, see table below). The clinical relevance of this change in basophil count is unclear.

Table 67. Change in absolute basophil count in study 2301

		Baseline			Post-baseline			Percent of Baseline				
Treatment	n	Mean	SD	Med	Mean	SD	Med	Mean	SD	Min	Med	Max
Month 6												
FTY720 1.25mg(N=429)	170	0.0994	0.01918	0.1000	0.0150	0.03503	0.0000	14.74	34.514	0.0	0.00	100.0
FTY720 0.5mg (N=425)	205	0.1005	0.01735	0.1000	0.0187	0.03914	0.0000	19.22	41.638	0.0	0.00	250.0
Placebo (N=418)	196	0.1011	0.02166	0.1000	0.0664	0.05469	0.1000	65.87	54.632	0.0	100.00	200.0

Source: Table 14.3-2.2d (pg 14) of ISS

A subset of patients in safety pool E was followed up after drug discontinuation (n=516 subjects). Analysis of % change from baseline in lymphocyte counts in this population is presented below.

Table 68. Change in lymphocyte % in E follow up cohort

Visit		Baseline			Post baseline					
					Endpoint			Change from Baseline		
Treatment Group	n	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
TEP										
FTY720 5 mg - 1.25 mg (N=47)	46	28.45	8.920	26.95	11.98	6.163	11.50	-16.47	10.162	-17.80
FTY720 1.25 mg (N=297)	281	29.30	7.945	29.00	11.72	7.042	10.00	-17.57	8.239	-18.00
FTY720 0.5 mg (N=194)	189	28.42	7.825	29.00	12.15	6.930	11.00	-16.27	7.889	-16.00
Total (N=538)	516	28.90	7.988	28.45	11.90	6.917	11.00	-17.00	8.309	-17.00
Day 1-45 after drug discontinuation										
FTY720 5 mg - 1.25 mg (N=47)	24	27.57	10.840	25.25	12.58	6.128	12.90	-15.00	10.121	-12.45
FTY720 1.25 mg (N=297)	174	28.23	7.409	28.00	14.92	8.409	14.00	-13.31	10.737	-13.28
FTY720 0.5 mg (N=194)	96	28.10	7.425	28.00	16.08	8.081	15.00	-12.03	8.143	-11.25
Total (N=538)	294	28.14	7.716	28.00	15.11	8.169	14.00	-13.03	9.915	-13.00
Month 3 after drug discontinuation										
FTY720 5 mg - 1.25 mg (N=47)	33	28.76	9.276	25.50	17.84	6.451	17.30	-10.92	9.521	-10.30
FTY720 1.25 mg (N=297)	199	28.91	7.570	28.00	23.49	7.802	22.60	-5.42	8.161	-5.00
FTY720 0.5 mg (N=194)	124	28.35	7.277	28.50	23.48	7.374	24.00	-4.87	7.280	-5.00
Total (N=538)	356	28.70	7.625	28.00	22.96	7.696	22.00	-5.74	8.155	-5.00
Month 6 after drug discontinuation										
FTY720 5 mg - 1.25 mg (N=47)	12	31.73	14.011	28.30	18.67	7.038	20.85	-13.07	11.663	-11.05

FTY720 1.25 mg (N=297)	72	28.22	7.977	27.00	24.94	8.710	24.50	-3.28	9.139	-3.00
FTY720 0.5 mg (N=194)	47	28.57	6.477	28.00	25.10	7.938	25.00	-3.48	7.160	-4.00
Total (N=538)	131	28.67	8.197	28.00	24.42	8.443	24.00	-4.25	9.120	-4.00
Month 9 after drug discontinuation										
FTY720 5 mg - 1.25 mg (N=47)	3	33.07	10.909	28.60	26.53	6.018	26.00	-6.53	12.007	-4.30
FTY720 1.25 mg (N=297)	43	28.38	7.455	28.00	25.91	8.706	24.00	-2.47	8.170	-3.00
FTY720 0.5 mg (N=194)	27	29.30	7.384	31.00	27.04	8.746	25.00	-2.26	8.036	-4.00
Total (N=538)	73	28.91	7.507	28.30	26.35	8.552	25.00	-2.56	8.183	-3.00
Month 12 after drug discontinuation										
FTY720 1.25 mg (N=297)	35	29.77	7.656	30.00	27.46	8.045	26.00	-2.32	7.523	-2.00
FTY720 0.5 mg (N=194)	20	27.35	7.132	26.00	26.85	9.708	29.00	-0.50	10.092	1.00
Total (N=538)	55	28.89	7.496	27.00	27.24	8.602	28.00	-1.66	8.500	-1.00
Month 15 after drug discontinuation										
FTY720 1.25 mg (N=297)	14	27.21	7.062	26.50	26.64	8.391	27.50	-0.57	7.439	0.50
FTY720 0.5 mg (N=194)	6	30.83	8.565	29.00	26.50	10.213	26.50	-4.33	10.152	-2.00
Total (N=538)	20	28.30	7.505	27.00	26.60	8.696	27.50	-1.70	8.253	-1.00
Month 18 after drug discontinuation										
FTY720 1.25 mg (N=297)	19	29.26	7.759	26.00	28.42	8.402	25.00	-0.84	7.625	-1.00
FTY720 0.5 mg (N=194)	10	27.60	6.150	26.00	25.00	9.580	27.00	-2.60	6.186	-1.50
Total (N=538)	29	28.69	7.177	26.00	27.24	8.810	26.00	-1.45	7.099	-1.00
Month 21 after drug discontinuation										
FTY720 1.25 mg (N=297)	7	26.57	6.161	25.00	29.21	8.999	28.50	2.64	9.059	0.00
FTY720 0.5 mg (N=194)	2	40.50	6.364	40.50	35.50	7.778	35.50	-5.00	1.414	-5.00
Total (N=538)	9	29.67	8.441	29.00	30.61	8.717	30.00	0.94	8.553	-2.00
Month 24 after drug discontinuation										
FTY720 1.25 mg (N=297)	9	31.00	8.201	27.00	30.22	6.741	31.00	-0.78	10.208	-2.00
FTY720 0.5 mg (N=194)	2	24.00	1.414	24.00	26.50	6.364	26.50	2.50	4.950	2.50
Total (N=538)	11	29.73	7.875	26.00	29.55	6.532	31.00	-0.18	9.358	-2.00

Source: Post Table 11.1-2 (pg 12 of 15), ISS. Change from baseline = endpoint - baseline. - For each laboratory test, only patients with a value at both baseline and post-baseline are included. - The last non-missing value on treatment is summarized in TEP (treatment end timepoint).

Analysis in this population shows that at the end of study evaluation in safety pool E, the lymphocyte count had decreased by 17 or 18%. By 3 months after drug discontinuation, the mean lymphocyte counts were still 5% (FTY 0.5 and FTY 1.25mg) or 10% (FTY 5-1.25 mg group) below baseline. A tiny effect in mean % lymphocyte count seems still present by 1 year and 18 months after drug discontinuation (<2% decrease from baseline). Such a small decrease in % of peripheral lymphocyte count as compared to baseline seems to be of no clinical relevance; however, it would suggest that the pharmacological effects of fingolimod might extend beyond the 45-day (5 half lives) period, at least in lymphoid tissues. Interpretation of these data are limited by the lack of a control arm.

- Analysis of outliers for hematologic abnormalities

Outlier analysis in Group D are presented in the following table.

Table 69. Outlier analysis of hematologic abnormalities, safety pool D

		FTY720 5 mg (N=94)	FTY720 1.25 mg (N=943)	FTY720 0.5 mg (N=854)	Placebo (N=511)	Interferon (N=431)
Parameter	**Criterion**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
WBC (total)	Total	93	934	851	506	429
	≤ 2.0x10E9/L	8 (8.6)	100 (10.7)	64 (7.5)	0	0
	≥ 15x10E9/L	0	6 (0.6)	3 (0.4)	12 (2.4)	7 (1.6)
Absolute Lymphocytes	Total	93	934	850	506	429
	< 0.2x10E9/L	10 (10.8)	273 (29.2)	142 (16.7)	0	3 (0.7)
	≥ 8x10E9/L	0	0	0	0	0
Absolute Neutrophils (Seg. + Bands)	Total	93	934	850	506	429
	≤ 1x10E9/L	3 (3.2)	30 (3.2)	17 (2.0)	6 (1.2)	5 (1.2)
	≥ 12x10E9/L	0	11 (1.2)	9 (1.1)	12 (2.4)	7 (1.6)
RBC	Total	0	840	851	414	429
	< 3.3x10E12/L		2 (0.2)	0	1 (0.2)	0
	> 6.8x10E12/L		0	0	0	1 (0.2)
Haemoglobin	Total	93	934	851	506	429
	≤ 100 g/L	4 (4.3)	12 (1.3)	14 (1.6)	12 (2.4)	8 (1.9)
Platelet count (direct)	Total	93	934	850	506	429
	≤ 100x10E9/L	2 (2.2)	2 (0.2)	5 (0.6)	5 (1.0)	1 (0.2)
	≥ 600x10E9/L	1 (1.1)	2 (0.2)	1 (0.1)	3 (0.6)	1 (0.2)

Source: Post text Table 5.8-3, ISS. Submitted as Addendum ISS on February 2010. n = number of patients with the notable abnormality criterion. Total = Total number of patients with the parameter value Percentages are calculated as n/Total*100

Analysis of outliers for hematologic parameters did not suggest a safety signal other than the known effect on lymphocyte counts.

An analysis of frequency distribution of neutrophil counts in study 2301 included in Novartis' background package for the FDA AC meeting (see Table 70 below) suggests that in addition to lymphocytes, neutrophils were also decreased in the fingolimod treatment groups, although there were no cases of absolute neutropenia (neutrophil count less than 0.5 x $10^{9/}$ L) in the FTY 0.5 mg group or placebo, and only one case on FTY 1.25.

Table 70. Frequency distribution of neutrophil count in study 2301

Criterion	FTY 1.25 N=429 n(%)	FTY 0.5 N=425 n(%)	Placebo N=418 n(%)
Patients with available values	425	424	424
$\leq 1.5 \times 10^9$/L	63 (14.8)	64 (15.1)	16 (3.9)
$< 1.0 \times 10^9$/L	12 (2.8)	5 (1.2)	4 (1.0)
$< 0.5 \times 10^9$/L	1 (0.2)	0	0

Source: Table 6-22, Novartis background package to FDA June 10, 2010 AC.

Analysis of notable hematologic abnormalities in group E were consistent with those in the core studies.

- Shift analyses of hematologic values:

Shift analyses for hematologic values were unremarkable, other than the change from normal to below normal for WBC and lymphocyte count (data not shown).

- Chemistry evaluations

As discussed in section 7.2 Adequacy of routine testing, routine hematology, some chemistry (including cholesterol, triglycerides, albumin, creatinine and liver enzymes) and UA were conducted throughout the studies. However, electrolytes (sodium, potassium, bicarbonate, calcium, magnesium) were not collected in the phase 2 and 3 MS studies. The lack of electrolyte evaluations in this program is of concern, particularly the fact that electrolytes are missing from the narratives and patient profiles of patients who developed adverse events that could be associated to electrolyte disturbances (e.g. bradycardia, extrasystoles, seizures).

In the renal transplant studies, there were some differences between the FTY 5 mg and the MMF groups in mean changes from baseline to Month 12, i.e., a larger mean increase in sodium, a larger mean decrease for calcium, and lower mean decreases for magnesium and potassium on FTY 5 mg compared to the MMF group (none of these differences were seen between FTY 2.5 mg and MMF). These differences were not considered clinically relevant and could be explained by the increased incidence of rejections in the FTY 5 mg treatment group which were treated with steroids.

An analysis of electrolytes was conducted in study 2113, a 28-day clinical pharmacology study. Standard analyses of mean changes from baseline, outlier analyses and shift analyses for sodium, potassium, magnesium, bicarbonate and calcium were unremarkable in this study (data not shown).

A retrospective analysis of electrolytes in a subset of blood samples from patients in study 2301 was submitted with the 120-day SUR, including BUN, sodium, potassium, chloride, phosphate, magnesium and calcium, but the number of patients is small (approximately 10-15 subjects per treatment group at 12 months and 25-30 per treatment group at 24 months) (data not shown).

Analyses of changes on bicarbonate were not submitted because bicarbonate could not be measured in stored blood samples.

The analysis of electrolytes from the subset of patients in study 2301 is as follows.

Table 71. Analysis of electrolytes from study 2301

Parameter	Criterion	FTY720 1.25mg (N=429) Total n (%)	FTY720 0.5mg (N=425) Total n (%)	Placebo (N=418) Total n (%)
Calcium (mmol/L)	<LLN	108 6 (5.6)	122 4 (3.3)	108 5 (4.6)
	>ULN	108 2 (1.9)	122 3 (2.5)	108 3 (2.8)
Chloride (mmol/L)	<LLN	108 1 (0.9)	122 1 (0.8)	108 2 (1.9)
	>ULN	108 14 (13.0)	122 15 (12.3)	108 11 (10.2)
Magnesium (mmol/L)	<LLN	108 14 (13.0)	122 16 (13.1)	108 19 (17.6)
	>ULN	108 0 (0.0)	122 4 (3.3)	108 0 (0.0)
Phosphate (Inorganic Phosphorus) (mmol/L)	<LLN	108 7 (6.5)	122 11 (9.0)	108 9 (8.3)
	>ULN	108 2 (1.9)	122 1 (0.8)	108 5 (4.6)
Potassium (mmol/L)	<LLN	106 2 (1.9)	122 1 (0.8)	108 0 (0.0)
	>ULN	106 1 (0.9)	122 2 (1.6)	108 2 (1.9)
Sodium (mmol/L)	<LLN	108 0 (0.0)	122 0 (0.0)	108 0 (0.0)
	>ULN	108 18 (16.7)	122 20 (16.4)	108 10 (9.3)

This analysis suggests a higher risk of sodium above 155 meq/L in the FTY 1.25 and 0.5 mg groups (approximately 16%) as compared to placebo (9%). This application is missing data on bicarbonate levels.

The FDA requested Novartis to submit information on patients who received electrolyte replacement during fingolimod treatment (pool E), including baseline values and values at the time when there was need for electrolyte replacement, along with the context in which electrolyte replacement was done. Novartis responded on May 28, 2010 as follows:

> "A total of 59 patients received electrolyte solutions, including a few patients who received nasal sprays and eye drops, during FTY720 treatment, the majority of them either potassium chloride or sodium chloride. The most frequent reason for administering electrolytes (in 27 of the 59 patients) was prophylaxis for steroid-induced hypokalemia. Among the remaining 32 patients, there was no predominant reason for receiving electrolytes. Electrolyte values at baseline and at the time of electrolyte replacement cannot be provided for these patients because most of them (52/59) were enrolled in studies D2201 and D2302. The only MS patients for whom electrolyte data are available comprise a small subset of patients in study D2301 for whom stored blood samples from the study could be retrospectively tested. The electrolyte data are available only for two of the seven D2301 patients, and only one of the two had a baseline measurement. Therefore, the relationship between electrolyte values and electrolyte replacement therapy cannot be evaluated in our database."

The lack of data on electrolytes is troublesome. If any electrolyte were to be affected significantly, it is likely that there would have been some clinical manifestations. Still, the chronic effects on electrolytes in patients with MS should be measured. The applicant has

recently amended all ongoing MS protocols to include electrolyte measurements. Additionally, electrolytes will be included in the prospective study that will evaluate the lower dose of fingolimod.

- Liver enzymes

Evaluation of liver enzymes indicated that fingolimod is associated with an increase in transaminases, mostly ALT and GGT. There was also a mild increase in mean alkaline phosphatase. There were no changes from baseline in mean total or direct BR.

Change from baseline in ALT are presented in the following table.

Table 72. Change from baseline in ALT at time of last available measurement, pool D

Visit / Treatment Group	n	Baseline Mean	Baseline SD	Baseline Median	Post baseline Endpoint Mean	Post baseline Endpoint SD	Post baseline Endpoint Median	Change from Baseline Mean	Change from Baseline SD	Change from Baseline Median
TEP										
FTY720 5 mg (N=94)	92	20.03	9.622	17.50	35.42	23.954	27.50	15.39	20.842	9.00
FTY720 1.25 mg (N=943)	925	20.58	12.005	17.00	40.05	41.436	27.00	19.48	37.160	9.00
FTY720 0.5 mg (N=854)	848	20.89	12.207	17.00	38.32	40.030	26.00	17.44	38.281	8.00
Placebo (N=511)	505	20.85	13.154	17.00	21.93	19.620	17.00	1.08	20.244	0.00
Interferon (N=431)	428	24.78	62.003	18.00	30.90	77.196	19.00	6.11	97.535	1.00

Source: Post text Table 5.9-2 ISS.

Table 73. Mean changes from baseline in BR at last available measurement, safety pool D

Visit / Treatment Group	n	Baseline Mean	Baseline SD	Baseline Median	Post baseline Endpoint Mean	Post baseline Endpoint SD	Post baseline Endpoint Median	Change from Baseline Mean	Change from Baseline SD	Change from Baseline Median
TEP										
FTY720 5 mg (N=94)	92	7.03	3.110	6.80	8.17	4.272	6.80	1.14	3.462	0.00
FTY720 1.25 mg (N=943)	925	8.78	4.860	8.00	9.34	5.264	8.00	0.56	4.295	0.00
FTY720 0.5 mg (N=854)	848	9.24	4.427	8.00	9.86	5.428	8.00	0.62	4.154	0.00
Placebo (N=511)	505	8.87	4.619	8.00	8.86	5.632	7.00	-0.01	3.915	0.00
Interferon (N=431)	428	9.09	5.642	8.00	8.69	5.024	8.00	-0.41	3.975	0.00
TEP										
FTY720 1.25 mg (N=943)	823	2.37	1.299	2.00	2.43	1.326	2.00	0.06	1.181	0.00
FTY720 0.5 mg (N=854)	842	2.43	1.228	2.00	2.53	1.354	2.00	0.10	1.159	0.00
Placebo (N=511)	406	2.44	1.317	2.00	2.30	1.276	2.00	-0.15	1.161	0.00
Interferon (N=431)	428	2.36	1.455	2.00	2.24	1.339	2.00	-0.12	1.212	0.00

Source: Post text Table 5.9-2 ISS.

Table 74. Mean changes from baseline in serum Alkaline phosphatase at last available measurement, safety pool D

Visit / Treatment Group	n	Baseline Mean	Baseline SD	Baseline Median	Post baseline Endpoint Mean	Post baseline Endpoint SD	Post baseline Endpoint Median	Change from Baseline Mean	Change from Baseline SD	Change from Baseline Median
TEP										
FTY720 5 mg (N=94)	92	64.48	20.019	62.00	67.36	24.598	62.50	2.88	15.273	1.50
FTY720 1.25 mg (N=943)	925	63.43	19.043	61.00	67.99	27.183	62.00	4.55	19.597	1.00
FTY720 0.5 mg (N=854)	848	63.31	17.937	61.00	66.64	24.517	62.00	3.33	18.690	0.00
Placebo (N=511)	505	63.59	19.500	61.00	63.16	18.787	60.00	-0.43	11.281	0.00
Interferon (N=431)	428	63.86	20.548	61.00	62.32	24.704	58.00	-1.53	19.793	-2.00

Distribution of patients with liver enzyme abnormalities in fingolimod controlled studies is presented in the following table.

Table 75. Distribution of patients with liver enzyme abnormalities, pool D

Parameter	Criterion	FTY720 5 mg (N=94) n (%)	FTY720 1.25 mg (N=943) n (%)	FTY720 0.5 mg (N=854) n (%)	Placebo (N=511) n (%)	Interferon (N=431) n (%)
ALT	Total	93	934	851	506	429
	No abnormalities	40 (43.0)	505 (54.1)	461 (54.2)	388 (76.7)	322 (75.1
	> 1 x ULN	53 (57.0)	429 (45.9)	390 (45.8)	118 (23.3)	107 (24.9)
	≥ 2 x ULN	20 (21.5)	173 (18.5)	148 (17.4)	29 (5.7)	26 (6.1)
	≥ 3 x ULN	11 (11.8)	91 (9.7)	72 (8.5)	8 (1.6)	10 (2.3)
	≥ 5 x ULN	1 (1.1)	21 (2.2)	14 (1.6)	4 (0.8)	6 (1.4)
	≥ 10 x ULN	0	0	1 (0.1)	0	2 (0.5)
	≥ 20 x ULN	0	0	0	0	1 (0.2)
AST	Total	93	934	851	506	429
	No abnormalities	69 74.2)	673 (72.1)	636 (74.7)	455 (89.9)	370 (86.2)
	> 1 x ULN	24 (25.8)	261 (27.9)	215 (25.3)	51 (10.1)	59 (13.8)
	≥ 2 x ULN	6 (6.5)	50 (5.4)	36 (4.2)	8 (1.6)	13 (3.0)
	≥ 3 x ULN	1 (1.1)	14 (1.5)	17 (2.0)	5 (1.0)	8 (1.9)
	≥ 5 x ULN	0	2 (0.2)	2 (0.2)	1 (0.2)	3 (0.7)
	≥ 10 x ULN	0	0	0	0	2 (0.5)
	≥ 20 x ULN	0	0	0	0	1 (0.2)
GGT	Total		840	851	414	429
	No abnormalities		537 (63.9)	580 (68.2)	378 (91.3)	383 (89.3)
	> 1 x ULN		303 (36.1)	271 (31.8)	36 (8.7)	46 (10.7)
	≥ 2 x ULN		144 (17.1)	119 (14.0)	10 (2.4)	16 (3.7)
	≥ 3 x ULN		72 (8.6)	56 (6.6)	3 (0.7)	6 (1.4)
	≥ 5 x ULN		23 (2.7)	15 (1.8)	0	2 (0.5)
	≥ 10 x ULN		0	1 (0.1)	0	1 (0.2)
	≥ 20 x ULN		0	1 (0.1)	0	0
Total Bilirubin	Total	93	934	851	506	429
	No abnormalities	90 (96.8)	854 (91.4)	763 (89.7)	463 (91.5)	398 (92.8)
	> 1 x ULN	3 (3.2)	80 (8.6)	88 (10.3)	43 (8.5)	31 (7.2)
	≥ 2 x ULN	0	7 (0.7)	8 (0.9)	3 (0.6)	2 (0.5)

Source: ISS addendum, submitted February 2010.

ALT ≥3xULN was shown by 9.7% and 8.5% of subjects in the FTY 1.25 and 0.5 mg groups, respectively, as compared to 1.6% of those in the placebo group, in the controlled studies. The percentage of patients with ALT ≥5xULN was also higher in the FTY groups (2.2% and 1.6%)

as compared to placebo (0.8%). Therefore, there is a clear effect on increase in liver enzyme elevations. However, the great majority of these cases had normal BR and ALK Phosphatase.

There were five cases in the entire ISS in which there was increase in transaminases ≥3xULN and increase in BR ≥ 2x ULN. One of them was the case of hepatic necrosis in a patient who died of disseminated herpes zoster; one was a patient who received intravenous paracetamol for hip pain; 2 cases occurred in subjects suspected of having Gilbert's disease, and one occurred in a patient after completing treatment with placebo.

Additional cases of transaminase elevation occurred in study 2309. These cases are blinded, except for the case of the patient who developed elevated ALT and jaundice while on FTY 0.5 mg and was found to have acute Hepatitis E.

> *Of note, the ISS datasets submitted by the applicant did not always include values for transaminases and bilirubin obtained at timepoints other than the scheduled protocol. For instance, no liver-enzyme related values were included in the datasets for the patient who died of disseminated varicella zoster infection and hepatic necrosis. Similarly, the patient who developed cytolytic hepatitis after receiving intravenous paracetamol had ALT's in the 4000 range. The ALT values are mentioned in the narrative, but not included in the datasets. That means that the analyses of changes from baseline and outlier analyses of liver related enzymes were biased by not including these values. In further submissions, the applicant's dataset should include all values (or at least one maximum/minimum value) on laboratory analyses done outside the protocols.*

- Analyses of metabolic parameters in pool D

There were no clinically relevant changes in mean changes from baseline in total cholesterol, HDL, LDL or TG, creatinine, estimated creatinine clearance (Cockcroft-Gault), glucose or albumin in safety pool D (data not shown).

Outlier analyses of metabolic parameters in pool D are shown as follows:

Table 76. Outlier analysis of metabolic parameters, safety pool D

		FTY720 5 mg (N=94)	FTY720 1.25 mg (N=943)	FTY720 0.5 mg (N=854)	Placebo (N=511)	Interferon (N=431)
Parameter	**Criterion**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Cholesterol (total)	Total	93	934	851	506	429
	≥ 6.21 mmol/L	22 (23.7)	306 (32.8)	313 (36.8)	157 (31.0)	63 (14.7)
Triglycerides	Total	93	934	851	506	429
	≥ 3.39 mmol/L	7 (7.5)	113 (12.1)	95 (11.2)	39 (7.7)	54 (12.6)
Glucose	Total	0	840	851	414	429
	≥ 11.11 mmol/L		4 (0.5)	4 (0.5)	1 (0.2)	2 (0.5)
Amylase	Total	0	840	851	414	429
	≥ 300 U/L		2 (0.2)	1 (0.1)	0	0
Creatinine	Total	93	934	851	506	429
	≥ 176 umol/L	0	0	1 (0.1)	0	0

Source: ISS addendum 1 submitted February 2010.

The analysis of outliers suggests that a few more patients developed elevated glucose in the FTY groups as compared to placebo, but the numbers are small for definitive conclusions. This evaluation also suggests a greater number of subjects developed markedly elevated triglycerides in the FTY groups (12.1% and 11.2%) and the IFN group (12.6%), as compared to placebo (7.7%), but the clinical significance of this difference is unclear. The analysis of cholesterol, amylase and creatinine outliers was unremarkable.

- Urinalysis

A categorical analysis of proteinuria was conducted in the clinical studies in the ISS. No other urinalysis results were provided.

The frequency of patients with urine protein in Safety pool D is presented in the following table

Table 77. Percentage of patients with protein in urine in Safety pool D

Post-baseline extreme value	FTY720 5 mg (N=94) n	(%)	FTY720 1.25 mg (N=943) n	(%)	FTY720 0.5 mg (N=854) n	(%)	Placebo (N=511) n	(%)	Interferon (N=431) n	(%)
Patients with any urine protein value	93		869		820		489		404	
-	89	(95.7)	775	(89.2)	745	(90.9)	445	(91.0)	385	(95.3)
+	4	(4.3)	76	(8.7)	57	(7.0)	38	(7.8)	17	(4.2)
++	0	(0.0)	12	(1.4)	14	(1.7)	5	(1.0)	2	(0.5)
+++	0	(0.0)	5	(0.6)	4	(0.5)	1	(0.2)	0	(0.0)
++++	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)

Source, ISS table.

In the controlled studies, there were more cases of 2+, 3+ and 4+ proteinuria in the FTY 1.25 and 0.5 mg groups as compared to placebo or IFN, but the numbers are small to draw definitive conclusions.

> *The applicant was asked to provide full urinalyses, chemistries and clinical correlation for patients with 3+ and 4+ proteinuria. Available electrolytes, creatinine and estimated creatinine clearance were normal in these patients, however it is unclear if these measurements were taken on the same date as the event of 3+ or 4+ proteinuria. Overall, the data submitted did not help in the evaluation of proteinuria. None of the subjects had 24 hour protein collection.*

Evaluation of individual study reports:

Analysis of shifts in proteinuria in study 2301 is shown below:

Table 78. Shift table of urine protein by treatment, study 2301

Treatment		Baseline	n (%)	Extreme value: NEG n (%)	+ n (%)	2+ n (%)	3+ n (%)	4+ n (%)
FTY720 1.25mg	(N=429)	NEG	364 (94.8)	315 (82.0)	42 (10.9)	3 (0.8)	4 (1.0)	0 (0.0)
		+	18 (4.7)	7 (1.8)	8 (2.1)	2 (0.5)	1 (0.3)	0 (0.0)
		2+	2 (0.5)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		3+	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		4+	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Total	384 (100.0)	324 (84.4)	50 (13.0)	5 (1.3)	5 (1.3)	0 (0.0)
FTY720 0.5mg	(N=425)	NEG	390 (94.7)	342 (83.0)	37 (9.0)	10 (2.4)	1 (0.2)	0 (0.0)
		+	17 (4.1)	11 (2.7)	5 (1.2)	0 (0.0)	1 (0.2)	0 (0.0)
		2+	4 (1.0)	3 (0.7)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
		3+	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		4+	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Total	412 (100.0)	357 (86.7)	43 (10.4)	10 (2.4)	2 (0.5)	0 (0.0)
Placebo	(N=418)	NEG	374 (94.4)	341 (86.1)	30 (7.6)	3 (0.8)	0 (0.0)	0 (0.0)
		+	19 (4.8)	12 (3.0)	6 (1.5)	1 (0.3)	0 (0.0)	0 (0.0)
		2+	3 (0.8)	3 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		3+	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		4+	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Total	396 (100.0)	356 (89.9)	36 (9.1)	4 (1.0)	0 (0.0)	0 (0.0)

- A patient must have both baseline and post-baseline values to be included in the summary.
- A patient is counted in the highest category. - n=number of patients with the given value.
Source: original ISS.

This analysis shows a shift from normal to 3+ proteinuria in 4 subjects on FTY 1.25 and 1 subject on FTY 0.5 mg, and none on placebo. There is also a shift from 1+ proteinuria to 3+ proteinuria in one subject on FTY 1.25 and 1 subject on FTY 0.5. But there are also switches from 2+ to 0 in several subjects on fingolimod and placebo. Overall, 2.6% of patients on FTY 1.25, 2.9% of patients on FTY 0.5 and 1% of patients on placebo presented 2+ or 3+ proteinuria at some point in study 2301.

Analyses of proteinuria in studies 2302 and 2201 were not included in the original study reports but were submitted at the FDA request on 5/26/10, as follows.

Table 79. Shift table of urine protein by treatment, study 2302

Treatment		Baseline	n (%)	Extreme value: NEG n (%)	1+ n (%)	2+ n (%)	3+ n (%)	4+ n (%)
FTY720 1.25 mg	(N=420)	NEG	362 (93.3)	336 (86.6)	19 (4.9)	6 (1.5)	0 (0.0)	1 (0.3)
		1+	19 (4.9)	16 (4.1)	3 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
		2+	6 (1.5)	5 (1.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
		3+	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		4+	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Total	388 (100)	358 (92.3)	23 (5.9)	6 (1.5)	0 (0.0)	1 (0.3)
FTY720 0.5 mg	(N=429)	NEG	384 (94.3)	368 (90.4)	11 (2.7)	3 (0.7)	2 (0.5)	0 (0.0)
		1+	21 (5.2)	18 (4.4)	2 (0.5)	1 (0.2)	0 (0.0)	0 (0.0)
		2+	2 (0.5)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
		3+	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		4+	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Total	407 (100)	387 (95.1)	14 (3.4)	4 (1.0)	2 (0.5)	0 (0.0)
Interferon	(N=431)	NEG	376 (93.1)	361 (89.4)	14 (3.5)	1 (0.2)	0 (0.0)	0 (0.0)
		1+	25 (6.2)	23 (5.7)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
		2+	3 (0.7)	1 (0.2)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
		3+	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		4+	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Total	404 (100)	385 (95.3)	17 (4.2)	2 (0.5)	0 (0.0)	0 (0.0)

Source: response to FDA submitted 5/26/10.

Table 80. Shift table of urine protein by treatment in study 2201.

Treatment		Baseline		Extreme value: NEG		1+		2+		3+		4+	
			n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
FTY720 5 mg	(N= 94)	NEG	91	(97.8)	87	(93.5)	4	(4.3)	0	(0.0)	0	(0.0)	0	(0.0)
		1+	2	(2.2)	2	(2.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
		2+	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
		3+	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
		4+	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
		Total	93	(100)	89	(95.7)	4	(4.3)	0	(0.0)	0	(0.0)	0	(0.0)
FTY720 1.25 mg	(N= 94)	NEG	91	(96.8)	89	(94.7)	2	(2.1)	0	(0.0)	0	(0.0)	0	(0.0)
		1+	2	(2.1)	2	(2.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
		2+	1	(1.1)	0	(0.0)	0	(0.0)	1	(1.1)	0	(0.0)	0	(0.0)
		3+	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
		4+	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
		Total	94	(100)	91	(96.8)	2	(2.1)	1	(1.1)	0	(0.0)	0	(0.0)
Placebo	(N= 93)	NEG	91	(98.9)	88	(95.7)	2	(2.2)	0	(0.0)	1	(1.1)	0	(0.0)
		1+	1	(1.1)	0	(0.0)	0	(0.0)	1	(1.1)	0	(0.0)	0	(0.0)
		2+	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
		3+	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
		4+	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
		Total	92	(100)	88	(95.7)	2	(2.2)	1	(1.1)	1	(1.1)	0	(0.0)

Source: response to FDA submitted 5/26/10.

In all studies, shifts from a normal baseline to abnormal findings on treatment were rare but slightly more frequent on FTY 1.25 as compared to FTY 0.5 or the control group (INF or placebo). There was no notable difference in the incidence of treatment-emergent abnormal urine protein findings between the 0.5 mg dose and interferon in study 2302.

Comment regarding potential reno-vascular toxicity:

In the renal transplant population, there more patients with SAE of transplant rejection in FTY 5mg and 2.5mg as compared to MMF. A possible explanation is that FTY is less immunosuppressive than MMF. Another possibility that has been entertained by the sponsor is that it could be related to "slower and incomplete recovery of renal function in the de novo transplantation setting, possibly explained by impaired recovery from ischemia reperfusion injury." (Source: response to FDA request for information. White paper on the effect of S1P receptor modulation on vascular physiology, dated May 13, 2010).

No patient developed renal failure in the MS program. Analyses of creatinine changes from baseline and outliers as well as changes in estimated creatinine clearance did not show a signal for renal toxicity in the MS program. Analyses of electrolytes in studies 2113 (a 28-day clinical pharmacology study) were unremarkable. Standard data on electrolytes were not collected in phase 2&3 studies. However, I am more concerned about the potential vascular effect of S1P modulation in the glomerulus rather than the immediate effect on the renal function. (In patients with diabetes, proteinuria appears before any evidence of renal failure.)

Three cases of unexplained edema (one of them with 8 kg weight gain) were observed in the fingolimod MS database shortly after initiation of treatment. These patients improved after diuretic treatment. Urinalyses (looking for protein) were not available from these

patients. Another patient discontinued because of upper and lower extremity edema in study 2309.

An increasing body of literature indicates that S1P is involved in the regulation of vascular permeability and vascular tone. This might in part explain the finding of macular edema observed with FTY. Another target organ that could be affected by S1P modulation could be the glomerulus. 24 hour protein was not collected in the MS program. The risk for renal toxicity would be increased in patients with underlying vascular problems, such as those with diabetes, but they were excluded from the phase 3 studies. The potential renal toxicity of fingolimod should be studied further. It could be done postmarketing.

As per discussions at the FDA AC meeting of June 10, 2010, a study evaluating the efficacy and safety of fingolimod 0.25 mg should be conducted postmarketing. Such a study should include measurement of 24 hour protein in patients who develop edema during the study.

- Coagulation parameters

S1P has been implicated in the process of thrombogenesis. S1P accumulates in platelets and induces platelet aggregation. PT and PTT were unremarkable in study 2113, a 28-day study. PT and PTT were not collected in phase 2 & 3 studies.

As per Dr. Fitter, a stroke expert, a standard hypercoagulable workup would include PT/PTT, TT, Fibrinogen, Antithrombin 3, Protein C, Protein S, activated protein C resistance, APLA, LA, Homocysteine. The mutations associated with hypercoagulability and pregnancy are Factor V Leiden, Prothrombin G20210A mutation and MTHFR mutation. All these tests should be performed in patients suspected of being hypercoagulable (e.g. those with stroke or with arterial occlusions).

It is unclear which coagulation parameters other than PT/PTT should be measured routinely in a clinical study. Of note, the NDA applicantion was supposed to include a drug interaction study in patients taking fingolimod and oral contraceptives. Such study has not been submitted in the current application but will be requested as a postmarketing requirement. This study is very relevant because given the teratogenecity risk, it is anticipated that many patients with MS who take fingolimod will also be taking oral contraceptives. An oral contraceptive interaction study could include some of the sophisticated laboratory evaluations mentioned above. At a minimum, PT/PTT, Protein C, Protein S, activated Protein C resistance, antiphospholipid antibodies and homocysteine should be included in such a study.

7.4.3 Vital Signs

Evaluation of vital signs indicates that chronic use of fingolimod increases systolic and diastolic blood pressure in a dose-response manner. However, the immediate effect upon first dose is a decrease in BP. Evaluation of BP over time showed that the effect on BP was evident in the 1 month evaluation, reached plateau at 6 months and was maintained throughout the end of the

evaluations. Changes in BP are presented in the following table. Of note, the 6 month evaluation includes all 3 studies; the 12 month evaluation includes only studies 2301 and 2302; the 24 month evaluation includes only study 2301.

Table 81. Changes from baseline in Systolic and diastolic blood pressure, safety pool D

Visit		Baseline			Endpoint			Post baseline Change from baseline		
Sitting Systolic BP		Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Month 6										
FTY720 5 mg (N=94)	84	116.07	15.336	115.50	123.33	15.821	120.00	7.26	12.402	6.58
FTY720 1.25 mg (N=943)	856	117.78	13.311	117.33	121.06	14.352	120.00	3.28	12.649	3.33
FTY720 0.5 mg (N=854)	808	118.14	12.648	117.67	119.88	13.373	120.00	1.74	11.522	1.67
Placebo (N=511)	476	117.80	12.889	117.67	117.38	12.685	118.00	-0.42	11.799	0.00
Interferon (N=431)	401	116.59	12.288	115.33	116.42	13.324	115.33	-0.17	12.642	0.00
Month 12										
FTY720 1.25 mg (N=943)	716	117.53	13.042	117.50	120.48	13.203	120.00	2.95	12.204	3.00
FTY720 0.5 mg (N=854)	773	118.03	12.609	117.33	119.72	12.490	120.00	1.69	11.789	1.33
Placebo (N=511)	362	118.28	12.844	118.33	118.30	12.934	118.67	0.03	11.665	0.00
Interferon (N=431)	383	116.43	12.285	115.00	115.65	12.897	115.00	-0.78	12.480	0.00
Month 24										
FTY720 1.25 mg (N=943)	306	117.97	13.267	117.50	121.59	12.196	120.50	3.62	12.994	4.33
FTY720 0.5 mg (N=854)	349	118.47	12.633	118.33	120.38	12.840	120.00	1.91	12.082	1.67
Placebo (N=511)	313	117.88	12.793	118.00	117.47	12.571	118.33	-0.41	12.516	1.00
Sitting Diastolic BP										
Month 6										
FTY720 5 mg (N=94)	84	73.94	10.477	75.00	79.16	10.601	79.00	5.22	8.842	3.75
FTY720 1.25 mg (N=943)	856	75.48	10.048	75.33	77.54	9.964	78.00	2.07	9.563	1.67
FTY720 0.5 mg (N=854)	808	75.90	9.421	76.50	77.24	9.630	77.33	1.35	8.902	0.67
Placebo (N=511)	476	75.64	9.802	75.00	75.24	9.473	75.33	-0.40	9.229	0.00
Interferon (N=431)	401	74.89	9.214	74.33	75.18	9.190	75.00	0.29	9.218	0.00
Month 12										
FTY720 1.25 mg (N=943)	716	75.41	9.729	75.00	77.29	9.631	78.08	1.88	9.432	1.67
FTY720 0.5 mg (N=854)	773	75.80	9.436	76.33	76.41	9.170	76.67	0.61	9.262	0.33
Placebo (N=511)	362	76.19	9.473	76.33	75.27	8.797	75.00	-0.93	9.043	-0.33
Interferon (N=431)	383	74.78	9.293	74.00	74.78	9.401	74.00	0.00	10.057	0.00
Month 24										
FTY720 1.25 mg (N=943)	306	75.49	9.784	74.67	77.61	8.188	78.33	2.12	8.972	2.67
FTY720 0.5 mg (N=854)	349	76.03	9.367	76.67	76.77	9.532	76.67	0.74	8.850	0.00
Placebo (N=511)	313	76.05	9.326	76.67	75.55	8.939	76.67	-0.50	9.673	0.00

Change from baseline in SBP * DBP in Safety Pool D: Last non-missing value on treatment

Sitting Systolic BP										
TEP										
FTY720 5 mg (N=94)	92	116.13	15.151	115.00	123.51	16.647	120.00	7.38	13.352	7.50
FTY720 1.25 mg (N=943)	924	117.67	13.270	117.33	121.30	13.224	120.00	3.63	12.242	3.33
FTY720 0.5 mg (N=854)	850	118.35	12.817	118.00	120.37	12.716	120.00	2.02	12.394	1.67
Placebo (N=511)	504	117.98	13.035	118.00	117.35	12.877	118.33	-0.63	12.946	0.00
Interferon (N=431)	429	116.81	12.539	115.33	115.89	12.784	115.00	-0.92	12.057	0.00
Sitting Diastolic BP										
TEP										
FTY720 5 mg (N=94)	92	73.98	10.072	74.50	79.25	11.106	79.00	5.27	9.931	6.00
FTY720 1.25 mg (N=943)	924	75.52	10.030	75.33	77.77	9.493	78.33	2.25	9.584	1.67
FTY720 0.5 mg (N=854)	850	76.07	9.527	76.67	77.04	9.497	77.67	0.97	9.543	1.00
Placebo (N=511)	504	75.80	9.789	75.33	75.40	9.147	75.83	-0.40	9.687	0.00
Interferon (N=431)	429	75.04	9.243	74.33	74.97	9.176	74.67	-0.07	9.850	0.00

Source, Post text Table 6.3-2. ISS.

There was a clear dose-related increase in systolic and diastolic blood pressure. The mean change from baseline to the last non missing value on treatment in the fingolimod 0.5 mg group was 2 mmHg increase in SBP and 1 mmHg increase in DBP, which is a small change.

Table 82. Distribution of change from baseline in systolic and diastolic blood pressure by visit LOCF, safety pool D

Visit: Month 6

		FTY720 5 mg (N=94) n	%	FTY720 1.25 mg (N=943) n	%	FTY720 0.5 mg (N=854) n	%	Placebo (N=511) n	%
Patients with any SBP or DBP value		93		934		852		506	
Systolic BP (mmHg)	<= 0	30	(32.3)	370	(39.6)	393	(46.1)	276	(54.5)
	> 0 to < 5	11	(11.8)	152	(16.3)	127	(14.9)	54	(10.7)
	>= 5 to < 10	12	(12.9)	129	(13.8)	133	(15.6)	78	(15.4)
	>= 10	40	(43.0)	283	(30.3)	199	(23.4)	98	(19.4)
Diastolic BP (mmHg)	<= 0	28	(30.1)	429	(45.9)	413	(48.5)	288	(56.9)
	> 0 to < 5	21	(22.6)	162	(17.3)	152	(17.8)	78	(15.4)
	>= 5 to < 10	13	(14.0)	165	(17.7)	136	(16.0)	77	(15.2)
	>= 10	31	(33.3)	178	(19.1)	151	(17.7)	63	(12.5)

Visit: Month 12

		FTY720 5 mg (N=94) n	%	FTY720 1.25 mg (N=943) n	%	FTY720 0.5 mg (N=854) n	%	Placebo (N=511) n	%
Patients with any SBP or DBP value		0		841		852		414	
Systolic BP (mmHg)	<= 0	0		358	(42.6)	401	(47.1)	223	(53.9)
	> 0 to < 5	0		109	(13.0)	105	(12.3)	62	(15.0)
	>= 5 to < 10	0		134	(15.9)	130	(15.3)	54	(13.0)
	>= 10	0		240	(28.5)	216	(25.4)	75	(18.1)
Diastolic BP (mmHg)	<= 0	0		383	(45.5)	417	(48.9)	244	(58.9)
	> 0 to < 5	0		149	(17.7)	174	(20.4)	73	(17.6)
	>= 5 to < 10	0		145	(17.2)	116	(13.6)	48	(11.6)
	>= 10	0		164	(19.5)	145	(17.0)	49	(11.8)

Visit: Month 24

		FTY720 5 mg (N=94) n	%	FTY720 1.25 mg (N=943) n	%	FTY720 0.5 mg (N=854) n	%	Placebo (N=511) n	%
Patients with any SBP or DBP value		0		425		424		414	
Systolic BP (mmHg)	<= 0	0		167	(39.3)	199	(46.9)	211	(51.0)
	> 0 to < 5	0		68	(16.0)	59	(13.9)	63	(15.2)
	>= 5 to < 10	0		62	(14.6)	59	(13.9)	59	(14.3)
	>= 10	0		128	(30.1)	107	(25.2)	81	(19.6)
Diastolic BP (mmHg)	<= 0	0		186	(43.8)	213	(50.2)	224	(54.1)
	> 0 to < 5	0		83	(19.5)	79	(18.6)	76	(18.4)
	>= 5 to < 10	0		76	(17.9)	59	(13.9)	54	(13.0)
	>= 10	0		80	(18.8)	73	(17.2)	60	(14.5)

Source: response to FDA request for information submitted 5/13/10.

Analysis of the distribution of BP values by visit shows that a slightly higher percentage of patients presented an increase from baseline of ≥ 10 mm Hg in systolic and diastolic BP in the

FTY groups as compared to placebo, with evidence of a dose response. There does not seem to be an increase in risk over time.

- Mean changes in pulse and weight

Mean changes in pulse and weight with chronic use were unremarkable

- Outlier analyses of vital signs

Outlier analyses of vital signs with chronic use are consistent with the analyses of mean changes and suggest that more patients fulfilled "notable criteria" (as defined in the table below) for high blood pressure in the FTY groups, particularly FTY 1.25 and FTY 5 mg.

Table 83. Outlier analyses of vital signs

Vital Sign Variable	Notable Criteria
Sitting systolic BP (mmHg)	≥ 160 mmHg or Increase of ≥ 20 mmHg from baseline or ≤ 90 mmHg or Decrease of ≥ 20 mmHg from baseline
Sitting diastolic BP (mmHg)	≥ 100 mmHg or Increase of ≥ 15 mmHg from baseline or ≤ 50 mmHg or Decrease of ≥ 15 mmHg from baseline
Sitting pulse (beats/min)	> 120 bpm or Increase of≥ 15 bpm from baseline or < 50 bpm or Decrease of≥ 15 bpm from baseline
Body weight (Kg)	± 7% from baseline weight

Table 84. Notable abnormalities in vital signs, safety pool D

Parameter Criterion	FTY720 5 mg N=94	FTY720 1.25 mg N=943	FTY720 0.5 mg N=854	Placebo N=511	Interferon N=431
Sitting systolic BP (mmHg) - n(%)					
Low: <=90 or >=20 decrease from baseline	16(17.0%)	158(16.8%)	158(18.5%)	137(26.8%)	88(20.4%)
<=90	6(6.4%)	46(4.9%)	42(4.9%)	45(8.8%)	33(7.7%)
>=20 decrease from baseline	11(11.7%)	132(14.0%)	130(15.2%)	114(22.3%)	68(15.8%)
High: >=160 or >=20 increase from baseline	39(41.5%)	264(28.0%)	193(22.6%)	101(19.8%)	67(15.5%)
>=160	6(6.4%)	49(5.2%)	22(2.6%)	11(2.2%)	7(1.6%)
>=140	30(31.9%)	225(23.9%)	176(20.6%)	94(18.4%)	62(14.4%)
>=20 increase from baseline	38(40.4%)	256(27.1%)	188(22.0%)	101(19.8%)	65(15.1%)
Sitting diastolic BP (mmHg) - n(%)					
Low: <=50 or >=15 decrease from baseline	13(13.8%)	156(16.5%)	150(17.6%)	128(25.0%)	81(18.8%)
<=50	5(5.3%)	19(2.0%)	9(1.1%)	20(3.9%)	3(0.7%)
>=15 decrease from baseline	9(9.6%)	146(15.5%)	146(17.1%)	118(23.1%)	79(18.3%)
High: >=100 or >=15 increase from baseline	39(41.5%)	260(27.6%)	213(24.9%)	115(22.5%)	80(18.6%)
>=100	12(12.8%)	78(8.3%)	55(6.4%)	24(4.7%)	18(4.2%)
>=90	29(30.9%)	271(28.7%)	257(30.1%)	120(23.5%)	92(21.3%)
>=15 increase from baseline	34(36.2%)	231(24.5%)	187(21.9%)	103(20.2%)	71(16.5%)

Source: Post text Table 6.3.3 ISS

- Notable abnormalities in vital signs upon first dose administration

Notable abnormalities in systolic and diastolic BP and pulse upon first dose in safety pool A are presented in the following table. (Since study 2201 did not have the same ECG monitoring as the phase 3 studies, only studies 2301 and 2302 presented, instead of pool D).

Table 85. Notable abnormalities upon first dose administration, safety pool A

Parameter Criterion	FTY720 1.25 mg N=849	FTY720 0.5 mg N=854	Placebo N=418	Interferon N=431
Sitting systolic BP (mmHg) - n(%)				
Low: <=90 or >=20 decrease from baseline	195(23.0%)	158(18.5%)	67(16.0%)	55(12.8%)
<=90	95(11.2%)	65(7.6%)	30(7.2%)	21(4.9%)
>=20 decrease from baseline	129(15.2%)	114(13.3%)	47(11.2%)	38(8.8%)
High: >=160 or >=20 increase from baseline	94(11.1%)	96(11.2%)	48(11.5%)	73(16.9%)
>=160	18(2.1%)	21(2.5%)	8(1.9%)	11(2.6%)
>=140	158(18.6%)	142(16.6%)	69(16.5%)	75(17.4%)
>=20 increase from baseline	86(10.1%)	89(10.4%)	46(11.0%)	67(15.5%)
Sitting diastolic BP (mmHg) - n(%)				
Low: <=50 or >=15 decrease from baseline	244(28.7%)	195(22.8%)	70(16.7%)	60(13.9%)
<=50	56(6.6%)	36(4.2%)	13(3.1%)	13(3.0%)
>=15 decrease from baseline	211(24.9%)	180(21.1%)	67(16.0%)	52(12.1%)
High: >=100 or >=15 increase from baseline	71(8.4%)	85(10.0%)	47(11.2%)	54(12.5%)
>=100	21(2.5%)	28(3.3%)	18(4.3%)	15(3.5%)
>=90	128(15.1%)	181(21.2%)	86(20.6%)	82(19.0%)
>=15 increase from baseline	55(6.5%)	64(7.5%)	35(8.4%)	43(10.0%)
Sitting pulse (bpm) - n(%)				
Low: <50 or >=15 decrease from baseline	404(47.6%)	283(33.1%)	54(12.9%)	36(8.4%)
<50	93(11.0%)	52(6.1%)	9(2.2%)	2(0.5%)
>=15 decrease from baseline	382(45.0%)	258(30.2%)	48(11.5%)	36(8.4%)
High: >120 or >=15 increase from baseline	19(2.2%)	36(4.2%)	54(12.9%)	175(40.6%)
>120	0(0.0%)	0(0.0%)	0(0.0%)	1(0.2%)
>=15 increase from baseline	19(2.2%)	36(4.2%)	54(12.9%)	175(40.6%)

Source: Post text Table 10.1-5b.

Of those subjects who presented marked VS abnormalities upon first dose, 10 to 25% presented VS abnormalities upon the second dose on Day 2.

Parameter Criterion	FTY720 1.25 mg N=59	FTY720 0.5 mg N=18	Placebo N=3	Interferon N=4
Sitting systolic BP (mmHg) - n(%)				
Low: <=90 or >=20 decrease from baseline	14(23.7%)	2(11.1%)	1(33.3%)	0(0.0%)
<=90	4(6.8%)	1(5.6%)	1(33.3%)	0(0.0%)
>=20 decrease from baseline	13(22.0%)	2(11.1%)	1(33.3%)	0(0.0%)
High: >=160 or >=20 increase from baseline	3(5.1%)	2(11.1%)	1(33.3%)	0(0.0%)
>=140	12(20.3%)	3(16.7%)	0(0.0%)	0(0.0%)
>=20 increase from baseline	3(5.1%)	2(11.1%)	1(33.3%)	0(0.0%)
Sitting diastolic BP (mmHg) - n(%)				
Low: <=50 or >=15 decrease from baseline	21(35.6%)	3(16.7%)	0(0.0%)	1(25.0%)
<=50	6(10.2%)	1(5.6%)	0(0.0%)	0(0.0%)
>=15 decrease from baseline	18(30.5%)	2(11.1%)	0(0.0%)	1(25.0%)
High: >=100 or >=15 increase from baseline	5(8.5%)	4(22.2%)	0(0.0%)	0(0.0%)
>=100	1(1.7%)	1(5.6%)	0(0.0%)	0(0.0%)
>=90	6(10.2%)	4(22.2%)	0(0.0%)	0(0.0%)
>=15 increase from baseline	5(8.5%)	4(22.2%)	0(0.0%)	0(0.0%)
Sitting pulse (bpm) - n(%)				
Low: <50 or >=15 decrease from baseline	46(78.0%)	12(66.7%)	0(0.0%)	0(0.0%)
<50	12(20.3%)	2(11.1%)	0(0.0%)	0(0.0%)
>=15 decrease from baseline	45(76.3%)	11(61.1%)	0(0.0%)	0(0.0%)
High: >120 or >=15 increase from baseline	0(0.0%)	0(0.0%)	1(33.3%)	1(25.0%)
>=15 increase from baseline	0(0.0%)	0(0.0%)	1(33.3%)	1(25.0%)

Source: ISS Post text Table 10.1-6a. N= number of subjects with 2nd day data.

7.4.4 Electrocardiograms (ECGs)

- **Study FTY720D 2101: Thorough QT study**

This was a randomized, parallel group, multiple-dose study to evaluate the effects of fingolimod on cardiac safety in healthy subjects vs. placebo, with positive Moxifloxacin control. Participating subjects were to be randomized to one of four treatment groups: moxifloxacin, placebo, FTY 1.25 mg, or FTY 2.5 mg group (21 to Moxifloxacin and 56 to each of the other groups). For the FTY treatment groups, a loading dose regimen was used over a 4 day period to achieve concentrations that would be expected at steady state before the 1.25 mg and 2.5 mg doses were administered from Day 5 to Day 7. For details about the study design the reader is referred to the Interdisciplinary Review Team (IRT) review dated October 10, 2008. The following are excerpts from the IRT Overall Summary of Findings):

"This study failed to exclude a 10 ms prolongation of the QT interval for both doses of FTY720 (1.25 and 2.5 mg). At 6 hours post-dosing on Day 7, the maximum mean ΔΔQTcI for both 1.25- and 2.5-mg doses was 10 ms with an upper one-sided 95% CI of~14 ms (see Table 1).

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for FTY720 (1.25 mg and 2.5 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcI (ms)	90% CI (ms)
FTY720 1.25 mg	6	10.0	13.6
FTY720 2.50 mg	6	10.5	14.0
Moxifloxacin 400 mg*	6	10.5	5.7

* Multiple endpoint adjustment is not applied. The largest lower bound after Bonferroni adjustment for 3 timepoints is 4.3 ms. Note: The sponsor specified times 1.5, 3, and 6 as the times to be tested for Moxifloxacin. At 8 hours the estimated ΔΔQTc was 11.0 ms and the unadjusted lower bound of the 90% C.I. was 7.5 ms.
Source: IRT review dated 10/20/08.

We do not have confidence in the accuracy of the estimated effect of administering FTY720 on the QTc interval for the following reasons:

1. The positive control, a single oral dose of 400 mg moxifloxacin, failed to have the expected effect on ΔΔQTcI (change from baseline and placebo corrected); the largest ΔΔQTcI for moxifloxacin was about 10.5 ms and occurred at 6 and 8 hours post-dose. This profile is not likely since the Tmax of moxifloxacin observed in this study was 3 hours (see Figure 5). This is especially relevant, since the largest ΔΔQTcI for FTY720 was of the same magnitude and occurred at the same time points as that observed for moxifloxacin.

2. Despite a 2-fold increase in the exposure to FTY720 plasma concentrations, there was no dose-response relationship for QT prolongation. There was also not a concentration-QTc relationship for FTY720 and its metabolite FTY720-P. This does not, however, rule out the existence of a positive exposure-response relationship because of the small range of steady-state concentrations observed on Day 7.

We recommend baseline and periodic on-therapy ECGs are collected for safety assessments in clinical trials irrespective of the results of the TQT study because bradycardia and conduction

defects have been noted in the clinical program (although there have been no cases of Mobitz II or 3rd degree blocks). According to the guidance to investigators in the current IB, vitals signs (including BP, HR and ECG) are being monitored pre-dosing and following a 6-hour observation period after administration of FTY720."

The ICH Guidance E14 states the following:

- If the "thorough QT/QTc study" is positive, analyses of the ECG and adverse event data from certain patient sub-groups are of particular interest, such as:
  - Patients with electrolyte abnormalities (e.g., hypokalemia)
  - Patients with congestive heart failure
  - Patients with impaired drug metabolizing capacity or clearance (e.g., renal or hepatic impairment, drug interactions)
  - Female patients
  - Patients aged <16 and over 65 years

- Even if the "thorough QT/QTc study" is negative, if other evidence of an effect in a patient population from subsequent studies (e.g., marked QT/QTc interval prolongation, TdP) were to emerge, then additional investigation would be needed".

In the case of fingolimod, the TQT could not rule out a >10msec prolongation of the the QT interval at doses of 1.25 and 2.5 mg. Review of the available data (adverse events, ECG and Holter evaluations) from this clinical program does not suggest an increase risk of QT interval prolongation (see section below, Standard ECG data analysis). However, the population at risk for developing QT prolongation was not included in these trials, therefore, a significant effect on the QT interval can not be ruled out in these patients.

- **Standard ECG data analysis**

- ECG upon first dose administration

In study 2201, patients were monitored for 4 hours. Monitoring outcomes, symptomatic bradycardia AE and medications for bradycardia after the first dose were not captured as well or were captured differently than in the phase 3 studies.

Patients in studies D2301, and D2302 (as well as in extension studies D2201E1 and D2302E1) were monitored in the clinic for at least the first 6 hours after taking the first dose of study drug with hourly heart rate and BP. After 6 hours of observation, patients could be discharged if the maximal lowering effect on heart rate had already been observed (i.e. after observing a decrease, heart rate should already have been increasing at the time of discharge), the patient was asymptomatic, and the 6-hour ECG did not show any new relevant abnormality. Patients not meeting the per protocol predefined criteria had to be observed longer until criteria were met (even if it required overnight hospitalization).

In order to avoid unnecessary unblinding, monitoring after the first intake of the study drug was performed under the responsibility of an independent physician called the First Dose

Administrator. This physician reviewed vital signs during 6-hour monitoring, post-dose ECG, assessed discharge criteria at 6 hours post-dose, and managed cardiac events when they occurred. The investigator/treating physician was informed of any SAEs that may have occurred, remaining otherwise blinded to the cardiac events happening on the first day. In addition, patients showing a strong sensitivity to the drug, defined as a heart rate decrease of more than 30% or the presence of symptomatic bradycardia, had to return to the clinic for the same 6-hour monitoring for the second dose of study drug.

Data recorded as part of the first dose administration monitoring included hourly vital signs, ECG, and summaries of bradycardia events, symptoms, and medication. Bradycardia events were defined according to the investigator's clinical judgment and not pre-defined criteria. The following is an analysis of changes in ECG parameters upon first dose in safety pool A (both phase 3 studies).

Table 86. First dose administration experience in safety pool A

	FTY720 1.25 mg (N=849) n (%)	FTY720 0.5 mg (N=854) n (%)	Placebo (N=418) n (%)	Interferon (N=431) n (%)
Discharged at 6 hours	645 (76.0)	700 (82.0)	356 (85.2)	422 (97.9)
Required extended monitoring after 6 hours	153 (18.0)	105 (12.3)	14 (3.3)	6 (1.4)
Hospitalized	23 (2.7)	15 (1.8)	0	2 (0.5)
Required Day 2 monitoring	62 (7.3)	19 (2.2)	3 (0.7)	4 (0.9)
Study drug permanently discontinued	12 (1.4)	2 (0.2)	1 (0.2)	0

Source: ISS. Required extended monitoring after 6 hours: patients who did not meet discharge criteria (i.e. maximal lowering effect on HR already been observed within 6 hours, HR at least 51 bpm, asymptomatic, 6 hour ECG did not show new relevant abnormality). Required Day 2 monitoring: Patients with HR decrease >30% or presence of symptomatic bradycardia

More patients in FTY 1.25 and FTY 0.5 required extended monitoring and hospitalization, particularly the 1.25 mg dose. AE after first dose led to drug discontinuation in 1.4%, 0.2%, 0.2% and 0 subjects in the FTY 1.25, FTY 0.5, placebo and IFN groups.

Table 87. ECG abnormalities upon first dose fingolimod in safety pool A

Timepoint Abnormality type	Finding	FTY720 1.25 mg (N=849) n (%)	FTY720 0.5 mg (N=854) n (%)	Placebo (N=418) n (%)	Interferon (N=431) n (%)
Day 1 pre-dose					
No. of patients with ECG		848	852	418	431
Any abnormality		56 (6.6)	63 (7.4)	33 (7.9)	36 (8.4)
Conduction	Total	34 (4.0)	34 (4.0)	20 (4.8)	25 (5.8)
	LAH	13 (1.5)	15 (1.8)	12 (2.9)	6 (1.4)
	First degree AV block	12 (1.4)	17 (2.0)	6 (1.4)	15 (3.5)
	IVCD	6 (0.7)	2 (0.2)	1 (0.2)	1 (0.2)
	RBBB	3 (0.4)	4 (0.5)	0	2 (0.5)
	IRBBB	2 (0.2)	0	1 (0.2)	1 (0.2)
Ectopy	Total	4 (0.5)	2 (0.2)	0	0

Timepoint Abnormality type	Finding	FTY720 1.25 mg (N=849) n (%)	FTY720 0.5 mg (N=854) n (%)	Placebo (N=418) n (%)	Interferon (N=431) n (%)
	APC	2 (0.2)	0	0	0
	VPC	2 (0.2)	2 (0.2)	0	0
Morphology	Total	1 (0.1)	0	0	0
	LAA	1 (0.1)	0	0	0
	LVH	1 (0.1)	0	0	0
Myocardial infarction	Total	2 (0.2)	1 (0.1)	1 (0.2)	0
	Antero septal MI V1-V4	1 (0.1)	0	0	0
	Septal MI V1, V2, (V3)	1 (0.1)	1 (0.1)	1 (0.2)	0
Rhythm	Total	10 (1.2)	7 (0.8)	6 (1.4)	1 (0.2)
	Ectopic Supraventricular Rhythm	5 (0.6)	2 (0.2)	2 (0.5)	1 (0.2)
	Sinus tachycardia	2 (0.2)	3 (0.4)	4 (1.0)	0
	Junctional rhythm	1 (0.1)	0	0	0
	Other Rhythm	1 (0.1)	2 (0.2)	0	0
	Sinus bradycardia	1 (0.1)	0	1 (0.2)	0
ST segment	Total	3 (0.4)	5 (0.6)	6 (1.4)	0
	Depressed ST segment	3 (0.4)	5 (0.6)	5 (1.2)	0
	Elevated ST segment	0	0	1 (0.2)	0
T waves	Total	10 (1.2)	20 (2.3)	6 (1.4)	10 (2.3)
	Flat T waves	7 (0.8)	13 (1.5)	2 (0.5)	4 (0.9)
	Inverted T waves	3 (0.4)	3 (0.4)	3 (0.7)	5 (1.2)
	Biphasic T waves	0	4 (0.5)	1 (0.2)	1 (0.2)
U waves	Total	0	0	1 (0.2)	0
	Abnormal	0	0	1 (0.2)	0
Day 1 post-dose (6 hours)					
No. of patients with ECG		840	837	413	422
Any abnormality		134 (16.0)	80 (9.6)	26 (6.3)	38 (9.0)
Conduction	Total	108 (12.9)	59 (7.0)	17 (4.1)	19 (4.5)
	First degree AV block	82 (9.8)	39 (4.7)	6 (1.5)	12 (2.8)
	LAH	15 (1.8)	16 (1.9)	9 (2.2)	5 (1.2)
	AV Mobitz I	6 (0.7)	2 (0.2)	0	0
	IVCD	3 (0.4)	2 (0.2)	1 (0.2)	0
	2:1 AV block	2 (0.2)	0	0	0
	IRBBB	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.2)
	RBBB	1 (0.1)	3 (0.4)	0	2 (0.5)
Ectopy	Total	4 (0.5)	2 (0.2)	1 (0.2)	0
	APC	3 (0.4)	0	0	0
	VPC	1 (0.1)	2 (0.2)	1 (0.2)	0
Myocardial infarction	Total	2 (0.2)	1 (0.1)	0	0
	Antero septal MI V1-V4	1 (0.1)	0	0	0
	Septal MI V1, V2, (V3)	1 (0.1)	1 (0.1)	0	0
Rhythm	Total	25 (3.0)	7 (0.8)	3 (0.7)	7 (1.7)
	Sinus bradycardia	19 (2.3)	5 (0.6)	2 (0.5)	0
	Other Rhythm	3 (0.4)	1 (0.1)	0	0
	Ectopic Supraventricular Rhythm	2 (0.2)	0	1 (0.2)	1 (0.2)

Timepoint Abnormality type	Finding	FTY720 1.25 mg (N=849) n (%)	FTY720 0.5 mg (N=854) n (%)	Placebo (N=418) n (%)	Interferon (N=431) n (%)
	Junctional rhythm	1 (0.1)	0	0	0
	Junctional Tachycardia	0	1 (0.1)	0	0
	Sinus tachycardia	0	0	0	6 (1.4)
ST segment	Total	4 (0.5)	2 (0.2)	1 (0.2)	5 (1.2)
	Depressed ST segment	4 (0.5)	2 (0.2)	1 (0.2)	5 (1.2)
T waves	Total	10 (1.2)	17 (2.0)	9 (2.2)	11 (2.6)
	Flat T waves	6 (0.7)	11 (1.3)	3 (0.7)	6 (1.4)
	Inverted T waves	4 (0.5)	4 (0.5)	5 (1.2)	4 (0.9)
	Biphasic T waves	0	2 (0.2)	1 (0.2)	1 (0.2)
U waves	Total	3 (0.4)	0	0	0
	Abnormal	3 (0.4)	0	0	0
Day 1 post-dose (>6 hours)					
No. patients with ECG		61	47	10	14
Any abnormality		18 (29.5)	8 (17.0)	0	1 (7.1)
Conduction	Total	17 (27.9)	7 (14.9)	0	1 (7.1)
	First degree AV block	12 (19.7)	4 (8.5)	0	1 (7.1)
	AV Mobitz I	4 (6.6)	1 (2.1)	0	0
	LAH	2 (3.3)	0	0	0
	IVCD	0	1 (2.1)	0	0
	Prolonged QTc	0	1 (2.1)	0	0
Ectopy	Total	1 (1.6)	1 (2.1)	0	0
	APC	1 (1.6)	0	0	0
	VPC	0	1 (2.1)	0	0
Rhythm	Total	2 (3.3)	0	0	0
	Sinus bradycardia	2 (3.3)	0	0	0
T waves	Total	2 (3.3)	1 (2.1)	0	0
	Flat T waves	2 (3.3)	0	0	0
	Biphasic T waves	0	1 (2.1)	0	0

Source: ISS table 4-51 and PT-Table 10.1-10.Abnormality types are presented alphabetically; findings are sorted within abnormality type by frequency from highest to lowest in the FTY 1.25 mg group. A patient with multiple occurrences of an abnormality is counted only once in the corresponding category. A patient with multiple findings within an abnormality type is counted only once in the total row of this abnormality type.

The incidence of ECG abnormalities at post-dose timepoints was higher than at pre-dose. The most frequently observed findings in the 6 hours post first dose ECG were related to conduction and rhythm disturbances (mostly AVB and sinus bradycardia) and were more frequently reported in the FTY 1.25 mg group compared to the FTY 0.5 mg, placebo and interferon groups. This finding is consistent with the review of SAEs in the Cardiac SOC). A few subjects had second degree AVB (Mobitz 1 and 2:1 AVB) in the 6-hour post dose ECG. Four subjects had second degree AVB among 61 who underwent >6hours post-dose ECG.

Changes from baseline in mean ECG parameters after first dose in safety pool A are presented in the following table.

Table 88. Changes from baseline in ECG parameters after first dose, safety pool A

	FTY720 1.25mg N=849		FTY720 0.5mg N=854		Placebo N=418		Interferon N=431	
Hour post-dose	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**
QT interval (ms)								
6 hours	835	32.8 (21.02)	826	24.8 (20.46)	413	4.1 (18.25)	420	-19.1 (24.73)
> 6 hours	61	28.0 (30.42)	47	27.8 (26.13)	10	4.8 (23.19)	14	-17.0 (26.34)
QTc interval – Bazett (ms)								
6 hours	834	-3.6 (17.84)	826	-1.4 (17.93)	413	1.6 (17.28)	420	3.6 (17.05)
> 6 hours	61	0.4 (17.50)	47	-4.5 (18.38)	10	6.9 (17.02)	14	-1.7 (18.23)
QTc interval – Fridericia (ms)								
6 hours	834	8.8 (14.52)	826	7.6 (14.39)	413	2.5 (13.53)	420	-4.6 (14.75)
> 6 hours	61	9.7 (16.32)	47	6.5 (17.22)	10	6.3 (10.26)	14	-6.9 (17.27)
PR interval (ms)								
6 hours	834	11.3 (23.80)	825	4.5 (16.70)	413	-0.8 (12.17)	420	-3.2 (12.10)
> 6 hours	60	10.7 (25.25)	47	5.1 (16.19)	10	-4.2 (9.83)	14	-4.6 (10.99)
RR interval (ms)								
6 hours	835	172.6 (122.26)	826	122.8 (119.72)	413	11.3 (103.40)	420	-97.5 (123.49)
> 6 hours	61	131.1 (153.19)	47	153.4 (128.08)	10	-8.4 (144.15)	14	-67.2 (118.50)
QRS duration (ms)								
6 hours	835	1.0 (6.84)	826	1.3 (6.76)	413	0.3 (6.56)	420	0.0 (6.91)
> 6 hours	61	1.6 (7.06)	47	-0.1 (7.62)	10	3.5 (5.13)	14	0.6 (8.93)
Heart rate (bpm)								
6 hours	835	-12.0 (8.76)	826	-9.0 (8.87)	413	-1.1 (8.60)	420	9.6 (11.85)
> 6 hours	61	-9.1 (12.96)	47	-10.9 (9.54)	10	0.0 (13.40)	14	6.9 (12.69)

Source: ISS Table 4-52. ECG > 6 hours post dose were done only in patient who meet Day 1 protocol monitoring guidelines [5]

Upon initiation of FTY treatment, there was a decrease in mean heart rate on ECGs at 6 hours and > 6 hours after the first FTY dose (which was done only in subjects who met monitoring guidelines to stay > 6 hours[7]). This decrease in heart rate appeared to be dose dependent but was attenuated on chronic dosing.

There was a prolongation in the mean PR and RR intervals for both FTY groups in the 6 hours or longer post-dose ECGs, consistent with the observed AE of first and second degree AVB.

No relevant change was seen in the mean QRS duration upon first dose.
Mean QTc intervals by Bazett's correction show decreases from baseline (pre-dose) in both FTY

[7] Patients might be discharged after 6 hours only if all of the following criteria were met: Heart rate at least 51 bpm; HR greater than 80% of baseline value; HR must not be the lowest hourly value measured during the observation period; patients must have no symptoms of bradycardia; ECG at 6 hours should not show any new significant abnormalitites other than sinus bradycardia not observed at the pre-dose ECG)

groups on the 6 hours post-dose ECG. However, mean QTc intervals by Fridericia's correction, which provide a more accurate correction in subjects with heart rates below 60 bpm, show increases from baseline in both FTY groups on the 6 hours post-dose ECGs (8.8 msec, 7.6 msec and 2.5 msec in the FTY 1.25, FTY 0.5 and placebo groups). At >6 hours post dose, increases in QTc intervals adjusted with Fridericia's formula were seen in both FTY groups and placebo. (The FTY groups continued to show small increases in QTc intervals by Fridericia's correction on chronic dosing, although the increases from baseline were less than 4 ms at all timepoints.)

- ECGs with chronic use

ECG evaluations were done at baseline, 1 week, 1 month, 3 months, 6 months and 12 months for studies 2301 and 2302; plus at 18 and 24 months for study 2301; and baseline, 2 weeks, 1 month, and 6 months for 2201. Except data for week 1-2 and 3 months, ECG data was pooled for analysis in all pre-specified safety populations. I will present the data from safety pool D.

The most common abnormalities at baseline were conduction abnormalities (in particular first degree AV block and left anterior hemiblock) and T wave abnormalities (flat T waves). Four subjects had evidence of a prior myocardial infarction (2 on FTY 1.25, 1 on FTY 0.1 and one on placebo). The number of patients with abnormal ECGs in safety pool D is presented in the following table.

Table 89. **Number of patients with abnormal ECG parameters in safety pool D by visit**

	FTY **1.25 (N=943) n (%)**	**FTY 0.5 (N=854) n (%)**	**Placebo (N=511) n (%)**	**Interferon (N=431) n (%)**
Baseline				
Number of patients with ECG	942	852	511	431
Any abnormality	62 (6.6)	63 (7.4)	40 (7.8)	36 (8.4)
Conduction	34 (3.6)	33 (3.9)	23 (4.5)	25 (5.8)
Month 1				
Number of patients with ECG	942	852	511	431
Any abnormality	68 (7.4)	65 (7.8)	38 (7.6)	33 (8.0)
Conduction	39 (4.3)	37 (4.4)	24 (4.8)	23 (5.6)
Month 6				
Number of patients with ECG	847	792	478	393
Any abnormality	71 (8.4)	64 (8.1)	35 (7.3)	44 (11.2)
Conduction	36 (4.3)	33 (4.2)	21 (4.4)	26 (6.6)
Month 12				
Number of patients with ECG	698	750	356	359
Any abnormality	64 (9.2)	69 (9.2)	32 (9.0)	37 (10.3)
Conduction	24 (3.4)	34 (4.5)	20 (5.6)	24 (6.7)
Month 24				
Number of patients with ECG	300	343	311	0
Any abnormality	33 (11.0)	39 (11.4)	34 (10.9)	0 (0.0)
Conduction	12 (4.0)	15 (4.4)	16 (5.1)	0 (0.0)

Source: ISS Post text table 7.3-4.

As seen in this table, the total number of patients with ECG abnormalities increased over time, but the percentage was similar in all treatment groups.
Analyses of number of patients with ECG changes over time did not reveal major differences between treatment groups in any of the areas that were evaluated (conduction, morphology, ectopy, ST changes, T wave abnormalities, U waves), however, by looking at the tables it is unclear if all the events observed at certain timepoint are the same as those at earlier timepoints, or not, as the pool of patients having ECGs changes (decreases) over time.

- Mean changes from baseline in PR and QRS intervals in safety pool D:

There were no relevant changes from baseline in PR and QRS duration for FTY 0.5 mg. At the one month ECG, there was a small increase from baseline in the point estimate for the PR interval (2 msec for FTY 5 and 1.25 mg), and a small decrease in the point estimate for the QRS interval (<1 msec for FTY 5 and 1.25mg), with large standard deviations. At the 12 month ECG and beyond, the duration of PR and QRS intervals was similar to that of placebo (data not shown).

- QT changes with chronic use

Evaluation of QT changes with chronic use did not show relevant differences among treatment groups. Again, it is unclear if some of the events observed at a certain timepoint are new or correspond to those observed at prior timepoints. Changes from baseline in QTc parameters by visit in safety pool D are presented in the following table.

Table 90. Changes from baseline in ECG parameters by visit for safety pool D

	FTY720 5 mg (N = 94) n (%)		FTY720 1.25 mg (N = 943) n (%)		FTY720 0.5 mg (N = 854) n (%)		Placebo (N = 511) n (%)		Interferon (N = 431) n (%)	
Parameter Visit	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
QTc interval (Bazett) (ms)										
Month 1	92	2.9 (16.84)	915	0.3 (18.27)	834	0.9 (17.80)	498	-1.3 (18.46)	414	-1.4 (19.92)
Month 6	82	4.7 (19.42)	845	1.5 (18.27)	792	1.5 (18.55)	478	-1.2 (19.46)	392	-1.0 (19.42)
Month 12			697	1.6 (18.81)	748	2.3 (18.32)	356	-1.1 (18.88)	358	0.9 (19.39)
Month 18			321	0.9 (17.75)	366	2.3 (19.25)	332	-2.1 (18.22)		
Month 24			299	-0.5 (17.53)	342	2.0 (19.32)	310	-2.0 (17.62)		
Treatment endpoint	93	3.1 (16.42)	912	1.1 (19.28)	841	1.8 (18.59)	502	-1.2 (19.64)	423	0.5 (19.73)
QTc interval (Fridericia) (ms)										
Month 1	92	6.1 (14.45)	915	2.1 (14.92)	834	3.2 (14.49)	498	0.9 (14.19)	414	0.2 (15.50)
Month 6	82	6.1 (15.06)	845	2.7 (15.30)	792	2.7 (15.34)	478	0.7 (15.63)	392	1.3 (15.09)
Month 12			697	3.0 (15.88)	748	3.8 (15.71)	356	0.5 (15.09)	358	3.2 (15.20)
Month 18			321	2.8 (14.88)	366	3.7 (15.88)	332	-0.1 (14.70)		
Month 24			299	1.4 (14.79)	342	3.0 (16.12)	310	0.1 (14.80)		
Treatment endpoint	93	5.6 (12.82)	912	2.9 (16.04)	841	3.5 (15.64)	502	0.9 (16.15)	423	2.5 (15.29)
Heart rate (bpm)										
Month 1	92	-3.6 (9.92)	915	-2.1 (8.94)	834	-2.6 (9.12)	498	-2.4 (9.81)	414	-1.5 (10.74)
Month 6	82	-1.7 (9.95)	845	-1.4 (9.32)	792	-1.4 (9.23)	478	-2.0 (10.88)	392	-2.3 (10.46)
Month 12			697	-1.6 (9.88)	748	-1.7 (9.44)	356	-1.7 (10.03)	358	-2.4 (10.16)
Month 18			321	-2.0 (8.85)	366	-1.7 (9.52)	332	-1.9 (10.39)		
Month 24			300	-2.2 (9.12)	342	-1.3 (9.57)	310	-2.2 (10.10)		
Treatment endpoint	93	-2.8 (10.12)	912	-2.0 (9.82)	841	-2.0 (9.44)	502	-2.2 (10.83)	423	-2.1 (10.64)

Change from baseline = timepoint – baseline. - Treatment endpoint includes the last non-missing value on treatment. - For each ECG, only patients with a value at both baseline and post-baseline are included. Source: [ISS PT-Table 7.3-2 and Table 22-1, ISS addendum 1]

Table 91. Outlier analysis of QT changes in safety pool D

		FTY720 5 mg (N=94) n %	FTY720 1.25 mg (N=943) n %	FTY720 0.5 mg (N=854) n %	Placebo (N=511) n %	Interferon (N=431) n %
Month 1						
No. of patients with any QT interval value		92	916	835	498	414
Bazett Correction	Maximum increase from baseline					
	< 30 msec	86 (93.5)	858 (93.7)	784 (93.9)	470 (94.4)	383 (92.5)
	30-60 msec	6 (6.5)	55 (6.0)	49 (5.9)	28 (5.6)	30 (7.2)
	> 60 msec	0 (0.0)	2 (0.2)	1 (0.1)	0 (0.0)	1 (0.2)
	Number of patients with QTc values					
	> 450 ms (male) or 470 ms (female)	0 (0.0)	3 (0.3)	4 (0.5)	2 (0.4)	2 (0.5)
	> 500 ms (male) or 520 ms (female)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

		FTY720 5 mg (N=94) n %	FTY720 1.25 mg (N=943) n %	FTY720 0.5 mg (N=854) n %	Placebo (N=511) n %	Interferon (N=431) n %
Bazett Correction	Maximum increase from baseline					
	< 30 msec	0	643 (92.1)	706 (94.4)	336 (94.4)	336 (93.9)
	30-60 msec	0	52 (7.4)	40 (5.3)	20 (5.6)	20 (5.6)
	> 60 msec	0	2 (0.3)	2 (0.3)	0 (0.0)	2 (0.6)
Bazett Correction	Number of patients with QTc values					
	> 450 ms (male) or 470 ms (female)	0	5 (0.7)	4 (0.5)	1 (0.3)	1 (0.3)
	> 500 ms (male) or 520 ms (female)	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fridericia Correction	Maximum increase from baseline					
	< 30 msec	0	661 (94.7)	707 (94.5)	349 (98.0)	345 (96.4)
	30-60 msec	0	35 (5.0)	40 (5.3)	7 (2.0)	12 (3.4)
	> 60 msec	0	1 (0.1)	1 (0.1)	0 (0.0)	1 (0.3)
	Number of patients with QTc values					
	> 450 ms (male) or 470 ms (female)	0	0 (0.0)	3 (0.4)	0 (0.0)	0 (0.0)
	> 500 ms (male) or 520 ms (female)	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Month 24						
No. of patients with any QT interval value		0	300	342	310	0

Bazett Correction	Maximum increase from baseline					
	< 30 msec	0	286 (95.3)	316 (92.4)	297 (95.8)	0
	30-60 msec	0	13 (4.3)	25 (7.3)	12 (3.9)	0
	> 60 msec	0	0 (0.0)	1 (0.3)	1 (0.3)	0
Bazett Correction	Number of patients with QTc values					
	> 450 ms (male) or 470 ms (female)	0	0 (0.0)	3 (0.9)	0 (0.0)	0
	> 500 ms (male) or 520 ms (female)	0	0 (0.0)	0 (0.0)	0 (0.0)	0
Fridericia Correction	Maximum increase from baseline					
	< 30 msec	0	291 (97.0)	323 (94.4)	302 (97.4)	0
	30-60 msec	0	8 (2.7)	18 (5.3)	8 (2.6)	0
	> 60 msec	0	0 (0.0)	1 (0.3)	0 (0.0)	0
	Number of patients with QTc values					
	> 450 ms (male) or 470 ms (female)	0	0 (0.0)	1 (0.3)	0 (0.0)	0
	> 500 ms (male) or 520 ms (female)	0	0 (0.0)	0 (0.0)	0 (0.0)	0
Overall Worst Case *						
No. of patients with any QT interval value		94	931	848	505	426
Bazett Correction	Number of patients with QTc values					
	> 450 ms (male) or 470 ms (female)	0 (0.0)	13 (1.4)	13 (1.5)	6 (1.2)	4 (0.9)
	> 500 ms (male) or 520 ms (female)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Number of patients with QTc values					
Fridericia correction	> 450 ms (male) or 470 ms (female)	0 (0.0)	3 (0.3)	5 (0.6)	0 (0.0)	1 (0.2)
	> 500 ms (male) or 520 ms (female)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

* Overall Worst Case counts the worst case over all post-baseline visit timepoints per patient. Source: [ISS PT-Table 7.3-3]

Of note, the TQTc study was not able to exclude the possibility of QTc prolongation >10 msec. The clinical database does not suggest an association with QTc prolongation.

A total of 9 subjects were identified to have QTc Fridericia correction >450 msec (male) or 470 ms (female) in the ISS. As per information submitted on April 29, 2010, they were 6 females (2 on FTY720 1.25 mg, 3 on FTY720 0.5 mg, and one on interferon) and 3 males (one on FTY720 1.25 mg and 2 on FTY720 0.5 mg). Of these 9 cases, only 2 had cardiac AEs at any time during the study both at the 1.25 mg dose, but none was the kind associated with prolonged QTc (2301/0304/00018, cardiac valve incompetence; and 2302/0423/00001, first degree AV block).

7.4.5 Special Safety Studies

The following pre-scheduled special safety evaluations were incorporated into the phase 2 and 3 protocols:
1. 24-hour Holter monitoring
2. Echocardiogram
3. Chest high resolution computerized tomography (HRCT)
4. Pulmonary function tests

5. Ophthalmologic evaluations
6. Dermatologic evaluations

1) **24 hour Holter monitoring ((**2201, 2302 and 2309)

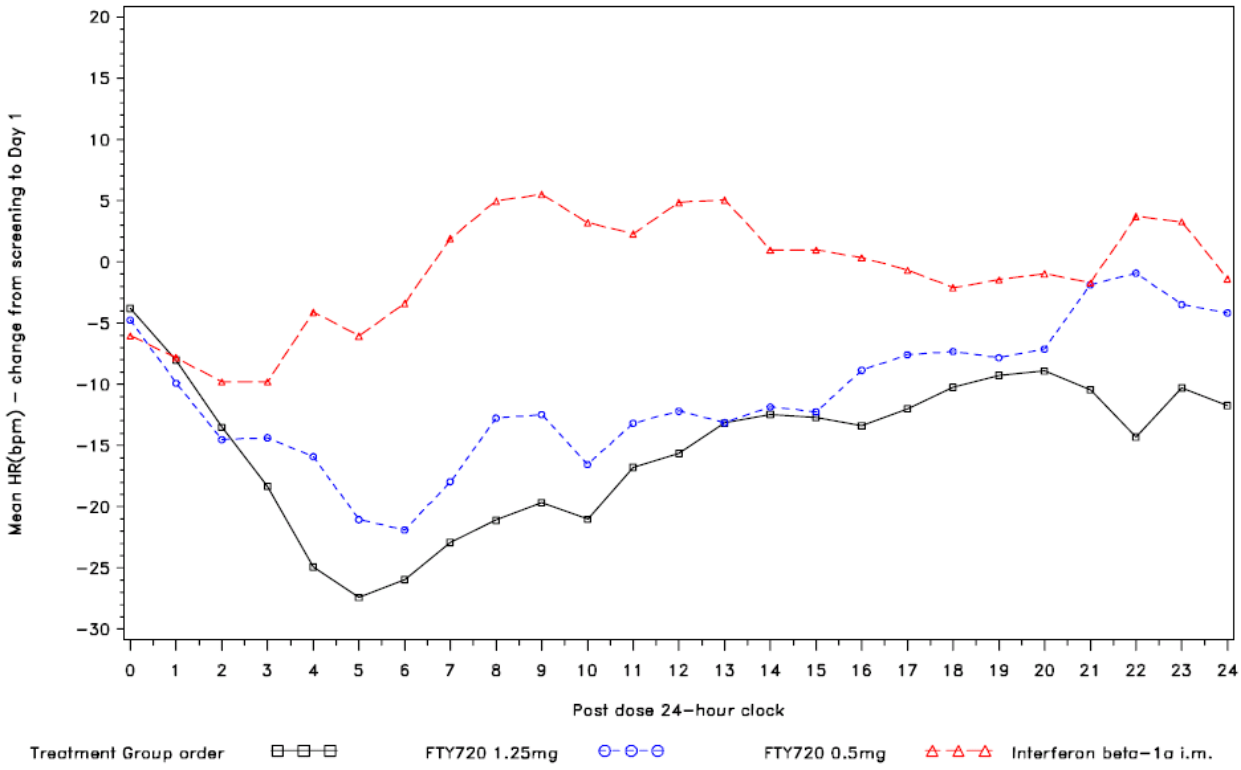
24-hour Holter ECGs were to be done at screening, Day 1 and Month 3 in all patients in study 2309 and at selected sites in study 2302 (all US sites and selected sites outside the US). The Holter ECGs data were collected and analyzed by a central reader. Holter was also done in study 2201 in some subjects. There was no Holter monitoring in study 2301.

- **Holter ECG in study D2302**

In total, 129 patients (42–45 per treatment group) participated in the 24-hour Holter monitoring. On Day 1, consistent with the observations of pulse and heart rate on the 6-hour ECGs, a decline in mean hourly heart rate was observed in the FTY720 groups as early as 1 hour post-dose, reaching a maximum decrease at 5 hours post-dose in the FTY720 1.25 mg group (mean drop of approximately 28 bpm) and at 6 hours post-dose in the FTY720 0.5 mg group (mean drop of approximately 22 bpm). The corresponding mean heart rate at 5 hours post-dose was 67.4 bpm for the FTY720 1.25 mg and and 67.6 bpm for the 0.5 mg groups. At the Month 3 Visit, the mean hourly heart rates were similar across the groups at all post-dose hours.

Graphical presentations of mean hourly heart rate by 24 hour Holter monitoring are as follows:

Figure 2. Line plot of change from screening to Day 1 in Holter hourly mean heart rate, study 2302



The most commonly reported finding was frequent ventricular premature complexes (4.8%, 4.8% and 2.2% in FTY 1.25, 0.5 and IFN, respectively) but in fewer patients at Day 1 than at screening in each group (7.1%, 4.8% and 6.7%, respectively).

Nonsustained ventricular tachycardia was observed in two patients on Day 1, one in each FTY720 group. For patient 2302-0514-00001 receiving FTY 0.5 mg, the nonsustained ventricular tachycardia was also reported as an AE along with angina pectoris which resolved on the same day as onset. Patient 2302-0505-00010 receiving FTY 1.25 mg appeared to be asymptomatic, with no AEs reported on Day 1. Both patients had normal Holter findings at Month 3. Seven subjects had second degree AVB (4 had Mobitz I [9.5%] and 3 had 2:1 AVB [7.1%] in the FTY 1.25 mg group). There was also intermittent ectopic atrial rhythm in one subject in the 1.25 mg group (2.4%).

There were no cases of sustained supraventricular tachycardia, ventricular tachycardia, ventricular fibrillation or flutter, Torsades de Pointes, atrial fibrillation or flutter, high grade or complete AVB.

At the month 3 Holter, again, frequent PVCs and non sustained ventricular tachycardia (3-10 beats) were observed with FTY and IFN, without clinical complaints at the time of the event.

- **Holter in study 2201**

In study 2201, 96 patients had 24 hour Holter monitoring (approximately 30 subjects per treatment group). Mean hourly heart rate is presented as follows.

Table 92. Mean hourly rate (bpm) for 24 hour Holter in study 2201

Time Post-Dose	FTY720 5 mg (N=34) † mean (SD)	FTY720 1.25 mg (N=31) † mean (SD)	Placebo (N=31) † mean (SD)	P-value*	P-value*
00:00	72.3 (11.16)	78.7 (12.45)	79.9 (10.80)	a=0.710	b=0.015
01:00	66.0 (12.08)	75.0 (11.38)	83.4 (11.70)	a=0.011	b=<0.001
02:00	60.2 (11.28)	66.6 (9.80)	81.4 (10.32)	a <0.001	b <0.001
03:00	58.7 (9.85)	63.0 (10.21)	82.0 (10.86)	a <0.001	b <0.001
04:00	57.4 (7.93)	63.2 (10.58)	82.3 (9.24)	a <0.001	b <0.001
05:00	59.9 (8.28)	65.0 (9.22)	81.1 (10.07)	a <0.001	b <0.001
06:00	62.5 (10.85)	67.9 (8.51)	83.2 (13.02)	a <0.001	b <0.001
07:00	63.3 (15.37)	66.0 (9.09)	82.0 (11.23)	a <0.001	b <0.001
08:00	63.8 (14.15)	65.5 (9.53)	80.5 (11.93)	a <0.001	b <0.001
09:00	63.3 (14.67)	62.7 (9.10)	81.2 (13.72)	a <0.001	b <0.001
10:00	61.4 (14.75)	61.6 (9.59)	79.3 (12.13)	a <0.001	b <0.001
11:00	60.2 (13.85)	62.2 (9.07)	77.3 (11.13)	a <0.001	b <0.001
12:00	57.5 (12.04)	61.3 (9.34)	75.7 (10.13)	a <0.001	b <0.001
13:00	55.6 (10.17)	60.4 (8.29)	72.8 (9.48)	a <0.001	b <0.001
14:00	54.7 (9.33)	59.0 (9.14)	70.8 (9.24)	a <0.001	b <0.001
15:00	54.6 (9.68)	59.1 (11.06)	70.5 (9.88)	a <0.001	b <0.001
16:00	53.8 (9.65)	60.0 (11.61)	69.8 (9.43)	a=0.001	b <0.001
17:00	53.3 (9.42)	61.9 (13.31)	69.4 (10.88)	a=0.028	b <0.001
18:00	54.5 (9.65)	62.0 (11.19)	68.9 (10.86)	a=0.024	b <0.001
19:00	56.3 (9.69)	63.4 (11.20)	69.7 (9.30)	a=0.029	b <0.001
20:00	57.5 (9.36)	66.8 (11.99)	72.4 (10.70)	a=0.077	b <0.001
21:00	58.8 (9.75)	67.8 (13.82)	75.9 (12.84)	a=0.032	b <0.001
22:00	63.2 (11.74)	66.3 (11.64)	78.0 (12.14)	a=0.001	b <0.001
23:00	65.4 (13.79)	68.1 (11.92)	82.5 (13.47)	a <0.001	b <0.001
24:00	70.4 (10.16)	68.4 (14.75)	86.9 (18.81)	a=0.037	b=0.053
Overall	60.4 (8.22)	65.5 (7.68)	77.3 (7.10)	a <0.001	b <0.001

* P- values represent pairwise comparisons, a= FTY720 1.25mg vs Placebo; b= FTY720 5.0mg vs Placebo
† Patients are summarized if they are in the Holter Monitor population

Source: Table 4-23, ISS.

This table shows a dose-related response in decreased heart rate, with FTY 5 mg showing the most decrease. For the 5 mg dose there seems to be a dip at 4 hours, with a HR of 57.4 bpm, and another dip at 18 hours with HR of 53.3 bpm (overall HR over 24 hours= 60.4 bpm). For the FTY 1.25 mg dose, the maximum decrease was at 12 hours, with a mean HR of 59 bpm at that time (mean overall HR of 65.5 bpm). For placebo the maximum decrease was at 17 hours, with a HR of 69.4 bpm (mean overall HR = 77.3 bpm). The mean hourly HR by Holter from time post dose at Month 3 was no different from placebo.

Notable Holter findings in study 2201 are summarized in the following table.

Table 93. Summary of notable Holter findings, study 2201

Finding	FTY720 5 mg n (%)	FTY720 1.25 mg n (%)	Placebo n (%)
Baseline (n):	24	28	23
Sinus pause 2-3 seconds	0	0	0
Sinus pause >3 seconds	0	0	0
2nd degree AV block	1 (4.2)	2 (7.1)	0
Sustained bradycardia	0	0	0
Day 1 (n):	28	27	31
Sinus pause 2-3 seconds	3	1	0
Sinus pause >3 seconds	0	0	0
2nd degree AV block	5 (17.9)	3 (11.1)	0
Sustained bradycardia	1 (3.6)	0	0
Month 3 (n):	28	26	26
Sinus pause 2-3 seconds	0	0	0
Sinus pause >3 seconds	0	0	0
2nd degree AV block	0	0	0
Sustained bradycardia	0	0	0

Source: ISS Table 4-25. Patients are summarized if they are in the Holter monitor population.

On Day 1 Holter monitoring, a sinus pause of a maximal duration of 3 seconds was reported in 1 FTY720 5 mg patient and sinus pauses of a maximal duration of 2 seconds were reported in 1 patient on FTY720 1.25 mg and 2 patients on FTY720 5 mg. No sinus pauses were observed during the Month 3 Holter monitoring. Further evaluation of the events showed that the reported sinus pauses were not "real" sinus pauses but non-conducting P waves in the context of a second degree AV block (3 events) or a sinus arrhythmia superimposed onto a sinus bradycardia (1 event). No sinus pauses lasting more than 3 seconds were reported.

There was no second degree AV block Mobitz II or third degree AV block on Day 1. Of the 8 patients with second degree AV block Mobitz I on Day 1, one patient in each of the FTY720 groups had a second degree AV block Mobitz I also in the baseline Holter. No patient had second or third degree AV block at Month 3 Holter monitoring. There were no findings in the Holters suggestive of ischemic events.

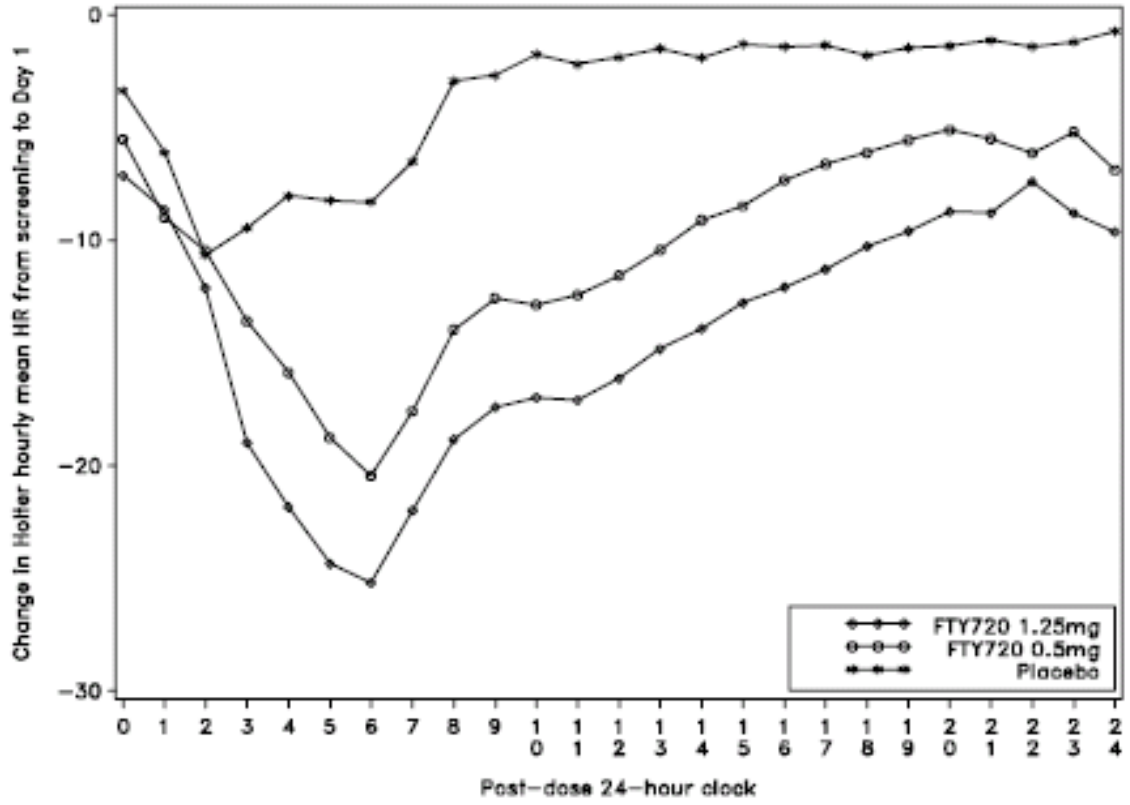
- **Holter ECG in study D2309**

Results of 24-hour Holter ECG evaluations are available for a total of 1075 patients (366 on FTY720 1.25 mg, 356 on FTY720 0.5 mg, 353 on placebo) from study D2309.

The line plot of change from baseline in hourly mean heat rate in study 2309 is presented as follows:

Figure 3. 24 hour Holter in study 2309

Figure 2-1 Line plot of change in Holter hourly mean heart rate (bpm) from screening to Day 1 by post-dose 24-hour clock (Holter ECG analysis set in study D2309)



Source: Special Safety Interim Report, original submission.

- Evaluation of Holter abnormalities

In study D2309, second degree AV blocks (Mobitz I only) were seen in approximately 1% of patients in all treatment groups during 24-hour monitoring before starting study drug. Upon treatment initiation, second degree AV blocks (Mobitz I or 2:1 blocks) were observed 6.6% of subjects on FTY 1.25, 3.4% of those on FTY 0.5 and 2.0% of those on placebo. For the majority of patients on FTY720, the second degree AV blocks were first seen within 6 hours post-first dose, whereas for the placebo-treated patients, these events first occurred >12 hours post-dose during the night.

Bradycardia, defined as average heart rate of 40 bpm for any one hour during 24-hour Holter monitoring, was observed in 1.4% of patients on FTY 1.25 mg, 0.3% of those on FTY 0.5 mg and none on placebo, after the first dose only.

Mobitz I, 2:1 AV block and bradycardia within 6 hours of the first dose of FTY 1.25 mg were reported as SAEs for 3 patients who were symptomatic and hospitalized for observation. They fully recovered by Day 2 and discontinued study drug.

One patient on FTY720 0.5 mg had ventricular tachycardia during Holter monitoring on Day 1 (scheduled) and Day 44 (unscheduled) which was reported as an SAE. The patient was asymptomatic, however study drug was discontinued on Day 65 due to this event. A repeat Holter 33 days after the last dose of study drug was normal.

At Month 3, neither Mobitz I nor 2:1 AV block was observed in the FTY720-treated patients, whereas Mobitz I occurred in 4 (1.1%) of patients on placebo. There was no evidence of newly occurring high grade AV blocks, torsades de pointes, ventricular fibrillation or flutter with FTY720 treatment.

Table 2-5 **Number (%) of patients with predefined Holter ECG findings by finding, visit and treatment (Holter ECG analysis set in study D2309)**

	Screening			Day 1			Month 3		
Predefined Holter ECG finding	FTY720 1.25 mg N=366 n (%)	FTY720 0.5 mg N=356 n (%)	Placebo N=353 n (%)	FTY720 1.25 mg N=366 n (%)	FTY720 0.5 mg N=356 n (%)	Placebo N=353 n (%)	FTY720 1.25 mg N=366 n (%)	FTY720 0.5 mg N=356 n (%)	Placebo N=353 n (%)
Frequent VPCs	28 (7.7)	31 (8.7)	30 (8.5)	29 (7.9)	30 (8.4)	25 (7.1)	24 (6.6)	27 (7.6)	29 (8.2)
Non-sustained VT 3-10 beats	4 (1.1)	2 (0.6)	3 (0.8)	6 (1.6)	6 (1.7)	4 (1.1)	6 (1.6)	2 (0.6)	5 (1.4)
Torsade de pointes	0	0	0	1 (0.3)*	0	0	0	0	0
Frequent short episodes of non-sustained SVT	0	1 (0.3)	2 (0.6)	2 (0.5)	2 (0.6)	4 (1.1)	0	0	2 (0.6)
Atrial fibrillation	0	0	1 (0.3)	0	0	0	0	0	0
Mobitz I (Wenckebach) 2nd degree AV block	4 (1.1)	4 (1.1)	4 (1.1)	24 (6.6)	12 (3.4)	7 (2.0)	0	0	4 (1.1)
2:1 AV block	0	0	0	12 (3.3)	6 (1.7)	0	0	0	0
High grade AV block	0	0	0	1 (0.3)*	0	0	0	0	0
Complete heart block	0	0	0	1 (0.3)*	0	0	0	0	0
Pause > 3.0 seconds	0	0	1 (0.3)	1 (0.3)	0	0	0	0	0
Average heart rate ≤40 for any one hour †	0	0	0	5 (1.4)	1 (0.3)	0	0	0	0
Marked sinus bradycardia (HR < 30)	0	1 (0.3)	0	0	0	0	0	0	0
Intermittent ectopic atrial rhythm	1 (0.3)	4 (1.1)	5 (1.4)	0	4 (1.1)	4 (1.1)	5 (1.4)	1 (0.3)	1 (0.3)
Intermittent junctional rhythm	1 (0.3)	0	1 (0.3)	2 (0.5)	0	1 (0.3)	0	0	0
Other	29 (7.9)	23 (6.5)	26 (7.4)	32 (8.7)	33 (9.3)	31 (8.8)	30 (8.2)	30 (8.4)	42 (11.9)
Nonsustained VT >10 beats, Sustained VT, Ventricular fibrillation, Ventricular flutter, Atrial flutter, Mobitz II AV block **	0	0	0	0	0	0	0	0	0

ECG = electrocardiogram; SVT = supraventricular tachycardia; VPC = ventricular premature complex; VT = ventricular tachycardia, HR = heart rate
* Patient 0537-00001: abnormalities occurred prior to study drug - refer to textual narrative in Section 2.2.3.
** All predefined Holter ECG findings for which there were no cases at any time point.
† For Patient 0567-00018 in the FTY720 1.25 mg group, the Holter ECG finding on day 1 of "Average heart rate ≤40 for any one hour" is counted twice, once in the "Average heart rate ≤40 for any one hour" category of predefined findings and once in the "Other" findings, due to a data entry error in the clinical database.

Source: PT-Table 14.3-2.6, PT-Listing 14.3-2.1

As noted in this table, several patients had an abnormal Holter at screening. In response to the FDA request for information the applicant clarified that these patients entered the study, and only one discontinued on Day 1 due to a SAE of bradycardia and 2:1 AV block (2309 559 0041, who had Mobitz 1 at screening). A few patients discontinued from the study for non-cardiac reasons and the others are still receiving treatment in the trial (Source: Response submitted 5/17/10)

> *In summary, Holter monitoring from the three studies show a drop in heart rate that is dose related. For the FTY 0.5 mg dose, the maximum change from baseline was around 20-22 bpm at 6 hours post dose in both, 2302 and 2309. By the end of the 24 hour period, the mean HR was similar to that at pre-dose.*
>
> *Average heart rate ≤40 bpm for any hour was observed in 5 (1.4%) and 1 (0.3%) of patients in the FTY 1.25 and FTY 0.5 during the first 24 hour Holter, but not at the 3 months Holter. The risk of second degree AV block (Wenckeback and 2:1*

block) was higher in the FTY groups, with evidence of a dose response during the first 24 hour Holter, but not at the 3 months Holter. There were no cases of non-sustained VT> 10 bpm, sustained VT, ventricular fibrillation/fluter, atrial fibrillation/flutter, Mobitz II AV block or complete AV block.

2) Echocardiography evaluations

- Echocardiography (2302 and 2309)

Echocardiography (echo) assessments were performed in studies 2302 (1-year, IFN-controlled) and 2309 (2-year, placebo-controlled) at selected US sites at Screening, Month 3, and Month 12. In 2309 there was also done at Month 24. They included assessment of myocardial function and estimation of pulmonary arterial pressure by echocardiography-doppler. Data were collected and analyzed by a central reader who was blinded to treatment. The original pooled echo analysis population included 183 subjects (152 subjects from study 2309 and 31 from 2302). At the time of the interim analysis data cut-off, there were 140 subjects with a Month 3, 84 with a Month 12 and 17 with a Month 24 echocardiography assessment. At the time of the Updated Special Safety interim report, the total number of patients with echocardiograms at Month 12 is 101 and at Month 24 is 31. Analyses were presented for the individual studies as well as pooled.

No clinically meaningful changes were found in the analyses of mean changes from baseline and outlier analyses in left ventricular ejection fraction, cardiac output, cardiac index, stroke volume, LV end diastolic and systolic volume, left posterior wall thickness or inter-ventricular wall thickness (data not shown). A small increase from baseline (approximately 10%) in Left atrial volume was observed. The clinical significance of this small change is unclear. The following table shows changes from baseline for the estimated pulmonary artery pressure (PaP) for the pooled echo analysis set (Updated report).

Table 94. Change from baseline for estimated pulmonary artery pressure (mm(Hg), pooled echo analysis set.

Visit Treatment	n*	Baseline Mean (SD)	Visit Mean (SD)	Change from baseline Mean (SD)	 Median	 Range
Estimated pulmonary artery pressure (mmHg)						
Month 3 †						
FTY720 1.25 mg (N=71)	15	26.26 (2.951)	27.30 (3.415)	1.04 (3.364)	0.70	-4.8 - 7.4
FTY720 0.5 mg (N=69)	16	27.09 (3.705)	27.91 (4.307)	0.82 (4.465)	0.50	-7.0 - 13.3
Placebo (N=57)	9	30.30 (3.136)	28.16 (4.555)	-2.14 (2.468)	-2.10	-5.8 - 1.6
Interferon beta (N=11)	4	27.63 (4.033)	25.45 (3.389)	-2.18 (2.871)	-1.15	-6.4 - 0.0
Month 12 †						
FTY720 1.25 mg (N=71)	11	26.13 (3.593)	27.43 (7.692)	1.30 (6.787)	-1.00	-4.2 - 20.1
FTY720 0.5 mg (N=69)	13	27.42 (2.573)	27.70 (4.127)	0.28 (3.791)	-0.70	-5.6 - 9.3
Placebo (N=57)	5	26.04 (4.337)	24.82 (2.955)	-1.22 (4.209)	-0.80	-7.0 - 3.8
Interferon beta (N=11)	4	25.08 (4.472)	26.63 (2.611)	1.55 (2.791)	1.80	-1.7 - 4.3
Last post-baseline †						
FTY720 1.25 mg (N=71)	17	25.97 (2.956)	27.93 (6.837)	1.96 (5.863)	1.00	-4.2 - 20.1
FTY720 0.5 mg (N=69)	20	26.87 (3.635)	28.11 (3.975)	1.24 (3.993)	2.10	-7.0 - 9.3
Placebo (N=57)	11	28.81 (4.345)	27.28 (4.444)	-1.53 (2.111)	-1.30	-4.5 - 1.6
Interferon beta (N=11)	5	26.24 (4.668)	26.20 (2.453)	-0.04 (4.299)	0.20	-6.4 - 4.3

Source: Table 3-4, Special safety interim report update 4/21/10. Only patients with evaluable data at both baseline and the post-baseline visit are included in the summaries. † At month 3, month 12 and the last post-baseline assessment up to cut-off date of 10-Mar-2010, data from patients in study D2309 ad D2302 are included. Only patients from study D2309 contributed data at month 24 (8 patients total, data not shown). Normal range for estimated systolic pulmonary artery pressure is 15 to 25 mmHg.

> *A small increase in mean values for systolic pulmonary artery pressure was observed in this database in the last post-baseline analysis, for both FTY 1.25 and FTY 0.5 mg, as compared to a small decrease on placebo (3 mmHg difference with placebo). The clinical significance of these small changes is unclear. Echocardiography only provides an estimate of the pulmonary pressure value and requires that some degree of tricuspid regurgitation be present. Pulmonary artery pressure could not be estimated in 2/3 of patients in this database because they did not have tricuspid regurgitation.*

One patient in the echo safety population discontinued from study 2309 because of pulmonary hypertension that improved after drug discontinuation (2309 0528 00003, case was discussed under AE leading to drug discontinuation in the Cardiac SOC, study 2309). Additional information on this patient was submitted on 5/27/10 at the FDA request, as follows:

> She developed mild hypertension, later diagnosed as labile hypertension. Then she developed shortness of breath. PFT found diminished PE max that was considered to be severe. The echography at 12 months showed mild diastolic left ventricular dysfunction, thickening of the anterior and posterior mitral valve leafleats, moderate to severe tricuspid regurgitation (which had worsened from baseline) with mixomatous changes of both the mitral and tricuspid valves. These events were reported as non-serious adverse events. Pulmonary hypertension was diagnosed when the cardiologist saw the results of the 12-month echocardiogram (increase in PaP of 20mmHg and worsening tricuspid regurgitation). Follow up echocardiogram done 2 months after drug discontinuation showed mildly dilated left and right atrium, with normal LV ejection fraction and mild tricuspid regurgitation. There is no mention of abnormal mitral or tricuspid valve morphology.

A subject with a SAE of papillary muscle disorder was also identified from study 2309 during a non-scheduled echochardiogram done for evaluation of tachycardia (identified by Holter monitoring). The echo showed a questionable mass initially thought to be an atrial mixoma or lymphoma and later determined to be a prominent papillary muscle. The patient did not have a baseline echo because he was not part of the echo safety population, and was eventually discontinued from the trial because of a new diagnosis of asthma. There are no follow up echocardiograms in this patient.

As per the updated Echo dataset submitted with the SUR, in addition to the patient with diagnosis of pulmonary hypertension mentioned above two patients had an increase from baseline in systolic PaP > 10 mmHg in study 2309 (2309 0567 00002 and 2309 0599 00002). As per the listings submitted with the Updated special safety interim report, they were asymptomatic.

- 2309 0567 0002, on FTY 0.5 mg. PaP increased by 13.3 mmHg (from 28.30 at screening to 41.6 at the 3 months echo). She had AE reports of mitral and pulmonic regurgitation

but no symptoms. At month 12 Her PaP was 22.7. One year later, at the end of study, the PaP was not measurable. As per the patient profile submitted on May 2010 the patient had not discontinued fingolimod treatment before month 12.

- 2309 0599 00002, on FTY 1.25. She had an increase of 11.30 mmHg from 28.5 at screening, unchanged at month 3 and 12, and to 39.6 at the end of study (at month 24). She had a bronchial upper respiratory infection and thromboflebitis of the R leg but no symptoms suggestive of pulmonary HTN.

Additionally, two patients had no measurable PaP at baseline and a PaP >35 mmHg at a follow up visit (2309 0600 00007 and 2309 0567 00007). As per the listings submitted with the updated special safety interim report, one had complaints of laryngeal spasm and the other had syncopal episodes.

- 2309 06000 00007 – 55 F, FTY 1.25 mg. Non measurable PaP at screening to 37.5 mmHg at month 12 and decreased to 30.9mmHg at month 24. She reported "laryngeal spasm" starting on Day 413, with no reported date of resolution. She discontinued because of abnormal lab value (LFT abnormal). Therefore, the PaP value at month 12 was on drug, and the one at month 24 was off drug. She also had gastritis, nausea, fatigue and urinary tract infection. LFT elevation started on Day 336 and was reported to be resolved on Day 450. Complete echocardiographic results are as follows:

Visit (VISNAM1A)	LV end diastolic volume (ml) (LVAEDV1N)	LV end systolic volume (ml) (LVAESV1N)	LV end diastolic dimension (cm) (LVAEDD1N)	LV end systolic dimension (cm) (LVAESD4N)	LV posterior wall thickness (cm) (PSRTCK1N)	IV septum thickness (cm) (SEPTCK4N)	Left atrial volume (ml) (ARLVOL1N)	Stroke volume (ml) (STKVOL1N)	Cardiac output (l/min) (CACOUT1N)
Screening D-28 to -2	95	38					39	57	4.58
Month 12	87	29	4.3	2.88	1.3	1.19	42	59	3.7
END OF STUDY	71	35	4.7	2.93	1.13	1.11	34.1	36	2.36

Visit (VISNAM1A)	Cardiac index (l/min/m^2) (CACIDX1N)	LV fractional shortening (%) (LVAFRS1N)	LV ejection fraction (%) (LVAEJF2N)	SVR (Dyn.s/cm^5) (SVR1N)	SVR index (Dyn.s/cm^5/m^2) (SVRIDX1N)	LV mass (g) (LVAMAS1N)	LV mass index (g/m^2) (LVAIDX1N)
Screening D-28 to -2	2.33		60	19	10		
Month 12	1.92	33.4	67	24	12	196.286	101.7
END OF STUDY	1.21	37.8	51	35	18	192.32	98.12

- 2309 0567 00007. 49 F on placebo. No measurable PaP at baseline. PaP was 32.3 mmHg at month 3 and 36.6 at month 12. She reported fatigue and syncopal episodes during the study which could be consistent with pulmonary HTN, but she was on placebo.

Dr. Shari Targum, FDA cardiologist, concluded the following regarding echocardiogram data:

> "The available echocardiographic data do not reveal a large safety signal. Despite the preclinical signal of myocardial fibrosis, depressed left ventricular systolic function is not observed in this sample. However, the available echocardiographic evaluations are limited. The application did not include the actual echocardiograms. This reviewer is unable to comment on image quality of the images, or methods of calculation. We were not given the extent of intra-reader or inter-reader variability. In addition, no Doppler results or any evaluations of valve morphology were submitted. If one were concerned about papillary muscle fibrosis, one would have evaluated the mitral and tricuspid valves,

> including an assessment of regurgitation. Those examinations were not part of this application. If there were a large signal—for example, an imbalance in severe chronic mitral regurgitation in the FTY720 group--one would have expected consequences of chronic volume overload such as left ventricular and left atrial dilatation, in addition to a holosystolic murmur heard best at the apex. It is therefore somewhat reassuring that the 12 month left atrial volume, end-diastolic and end-systolic dimensions are not increased from baseline. However, one cannot exclude a smaller signal, or a signal appearing over a longer time period. Finally, since the study population excluded diabetics and subjects with significant heart disease, one cannot exclude safety signals that might surface in a more vulnerable population."

A retrospective evaluation of the morphology of the valves was requested by FDA. This analysis was submitted to FDA on May 19, 2010 and did not find any significant valvular changes. A summary of the findings, excerpted from Dr. Shari Targum's review is as follows:

> "An independent cardiologist conducted a review that was blinded to subject name, treatment arm, investigational site, examination date and reason for examination. Echocardiograms were reviewed at baseline and month 12 to assess morphology of mitral, aortic and tricuspid valves; the data were not appropriate to assess the pulmonic valve. Valves were evaluated with respect to mobility, thickness, calcification and reduction in excursion; extent of changes was assessed as trace, mild, moderate or severe or diffuse/focal as appropriate. The mitral and tricuspid valves were evaluated for the presence of stenosis or regurgitation.
>
> Results:
> Mitral, tricuspid and aortic valves were evaluable in most of the echocardiograms in this subset.
>
> No calcification or reductions in valve excursion were observed; no mitral or tricuspid stenosis was observed in any treatment group. No moderate or severe mitral or tricuspid regurgitation was observed in any treatment group at Month 12. The aortic valve could not be assessed for stenosis or regurgitation. At Month 12, four patients on fingolimod 1.25 mg, 2 patients on fingolimod 0.5 mg, and 3 patients on placebo had mild thickening of the mitral valve; no moderate or severe thickening of the mitral valve was observed in any treatment group. At Month 12, mild mitral regurgitation was observed in two patients on fingolimod 1.25 mg, three patients on fingolimod 0.5 mg and one patient on placebo.
>
> No tricuspid thickening was observed in any treatment group. At Month 12, trace tricuspid regurgitation was observed in 37 patients (88.1%) on fingolimod 1.25 mg (N=71), 32 patients (80.0%) on fingolimod 0.5 mg (N=69), 16 patients (75.0%) on placebo (N=57) and 6 patients (87.5%) on Avonex (N=7). Mild tricuspid regurgitation was observed in 3 patients on fingolimod 1.25 mg, 6 patients on fingolimod 0.5 mg, and 3 patients on placebo. No moderate or severe tricuspid regurgitation was observed.
>
> At Month 12, no thickening of the aortic valve was observed in any treatment group."

Dr. Targum's comments:

1. While there may be a numerical imbalance in "trace" tricuspid regurgitation in patients on fingolimod 1.25 mg vs. placebo, trace tricuspid regurgitation is not generally considered clinically significant and may be a function of the high sensitivity of Doppler testing; one should also note a similar incidence of trace tricuspid regurgitation in the Avonex group.
2. No clinically meaningful signal for valvular abnormalities was observed in this analysis.

My comment: Again, one needs to keep in mind the small number of patients available for echocardiogram evaluation at 1 and 2 years, and that many patients discontinued from 2309 because of respiratory related events, particularly in the FTY 1.25 mg group, depleting the sample of patients who could potentially have pulmonary hypertension.

3) Pulmonary Function Tests (PFTs)

In studies D2301, D2302, and D2201, PFTs evaluating FEV1, FVC, and carbon monoxide diffusing capacity (DLCO) were performed at the following time points:
• Study D2201: screening and Month 6
• Study D2301: screening, Month 1, 3, 6, 12, 18, and 24
• Study D2302: screening, Month 1, 3, 6, and 12
For the extension study D2201E1, PFTs were assessed every 3 months starting at Month 9.
For the extension study D2302E1, PFTs were assessed at Month 13, 15, 18, and 24.

As PFT data in study 2201 were collected differently from studies 2301 and 2302, data from 2201 and the extension study 2201E1 were not included in pooled analyses.

FEV1 and DLCO changes from baseline in study 2201 are presented as follows:

Table 10-18 Characteristics of change from baseline in FEV_1 (Safety population)

	Placebo n=37	FTY720 1.25mg n=40	FTY720 5.0mg n=34	P-value*
Change from baseline at month 6 (% predicted)				
Mean (median)	-1.75 (-1.30)	-2.82 (-3.60)	-8.76 (-8.75)	a= 0.624
SD	10.953	8.054	7.760	b=0.003
				c=0.002
% decline from baseline				
≥ 5 - 15%	12 (32.4%)	13 (32.5%)	20 (58.8%)	
≥ 15 - 25%	3 (8.1%)	1 (2.5%)	6 (17.6%)	
≥ 25%	0	0	0	

* Pairwise comparison using two-sample t-rest a= FTY720 1.25mg vs Placebo; b= FTY720 5.0mg vs Placebo; c= FTY720 1.25mg vs. 5.0mg

Table 10-20 Intervals of incremental change from baseline (DLCO) (Safety population)

	Placebo n=25	FTY720 1.25mg n=26	FTY720 5.0mg n=27	P-value*
Change from baseline at month 6 (% predicted)				
Mean (median)	-4.50 (-6.0)	-12.75 (-10.75)	-10.91 (-10.20)	a= 0.137
SD	19.340	19.654	12.095	b=0.155
				c=0.682
% decline from baseline				
≥ 5 to 15%	11 (44.0%)	6 (23.1%)	12 (44.4%)	
≥ 15 to 25%	2 (8.0%)	6 (23.1%)	4 (14.8%)	
≥ 25 to 35%	0	1 (3.8%)	3 (11.1%)	
≥ 35 to 55%	1 (4.0%)	0	0	
≥ 55%	0	2 (7.7%)	1 (3.7%)	

* Pairwise comparison using two-sample t-rest a= FTY720 1.25mg vs Placebo; b= FTY720 5.0mg vs Placebo; c= FTY720 1.25mg vs. 5.0mg

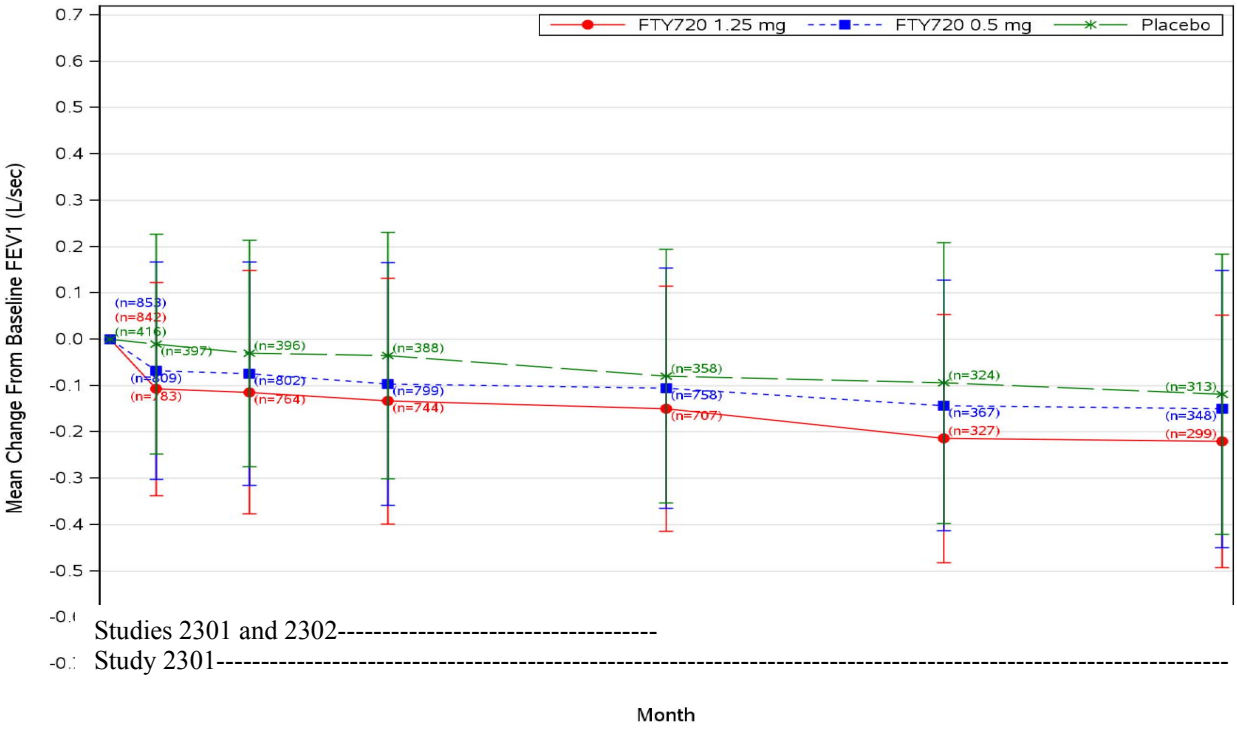
Source: Study 2201 CSR.

The numbers are small but indicate that more patients had decreased FEV1 and DLCO ≥ 15 % of baseline in the FTY 5 mg and FTY 1.25 mg, as compared to placebo. The changes in FVC were no different from placebo (data not shown).

PFT evaluation over time showed an initial sharp decrease within the first month followed by a progressive decrease in FEV1 and DLCO over time, in both, the pooled phase 3 studies and in study 2309.

PFTs in pooled studies 2301 and 2302 (controlled, core studies) are presented as follows:

Figure 4. Changes from baseline in FEV1 in pooled studies 2301 and 2302 core studies



Source: Response to FDA request for information dated 4/8/10. FEV_1=forced expiratory volume in 1 second (L/sec)

Table 95. Change from baseline in Percentage of predicted FEV 1, studies 2301 and 2302

Visit	n	Baseline Mean (SD)	Δ from baseline Mean (SD)
Month 1			
FTY 1.25 (N=849)	781	102.4 (14.0)	- 3.2 (6.7)
FTY 0.5 (N=854)	806	102.0 (14.4)	- 2.0 (6.9)
Placebo (N=418)	397	105.1 (13.9)	- 0.1 (7.2)
Month 12			
FTY 1.25 (N=849)	706	103.9 (13.6)	- 3.8 (8.2)
FTY 0.5 (N=854)	755	103.6 (14.4)	- 2.3 (7.7)
Placebo (N=418)	358	105.3 (14.1)	- 1.5 (8.2)
Month 24			
FTY 1.25 (N=849)	299	104.3 (13.7)	- 5.3 (8.4)
FTY 0.5 (N=854)	348	103.7 (14.5)	- 3.1 (8.7)
Placebo (N=418)	313	105.2 (13.9)	- 2.0 (9.3)

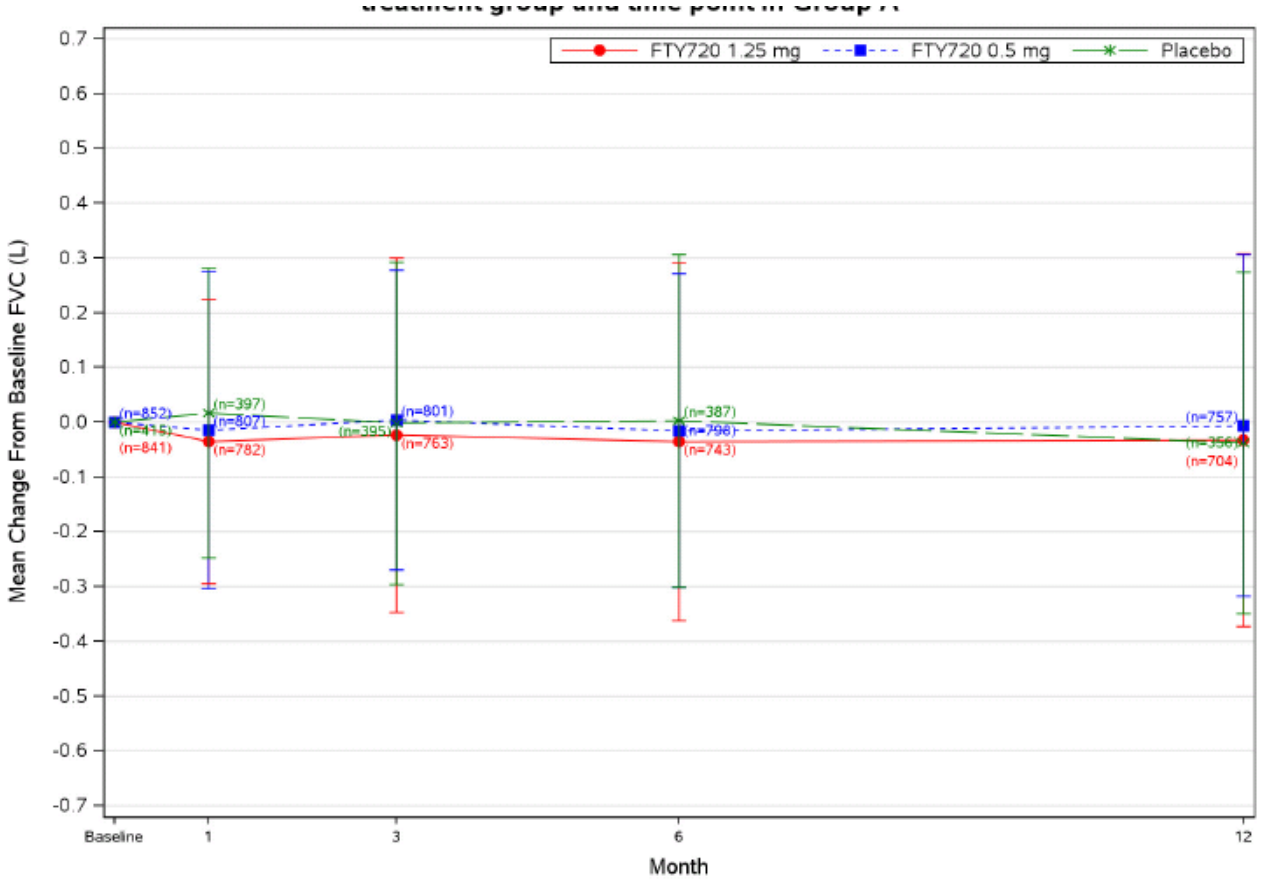
Source: modified from Table 8.1-1 submitted on 3/31/10.

All groups have a very high percentage of predicted FEV1 value at baseline. There is an overlap of confidence intervals and SDs, but the point estimates clearly show a decrease for FTY 1.25, and to a smaller extent for FTY 0.5, as compared to placebo for FEV1.

Dr. Porter, the FDA pulmonologist consultant noted that the change in FEV1 for FTY 0.5 was >100 ml at 6 months, which is greater than the annual decline in FEV1 seen in healthy patients, patients with COPD or MS patients in general. Also of note, PFTs did not correlate with symptoms; this may be due in part at the high percentage of predicted value for PFTs at baseline in these studies.

Changes in FVC are presented in the following figure and table.

Figure 5. Changes from baseline in FVC in pooled studies 2301 and 2302



Source: Response to FDA request for information submitted 4/8/10. FVC: forced vital capacity (L)

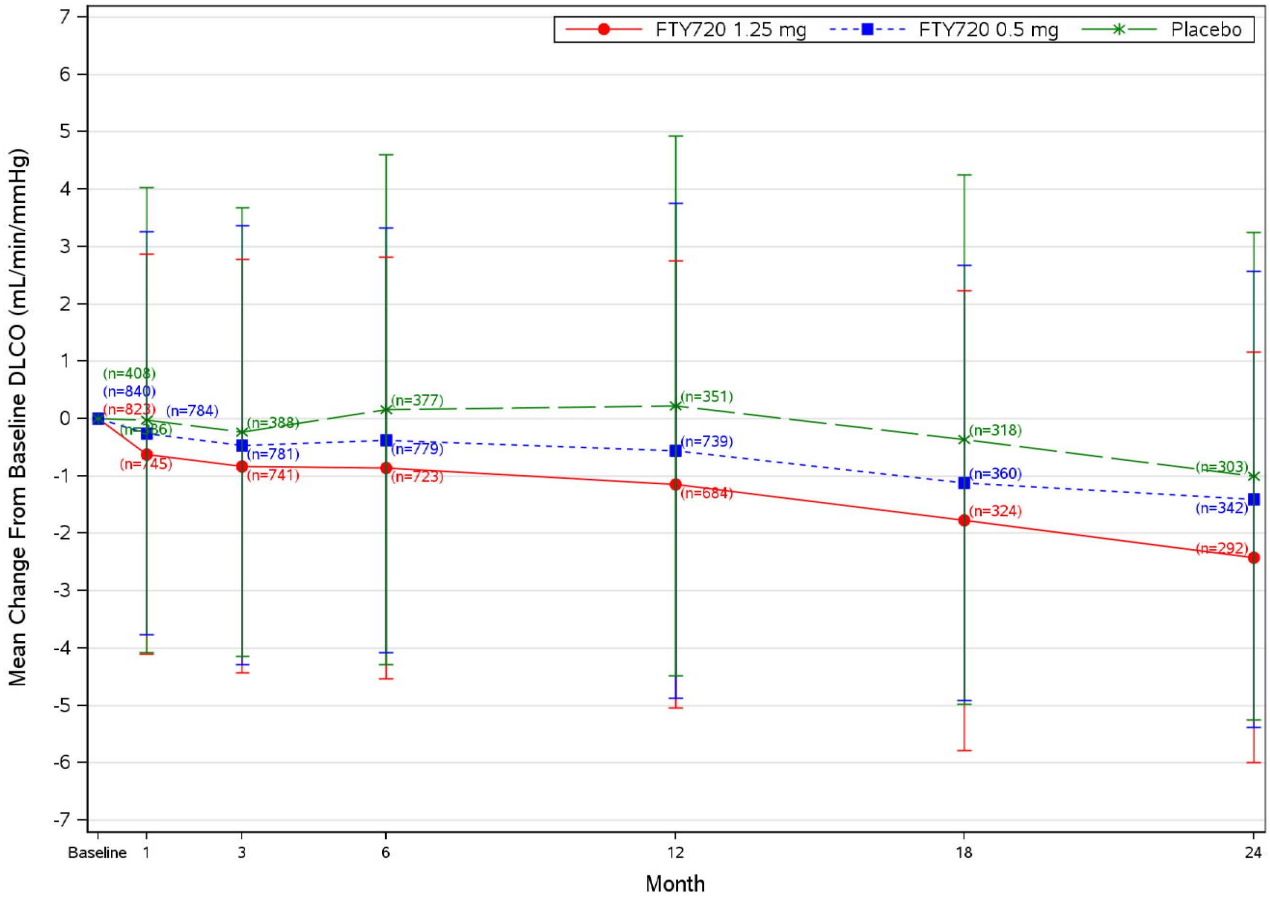
Table 96. Percentage of predicted FVC in 2301 and 2302

Visit / Treatment Group	n	Baseline Mean	Baseline SD	Baseline Med	Post-baseline Endpoint Mean	Post-baseline Endpoint SD	Post-baseline Endpoint Med	Post-baseline Change from baseline Mean	Post-baseline Change from baseline SD	Post-baseline Change from baseline Med
Month 24										
FTY720 1.25 mg (N=849)	298	107.75	15.265	106.61	107.37	16.279	106.49	-0.38	11.659	-0.63
FTY720 0.5 mg (N=854)	348	107.51	14.124	106.99	108.05	14.754	106.92	0.54	9.537	0.07
Placebo (N=418)	312	108.25	14.795	107.49	107.91	14.725	107.53	-0.34	9.104	0.24
Interferon (N=431)	0									

Source: Response to FDA submitted 3 31 10

There was no change from baseline in FVC in this database.

Figure 6. Changes from baseline in DLCO in pooled studies 2301 and 2302 core studies.



Source: response to FDA request submitted 4/8/10. DLCO=diffusion capacity for carbon monoxide.

Table 97. Change from baseline in Percentage of predicted DLCO, studies 2301 and 2302

Visit	n	Baseline Mean (SD)	Δ from baseline Mean (SD)
Month 1			
FTY 1.25 (N=849)	743	86.1 (15.7)	- 2.0 (12.1)
FTY 0.5 (N=854)	781	84.7 (15.7)	- 1.0 (12.0)
Placebo (N=418)	386	87.8 (17.8)	0.0 (15.0)
Month 12			
FTY 1.25 (N=849)	683	86.1 (15.7)	-3.3 (13.7)
FTY 0.5 (N=854)	736	84.7 (15.7)	-1.5 (12.8)
Placebo (N=418)	351	87.8 (17.8)	1.3 (17.1)
Month 24			
FTY 1.25 (N=849)	292	88.8 (14.9)	- 7.3 (12.2)
FTY 0.5 (N=854)	342	86.3 (15.0)	- 3.8 (13.4)
Placebo (N=418)	303	88.0 (17.8)	- 2.7 (15.8)

Source: FDA response for information submitted 3 31 10

There is a decrease in mean absolute and percentage values in DLCO in this database, with a suggestion of a dose response.

Table 98. PFT outlier analysis in studies 2301 and 2302

		FTY720 1.25 mg (N=849) n (%)	FTY720 0.5 mg (N=854) n (%)	Placebo (N=418) n (%)	Interferon (N=431) n (%)
<80% of baseline PFT absolute values at any post-baseline visit					
	FEV1	64 (7.5%)	39 (4.6%)	24 (5.7%)	15 (3.5%)
	FVC	36 (4.2%)	23 (2.7%)	17 (4.1%)	11 (2.6%)
	DLCO	157 (18.5%)	133 (15.6%)	50 (12.0%)	62 (14.4%)

Source: response to FDA request submitted 3/31/10.

The outlier analysis of PFTs in studies 2301 and 2302 suggests a slightly higher risk of decreased FEV1 and DLCO >20% for FTY 1.25 mg as compared to placebo, but not for FTY 0.5. There is no difference for FVC for any dose.

- PFT changes in safety pool E

The change from baseline in percent PFTs in safety pool E (all controlled and extension studies) in the safety update report is presented as follows.

Table 99. Percentage of PFT changes from baseline, safety pool E (SUR)

Variable Visit	FTY720 1.25 mg N=1168		FTY720 0.5 mg N=1176	
	n	Mean (SD)	n	Mean (SD)
FEV_1 (%)				
Month 1	1068	−3.15 (6.59)	1105	−1.97 (6.71)
Month 3	1008	−3.12 (7.76)	1059	−2.14 (6.88)
Month 6	953	−3.59 (7.56)	1014	−2.58 (7.65)
Month 12	860	−3.66 (7.99)	913	−2.38 (7.70)
Month 18	625	−4.46 (8.81)	695	−2.96 (8.09)
Month 24	557	−4.45 (8.24)	634	−2.66 (8.45)
Treatment endpoint	1107	−4.04 (8.37)	1151	−2.50 (8.08)
FVC (%)				
Month 1	1067	−1.01 (6.62)	1104	0.97 (49.24)
Month 3	1007	−0.54 (8.05)	1058	−0.03 (6.79)
Month 6	952	−0.65 (7.90)	1013	−0.33 (7.30)
Month 12	859	−0.34 (8.48)	914	0.29 (7.87)
Month 18	624	−0.35 (9.35)	695	0.02 (8.09)
Month 24	557	−0.09 (10.15)	634	0.96 (9.01)
Treatment endpoint	1106	−0.54 (9.07)	1150	1.45 (48.37)
D_LCO corrected for hemoglobin (%)				
Month 1	1027	−2.30 (12.69)	1078	−0.63 (11.40)
Month 3	979	−3.09 (12.26)	1031	−1.26 (12.44)
Month 6	929	−2.98 (13.08)	991	−0.83 (12.16)
Month 12	835	−3.18 (13.41)	893	−1.42 (14.08)
Month 18	603	−4.14 (13.30)	674	−2.71 (14.79)
Month 24	539	−5.12 (12.38)	619	−3.57 (14.00)
Treatment endpoint	1085	−4.47 (14.25)	1138	−2.62 (13.53)

Source: Table 4-7. Safety Update Report, 4/22/10. (There is no placebo in pool E)

The analysis indicates a decrease from baseline in FEV1 and DLCO (but not for FVC), for both, FTY 1.25 and FTY 0.5, with a suggestion for a dose response, which is consistent with the analyses in the core studies and in study 2309.

The outlier analysis of decreased PFTs for safety pool E is as follows (SUR)

Table 100. Outlier analysis, PFTs in safety pool E (SUR)

	FTY720 1.25 mg (N=1168) n (%)	FTY720 0.5 mg (N=1176) n (%)
<80% of baseline PFT absolute values at any post-baseline visit		
FEV_1	94 (8.0)	63 (5.4)
FVC	49 (4.2)	32 (2.7)
D_LCO	262 (22.4)	223 (19.0)

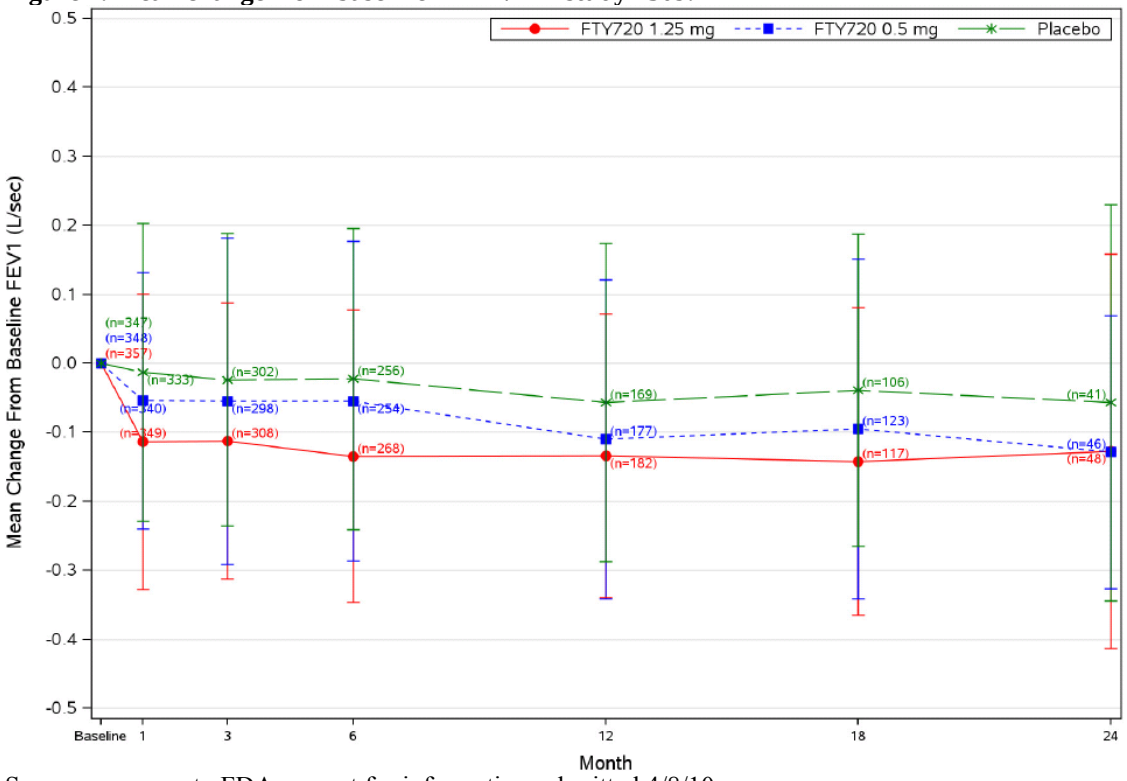
Source: Table 4-8, safety update report (4/22/10)

This analysis suggests that a slightly higher percentage of patients had decreased FEV1, FVC and DLCO in the FTY 1.25 mg group, as compared to FTY 0.5 mg (there is no placebo in pool E).

- PFT changes in study 2309

The following figures represent change from baseline in FEV1 and DLCO in study 2309. Consistent with the findings in the phase 3 studies, there is no decline in FVC in 2309 (data not shown).

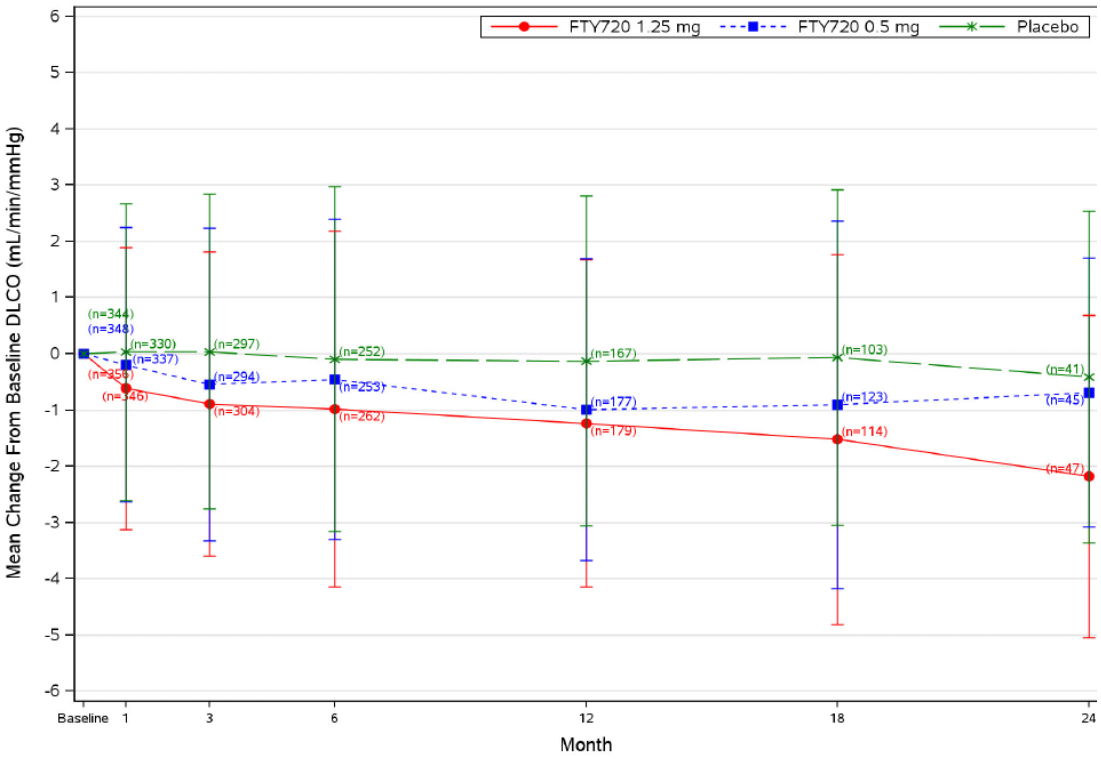
Figure 7. Mean change from baseline in FEV1 in study 2309.



Source: response to FDA request for information submitted 4/8/10

There is a decrease from baseline in mean FEV1 for FTY 1.25 mg and 0.5, as compared to placebo (of course, with wide confidence intervals). The change is observed already at the 1 month evaluation and it is maintained until the 24 month evaluation.

Figure 8. Mean change from baseline in absolute value DLCO in study 2309.



Source: response to FDA request for information submitted 4/8/10

The decrease in DLCO in study 2309 is consistent with the analysis in 2301 and 2302. There is a suggestion for some decline in DLCO over time particularly for the 1.25 mg dose.

Table 101. Outlier analysis of PFTs in study 2309, PFT analysis set.

	FTY 1.25 N=358	FTY 0.5 N=348	Placebo N=347
FEV1	5.6%	3.2%	2.3%
FVC	3.4%	1.7%	1.4%
DLCO	13.1%	11.8%	7.2%

Source: Response to FDA request for information submitted 2/9/10.

The PFT analyses (mean and outlier) indicate a decline in lung function for FTY 1.25 mg, particularly for FEV1 and DLCO, suggesting some degree of lung toxicity. This is observed in the phase 3 studies, pool E and study 2309. In study 2309, there also seems to be a higher risk of decrease FVC with FTY 1.25 mg.

The decrease in FEV1 may be in part explained by the known pharmacologic bronchoconstrictive effects of fingolimod. The reason for the decreased diffusion capacity observed in these studies is not clear.

It has recently been shown that prolonged S1P antagonist exposure increases the damage in mice with bleomycin - induced lung injury.[8] The authors hypothesize that the increase in AE of dyspnea and decreased PFTs observed in study 2201 with FTY 5 mg dose as compared to placebo (from an article published in the NEJM in 2006) could be explained by "minor perturbations in lung endothelial barrier function" This is a very interesting hypothesis. However, the available database is insufficient to test that hypothesis.

- HRCT in patients having decreased PFTs

Per protocol, patients in study 2309 with FEV1, FVC or DLCO below 80% of the baseline value were to have HRCT. The listing of patients whose PFT values satisfied abnormal criteria along with the HRCT scan results in study 2309 was submitted at the FDA request. Review of this listing indicates that:

- a higher percentage of patients fulfilled PFT abnormal criteria (any FEV1, FVC or DLCO) in the FTY groups, with suggestion of a dose-response
- many patients who fulfilled abnormal PFT criteria did not get a follow up HRCT after the abnormal PFT (at least 50% of patients with abnormal PFTs are missing a follow up HRCT).

Table 102. Patients with PFT decrease of >20% of baseline in study 2309

	FTY 1.25 mg N= 358 n (9%)	**FTY 0.5 mg N=348 n (%)**	**Placebo N=347 n (%)**
Patients with decrease in PFT value >20% of baseline	65 (18.2)	50 (14.4)	32 (9.2)
Patients who did not have follow up HRCT after abnormal PFT value	*34 (52.3)*	*31 (62.0)*	*20 (62.5)*

Source: Listing 14.3-4.3. Response to FDA request for information submitted February 2010. N= PFT analysis population.

Of patients on FTY 0.5 mg, 11 had decreased FEV1; 7 had decreased FVC, and 39 had decreased DLCO >20% from baseline. Some had decrease of >20% in more that one parameter. One patient had decrease of >20% in all 3 parameters (ID 0511 00002, 47 F). No clinical history was available to correlate with PFT information in the original ISS.

PFT changes in selected patients receiving FTY 0.5 mg in study 2309 are as follows:

[8] Shea et al. Prolonged S1P antagonist exposure may exacerbate vascular leak, fibrosis and mortality after lung injury. Am J. Resp.Cell.Mol. Biology. January 15, 2010.

Treatment: FTY720 0.5mg Country/Center/Subject: USA/0511/00002 Age/Sex/Race: 47/F/Ca

	Absolute values				Percent of predicted					
Study day	FEV1 [L]	FVC [L]	DLCO [ml/ min/ mmHg]	FEV1/ FVC [%]	FEV1 [%]	FVC [%]	DLCO [%]	FEV1/ FVC [%]	HRCT result	HRCT findings
-17	3.26	4.17	26.38	78.18	141.25	153.86	116.51	79.75	Normal	
33	2.97	3.83	27.21	77.55	128.68	141.32	120.17	79.10		
96	3.13	4.19	23.27	74.70	135.62	154.60	102.77	76.20		
194	2.60*	3.37	22.21	77.15	113.89	125.55	98.72	78.55		
369	2.82	3.62	23.85	77.90	123.52	134.86	106.01	79.31		
551	2.41*	3.14*	20.92*	76.75	106.73	118.13	93.58	77.99		
728	2.93	3.89	27.24	75.32	129.76	146.34	121.85	76.54	Radiological findings	RIGHT MIDDLE LOBE LINEAR OPACITY
728	2.93	3.89	27.24	75.32	129.76	146.34	121.85	76.54	Radiological findings	RIGHT LOWER LOBE SUBPLEURAL 4 MM NODULE

Comment: It is unclear if the drug was discontinued or not. The patient was probably asymptomatic, as she started with very high PFT values. At last available follow up PFT there was improvement in PFTs but there were abnormal HRCT findings that were considered to be of no clinical significance. There is no follow up HRCT that shows resolution of findings.

Treatment: FTY720 0.5mg Country/Center/Subject: USA/0512/00008 Age/Sex/Race: 47/M/Ca

	Absolute values				Percent of predicted					
Study day	FEV1 [L]	FVC [L]	DLCO [ml/ min/ mmHg]	FEV1/ FVC [%]	FEV1 [%]	FVC [%]	DLCO [%]	FEV1/ FVC [%]	HRCT result	HRCT findings
-25	3.68	4.70	30.40	78.30	97.56	100.75	96.17	99.65	Normal	
46	3.10	4.08	23.50*	75.98	82.18	87.46	74.34	96.70		
74	3.23	4.24	26.70	76.18	85.63	90.89	84.46	96.96		
291@	3.47	4.57	26.20	75.93	91.99	97.97	82.88	96.64		

There was a decrease in DLCO on Day 46. It is unclear if value on Day 74 was on drug or after drug dc. The value at last FU on Day 291 was after drug discontinuation. There is improvement from Day 46 but there is no full recovery. There was no HRCT after decrease in PFTs.

Treatment: FTY720 0.5mg Country/Center/Subject: USA/0536/00001 Age/Sex/Race: 37/F/Ca

	Absolute values				Percent of predicted					
Study day	FEV1 [L]	FVC [L]	DLCO [ml/min/mmHg]	FEV1/FVC [%]	FEV1 [%]	FVC [%]	DLCO [%]	FEV1/FVC [%]	HRCT result	HRCT findings
-24	3.00	3.58	24.70	83.80	101.59	104.89	93.14	87.17	Normal	
29	2.80	3.35	18.20*	83.58	94.82	98.15	68.63	86.95		

This patient appears to have been discontinued. DLCO decreased by 25%; there was no follow up HRCT or PFT.

Treatment: FTY720 0.5mg Country/Center/Subject: USA/0577/00005 Age/Sex/Race: 32/F/Ca

	Absolute values				Percent of predicted					
Study day	FEV1 [L]	FVC [L]	DLCO [ml/min/mmHg]	FEV1/FVC [%]	FEV1 [%]	FVC [%]	DLCO [%]	FEV1/FVC [%]	HRCT result	HRCT findings
-9	3.20	3.80	31.00	84.21	90.49	93.66	103.10	88.48	Normal	
34	3.66	4.35	23.40*	84.14	103.50	107.22	77.82	88.40		
91	4.04	4.84	28.50	83.47	114.25	119.30	94.78	87.70		
188	4.04	4.95	26.20	81.62	114.25	122.01	87.13	85.75		

This patient had >20% decrease in DLCO. The drug was probably discontinued, as there is no further PFTs after Day 188. There was some improvement on DLCO at last evaluation, although it did not fully recovered. There is no HRCT after PFT decreased.

In summary, in study 2309, contrary to what was established in the protocol, less than 40% of patients who had decreased PFTs >20% had a follow up HRCT scan at the time of the event. We do not have the full clinical picture for the risk of lung toxicity with FTY.

- Reversibility of effect on PFTs in safety pool E follow up population

A subset of patients in safety pool E (288 patients on FTY 1.25mg and 211 on FTY 0.5mg), was followed up after discontinuation (mean of 4 months). Change from baseline in FEV_1 and D_LCO in this population are presented by visit and treatment as follows.

Table 103. Percentage of predicted FEV1 in E follow up population (SUR)

Visit / Treatment Group	n	Baseline Mean	Baseline SD	Baseline Med	Post-baseline Endpoint Mean	Post-baseline Endpoint SD	Post-baseline Endpoint Med	Change from baseline Mean	Change from baseline SD	Change from baseline Med
TEP										
FTY720 1.25 mg (N=288)	248	102.08	14.871	101.00	98.11	14.467	98.30	-3.96	9.871	-3.69
FTY720 0.5 mg (N=211)	194	99.55	14.743	99.85	97.04	13.810	97.39	-2.51	8.316	-2.38
Day 1-45 after drug discontinuation										
FTY720 1.25 mg (N=288)	136	102.39	13.522	101.50	99.80	14.302	100.49	-2.58	8.371	-2.56
FTY720 0.5 mg (N=211)	92	103.00	15.191	104.12	101.76	14.372	101.84	-1.25	8.963	-0.70
Month 3 after drug discontinuation										
FTY720 1.25 mg (N=288)	163	101.92	14.671	100.87	100.55	14.364	99.79	-1.37	8.280	-2.16
FTY720 0.5 mg (N=211)	116	100.74	14.713	100.87	100.52	13.917	100.21	-0.22	7.547	-0.27

Source: post table 11.4-2 Safety Update Report (4/22/10). TEP: treatment endpoint; last non-missing value. Only patients with both, baseline and post-baseline are included.

Table 104. Percentage of predicted DLCO corrected for Hg in E follow up population (SUR)

Visit / Treatment Group	n	Baseline Mean	Baseline SD	Baseline Med	Post-baseline Endpoint Mean	Post-baseline Endpoint SD	Post-baseline Endpoint Med	Change from baseline Mean	Change from baseline SD	Change from baseline Med
TEP										
FTY720 1.25 mg (N=288)	244	86.48	18.136	84.79	82.21	17.774	80.86	-4.27	16.449	-3.95
FTY720 0.5 mg (N=211)	193	83.57	17.742	81.97	80.46	15.521	80.01	-3.12	17.754	-1.96
Day 1-45 after drug discontinuation										
FTY720 1.25 mg (N=288)	134	86.37	17.558	85.86	79.58	15.079	79.14	-6.79	11.792	-5.76
FTY720 0.5 mg (N=211)	90	83.45	15.529	82.68	82.05	15.208	81.32	-1.40	10.904	-2.78
Month 3 after drug discontinuation										
FTY720 1.25 mg (N=288)	159	86.26	17.539	85.40	81.94	17.806	79.76	-4.31	15.120	-3.52
FTY720 0.5 mg (N=211)	115	84.23	19.028	80.85	80.63	14.018	79.66	-3.61	18.385	-1.62

Source: post table 11.4-2. Safety Update Report (4/22/10). TEP: treatment endpoint; last non-missing value. Only patients with both, baseline and post-baseline are included.

The analyses in the E follow up population suggest that the changes from baseline to the last available measurement in FEV1 are reversible, however, the DLCO changes do not appear to be reversible. Some patients were followed beyond 3 months but the numbers become too small (there were 56 patients at 6 months and 3 patients at 18 months). Additional analyses have been requested.

In summary, evaluation of scheduled PFTs indicates a dose response in the number of patients with PFT decrease >20% from baseline for FEV1 and DLCO. Many patients who discontinued because of dyspnea or had PFT >20% decrease from baseline did not have a follow up HRCT. This was observed in the ISS (Studies 2301 and 2302) as well as

study 2309. The effect on DLCO did not appear to be fully resolved at the time of last available PFT value in the Pool E follow up population. In my opinion, the lung toxicity of fingolimod has not been fully characterized. This finding does not preclude approval of the drug, but will require awareness in the part of the physicians and patients who use it. I recommend that it should be part of the REMS.

Fingolimod lung toxicity was discussed at the FDA AC meeting of June 10, 2010. Dr. Redlich, the pulmonologist at the FDA AC meeting was concerned about the findings, particularly the lack of information in patients at increased risk. She recommended that PFT's be obtained at baseline in all patients.

3) Chest high resolution computer tomography

- In 2201 Chest X-rays were done but HRCT were not part of the protocol.
- In 2301 chest X-rays were done at screening, month 12, 18 and 24. As per a protocol amendment (April 2006) chest HRCT were done instead of X-rays at screening and month 24 at selected sites and read by local radiologists. HRCT could be required at other visits in case of confirmed ≥20% reduction of baseline PFTs (unscheduled HRCTs).
- In study 2302, chest X-rays were done at Screening and Month 12. HRCT were done instead of the X-rays at all US sites and selected sites outside the US where feasible, and interpreted by local radiologists. HRCT was to be done if PFT reduction of ≥20%.
- In 2309 HRCT was to be done in all subjects at screening and Month 24. Additionally, chest HRCT was to be performed at visit 14 (12 months) in the first 360 (approximately) randomized patients, and interpreted by a central reader.

The investigator was requested to specify for each finding recorded on CRF whether it was clinically significant according to his/her clinical judgment. However, no specific guidance as to which HRCT findings were to be considered "clinically significant" was given to the investigators. HRCT findings that were not rated as clinically significant by the investigator were classified as "clinically insignificant" in the analyses.

- Chest HRCT in study D2301

In total, 360 patients (one third of those randomized) had chest HRCT scans at screening in study 2301. Of these, 259 patients had the assessment at Month 24 visit, 34 patients had an end-of-study chest HRCT scan performed outside of the 24-month visit window and 67 had no post-baseline chest HRCT scan. Chest HRCT results in study D2301 as judged by the local radiologist at screening and at Month 24 are summarized the following table.

Table 105. HRCT abnormalities in 2301 by visit

	FTY 1.25 N=429 n (%)	FTY 0.5 N=425 n (%)	Placebo N=418 n (%)
Screening			
Number of patients	122	120	118
Abnormal findings	35 (28.7)	27 (22.5)	31 (26.3)
Clinically significant abnormality	0	1 (0.8)	0
Month 24			
Number of patients*	85	90	95
Abnormal	24 (28.2)	23 (25.6)	22 (23.2)
Abnormality compared to baseline:			
Unchanged	9 (10.6)	9 (10.0)	12 (12.6)
New or worsened	**12 (14.1)**	**13 (14.4)**	**9 (9.5)**
Clinically significant	**4 (4.7)**	**4 (4.4)**	**2 (2.1)**
Unscheduled			
Number of patients	8	11	10
Considered clinically significant	**1**	**3**	**2**

Source: Modified from ISS Table 4-35 and ISS text. * includes 11 patients (3 in FTY720 1.25 mg, 3 in FTY720 0.5 mg and 5 in placebo) who did not have baseline chest HRCT assessment. Screening and Month 24 results do not include unscheduled results.

At screening, the proportion of patients with abnormal chest HRCTs was similar across the treatment groups. The majority of abnormal readings were related to prior-inflammatory events or to small nodular changes. At Month 24, the percentage of patients with chest HRCTs showing new or worsened abnormalities compared to baseline was higher in the FTY groups than the placebo group (14.1% in the FTY1.25 mg, 14.4% in the FTY 0.5 mg, and 9.5% in the placebo group). Of those patients with new or worsened abnormalities, clinically significant pulmonary changes (as interpreted by the local radiologist) were seen in 2 patients on FTY 1.25 mg (benign cysts lower lobe, apical scarring and ground glass appearance), 3 patients on FTY0.5 mg (pneumofibrosis, suspected pneumonia, cysts/unknown abnormality) and 2 patients on placebo.

A similar number of patients had unscheduled HRCT (because of a clinical indication or because of decreased PFTs >20% from baseline). Among the 29 subjects with unscheduled chest HRCT, seven were considered clinically significant by the investigator: 1 (pericarditis/pleurisy/ pneumonia) in the FTY 1.25 mg group, 3 (node enlargement, panbronchiolitis, and pneumonic infiltration) in the FTY 0.5 mg group and 2 (mild bronchial wall thickening in both lungs/bilateral glass appearance) in the placebo group.

Shifts from normal to abnormal on Month 24 chest HRCTs occurred slightly more frequently in the FTY 1.25 mg [8/56 (14.3%)] and FTY 0.5 mg [13/70 (18.6%)] than in the placebo group [8/67 (11.9%)]. Approximately half of the patients with an abnormal HRCT scan at baseline had a normal HRCT scan at Month 24 across the 3 treatment groups.

- Chest X-rays

The patients who did not have a chest HRCT assessment underwent a chest X-ray at Screening and Month 24 (read by local radiologist). At Screening, less than 10% of the patients had an abnormal chest X-ray in each group. At Month 24, there was a lower percentage of abnormal chest X-ray in all groups, lowest in the FTY 0.5 mg group; i.e. 8.4% in the FTY 1.25 mg group, 3.3% in the FTY 0.5 mg group, and 6.1% in the placebo group. There was

no difference in the number of patients with clinically significant findings at Month 24 (2 patients in the FTY 1.25 mg group, 1 patient in the FTY 0.5 mg group, and 1 patient in the placebo group).

Therefore, evaluation of HRCT in this 2-years study suggests a slightly higher risk of pulmonary toxicity for FTY as compared to placebo, however, there was no particular pattern of toxicity and there was no evidence of pulmonary fibrosis.

- **Chest HRCT in study 2302**

In study D2302, chest HRCT was performed at all US sites and at sites outside the US where feasible and permitted per local regulations instead of chest X-ray. Chest HRCTs were performed in 478 patients at screening and 421 patients at Month 12. Chest HRCT results as judged by the local radiologist are presented by visit and treatment in the following table. The proportion of patients with chest HRCTs showing new or worsening abnormalities compared to baseline was similar across groups at each visit.

Table 106. Table Chest HRCT in 2302 by visit

	FTY720 1.25 N=420	FTY720 0.5 N=429	Interferon N=431
Baseline			
Number of patients	157	161	160
Abnormal findings	24 (15.3)	35 (21.7)	26 (16.3)
Clinically significant	0	0	1 (0.6)
Month 12			
Number of patients	135	139	147
Abnormal	24 (17.8)	25 (18.0)	25 (17.0)
Abnormality compared to baseline			
Unchanged	8 (5.9)	13 (9.4)	7 (4.8)
New or worsened	**12 (8.9)**	**11 (7.9)**	**15 (10.2)**
Not compared	4 (3.0)	1 (0.7)	3 (2.1)
Abnormality			
Clinically significant	**3 (2.2)**	**1 (0.7)**	**3 (2.0)**
Missing assessment	0	1 (0.7)	1 (0.7)
Unscheduled chest HRCTs			
Number of patients	9	14	6
Number of HRCT scans	10	15	9
Normal	7	13	2
Abnormal	3	2	7
Clinically significant	**0**	**1**	**1**
Abnormality compared to baseline:			
Unchanged	0	1	0
New or worsened	**2**	**1**	**2**
Not compared	1	0	5

Modified from ISS Table 4-36.

As per the complete study report, seven subjects with HRCT abnormalities were considered to have clinically significant changes: 3 on FTY 1.25 (bronchopathy, atelectactic strias with tubular bronchiectasis and pulmonary nodules with patchy nodular infiltrate in R middle lobe), one on 0.5 (pulmonary nodules, hepatic nodules) and 3 in the interferon group (pulmonary nodules, emphysema). As per an interim report submitted to the IND, three additional patients had clinically significant new findings in FTY 0.5: a case of acute bronchopneumonia (#2302

822/00003) and a case of small nodule in the lingual, may be atelectasias" (# 2303 0535 00005) and bilateral mild bronchial wall thickening (#2302 0538 0003), but it is unclear if they were among the scheduled or unscheduled findings.

Among the 29 subjects who underwent unscheduled HRCT testing, 9 were in the FTY 1.25mg group, 14 in the TY 0.5 mg group and 6 in the IFN group. Only one in the FTY 0.5 mg and one in the IFN group were considered by the investigator be clinically significant changes.

Overall, there was no increased risk of pulmonary toxicity as compared to interferon, and there were no changes consistent with pulmonary fibrosis.

- **HRCT in 2309**

Results of HRCT in 2309 are presented in the following table.

Table 107. Chest high resolution CT in 2309

	FTY720 1.25 mg N=132 n (%)	FTY720 0.5 mg N=133 n (%)	Placebo N=144 n (%)
Baseline			
Number of patients	132	132	141
Normal	80 (60.6)	75 (56.8)	86 (61.0)
Abnormal	52 (39.4)	57 (43.2)	55 (39.0)
Clinically significant	0	2 (1.5)	3 (2.1)
Clinically insignificant	52 (39.4)	55 (41.7)	52 (36.9)
Month 24 for completers on study drug			
Number of patients	80	87	82
Normal	51 (63.8)	56 (64.4)	45 (54.9)
Abnormal	29 (36.3)	31 (35.6)	37 (45.1)
Clinically significant	2 (2.5)	2 (2.3)	7 (8.5)
Clinically insignificant	27 (33.8)	29 (33.3)	30 (36.6)
Abnormality compared to baseline			
Unchanged	8 (10.0)	12 (13.8)	18 (22.0)
Improved	0	1 (1.1)	0
New or worsened	17 (21.3)	16 (18.4)	18 (22.0)
Comparison not required	0	0	0
Not compared	3 (3.8)	2 (2.3)	1 (1.2)
Missing	1 (1.3)	0	0
End of study			
Number of patients	107	109	117
Missing	0	0	1 (0.9)
Normal	65 (60.7)	66 (60.6)	71 (60.7)
Abnormal	42 (39.3)	43 (39.4)	45 (38.5)
Clinically significant	3 (2.8)	4 (3.7)	9 (7.7)
Clinically insignificant	39 (36.4)	39 (35.8)	36 (30.8)
Abnormality compared to baseline			
Unchanged	16 (15.0)	18 (16.5)	21 (17.9)
Improved	0	1 (0.9)	0
New or worsened	20 (18.7)	22 (20.2)	20 (17.1)
Comparison not required	0	0	0
Not compared	5 (4.7)	2 (1.8)	4 (3.4)
Missing	1 (0.9)	0	0

	FTY720 1.25 mg N=132 n (%)	FTY720 0.5 mg N=133 n (%)	Placebo N=144 n (%)
Unscheduled chest HRCT			
Number of patients	11	11	12
Number of HRCT scans	13	15	12
Missing	1 (7.7)	0	0
Normal	3 (23.1)	10 (66.7)	7 (58.3)
Abnormal	9 (69.2)	5 (33.3)	5 (41.7)
Clinically significant	1 (7.7)	1 (6.7)	0
Clinically insignificant	8 (61.5)	4 (26.7)	5 (41.7)
Abnormality compared to baseline			
Unchanged	4 (30.8)	3 (20.0)	1 (8.3)
Improved	0	0	2 (16.7)
New or worsened	5 (38.5)	2 (13.3)	2 (16.7)
Comparison not required	0	0	0
Not compared	0	0	0

The number of patients in end of study includes the study 2309 patients who had a chest HRCT at the end of the study, i.e. completed 24 month visit or discontinued early. Many patients had not reached end of study at the time of the interim analysis cut-off date of 11-Sep-2009. Patients are listed under “clinically significant” category if any of the radiological findings were clinically. significant. Same rules apply for the category of "Abnormality compared to baseline". Patients are listed under the worst category if they had multiple abnormal findings. For baseline and end of study chest HRCTs, the number of patients is the denominator for the percentages. For unscheduled chest HRCT, the number of HRCT scans is the denominator for the percentages. Chest HRCT results obtained more than 45 days after the last dose of study drug are not included in the summary tables, but are included in the patient listings.
Source: Special safety interim report, original application.

Evaluation of the HRCT data did not suggest pulmonary fibrosis, which is reassuring. However, the non-clinical toxicity studies were never described as showing pulmonary fibrosis. They did show increased weight and increased collagen deposition, and subpleural fibrosis, but no parenchymal lung fibrosis.

The number of abnormal HRCT at the end of study is similar among treatment groups (40-42%) among scheduled studies. The percentage of abnormal HRCT among unscheduled tests is higher in the FTY 1.25 mg group, as compared to FTY 0.5 and placebo but most are clinically insignificant. However, there was no definition of what clinically significant meant. No specific guidance was provided to the investigators as to how to determine if a HRCT finding was clinically significant or not. Ideally, HRCT should have been read blindly by at least 2 different readers (the same for all tests) but there was no central reading except for study 2309. The number of new or worsened abnormalities as compared to baseline also is higher in FTY 1.25 as compared to FTY 0.5 and placebo, but the numbers are small.

5) Ophthalmologic evaluations

A comprehensive ophthalmic examination was performed in all studies by an ophthalmologist at Screening and end of study, and regularly throughout the study, depending on the study. It included an eye history, visual acuity measurement and dilated ophthalmoscopy. For study 2309

ophthalmologic evaluations were at screening, month 1, 3, 6, 12, 18 and 24. For other studies, the original schedule of visits was less often, but a schedule similar to 2309 was implemented after the protocols were ongoing.

Study 2301 included OCT (optic coherence tomography) to determine central foveal thickness (CFT) at screening and Month 24. It could be required at other visits to evaluate macular thickness, if indicated.

In study 2302, OCT was done at screening and 12 months. Patients in the United States also had an OCT performed at Month 1, Month 3, Month 6, and if technically feasible, total macular volume and retinal nerve fiber layer (RNFL) thickness (requires OCT-3, done in US centers only). Patients with a medical history of uveitis or newly-diagnosed uveitis at Screening or after initiation of study drug required additional ophthalmic evaluations.

In study 2309, CFT and RNFL thickness by OCT was to be performed at each visit for the first 300 randomized patients and in all patients with history of uveitis or active uveitis, and at screening, Month 12 and Month 24 for the remaining randomized patients.

Results of CFT by OCT in study 2301 are presented as follows.

Table 108. Mean changes from baseline in CFT in Study 2301

Visit	Statistics	FTY720 1.25mg N=429	FTY720 0.5mg N=425	Placebo N=418
Baseline	n (eyes)	784	779	771
	Mean (SD)	169.2 (25.16)	168.7 (24.70)	169.5 (25.24)
Month 24	n (eyes)	566	637	557
	Mean (SD)	174.8 (31.16)	172.6 (30.41)	169.7 (30.78)
Change from baseline	n (eyes)	520	581	511
	Mean (SD)	5.45 (28.834)	4.08 (27.025)	0.85 (29.028)

Source: Table 4-41 ISS

Evaluation of mean changes in CFT indicates an increase in mean CFT for both FTY doses compared to placebo; however, more informative is the evaluation of the distribution of changes in study 2301 (2 year study) which shows a higher number of patients in the FTY 1.25 mg group had changes from baseline >40 microns at the 24 months evaluation.

Table 109. Distribution for change from baseline in central foveal thickness, study 2301

Table 14.3-6.6 (Page 1 of 2)
Frequency (%) distribution for change from baseline in central foveal thickness, by visit and treatment
Safety population

Visit		FTY720 1.25mg N=429	FTY720 0.5mg N=425	Placebo N=418
Month 24	Number of eyes with OCT performed at baseline and this visit	520	581	511
	Change from baseline in central foveal thickness			
	<-40	15 (2.9%)	20 (3.4%)	23 (4.5%)
	>=-40 to <=-21	40 (7.7%)	38 (6.5%)	33 (6.5%)
	>-21 to <=20	375 (72.1%)	417 (71.8%)	376 (73.6%)
	>20 to <=40	45 (8.7%)	69 (11.9%)	54 (10.6%)
	>40	45 (8.7%)	37 (6.4%)	25 (4.9%)
Last assessment on study drug *	Number of eyes with OCT performed at baseline and this visit	554	563	538
	Change from baseline in central foveal thickness			
	<-40	15 (2.7%)	19 (3.4%)	19 (3.5%)
	>=-40 to <=-21	43 (7.8%)	38 (6.7%)	35 (6.5%)
	>-21 to <=20	396 (71.5%)	415 (73.7%)	408 (75.8%)
	>20 to <=40	54 (9.7%)	57 (10.1%)	55 (10.2%)
	>40	46 (8.3%)	34 (6.0%)	21 (3.9%)

Source: PT table 14.3-6.6 CSR.
- The percentages are based on the number of eyes with OCT performed for each visit.
- The highest value is used if two or more unscheduled values exist for a patient.
- Only the worst case is counted in unscheduled visit.
- * The last central foveal thickness value taken at or before last day of study drug is summarized in row 'Last assessment on study drug'.

In study 2302 mean changes from baseline in CFT showed a slight increase in CFT for FTY 0.5 mg (2.5-4 microns) that was maximum at the 1 month evaluation, but not for FTY 1.25mg or IFN (data not shown). (Only US patients had measurement at 1, 3 and 6 months).

- OCT in 2309

As per the Updated Special safety interim report, the following number of AE of macular edema were reported in study 2309: 7 on FTY 1.25mg, 5 on FTY 0.5 and 2 on placebo. Macular edema was diagnosed within the first six months of treatment with FTY720 in all patients, except one. DSMB has confirmed macular edema for 8 of these 14 patients: 4 on FTY720 1.25 mg, 3 on FTY720 0.5 mg and 1 on placebo. Six of the 14 patients had absolute CFT >300 μm newly occurring, post-baseline (3 in each of the FTY720 groups). Out of the other 8 patients whose CFT data did not meet this notable CFT criterion, 3 had a change from baseline >40 μm, while 5 patients had only subtle changes in CFT.

Mean changes from baseline in central foveal thickness (microns), and distribution of changes in study 2309 is presented in the following tables (Updated Report).

Table 110. Change from baseline in central foveal thickness (microns), Ophthalmology analysis set, study 2309

Visit Treatment	n	Baseline Mean	Visit Mean	Change from baseline Mean (SD)	Median	Range
Month 1						
FTY720 1.25 mg (N=359)	464	174.61	176.85	2.24 (23.858)	2.00	-83.0 - 150.0
FTY720 0.5 mg (N=350)	434	176.77	177.58	0.81 (25.642)	0.00	-121.0 - 257.0
Placebo (N=350)	426	176.86	175.96	-0.89 (20.840)	-1.00	-115.0 - 117.0
Month 12						
FTY720 1.25 mg (N=359)	392	175.33	180.23	4.90 (25.808)	4.00	-77.0 - 147.0
FTY720 0.5 mg (N=350)	388	173.44	178.08	4.63 (30.088)	2.00	-110.0 - 154.0
Placebo (N=350)	384	177.60	179.85	2.25 (28.886)	0.00	-119.0 - 137.0
Month 24						
FTY720 1.25 mg (N=359)	156	173.38	182.99	9.62 (31.638)	5.00	-73.0 - 108.0
FTY720 0.5 mg (N=350)	172	173.70	176.97	3.26 (34.082)	0.00	-99.0 - 175.0
Placebo (N=350)	158	175.20	177.70	2.51 (33.535)	1.00	-121.0 - 126.0

Table 5-1, Special safety interim report (Updated report). Source: N = number of patients in the OPH analysis set
n = number of eyes evaluated by optical coherence tomography at baseline and the respective visit.
Baseline assessment is the last ophthalmic assessment prior to initial dose of study medication.

Table 111. Distribution of change from baseline in central foveal thickness, study 2309

Visit	Change from baseline in CFT (µm)	FTY720 1.25 mg N=359, n (%)	FTY720 0.5 mg N=350, n (%)	Placebo N=350, n (%)
Month 1	n	464	434	426
	< -40	17 (3.7)	18 (4.1)	14 (3.3)
	≤ -40 to ≤ -21	24 (5.2)	33 (7.6)	27 (6.3)
	> -21 to ≤ 20	378 (81.5)	334 (77.0)	352 (82.6)
	> 20 to ≤ 40	26 (5.6)	34 (7.8)	22 (5.2)
	>40	19 (4.1)	15 (3.5)	11 (2.6)
Month 3	n	400	392	386
	< -40	16 (4.0)	16 (4.1)	21 (5.4)
	≤ -40 to ≤ -21	24 (6.0)	37 (9.4)	43 (11.1)
	> -21 to ≤ 20	308 (77.0)	294 (75.0)	288 (74.6)
	> 20 to ≤ 40	32 (8.0)	30 (7.7)	24 (6.2)
	>40	20 (5.0)	15 (3.8)	10 (2.6)
Month 24	n	156	172	158
	< -40	8 (5.1)	14 (8.1)	14 (8.9)
	≤ -40 to ≤ -21	11 (7.1)	12 (7.0)	14 (8.9)
	> -21 to ≤ 20	98 (62.8)	116 (67.4)	103 (65.2)
	> 20 to ≤ 40	24 (15.4)	14 (8.1)	13 (8.2)
	>40	15 (9.6)	16 (9.3)	14 (8.9)

Source: Updated Special safety interim report (submitted 4/22/10)

The number of patients with change from baseline in CFT >40 µm *was higher for FTY 1.25 and 0.5 as compared to placebo at 1 month and 3 months. For other assessments (month 6, 12 and 18) and at the Month 24 visit, there was no difference. However, the number of eyes available for evaluation decreases with time, and patients with macular edema are withdrawn from the pool.*

The protocols included measurement of RNFL (retinal nerve foveal layer) thickness at selected centers as an exploratory analysis. The FDA inquired whether this analysis had been conducted. On July 7.2010 the applicant submitted this analysis. A total of 350 patients had RNFL data at baseline and at Month 12 or at Month 24, and 189 patients had measurements at all three time-points. Review of the data did does not demonstrate any clear differences between treatment groups particularly when examining change over time in patients with observations at each of the relevant time-points.

Dr. Wiley Chambers, FDA ophthalmologist consultant recommended that all visual acuity analyses be re-done in the application. The applicant tables report means using a method which is not scientifically correct without having converted the acuities to LogMAR first. A request that all analyses of visual acuity be converted to LogMAR was sent to Novartis on June 14, 2010. The response was submitted on July 6, 2010, wich included tables with summary statistics and changes from baseline in visual acuity in populations A, B, and E (not D). Evaluation of mean and median changes do not suggest worsening VA (data not shown).

6) Dermatologic examination

Following the report of skin malignancies from the study 2201E1, dermatological exams performed by a dermatologist were implemented when studies 2301 and 2302 were ongoing. Thus, while a number of cases were detected on study, no pre-study assessment was available to determine that the lesions were not present prior to initiation of study medication. In study 2302, the majority of patients had only one exam in the study, in most cases at the end of the study. In study 2301, the mean time to the first assessment (1119 patients) was 10 months for all treatment groups. At this time, approximately 70% of patients had normal examinations. Of the abnormal findings, most were benign. Any finding of cancerous skin disorders resulted in permanent study drug discontinuation. Skin neoplasms have been discussed in the Other significant events, serious and non-serious neoplasms.

In study 2309 a complete dermatological examination is being performed at screening and Month 24 or end of study.

> *Whether the risk of skin malignancies is increased in patients taking fingolimod should be studied in larger population, in the postmarketing setting. In my opinion, a baseline dermatologic examination should be recommended for all patients who start fingolimod treatment.*

7.4.6 Immunogenicity

Fingolimod is a small molecule. Antibody generation to fingolimod is not expected.

Given the effect on the redistribution of lymphocytes and a possible effect on immunosurveillance, the applicant conducted a clinical pharmacology study to evaluate the impact of fingolimod on neoantigen immunogenicity and recall immunogenicity.

StudyD2109 was an exploratory, randomized, double-blind, placebo controlled, parallel group, multiple dose study to assess the pharmacodynamic effect of fingolimod given for 4 weeks, on antibody response following multiple immunizations in healthy volunteers. The study included 72 healthy subjects (24 on FTY 1.25mg, 24 on FTY 0.5 mg and 24 on placebo).
Objectives included:
Primary
To measure the effect of once daily dosing of fingolimod for 4 weeks on the capacity to mount a T-cell dependent antibody response to KLH (Keyhole limpet hemocyanin) immunization.
Secondary
• To measure the effect of FTY on the capacity to mount
- A T-cell independent antibody response to PPV-23 (pneumococcal polysaccharides vaccine) immunization.
- A recall antibody response to TT (tetanus toxoid) immunization
- A cellular immune response (as measured by delayed type hypersensitivity using a KLH skin test)

• To assess the effect of FTY on common antigen skin test as measured by delayed type hypersensitivity
• To assess the safety and tolerability of fingolimod following once daily dosing for 4 weeks, including ambulatory blood pressure monitoring on Day 1 and at the end of study.

The study consisted of a 21-day screening period (maximum), a baseline visit (day -1), a treatment period of 4 weeks followed by a follow-up visit 2 weeks after last dose and a Study Completion evaluation approximately 4 weeks after the last drug administration. Subjects were domiciled in the center on days 1-4 for the loading dose regimen and also overnight on Day 28 to complete PK profiling. The subjects were discharged from the center 6 hours post-dose on Day 4 if they had normal vital signs, normal physical exam of the heart and lung, and no Atrioventricular (AV) block on ECG. The subjects returned to the study center on days 7, 14, 21, and 28 for study assessments, review of their drug administration diary and a pill count, and on days 29, 30, 42 and 56 for study assessments.

Subjects received intra-muscular injections of KLH adsorbed to aluminium hydroxide on days 7, 14 and 21, an intra-muscular injection of PPV-23 on day 7, and an intra-muscular injection of Tetanus toxoid on day 14. Blood samples were collected at various points throughout the study to assess levels of vaccine-specific IgM and/or IgG.

KLH alone (i.e. not adsorbed to aluminium hydroxide), *Candida albicans* and Tetanus toxoid were also administered to subjects intra-dermally during Screening and at day 28 to assess immediate and delayed hypersensitivity response, with delayed-type hypersensitivity measurements being assessed in the 2 days post each administration.

Eligibility criteria
Eligibility criteria were similar to that in the phase 2 & 3 studies. All subjects had a previous tetanus vaccination prior to entry to the study, confirmed by antitetanus IgG measurement during Screening. Key exclusion criteria for the study included: smokers, subjects vaccinated with live-attenuated vaccines within 2 months of screening, subjects with negative serology test for varicella-Zoster virus, subjects with allergy to shellfish, subjects with pathological features of the

retina or other eye disease, or abnormal corrected visual acuity, history of bronchospastic disease or other significant past medical history, presentation of skin lesions or unusual nevi.

Pharmacodynamic evaluation
Primary
To assess the primary objective, blood samples were collected at timepoints throughout the study to measure levels of KLH specific IgG and IgM following administration of KLH via intramuscular injection.
Secondary
• Blood samples were collected at timepoints throughout the study to measure levels of PPV-23-specific IgG and IgM, and Tetanus toxoid-specific IgG following administration of PPV-23 and TT via intramuscular injection.
• Immediate and delayed type hypersensitivity was assessed by investigator site staff by the measurement of wheal and erythema present on the arm of each subject following intradermal administration of antigens KLH, TT and *Candida albicans*.

Pharmacodynamic results are summarized in the following table.

Table 112. Summary results of study D2109

Test	Placebo N= 24	FTY 1.25 N= 24	FTY 0.5 N= 24
Primary endpoint			
KLH[1] neoantigen immunogenicity[2]	Detected at Day 14, maximum at Day 56	Reached maximum at Day 56	Reached maximum at Day 56
IgG antibody levels		31% of placebo	83% of placebo
IgM antibody levels		9% of placebo	9% of placebo
KHL responder rate[3]			
IgG antibody	>90%	57%	>90%
IgM antibody	>90%	0%	23%
Secondary endpoints			
PPV-23[4] neoantigen immunogenicity	Detected at D 14, maximum at D 21, persistent.	Reached maximum at week 4:	Reached maximum at week 4:
IgG antibody level	5 fold increase	50% of placebo	50% of placebo
IgM antibody level	5 fold increase	75% of placebo	30% of placebo
PPV-23 responder rate			
IgG antibody	54%	10%	41%
IgM antibody	68%	43%	41%
Tetanus recall[5] immunogenicity	Maximum detected:	Maximum detected:	Maximum detected:
IgG antibody level	5.5 IU/ml (31% increase from bsl)[6]	2.1 IU/mL (40 % increase from bsl)	3.7 IU/mL (19% increase from bsl)
Tetanus booster response rate	15%	5%	5%
Delayed type hypersensitivity[6]	Evaluation at week 4:	A week 4:	At week 4:
Positive Candida skin test	50% lost reaction	91% lost reaction	64% lost reaction
Positive Tetanus skin test	40% lost reaction	79% lost reaction	53% lost reaction

[1] KLH: keyhole limpet hemocyanin. [2] Neoantigen immunogenicity: ability to mount IgG and IgM response to neoantigen (an antigen to which there has not been prior exposure). [3] Responder rate: ability to mount a >4 fold increase in antibody levels (in the clinic >4 fold increase is considered "protective"). [4] PPV-23: pneumococcal vaccine. [5] Recall immunogenicity: ability to mount IgG response to booster immunization. [6] Similar number of

patients had baseline positive skin reactions (induration) to the two antigens in each treatment group. KLH immunization was also done but did not result in appreciable hypersensitivity reaction in either treatment.

In summary, there was a decrease in immune response to neoantigen immunization (more marked for IgM response), IgG recall antigen inmmunization and cellular immunitiy as compared to placebo, with evidence of a dose response.

- The capacity to mount a primary response to neoantigen KLH immunization was the primary endpoint of the study. IgG levels at maximum point were 31% of placebo in the FTY 1.25 mg, and 83% of placebo in FTY 0.5 mg. The IgM levels were only 9% of placebo for both, FTY 1.25 and 0.5 mg. The responder rate (the capacity to mount a > 4 fold increase antibody level) to KLH immunization was >90% for both placebo and FTY 0.5mg for Ig G antibodies; the IgG response rate with FTY 1.25 was only 57%. The IgM response rate to KLH was >90% for placebo, 23% for FTY 0.5 and 0% for FTY 1.25. This finding suggests a marked impaired response to KLH neoantigen response particularly for IgM, for the 1.25 mg dose, but also for FTY 0.5. *It is likely that patients will have a decreased response to vaccination.*

• Anti-tetanus toxoid IgG response was observed in a small number of patients over the course of the study in all treatment groups: 15% on placebo and 5% on fingolimod groups.

• The capacity to mount skin delayed type hypersensitivity was decreased in subjects receiving fingolimod treatment compared to placebo treatment, more marked in the fingolimod 1.25 mg treatment group.

A secondary endpoint in this study was the evaluation of 24 hour Ambulatory blood pressure monitoring. Compared to placebo treatment, fingolimod treatment resulted in an increase in mean systolic BP of approximately 2-3 mmHg (p=0.38 and p=0.61 for fingolimod 0.5mg treatment and fingolimod 1.25mg treatment) and in mean diastolic BP of approximately 5-6 mmHg (p=0.03 and p=0.08 for fingolimod 0.5mg treatment and fingolimod 1.25mg treatment) which is higher than what was observed in the phase 2 and 3 studies. Evaluation of the data suggests that night time rather than daytime contributes more to the increase in blood pressure seen with fingolimod treatment.

7.4.7 Evaluation of safety in phase 1 studies

- SAE in the Phase 1 clinical pharmacology studies.

This database includes studies that were uncontrolled as well as crossover studies, therefore, comparisons of risk/rate between FTY and placebo in the overall database can not be done. Twelve subjects had SAE in this database. Five were in placebo treated subjects and seven in FTY treated subjects.

Table 113. SAE in clinical pharmacology studies

Patient No.	Age/Sex	Study medication	Serious adverse event/infection	Day reported	Relationship to study medication
01-003	58/Male	FTY720 0.125 mg	Pneumonia	21	Not suspected
01-008	50/Female	FTY720 0.125 mg	Urinary tract infection	32	Not suspected
02-001	54/Female	FTY720 0.125 mg	Dyspnea	2	Suspected
04-001	21/Female	FTY720 0.25 mg	Gastroenteritis	33	Not suspected
01-032	50/Female	FTY720 5 mg	Herpes zoster	7	Not suspected
06-001	51/Female	FTY720 5 mg	Hepatic enzymes increased	3	Suspected
01-009	47/Female	Placebo	Cerebrovascular disorder	24	Not suspected
01-025	63/Female	Placebo	Tachycardia supraventricular	37	Not suspected
05-002	30/Male	Placebo	Gastroenteritis	4	Not suspected

Source: Table 2-98, ISS.

Findings in this dataset were consistent with those in the phase 2 and 3 studies, with events of bradycardia, AV Block, and hepatic enzyme increased (data not shown).

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There was a clear dose-response in terms of adverse events in this application, particularly for the serious events of macular edema, bradycardia and AV bloc as well as in liver enzyme elevations and decrease in pulmonary function tests.

7.5.2 Time Dependency for Adverse Events

Some events occurred immediately such as bradycardia and AV block. They were transient and mostly recovered without specific treatment, however, some required treatment or led to drug discontinuation. Other events tend to occur early, during the first few months of treatment, such as macular edema but they also occurred later. Some events are likely to occur with time and will need longer follow up (e.g. cardiac function, malignancies).

7.5.3 Drug-Demographic Interactions

Gender: Increased LFT was observed more in males as compared to females (See table below).

Table 2-30 Number (%) of patients with liver enzyme elevation AEs by gender in Group A (12-month safety population)

Primary system organ class Preferred term	Male FTY720 1.25 mg (N=266) n (%)	Male FTY720 0.5 mg (N=277) n (%)	Male Placebo (N=120) n (%)	Male Inter-feron (N=139) n (%)	Female FTY720 1.25 mg (N=583) n (%)	Female FTY720 0.5 mg (N=577) n (%)	Female Placebo (N=298) n (%)	Female Inter-feron (N=292) n (%)
Investigations	90 (33.8)	102 (36.8)	24 (20.0)	14 (10.1)	108 (18.5)	99 (17.2)	57 (19.1)	24 (8.2)
ALT increased	41 (15.4)	42 (15.2)	4 (3.3)	4 (2.9)	25 (4.3)	19 (3.3)	7 (2.3)	4 (1.4)
GGT increased	23 (8.6)	17 (6.1)	1 (0.8)	1 (0.7)	23 (3.9)	11 (1.9)	2 (0.7)	0
Hepatic enzyme increased	17 (6.4)	22 (7.9)	1 (0.8)	2 (1.4)	6 (1.0)	8 (1.4)	0	1 (0.3)
AST increased	8 (3.0)	10 (3.6)	0	2 (1.4)	15 (2.6)	5 (0.9)	2 (0.7)	3 (1.0)
Transaminases increased	8 (3.0)	5 (1.8)	0	0	3 (0.5)	4 (0.7)	0	1 (0.3)
Liver function test abnormal	4 (1.5)	6 (2.2)	0	0	5 (0.9)	2 (0.3)	0	2 (0.7)

A patient with multiple AEs within a primary SOC is counted only once in the total row.
A patient with multiple occurrences of an AE under one treatment group is counted only once in the AE preferred term for that treatment group.

Source: ISS.

No gender differences were found in the risk/rate of adverse events.

Analyses of mean change from baseline in PFT values by gender submitted on June 29, 2010 at the FDA request suggests a gender effect for FEV1 but not for DLCO. The drop in FEV1 absolute value was greater in females (160 ml for FTY 0.5 mg and 240 ml for FTY 1.25 mg) as compared to males (100 for FTY 0.5 mg to 150 ml for FTY 1.25 mg) at the 24 month evaluation. The changes in % of predicted DLCO or forced vital capacity were similar in males and females at 24 months.

7.5.4 Drug-Disease Interactions

Of note, certain patient groups were excluded from the Phase III clinical studies in MS. Based on the known pharmacological effects occurring after the first dose of fingolimod, patients with relevant cardiac conditions (symptomatic bradycardia, sino-atrial heart block, second or third degree AV block or vasovagal syncope, treatment with Class III antiarrhythmic drugs) were excluded. Based on previous clinical experience, patients with relevant pulmonary conditions, macular edema, diabetes mellitus and low white blood cell or lymphocyte counts were also excluded.

It is likely that these patients will have a greater risk of events than the healthy population included in this application. The proposed label recommends caution in use of fingolimod in such patients until experience is gained in those settings. My original recommendation was that fingolimod should be contraindicated in patients that were excluded from fingolimod studies, in particular, patients with diabetes and patients taking medications that were not allowed in the studies. Upon discussion at the FDA June 10, 2010 AC, it is recommended that patients at risk of developing serious events, particularly cardiovascular and respiratory events, be allowed to

use the drug with caution and be specifically studied in the postmarketing setting, such as in a study evaluating lower doses of fingolimod.

7.5.5 Drug-Drug Interactions

In the Phase III program, patients having used other MS therapies were allowed into the study, either directly after stopping prior therapy, or within a specified timeframe. However, no concomitant use of other currently approved immunosuppressants was allowed during the study. For results of drug-drug interaction studies the reader is referred to the Clinical pharmacology review.

> *At the FDA June 10, 2010 AC meeting it was recommended that concomitant use with other immunosupressants be evaluated, such as in the case when a patient needs to discontinue from fingolimod because of intolerance. It appears that since data are not available, those patients should undergo a washout before being treated with other immunosuppressants other than corticosteroids.*

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Increased risk of lymphoma was observed in carcinogenicity studies in mice. See review by Pharmacology toxicology reviewer.

No evidence of increased risk of malignancy was observed in the MS database, except for a potential increase in basal cell carcinoma. However, exposure is relatively short. See SAE of Neoplasms in this review. This issue should be addressed in longer term postmarketing studies.

7.6.2 Human Reproduction and Pregnancy Data

As of 29-Jan-10, a total of 30 pregnancies were reported in FTY720-treated patients. Of these, 13 resulted in successful delivery, 5 in spontaneous abortions and 8 in elective abortions. Four pregnancies are still ongoing. The 13 term deliveries included 12 normal newborns and 1 with a congenital abnormality: One 29-year-old female, who had received FTY720 0.5 mg for approximately 9 months in Study D2301 before she became pregnant, gave birth to a premature baby with a congenital shortening of the right leg (congenital posteromedial bowing of the tibia).

An updated report submitted on July 30, 2010 in response to the FDA request for information the applicant indicated that a total of 60 pregnancies have occurred in the Fingolimod MS program. A summary of the treatment group and outcome is presented below.

	Pregnancy outcome					
Treatment	Normal birth	Abnormal offspring	Elective abortion	Spontaneous abortion	Ongoing	Total
Fingolimod	13 [3]	1	9	6	5 [3]	34
Interferon beta-1a	2 [1]	0	2	0	0	4
Placebo	0	0	7	1	0	8
Still blinded	6	0	4	0	4	14
Total	21	1	22	7	9	60

[] = patient had already discontinued treatment by the time the pregnancy was detected.

A report of a baby with Fallot's tetralogy in a patient who had received fingolimod 1.25 mg/day was recently submitted to the IND as a 15-day report. It is unclear whether this case is related to fingolimod use. Sphingosine 1-phosphate is known to be involved in angiogenesis and vascular development, however, this is the first case of reported cardiovascular malformation.

Azoospermia was reported in two patients undergoing fingolimod treatment, in non ISS studies.

> *Although patients were supposed to follow adequate contraception, a high number of pregnancies was observed in the MS program. A consultation to the Maternal Health Team has been placed and is pending at the time of this review.*

7.6.3 Pediatrics and Assessment of Effects on Growth

Were not conducted in the application.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The assessment of abuse potential of fingolimod was reviewed by the Controlled Substance Staff. There does not appear to be potential for abuse with fingolimod.

7.7 Additional Submissions

The DNP and FDA consultants requested several request for information and additional analyses. The applicant has responded in a timely manner to the FDA requests. The 4-month Safety Update Report was submitted on April 21, 2010. Review of the SUR, updated special safety interim report and responses to FDA requests for information have been incorporated throughout this review up to June 10, 2010.

8 Postmarketing Experience

There is no postmarketing experience with fingolimod.

9 Appendices

9.1 Literature

Literature citations have been incorporated into the body of the review.

9.2 Labeling Recommendations

Draft labeling recommendations were sent to the team in a separate document on July 15, 2010.

9.3 Advisory Committee Meeting

The Peripheral and Central Nervous System Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research, met on June 10, 2010, at the Hilton Washington DC/Silver Spring,, MD., to discuss NDA 22-257.

The committee unanimously voted that fingolimod 0.5 mg had demonstrated substantial evidence of efficacy in reducing the rate of MS relapse, and 24/1 that it had demonstrated evidence of effectiveness in delaying the accumulation of physical disability, and that fingolimod could be used as first line therapy.

The majority of the committee agreed that studies should be conducted to evaluate the effects of doses lower than 0.5 mg once daily to see if efficacy would be maintained while reducing adverse events, and that such a study could be done as a postmarketing study.

The committee members agreed that patients should be required to receive the first dose in a monitored setting due to the risk of bradycardia and heart conduction abnormalities. The cardiologists on the committee recommended that only a specific subset of patients be monitored: groups excluded from the studies, patients with heart rate <60 bpm, patients on beta blockers and/or calcium channel blockers concomitantly. However, the majority of the committee members agreed that all patients should be required to receive the first dose in a monitored setting. ECG before starting fingolimod therapy was also recommended.

The majority of the committee agreed that routine ophthalmologic assessments of M.S. patients are not being performed by neurologists and thus recommended that patients should have a baseline ophthalmologic evaluation by an ophthalmologist, and neurologists should monitor visual acuity in patients treated with fingolimod.

The committee's pulmonologist recommended baseline pulmonary function tests (PFTs). The majority of the panel agreed with this recommendation.

The committee agreed that postmarketing safety studies should be required, and noted a number of specific safety concerns. They were particularly interested in data on the use of fingolimod in patients excluded from the trials, notably patients with diabetes and cardiovascular disease . They were also particularly interested in establishing optimal screening and surveillance practices, especially in populations deemed to be at higher risk due to preexisting conditions,

comorbidities, concomitant therapies, and duration of therapies. The majority of the committee agreed that routine pharmacovigilance (spontaneous postmarketing AE reporting) is not sufficient to mitigate the risks associated with the pulmonary toxicity of fingolimod.

9.4 Narratives from multiple sclerosis studies

9.4.1 Additional details for selected narratives of Death.

- 2302-0212-00021: Herpes zoster disseminated, acute hepatic failure, multiorgan failure

29 year old female, randomized to FTY 1.25 mg in study 2302. She was diagnosed 1 year prior to study entry but symptoms had started 2 years before diagnosis. She had 3 relapses in the 2 years prior to study entry and 3 relapses in the year prior to study entry. She received the last course of steroids 1 year prior to study entry. The patient had been treated with INF β1-a s.c (Rebif) at some point before study entry (date not reported). At baseline the EDSS score was 1. She worked as a teacher in a local nursery for children 0-3 years. (She had not have varicella as a child. She was VZV IgG negative).

On Day 212 she complained of 6-day history of progressive weakness of the limbs. Blood tests were performed. The investigator suspected a relapse and started treatment with intravenous (iv) methylprednisolone (MP) 1 g daily. On Day 231 she was reported to have complete recovery from MS relapse. On Day 272, at visit 9, she reported no symptoms.

On Day 300, 70 days after recovery from the previous relapse she was suspected to have another relapse. She had paresthesias and hypoesthesia in both feet. She received no treatment and continued working. On Day 306 she reported worsening symptoms. On Day 309, iv MP 1 g daily for five days was started. She continued to work at the nursery. (She subsequently reported that there was a varicella outbreak in the nursery at that time.) On Day 310 she reported epigastric pain, treated with omeprazole. On Day 314, after completing the 5-day iv MP course she continued oral steroid therapy 48 mg daily without the knowledge of the investigator.

On Day 317 she developed increasing epigastric pain and went to the emergency department. At that time she was found to have increased transaminases (“approx. 300”) and was admitted to the hospital. Drug induced liver injury was suspected. Study medication was discontinued on Day 317 due to herpes zoster disseminated. In addition to increased liver enzymes (“approx 1200”), she was found to have vesicles in her throat and a vesicular eruption on the trunk. She was treated with intravenous Acyclovir. Later that evening she developed acute liver failure and disseminated intravascular coagulation. Serology for hepatitis viruses A, B and C were negative. Herpes virus serology and aspiraton of skin lesions were performed and reported to be positive for varicella zoster virus (VZV). On Day 320 her condition deteriorated, with multiorgan failure. The cause of death was acute hepatic failure.

An autopsy showed massive hepatic necrosis with giant mononuclear cells with morphological alterations consistent with herpetic infection (possible VZV); non-alcoholic steatosis perivenular centrolobular fibrosis and neofibrillogenesis. Kidneys had signs of shock. Lungs revealed edema and endoalveolar hemorrhagic effusions. Heart had subendocardial and subpericardial hemorrhages and fibrinous pericarditis. The esophagus had subepithelial mucosal hemorrhages, “occasional aspect of viral esophagitis (possible herpes virus/VZV).” The diagnosis was reported as massive hepatic necrosis consistent with viral herpetic infection complicated by consumption

coagulopathy in a patient with MS; viral esophagitis and steatotic non-alcoholic hepatopathy. The event was considered related to study medication.

Although drug toxicity was suspected at some point, she was found to have active disseminated VZV infection that could explain liver necrosis and multiorgan failure.

- **2302-0821-00007**: Herpes simplex encephalitis, grand mal convulsion, coma

23 year-old Asian male, randomized to FTY 1.25 mg in study 3202. The patient had been diagnosed 2 ½ months prior to study entry. He had 3 relapses in the 2 years prior to study entry and 3 relapses in the year prior to randomization. His last relapse occurred 2 months prior to entry and was treated with steroids. He received INF beta 1b before entering the study. Baseline EDSS score was 3. He had no other significant medical history.

Approx. 11 months into treatment (Day 255) he experienced fever, headache and upper respiratory symptoms. Drug was permanently discontinued. The following day he developed sudden generalized tonic-clonic seizures and was hospitalized. Blood testing was unremarkable. CSF tests did not reveal any significant findings except for an increased opening pressure of 22 cmH_20. In the CSF, microbiological analysis was negative. On Day 278, HSV 1 & 2, IgG was negative, IgG antibody to VZV was positive. A brain MRI scan showed diffuse low intensity lesion at the left temporal and parietal cortex and subcortical white matter. No specific diagnosis was made and the patient was treated with oxcarbazepine. He continued to have intermittent high fevers and partial seizures with secondary generalization, treated with phenobarbital. His level of consciousness rapidly deteriorated. A follow-up MRI revealed a markedly progressed confluent cortex and subcortical white matter lesion with extensive gyral swelling. The patient received antibiotics for aspiration pneumonia and high dose methylprednisolone. He was transferred to another hospital. A second CSF sample supported the diagnosis of a viral encephalitis (PCR was positive for HSV-1). He was treated with acyclovir. Additional CSF from this second sample was sent to the NIH and was negative for JC virus.

His condition deteriorated and he died 2 months after study drug discontinuation. An autopsy was not performed. Last available lymphocyte count was 0.43 x 10^9/L on day 183 (nl 0.8 – 2.8). No additional values are available after this visit.

- **2302-0254-00011 –** Acute Disseminated Encephalomyelitis (ADEM) and aspiration pneumonia

A 42 year old, Caucasian male (0254/00011) with RRMS was enrolled in study FTY720 D2302 and randomized to FTY 1.25 mg/day. He had been diagnosed with MS 2 and ½ years prior to study entry. He initially presented with quadriparesis. He had four additional relapses (two in the 2 years prior to randomization and two in the year prior to randomization) treated with steroids. Immunomodulators used prior to entering the study were INF β 1-a s.c (date not known), and azathioprine (two years prior to entry for about 2 months). No concomitant immunomodulators were taken at the time of the study. The last steroid course had been completed 9 months prior to entry. At the time of screening he had an EDSS of 5. The patient's VZV IgG antibody status was negative. No other medical history was reported for this patient.

On Day 348, approximately 11 months into FTY treatment he was hospitalized with fever, headache, cough, and mild hemoptysis. The hemoptysis initially reported by the patient was not

persistent, not detected on examination and determined to be non-clinically significant. A chest x-ray revealed increased bronchovascular markings. AE was coded as chest infection. He was treated with paracetamol and antibiotics. The study medication was permanently discontinued.

On Day 351 he was transferred to the neurology department because of generalized tonic-clonic seizures associated with fever of 39.5C, hypertension (170/110), hyperglycemia (450 mg/dL) and hypocalcemia (3.31 mg/dL: nl 8.4-10.3). He was treated with phenytoin and seizures stopped. He regained consciousness but remained confused. A brain CT scan without contrast was reported as normal. A lumbar puncture was performed and the CSF was clear, colorless, with no cells; glucose 86 mg/dl (nl 60-90 mg/dl); protein 13 mg/dl (nl 15-45 mg/dl); LDH 35 U/L (nl 12-24 U/L); culture no growth; and cytology no cells. PCR for HSV-1, HSV-2, and JC virus testing (*not at NIH*) were negative. A brain MRI read by the local neuroradiologist showed bilateral deep and high parietal, bilateral frontal, basal ganglia and pontine foci of altered MRI signal surrounded by abnormal periventricular white matter signal intensity, suggestive of multiple demyelinating foci (MS) vs. ischemic foci (lacunar infarcts).

The central MRI reader subsequently reviewed the current MRI and compared it to the baseline MRI. On the current MRI scan, there was one new T2 lesion in the left frontal region, which could not readily explain the patient's clinical presentation. Otherwise, there were no remarkable findings, especially no evidence for infections. On both the baseline and current MRI scans, there were numerous T2 lesions in the periventricular region, deep white matter, and infratentorially. The distribution and appearance of most lesions was consistent with MS, but additional pathology, such as vascular lesions or metabolic disease, could not be ruled out.

On Day 353 the patient was transferred to the neurology intensive care unit. EEG showed diffuse slowing at theta rhythm. His level of consciousness appeared to improve, but on Day 359 started to deteriorate again. At that time he was found to have a urinary tract infection. On day 363 he again developed generalized tonic clonic seizures, with further deterioration in his level of consciousness. Glasgow Coma Scale (GCS) was 8-9. He was subsequently treated with MP 1 g/day for 5 days, followed by an oral steroid taper. On Day 366 he developed metabolic acidosis. On Day 367 he improved his GCS score to 11-12.

On Day 373 he was able to go to the bathroom on his own. Follow up tests performed as part of a vasculitis work-up were negative for autoantibodies (ANA, Ds-DNA, SM, SSA, and SSB). Viral serology tests suggested prior exposure to CMV and EBV IgG(+) , with CMV, EBV, HSV-1 and HSV-2 IgM(-). As per the patient profile, on Day 369 IgG antibody to Varicella Zoster virus was 661 U/L. On Day 379 he was fully conscious with a mini mental status exam of 19/30. He had intermittent coarseness and emotional liability, but otherwise no changes in neuro exam. He was discharged from the hospital with a plan to be re-admitted after a holiday. He was able to stand but required assistance with walking. The patient was re-admitted to the hospital after the local holiday period. The diagnosis on the SAE follow-up form was 'acute disseminated encephalomyelitis (ADEM) on top of multiple sclerosis'. According to the investigator, the diagnosis was made according to the clinical picture: 1) disturbed consciousness level – delirious state and 2) convulsions.

On Day 395, a follow-up brain MRI showed no changes since the previous examination. On Day 425, while still hospitalized, the patient was noted by his wife to have mental and behavioral changes. He became more aggressive with her and others. He subsequently developed urinary and fecal incontinence. On Day 427 his medications were adjusted: reduction of prednisolone dose from 40mg to 30mg po daily, addition of risperidone to control his recent aggression and behavioral changes, discontinuation of SSRI antidepressant, and continuation of antiepileptic

medication. A neurological examination revealed new findings of decreased attention and disorientation to place and time. On Day 435, the patient was discharged home at the request of his family.

On Day 530, the patient's caregiver reported to the investigator that the patient's movement was now difficult with weakness of both upper and lower limbs to the extent that he could not move without support. Superficial bed sores were present on the patient's back. Mental and behavioral changes were also noted in the form of aggression towards the patient's caregiver. The patient's orientation was not normal and he had bouts of confusion.

On Day 535 of the study, 187 days after fingolimod discontinuation, the patient died due to aspiration pneumonia. Prior to his death he was reported to be dehydrated and feverish and have bulbar symptoms. No autopsy was performed. According to the investigator, the events (acute disseminated encephalomyelitis, lower respiratory tract infection) required hospitalization, while the event (aspiration pneumonia) resulted in death, and all three were related to study medication.

This event was reviewed by an independent Data and Safety Monitoring Board (DSMB). According to the DSMB neurologists, although the patient's neurological history and baseline MRI scan may be consistent with a diagnosis of MS, there were atypical features in both the clinical presentation and baseline MRI scan. The normal CSF and a brain MRI at the time of the adverse event with no relevant changes do not support an infection and make a MS relapse unlikely as the cause of the events that started almost one year into fingolimod treatment. According to the DSMB neurologists, ADEM is not usually diagnosed in the context of already established MS. ADEM is a diagnosis of exclusion and is usually associated with large, often confluent new MRI abnormalities, with or without enhancement.

In summary this was a 42 year old male with a 3 year history of MS, who presented an ADEM-like clinical picture while on treatment with fingolimod 1.25 mg/day. The MRI showed a new T2 lesion that did not explain the extent of neurologic changes. JC virus testing done at a laboratory in Europe was negative. No samples remain for additional testing. The last available lymphocyte count in the patient profile on Day 105 was 0.4 x 10^9/L (normal 0.l8-2.8) but neurologic changes occurred on Day 348. This case was evaluated by Dr. Heather Fitter, DNP neurologist, who offered the following differential diagnoses: MS relapse in the setting of multiple infections, seizures and steroid induced encephalopathy, and PML.

- **2306-0362-0005:** rapidly deteriorating MS

46 year old male, enrolled in study 2306 (ongoing study). The patient reported first MS symptoms four years prior and was diagnosed with MS approximately 2 and ½ years prior to entering the trial, based on at least one year of disease progression, presence of at least nine T2 lesions in the brain MRI, at least two T2 lesions in the spinal cord MRI and oligoclonal bands in the CSF. The EDSS at baseline was 4.0 due to a visual acuity deficit (FS 2), a mild pyramidal deficit (FS 2), mild ataxia (FS 2), symptomatic mild sensory deficit (FS 2) and mild to moderate cognitive deficit or fatigue (FS 2) associated to restricted walking (>500 m). The patient was not treated with MS disease modifying therapies prior to study entry. Concomitant medications taken prior to randomization included: amantadine for fatigue, fesoterodine and tamsulosin for mictional urgency and citalopram for mood swings, all of them taken for approx 1 ½ years prior to study entry.

After 9 days on study drug, the patient presented with an AE of "muscle spasm left leg" that was treated with Baclofen (two days before the patient had been treated with Botulinium toxin for spasticity, location unknown). Approximately 1 month into study drug treatment, he was not able to walk 100 meters without assistance (EDSS 6). On Day 39 into study drug treatment, the patient presented with urinary tract infection treated with antibiotics.

On Day 49, the patient experienced “pain all over the body”. The activities of daily living had become more difficult. There was frequent urinary incontinence. Spastic contraction of muscles of hand and feet were reported. No other relevant AE is reported in the clinical data base. Around this time, the patient started treatment with miconazole for "prevention of mucositis".

On Day 59, a neurological examination showed signs and symptoms of general deterioration that was considered to be consequence of the previous urinary tract infection and required hospitalization. However, the patient did not agree to an admission to hospital and wanted to stay at home. The investigational site advised the patient to stop study medication. The patient continued to take study medication until the supply was exhausted (unclear how many days).

The patient became gradually worse. A month after the neurology visit the patient experienced a severe lower respiratory infection. On Day 103 of the study, the patient died due to rapidly deteriorating MS. No autopsy was performed. The investigator indicated that the event was due to progression of underlying illness. The investigator did not suspect a relationship between the event and the study medication.

In summary, this was a 46 year old male with 2 and ½ years history of MS, who had not received immunomodulators for MS, who 9 days into fingolimod treatment developed muscle spasm and deterioration of neurologic status that was thought to be related to a urinary infection. Three months into fingolimod treatment he developed a severe respiratory tract infection. There was no autopsy, no following MRI, no adequate work up to rule out opportunistic infections, no information on level of immunosuppression achieved by this patient.

In my opinion, these two last cases may represent MS relapse/progression of disease but another cause, such a CNS opportunistic infection can not be ruled out. In one case, extensive work up was done and an infection was not identified (however, PML is not completely ruled out as JC virus PCR testing was not done at the NIH). In the second case, there was worsening of the neurologic condition without any assessments to rule out causes other than MS progression. Both cases were complicated by fatal respiratory infections. No data on lymphocyte counts are available at the time of the deaths.

Deaths reported subsequent to the original submission

- **1201E-0005-00001:** Multiple sclerosis relapse, possible malignant kidney, lung, brain tumor, and lymphoma, coagulopathy, pancytopenia. Aspiration bronchopneumonia.

  42 year old Japanese M, randomized to FTY 1.25 mg in study D1201. He completed the 6-month core study and received FTY 0.5 mg during the extension study. He was diagnosed with MS five years prior to entry and had had 6 relapses treated with steroids since diagnosis. He did not receive other immunosuppressants prior to randomization. Baseline EDSS score was 4. He had

no significant medical history. At the end of the core study an MRI showed new T2 weighted lesions in the deep white matter of the anterior horn of the right lateral ventricle and left centrum semiovale. These lesions showed clear ring shaped enhancement on Gd-enhanced T1 weighted scan, suggesting the destruction of the blood brain barrier (BBB). These lesions were considered to be new MS lesions. He entered the extension study and continued taking FTY.

Approx. 1 ½ months into the extension study he was admitted for a course of steroid pulse (MP 1 g/day x 3 days) for MS relapse. MS symptoms deteriorated and he became unable to walk. He was admitted to the hospital with right hemiparesis and received a second course of steroid pulse. He was discharged from the hospital unable to walk, with decreased cognitive function and steroid psychosis, but readmitted a week later for worsening paresis. A repeat MRI showed spreading of the demyelinating lesion on the left parietal lobe with strong inflammation causing Blood Brain Barrier (BBB) destruction in the central area.

One month later, study drug was discontinued and the patient received three more courses of steroid pulse therapy. MRI was unchanged.

One month after drug discontinuation, based on the MRI scans, the possibility of brain malignant lymphoma in addition to MS was considered, however, CSF testing showed an extremely small quantity of lymphocytes with no malignant cells. Two more courses of IV pulse steroids were given (total of seven pulses within 2 ½ months), followed by oral prednisolone 60 mg/day for 3 more months.

Right after the seven IV steroid pulses, a brain MRI showed that the lesions "were disappearing to some extent". Magnetic resonance spectroscopy (MRS) showed no increase in choline. At this time the probability of malignant lymphoma was considered to be low, although it could not be ruled out. A biopsy was not performed. In the investigator's opinion the relationship to the event of MS progression and study drug could not be ruled out. *FDA reviewer's comment: high dose steroid treatment may certainly have reduced the size/number of lesions and tumor activity if this were a malignant lymphoma.*

Seven months after drug discontinuation (two months after completing high dose oral steroids) the patient was readmitted to the hospital with suspected malignancy of the lungs, based on a chest X-ray with multiple irregularly shaped tumor lesions. The patient had concurrent aspiration pneumonia. A CT scan of the chest and abdomen showed multiple low absorption regions and nodules in both lungs and both kidneys, pleural effusions and atelectasies. Small scattered lymph nodes were found in the pulmonary hilum, mediastinum, neck and axilla and paraaortic area along with hepatosplenomegaly. The findings suggested an atypical malignant lymphoma or metastases of malignant tumors. The patient was pancytopenic and lab tests showed abnormal coagulation.

A kidney biopsy was performed (8 months after study drug discontinuation). An Epstein-Barr (EB) virus related lymphoproliferative disorder was possible. However, the diagnosis could not be confirmed because tissue was not available for additional staining. Results of the kidney biopsy, as reported in MedWatch report):

Sample 1 tumour tissue showed cells with large irregular abnormally shaped cores with high solidity. The cell cytoplasm with either clear or acidophillic. In the inner portion of the tumour, tubule tissue that had been taken in was present. From hematoxylin and eosin (HE) staining, renal cell carcinoma G3 appeared most likely. In some areas, cells were also lymphoid. Sample 2 kidney tissue showed no clear invasion of tumour cells. Immunostaining of sample 1 showed negative keratin. It had been hypothesized that the

structure originated in the epithelium but from HE staining, this appeared unlikely. Vimentin was positive, but desmin and alpha smooth muscle actin were negative. L26 was negative and CD3 was partially positive. However, it was not possible to make a clear determination. Ki-67, CD-68 and EB (Epstein-Barr) virus were positive. An EB virus related lymphoproliferative disorder was possible, but since only a small amount of biopsy tissue was available and additional staining was not possible, a determination could not be made.

An MRI of the brain showed demyelinating lesion was in remission after steroid therapy, although gliosis and hemosiderin deposits remained. Multiple nodular lesions with ring enhancement and micro hemorrhages were identified. A new, similar lesion with edematous changes was identified. A MR spectroscopy then revealed that the lesion showed an increase in choline and a decrease in N-acetyl aspartate (NAA). The ring enhancement and the fact that many lesions were in the cortical white matter was typical of metastases to the brain. So, the radiologist noted that it was possible that the lesions in either the chest or abdomen were the primary site. A repeat CT of the abdomen showed persistent kidney tumors and lymph node enlargement, and new multiple liver tumors. The finding was consistent with possible metastasis or malignant lymphoma.

An upper endoscopy was conducted and identified a possible tumor in the esophageal mucosa and multiple polyps in the stomach. A biopsy showed no malignancy, but tested positive for H pylori. A gallium scintigraphy showed increase in uptake to the upper left abdomen (probably the stomach) and to both kidneys. Suspected illnesses included interstitial pneumonia, malignant lymphoma of the kidneys and leukemia invasion of the kidneys. Possible determinations for the uptake to the stomach included gastritis and malignant lymphoma. Because of the low platelet count, a repeat biopsy or a bone marrow aspiration were not conducted. The investigator suspected a relationship between the ongoing events and study drug.

Eleven months after drug discontinuation and approximately 5 month after completion of high dose oral steroid treatment the patient showed invasive erythematous eruptions. A skin biopsy was "highly suspicious of T cell lymphoma" of the skin based on both immunostaining results and gene rearrangement using skin tissues. A CT scan showed that nodules in lung and kidney were increased in size/number (although at some point they had been reported to be somewhat decreased). The patient died approximately 1 year after drug discontinuation, after receiving FTY 0.5 mg daily for 8 ½ months.

Appendix 9.4.2 Brief narratives of SAEs in the Cardiac disorders SOC (Rhythm and conduction disorders), Safety pool D

Patient ID	Age /sex	Preferred term	Rel Study day		Comment
Placebo					
2301 0312_00004	31 M	AVB 2nd degree sick sinus syndrome	DAY 684	-	History of Borrelia myocarditis; reported prior episodes of AVB 2nd and 3rd (not documented). No concomitant meds. On Day 684 admitted to pre-collapse ECG sinus rhythm, 52 /min. Chest Xray normal. During monitoring found to have intermittent 2nd degree AVB, type 1 (Wenkebach). Asymptomatic during these episodes. Echo: mild mitral insuff. Recovered, completed core and entered extension.
2301 0909_00006	36 M	Palpitations Bradycardia Presyncope	121	dc	History of non-cardiac chest pain 7 years prior. History of orthostatic dizziness. Concomitant meds: tadalafil, gabapentin and citalopram. Baseline HR= 54-66 bpm. On Day 1 he had non-cardiac chest pain that recovered by Day 8. On Day 120 he had pre-syncopal episodes and bradycardia, with dizziness, sharp central chest pain and palpitations. Ten days before the event he had discontinued citalopram. ECG on Day 121, HR= 42 rpm, QT prolongation= 516ms and QTcB=430 ms. Study drug was discontinued. Repeat ECG: sinus bradycardia, otherwise normal. Echocardiography on Day 122 was normal. The event was not considered related to study drug.
FTY720 5 mg					
2201 0019_00006	26 F	Ventricular extrasystoles Bradycardia	1	dc	No CV history. ECG at 6 hours post dose showed arrhythmia; ventricular premature complexes. Bigeminism with moderate bradycardia. Drug was discontinued. No follow up.
2201 0025_00016	52 F	Bradycardia also chest pain & dyspnea	1	dc	History of intermittent dizziness with syncope. Baseline pulse: 73; BP 115/76. 2 hours after dose, pulse dropped to 47 bpm, BP 122/80. Lowest pulse was 43, 4 hours post dose. Six hours post dose, pulse was 48 and BP was 124/77. ECG showed sinus bradycardia. Symptoms: cold sensation, dizziness, flushing, oppression in chest. On Day 4 patient presented sharp chest pain and dyspnea. Study drug was discontinued. No cardiac enzymes available. On day 31 she was still not feeling well but ECG and chest X-ray were normal.
2201 0066_00006	41 F	Bradycardia	**2**	-	No CV history. Baseline pulse: 68, BP 120/60. Day 1, 4 hours after dose, pulse: 54; BP 110/60. She went home after 6-hour observation. She had a Holter monitor. She woke up at 2 am with oppressive thoracic pain extending to both arms associated with nausea and vomiting that lasted for 5-6 hours. At the ER her BP was normal, pulse was 45 bpm. ECG showed sinus bradycardia. CK and troponin were normal.

					Cardiologist saw her within the first 24 hours, ECG sinus rhythm 55 bpm, otherwise normal. Echocardiography was normal. Stress test was submaximum, but negative. Diagnosed as non-anginal chest pain. Recovered. The Holter ECG recorded during the first 24 hours after study drug initiation showed no rhythm or conduction abnormalities. Mean HR decreased in the first 10 hours. The lowest HR registered was 34 bpm at 1:59 am. Drug was interrupted and re-started on Day 8, at 1.25 mg, and increased to 5 mg one week later. ECG at beginning of extension phase showed inverted T waves. She has remained in the study with no other cardiac symptoms. She is currently participating in the extension study. (updated narrative 4/22/10)
FTY720 1.25 mg					
2201 0018_00003	44 F	AVB first degree	1	-	History of HTN. Day one, baseline pulse= 81; BP 156/110; 4 hours post dose pulse dropped to 64, BP 147/75. ECG at 6 hours: 1st degree AVB. Symptoms: chest pain at 3 hours post dose. Recovered. Drug not discontinued. She is still in the study.
2301 0101_00003	42 M	Bradycardia	1	**dc**	No CV history. Active smoker. Baseline HR 76 pm. He experience bradycardia with the lowest heart rate=49 bpm registered 13.5 hours after first dose. Hospitalized. Asymptomatic. ECG not performed at the time of event. Study medication was discontinued on Day 2. Pt recovered.
2301 0176_00001	45 F	Bradycardia & dyspnea	1 11 (1st re-dose)	- **dc**	No CV medical history. Smoker. Day 1 pre dose, HR- 72-74, and BP 95/62 - 112/48 mmHg. 2 hours post dose both variables started to decrease. Lower HR recorded was 52 bpm 5 hrs post dose. Lowest BP 94/52. Asymptomatic. Hospitalized. On Day 2, mild dyspnea and bradycardia. Drug interrupted. Events resolved on day 9. Drug re-started on Day 11 noted to have other event of bradycardia and dyspnea which led to permanent drug discontinuation. All ECGs were normal. No change in PFTs. Pt discontinued study on day 12.
2301 0180_00007	53 M	Bradycardia	1	**dc**	No CV history. Smoker. Concomitant medications amitriptyline, ibuprofen. Baseline ECG: L anterior hemiblock. Day 1 Baseline HR= 64 bpm; BP 114/74. After first dose developed bradycardia. Lowest HR recorded was 38 bpm (4 hours post dose), lowest BP 96/54. Study drug permanently discontinued because of this event. Patient was asymptomatic. He was not hospitalized and did not undergo further monitoring. Even considered resolved the same day. Four days after drug discont, pulse was 58bpm.
2301 0404_00002	49 F	Bradycardia	1	-	History of HTN, MI (7 years prior) on captopril, HCTZ, thyroid replacement and venlafaxine. Non-smoker. Baseline HR 58-68 pm. 4 hours after first dose HR= 46 pm. Asymptomatic. Hospitalized. Recovered day 2 without specific treatment. No action taken with study drug
2301	25 F	AVB first	1	**dc**	No CV history. Non-smoker. Four days prior to randomization reported nausea. First

0405_00001		degree			dose, during first 6 hrs HR 56-64 bpm, BP 90/60-120/60. 1-2 hours post dose had nausea. At 6 hours HR=50 bpm. ECG post dose showed prolonged PR interval of 40 ms compared to pre-dose. She was hospitalized. At 7 hrs HR=45 bpm. Second ECG showed PR= 300 msec (First degree AVB). Patient transferred to ICU. She was given IV potassium. She complained of dizziness. The following morning HR=56 bpm at 7 am, with normalization of PR to 180 ms. At 10 am HR=60 bpm. Study drug was discontinued.
2301 0612_00002	46 M	Bradycardia	1	-	No history of heart disease. Smoker ½ pack daily for 3 years. No concomitant meds. Baseline HR before first dose= 80 bpm. Pt was hospitalized with asymptomatic bradycardia for overnight monitoring. Lowest HR= 48 bpm at 10 hrs post dose. Gradually recovered after 15 hrs post dose. Completely recovered on day 3. No action taken with study drug.
2301 0651_00016	27 F	Angina pectoris & AVB 2nd degree	1 16	- **dc**	Symptomatic 1st degree AV block" 4 years prior (as per narrative; not in patient profile). History of asthma (as per patient profile). Non smoker. Pre-dose HR=83 bpm; ECG: 1st degree AVB, PR 208, QTc 448. Day 1: 3.5 hours after first dose developed shortness of breath, chest pain and irregular pulse. ECG showed first degree AVB (PR 344 ms). Repeat ECG 6 hrs post-dose showed 2nd degree AVB (type 1). Pt hospitalized. At 9 hrs post-dose, she felt chest discomfort and dyspnea. She received treatment with atropine and symptoms improved. She recovered completely within 24 hrs. The following day she received 2nd dose and did not have any symptoms. She continued taking fingolimod at home. On day 4 she was readmitted with "flashes" in the eyes and painful eye movements, dyspnea and overall feeling unwell. Symptoms resolved by Day 6 and she went home. On Day 16 reported chest pain and pressure similar to those after first dose. An ECG done in an ambulance showed unspecified abnormalities. Admitted to hospital, ECG showed "increase in conduction disorder". Cardiologist advised the patient to stop study medication. She was discharged home. On Day 17 again had chest pain but ECG showed no AVB. On Day 19 she was given low dose of nitrates IV and was discharged. DSMB cardiologist agreed with diagnosis of AVB 2nd degree type 1 and thought that prior history of symptomatic first degree AVB may indicate chronic AV nodal disease or dysfunction. PFTs done on Day 62 showed decreased DLCO >20%. *(As per the patient profile drug was discontinued after the first dose. Upon FDA request for clarification the applicant confirmed that there was no interruption of treatment from Day 1 to Day 17. The AVB occurred one day after study drug dc).*
2302 0211_00003	41 F	Arrhythmia Bradycardia	1 1	**dc**	No CV history. On Day 1 hospitalized with first degree AVB with bradycardia/ arrhythmia. Medication was kept on hold and then discontinued due to these events.

		AVB 1st degree	1		She recovered within 24 hours. No treatment details available.
2302 0219_00010	28 F	AVB 2nd degree	1	**dc**	No CV history. On Day 1, six hrs after first dose she developed severe AVB 2nd degree (Mobitz type 1) and was hospitalized. At the time she had chest discomfort. Drug was discontinued due to this event. Event recovered the same day without specific treatment.
2302 0326_00010	38 F	AVB 2nd degree	1	-	No CV history. Smoker 20 cigarettes/day x 15 years. On Day 1, 4 hrs after first dose experienced chest discomfort, palpitations, bradycardia and decreased BP. Hospitalized with 2nd degree AVB confirmed by ECG. She recovered without specific treatment. DSMB cardiologist stated ECG showed Wenkebach 3:2 AVB with narrow QRS. Patient is currently in extension study.
2302 0333_00007	29 F	Bradycardia	1	-	No CV history. HR at baseline was 89 bpm. On Day 1, hospitalized for arrhythmia, sinoatrial block and bigeminy. No action taken to study drug. Event resolved the next day. DSMB cardiologist noted that one of ECGs taken had shown atrial bigeminy (9/20 At 5:39); all others show right atrial rhythms with normal rates and some subtle shifts in P wave morphology that could be due to changes in posture or shift in the primary pacing site within the sinus node complex (usually of no clinical significance). Patient discontinued study drug in core phase, on Day 47.
2302 0361_00009	31 F	Bradycardia	1	-	No CV history. On Day 1, 6 hrs after first dose hospitalized due to asymptomatic bradycardia. Minimum HR 50 bpm. No specific treatment or action taken with study drug. Event resolved on Day 2.
2302 0361_00013	36 F	Bradycardia	1	-	History of depression and smoking. Conc meds: trazodone. On Day 1, after first dose, hospitalized for asymptomatic bradycardia. Lowest HR was 51 bpm at 10 hrs. (baseline HR was 84). No specific treatment or action taken with study drug. She recovered on Day 2. She discontinued on Day 140.
2302 0364_00007	44 F	Sinus bradycardia	1	N	History of diabetes, hypercholesterolemia and obesity. On Day 1, hospitalized with sinus bradycardia. Lowest HR= 55 bpm (baseline HR=82). No specific treatment or action taken with study drug. Patient recovered the same day.
2302 0364_00008	34 M	Sinus bradycardia	1	-	No CV history. Active smoker. On Day 1, hospitalized with sinus bradycardia. Lowest HR was 52 bpm after 4 hrs of first dose (baseline 82 No specific treatment or action taken with study drug. Event resolved same day.
2302 0381_00003	43 F	Bradycardia AVB 1st degree	1	-	No CV history. Non smoker. On Day 1, hospitalized due to asymptomatic bradycardia. Lowest HR was 38 bpm after 8 hours of first dose (baseline was 56). ECG after 6 hours of first dose showed AVB "grade 1". No action
2302 0443_00005	54 M	Bradycardia	1	-	No CV history. Non smoker. Concomitant med: baclofen. On Day 1 experienced low heart rate. 7 hrs after first dose, HR was 44 bpm. ECG showed no abnormalities. Hospitalized overnight for monitoring. No specific treatment or action taken with

					study drug. His HR on Day 2 was 60 bpm with normal ECG.
2302 0444_00003	48 F	AVB 1st degree	1	-	No CV history. On Day 1, an ECG showed 1st degree AVB that was asymptomatic. No action taken with study drug. No treatment details are available. Patient recovered the same day.
2302 0445_00006	43 M	Bradycardia	1	-	No CV history. Non smoker. On Day 1, 6 hours after first dose patient noted decrease in heart rate (47 bpm) (baseline was 69). Patient hospitalized with diagnosis of asymptomatic bradycardia confirmed by ECG. No action taken with drug. Treatment details are not available. He recovered the next day.
2302 0601_00009	41 M	AVB 2nd degree	1	**dc**	No CV history, On Day 1, 6 hrs after first dose he had irregular pulse, dizziness and shortness of breath. BP was 110/70. ECG showed HR 46 bpm with 2nd degree AVB (Wenkebach). He received iv NaCl. At baseline HR was 74 bpm and systolic BP was 120-135 mmHg. By 7 hrs after dose he was back to sinus rhythm. He had two more 15-minute episodes of Wenkebach AVB 11 and 14 hours after first dosing. BP remained stable. No treatment was given. The patient decided to discontinue from the study.
2302 0903_00005	39 F	Bradycardia Bradycardia	1 12	- **dc**	No CV history. Smoker. On Day 1 patient experienced bradycardia requiring hospitalization. Drug was interrupted. The event resolved completely on Day 2. PR interval ranged from 204 to 209 msec. Drug was re-started on Day 12. The patient had an episode of asymptomatic sinus bradycardia. ECG showed borderline AVB. The patient discontinued from the study due to this event.
2301 0707_00049	55 M	Supraventricular extrasystoles Arrhythmia	1 1	-	History of hypertension treated with cilazapril and metoprolol. Smoker 1 ½ pack for 30 years. Baseline ECG was normal. After first dose, 1 hr post-dose he had arrhythmia and supraventricular extrasystole. The same day he had a second run of paroxysmal ectopic supraventricular beats at an unspecified time. He was admitted to the hospital due to the event. He received oral calcium on Day 1, 2 and 3. He was completely recovered by Day 2. On Day 2 and 3 the ECG were normal. No action taken with study drug.
2302 0307_00001	24 F	Sinus tachycardia Supraventricular extrasystoles Ventricular extrasystoles	344 344 344	- - -	No CV history. Smoked 3 cigarettes/day. Meds: aspirin for headaches and oral contraceptive. On Day 216 presented episode of dyspnea/hyperventilation. On Day 344 sinus tachycardia with extrasystoles and hyperventilation. Reported palpitations for 2 weeks. ECG on Day 353: sinus rhythm up to 150 bpm, rare SVES and many polytopic VES and one couplet. Drug interrupted til Day 362. Events resolved on Day 373 without specific treatment. *Patient is currently in extension study.*

Source: original AE datasets submitted 12/18/09. Narratives (12/18/09) & patient profiles (2/16/10). Rel study day: relative day of study at onset of study day. Rel day FTY: relative day on fingolimod treatment during extension study. DC: drug discontinuation Y= yes; N= no.

SAE in Cardiac disorders SOC (Rhythm and conduction disorders related) in extension studies.

EXTENSION STUDIES						
Patient ID	**Age /sex**	**Preferred term**	**Rel Study day**	**Rel day FTY**	**DC**	**Narrative**
FTY 1.25 mg						
2302E 0141_00004	39 F	AVB 3rd degree	372	**1**	**dc**	Received IFN during core. No cardiovascular history. Non smoker. Concomitant meds included oral contraceptive, magnesium-vitamin B. On Day 1, 2 hrs after first dose the patient had no complaints but her pulse went from 74 at baseline to 50 bpm, irregular. An ECG showed 1st degree AVB, 59 bmp. One minute later, an ECG showed 2nd degree AVB type I (wenckebach) with a heart rate of 55 bpm. No meds were given. Approx. 3 hours after the first dose the patient complained that she was not feeling well and reported having strange dreams. She lost consciousness. A heart monitor showed 3rd degree AVB which lasted 30 seconds, followed by an escape rhythm for 19 seconds. She recovered spontaneously and hear rate returned to the 40's. Heart monitoring showed irregular rhythm with 2nd degree AV B type II. BP was low. Atropine 0.125 mg was given because of low heart rate. Potassium was 3.4. She was transferred to ICU. 11 hours post dose, monitor showed 2nd degree AVB type I. Few minutes later she was in sinus rhythm. An echo showed mild mitral valve insufficiency that was not considered to be significant. The drug was discontinued (she only received one dose) . The patient recovered completely and was discharged home the day after the event.
2302E 0211_00002	30 M	AVB 2nd degree	376	**1**	**dc**	Received IFN during core. Prior history of first degree AVB for about 1 year. Concomitant med included lamotrigine. No history of diabetes. Non smoker. ECG pre-dose at 9:17am was 60, sinus rhythm first degree AVB; 6 hours after drug, at 15:43, sinus rhythm 56 bpm, 3:2 Wenckebach type 2nd degree AVB; 8 hours after dose, sinus arrhythmia with both 2:1 AVB and variable ratio Wenckebach type, 2nd degree AVB. QRS normal. At times HR was as low as 31 bpm. He was asymptomatic and did not receive medication for this event. The event of 2nd degree AV B type I resolved on Day 3. An ECG before discharge showed 1st degree AVB. A 24-hour Holter done **15 days after drug discontinuation** showed bradycardia with mean HR of 68 (range 38 to 120 bpm), 1st degree AVB and 4 nocturnal

						episodes of 2nd degree AVB.
2302E 0426_00006	26 M	AVB 2nd degree palpitations	361	**1**	**dc**	Received IFN during core. Prior history of optic neuritis. No CV history. Pre-dose, pulse was 57 bpm, ECG normal sinus, HR 65pm. There was no AVB but 1st degree AVB had been seen during core study. Six hour after receiving drug, he had palpitations. HR was as low as 37 bpm and BP was 100/60. ECG showed sinus bradycardia with occasional supraventricular premature complexes and second degree AVB Type I. No treatment was given. The event resolved completely the following day, and the patient was discharged home. Drug was discontinued.
2302E_ 0801_00009	39 M	Bradycardia	388	**1**	**dc**	Received IFN during core.
2201E_ 0025_00006	45 F	Extrasystoles Bradycardia palpitations	190	**1**	**dc**	Received placebo during core. First fingolimod dose: pre-dose pulse was 77, BP 119/90. Four hours post dose, pulse dropped to 54, BP 104/63. At 5 hours pulse was 35. 6 hrs post dose ECG showed ventricular rate of 30 bpm. Otherwise normal morphology. No further pulse/BP readings available. Symptoms: cold sensation, loss of heart beats, palpitations. Drug was discontinued.
FTY 0.5 mg						
2302E_ 0252_00002	42 F	Bradycardia	372	**1**	-	Received IFN during core. HR down to 36 bpm after 1st dose. No narrative or pt profile available.

Several SAEs in the Cardiac disorders SOC have been reported from the ongoing blinded studies, including a case of 2nd degree AVB with nodal rhythm, summarized as follows:

2301 E 0707 00055 (BLINDED)	26 F	AVB 2nd degree, bradycardia, nodal rhythm, blood pressure decrease	Received placebo during core study. Medical history of depression, optic neuritis, AVB first degree for 2 years. No other CV history. Non smoker. Baseline HR: 72 bpm. Six hours after first drug administration she developed bradycardia (46 bpm) and 2nd degree AVB. After 14 hours, "the AVB seemed to progress to 3rd degree AVB." Patient was asymptomatic and was treated with atropine for bradycardia. The AVB fully resolved 6 hours later. The DSMB cardiologist interpreted this ECG as 2:1 block with a competing junctional rhythm, which technically could not be interpreted as third degree AV block. The drug was reintroduced on Day 10 of the extension study, and the patient dropped the HR to 44 bpm (from 73 before drug). ECG showed 2nd degree AVB, but there were no changes in BP. Drug was interrupted again. Drug was reintroduced 8 days later. Apparently the patient continued to take study medication without further episodes

Appendix 9.4.3. Brief narratives of subjects with serious AE of ischemic heart disease events in safety pool D

Placebo
2301 0703_00005. 45 M. Myocardial infarction, on Day 44. No history of ischemic heart disease. Depression and nicotine dependence. Smoker 25 pck/year. Meds: mianserin. On Day 44 symptoms suggestive of MI, found to have ECG consistent with acute MI and underwent angioplasty. No action taken with study drug.
2301_0309_00005. 42 M. MI occurred 50 days after drug dc. No previous history of heart disease. On day 729 discontinued because of hyperbilirubinemia. On day 775, 50 days after drug dc he had ventricular tachycardia and myocardial infarction .
IFN
2302 0314_00008. 55 M. Angina unstable on Day 337. Medical history of Myocardial infarction with stent 7 years prior to entry, HTN, hyperlipidemia, diabetes mellitus. On ramipril, metoprolol, simvastatin. On Day 337 had retrosternal chest pain and hospitalized with angina pectoris. ECG unchanged and echo was normal. No action taken with study drug.
F**TY 1.25 mg**
2301 0651_00016. 27 F. Angina pectoris & AVB 2nd degree on Day 1. Recurrent event on Day 16. Drug discontinued (unclear if upon first or second event). *This case was also included in Table 16 of conduction disorders)*
FTY 0.5 mg
2301 0651_00005. 34 F. Angina pectoris on Day 573 (2 days after dc) History of pregnancy-induced HTN and palpitations. Non-smoker. On Day 573 of the study, two days after last dose of FTY 0.5 she was admitted to hospital with severe chest pain radiating to L arm. Cardiac enzymes elevated and returned to normal within next 2 days. Two days later, she had recurrent episode. On PExam, a cardiac murmur was noted. Cardiac catheterization found normal coronary arteries. There had not been ECG or PFT changes during the study. Review of labs indicate that she dropped her HTC from 41% at screening to 36% at end of study (nl 35 to 49%). In response to FDA informational request, the sponsor provided the following information on 3/4/10: Results of echocardiography were normal. Repeated ECG, ergometry and 24 hour Holter were normal. Other than MS, the patient had no complaints.
2301 0454-00002. 44 F. Dyspnea, chest pain, ventricular hypokinesia, myocardial ischemia on Day 449. Led to drug discontinuation. MS diagnosed 6 years prior to study entry. Prior treatments for MS included IFN and glatiramer acetate. Medical history included LDL elevated, febrile convulsion, optic neuritis and hepatitis. No history of heart disease or diabetes. No use of contraceptives. Active smoker (20 pack/year). On day 449 she had episode of "precordialgia" and dyspnea that lasted for 3 hours. Hospitalized, ECG showed T wave inversion in AVF and DIII. One month later echocardiography showed posterior wall hypokinesia consistent with coronary insufficiency (R coronary artery). This was considered to be the cause of the precordial pain. One week later she developed chest pain on exertion radiated to jaw, throat, arm and back. ECG showed isolated negative T waves and residual retrosternal oppression. Study medication was discontinued on Day 489. One month after drug discontinuation, a stress test was normal. The investigator suspected the event to be related to study drug.*44 year old female, no cardiovascular history but risk factors (smoking, elevated LDL) presented episode of chest pain associated with inverted T waves and posterior wall hypokinesia consistent with myocardial ischemia. There was no evidence of ischemia on stress test, one month after drug discontinuation.*

Appendix 9.4.4.

Listing of SAES of MS or MS relapse in ISS

ID	Age Sex	PT	Verbatim	Rel day	dc
CONTROLLED					
Placebo					
2201_0074_00003	42 F	MS relapse	Relapse multiple sclerosis	26	Y
2301_0851_00010	23 F	MS relapse	Worsening of retrobulbar neuritis in the context of a MS relapse	43	Y
IFN					
2302_0331_00003	37 F	MS relapse	Frequent relapses [due to MS]	298	.
FTY 1.25		MS relapse			
2301_0409_00008	27 F	MS relapse	Unusual MS relapse	193	.
2301_0413_00001	43 F	MS relapse	Ms relapse	744	.
FTY 0.5					
2302_0310_00004	46 M	MS relapse	Ms relapse	222	Y
2301_0310_00009	44 F	MS relapse	Ms relapse	246	.
2301_0413_00005	20 F	MS relapse	Ms relapse	267	.
2301_0105_00007	36 F	MS	Worsening of MS	120	.
EXTENSIONS					
2201 0001 00012 FTY 1.25	42 F	MS relapse	Relapse	263	Y
2302 0202 00010 FTY 0.5	33 F	MS relapse	Unusually severe MS relapse	590	Y

Listing of as SAE of MS relapse after drug discontinuation.

After drug DC	**Age sex**	**PT**	**Verbatim**	**Comment**
2301_0412_00004	45 F	MS	Chronic progression of MS	Received FTY 0.5. Discontinued on Day 203 because of multiple basal cell carcinoma (at 3 sites). Relapsed 2 months after dc
2301_0407_00021	34 M	MS relapse	Unusually severe MS relapse	Received FTY 1.25. Discontinued because of lack of efficacy. Received Rebif for 5 months after FTY. Had unusually severe relapse after stopping Rebif.
2201_0051_00001	37 F	MS relapse	Ms relapse	Received FTY 5 during core, and 1.25 during the extension. Relapsed 3 months after drug dc
2201E1_0029_00008	33 F	MS relapse	Progression of MS	Received placebo during core and FTY 1.25 in the extension. Relapsed 57 days after last dose of study drug. Treated with acyclovir and steroids.

Appendix 9.4.5.

Serious ischemic/thrombotic events in the Nervous system disorders SOC

CONTROLLED STUDIES
2301_0108_00010. 40 F. Ischemic stroke. Cerebrovascular accident, on Day 393 of FTY 1.25 mg. MS diagnosed approx. 1 ½ years prior to entry. Her last relapse was 8 months prior to entry. She had received Betaseron until 3 months prior to entry. Medical history: obesity and depression. No history of HTN or DM. Non smoker. No family history of coronary disease. On Day 393 she collapsed in the dermatology clinic after undergoing a shaving biopsy of two nevus. She had global aphasia and paralysis of the right arm. Study drug was dc. During hospitalization she presented with a focal motor seizure in the right face/hand. One week later, a brain MRI was compatible with an extensive middle cerebral artery infarction in the subacute phase. An angiogram was negative for carotid artery dissection. Transthoracic echocardiography showed no evidence of embologenic source, with normal LV function and valves. Hypercoagulability work-up showed negative lupus anticoagulant, normal APC resistance, normal Protein C and S, normal antithrombin activity, anticardiolipin IgG and IgM negative, elevated homocysteine 28 µmol/L (nl 5-15 µmol//L), other results pending. Other test results: normal lipid profile; negative hepatitis C serology; negative rheumatoid factor; ANA positive at 1/80 titer; ENA negative. The diagnosis provided by the investigator is "ischemic stroke of unknown origin". He did not suspect a relationship between the study drug and this event. A Data Safety Monitoring Board (DSMB) neurologist reviewed this case. According to his review, the CT angiography done the day after the event, showed irregularity and narrowing of the M1 segment of the left middle cerebral artery with attenuation of flow distally. In his opinion, this abnormality could be due to an arteriopathy or residual thrombus following spontaneous thrombolysis. He concluded that the cause of the ischemic stroke is unknown, although the history and work-up are suggestive of an embolic stroke. Other possible causes include an arteriopathy/vasospasm disorder or unknown coagulopathy.
EXTENSION
#2302E1_0365_00002. 40 M. Carotid artery occlusion, Cerebral ischaemia on Day 682 of FTY 1.25 mg. Diagnosed with MS 7 years prior to randomization. Most recent relapse was 1 year prior to randomization. He had received Rebif and Betaseron in the past. History of optic neuritis, hypertriglyceridemia and depression. No history of HTN or DM. He was a smoker. On Day 532 he presented herpes zoster ophthalmicus L side, treated with IV acyclovir. He recovered on Day 681. On Day 682 of FTY 1.25 mg he presented with subacute loss of vision in the R visual field and hypesthesia in R arm, with R-sided homonymous hemianopsia. Patient was hospitalized with the diagnosis of left internal carotid artery dissection. The DSMB and an independent neuroradiologist with expertise in vascular disease felt that the arterial occlusion was due to an embolus or in situ thrombosis and not dissection, but source was not found. Study medication was discontinued after the event.
#2302E1_0142_00005. 25 F. Vascular disorder. Cerebral ischaemia on day 60 of FTY 1.25 mg. MS diagnosed 5 years prior. Last relapse 3 months prior to entry. She had received Avonex and Rebif in the past. Medical history optic neuritis, dysmenorrhea and headaches. No history of ischemic events, HTN or diabetes. Concomitant medications included ibuprofen and oral contraceptive. She received IFN during core study. On extension Day 60 she presented acute L sided headache with

photophobia followed by tingling on R side of body, heavy limbs and dysarthria. Most symptoms resolved within 1 hour; mild headache persisted for some days. Drug was discontinued. A vascular event was suspected but MRI was negative for ischemic event and carotid ultrasound was negative for stenosis or dissection. MRA was negative for vascular stenosis. ECG was normal. Drug was re-started on Day 101. The case was reviewed by DSMB neurologist who concurred with "no evidence of infarction in the acute clinical phase" and concluded that event may have been "a complicated migraine".

The following cases were reported from the ongoing study 2309:

- **2309 0567 00008-** Stroke (Case recently unblinded: on FTY 1.25 mg)

41 year old Caucasian female (US 2309 567-8) diagnosed with MS approximately 3 ½ years prior to entry. Treated with Rebif one year prior to study entry. Medical history included severe migraine and meningioma, mitral and tricuspid valve incompetence. No history of HTN or diabetes. No previous ischemic event. Baseline EDSS score= 1.5. One month into FTY720 1.25 mg she had a severe headache, left hemiplegia and L homonymous hemianopia. MRI showed a 6.8 x 4.0 x 4.5 cm hemorrhagic stroke of the right occipital lobe. No immediate etiology was apparent but study medication was discontinued. A transesophageal echocardiogram showed no signs of left atrial appendage thrombus, atrial septum defect or patent foramen ovale; valves, chambers size all ok, no pericardial effusion and normal left and right ventricle. A work-up for hypercoagulable risk factors was negative. The DSMB neurologist evaluated the case and suspected embolic stroke affecting both the right and left posterior hemispheres with secondary hemorrhagic transformation in the right parietal lobe. No clear source of thromboembolism has been identified.

- **2309 0551 00022** - IND report of TIA, IND report PHHO2009US08314, 4 9 10. (Case recently unblinded: on placebo)

40 year old woman with MS developed left side weakness, paresthesias of lip and hand and ataxia. Initially reported as stroke. An MRI and MRA of the brain and CT were done (and were apparently negative because the investigator changed the diagnosis to TIA). Carotid artery duplex examination showed less than 20% stenosis in the internal carotid arteries. ECG and echocardiogram showed normal sinus rhythm, normal size left ventricle, normal left ventricular systolic function, an ejection fraction (EF) between 60% and 65%, normal left atrium, normal right ventricle, normal aortic valve with no aortic regurgitation or stenosis, mild mitral regurgitation, mild tricuspid regurgitation, mild pulmonary hypertension, no pericardial effusion and no masses, thrombus or vegetations. Drug screen was negative for phencyclidine, benzodiazepines, cocaine, amphetamines, THC, opiates and barbiturates. The patient recovered 2 days after the onset of the event.

Appendix 9.4.6. Listing of patients with SAE of infections and infestations, pool D

Placebo					
2301_0757_00012	52	M	Appendicitis	458	.
2301_0708_00024	52	M	Clostridial infection	652	.
2301_0803_00019	32	F	Gastroenteritis	109	.
2301_0757_00012	52	M	Peritoneal abscess	458	.
2301_0405_00010	41	M	Peritonsillitis	229	.
2301_0252_00002	22	F	Pharyngitis	466	.
2301_0803_00008	22	F	Pharyngotonsillitis	5	.
2301_0758_00002	45	F	Pyelonephritis	614	.
2301_0606_00004	27	F	Upper respiratory tract infection	84	.
Interferon					
2302_0444_00005	31	F	Administration site infection	353	.
2302_0444_00005	31	F	Administration site infection	353	.
2302_0444_00005	31	F	Administration site infection	353	.
2302_0315_00006	28	M	Appendicitis	125	Dc
2302_0421_00020	30	M	Appendicitis	321	.
2302_0603_00002	45	F	Bartholin's abscess	264	.
2302_0202_00016	34	F	Herpes virus infection	187	.
2302_0724_00011	23	F	Incision site abscess	200	.
2302_0444_00005	31	F	Urinary tract infection	352	.
FTY 1.25 mg					
2301_0408_00005	37	M	Abscess	520	.
2301_0651_00017	33	F	Abscess jaw	85	.
2301_0757_00016	45	F	Acute sinusitis	205	.
2302_0407_00001	42	M	Appendicitis	314	.
2302_0604_00014	34	M	Appendicitis	280	.
2301_0453_00009	40	M	Dermo-hypodermitis	563	.
2302_0821_00007	23	M	Encephalitis viral	339	Dc
2301_0303_00018	33	F	Genital herpes	106	.
2302_0308_00006	47	F	Helicobacter gastritis	237	.
2302_0318_00005	25	M	Herpes zoster	230	.
2302_0212_00021	29	F	Herpes zoster disseminated	319	Dc

2302_0254_00011	42	M	Lower respiratory tract infection	348	Dc
2301_0757_00016	45	F	Mastoiditis, otitis media	205	.
2301_0601_00012	24	F	Pneumonia	65	Dc
2301_0757_00016	45	F	Pyelonephritis acute	344	.
2301_0757_00016	45	F	Pyelonephritis chronic	683	.
2301_0501_00003	50	F	Respiratory tract infection	643	.
2301_0453_00009	40	M	Streptococcal abscess	563	.
2301_0307_00015	32	M	Tonsillitis	100	.
2301_0252_00008	41	M	Tooth abscess	219	.
FTY 0.5 mg					
2301_0801_00021	45	F	Cystitis	481	.
2301_0652_00013	49	F	Herpes virus infection	622	Dc
2302_0442_00005	46	M	Herpes zoster ophthalmic	186	.
2301_0304_00030	32	M	Pharyngitis	493	.
2301_0652_00013	49	F	Pneumonia x 2	567 & 622	dc
2301_0752_00014	28	M	Sinusitis	718	.
2301_0501_00006	35	F	Urinary tract infection	385	.
2301_0926_00003	28	F	Urinary tract infection	236	.

Brief narratives of serious herpes viral infections in fingolimod extension studies

FTY 5 to 1.25 mg
2201E1_0038_00004 - Herpes zoster, facial paresis 42 F. MS dx 9 years prior. Treated with Rebif until 4 months prior to study entry. Received placebo during core. On Day 209 of FTY treatment she developed facial zona and external R otitis, hospitalized with facial paresis. She presented transient deafness and elevated transaminases. Skin lesions were confirmed by dermatologist, treated with acyclovir. Drug was dc due to the AE.
FTY 1.25 mg
2302E1_0365 00002 - Herpes zoster ophthalmic. 40 M. On Day 532 developed left side herpes zoster ophthalmicus that required hospitalization. He recovered with sequelae on Day 681. No action taken with study drug. (same patient who had cerebral ischemia on Day 682).
2302E1_0121_0000720 F. – Herpes zoster (possible reactivation). FTY 1.25 in core. On Day 388 developed herpes zoster with pulmonary lesions. DC due to AE (narrative provided as blinded IND report). Unclear if it is primary infection or reactivation. See text after table.

2302E1_0324_00019 – Herpes zoster 35 M. Treated with IFN beta 1a until one year prior to entry. Received FTY 1.25 in core. On Day 405 developed skin rash in left 5th thoracic segment and neck pain. Hospitalized with herpes zoster. No action taken with study drug. Event considered resolved after 38 days.
2302E1_0212_00007 – herpes zoster ophthalmic 42 M. Received IFN during core. On Day 200 of FTY required hospitalization and iv acyclovir. Drug discontinued due to AE. Patient recovered after 18 days.
2302E1_0608_00012 – Herpes zoster L eye, arm and face. 33 F. On Day 87 of FTY treatment she had decreased lymphocyte and neutrophil counts. On Day 92: sinusitis. On Day 100: vaginal infection. All were non-serious. On Day 193 of FTY treatment she had pain under her left arm and spots extending from under her arm to her face, including the left eye, diagnosed as herpes zoster. The study medication was temporarily interrupted. The event was considered to be medically significant and serious. It is unclear how it was treated. There was no evidence of visceral involvement. In a follow up report, the investigator stated that the patient had a history of varicella infection (chicken pox) and the shingles were originally thought to be serious but had been downgraded to moderate in severity and non-serious.
FTY 0.5 mg
2302E1_0404_00001 – herpes zoster disseminated 47 F. Received IFN in core for 1 year. Six months into the extension, she presented with a fever of 38.8C and diarrhea diagnosed as gastroenteritis. Laboratory tests revealed low lymphocyte count. Two weeks later, the patient was admitted to the emergency department due to facial pain and vesicles on her face and eyelid as well as her trunk, arms and legs, typical of varicella zoster. She was lucid with normal vital signs. An ophthalmologist determined that there was no eye involvement. The patient was treated with intravenous acyclovir. Study drug was interrupted and then discontinued. Event lasted 30 days. There was not any evidence of visceral involvement and laboratory tests during the patient's hospitalization were normal (no hepatomegaly). Lumbar puncture was also normal-(white cells: 3, proteins: 31, glucose: 59). She did have a history of Varicella as a child. Laboratory testing 2 months after the episode revealed Varicella zoster IgG of 2.00 (positive > 1.10).

The following is a case of herpes zoster infection from the above table, in which viral reactivation is suspected.

- **Subject 2302E 0121 00007 (extension study) - Herpes zoster (VZ reactivation)**

  20 year old female, Relative study day 388. (The narrative for this event was blinded in the original ISS.
  As per the AE datasets this event occurred on FTY 1.25 after receiving 1.25 during the core study. Relative days estimated from information in datasets.)

MS diagnosed 3 years prior, manifested as retrobulbar neuritis. She had 7 relapses treated with steroids. She received IFN until 1 year prior to study entry. She has not received varicella zoster vaccination but medical history included scattering of vesicles and red papules in small number which were possibly related to VZV (varicella zoster virus) when she was 9 years old.

On Day 386 of study treatment she presented weakness, dysarthria and shortness of breath, preceded by 1 week of asthenia. On Day 387, she experienced scattering of vesicles that started as red itchy papules, fever, headache and cold like symptoms. On day 390, neurologic exam was normal and the patient had no oropharyngeal or urogenital ulcers, but she had erythematous macules, papules, clear vesicles and pustules, intense pruritus and dyspnoea. The patient was hospitalized due to this event. The study medication was temporarily interrupted.

Laboratory results on day 390 showed neutropenia and Lymphopenia and mild transaminase elevation with normal bilirubin (BR). Immunological examination of CSF showed an intrathecal inflammatory process (positive IgG index at 88% with oligoclonal strips). Herpes group (VZV, HSF, CMV) PCR in CSF were negative. The patient was treated with intravenous Acyclovir 800mg three times daily for 10 days and Zovirax for 10 days. The patient's clinical condition improved. The patient's neurologic and pulmonary exams were normal since the first day of her hospitalization. On Day 391 (one day after drug discontinuation), a thoracic scan showed nodular and micronodular lesions in the pulmonary parenchyma, that evoked an acute viral disease. Arterial blood gases showed mild respiratory alkalosis consistent with hyperventilation. A control thoracic scan one week later showed that the number of lesions had decreased.

Plasma VZV serology showed that plasma VZV IgG was low positive on Day 391 and positive on Day 400. Plasma VZV IgM was reported as positive on both days. Ratio VZV IgG was 724.81 on Day 391 and 3541.3 on Day 400. Ratio VZV IgM was 1.1 on Day 391 and 4.57 on Day 400. IgG versus IgM was reported as IgG > IgM on both days. The serology report could not confirm a primary infection and concluded that the serum profile was in favor of a reactivation. The investigator did suspect a relationship between the event and the study medication.

The hospital report concluded that the patient experienced a spread vesicular cutaneous eruption in relation to a VZV reactivation. There was lung involvement with normal blood gases. There was no evidence of viral encephalitis. The patient recovered approximately 1 months after admission to the hospital.

On follow up report, Varizella zoster virus IgG tests on stored sera from a few months before this episode were negative (both less than 50 IU/L). In order to be positive, the IgG result should have been greater than or equal to 150 IU/L. The results indicated inadequate immune protection against varicella-zoster virus.

The case suggests that even patients who had prior immunity to VZ virus may have an increased risk of herpes infection.

Appendix 9.4.7.a. Brief narratives of cases of SAE of macular edema in the controlled studies with FTY 1.25 mg.

FTY 1.25 mg
2302_0915_00006. 46 F. Macular edema on Day 54. Led to drug dc History of vitreous floaters for 10 years. Optic neuritis R eye 6 years prior. Blurred vision at entry. Dilated ophthalmoscopy at screening and 1 month: No hx of ME. Visual acuity (VA): 5/10, L; 10/10 R. Screening Central Foveal thickness (CFT) was 174/190 L/R. On Day 54 progressive deterioration in visual acuity R eye. On Day 72 OTC showed cystic macular edema with CFT of 182/418 L/R. Drug dc on Day 79 because of ME. 92 days after drug dc OCT showed CFT 188/193 L/R. However, Fluorescein Angiography (FA) showed capillary leakage R eye. Event was considered recovered with some decreased vision.
2301_0701_00033. 39 F. Uveitis on Day 52. Macular edema on Day 99, 33 days after drug discontinuation. No history of eye problems. No ME on dilated ophthalmoscopy. Screening: Visual acuity 0.8 L/0.9 R; CFT was 185/193 L/R. On Day 65 found to have elevated LFTs; drug discontinued. On Day 99 (end of study visit 33 days after last dose): visual acuity decreased: 0.6 L/ 0.7 R. Macular edema both eyes. CFT 483/355 L/R. *DSMB ophthalmologist thought it was MS-related uveitis based on pattern of fluoroscein angiography.* Treated with dexamethasone and hydrocortisone iontophoresis. Macular edema reported as resolved on Day 150 (by OCT and ophthalmoscopy) but visual acuity still decreased as compared to screening (0.7/0.6 L/R).
2301_0708_00020. 21 M. Vitreo retinitis on Day 15. Macular edema on Day 90. Drug dc. No history of eye problems. MS dx 2 months prior to study entry. Most recent relapse 3 months prior to entry, treated with steroids. Screening CFT: 196/182 L/R; visual acuity: 0.9/1.0 L/R. On Day 13, decreased visual acuity L eye. On Day 15, dilated ophthalmoscopy showed bilateral vitreoretinitis with left ME which led to drug discontinuation. Visual acuity l eye was 0.1 as compared to 0.9 at screening; Events treated with iv MP, dexamethasone, topical depo-medrol, diclofenac. The PI thought this was ocular inflammation due to MS. A drug effect could not be excluded. FU exam 17 days after drug dc, visual acuity was 0.7/1.0 L/R. FA showed retinal capillary leakage in both eyes. The R eye had vasculitis in the lower part of the retina. End of study (D 46) CFT was 210/194 L/R. 92 days after last dose there was resolution of ME; visual acuity was decreased (0.7/0.9 L/R). DSMB ophthalmologist thought that this was MS-related uveitis.
2301_0904_0000377. 41 M. On Day 36, macular edema, retinal disorders, visual acuity reduced. Drug dc. MS diagnosed 11 years prior. No history of optic neuritis but intermittent double vision for 4 years. Visual acuity at screening: 1/1, L/R. Screening OCT FT: 187/192 L/R. On Day 36, macular edema. FA showed retinal capillary leakage of R eye. ME worse at R without reported symptoms of vision impairment. End of study OCT FT (D36): 203/259. Visual acuity on day 63: 1.0/0.6 L/R.; 66 days after drug dc, OCT CFT 175/200 L/R, visual acuity 1/1. As per DSMB ophthalmologist ME was consistent with pattern of FTY retinal toxicity.

Appendix 9.4.7. b. Brief narratives of SAE of macular edema in extension studies in the fingolimod ISS, FTY 5-1.25 and FTY 1.25 mg dose groups

FTY 5- 1.25 mg
2201_E1 0052_00001. 38 F. Received FTY 5 mg during core study, and FTY 1.25 during extension. On day 476 diagnosed with ME. Duration 64 days. No dc.
FTY 1.25 mg
2201 E 0023_00003. 12 year diagnosis of MS. On Day 932 of study treatment he had 30 month ophthalmic assessment. Visual acuity was 20/30 R and 20/20 L. He had no visual complaints. Dilated ophthalmoscopy was indeterminate for ME both eyes. Retinal thickness by OCT-2 showed increased CFT as compared to month 24 (current 246/210 L/R), which led to the diagnosis of macular edema. Drug was discontinued due to the event. The event was considered resolved 28 days after the last dose, although no value for repeat OCT is available. A DSMB ophthalmologist opined that the change in CFT were within the range expected for noise. *(ME not confirmed)*
2201 E 0043_00001. 40 F. 13 years history of MS. No history of ocular problems with MS. She received FTY 1.25 during core study. On Day 575 as part of the protocol examination she underwent Retinal Thickness Analyzer (RTA) and dilated ophthalmoscopy and was diagnosed with macular edema R eye. Drug was discontinued. Two weeks after drug discontinuation a second ophthalmic assessment was done and no ME was detected. An OCT showed CFT < 160 in both eyes *(ME not confirmed)*.
2302E1_0145_00004. 53 F. 40 years history of MS. Previous history of uveitis of left eye 13 years prior, and uveitis right eye 5 years prior. History of depression. On gabapentin, oral contraceptive for menopausal complaints, trazodone and bupropion. She received IFN during the core study. On day 40 of FTY 1.25 during the extension study, at a scheduled visit, mild decreased visual acuity on right eye (from 0.6 to 0.5). An OCT showed CFT of 304 microns, from 156 microns at screening. Along with the use of FA, a diagnosis of lamellar macular hole with surrounding cystic macular edema of the right eye" was made. Drug was discontinued. She was treated with acetazolamide, prednisolone and indomethacin for 2 months. 68 days after drug discontinuation, the patient had recovered from the macular edema in the right eye. The investigator suspected the event to be related to study drug. The DSMB ophthalmologist confirmed the diagnosis of macular edema, but not that of "lamellar macular hole".
2302E1_0324_00008. 50 M. Received IFN during core study. MS dx 7 years prior. Five relapses treated with CS. Hx of HTN, strabismus and amblyopia in R eye since birth, uveitis since 3 years prior. No macular edema. No diabetes or retinopathy. Smoker (20 cigarettes/day). Screening visual acuity was 0.05 OD and 0.8 OS. On Day 312 of FTY therapy c/o blurred vision L eye. Visual acuity at that time not available. She was dx with macular edema by fundoscopy and OCT by local ophthalmologist. She also developed uveitis L eye. Drug was dc on Day 317 of FTY treatment. She was hospitalized, treated with acetazolamide, prednisone, MP and potassium bicarbonate. Two months later, visual acuity was 0.05 OD and 0.5 OS (decreased compared to screening). At time of last reporting she was considered recovered.
2302E1 0610_00001. 37 M. Diagnosed with MS 1 ½ years prior to entry. History of optic neuritis 7 years prior with left eye mild optic atrophy diagnosed 1 year prior. He received FTY 1.25 during core study. On Day 359, during the extension study he experienced blurred vision of the right eye. An examination a week later showed no change in visual acuity (20/20). An OCT showed intra-retinal cyst of the right eye (CFT not available). A FA showed bilateral cystoid macular edema. Drug was discontinued. No treatment was given. OCT done one month after drug dc showed persistent cyst. 59 days after the last dose of FTY, an ophthalmic assessment showed resolution clinical symptoms. Follow up OCT and FA were scheduled, results pending.

Appendix 9.4.8. a. Brief narratives of patients with SAE in the Respiratory, thoracic and mediastinal disorders SOC, safety pool D

Placebo
2301_ 0552_00006. 42 F. COPD dx on day 230. did not lead to drug dc.
2301_0307_00031. 53 F. Asthma on Day 493. History of asthma and optic neuritis. Non smoker. Presented two decompensations treated with bronchodilators. While in hospital also diagnosed with COPD. HRCT was not done.
2301_0304_00045. 52 M. Pulmonary embolism on day 657. Patient died of PE. Narrative included in table of deaths.
IFN
2302_0608_00004, 36 M. Pneumothorax,on Day 105 (motor vehicle accident, rib fracture and pneumothorax).
FTY 5 mg
2201_0025_00016. 52 F. Dyspnoea, chest pain and bradycardia on Day 5. Led to drug dc. She presented bradycardia on first day of treatment 2 hours after first dose, with dizziness and chest pain. *Case described under serious cardiac events.*
FTY 1.25 mg
2302_0521_00001. 51 F. Pleurisy, dyspnea. No significant medical history. On Day 116 she presented shortness of breath and chest pain and was diagnosed with severe pleurisy, treated with oxycodone. Chest Xray and labs were normal and stress test was negative. Event resolved on Day 126. On Day 198 the patient FEV1 was decreased from 2.44L at screening to 1.89 L. On Day 442 FEV1 was 1.77 L. HRCT at baseline and on Day 365 was normal. She discontinued from the study due to FEV decreased. Last dose of study drug was on Day 484 during extension study. 20 days after drug dc FEV1 was 1.58 L. *UNEXPLAINED DECREASE in FEV_1 on day 198. No HRCT or echocardiogram at time of the event or later.*
2302_0307_00001. 24 F. Hyperventilation and Dyspnoea No significant medical history. Smoker (3 cigarettes per day). Taking oral contraceptive. On day 216 of study presented dyspnea and hyperventilation. Treated with lorazepam, the event resolved on Day 220 and drug was re-started on Day 221. *Chest Xary, PFTs or HRCT are not available for this subject.*
2302_0125_00001. 34 F. Dyspnea, lung disorder on Day 1. Recurrent dyspnea on Day 140 led to drug dc. Smoker 10 cigarettes/day for 20 years. Baseline PFTs: FEV 4.34L, FVC 4.49 L, DLCO 69. On Day 1 the patient experienced dyspnea and dysgeusia, initially mild but worsening to the point of dyspnea on minimal exertion. One month into the study she had mild decreased DLCO (13% from baseline). On Day 139 she was hospitalized for dyspnea. An scintigraphy showed a non-specific pulmonary segmental dorsal defect compatible with pulmonary embolus (a definitive diagnosis was not made). Drug was dc on Day 140. 15 days after the last dose of study medication she experienced myocardial ischemia. 62 days after last dose of study drug, the event of dyspnea and dysgeusia completely resolved. A HRCT done 2 ½ months after drug dc was normal. The DSMB pulmonologist reviewed this case and found no etiologic cause, although the fact that it started after study drug initiation and improved after discontinuation suggests a causal relationship. *No HRCT available at time of the event. No echocardiogram or further cardiac workup available for this subject.*
2301_0601_00012. 24 F. Pneumonic infiltration. Pleurisy on Day 65. *Also associated with pericarditis. This case has been described under serious cardiac disorders and mentioned under infections. It was thought to be viral.*

FTY 0.5 mg
2302_0145_00003, 42 M. Pneumothorax. Day 85. No dc. History of hypertension and spontaneous pneumothorax. On Day 85 he was hospitalized due to spontaneous pneumothorax. Patient completed core phase and entered the extension.
2301_0454_00002. 44 F. Dyspnea Chest pain, myocardial ischemia on Day 449. No dc. Described under serious cardiac events.
2301_0408_00009, 21 F. Pulmonary oedema,(?myocardial ischemia) on Day 7. Led to drug dc. This cases was discussed under serious cardiac events because it was associated with LV dysfunction and increased cardiac enzymes. Etiology of the pulmonary edema is unclear, perhaps related to transient ischemia, confounded by the use of "varnish" prior to the event.

Appendix 9.4.8.b. Brief narratives of SAE in the Thoracic system disorders SOC in the extension studies, original ISS.

FTY 5 to 1.25 mg
2201E1_0003_00008, 44 F. Asthma on Day 349. Drug dc. MS symptoms for 4 years. No history of asthma. Non smoker. On Day 349 of FTY treatment she presented with asthma, treated with prednisone budesonide-formoterol, salbutamol and fluticasone. She returned to the ER the day after, and was hospitalized overnight for close monitoring. The event resolved on Day 351. Subject withdrew consent in discontinued from the study. PFTs not available. *NEW ONSET of ASTHMA.*
2201E1_0038_00010, 27 F. Asthma. Day 209. Drug dc. Medical history of asthma since 15 years prior to entry. On Day 27 he experienced mild dyspnea. On Day 209 of FTY treatment she experienced moderate exacertbation of asthma. She was hospitalized for 4 days and treated with prednisome, salbutamol, terbutaline. Study drug was interrupted from Day 241 to 275. Study drug was re-started on Day 276 but then discontinued on Day 278 due to the event of asthma. The investigator suspected a relationship between the event and the study medication. *EXACERBATION of ASTHMA.*
2201E1_0037_00013. 40 F. Bronchospasm on Day 8. Drug dc. MS diagnosed 5 years prior to entry. Non smoker. No history of asthma or respiratory disease. Concomitant medication: oral contraceptive. She received placebo during core study. On Day 8 of the extension she developed severe bronchospasm. PFT showed decreased FEV1 and DLCO. "Discrete obstructive syndrome" was diagnosed. Study drug was discontinued on extension day 183. A chest CT done on an unknown date showed no pleural or parenchymatous abnormalities. The event of bronchospasm resolved completely 63 days after last dose of study drug. *NEW ONSET BRONCHOSPASM, reversible upon drug discontinuation.*
FTY 1.25 mg
2302E1_0124_00001, 43 F. Dyspnea, hypoxia, lung disorder, day 570. Drug dc.History of optic neuritis, migraine and hyperlipidemia. Smoker. On day 570 of FTY 1.25 developed acute chest pain, dyspnea and severe hypoxia (66mm Hg). A CT scan showed bilateral pneumopathy with basal infiltrates and mediastinal lesion/parenchymatous opacities (L side) and pleural disorder. No PFTs are available at the time of the event. BAL showed hypercellularity (750/mm^2) and eosinophilia (4%). Study drug discontinued. Chest pain and dyspnea resolved on the same day. A CT scan repeated 8 days after drug discontinuation showed comlete recovery from parenchymatous and pleural lesions, and PFTs were normal. There is no additional information about this event. One month later he presented fever and left lumbar pain and was diagnosed with pyelonephritis requiring hospitalization.

2302E1_0525_00002, 41 F. Pneumothorax (acinetobacter pneumonia), Day 400. Drug dc. R middle lobe "lung neoplasm" diagnosed by HRCT without biopsy. One month later, bronchoscopy + biopsy for evaluation of bronchiectasis. Culture from the day of bronchoscopy grew acinetobacter. Dx as acinetobacter pneumonia, complicated with pneumothorax during bronchoscopy *Case also described under infections.*
2302E1_0604_00010. 34 F. Asthma on day 494. No drug dc. Pt had history of mild asthma for 20 years, treated with fluticasone and salbutamol. One week prior to the event had common cold symptoms. On Day 118 presented asthma attack and was hospitalized with dyspnea & wheezing. Decreased FEV and FVC.
FTY 0.5 mg
2302E_0442_00012, 41 F. Pulmonary embolism 58. No dc. MS diagnosed 7 yrs prior to entry. Prior treatment with Avonex, Betaseron and Rebif. Medical history included varicose vein embolectomy, tachycardia, depression, optic neuritis. Family history of clots, stroke and heart attack. Active smoker. During study received perindopril for HTN, carbamazepine and pregabalin for MS pain, atorvastatin for high cholesterol and varenicline for cessation of smoking. On Day 58 of FTY 0.5 mg treatment she presented left sided chest pain and heaviness in her leg. ECG and blood tests, and comput ed tomography angiogram were done. She was treated with glyceryl trinitrate, morphine, aspirin. She improved and was discharged the next day with diagnosis of musculoskeletal chest pain. At home she continued with intermittent chest pain and dyspnea. On Day 62 of FTY treatment she was re-hospitalized. A VQ lung ventilation perfusion scan showed PE. She was treated with heparin followed by warfarin. At the time of last reporting, condition was improving. Drug was not discontinued. Follow up information is pending.
2301E_0851_00009. 33 M. Snoring. Day 164 of FTY 0.5 treatment (after receiving placebo in core study)
2302E1-0521-00001. 1) Pleurisy (Core), 2) Forced expiratory volume decreased (Extension)

Appendix 9.4.9. Brief narratives of patients with SAE of chest pain, pool D

Placebo
2301_0206_00029 – 38 M. Non-cardiac chest pain on Day 561 2301_0909_00006 – 36 M. Non-cardiac chest pain on Day 120
FTY720 5 mg
2201_0025_00016. 57 F. Bradycardia on Day 1. Chest pain, dyspnea, tachycardia on Day 4. Patient had bradycardia on first day (<50 bpm), with dizziness and chest pain/pressure. HR back to normal 12 hours later. She continued treatment. On day 3 she had watery diarrhea; on day 4 she was tachycardic with sharp chest pain and dizziness and dyspnea and was withdrawn from the study. She recovered after 10 weeks. *Cardiology workup suggested non-anginal chest pain This case was included in Table 16 among cases of bradycardia. Narrative updated 4/22/10.*
2201_0066_00006 – 41 F. Chest pain, bradycardia on Day 2. On 2nd day of treatment had unspecific thoracic pain spreading to arms, bradycardia, vomiting, normal CK and troponin. Chest pain though to be due to vomiting. Drug interrupted and restarted a week later. At 6 months, ECG showed inverted T waves. *Pt continues in the extension study as per 4/22/10 narrative update. Case is also included in Table 16.*
FTY 1.25 mg
2201_0018_00003 - 44 F. Chest pain, bradycardia, Day 1 44 F . History of HTN. Had chest pain 3 hours after first dose. ECG showed first degree AVB. No symptoms with further doses. She received diazepam. Troponin level was normal. After the second dose, all subsequent ECGs were normal with no cardiac or respiratory symptoms. She is still in the study. She has have episodes of neck pain and anxiety but no cardiac chest pain. *Case included in Table 16. She is still in the extension study as per 4/22/10 updated narrative.*
FTY720 0.5 mg
2301_0459_00004 – 34 F. Chest pain on day 357 Medical hx: Restless leg syndrome; Botallo's foramen ovale, atrial septal aneurysm. No hx of HTN or diabetes. Smoker ½ pack x 23 years. On Day 358 she had constrictive chest pain with palpitations that lasted 5 hours. Hospitalized. P exam, cardiac enzymes, troponin and ECG were normal. She recovered the same day and was discharged. Cause of pain was unknonwn. No further workup was done. *As per 4/22/10 follow up, she has not experienced further episodes of chest pain.*
2301_0413_00004 – 47 F. "Non-cardiac chest pain" and increased BP on Day 638. History of HTN. No diabetes or heart disease. Concomitant meds: carbamazepine, amantadine and estradiol-norethisterone. Prior to the study entry, the patient's blood pressure was 140/90 mmHg. On Day 638 had sudden onset of "non-anginal" thoracic pain. Hospitalized. Found to have high blood pressure. Treated with niroglycerine and amlodipine. The event of chest pain and increased BP resolved on the next day. ECG, Echocardiogram and lab evaluations showed no evidence of myocardial infarction. *Subject still in the trial as per 4/22/10 follow up.*

2301_0651_00001 - 34 M, "Non-cardiac chest pain", day 514
History of varicose veins and thrombophlebitis. No HTN or diabetes. Non smoker. No concomitant meds. On Day 514 he had chest pain with radiation to R jaw and arm. Hospitalized, ECG and cardiac enzymes were normal. Nitroglycerin and unspecified analgesics were given. Over the ensuing 2 months he complained of intermittent light pressure. No additional work up was reported. *As per follow up on 4/22/10, the subject is still in the study.*

Appendix 9.4.10. Narrative of selected SAE in the Hepatobiliary disorders SOC and (hepatobiliary) Investigations SOC in fingolimod controlled studies.

FTY 1.25 mg
2201 0002_0001. 55 F. Hepatitis toxic on Day 36. Led to drug dc. MS diagnosed 1 year prior to entry. Previously treated with glatiramer. Medical history included type 2 diabetes mellitus, osteoarthritis, urinary frequency, HTN, intermittent cough, depression. Concomitant medications: methylsulfonylmethane, rofecoxib, oxytutynin, ramipril, triamterene for many years. Other prior meds were *Oenothera Biennis* oil, *Linum Usitatissimum* seed oil, erythromycin, but were discontinued within the first 10 days of the study. Baseline liver enzymes were normal (ALT 17 U/L –nl 1 to 30-, AST 19 U/L –nl-32-, BR 6.8 µmol/L –nl 1.7-18.8) and ALK Phos 94 U/L –nl 31-121-). On Day 36 she had an increase in ALT (123 U/L) associated with BR 5.1, ALK Phos 147 U/L. She was diagnosed with "chemical hepatitis". Study medication was interrupted from Day 102 to Day 113 due to this event. Treatment was re-started on Day 114, and permanently dc on Day 119 due to this event. On Day 120, ALT rose again to 106 U/L. The toxic hepatitis resolved 41 days after drug discontinuation. The investigator did suspect a relationship between the event (toxic hepatitis) and the study medication.
2201_0074_00005. 30 M. ALT increased on day 148. Led to drug dc. (ALT baseline value: 32 U/L), presented with elevated ALT levels of 111 U/L on day 85, and 119 U/L after 4.5 months on study drug. A follow-up monitoring of the patient again showed raised ALT which was reported as a serious adverse event on day 148. Initially it was believed that this was due to the drug taken for body building, Norateen, which was discontinued. As ALT raised further to 474 U/L, the study drug was permanently discontinued on day 154. The patient was lost to follow-up.
2301_0152_00011. 40 M. ALT & GGT increased on Day 168. Led to drug dc. In accordance with protocol guidelines, drug dc on Day 175 due to ALT=217 (nl 0-45 U/L)(5x ULN). GGT was 2x ULN. BR was normal. Two months after drug dc, ALT was normal.
2301_0601_00012. 24 F. Liver function test abnormal on Day 65. Led to dc. On Day 65 she experienced chest pain, dyspnea, nausea and vomiting. Echocardiography showed pericarditis and pleuritis with mild pneumonic infiltrate. Labs showed ALT 122 (3xULN), AST 88 (2x ULN) and ALKP 446 (4x ULN). Drug was discontinued. Event was thought to be viral, but no definitive agent was identified.
2301_0903_00010. 29 F. Liver function test abnormal on Day 190. Concomitant meds included ibuprofen and oral contraceptive. On Day 190 during routine visit, ALT=96 U/L (2x ULN) with normal BR. On Day 281 liver enzymes continued to rise, with ALT 114 U/L (<3x ULN), AST 53 U/L and normal BR. Liver US was normal, hepatitis serology was negative. Drug was interrupted. On day 304 she had myalgias and arthralgias, upper limb weakness, sore throat and chest pain when breathing that lasted for five days. She was admitted to the hospital on Day 311. On day 316, ALT was 143 U/L; AST 79 U/L, with normal BR and ALK P. Study medication was resumed on Day 371.
2302_0145_00007. 46 F. Hepatic enzyme increased on Day 247. Led to dc. Medical history scoliosis, bronchitis and HTN. During the study she received nifedipine, ibuprofen and amoxicillin for periodonditis At screening she had elevated ALT (104 U/L) and AST (53 U/L); at baseline, ALT,AST , GGT, BR and ALK P were normal. (Day 25), the patient was noted with elevated ALT (125 U/L, >2x ULN, AST (63 U/L > ULN), ALK P (112 U/L), total bilirubin (26 µmol/L > ULN) GGT 121 U/L > ULN). During the study ALT, AST, ALK P, total BR and GGT levels fluctuated. On Day 247 ALT= 252 U/L (>5x ULN), AST= 129 U/L (<3x ULN) AlK P= 177 U/L and GGT 282 U/L, <4x ULN). TBilirubin was within the normal range. Study drug was dc. Eleven days after last dose, GGT was still elevated (164 U/L) but other enzymes were normal.
FTY 0.5 mg
2302_0330_00004. 37 M. Hepatic enzyme increased on Day 19. Led to study dc. No concomitant medications. Liver enzymes at screening were normal. On Day 19 mild he was noted to have ALT =147 U/L (3xULN). BR and ALk P were normal. Drug was discontinued due to the event on day 36. Eleven days after last dose, ALT was 359 (>7xULN), AST was 147 U/L (>3xULN), and GGT was 224 (>3x ULN). Liver enzymes

normalized 69 days after drug dc.

Appendix 9.4.11a. Listing of SAEs in the Blood and Lymphatic system disorders SOC and Investigation (hematology related) SOC

FTY 1.25 mg	
2301_ 0419_00001. 28 F. Leukopenia & Lymphopenia on Day 199. Per laboratory samples collected on Day 197 of FTY 1.25 mg**,** the patient presented with leucopenia 1.3x 109/L and lymphopenia 10.4% which were considered medically significant.The study medication was temporarily interrupted Day 244. The patient was treated with sulfamethoxzole 800mg and trimethoprim 160mg for a few days and did not have any signs/symptoms associated with the leucopenia and lymphopenia. The study medication was restarted on Day 351. On Day 393, laboratory tests showed normal values in all relevant samples.	
2301 0459_00005. 26 F. Lymphopenia on Day 635. Led to drug dc. Diagnosed with MS 4 years prior. Received IFN B 1a s.c for 5 months, til 4 months prior to entry. On Day 635 of FTY 1.25 mg, the patient was noted to have decreased lymphocyte count to 0.19x109/L (0.85-4.10x109/L). and persistent, productive cough. Hospitalized due to productive cough and bronchitis. Found to have low CD4 (11 cells; normal above 490). Treated with bactrim for "toxoplasm prophylaxis." FTY interrupted for 3 weeks. Patient recovered from lymphopenia and cough. Drug re-started, and he entered extension study. On day 12 he developed Lymphopenia again and was discontinued from the study. He recovered from lymphopenia one month after drug discontinuation.	
2302 0361_00007. 33 F. Lymphopenia on Day 124	

Appendix 9.1.11. b. Listing of SAE in the Blood and lymphatic disorders SOC, extension studies

2201E_0002 00002. FTY 1.25. 37 F. Neutropenia on Day 309 of FTY treatment. Drug dc. Received FTY 5 mg during core.
1202E_0106 00009. FTY 1.25. 37 F. Lymphopenia on Day 302 of FTY treatment. Drug not dc. Received IFN during core.
2302E1-0316-00010. FTY 1.25 mg . 44 F Idiopathic thrombocytopenic purpura on Day 181 of FTY treatment. Received IFN during core study. MS dx 10 years prior to randomization. Hx of hyperthyroidism and menopause, taking levothyroxine and estrogents. During screeing platelet count was 236 $x10^9$/L. On day 487 it was 209 x $x10^9$/L. On day 181 of FTY treatment platelet count was 4 $x10^9$/L. A hematologist diagnosed ITP. Drug was discontinued and patient was treated with steroids. At the time of last reporting, 5 months after drug dc the patient was considered completely recovered from ITP.
2302E_0510 00001. 50 F. On FTY 0.5. 50 F. Lymphadenopathy on Day 222 of FTY treatment. Received IFN during core. Left axillary lymph node enlargement. Drug not dc.
2302E_0303_00013. 48 F. Leukopenia on Day 548 of FTY treatment. On day 547 WBC was 1.6 $x10^9$/L. Drug was interrupted for one week. WBC was 3.0 $x10^9$/L. Drug re-started without further problems.

Source: AE datasets submitted 12/18/10 *and* selected patient narratives.

Appendix 9.4.12. Non-seriousAE leading to drug discontinuation in the EYE system disorders SOC

FTY 1.25 mg
2301 0151_00003, 50 F. Macular edema on Day 19, duration 72 days. Prior history of Guillain Barre and optic neuritis 4 years prior. Screening CFT 125/186 microns L/R. On Day 19 c/o eye pain and blurred vision. One week later visual acuity decreased 20/40; macular edema Left eye; CFT 416/186 L/R. Drug was discontinued. 23 days after drug dc visual acuity was normal and ME had improved. 3 months after drug discont FA demonstrated bilateral parafoveal dye leakage from the retinal capillaries R>L as well as mild bilateral dye leakage from the optic nerve heads.
2301 0651_00024, 38 M. Macular edema on Day 15, duration 40 days History of optic neuritis and uveitis prior to entry. At screening eye exam showed uveitis but no macular edema (CFT was 198/185 micron L/R). Visual acuity was 1.0 R and 0.8 L. He was treated with topical steroids. On Day 15 of FTY treatment, dilated ophthalmoscopy showed bilateral macular edema, confirmed with OCT and FA (bilateral leakage). CFT by OTC was 297/329 L/R. Visual acuity was normal. On Day 17 drug was discontinued. Ten days after drug discontinuation, visual acuity was 0.6 R, 0.8 L, ME still present. Event resolved 40 days after drug discontinuation . DSMB ophthalmologist confirmed that macular edema developed after drug started and thought could be related to therapy.
2301 0953_00007, 27 M, Macular edema on Day 173. Not recovered. May be not drug related. Prior history of optic neuritis Left eye and bilateral abnormal foveal thickness 2 months prior to entry. At screening pt already had significant reduction of visual acuity (0.05 both eyes) and increased thickness of paramacular area of L eye. Fluorescein angiography showed no leakage consistent with ME, then the patient was enrolled into the study. On Day 43 visual acuity was unchanged. No ME was detected by dilated ophthalmoscopy. OCT and FA were not done. On Day 173 ophthalmic examination by local ophthalmologist showed bilateral macular edema and drug was discontinued. The PI disagreed with the diagnosis of macular edema. The DSMB ophthalmologist reviewed all records and concluded that one month into treatment, the patient had bilateral papillitis and periphlebitis L>R. 9 months later, periphlebitis was less but still present, additionally there were two areas of retinal pigment epithelium (RPE) depigmentation inside the temporal arcades. He suspected that the patient had active uveitis at the time of enrollment and agreed that he should be off study drug. An uveitis specialist concluded that there was no doubt that the patient had cystoid macular edema of the left eye which would be typical of the intermediate uveitis seen in MS patients. Seven months after study drug discontinuation he withdrew from the study. At this visit, his visual acuity was “hand motion” both eyes, macular edema was present, assessed by dilated ophthalmoscopy, OCT showed normal CFT and FA showed no retinal capillary leakage. He showed no improvement after several months of discontinuation and local and systemic treatment for macular edema. At the end, the investigator suspected that it was not drug related.
2301 0952_00006. 42 F. Macular edema on Day 37. Duration 140 days. Prior history of uveitis for the last 2 years. No evidence of active retinopathy prior to study entry. At screening there was uveitis but no evidence of macular edema. A FA was normal with no retinal capillary leakage. On Day 37 of FTY 1.25 treatment a repeat OCT was still normal, but because of the uveitis a fluorescein angiogram was done which showed mild, very late, capillary leakage consistent with macular edema. The local ophthalmologist suggested that the leakage was related to the uveitis and not to the drug. The drug was discontinued on Day 85 due to macular edema. This date, opht evaluation showed improvement in the uveitis while the condition with respect to macular edema remained the same. She received topical treatment with dexamethasone and diclofenac. She had follow up ophth evaluations. She recovered completely from the event of macular edema 98 days after the last dose of study drug. The DSMB ophthalmologist confirmed that the FA at screening was normal and on Day 37 showed bilateral perifoveal dye leakage in the late frames, and that the patient should stay off drug.

2302 0106 00005, 37 F. Macular edema on Day 99 – no recovery date in dataset. History of optic neuritis and decreased VA in L eye. At screening, VA was 1 in the R eye and 0.67 in the L eye. DO was normal. CFT was not reported for the L eye. On Day 29, the patients VA in L eye decresed to 0.25. ON DO he was noted to have cicatrictial retinitis in the left eye, but macular edema was not confirmed (entered as 'unknown'). OCT and FA of the left eye were not available. On Day 92 the patient's visual acuity in the left eye was 0.30. On dilated ophthalmoscopy, the patient was noted to have macular edema and cicactricial retinitis in the left eye. Central foveal thickness on OCT of the left eye was 462 um. One month later, his VA in L eye had decreased to 0.15. CFT on L was 407 um. FA was not performed. Study drug was discontinued due to ME on Day 295. 34 days after drug dc VA was 0.8 in R and 0.5 in the L eye. ophthalmologic evaluation showed that the optic fundus was normal in the right eye and the left eye showed atrophy with macular edema and periferic speculated pigment. OCT foveal thickness was 149 +/- 10 in the right eye and 242 +/- 12 in the left eye. FA showed cystic macular edema in the left eye. The investigator did not suspect a relationship between the event (macular edema) and the study medication, and assessed the event (macular edema) to be secondary to cicatricial chorioretinitis. ME was confirmed by DSMB ophthalmologist.
2302 0251 00002. 32 M. Macular edema on Day 99 diagnosed by dilated ophthalmoscopy. No ocular symptoms. Drug was dc on day 145. No treatment given. Limited data in narrative. Not confirmed by DSMB ophthalmologist.
2302 0524 00005 . 36 M. Macular edema on Day 98, lasted 33 days. Confirmed by DSMB ophthalmologist.
2302 0602 00005, 44 F. Macular edema on Day 99, lasted 85 days. Presented with visual blurring on Day 80. D) on Day 92 showed ME on left eye. It was treated with ketorolac drops. It resolved 84 days after drug discontinuation. Visula problems persisted. There is no available visual acuity measurement. It was confirmed by DSMB ophthalmologist.

Appendix 9.4.13.a. Listings and brief comments on non-serious events that led to discontinuation due to respiratory related symptoms are presented in the following table for the controlled studies.

Placebo
2301_0251_00002, 38 F. Dyspnea on Day 17; duration 17 days
2201_0025_00016, 31 F. Dyspnea on Day 12; duration 26 days
2301_0607_00009, 40 F. Spirometry (abnormal) on Day 555; duration 1 day. CT abnormal on day 576. Depression treated with amitriptyline. Other meds: tizanidine. Non smoker. No other significant history. During the study she had an upper respiratory tract infection. On Day 557 she was noted to have a decreased DLCO, from 23.7 mmol/min/Kpa at screening, to 17.6 mmol/min/KPa (less than 80% of screening value). HRCT showed bilateral ground glass areas. Drug was discontinued. No date of recovery.
2301_0751_00008, 28 M. DLCO decreased on Day 107; duration 202 days. Smoker, 1 pack day for 14 years. At screening DLCO was 0.68 mmol/min/KPa. On Day 107 DLCO was 6.52 (60% of predicted) but he did not have any respiratory symptoms. Drug was discontinued and DLCO improved after discontinuation. Chest Xrays and HRCT done 190 days after drug dc showed no significant abnormalitities.
2301_0756_00004, 27 M. DLCO decreased on Day 548; no date of recovery. Non smoker, no hx of asthma, history of + antiphospholipid antibodies. During the study she had flu like symptoms and chest infection from day 503 to 527, treated with antibiotics. On Day 527 FEV1 was decreased 64%. Study drug was discontinued. 119 days after drug discontinuation the patient was diagnosed with asthma. Chest X-ray at screening and end of study visit (196 days after study dc) were normal.
IFN 2302_0220_00002, 43 F. DLCO decreased on Day 108; no date of recovery 2302_0220_00014, 43 F. DLCO decreased on Day 32; no date of recovery
FTY 5 mg 2201_0072_00003, 55 F. Dyspnea on Day 5; duration 16 days Baseline values of FEV1 2.58 L (110% of expected), FVC 3.29 L (119% of expected) and DLCO 24.78 ml/min/mmHg (108% of expected), presented with symptoms of moderate dyspnea on day 5. The investigator suspected a relationship with the study medication. Treatment with study medication was discontinued on day 16. The patient discontinued the study on day 63 after withdrawal of consent. There is no follow up PFT or HRCT for this patient.
FTY 1.25 mg
2301_0176_00001, 45 F. Dyspnea on Day 11; duration 2 days Smoker. No other significant medical history. On day 1, upon first FTY dose he presented asymptomatic bradycardia 6 hours post dose. The second day, he presented mild dyspnea. The patient adjusted his own dosing because of the AE. On Day 11 he had another event of bradycardia and dyspnea, which led to permanent drug discontinuation. *(In this case the dyspnea seems to be cardiac-related)*
2302_0311_00002, 49 F. Obstructive airways disorder on Day 178; no date of recovery
2302_0333_00008. Narrative was provided in NDA but case was not in AE datasets. 32 F, developed abnormal DLCO values on day 177. At screening DLCO was 10.07 mmol/min/KPa. On Day 177 DLCo was 6.19. No changes in FEV1 an FVC. HRCT not done at baseline. 72 days after drug discontinuation DLCO was 6.6. HRCT done 16 days after drug dc showed "residuals of outdated infiltration". *No fu HRCT available.*

Appendix 9.4.13.b. Discontinuations due to AE in Respiratory SOC in Extension studies

2302E1-0307-00002 – Dyspnea. 42 F. Medical history included psoriasis, headache, intercostal neuralgia and migraine. No history of diabetes mellitus, HTN or cardiovascular disease. She received IFN during the core study. On Day 486 (109 of the extension study on FTY 0.5 mg) she experienced mild dyspnea, asthenia, hypertension and diarrhea. She received last dose of study drug on extension Day 122. The event of dyspnea resolved 5 days after the last dose of study drug. The narrative does not provide any information about work-up conducted in this patient. *Additional information provided on May 21, 2010:* the dyspnea symptoms were mild and stopped a few days after onset and did not require any additional follow-up. A retest of the original PFT assessments with a pulmonologist was also not performed, as the patient's condition improved and the AE (dyspnea) was only of mild intensity. Fourteen days after study drug discontinuation, the patient came back to the clinic to have the end of study visit which included PFT, lab and ECG assessments. No chest x-ray or HRCT was performed. At this visit the patients DLCO was 79.7% of the baseline value. However, review of PFTs done at the end of the core study (Day 366 shows that the decrease in DLCO preceded the first dose of FTY. 105 days after drug discontinuation at the 3-month follow-up visit the patients DLCO was still 78% of the screening value.
2302E1-0609-00006 –Fatigue, dyspnea, non-cardiac chest pain on FTY 0.5 mg. 41 F, MS diagnosed 14 years earlier. Medical history headaches, dysmenorrhea, seasonal allergy, optic neuritis, bronchitis. No diabetes, HTN, CV or respiratory disease. Smoker. She received IFN during core. On E Day 4 of FTY 0.5 mg, she experienced mild fatigue and dizziness. On E Day 14 increased fatigue and headache. On E Day 35 mild dyspnea and non-cardiac chest pain. Drug was discontinued on E Day 38. No treatment was given. The narrative has no information about work-up done in this patient. *Additional information provided on May 21, 2010:* Physical exam, PFT and ECG were normal. The investigator concluded that the patient had intolerance to FTY and decided to stop study medication and switch to IFN. The patient did not see a pulmonologist or cardiologist as it was not deemed necessary by the investigator. Evaluation of PFTs indicate that the patient had a decrease in DLCO during the core phase (from 24.23 ml/min/mmHg to 21.92), with normal Xray. PFTs done on E day 38 showed DLCO of 24.72 ml/min/mmHg. No Xray was done at that time.
Patient 2302E1-0543-00003 – Dyspnea (IFN in core, FTY 1.25 in extension) 44 F, MS for 15 years. Medical history fibromyalgia, hypersensitivity to sulfa drugs, optic neuritis, sleep apnea syndrome, GERD. No history of diabetes or CV disease. She received IFN during core. On E day 58, while on FTY 1.25 mg she experienced dyspnea of moderate severity. Drug was discontinued on E day 68. Not treatment give. Event was ongoing at time of last available report. *Additional information submitted May 21, 2010:* Prior to the event on Day 351 the patients FVC and FEV-1 scores were both over 100% of predicted value, but the patients DLCO was less than 80% (73.8%) of the predicted value. A approximately a month later the patient had an unscheduled PFT assessment to follow-up on pulmonary function tests because of a more than 20% DLCO reduction from core phase baseline value at previous study visit (77% baseline at month 13 visit). At this visit, the patient informed the investigator that she also experienced dyspnea since extension Day 58. A repeated PFT at this visit showed a persistent DLCO reduction (79.9% of BL, FEV1 82% BL and FVC 94.3% BL). No workup was done to specifically investigate the dyspnea and the patient was not seen by a pulmonologist. There were no dyspnea complaints and the PFT were greater than 80% of baseline. The event (dyspnea) completely resolved completely by 3 months post drug discontinuation.
Patient 2302E1-0222-00002 – Dyspnea, FTY 1.25 31 F. MS dx 2 years earlier. Medical history Gilbert. No other relevant history. On E day 22 she experienced moderate dyspnea. Drug discontinued on E Day 23. Dyspnea was ongoing at time of the last available report. *Additional information submitted May 21 2010:* This event was evaluated by a pulmonologist. Physical exam was normal, pulmonary function test was considered to be normal (DLCO 85% BL), and bronchodilatator reversibility test were negative. Saturation of O2 in ambient was 98%". No chest xRay or HRCT was performed after drug discontinuation.

2302E1 0521 00001 – Pleurisy (core) Forced expiratory volume decreased (extension). FTY 1.25mg core and extension. 51 F, past medical history of melanocytic nevus and pleurisy, irritable bowel syndrome. During the study she received desvenlafaxine, bupropion, estradiol, gabapentin, nystatin (for thrush), valacyclovir for herpes zoster and oxycodone for zoster pain. Prior to sutyd entry FEV1 was 2.44 L/sec. FVC was 3.38 L and DLCO was 14 mmol/min/KPa. HRCT was normal. On Day 120 of core study she developed dyspnea and chest pain and was dix with pleurisy. Chest xray, lab test and stress test were reportedly normal. The event resolved 6 days later. During the extension study, on Day 198, the patient was noted to have decreased FEV1 at 1.89 L/sec. On Day 442, the FEV1 was further decreased to 1.77 L. On day 469 she was diagnosed again with pleurisy. Study drug was discontinued. FEV1 21 days after drug dc was 1.48 L, FVC was 3.16 L and DLCO was 13.32. There was no HRCT at the time of lowest FEV1 or after drug discontinuation. The cause of FEV1 decrease remains unexplained. Event was ongong at the time of last available follow up.

Appendix 9.4.14. Listing of subjects with serious and non-serious AE consistent with ischemic heart disease:

Placebo 2301_0703_00005	45 F	S	-	Serious Myocardial infarction on day 44
Placebo 2301_0309_00005	42 M	S	-	Serious Myocardial infarction on study day 775, 50 days after drug dc
Placebo 2301_0251_00010	46 F	-	-	Non-serious Angina pectoris, 1 month into study. History of heart murmur and intermittent chest pains/tightness for several years. No HTN or diabetes. Smoker. First report during the study was one month into treatment, when he reported that chest pains got worse since study medication started (from mild to moderate), but there was no chest pain with the first dose. The pain was considered to have cardiac origin but there is no documentation of a cardiac work up and there was no use of low dose aspirin. Concomitant meds included ibuprofen and paracetamol.
Placebo 2301_0402_00005	36 M	-	-	Non serious Angina pectoris, day 17. No hx of diabetes or HTN. Familial hyperlipidemia. Smoker. No concomitant meds. On day 1 he had asymptomatic first degree AV block by ECG at 6 hours post dose, with no decrease in HR. On Day 17 had "stenocardia" (angina pectoris) of moderate severity (chest pain/tightness). Stress test and cardiac ultrasound were normal. Cardiac enzymes not available. No action taken with study drug and no treatment given. Event resolved on Day 30. Other ECGs were normal, except first degree AVB again noted at Month 6 ECG.
Interferon 2302_0314_00008	55 M	S	-	Serious Angina unstable on day 337 (described under SAEs)
Interferon 2302_0253_00010	32 M	-	-	Non serious MI, day 204. No relevant medical Hx. No conc. meds. On Day 204 (6-mo ECG) had first degree AV block and suspected of mild anterior wall MI. No symptoms. A second ECG done a few days later showed no MI, just first degree AV block. The event of "acute MI" resolved on day 208. No action taken with study drug.
Interferon 2302_0407_00003	48 M	-	-	Non serious angina pectoris, day 383. No relevant medical Hx. Smoker. No conc. medications. 12 days after last dose in core study he had severe chest pain diagnosed as angina pectoris. No treatment given. ECG (ST elevation) and increased CK at the time suggested "cardiac ischemia" Echocardiogram was normal. He did not enter the extension because of abnormal ECG.
FTY 1.25 mg 2301_0651_00016	27 F	S	dc	Serious Angina pectoris on day 1 (described under SAEs)
FTY 1.25 mg 2302_0216_00013	30 M	-	dc	Non serious angina pectoris on day 56 and inverted T wave on day 62 leading to drug dc
FTY 1.25 mg 2302_0125_00001	34 F			Discontinued on Day 140 drug because of increasing dyspnea. Hypothyroidism. No diabetes or HTN. Smoker. On Day 1 had dyspnea and dysgeusia. Dyspnea increased progressively. At Month 1 DLCO had decreased by 13% and PEmax increased almost 3 fold. Scintigraphy was suggestive of P.E. Drug was dc. 13 days after drug dc she underwent multiple tests. Bronchial fibroscopy indicated a mild inflammation but the samples were negative; bronchial alveolar lavage revealed numerous macrophages

		-	-	and a transbronchial biopsy did not reveal any disorder. 15 days after drug dc she had an abnormal ECG. A cardiologist who saw the patient diagnosed sub-epicardial ischemia. The patient had no additional clinical symptoms. A HRCT done approx 2 months after drug dc was normal. The event of dyspnea resolved 62 days after last dose. Cause of dyspnea was not identified. The DSMB cardiologist reviewed the ECGs, persantin scan and echos and thought that the ECG changes were likely due to improper lead placements.
FTY 1.25 mg 2302_0382_00011	21 M	-	-	Non serious angina pectoris day 94. Hx of headaches, optic neuritis and abnormal chest X-ray. Smoker. No conc. meds. On Day 94 presented sharp pain in heart region, referred toa cardiologist who diagnosed angina pectoris of moderate severity. ECG and stress test showed no ischemic changes. The event resolved the same day. No action was taken with study drug. Patient entered the extension. Subsequent ECGs were normal.
FTY 1.25 mg 2302_0822_00005	37 F	-	-	Non serious angina pectoris on day 3. Medical Hx of HTN and optic neuritis. Mother had diabetes. Non-smoker. On Day 1, ECG showed transient first degree AV block. On Day 3 she had chest tightness and was dix with mild angina pectoris. No action taken with study drug. No treatment given. ECG on Day 3 showed bradycardia. Subsequent ECGs were normal. 2 weeks later, BP was 150/100 mmHg. On Day 35 she had 24 hour Holter, that showed no specific findings. On Day 36 BP was 150/100. She was treated with amlodipine and HCTZ. 2-D Doppler echo was done on Day 30 but results are not available. Event of angina resolved the same day that it started. HTN was ongoing. Pt completed the core phase and entered the extension.
FTY 0.5 mg 2301_0402_00010	29 F	-	-	Non serious angina pectoris on day 68. Hx of headaches, thrombocytosis, and "stenocardia" (angina pectoris), No diabetes, HTN or smoking. During study was taking oral contraceptives and multiple analgesics. On day 68 she had one episode of chest tightness with pain in left arm (angina pectoris) and elevated blood pressure (150/90 mmHg) that resolved spontaneously. No ECG or cardiac enzymes available at the time of the event. Subsequent ECGs were normal. No treatment given for angina pectoris. No further work up was done. Patient withdrew consent on Day 497.
FTY 0.5 mg 2301_0652_00008	44 F	-	-	Non serious angina pectoris on day 327. Hx of knee surgery and hip replacement. HTN and hypercholesterolemia were diagnosed after randomization, before initiation of study drug, HTN treated with HCTZ, metoprolol, amlodipine, lisinopril, irbesartan; high chol. treated with simvastatin. During study received oral contraceptive and tramadol. On Day 179 reported palpitations that lasted until Day 183. At Month 6 and 9 visits, BP was 157/103 and 158/91, respectively. On Day 327 experienced cardiac pain during cycling, diagnosed as angina pectoris. One month later saw a cardiologist, ECG and angiography were normal. No action taken with study drug. Event was resolved by Day 450 (Month 15 visit) without specific treatment. The patient withdrew consent because of HTN.
FTY 0.5 mg 2302_0514_00001	43 F	-	-	Non serious angina pectoris on day 1. Hx of ADHD, depression, GERD, restless legs syndrome, treted with multiple medications. No diabetes or HTN. At screening mild abnormality on valves on echocardiogram. At randomization visit, Day 1, Holter revealed 4 beat episode of non-sustained VT and 13 VPCs approximately 3.5 hours after start of monitoring. ECG showed first degree upon fist dose. Events resolved the same day. On Day 8 pt experienced mild chest discomfort. ECG showed bradycardia. No action taken with drug. Cardiac workup included normal cardiac enzymes and normal continuous cardiac monitoring. A week later a stress echo was within normal. On Day 98, echo showed mild abnormalities on valves, similar to screening echo. No action taken with drug. Pt completed core phase and entered the extension.

FTY 0.5 mg 2302_0535_00002	39 M	-	-	ECG ST segment elevation on day 1, with bradycardia and dizziness. Treated with aspirin and lisinopril. No cardiac workup available.
FTY 0.5 mg 2301_0651_00005	34 F	S	-	Angina pectoris (day 573, 2 days after dc)
FTY 0.5 mg 2301_0454_00002	44 F	S	dc	Dyspnea, chest pain day 449. Recurrent chest pain/pressure radiated to jaw (led to dc) Echo posterior wall hypokinesia.

Source: AE datasets. S= serious. Dc= led to discontinuation

Appendix 9.4.15a. Brief narratives of cases of serious and "non-serious" seizure in the fingolimod controlled studies

ID	AGE SEX	PT_TXT	DAY	Ser	DC	
FTY 5 mg						
2201_0062_00010	21 M	Epilepsy	112	N	.	
FTY 1.25 mg						
2301_0104_00007	31 M	Epilepsy	430	N	.	Ms dx 14 years prior. *Hx of epilepsy for 18 years*, treated with lamotrigine. During the study also received carbamazepine for trigeminal neuralgia. No action taken with study drug.
2301_0304_00005	28 F	Epilepsy	62 77	N N	. .	Ms dx 1 ½ years prior. Medical history included *epilepsy diagnosed 8 years prior* to entry, treated with lamotrigine. No action taken with study drug.
2301_0657_00019	34 F	Epilepsy Epilepsy Epilepsy	45 176 177	Y Y Y	. dc dc	MS dx 10 year prior. No hx of seizures. Most recent relapse 2 months prior to entry, treated with steroids. On day 45 had decreased consciousness and motor abnormalities c/w seizure. EEG showed varying epileptic activity. NO MRI or CT scan done during hospitalization. On Day 176 she had 2 epileptic attacks and developed a fever treated with paracetamol. She was treated with IV methylprednisolone x3 and drug was discontinued. MRI showed active MS lesions. Investigator stated that epileptic attack could be drug related but was probably 2nd to active MS. No additional work up provided for this patient.
2301_0707_00007	43 F	Grand mal convulsion Epilepsy Epilepsy Epilepsy	678 789 789 789	Y N N Y	. . . .	MS dx 8 years prior to entry. No hx of epilepsy. Most recent relapse was 3 months prior to randomiz, treated with steroids. Hx of optic neuritis and HTN. On Day 678 had grand mal Sz with nystagmus, ataxia and left sided hemiparesis. EEG showed "sharp waves of general nature, mostly in posterior regions bilaterally." She was found to have leukocytes & bacteria in urine, and she was treated for UTI. On Day 760 during extension phase she had 3 grand mal seizures. A CT scan showed cortical-subcortical brain and cerebellum atrophy and lesions with symmetric dilatation of the ventricular system and extracerebral fluid space. Also regions of reduced density around lateral ventricles associated with "chronic ischaemic processes" She was started on valproic acid. Final diagnosis was epilepsy and MS. The investigator stated that the reason for the seizure was not known and that there was no evidence to suggest an MS relapse.
2302_0253_00003	34 M	Grand mal convulsion Status epilepticus	33 358	N Y	. .	MS dx 13 years prior. Last relapse prior to random. Was 7months prior, treated with steroids. Patient also received IFN beta 1a in the past. No history of seizures. No concomitant meds. He had two relapses during the study, the second one on Day 118 was associated with generalized tonic clonic seizure and was treated with steroids and carbamazepine. On Day 369 he was hospitalized with status epilepticus. MRI was not done. The cause of status was thought to be non-compliance with his antiepileptic medication. The patient remains in the study.
2302_0821_00007	23 M	Grand mal convulsion Epilepsy Epilepsy	339 311 312	Y N N	dc . .	No history of seizures. Patient had fatal herpes simplex encephalitis. Case describe din more detail under deaths.

FTY 0.5 mg						
2301_0108_00002	42 F	Petit mal epilepsy	723	N	.	Ms dx 9 years prior. Last relapse prior to random was 4 months prior to random. Hx of temporal lobe epilepsy not ongoing at the time of study entry. On Day 723 experienced episodes of absence epilepsy. No action taken with study drug.
2301_0453_00003	19 M	Partial Sz Partial Sz Partial Sz w 2nd.generaliz.	483 496 308	N N Y	. . .	No history of seizures. Had 1 relapse in 2 yrs prior and one relapse in the year prior to randomization. Most recent relapse was 6 mo. prior to randomization. Treated with IFN and glatiramer up to 6 mo. prior to random. Hx of optic neuritis. Smoker. On Day 308 of FTY 0.5 mg he had partial seizure with secondary generalization. CT scan showed subarachnoidal bleeding thought to be due to head trauma during seizure. He recovered from the event. On Day 365 MRI showed an active MS lesion very close to the cortex. It was suggested that this lesion could be the cause of the seizure. This was considered an MS relapse and was treated with Methylprednisolone. The event did not lead to drug dc. The clinical course was favorable with recurrent partial seizures but no new neurological symptoms.

Source: AE datasets and patient profiles

Appendix 9.4.15b. Brief narratives of cases of seizure in the fingolimod extension studies

	AGE SEX	PT_TXT	DAY	Ser	DC	
FTY 5 mg-1.25						
2201_0011_00013	30 F	Epilepsy	1240	Y	-	
2201_0019_00023	44 F	Status epilepticus	682	Y	-	
FTY 1.25 mg						
2201_0050_00008	27 M	Convulsion	1479	Y	Y	No prior history of seizures. Herpes simplex encephalitis – fatal. Described under Deaths.
FTY 0.5 mg						
2301_0951_00001	22 M	Epilepsy	826	Y	-	

Appendix 9.4.15c. Brief narratives of cases of SAE of seizure in ongoing studies (doses other than FTY 0.5)

ID	AGE SEX	PT_TXT	DAY	Ser	DC	
FTY 1.25						
USA/2309 0587/00010	54 M	Ependimoma, Herpes simplex encephalitis	193 after drug dc	Y	N	MS dx 4 years prior. No history of seizures. He had a cyst near the choroidal fissuere in screening MRI. On day 58 he experienced an unexplained fall. On Day 182 during 6-month MRI, the lesion near choroidal fissure was noted to increase in size. On day 267 he underwent stereotactic biopsy of left temporal lobe, followed by surgery. Pathology showed low grade ependimoma. On Day 193 after last dose of study drug, he was hospitalized with new onset

						status epilepticus. Lumbar puncture was positive for HSV PCR. He was treated with iv acyclovir. CSF was negative for other organisms; cytology was negative. CBC reportedly showed normal lymphocyte count. *The case of viral encephalitis is unlikely to be related to fingolimod but the role of fingolimod can not be completely ruled out.*
BLINDED						
2309 558/00011	37 M	Grand mal convulsion	293	Y	N	MS dx 10 years prior. He received IFN beta 1b and glatiramer up to 3 months prior to study entry. Medical hx of optic neuritis and high cholesterol. No hx of seizures. Concomitant meds: modafinil and sildenafil. On Day 293 of treatment he experienced generalizecd tonic clonic seizure. He received acyclovir. At the time of reporting the patient's condition was improving. The investigator did not suspect a relationship to study drug. This case has been unblinded. The patient was receiving placebo.
1201E1 0019 00001 (Japan)	33 F	Convulsion. Loss of consciousness	10 months	Y	N	MS dx 16 years prior to study entry. Hx of optic neuritis, and depression. No history of seizures. Ten months into treatment had convulsion and loss of consciousness for several minutes. Hospitalized. MRI showed no new lesions in the brain. Started on phenytoin. An EEG showed abnormal slow waves in both temporal regions. The investigator concluded that this was likely an epileptic seizure due to an old MS lesion. He did not suspect a causal relationship. *The patient had MS for 18 years and never had a seizure; the MRI showed no new lesions. I would not rule out a causal relationship.*
D1201E1-0024-00002 (Japan)	55 M	Status epilepticus Urinary tract infection	8 months	S	N	MS dx 9 years prior to study entry. Previously treated with interferon beta-1 b and methotrexate (9 years prior). Medical history included depression, back pain and optic neuritis. No history of seizures. Eight months into treatment he fell out of bed and had "limb rigidity" and convulsions in the left arm and face for about 40 minutes. He did not respond when spoken to. He was treated with diazepam, and phenytoin. He had fever (38.7 C). Because of the possibility of aspiration pneumonia, he was give iv antibiotics. Durg was discontinued. MRI of brain showed no new lesions, therefore a relapse had not occurred. EEG showed multiple slow waves. Study drug was re-started when the patient consiousness improved. One week after the episode he was still febrile. He complained of difficult urinating. Urinalysis was consistent with a urinary tract infection. The antibiotic was changed to sultamycillin (Unasyn). A few days later he ws unable to urinate. Urinary catheterization was performed intermittently. The antibiotic was changed to levofoxacin. Two weeks after the initial partial seizure he recoverd and was discharged home. Study drug was not discontinued. Relationship to study drug was suspected. *The reason for the seizure remains unexplained.*

9.5 Information from the transplant population

- Studies conducted in the transplant population.

For completeness of this safety review, I am including relevant information from studies in the transplant population. We need to keep in mind that the renal transplant population is a sicker population than the MS population, includes post-surgical patients with end stage renal disease, with multiple co-morbidities and concomitant medications (cyclosporine A and corticosteroids) with their own set of complications. Interpretation of safety in these trials is complex. More importantly, the doses of fingolimod used in this program (5 and 2.5 mg/day) were higher than in the MS program (1.25 and 0.5 mg/day), therefore one can not extrapolate these findings to the MS population. Still, some patterns of toxicity may be of help in trying to identify potential safety issues in the MS population. In fact, the transplant studies preceded the MS studies and led to discontinuation of development in the transplant population, to the use of lower doses in the MS population and to the identification of AE that needed to be monitored in MS studies.

Studies contributing to safety in the renal transplant population are presented in the following table.

Table 114. Phase 2 & 3 studies of fingolimod in the transplant population

Study No.	Study design	Patients randomized	Treatment Duration	Study medication maintenance dose/day
Key controlled trials:				
0124	Phase III, randomized, partially-blinded efficacy/safety study in de novo adult renal Tx patients	682	1 year	#FTY720 5 mg + RDN + corticosteroids FTY720 2.5 mg + FDN + corticosteroids MMF 2 g + FDN + corticosteroids
†0124E1	Two-year, open-label extension to patients who completed one year study 0124	374	†2 years	#FTY720 5 mg + RDN + corticosteroids FTY720 2.5 mg + FDN + corticosteroids MMF 2 g + FDN + corticosteroids
†0125	Phase III, randomized, partially-blinded efficacy/safety study in de novo adult renal Tx patients	696	†1 year	#FTY720 5 mg + RDN + corticosteroids FTY720 2.5 mg + FDN + corticosteroids MMF 2 g + FDN + corticosteroids
†0125E1	Two-year, open-label extension to patients who completed one year study 0125	373	†2 years	#FTY720 5 mg + RDN + corticosteroids FTY720 2.5 mg + FDN + corticosteroids MMF 2 g + FDN + corticosteroids

Other controlled trials				
B201	Phase IIa, randomized, open-label dose-finding safety, tolerability, and efficacy study in *de novo* renal transplant recipients	208	12 weeks (+12 weeks FU)	FTY720 0.25 mg FTY720 0.5 mg FTY720 1.0 mg FTY720 2.5 mg MMF 2 g (all groups + FDN + corticosteroids)
A121	Phase II, randomized, partially-blinded efficacy/safety study in de novo adult renal Tx patients	270 (269~)	1 year	#FTY720 5 mg + RDN + corticosteroids #FTY720 2.5 mg + RDN + corticosteroids FTY720 2.5 mg + FDN + corticosteroids MMF 2-3 g +FDN + corticosteroids
A121E1	Two-year, partially-blinded, extension to patients who completed one year study A121	116	2 year	#FTY720 2.5 mg + RDN + corticosteroids #FTY720 5 mg + RDN + corticosteroids FTY720 2.5 mg + FDN + corticosteroids MMF 2-3 g + FDN + corticosteroids
†A121E2	Two-year, open-label second extension to patients who completed one year study A121 and two year A121E1	59	†2 year	#FTY720 5 mg + RDN + corticosteroids FTY720 2.5 mg + FDN + corticosteroids MMF 2 g + FDN + corticosteroids
†A121E2	Two-year, open-label second extension to patients who completed one year study A121 and two year A121E1	59	†2 year	#FTY720 5 mg + RDN + corticosteroids FTY720 2.5 mg + FDN + corticosteroids MMF 2 g + FDN + corticosteroids
A2216	24 hr Holter monitoring and observational ECG study in stable adult renal transplant patients maintained on Neoral® or MMF	308‡	2 day	Maintenance treatment: Neoral + MMF with or without corticosteroids
†A2218	Phase IIb, randomized, double-blind, double-dummy, efficacy/safety study in de novo adult renal Tx patients (including Japanese patients)	271	†1 year	FTY720 5 mg + FDN + corticosteroids FTY720 2.5 mg + FDN + corticosteroids MMF 2 g + FDN + corticosteroids
†A2218E1	Two-year, extension to patients who completed one year study A2218	121	†2 year	FTY720 5 mg + FDN + corticosteroids FTY720 2.5 mg + FDN + corticosteroids MMF 2 g + FDN + corticosteroids
†A2302	Phase III, randomized, open-label safety/efficacy study in combination with tacrolimus in de novo adult renal Tx patients	103	†1 year	FTY720 2.5 mg + tacrolimus + corticosteroids MMF 2 g + tacrolimus + corticosteroids
†A2302E1	Two-year, open-label extension to patients who completed one year study A2302	4	†2 year	FTY720 2.5 mg + tacrolimus + corticosteroids MMF 2 g + tacrolimus + corticosteroids

Other non-controlled trials				
A2202	Phase II, open-label safety/tolerability and efficacy study in de novo adult renal Tx patients at increased risk of DGF	56 (53*)	1 year	FTY720 2.5 mg + RAD 2 mg bid + corticosteroids
A2202E1	Two-year, open-label extension to patients who completed one year study A2202	27**	2 year***	FTY720 2.5 mg + RAD 2 mg bid + corticosteroids
†A2307	Phase III, randomized, open-label safety/efficacy study in combination with antibody induction in de novo adult renal Tx patients	9	†1 year	FTY720 5 mg + RDN + corticosteroids FTY720 2.5 mg + FDN + corticosteroid (in both groups + antibody induction)

Table. cont.

treatment arm was discontinued by protocol amendment & patients switched to center-specific standard care
†Study medication terminated by protocol amendment and patients switched to center-specific standard care. For Study 0125 at time of implementation only 2 MMF patients had not reached 12 months on study and were discontinued.
*Study A2202 was single-arm (non-randomized study) 56 patients were enrolled and treated but only 53 patients were transplanted and included in the safety analyzable population for the CSR.
~ Study 121 enrolled 270 patients who all took study drug but only 269 were randomized.
** Study A2202E1 was a single-arm (non-randomized study) 27 patients were included in the extension safety population
***Two year Study 2202E1 was stopped after 12 months.
‡Study A2216 was a non randomized study Data from A2216 (308 MMF patients) was combined with data from A121E1 (94 FTY720 patients and 19 MMF patients). Study A2216 was not included in the pooled populations.
Source: Table 2-1 of Transplant ISS

- Populations pooled for safety analyses in the transplant population.

- **The Key Safety population** included data from the two large, pivotal, Phase III transplantation trials 0124 and 0125, combined with their respective study extensions (0124E1 and 0125E1).
- **The Overall Safety population** pooled safety data from the 8 completed transplantation trials including 0124, 0125, A121, A2202, A2218, A2302, A2307 and B201 with core and extension phases combined.
- **The Ophthalmic population** included patients from all trials in which ophthalmic data were collected, including Studies 0124, 0125, A121, A2218, A2302, and A2307, with core and extension phases combined. All patients enrolled in these trials and who received study medication were included.

    - Exposure in Transplant population

Approximately 1600 subjects were exposed to fingolimod in renal transplant studies. Approximately 1000 subjects were exposed to doses of 5 mg and 2.5 mg daily for at least 6 months and 670 were exposed for at least a year, in the Key safety transplant population (controlled studies, up to 2 years); and approximately half that number was exposed to MMF. FTY and MMF were added to background Cyclosporin A and corticosteroids. Less than 10% of patients in any treatment group experienced 24 months or more cumulative exposure (source: table submitted on 12 2 09 at the FDA request).

Table 115. Key safety population (controlled data). Cumulative duration of exposure

Duration of exposure*	FTY720 5 mg (N=461) n (%) PYRs= 357.8	FTY720 2.5 mg (N=456) n (%) PYRs= 447.5	MMF (N=461) n (%) PYRs= 500.3
≥ 1 week	431 (93.5)	422 (92.5)	431 (93.5)
≥ 1 month	389 (84.4)	388 (85.1)	402 (87.2)
≥ 6 months	279 (60.5)	310 (68.0)	337 (73.1)
≥ 12 months	168 (36.4)	260 (57.0)	289 (62.7)
≥ 18 months	75 (16.3)	140 (30.7)	166 (36.0)
≥ 24 months	17 (3.7)	26 (5.7)	45 (9.8)
≥ 30 months	0	0	0
≥ 36 months	0	0	0

*any exposure (at least 1 dose)
Note: A patient is counted in the maximum category of duration which fits and in each lower category
Source: response to FDA request for information , December 2009.

Overall Renal transplant Safety Population. Cumulative duration of exposure

Duration of exposure*	FTY720 (N=1606) n (%)	MMF (N=689) n (%)
≥ 1 week	1506 (93.8)	652 (94.6)
≥ 1 month	1386 (86.3)	607 (88.1)
≥ 6 months	962 (59.9)	484 (70.2)
≥ 12 months	670 (41.7)	386 (56.0)
≥ 18 months	324 (20.2)	194 (28.2)
≥ 24 months	113 (7.0)	63 (9.1)
≥ 30 months	56 (3.5)	16 (2.3)
≥ 36 months	51 (3.2)	16 (2.3)

*any exposure (at least 1 dose)
Note: A patient is counted in the maximum category of duration which fits and in each lower category
Source: response to FDA request for information. December 2009.

- Adverse Events in the renal transplant population

Adverse events summaries are based on treatment emergent adverse events (events started or worsened on or after the first date of study medication or within 7 days after the last study medication). The adverse events tables that were based on all events, not only treatment emergent, are summaries of malignant neoplasm, deaths, and the incidence of macular edema.

- Deaths in the transplant program

Deaths in the Key Safety Population

Deaths as the primary cause of discontinuation was reported in 3.5% of patients in the key safety population (3.5% in each treatment group: fingolimod 5mg, fingolimod 2.5 mg and MMF). The most commonly reported causes of death in the key safety population were infections and

infestations, in all treatment groups. Deaths in the cardiac SOC occurred in 7 patients in the FTY720 5 mg (4 MI and 3 cardiac arrest). For most of these patients, the cardiac event leading to death was part of a wider pattern of symptoms, and all the patients had pre-existing cardiac risk factors. Additionally, two patients in the fingolimod 2.5 mg/day were found dead at home and are categorized as death or unknown reason, however, they should probably be categorized as sudden death. There were no cardiac deaths in the MMF group. There were no GI deaths in the fingolimod group. Otherwise, incidence of death by SOC is similar to those on MMF.

Table 116. Deaths in the renal transplant Key safety population

	FTY720 5 mg (N=461)	FTY720 2.5 mg (N=456)	MMF (N=461)
No. (%) who died	16 (3.5)	16 (3.5)#	15 (3.5)#
System organ class Preferred term	**n (%)**	**n (%)**	**n (%)**
Cardiac disorders	7 (1.5)	0	0
Cardiac arrest	3 (0.7)	0	0
Myocardial infarction	4 (0.9)	0	0
Gastrointestinal disorders	0	0	3 (0.7)
Intra-abdominal haemorrhage	0	0	1 (0.2)
Pancreatitis	0	0	1 (0.2)
Pancreatitis acute	0	0	1 (0.2)
General disorders and administration site conditions	2 (0.4)	4 (0.9)	1 (0.2)
Multi-organ failure	1 (0.2)	0	1 (0.2)
Catheter related complication	0	1 (0.2)	0
Death [unspecified]*	0	3 (0.7)	0
Sudden death	1 (0.2)	0	0
Infections and infestations	4 (0.9)	7 (1.5)	6 (1.3)
Septic shock	1 (0.2)	1 (0.2)	2 (0.4)
Brain abscess	0	0	1 (0.2)
Dengue fever	0	0	1 (0.2)
Sepsis	1 (0.2)	3 (0.7)	1 (0.2)
Urosepsis	0	0	1 (0.2)
Bronchopneumonia	1 (0.2)	0	0
Infection	1 (0.2)	1 (0.2)	0
Pneumonia cytomegaloviral	0	2 (0.4)	0
Injury, poisoning and procedural complications	0	1 (0.2)	0
Procedural complication	0	1 (0.2)	0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.4)	1 (0.2)	1 (0.2)
Central nervous system lymphoma	0	0	1 (0.2)
Lung neoplasm	1 (0.2)	0	0
Myelodysplastic syndrome	0	1 (0.2)	0
Neoplasm malignant	1 (0.2)	0	0
Nervous system disorders	1 (0.2)	1 (0.2)	2 (0.4)
Anoxic encephalopathy	0	0	1 (0.2)
Cerebral haemorrhage	1 (0.2)	0	1 (0.2)
Cerebral ischaemia	0	1 (0.2)	0
Respiratory, thoracic and mediastinal disorders	0	1 (0.2)	1 (0.2)
Respiratory failure	0	0	1 (0.2)
Acute pulmonary oedema	0	1 (0.2)	0
Unspecified deaths during follow-up#	0	1 (0.2)	1 (0.2)

- one patient died following a traumatic fall and 2 deaths occurred at home of unknown cause.

Sixteen (3.5%) FTY720 5 mg, 15 (3.3%) FTY720 2.5 mg and 14 (3.0%) MMF patients died as reported on the CRF study completion form. A further 1 patient each in the FTY720 2.5 mg and MMF groups were reported to have died during follow-up of unknown cause: FTY720 2.5 mg patient [124/0086/00017] died on Day 239 having discontinued study medication on Day 0and MMF patient [124/0052/00010] died on Day 311 having discontinued study medication on Day 14. Source: Table 4-8 of Transplant ISS.

- Deaths in Overall Transplant Population

Deaths in the overall transplant safety population occurred in 0.6% of fingolimod patients and 0.4% of MMF patients. As for AEs, cause of deaths were pooled according to groupings of studies which used the same version of the MedDRA dictionary. Deaths in two of these subpopulations are summarized here (data not shown).

- The analysis of death from studies 0124, 0125, A2218, A2302 and A2307 and their respective extension periods shows that the most common cause of death in this study was infections and infestations (1% of fingolimod, 1.3% of MMF patients) followed by cardiac disorders (0.7% of fingolimod and 0.2% of MMF patients). Fatal infections and infestations in the fingolimod group included 2 cases of septic shock, 4 of sepsis, one bronchopneumonia and 2 cytomegaloviral pneumonia.

- The analysis of deaths in study A121 and extension also showed infections and infestations (one bacterial sepsis, one lung infection and one mycotic spsis), one cardiac arrest, one respiratory arrest and one cardiogenic shock). No such cases occurred with MMF.

- Serious AES in the transplant Key Safety population

Serious AE in the transplant Key Safety population are presented in the following table.

Table 117. SAE in the Renal transplant Key Safety population by SOC

	FTY720 5 mg (N=461)	FTY720 2.5 mg (N=456)	MMF (N=461)
No. (%) with SAE(s)	278 (60.3)	273 (59.9)	249 (54.0)
No. (%) with SAEs leading to discontinuation	123 (26.7)	101 (22.1)	75 (16.3)
System organ class	**n (%)**	**n (%)**	**n (%)**
Blood and lymphatic system disorders	19 (4.1)	16 (3.5)	21 (4.6)
Cardiac disorders	36 (7.8)	25 (5.5)	18 (3.9)
Congenital, familial and genetic disorders	1 (0.2)	0	0
Ear and labyrinth disorders	1 (0.2)	2 (0.4)	2 (0.4)
Endocrine disorders	0	0	2 (0.4)
Eye disorders	23 (5.0)	22 (4.8)	8 (1.7)
Gastrointestinal disorders	30 (6.5)	28 (6.1)	43 (9.3)
General disorders and administration site conditions	25 (5.4)	29 (6.4)	21 (4.6)
Hepatobiliary disorders	5 (1.1)	3 (0.7)	5 (1.1)
Immune system disorders	36 (7.8)	21 (4.6)	16 (3.5)
Infections and infestations	71 (15.4)	80 (17.5)	116 (25.2)
Injury, poisoning and procedural complications	63 (13.7)	63 (13.8)	67 (14.5)
Investigations	40 (8.7)	47 (10.3)	27 (5.9)
Metabolism and nutrition disorders	27 (5.9)	26 (5.7)	20 (4.3)
Musculoskeletal and connective tissue disorders	7 (1.5)	4 (0.9)	9 (2.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9 (2.0)	11 (2.4)	10 (2.2)
Nervous system disorders	20 (4.3)	22 (4.8)	10 (2.2)
Pregnancy, puerperium and perinatal conditions	0	1 (0.2)	0
Psychiatric disorders	3 (0.7)	5 (1.1)	5 (1.1)
Renal and urinary disorders	72 (15.6)	72 (15.8)	60 (13.0)
Reproductive system and breast disorders	3 (0.7)	8 (1.8)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	28 (6.1)	34 (7.5)	10 (2.2)
Skin and subcutaneous tissue disorders	3 (0.7)	6 (1.3)	2 (0.4)
Social circumstances	0	1 (0.2)	0
Surgical and medical procedures	0	2 (0.4)	3 (0.7)
Vascular disorders	34 (7.4)	56 (12.3)	26 (5.6)

Note deaths specifically reported as SAEs i.e. preferred terms "death" or "sudden death" are not included.

Source: Table 4-14, Transplant ISS (SN 002)

Selected Serious AEs in the transplant Key Safety population are presented in the following tables (from Post-Text Table 4.4-2 of ISS):

Blood and lymphatic system disorders, renal transplant Key safety population

Body System	Preferred term	FTY 5mg (N=461) n (%)	FTY 2.5mg (N=456) n (%)	MMF (N=461) n (%)
-ANY BODY SYSTEM	-TOTAL	278 (60.3)	273 (59.9)	249 (54.0)
-Patient disc. drug due to SAE(s)		123 (26.7)	101 (22.1)	75 (16.3)
Blood and lymphatic system disorders	-TOTAL	19 (4.1)	16 (3.5)	21 (4.6)
	Leukopenia	8 (1.7)	3 (0.7)	8 (1.7)
	Anaemia	2 (0.4)	2 (0.4)	7 (1.5)
	Agranulocytosis	0	0	2 (0.4)
	Thrombocytopenia	2 (0.4)	2 (0.4)	2 (0.4)
	Coagulopathy	0	0	1 (0.2)
	Microangiopathic haemolytic anaemia	0	0	1 (0.2)
	Neutropenia	3 (0.7)	1 (0.2)	1 (0.2)
	Pancytopenia	0	0	1 (0.2)
	Polycythaemia	0	0	1 (0.2)
	Anaemia haemolytic autoimmune	1 (0.2)	1 (0.2)	0
	Haemolysis	1 (0.2)	1 (0.2)	0
	Haemolytic anaemia	0	3 (0.7)	0
	Haemolytic uraemic syndrome	4 (0.9)	2 (0.4)	0
Blood and lymphatic system disorders	Haemorrhagic anaemia	1 (0.2)	0	0
	Lymphopenia	0	1 (0.2)	0
	Splenomegaly	1 (0.2)	0	0
	Thrombotic microangiopathy	1 (0.2)	2 (0.4)	0

This table indicates that in addition to the expected leukopenia, there are other AEs such as thrombocytopenia and 6 cases of hemolytic uremic syndrome. These AEs are of interest, however, the relevance of this information at doses of 5 and 2.5 mg is unclear to the MS population (for which the only proposed dose for marketing is 0.5 mg). This comment applies to all tables shown below as well.

SAEs in Cardiac disorders SOC, renal transplant Key safety population.

Cardiac disorders	-TOTAL	36 (7.8)	25 (5.5)	18 (3.9)
	Myocardial infarction	10 (2.2)	1 (0.2)	5 (1.1)
	Angina pectoris	1 (0.2)	2 (0.4)	2 (0.4)
	Cardiac arrest	3 (0.7)	2 (0.4)	2 (0.4)
	Cardiac failure	2 (0.4)	1 (0.2)	2 (0.4)
	Cardiac failure acute	0	0	1 (0.2)
	Cardiac failure congestive	5 (1.1)	4 (0.9)	1 (0.2)
	Cardio-respiratory arrest	0	0	1 (0.2)
	Coronary artery insufficiency	0	0	1 (0.2)
	Coronary artery occlusion	0	0	1 (0.2)
	Myocarditis	0	0	1 (0.2)
	Pericarditis	2 (0.4)	1 (0.2)	1 (0.2)
	Sinus bradycardia	1 (0.2)	0	1 (0.2)

Cardiac disorders	Supraventricular tachycardia	1 (0.2)	1 (0.2)	1 (0.2)
	Tachyarrhythmia	0	0	1 (0.2)
	Ventricular hypertrophy	0	0	1 (0.2)
	Ventricular tachycardia	0	0	1 (0.2)
	Acute coronary syndrome	1 (0.2)	0	0
	Acute myocardial infarction	0	1 (0.2)	0
	Angina unstable	1 (0.2)	0	0
	Atrial fibrillation	2 (0.4)	3 (0.7)	0
	Bradycardia	7 (1.5)	9 (2.0)	0
	Brugada syndrome	0	1 (0.2)	0
	Cardiac aneurysm	0	1 (0.2)	0
	Coronary artery disease	2 (0.4)	0	0
	Coronary artery stenosis	0	1 (0.2)	0
	Coronary artery thrombosis	1 (0.2)	0	0
	Hypertensive heart disease	1 (0.2)	1 (0.2)	0
	Mitral valve incompetence	0	1 (0.2)	0
	Myocardial ischaemia	2 (0.4)	0	0
	Pericardial effusion	0	1 (0.2)	0
	Ventricular fibrillation	0	1 (0.2)	0

There is a signal for myocardial infarction for the fingolimod 5mg dose and for bradycardia for both 2.5 and 5 mg doses as compared to MMF. Of note, ECG and Holter monitoring were extensively conducted in the MS population. The DNP also requested that echocardiogram be conducted in a subset of patients.

SAE in Eye disorders SOC, renal transplant Key safety population

Eye disorders	-TOTAL	23 (5.0)	22 (4.8)	8 (1.7)
	Macular oedema	19 (4.1)	18 (3.9)	7 (1.5)
	Diabetic retinal oedema	1 (0.2)	1 (0.2)	1 (0.2)
	Blindness unilateral	0	1 (0.2)	0
	Glaucoma	0	1 (0.2)	0
	Maculopathy	1 (0.2)	0	0
	Retinal haemorrhage	0	1 (0.2)	0
	Retinal oedema	1 (0.2)	2 (0.4)	0
Eye disorders	Retinal telangiectasia	1 (0.2)	0	0
	Visual acuity reduced	0	2 (0.4)	0

There is a signal for increased macular edema for both doses of fingolimod 5mg and 2.5 mg as compared to MMF. Extensive ophthalmologic evaluations were conducted in the MS program.

Immune system disorders, renal transplant Key safety population)

Immune system disorders	-TOTAL	36 (7.8)	21 (4.6)	16 (3.5)
	Transplant rejection	31 (6.7)	18 (3.9)	14 (3.0)
	Kidney transplant rejection	4 (0.9)	2 (0.4)	2 (0.4)
	Anaphylactic reaction	1 (0.2)	1 (0.2)	0
	Serum sickness	1 (0.2)	0	0

There were a total of two cases of anaphylactic reactions and one serum sickness in the transplant key safety population in the fingolimod group and no such cases in the MMF group.

An increased risk of infections and infestations is expected with agents that cause immuno-suppression. In fact, 15.4% of fingolimod 5 mg treated patients and 17.5% of fingolimod 2.5mg treated patients had serious infections or infestations. Of note, 25% of those treated with MMF also had serious infections and infestations (data not shown).

In the Investigations SOC, the risk of SAEs was 8.7%, 10.3% and 5.9% in the fingolimod 5, fingolimod 2.5 and MMF groups, respectively, mostly related to blood creatinine increased in 7.4%, 8.6% and 3.9% of patients in the fingolimod 5, fingolimod 2.5 and MMF, respectively. (data not shown).

In the Neoplasms SOC, the overall risk of SAEs was similarly distributed among treatment groups (0.9%, 0.9 % and 0.7% for fingolimod 5, 2.5 and MMF, respectively). Of interest, there was one case of B-cell lymphoma, one T-cell lymphoma and one lymphoproliferative disorder among 456 patients in the fingolimod 2.5 mg. No such cases were observed in the fingolimod 5 mg or MMF groups, but there was a case of CNS lymphoma in the MMF group (data not shown). Fingolimod is supposed to inhibit peripheral circulation and it is not supposed to affect lymphocyte proliferation. These disorders were not observed in the higher fingolimod dose group. It is unclear if these events are related to fingolimod.

Regarding the Nervous system disorders SOC, overall, there were more SAEs in the fingolimod groups (4.3% and 4.8%, for the 5 and 2.5 mg doses, respectively) as compared to the MMF group (2.2%). A summary of these events is presented in the following table.

Serious AEs in the Nervous system disorders SOC. Renal transplant Key safety population.

Body System	Preferred term	FTY 5mg (N=461) n (%)	FTY 2.5mg (N=456) n (%)	MMF (N=461) n (%)
Nervous system disorders	-TOTAL	20 (4.3)	22 (4.8)	10 (2.2)
	Headache	1 (0.2)	3 (0.7)	2 (0.4)
	Cerebral haemorrhage	1 (0.2)	0	1 (0.2)
	Cerebrovascular accident	2 (0.4)	3 (0.7)	1 (0.2)
	Convulsion	5 (1.1)	6 (1.3)	1 (0.2)
	Dizziness	0	2 (0.4)	1 (0.2)
	Drop attacks	0	0	1 (0.2)
	Femoral nerve lesion	0	0	1 (0.2)
	Hypotonia	0	0	1 (0.2)
	Neurological symptom	0	0	1 (0.2)
	Transient ischaemic attack	1 (0.2)	0	1 (0.2)
	Benign intracranial hypertension	1 (0.2)	0	0
	Cerebral haematoma	0	1 (0.2)	0
	Cerebral ischaemia	2 (0.4)	0	0
	Cerebrovascular spasm	0	1 (0.2)	0
	Cognitive disorder	0	1 (0.2)	0
	Depressed level of consciousness	0	1 (0.2)	0
	Diabetic coma	1 (0.2)	0	0
	Dysarthria	0	2 (0.4)	0
	Encephalitis	2 (0.4)	0	0
Nervous system disorders	Encephalopathy	0	2 (0.4)	0
	Grand mal convulsion	2 (0.4)	0	0
	Haemorrhage intracranial	1 (0.2)	0	0
	Hypertensive encephalopathy	3 (0.7)	1 (0.2)	0
	Ischaemic cerebral infarction	0	1 (0.2)	0
	Locked-in syndrome	1 (0.2)	0	0
	Migraine	1 (0.2)	0	0
	Nervous system disorder	0	1 (0.2)	0
	Neurotoxicity	1 (0.2)	1 (0.2)	0
	Partial seizures	0	1 (0.2)	0
	Somnolence	1 (0.2)	0	0
	Subarachnoid haemorrhage	0	1 (0.2)	0
	Syncope	3 (0.7)	1 (0.2)	0
	Tremor	1 (0.2)	0	0

Source, Post-text Table 4.4-2, Transplant ISS.

Of note, SAEs of convulsions were reported by 5 (1.1%) and 6 (1.3%) of patients in the fingolimod 5mg and 2.5mg groups, as compared to 1 (0.2%) of the MMF group; grand mal convulsion was reported in 2 (0.4%) of the fingolimod 5mg and partial seizures in 1 (0.2%) of the fingolimod 2.5mg group. Additionally, one patient had a “locked-in syndrome” (I suspect it could have been post-ictal) and 2 (0.4%) reported encephalitis in the fingolimod 5mg group.

These events are of concern. It is unclear what the total number of events is. Additional information will be requested from these patients. This finding suggests that fingolimod, at the doses of 5 and 2.5 mg/day may be associated with seizures.

With regard to the Renal and Urinary disorders SOC, the risk of SAEs was slightly higher in the fingolimod groups (15.6% and 15.8% in the fingolimod 5 and 2.5 mg, respectively), as compared to the MMF treated group (13%). The difference seems to be driven by events of hydronephrosis and renal impairment, renal tubular necrosis, renal vein thrombosis and proteinuria in the fingolimod groups. Renal adverse events are very difficult to assess in the setting of failing transplanted kidneys. I have not conducted a full review of these cases.

In the Respiratory, thoracic and mediastinal disorders, the risk of SAEs was higher in the fingolimod groups. See table below.

SAEs in the Respiratory, thoracic and mediastinal disorders SOC. Renal transplant Key safety population.

Body System	Preferred term	FTY 5mg (N=461) n (%)	FTY 2.5mg (N=456) n (%)	MMF (N=461) n (%)
Respiratory, thoracic and mediastinal disorders	-TOTAL	28 (6.1)	34 (7.5)	10 (2.2)
	Cough	1 (0.2)	0	2 (0.4)
	Dyspnoea	6 (1.3)	6 (1.3)	2 (0.4)
	Non-cardiogenic pulmonary oedema	0	0	2 (0.4)
	Pharyngolaryngeal pain	2 (0.4)	0	2 (0.4)
	Respiratory failure	2 (0.4)	1 (0.2)	2 (0.4)
	Interstitial lung disease	2 (0.4)	2 (0.4)	1 (0.2)
	Pleuritic pain	0	0	1 (0.2)
	Respiratory distress	0	0	1 (0.2)
	Acute pulmonary oedema	1 (0.2)	3 (0.7)	0
	Acute respiratory distress syndrome	1 (0.2)	0	0
	Acute respiratory failure	1 (0.2)	0	0
	Alveolitis	1 (0.2)	0	0
	Asthma	0	4 (0.9)	0
	Atelectasis	1 (0.2)	1 (0.2)	0
	Bronchopneumopathy	0	2 (0.4)	0
	Bronchospasm	1 (0.2)	0	0
	Chronic obstructive pulmonary disease	1 (0.2)	0	0
	Dysphonia	0	1 (0.2)	0
Respiratory, thoracic and mediastinal disorders	Epistaxis	1 (0.2)	0	0
	Haemoptysis	0	1 (0.2)	0
	Hypoxia	1 (0.2)	1 (0.2)	0
	Laryngeal granuloma	0	1 (0.2)	0
	Obstructive airways disorder	1 (0.2)	0	0
	Orthopnoea	0	1 (0.2)	0
	Pneumonitis	0	1 (0.2)	0
	Pulmonary congestion	0	1 (0.2)	0
	Pulmonary embolism	2 (0.4)	1 (0.2)	0
	Pulmonary oedema	6 (1.3)	10 (2.2)	0
	Sleep apnoea syndrome	1 (0.2)	1 (0.2)	0

Of note, the risk of SAEs in the Respiratory, thoracic and mediastinal disorders was higher in the fingolimod 5 and 2.5 mg groups (6.1% and 7.5%, respectively) as compared to MMF (2.2%). Dyspnea was reported by 6 (1.3%), 6 (1.3% and 2 (0.4%) of patients in the fingolimod 5 mg, 2.5 mg and MMF groups, respectively. Pulmonary edema was reported by 6 (1.3%) and 10 (2.2%) of patients in the fingolimod 5 and 2.5 mg groups, as compared to 0 in the MMF group. Acute pulmonary edema was reported by 1 (0.2%), 4 (0.9%) and 0% in the fingolimod 5, 2.5 and MMF groups. Additionally acute respiratory failure, acute respiratory distress syndrome and alveolitis

(one case each) were reported in the fingolimod 5 mg group. It is possible that a single patient may have reported more than one of these events. Still, there is a clear signal of lung or may be cardiac toxicity for fingolimod in this database, at the 5 and 2.5 mg doses. This is consistent with the findings in non-clinical studies. Because of these findings, the sponsor conducted extensive lung assessments (including PFTs and HRCT) in the MS program. A small number of patients also underwent echocardiography.

Of note, S1P1 receptor modulators are expected to affect bronchoconstriction. In the key renal transplant database there is one case of bronchospasm in the fingolimod 5 mg group and 4 of asthma in the fingolimod 2.5 mg group, with no such cases in the MMF group.

With regards of the Vascular disorders SOC, the risk of SAEs was higher in the fingolimod groups (7.4% and 12.3% for the 5 and 2.5 mg doses, respectively) as compared to the MMF group (5.6%). The listing of SAEs in this SOC is presented as follows:

SAEs in the Vascular disorders SOC, renal transplant Key safety population.

Body System	Preferred term	FTY 5mg (N=461) n (%)	FTY 2.5mg (N=456) n (%)	MMF (N=461) n (%)
Vascular disorders	-TOTAL	34 (7.4)	56 (12.3)	26 (5.6)
	Lymphocele	9 (2.0)	17 (3.7)	11 (2.4)
	Deep vein thrombosis	2 (0.4)	3 (0.7)	4 (0.9)
	Hypertension	6 (1.3)	11 (2.4)	3 (0.7)
	Shock haemorrhagic	0	1 (0.2)	3 (0.7)
	Extremity necrosis	0	1 (0.2)	1 (0.2)
	Hypertensive crisis	2 (0.4)	3 (0.7)	1 (0.2)
	Hypotension	5 (1.1)	7 (1.5)	1 (0.2)
	Hypovolaemic shock	0	1 (0.2)	1 (0.2)
	Orthostatic hypotension	3 (0.7)	2 (0.4)	1 (0.2)
	Steal syndrome	0	0	1 (0.2)
	Arterial disorder	0	1 (0.2)	0
	Arterial occlusive disease	0	1 (0.2)	0
	Arterial thrombosis	2 (0.4)	0	0
	Blood pressure fluctuation	1 (0.2)	0	0
	Haematoma	1 (0.2)	0	0
	Hypertensive emergency	0	1 (0.2)	0
	Iliac artery stenosis	1 (0.2)	1 (0.2)	0
	Iliac artery thrombosis	0	1 (0.2)	0
	Intermittent claudication	0	1 (0.2)	0
Vascular disorders	Lymphoedema	0	1 (0.2)	0
	Lymphorrhoea	0	1 (0.2)	0
	Peripheral artery dissection	1 (0.2)	0	0
	Phlebitis	1 (0.2)	0	0
	Subclavian vein thrombosis	0	1 (0.2)	0
	Vascular pseudoaneurysm	1 (0.2)	0	0
	Venous stenosis	0	1 (0.2)	0
	Venous thrombosis	0	2 (0.4)	0
	Venous thrombosis limb	0	1 (0.2)	0

As seen in this table, SAEs related to changes in blood pressure were more common in the fingolimod groups. Hypertension was reported in 6 (1.3%), 11 (2.4%) and 3 (0.7%) of patients in the fingolimod 5, fingolimod 2.5 and the MMF groups, respectively. Hypotension was reported by 5 (1.1%), 7 (1.5%) and 1 (0.2%) of patients in the fingolimod 5, fingolimod 2.5 and MMF groups respectively. Overall, arterial ischemic and thrombotic events as well as venous thrombotic events appear to be somewhat more frequent in the fingolimod groups, but the number of individual events are small and some of them may have occurred in the same patient. No definitive conclusions can be drawn from this table of vascular events.

Laboratory evaluations

Larger mean increases for total cholesterol, triglycerides and sodium levels, a larger mean decrease for calcium, and lower mean decreases for magnesium and potassium occurred for the FTY720 5 mg group compared to the MMF group. However, mean values for sodium, potassium and calcium remained within normal range for all treatment arms at visits through Month 12 and Month 24. Some of the findings in the FTY720 5 mg group may be explained by the increased incidence of rejections in this treatment arm which were treated with steroids.

Table 5-7 Number (percent) of patients with at least one notable clinical chemistry abnormality – Key Safety Population

Variable (unit)	Notable criteria	FTY720 5 mg (N=461) n (%)	FTY720 2.5 mg (N=456) n (%)	MMF (N=461) n (%)
Alpha Amylase (Serum) (U/L)	High: >= 2 x ULN	108 (23.4)	128 (28.1)	123 (26.7)
Lipase (Blood) (U/L)	High: >= 2 x ULN	121 (26.2)	147 (32.2)	131 (28.4)
Cholesterol (total) (mmol/L)	High: >= 9.051	10 (2.2)	9 (2.0)	4 (0.9)
Triglycerides (mmol/L)	High: >= 8.5	3 (0.7)	5 (1.1)	5 (1.1)
Alkaline phosphatase, serum (U/L)	High: >= 3 x ULN	14 (3.0)	13 (2.9)	7 (1.5)
Bilirubin (total) (umol/L)	High: >= 34.2	11 (2.4)	49 (10.7)	31 (6.7)
AST (SGOT) (U/L)	High: >= 3 x ULN	22 (4.8)	26 (5.7)	19 (4.1)
ALT (SGPT) (U/L)	High: >= 3 x ULN	88 (19.1)	95 (20.8)	70 (15.2)
Calcium (mmol/L)	Low: <= 1.5	5 (1.1)	10 (2.2)	5 (1.1)
	High: >= 3.2	4 (0.9)	3 (0.7)	2 (0.4)
Glucose (mmol/L)	Low: < 2.5	36 (7.8)	41 (9.0)	44 (9.5)
	High: > 13.9	53 (11.5)	57 (12.5)	51 (11.1)
Glycosylated hemoglobin (HbA1c) (%)	High: > 6.4	82 (17.8)	94 (20.6)	100 (21.7)
Magnesium (mmol/L)	Low: < 0.4	1 (0.2)	1 (0.2)	4 (0.9)
	High: > 1.5	6 (1.3)	11 (2.4)	9 (2.0)
Potassium (mmol/L)	Low: <= 3	22 (4.8)	20 (4.4)	23 (5.0)
	High: >= 6	121 (26.2)	136 (29.8)	125 (27.1)
Sodium (mmol/L)	Low: <= 130	70 (15.2)	71 (15.6)	63 (13.7)
	High: > 145	72 (15.6)	75 (16.4)	70 (15.2)
Creatinine (umol/L)	High: > 30% above value from preceding visit or Day 1 to Week 4 > 354 or After Week 4 > 265	394 (85.5)	379 (83.1)	381 (82.6)
Uric Acid (umol/L)	High: Male >= 714 or Female >= 535	103 (22.3)	120 (26.3)	74 (16.1)

Source: PT-Table 5.2-2a

Source: Renal transplant ISS. SN 002.

This analysis suggests a higher risk of markedly abnormal increase in cholesterol, ALT, and uric acid as compared to MMF.

In summary, review of tables of deaths and serious AEs in the renal transplant population indicates an increased risk of cardiac events (MI, cardiac arrest), eye toxicity (macular edema), respiratory events (pulmonary edema vs cardiac failure) and neurologic events (seizures) for the fingolimod at the doses of 5 and 2.5 mg/day as compared to MMF. Additionally there is a suggestion for increased renal toxicity, lymphoproliferative disease and allergic reactions in fingolimod-treated patients as compared to MMF.

- Serious and non-serious AE of interest in Renal Key safety population.

- Macular Edema

Table 6-13 Number (percent) of patients with diagnosis of macular edema (Ophthalmic population)

	FTY720 5mg (N=625)	FTY720 2.5mg (N=757)	MMF (N=648)
Number of patients with ophthalmic evaluation	422	469	484
A. Number of patients with diagnosis of macular edema (any eye)	33 (7.8)	38 (8.1)	20 (4.1)
B. Bilateral macular edema	22 (66.7)	18 (47.4)	8 (40.0)
Unilateral macular edema	11 (33.3)	20 (52.6)	12 (60.0)
Macular edema diagnosed while on treatment	14 (42.4)	20 (52.6)	13 (65.0)
Diabetic patients with macular edema (any eye)	18 (54.5)	22 (57.9)	12 (60.0)
Non-diabetic patients with macular edema (any eye)	15 (45.5)	16 (42.1)	8 (40.0)
Patients with risk factors*	19 (57.6)	22 (57.9)	12 (60.0)
Diabetes	18 (54.5)	22 (57.9)	12 (60.0)
Diabetic retinopathy	11 (33.3)	10 (26.3)	5 (25.0)
Other retinal vascular disease	0	0	0
Previous ocular surgery	3 (9.1)	2 (5.3)	2 (10.0)
Uveitis	0	0	1 (5.0)

Percentages for A are based on the number of patients with ophthalmic evaluation.

Percentages for B are based on the number of patients with final diagnosis of macular edema, as assessed by the ophthalmologist.

Source: Renal transplant ISS (SN 002).

- Neoplasms including malignancies

Table 4-28 Number (percent) of patients with malignancies on study – Key Safety Population

Preferred term	FTY720 5 mg (N=461) n (%)	FTY720 2.5 mg (N=456) n (%)	MMF (N=461) n (%)
Any malignant neoplasm	**10 (2.2)**	**13 (2.9)**	**10 (2.2)**
Basal cell carcinoma	4 (0.9)	5 (1.1)	3 (0.7)
Kaposi's sarcoma	0	2 (0.4)	1 (0.2)
Squamous cell carcinoma	2 (0.4)	2 (0.4)	1 (0.2)
Lymphoproliferative disorder	0	1 (0.2)	1 (0.2)
B-cell lymphoma	0	1 (0.2)	0
Epithelioma	0	1 (0.2)	0
Papillary thyroid cancer	0	1 (0.2)	0
Squamous cell carcinoma of skin	0	1 (0.2)	0
T-cell lymphoma	0	1 (0.2)	0
Malignant melanoma	1 (0.2)	0	1 (0.2)
Renal cell carcinoma stage unspecified	1 (0.2)	0	1 (0.2)
Bowen's disease	1 (0.2)	0	0
Prostate cancer	1 (0.2)	0	0
Uterine cancer	1 (0.2)	0	0
Central nervous system lymphoma	0	0	1 (0.2)
Hepatic neoplasm malignant	0	0	1 (0.2)
Oesophageal neoplasm#	0	0	1 (0.2)

Malignancies are summarized which occurred within 7 days after the last dose of study drug.

Source. Renal transplant ISS (SN 002).

- Respiratory disorders

Table 4-24 Number (percent) of patients with respiratory disorders - Key Safety Population

	FTY720 5 mg (N=461) n (%)	FTY720 2.5 mg (N=456) n (%)	MMF (N=461) n (%)
Respiratory, thoracic and mediastinal disorders	217 (47.1)	200 (43.9)	170 (36.9)
Preferred term			
Cough	38 (8.2)	47 (10.3)	48 (10.4)
Dyspnoea	76 (16.5)	65 (14.3)	47 (10.2)
Pharyngolaryngeal pain	23 (5.0)	18 (3.9)	25 (5.4)
Pleural effusion	16 (3.5)	7 (1.5)	13 (2.8)
Nasal congestion	5 (1.1)	5 (1.1)	10 (2.2)
Dyspnoea exertional	16 (3.5)	15 (3.3)	8 (1.7)
Pulmonary oedema	21 (4.6)	23 (5.0)	7 (1.5)
Rhinorrhoea	10 (2.2)	4 (0.9)	7 (1.5)
Productive cough	13 (2.8)	9 (2.0)	6 (1.3)
Wheezing	4 (0.9)	4 (0.9)	6 (1.3)
Hiccups	7 (1.5)	6 (1.3)	5 (1.1)
Hypoxia	4 (0.9)	6 (1.3)	5 (1.1)
Asthma	7 (1.5)	13 (2.9)	4 (0.9)
Obstructive airways disorder	8 (1.7)	5 (1.1)	4 (0.9)
Pharyngeal erythema	0	2 (0.4)	4 (0.9)
Sinus congestion	4 (0.9)	3 (0.7)	4 (0.9)
Atelectasis	7 (1.5)	6 (1.3)	3 (0.7)
Lung disorder	1 (0.2)	3 (0.7)	3 (0.7)
Respiratory failure	5 (1.1)	5 (1.1)	3 (0.7)
Restrictive pulmonary disease	1 (0.2)	2 (0.4)	3 (0.7)
Rhinitis allergic	5 (1.1)	4 (0.9)	3 (0.7)
Bronchospasm	9 (2.0)	10 (2.2)	2 (0.4)
Epistaxis	6 (1.3)	10 (2.2)	2 (0.4)
Lung consolidation	0	0	2 (0.4)
Non-cardiogenic pulmonary oedema	0	0	2 (0.4)
Pleuritic pain	0	1 (0.2)	2 (0.4)
Rales	7 (1.5)	5 (1.1)	2 (0.4)
Haemoptysis	3 (0.7)	3 (0.7)	1 (0.2)
Hypoventilation	2 (0.4)	0	1 (0.2)
Increased viscosity of bronchial secretion	0	1 (0.2)	1 (0.2)
Interstitial lung disease	2 (0.4)	3 (0.7)	1 (0.2)
Lung infiltration	2 (0.4)	2 (0.4)	1 (0.2)
Nasal discomfort	1 (0.2)	0	1 (0.2)
Orthopnoea	3 (0.7)	3 (0.7)	1 (0.2)
Paranasal sinus hypersecretion	0	1 (0.2)	1 (0.2)
Pharyngeal polyp	0	0	1 (0.2)
Pneumothorax	0	3 (0.7)	1 (0.2)
Pulmonary congestion	5 (1.1)	3 (0.7)	1 (0.2)
Pulmonary granuloma	0	0	1 (0.2)
Pulmonary hypertension	2 (0.4)	4 (0.9)	1 (0.2)
Pulmonary vascular disorder	0	0	1 (0.2)
Respiratory depression	0	0	1 (0.2)
Sinus disorder	0	0	1 (0.2)
Vocal cord disorder	0	0	1 (0.2)
Acute pulmonary oedema	4 (0.9)	5 (1.1)	0

Source: Renal transplant ISS (SN 002).

In the renal transplant controlled key safety population there was an excess of cardiovascular death with FTY 5mg and increase risk of SAE in the cardiac, vascular, respiratory, neurologic and eye disorders SOCs with both FTY 5 and 2.5 mg as compared to MMF. There was also higher risk of Investigations, blood creatinine increased AE as compared to MMF, but there was also a higher rate of transplant failure as compared to MMF. Again, it is hard to extrapolate these findings to other population and to lower fingolimod doses.

9.6 Sponsor's proposed REMS

The sponsor proposes to address the following safety issues:

1. Bradycardia/bradyarrhythmia
2. Infections
3. Macular edema
4. Teratogenecity

In my opinion, respiratory and liver effects should also be included in the REMS.

The applicant proposes to have a MedGuide a Communication plan consisting on a Dear HCP letter and product Brochure, with no elements of safe use.

The applicant also proposes to conduct a 6,000 patient (4,000 newly treated with fingolimod and 2,000 already treated with other MS disease-modifying therapies), 5-year postmarketing registry (PASS= post-authorization safety study) to investigate the incidence of selected safety-related outcomes in patients with MS receiving fingolimod under conditions of routine clinical practice.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22527	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	FINGOLIMOD HCL ORAL CAPSULES

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/s/

MARIA L VILLALBA
08/25/2010

SALLY U YASUDA
08/25/2010

Shari L. Targum, M.D.
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, Maryland 20993
Tel (301) 796-1151

Memorandum

DATE: June 8, 2010

FROM: Shari L. Targum, MD, Team Leader
Division of Cardiovascular and Renal Products, HFD-110

THROUGH: Norman Stockbridge, MD, PhD, Director
Division of Cardiovascular and Renal Products, HFD-110

TO: Eric Bastings, M.D., Deputy Director, Division of Neurology

SUBJECT: NDA #022527

NAME OF DRUG: Fingolimod
TRADE NAME: Gilenia
FORMULATION: Oral
RELATED APPLICATIONS: IND #70,139; IND #70,407 (treatment of hepatitis C virus); IND #57,293 (organ rejection in transplantation).
APPROVED INDICATIONS: N/A

SPONSOR: Novartis

DOCUMENTS AVAILABLE FOR REVIEW: 1. Prior consultations; 2. edr submission, serial #078, 5/19/2010;
DATE CONSULT COMPLETED: June 8, 2010

REASON FOR CONSULTATION:
The Division of Neurology Products has asked for an evaluation of cardiovascular safety of fingolimod, an oral agent for the treatment of multiple sclerosis (MS), including an evaluation of echocardiography data submitted in this application. A presentation of the fingolimod NDA is planned at an advisory committee meeting on June 10, 2010.

This addendum is a review of valve data based on echocardiograms in selected sites in studies 2302 and ongoing study 2309. The requested retrospective analysis of cardiac valves was based on the following:

1. In nonclinical oral toxicity studies in the dog, microscopic examination showed vascular wall thickening and perivascular and focal perimysial fibrosis of the left ventricular papilla in the heart.
2. Several cases of heart failure, pulmonary edema, pulmonary congestion and fluid overload were observed in the transplant trials, at doses above the dose currently recommended for approval. The transplant program was developed in a different population (older, majority male, renal failure, diabetics included); however, an imbalance was observed with more cases on drug (prior

consultation by Dr. Desai). The Phase 3 MS program involved a lower fingolimod dose and different population and excluded diabetics.

Methods:

An independent cardiologist conducted a review that was blinded to subject name, treatment arm, investigational site, examination date and reason for examination. Echocardiograms were reviewed at baseline and month 12 to assess morphology of mitral, aortic and tricuspid valves; the data were not appropriate to assess the pulmonic valve. Valves were evaluated with respect to mobility, thickness, calcification and reduction in excursion; extent of changes was assessed as trace, mild, moderate or severe or diffuse/focal as appropriate. The mitral and tricuspid valves were evaluated for the presence of stenosis or regurgitation.

Results:

Mitral, tricuspid and aortic valves were evaluable in most of the echocardiograms in this subset.
No calcification or reductions in valve excursion were observed; no mitral or tricuspid stenosis was observed in any treatment group. No moderate or severe mitral or tricuspid regurgitation was observed in any treatment group at Month 12. The aortic valve could not be assessed for stenosis or regurgitation.

At Month 12, four patients on fingolimod 1.25 mg, 2 patients on fingolimod 0.5 mg, and 3 patients on placebo had mild thickening of the mitral valve; no moderate or severe thickening of the mitral valve was observed in any treatment group. At Month 12, mild mitral regurgitation was observed in two patients on fingolimod 1.25 mg, three patients on fingolimod 0.5 mg and one patient on placebo.

No tricuspid thickening was observed in any treatment group. At Month 12, trace tricuspid regurgitation was observed in 37 patients (88.1%) on fingolimod 1.25 mg (N=71), 32 patients (80.0%) on fingolimod 0.5 mg (N=69), 16 patients (75.0%) on placebo (N=57) and 6 patients (87.5%) on Avonex (N=7). Mild tricuspid regurgitation was observed in 3 patients on fingolimod 1.25 mg, 6 patients on fingolimod 0.5 mg, and 3 patients on placebo. No moderate or severe tricuspid regurgitation was observed.

At Month 12, no thickening of the aortic valve was observed in any treatment group.

Reviewer Comments:

1. While there may be a numerical imbalance in “trace” tricuspid regurgitation in patients on fingolimod 1.25 mg vs. placebo, trace tricuspid regurgitation is not generally considered clinically significant and may be a function of the high sensitivity of Doppler testing; one should also note a similar incidence of trace tricuspid regurgitation in the Avonex group.

2. No clinically meaningful signal for valvular abnormalities was observed in this analysis.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22527	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	FINGOLIMOD HCL ORAL CAPSULES

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/s/

SHARI L TARGUM
06/07/2010

NORMAN L STOCKBRIDGE
06/07/2010

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY

DATE: 27 May 2010

FROM: John R. Senior, M.D., Associate Director for Science, Office of Surveillance and Epidemiology (OSE)

TO: Russell Katz, M.D., Director, Division of Neurological Products (DNP)
Lourdes Villalba, M.D., Medical Safety Reviewer, DNP
Sally Yasuda, Pharm.D., Safety Team Leader, DNP

VIA: Gerald Dal Pan, M.D., Director, OSE

SUBJECT: New information on case of liver injury in German patient treated with fingolimod (FTY720) for reducing the relapse rate of multiple sclerosis

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Documents reviewed:

1) Updated MedWatch report dated 21 May from sponsor (Novartis), received yesterday (26 May), with results of further serum liver tests and viral antibody measurements
2) Revised narrative updated to 25 May, and received from sponsor 26 May 2010.
3) Selected medical literature articles on acute hepatitis E, and other items

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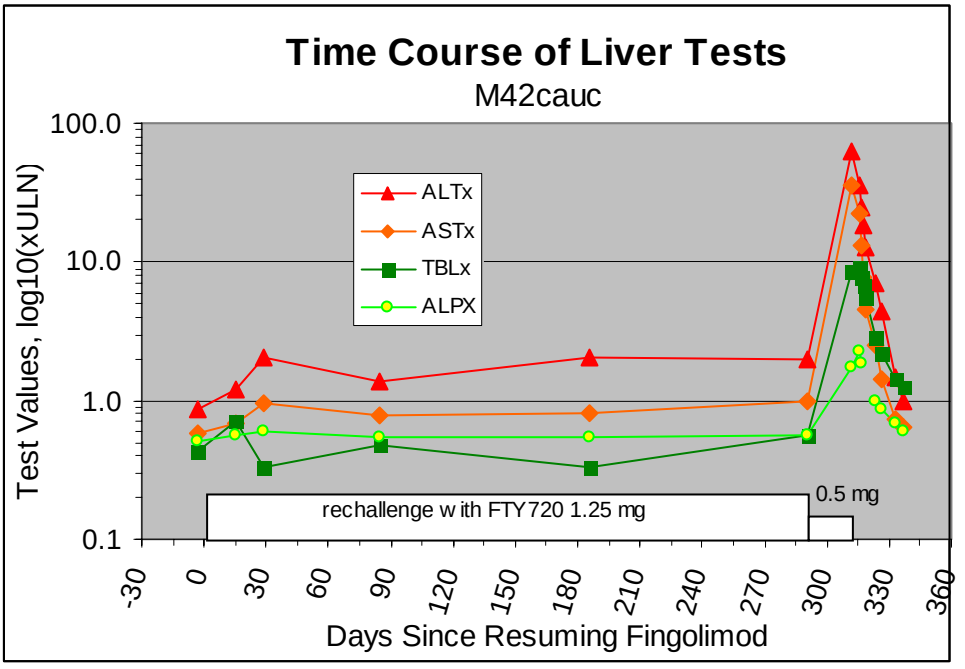
The conclusion of the consultation sent 25 May will have to be modified in light of the new information received yesterday from the sponsor, reporting the finding of viral hepatitis E RNA by PCR in the blood of the patient 2302E_330_21 in Henningsdorf, Germany, with confirming serum antibodies against hepatitis E, both IgG and IgM. The analyses were done in retrospect on stored serum samples from the central laboratory, as requested by the sponsor. Additional serum enzyme and bilirubin measurements were reported for 29 April, 6 and 10 May, as follows:

		ALT	AST	TBL	ALP	DAY	ALTx	ASTx	TBLx	ALPX
5-Jun-09	resume 1.25mg 6/8	39	24	9	64	-3	0.87	0 59	0.43	0.51
22-Jun-09		55	28	15	71	15	1.22	0.68	0.71	0.57
6-Jul-09		91	39	7	75	29	2.02	0 95	0.33	0.60
31-Aug-09		62	32	10	67	85	1.38	0.78	0.48	0.54
10-Dec-09		91	33	7	67	186	2.02	0.80	0.33	0.54
25-Mar-10	reduce FTY721 0 5mg	90	41	12	71	291	2.00	1.00	0.57	0.57
15-Apr-10	jaundice 4/12; stop 4/15	**2787**	**1466**	**177**	218	312	**61.93**	**35.76**	**8.43**	1.74
19-Apr-10	hospitalized	**2287**	**817**	**194**	273	316	**35.18**	**22.08**	**9.24**	2.28
20-Apr-10		**1624**	**493**	**164**	224	317	**24.98**	**13.32**	**7.81**	1.87
21-Apr-10		**1191**	**289**	**144**		318	**18.32**	**7.81**	**6.86**	
22-Apr-10	discharged 4/23	**818**	**167**	**116**		319	**12.58**	**4.51**	**5.52**	
26-Apr-10		**318**	103	**60**	122	323	**7.07**	2 51	**2.86**	0.98
29-Apr-10	*new data 5/26*	**201**	58	**46**	108	326	**4.47**	1.41	**2.19**	0.86
6-May-10	*new data 5/26*	67	30	30	85	333	1.49	0.73	1.43	0.68
10-May-10	*new data 5/26*	44	26	26	75	337	0.98	0.63	1.24	0.60

The follow-up tests show that the rapidly improving trend continued, with normalization of the serum enzyme activities for ALT, AST, and ALP, with TBL returning almost to normal. It may be seen in the truncated time-course graph below that rechallenge with 1.25 mg fingolimod daily was "positive" but weakly, compared to the initial rise seen previously when he was first exposed to fingolimod, at the same daily dose in September 2008, and the ALT rose to 5.5xULN when it stopped in November. The very sharp rise in all serum enzymes and total bilirubin in April 2010, shortly after reduction in daily fingolimod dose to 0.5 mg, was puzzling and not what might be expected if drug-induced, but rather suggested some other possible cause. It was suggested in the original consultation of 25 May that the investigator and sponsor should search for that, which apparently was already underway at the investigation site in Germany and in the sponsor's central laboratory. The findings of probable acute viral hepatitis E have resulted, and were just reported to us yesterday.



The updated narrative report from the sponsor that arrived yesterday showed appearance of both acute (IgM) and chronic (IgG) antibodies hepatitis E, and positive pcr RNA tests for the virus:

Visit	Date of sample	Hep E IgG Ab	Hep E IgM Ab	Hep E RNA pcr	Comment
18	31-Aug-09	negative	negative	negative	
19	10-Dec-09	negative	negative	negative	
20	25-Mar-10	negative	negative	positive** high	active or recent hepatic E infection
extra	15-Apr-10	positive* 1.99	positive* 2.63	positive** mod	active or recent hepatic E infection
extra	6-May-10	positive* 2.78	positive* 1.33	negative	subsiding hepatitis E infection

**ratio of observed to cut-off values; **PCR detection in blood (copy number)*

Comment: Hepatitis E has been known for decades to be common in southern Asia, North Africa, and Mexico, and has been reported to be particularly fulminant in pregnant women. However, it was not thought of as a disease seen in Europe or North America until quite recently. It is caused by an RNA virus transmitted orally by ingested water or food, especially by fecally contaminated water, as is hepatitis A. In the sporadic cases recently reported in the United States and Europe, ingestion of the uncooked meat of pig or boar or wild deer has been thought responsible. It has also been reported to be transmitted by blood transfusion, and vertically from infected mothers to infants. The incubation time from ingestion to clinical onset has been estimated as 28-40 days, with peak serum enzyme values at 42-46 days. Hepatitis E virus can be detected in blood before rise in serum enzymes or appearance of acute-phase IgM antibody, which then subsides along with or after the enzymes fall, as the chronic IgG antibodies are increasing. Some cases may show prolonged cholestasis with slow resolution, and anicteric, mildly symptomatic cases have been reported. Like hepatitis A, it does not appear to cause chronic liver disease or lead to cirrhosis, and if the acute infection is tolerated, recovery is complete. The clinical picture in this case appears to be that of an acute viral hepatitis E infection superimposed upon a mild and asymptomatic fingolimod-induced elevation of ALT only, from which the patient seems to be recovering satisfactorily. It will be of interest to follow this patient to complete recovery and full confirmation of the new diagnosis, including disappearance of IgM antibody and PCR evidence of blood infection.

Another finding in the work-up of this patient is the finding of low serum alpha-1-antitrysin levels, reported as 8 mg/dL, compared to a normal range of 90-180 mg/dL. Although deficiency in alpha-1-antitrypsin is a known liver disease, it is more often seen in children and more likely to be a chronic process leading eventual cirrhosis rather than as an acute presentation. This finding should also be repeated, and liver biopsy should be considered both for confirmation and to determine if asymptomatic chronic injury or fibrosis has occurred. Genetic testing for serum $\alpha_1 AT$ phenotype (PI type) electrophoresis is also suggested, along with characteristic finding on liver biopsy for diagnosis, and assessment of fibrosis. This may be of importance if resumption of fingolimod treatment of his multiple sclerosis is considered, assuming that the benefits of therapy so far have justified it.

Recommendations:

1) It will be important to be very sure that the diagnosis of acute hepatitis E is confirmed in subject 2302E_330-21 to reduce the likelihood of fingolimod causation to only possible.
2) Further inquiry into the question of $\alpha_1 AT$ deficiency liver disease should be done.
3) The question of restarting fingolimod remains uncertain, to be based upon additional findings and estimates of his chances for future benefits versus risks of harm, after complete resolution of the acute liver injury.

_____

John R. Senior, M.D.

cc: OSE 2010-956B
G. Dal Pan, OSE
L. Villalba, DNP
S. Yasuda, DNP

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22527	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	FINGOLIMOD HCL ORAL CAPSULES
IND-70139	SAFETYRPT-1	NOVARTIS PHARMACEUTICALS CORP	FTY 720D CAPSULES

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JOHN R SENIOR
06/15/2010

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY

DATE: 25 May 2010

FROM: John R. Senior, M.D., Associate Director for Science, Office of Surveillance and Epidemiology (OSE)

TO: Russell Katz, M.D., Director, Division of Neurological Products (DNP)
Lourdes Villalba, M.D., Medical Safety Reviewer, DNP
Sally Yasuda, Pharm.D., Safety Team Leader, DNP

VIA: Gerald Dal Pan, M.D., Director, OSE

SUBJECT: Cases of possible liver injury in patients treated with fingolimod (FTY720) for reducing the relapse rate of multiple sclerosis

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Documents reviewed:

1) E-mail alert that there might be a hepatoxicity safety concern for fingolimod sent 3 May from Dr. Heather Fitter of DNP
2) Formal consultation request dated 30 April 2010, sent 4 May and received 17 May with desired completion date 24 May, as OSE consultation #2010-956
3) Interim safety review by Dr. Lourdes Villalba dated 12 May and forwarded 18 May 2010; priority review for NDA 22-527 for use of fingolimod (Gilenia™, Novartis) for treatment of relapsing multiple sclerosis submitted 18 December 2009 with PDUFA goal date 21 June 2010 and advisory committee discussion scheduled for 10 June 2010.
4) Narrative case report for subject 330-21 from study 2302E, dated 29 April, received 17 May, and on 24 May a copy of 15-day follow-up MedWatch report from Germany dated 30 April.
5) DNP briefing package for Advisory Committee meeting 10 June, received 19 May, including reviews by Drs. Heather Fitter (efficacy), Lourdes Villalba (safety), and statistics (Sharon Yan), and brief summary material.
6) Sponsor's briefing package for AC meeting 10 June, received 24 May
7) Selected medical literature articles on fingolimod, FTY720, and multiple sclerosis

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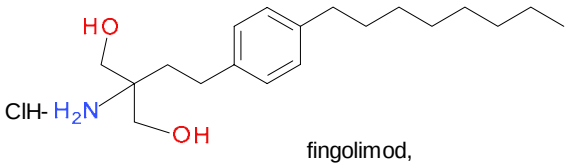
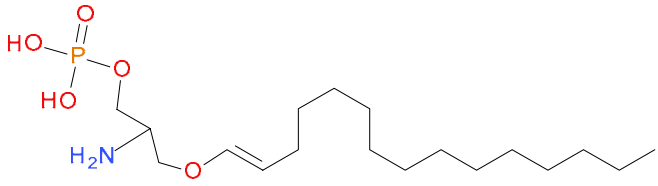
This request for consultation calls attention to a case of serious hepatotoxicity observed in study subject #303-21 in clinical study FTY720 D2302E, in addition to increased incidence of elevated serum aminotransferase activities to about 9% in subjects receiving daily fingolimod 1.25 mg or 0.5 mg orally, compared to about 2% in those randomized to placebo or interferon beta-1a in the controlled studies 2201, 2301, and 2302.

Fingolimod is an amphipathic compound consisting of a highly hydrophilic moiety of propane-2-amino-1,3-diol with a long hydrophobic 2-ethyl-phenyl-octyl side chain. It is taken by mouth and is rather slowly absorbed, then is phosphorylated stereospecifically at its 1-hydroxide to become an active modulator of sphingosine-phosphate receptors 1, 3, 4, and 5. This is believed to slow

egress of B- and T-lymphocytes from lymphatic tissues such as nodes, thymus, and gut Peyer's patches into the lymph and then into blood circulation, with the aim of reducing their aggressive attack on target cells in the nervous system and elsewhere. FTY720 was originally tested at 5 and 2.5 mg daily for preventing acute rejection after renal transplant, but its efficacy was not better than conventional treatment and did not justify further development. It has now been investigated for reducing the rate of relapses in multiple sclerosis as IND 70,139 since May 2005 and was submitted as NDA 22-527 on 21 December 2009 for priority review. An Advisory Committee hearing is scheduled for 10 June 2010.



fingolimod,
(FTY720, Gilenia; Novartis)



sphingosine-1-phosphate

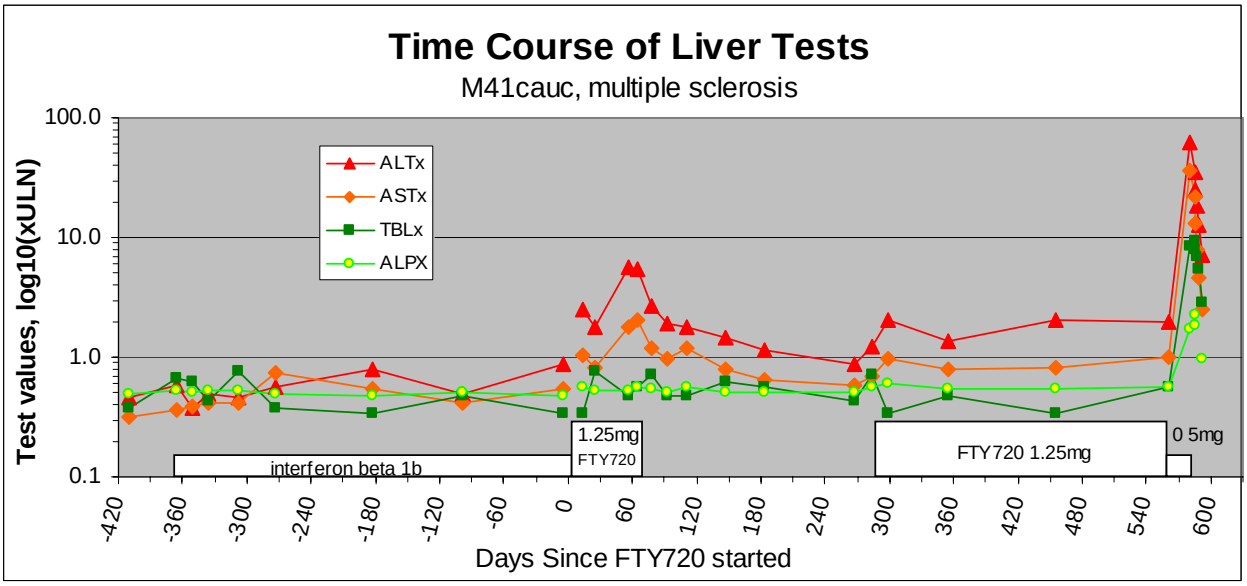
It has been known for decades that sphingosine-1-phosphate is an intracellular messenger, and more recently also that it is a circulating messenger that modulates a wide variety of effects by reacting at a set of receptor sites that modulate the effects. Fingolimod was discovered at the Yoshitomi Laboratories in Japan in 1995 (preliminary report: Adachi et al.) as a long-chain alkyl-phenyl hydrocarbon 2-substituent of propane-2-amino-1,3-diol that had more potent immunosuppressive activity than cyclosporine. A series of biochemistry papers (Kiuchi et al., 2000) showed that the ethyl-*p*-phenyl-octyl derivative was an especially active, potentially useful immunosuppressant. The drug was acquired by Novartis and was first investigated for the prevention of rejection after renal transplantation, but its development was discontinued, and subsequently it has been studied for effects in reducing relapses in multiple sclerosis, as the first oral agent for that indication.

As summarized in the interim medical efficacy review of Dr. Heather Fitter, FTY720 had many problems, included a prolonged clinical hold from June 2005 to June 2006 because of reports of cases of macular edema, plus concerns about cardiac and pulmonary adverse effects. An end-of-phase 2 meeting in March 2007 revealed that 85% of the subjects studied were outside the U.S. but fast-track status was granted in June 2007, and a rolling submission schedule was granted in February 2009. Because the data showed relatively little difference in efficacy between the two doses used in pivotal studies 2301 and 2302 but some increase in adverse effects at the higher dose, (b) (4)

As reviewers were completing their interim analyses in preparation for the Advisory Committee meeting of 10 June, a report was received 29 April 2010 of a serious case of hepatotoxicity that

was apparently induced by fingolimod. The report concerned a 41-year old white man (date of birth (b) (4) diagnosed with multiple sclerosis in April 2007. In retrospect, he had had three relapses in the previous two years and had two more before he was screened in June 2007 for study 2302, then randomized 13 September to receive interferon beta-1a 30 µg i.m. weekly for 12 months. He was an active smoker, but had no history of alcohol abuse, diabetes mellitus, liver disease, or retinopathy. He had taken ranitidine and prednisolone for multiple sclerosis, but no MS-disease modifying drugs. During the study the patient also received ibuprofen for flu like symptoms, mepivacaine hydrochloride as local anaesthetic, magnesium as health supplement, amantadine hydrochloride for fatigue, heparin fraction calcium salt for thrombosis prophylaxis, ranitidine for gastritis prophylaxis, homeopathic preparation as prophylaxis and influenza virus vaccine monovalent as vaccination swine influenza. During the study, the patient also underwent excision biopsy with histology of a histiocytoma (benign fibrous histiocytoma).

Serum liver tests (alanine and aspartate aminotransferase, ALT and AST; alkaline phosphatase, ALP; total and direct-reacting bilirubin, TBL and DBL) were in the normal range and remained so for the year he was given interferon. On 13 September 2008, he started taking oral fingolimod 1.25 mg daily, and 12 days later showed moderate elevation of his ALT activities to 2.5 xULN, suggesting some hepatocellular injury that persisted at subsequent visits on 6 October and 7 November, when his fingolimod was stopped 13 November because of ALT 5.6xULN, with only slight AST rise to 1.8xULN and normal values for ALP and TBL. No fingolimod was given for seven months while his ALT slowly declined to the normal range. On 5 June 2009 fingolimod administration was resumed at the same dose of 1.25 mg daily, and again he showed slight ALT increases up to about 2xULN over more than nine months. Because of change in policy, the dose of 1.25 mg daily was reduced to 0.5 mg daily on 25 March 2010, and 18 days later a coworker told him he was jaundiced. His fingolimod was immediately stopped on 14 April and recheck of serum tests on 15 April, three weeks after starting the 0.5 mg daily dose, showed ALT 62xULN, AST36xULN, TBL 8.4xULN, and ALP1,7xULN.



He was hospitalized (b) (4), at which time his ALT and AST had fallen somewhat (local laboratories were used because volcanic ash from Iceland prevented air transport of samples to the central laboratory) but TBL was higher. He reported symptoms of fatigue, dark urine, light stools, and right upper quadrant pressure sensation. On questioning he reported taking sodium bicarbonate and a magnesium-aluminum antacid before being sent to hospital, and took four capsules of an herbal remedy for digestive problems, "Holy Thistle," after hospitalization. An initial MedWatch report was submitted 19 April from the study site in Henningsdorf, Germany. Workup in hospital there showed no evidence for acute vital hepatitis A, B, C, D, or E, nor for autoimmune hepatitis, biliary tract disease, or circulatory disorders of congestive failure or hypotension. He had no evidence of liver failure, and recovered quickly in hospital, leading to discharge (b) (4), and then to further improvement as an outpatient on 26 and 29 April, after which the case was reported to Novartis. The time course of his liver tests is shown in the Excel graph inserted above.

Comment: The severity of this case is level three (hospitalization, gross jaundice, symptoms of hepatocellular liver injury without prominent cholestasis and no evidence of liver failure). The estimated probability that this was caused by fingolimod is very likely (category four on our FDA-NCI scale of likelihood, giving a severity-likelihood product of 3 X 4 = 12, or clinically important. This somewhat greater in severity than a simple "Hy's Law" case (level two severity) that calls for hepatocellular injury with ALT >3xULN AND TBL >2xULN and no significant cholestasis. The findings in the safety review that fingolimod causes increased incidence of ALT elevations without bilirubin increases supports the conclusion that it is a drug that can cause idiosyncratic liver injury in some recipients. The likelihood that the causality was as high as "very likely" is supported by the evidence that rechallenge with fingolimod caused recurrence of the ALT rises, although it is unclear why this patient showed the delayed aggravated rise with jaundice after dose reduction to 0.5 mg/day. No concomitant chemical agent seems to have been implicated, but it is still possible that he suffered an acute viral hepatitis for which the IgM antibodies had not yet risen. It will be advisable that they should be rechecked again before to AC meeting, to rule out that possibility. It was noted that his lady friend has chronic, low grade hepatitis C. If he were found to show acute hepatitis C, with IgM antibody, it would change the probable cause of the reaction to very likely that diagnosis, which would change the interpretation for regulatory purposes.

The other data on fingolimod that showed increased incidence of serum ALT increases seem quite consistent but not in themselves alarming if some other cause for the acute serious cases can be established. So, in addition to the anecdotal reports of cases of possible hepatotoxicity that might have been induced by fingolimod, routine monitoring of serum enzyme and bilirubin levels of activity and concentration yielded information from the trials on the relative incidence of elevattions during or after treatment with the experimental drug or control agents that can be taken as an indication of the drug's proclivity to cause liver injury in recipients. However, even cases in which functional disturbances such as impaired liver ability to clear bilirubin from the plasma and excrete it into bile that are associated with or follow hepatocellular injury need to be examined to determine the most likely cause of the problem, by excluding alternative causes. It has become clear that disturbed function of the whole liver is important in determining outcome and that serum enzyme elevations do not measure function at all. Impaired functions such as clearing bilirubin from plasma, synthesis of proteins such as prothrombin, are key.

In the sponsor's pooled data D set for studies 2201 (6 months: F5.0, F 2.5, PLA); 3201 (24 months: F1.25, F0.5, PLA); and 3202 (12 months: F1.25, F0.5, INF), reported in Table 20-1 in Addendum 1 to the Integrated Study of Safety in the NDA submission, the results show a clear dose-related excess of ALT elevations on fingolimod compared to placebo or interferon:

20 Tables for ISS Section 3.4.2.4

Table 20-1 Frequency (%) distribution of liver function tests in Group D (All double-blind, randomized, and controlled studies – safety population

Parameter	Criterion	FTY720 5 mg (N=94) n(%)	FTY720 1.25 mg (N=943) n(%)	FTY720 0.5 mg (N=854) n(%)	Placebo (N=511) n(%)	Interferon (N=431) n(%)
ALT	Total	93	934	851	506	429
	≥3 xULN	11 (11.8)	91 (9.7)	72 (8.5)	8 (1.6)	13 (2.3)
AST	Total	93	934	851	506	429
	≥2 xULN	6 (6.5)	50 (5.4)	36 (4.2)	8 (1.6)	13 (3,0)
TBL	Total	93	934	851	506	429
	≥2 xULN	0	7 (0.7)	8 (0.9)	3 (0.6)	2 (0.5)
GGT	Total		840	851	414	429
	≥3 xULN		72 (8.6)	56 (6.6)	3 (0.7)	6 (1.4)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBL, total bilirubin; GGT, gammaglutamyl transferase.

It may be seen that there was no observed effect on bilirubin concentrations, but a clear tendency for recipients of fingolimod to show elevated ALT and GGT levels, and somewhat lesser effects on AST. We are now assessing the data from those trials in the Group D set (studies 2201, 2301, and 2302) to look at peak values of ALT and TBL for each patient, for plotting the $\log_{10}$ values of elevations in multiples of the ULN as an x-y plot, to identify individual patients whose data need to be amplified by clinical narratives for estimation of the likelihood that fingolimod caused the problem. The first need is to establish the severity of the adverse liver effect, then to estimate likelihood that it was caused by the suspected drug, an often quite difficult exercise in medical differential diagnosis because there are no pathognomonic indications of drug-induced liver injury (DILI), and therefore depends on exclusion of other possible causes. Liver biopsy is not conclusive, because DILI may mimic any known liver disease, both histologically and clinically.

Comment: We have for some time graded severity of DILI into mild, moderate, serious, liver failure, and death or need for transplantation, using levels of 1 to 5 to describe them briefly. Mark Avigan and I have considered level 1 (mild) as enzyme elevations only, indicating some hepatocellular injury if ALT or AST and if not canalicular-cholestatic by ALP or GGT; level 2 (moderate) as "Hy's Law cases" in which hepatocellular injury with >3xULN of ALT is seen, along with TBL >2xULN with or following, but without significant cholestasis; level 3 (serious) requires clinical symptoms and either hospitalization or disability, but is not dependent on quantitative levels of ALT or TBL elevation; level 4 is reserved for acute liver failure, with encephalopathy, renal insufficiency, or coagulation problems and bleeding, not dependent on serum enzyme levels; and level 5, death in liver failure or need for liver transplantation. This

determination requires clinical information beyond simple serum chemistry values for level 3-5, and we have not graded severity based on highest levels of ALT activity observed. More difficult has been estimating the likelihood that the liver injury was caused by the drug suspected rather than by disease or some other drug or chemical agent, or combinations. This requires ruling out all reasonable alternative possible causes such as acute viral hepatitis A or C (less often C, D, or E), autoimmune or acute alcoholic hepatitis, biliary disease, and cardiovascular-pulmonary disorder that may cause liver hypoxia especially of the centrilobular hepatocytes around the central veins. Exclusion of other causes is based on the art of differential diagnosis, requiring both adequate information and the clinical experience to interpret it. We have used categories of likelihood, as proposed by the NCI in the mid-1980s, estimate whether it is unlikely (5-25%), possible (>25-50%), probable (>50 -75%), very likely (>75-95%), or almost certain/definite (>95%). We realize that exact percentage likelihood is beyond current art of diagnostic determination, but have added the numerical ranges to improve on the definitions by words only. We have used likelihood categories of 1 to 5 for the categories, as had the NCI, but the DILI Network has chosen to reverse the scale, so that our categories are 6- DILIN scale. When the severity and likelihood are multiplied together to form a product, we consider it to estimate the clinical importance of a case (for example, very likely drug-induced liver failure is 4 x 4 =16, quite compelling, while possible enzyme elevations (2 x 1 = 2) is of much less concern. SEVxLIK products of 10 or more (from definite Hy's Law case to possible fatal DILI) are most heavily weighted in making regulatory decisions.

To put these points into context of how adverse findings are graded, in 1982 the National Cancer Institute began to work on its common terminology criteria for adverse effects (CTCAE), and started a comprehensive consideration of and consensus development for both laboratory and clinical findings that physicians use for evaluating patients. For liver tests, they concluded:

grade	*definition*	ALT	AST	ALP	TBL
		all expressed in multiples of upper limit of normal (xULN)			
Grade 1 **mild**	*transient or mild discomfort, no disability, no treatment needed*	*>1 – 2.5*	*>1 – 2.5*	*>1 – 2.5*	*>1 – 1.5*
Grade 2 **moderate**	*some limitation in activity, may need assistance, minimal therapy*	*>2.5 - 5*	*>2.5 - 5*	*>2.5 – 5*	*>1.5 - 3*
Grade 3 **severe**	*marked limitation, assistance and therapy required, hospitalization*	*> 5 - 20*	*> 5 - 20*	*> 5 – 20*	*>3 - 10*
Grade 4 **life-threatening**	*disabled, need much assistance and treatment, threat of death*	*>20*	*>20*	*>20*	*>10*
Grade 5 **fatal**	*fatal*	*NA*	*NA*	*NA*	*NA*

Note: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase: all in units/L of activity; TBL, total serum bilrubin, in mg/dL; ULN, upper limit of normal range; NA, not applicable.

The origin of these values and definitions were derived from panels of experts who convened at the National Cancer Institute to classify and grade clinical symptoms/findings and laboratory data into grades of severity (0, none; 1, mild; 2, moderate; 3, severe; 4, life-threatening; and 5, fatal). For serum enzyme elevations, which do not measure any liver function or of themselves cause disease or symptoms, but simply give a rough, unspecific indication of cellular injury causing release of enzymes into plasma, the CTCAE grading is rather forced. However, when

jaundice is seen in a patient with drug-induced hepatocellular (but not cholestatic) injury, the damage to the liver is serious and has a potential mortality of 10 to 50%, as observed long ago by the late Hyman Zimmerman, which was the basis for the use by Dr. Robert Temple of the teerm "Hy's Law." It is instructive and worthwhile, to look more closely at the patients who showed these abnormalities during the clinical trials of fingolimod.

[Dr. T. Guo and I are preparing an "eDISH" plot of the ALT-TBL peak data as an x-y graph, but it is not yet ready. We shall try to provide it before the end of May.]

Once patients are identified who show both hepatocellular injury AND functional impairment of the liver by elevations in serum total bilirubin, it is necessary to examine those patients more closely to find out the most likely cause of the abnormal findings. This requires additional information, including both a time course of changes in the serum measures of ALT, AST, ALP, and TBL, and also a narrative description of clinical findings that helps greatly to determine the most likely cause. The diagnosis that the abnormalities were most likely caused by a suspected drug requires that alternative possible causes be excluded.

For the index case 2302E_330-21, the 41-year old patient from Hennigsdorf, Germany, we have asked for whatever additional information can be obtained about the period leading up to his acute rise in serum enzymes and bilirubin in early April 2010. A very good attempt was made to rule out viral hepatitis, autoimmune hepatitis, and other possible causes such as other drugs, herbal remedies, or chemicals, which were negative at the time from 15 to 29 April, including hospitalization from (b) (6). It has been observed that acute viral hepatitis may require some weeks before IgM antibodies appear, we have asked that those test be repeated to see if they have changed since initially. If not, we are left with no alternative cause being likely and so it would be concluded as very likely that the adverse hepatic reaction was fingolimod-induced.

Recommendations:

1) An additional, final effort should be made by the sponsor to rule out other causes of the acute and serious liver reaction in subject 2302E_330-21 by rechecking serum antibody tests for viral infections, and inquiring closely about any herbal, drug, chemical or other product he may have been exposed to prior to the findings that began in early April.
2) Failing discovery of any alternative cause, the case will have to be considered serious and very likely fingolimod-induced, and some mention of it will need to be in the labeling.
3) It is not clear that systematic monitoring of serum ALTs should be attempted. It has not been found to be effective in preventing serious problems for other drugs and generally is not well done. Warning physicians alert for early symptoms of liver dysfunction, and interrupting treatment promptly to investigate liver injury further, may be sufficient.

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John R. Senior, M.D.

cc: OSE 2010-956
G. Dal Pan, OSE
L. Villalba, DNP
S. Yasuda, DNP

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Appendix I.
Tabulation of Liver Tests by Date for Subject 2302E_330_21
(used for plotting the Time Course graph)

fingolimod case 303-21 male 41 caucasian StudyD2302E1

date of birth [redacted] relapsing-remitting multiple sclerosis since April 2007

		0 - 45	0 - 41	0 - 21	0 - 125						
date	event	ALT	AST	TBL	ALP	)the	DAY	ALTx	ASTx	TBLx	ALPX
30-Jul-07	screening	21	13	8	61		-410	0.47	0.32	0.38	0.49
13-Sep-07	baseline	26	15	14	66		-365	0.58	0.37	0.67	0.53
28-Sep-07	on interferon beta1b	17	16	13	64		-350	0.38	0.39	0.62	0.51
12-Oct-07		22	17	9	66		-336	0.49	0.41	0.43	0.53
9-Nov-07		21	17	16	65		-308	0.47	0.41	0.76	0.52
14-Dec-07		25	30	8	62		-273	0.56	0.73	0.38	0.50
14-Mar-08		35	22	7	60		-182	0.78	0.54	0.33	0.48
6-Jun-08		22	17	10	64		-98	0.49	0.41	0.48	0.51
8-Sep-08		39	22	7	60		-4	0.87	0.54	0.33	0.48
12-Sep-08	to FTY720 1.25mg						1				
24-Sep-08		113	43	7	71		13	2.51	1.05	0.33	0.57
6-Oct-08		79	34	16	65		25	1.76	0.83	0.76	0.52
7-Nov-08		**250**	74	10	66		57	**5.56**	1.80	0.48	0.53
14-Nov-08	stop FTY720 13Nov	**246**	**83**	12	70		64	**5.47**	**2.02**	0.57	0.56
27-Nov-08		119	48	15	68		77	2.64	1.17	0.71	0.54
12-Dec-08		85	40	10	64		92	1.89	0.98	0.48	0.51
30-Dec-08		81	48	10	70		110	1.80	1.17	0.48	0.56
5-Feb-09		66	32	13	63		147	1.47	0.78	0.62	0.50
13-Mar-09		51	26	12	63		183	1.13	0.63	0.57	0.50
5-Jun-09	resume 1.25mg 6/8	39	24	9	64		267	0.87	0.59	0.43	0.51
22-Jun-09		55	28	15	71		284	1.22	0.68	0.71	0.57
6-Jul-09		91	39	7	75		298	2.02	0.95	0.33	0.60
31-Aug-09		62	32	10	67		354	1.38	0.78	0.48	0.54
10-Dec-09		91	33	7	67		455	2.02	0.80	0.33	0.54
25-Mar-10	reduce FTY721 0.5mg	90	41	12	71		560	2.00	1.00	0.57	0.57
15-Apr-10	jaundice 4/12; stop 4/15	**2787**	**1466**	**177**	218		581	**61.93**	**35.76**	**8.43**	1.74
[redacted]	hospitalized	**2287**	**817**	**194**	273		585	**35.18**	**22.08**	**9.24**	2.28
20-Apr-10		**1624**	**493**	**164**	224		586	**24.98**	**13.32**	**7.81**	1.87
21-Apr-10		**1191**	**289**	**144**			587	**18.32**	**7.81**	**6.86**	
22-Apr-10	discharged [redacted]	**818**	**167**	**116**			588	**12.58**	**4.51**	**5.52**	
26-Apr-10		**318**	103	**60**	122		592	**7.07**	2.51	**2.86**	0.98

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22527	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	FINGOLIMOD HCL ORAL CAPSULES
IND-70139	SAFETYRPT-1	NOVARTIS PHARMACEUTICALS CORP	FTY 720D CAPSULES

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/s/

JOHN R SENIOR
06/15/2010

Medical Officer's Consult Review of NDA 22-527
Ophthalmology Consultation

Submission date:	10/27/09
Review date:	5/11/10
Sponsor:	Novartis Pharmaceuticals Corporation
Drug:	Gilenia (fingolimod)
Pharmacologic Category:	Sphingosine- 1- phosphate (S1P) modulator
Proposed Indication:	Multiple sclerosis

Requested:
We request evaluation of the ophthalmologic toxicity of fingolimod, an oral agent for the treatment of multiple sclerosis (MS) (NDA 22-527). Fingolimod is a sphingosine-1-phosphate (S1P) modulator that induces immunosuppression by reduction of circulating lymphocytes. The drug was initially developed in the renal transplant population at doses of 2.5 and 5 mg/day but that indication is no longer pursued. The dose proposed for approval in MS is 0.5 mg/day. This is a rolling NDA (\\CDSESUB1\EVSPROD\NDA022527). The clinical data in the MS population was submitted in 18 December, 2009 (SN 003 and 004). Clinical data in the transplant population was submitted in October 5, 2009 (SN 002). This application has a priority review (PDUFA goal date June 21, 2010) and will go to an advisory committee meeting (estimated date June 10, 2010). Several cases of macular edema were reported during the development of fingolimod for the renal transplant indication. Subsequently, ophthalmic screenings for macular edema were implemented in all MS studies. Ophthalmic evaluations in MS studies D2301, D2302, D2302E1 and D2201 Extension included assessment of visual acuity and dilated funduscopy. Additionally, study D2309 (an ongoing study of approximately 1080 subjects) included OCT in all patients to determine retinal (including central foveal) thickness. OCT analyses were submitted as part of a Special Safety Interim Report (SN 004), however, clinical safety data from this study is still blinded.

Study Populations:
The data from three completed, double-blind, controlled MS studies and interim data from two long-term extension studies in MS patients were pooled into 5 datasets to accommodate differences between studies in duration of treatment, doses, and comparators:

• Group A – all patients in double-blind, randomized, and placebo- or active-controlled studies – 12 months treatment data (studies D2301 and D2302 cut-off at the Month 12 visit).

• Group B – all patients in double-blind, randomized and placebo-controlled studies – 24- months treatment data (study D2301 with a cut-off at the Month 24 visit). This dataset enables characterization of the safety profile of Fingolimod versus that of placebo, and of the 0.5 mg and 1.25 mg doses of Fingolimod.

• Group C – all patients in the double-blind, randomized and placebo- or active-controlled studies – 6 months treatment data (studies D2301, D2302 and D2201 cut-off at the Month 6 visit). Group C allows evaluation of dose dependency of Fingolimod-related events over the entire dose range (0.5 mg to 5.0 mg) and comparisons between Fingolimod, placebo, and interferon for 6-month treatment.

• Group D – all patients in double-blind, controlled studies (D2301 cut-off at the Month 24 visit, study D2302 cut-off at the Month 12 visit, study D2201 cut-off at the Month 6 visit). This group contains all data from the randomized, double-blind and controlled studies regardless of differences in treatment duration or comparators.

• Group E – all Fingolimod-treated patients, including studies D2301, D2302, and D2201, extension studies D2302E1 with cut-off 01-Jun-2009 or visit Month 24 (12 month extension), whichever came first, and D2201E1 with cut-off at the Month 60 visit. Group E includes all safety data which were collected on Fingolimod treatment and up to 45 days after the discontinuation of Fingolimod treatment. It provides supplementary information on the long-term safety of the Fingolimod 1.25 mg and 0.5 mg doses.

• Group E follow-up population – all Fingolimod-treated patients from studies D2301 and D2302 who received a cumulative dose of at least 3 months (90 days) of study drug and had any follow-up data beyond 14 days after study drug discontinuation, and all patients who entered study D2201E1 and received a cumulative dose of at least 3 months (90 days) of Fingolimod and had any follow-up data beyond 14 days after study drug discontinuation.

Serious Adverse Events in the Eye disorders SOC

Safety pool D (all controlled studies, 6 months to 2 year data) is presented in the following table.

	Fingolimod 5 mg N=94	Fingolimod 1.25 mg N=943	Fingolimod 0.5 mg N=854	Placebo N=511	Interferon N=431
Eye disorders – total	0	7	2	1	0
Macular edema	0	4	1	0	0
Eye pain	0	1	0	0	0
Papilloedema	0	1	0	0	0
Photopsia	0	1	0	0	0
Retinal disorder	0	1	0	0	0
Retinitis	0	1	0	0	0
Iridocyclitis	0	0	0	1	0
Keratitis	0	0	0	1	0
Retinal detachment	0	0	1	0	0

Source: ISS Table 4.4-9. A patient with multiple occurrences of the same AE under one treatment is counted only once in the AE preferred term for that treatment. - A patient with different adverse events within a primary system organ class is counted only once in the total row.

Serious Adverse Events in Eye disorders SOC
Pool E, (all controlled and open-label extensions)

Preferred term	Fingolimod 1.25-5 mg N=137	Fingolimod 1.25 mg N=1157	Fingolimod 0.5 mg N=1021
Eye Disorders –Total	1	12	3
Macular edema	1	9	2
Eye pain	0	1	0
Papillodedema	0	1	0
Photopsia	0	1	0
Retinal disorder	0	1	0
Retinitis	0	1	0
Retinal detachment	0	0	1

Reviewer's Comments: *There is a dose dependent increase in cases of macular edema.*

All Ocular Adverse Events

Preferred term	Fingolimod 1.25-5 mg N=137	Fingolimod 1.25 mg N=1157	Fingolimod 0.5 mg N=1021
Total	**24** (18%)	**206** (18%)	**177** (17%)
Vision Blurred	6 (4%)	30 (3%)	33 (3%)
Conjunctivitis	2	25 (2%)	29 (3%)
Eye pain	3 (2%)	23 (2%)	20 (2%)
Dry eye	3 (2%)	15	9
Visual acuity reduced	2	15	8
Abnormal sensation in eye	0	1	6
Blepharspasm	0	1	6
Visual impairment	1	5	5
Uveitis	0	4	5
Presbyopia	0	3	5
Diplopia	1	10	4
Allergic conjunctivitis	1	6	4
Eyelid edema	0	5	4
Retinal hemorrhage	0	5	4
Keratoconjunctivitis sicca	0	3	4
Lacrimation increased	0	2	4
Optic atrophy	0	2	4

Preferred term	Fingolimod 1.25-5 mg N=137	Fingolimod 1.25 mg N=1157	Fingolimod 0.5 mg N=1021
Eye hemorrhage	1	0	4
Macular edema	**1**	**18 (2%)**	**3**
Myopia	0	3	3
Retinal disorder	0	3	3
Conjunctival hemorrhage	0	1	3
Chalazion	0	0	3
Scintillating scotoma	0	0	3
Accommodation disorder	0	0	2
Amblyopia	0	0	2
Blepharitis	1	3	2
Eye swelling	0	1	2
Eye irritation	1	3	2
Glaucoma	1	3	2
Retinal detachment	0	3	2
Cataract	0	2	2
Sicca syndrome	0	0	2
Retinal tear	0	3	1
Blindness unilateral	0	1	1
Ciliary muscle spasm	0	1	1
Eye disorder	1	1	1
Iridocyclitis	1	1	1
Miosis	0	1	1
Ophthalmoplegia	0	1	1
Photophobia	0	1	1
Blepharchalasis	0	0	1
Asthenopia	0	3	1
Corneal disorder	0	0	1
Corenal edema	0	0	1
RPE detachment	0	0	1
Eczema eyelids	0	0	1
Eye discharge	0	0	1
Eyelid ptosis	0	0	1
Macular degeneration	1	0	1
Ocular hyperemia	1	0	1
Ocular vascular disorder	0	0	1
Optic disc hemorrhage	0	0	1
Optic disc vascular disorder	0	0	1
Panophthalmitis	0	0	1
Retinal vasculitis	0	0	1
Scleral discoloration	0	0	1
Scotoma	0	0	1
Photopsia	1	3	1
Strabismus	0	0	1

Preferred term	Fingolimod 1.25-5 mg N=137	Fingolimod 1.25 mg N=1157	Fingolimod 0.5 mg N=1021
Uhthoff's phenomenon	0	0	1
Myodesopsia	0	7	1
Maculopathy	2	2	1
Arteriosclerotic retinopathy	0	1	0
Eye allergy	0	4	0
Eye pruritus	0	2	0
Retina aneurysm	0	2	0
Cataract subcapsular	0	1	0
Chorioretinal atrophy	0	1	0
Dacryostenosis	0	1	0
Episcleritis	0	1	0
Eye movement disorder	0	1	0
Eyelid cyst	0	1	0
Glare	0	1	0
Hyperemtropia	0	1	0
Iritis	0	1	0
Lacrimal disorder	0	1	0
Lens disorder	0	1	0
Meibomianitis	0	1	0
Optic disc drusen	0	1	0
Papilloedema	0	1	0
Refraction disorder	0	1	0
Retinal degeneration	0	1	0
Retinal exudates	0	1	0
Reinal pigment epitheliopathy	0	1	0
Retinal pigmentation	0	1	0
Retinitis	0	1	0
Retinopathy	0	1	0
Vitritis	0	1	0
Xanthopsia	0	1	0

Reviewer's Comments: *With the exception of macular edema, the reported events are consistent in frequency with the expected events for a population with multiple sclerosis.*

Visual Acuity

Summary statistics of visual acuity were presented by visit for Group A in PT-Table 9.1-1. Change from baseline in visual acuity was presented by visit for Group A in Table 4-37. Visual acuity was comparable across all 4 treatment groups and remained stable (all mean changes were less than ± 0.2 points in decimal score) at all timepoints during 12 months of treatment. At baseline, mean visual acuity was 0.967, 0.973, 0.964 and 0.969 for the Fingolimod 1.25 mg, Fingolimod 0.5 mg, placebo and interferon groups, respectively (PT-Table 9.1-1). At Month 12, mean visual acuity was 0.989, 0.990, 0.982 and 0.974, respectively.

Reviewer's Comments: *Visual acuity is not reported correctly. Letter size is being divided by the distance to the target, the decimal value needs to be transformed to a log value before averaging or reporting a difference between scores. It would be preferable to report the visual acuity as LogMAR scores.*

Central Macular thickness – Group B

At baseline, the majority of eyes tested presented a central foveal thickness ≤ 200 microns i.e. 90.1% of eyes for the Fingolimod 1.25 mg group, 89.3% for the Fingolimod 0.5 mg group, and 90.5% for the placebo group. At Month 24, a slightly lower percentage of eyes had a central foveal thickness ≤ 200 microns, i.e. 84.5% of eyes for the Fingolimod 1.25 mg group, 84.9% for the Fingolimod 0.5 mg group, and 88.9% for the placebo group. The main difference between treatment groups was a higher percentage of patients in the Fingolimod treatment groups had a central foveal thickness of > 200 but ≤ 250 microns than in the placebo group (12.5% in the Fingolimod 1.25 mg group, 13.0% in the Fingolimod 0.5 mg group, and 9.3% in the placebo group). There was no difference between groups with regard to the percentage of patients with a central foveal thickness of > 250 to ≤ 300 microns, and no patients in the Fingolimod 0.5 mg group had a central foveal thickness of greater than 300 microns at either Month 24 or the last visit on study drug, compared with 3 patients in the Fingolimod 1.25 mg group and 1 in the placebo group (last visit on study).

Frequency distribution of change from baseline in central foveal thickness for Group B is presented in below. Changes > 40 microns were reported for a higher percentage of Fingolimod treated patients than placebo, with the Fingolimod 1.25 mg group having a higher incidence than the Fingolimod 0.5 mg group.

	Fingolimod 1.25	Fingolimod 0.5mg	Placebo
Number of Patients	429	425	418
Number of Eyes	520	581	511
Change from baseline			
<-40	15 (3%)	20 (3%)	23 (5%)
≥-40 and ≤-21	40 (8%)	38 (7%)	33 (6%)
>-21 and ≤20	375 (72%)	417 (72%)	376 (74%)
>20 and ≤40	45 (9%)	69 (12%)	54 (11%)
>40	45 (9%)	37 (6%)	25 (5%)

Reviewer's Comments: *The mean and the distribution demonstrate small increases in macular thickness in patients on fingolimod.*

Central foveal thickness in study D2309

Frequent, serial OCT measurements of central foveal thickness were done in a total of 1053 patients from study D2309 (357 on Fingolimod 1.25 mg, 348 on Fingolimod 0.5 mg, 348 on placebo). OCTs were performed at screening, Month 1, Month 3, Month 6, Month 12, Month 18, and Month 24.

There were small, dose-dependent effects of Fingolimod on central foveal thickness (difference from placebo in mean/median change from baseline was 5 microns/4 microns for Fingolimod 1.25 mg, and 4 microns/3 microns for Fingolimod 0.5 mg). These effects were observed at Month 1 and did not increase over time.

Central foveal thickness >300 microns was observed in 3 patients on Fingolimod 1.25 mg, 3 patients on Fingolimod 0.5 mg, and 1 patient on placebo at Month 1. At Month 3, the number of patients with central foveal thickness >300 microns was 3, 1, and 1 for Fingolimod 1.25 mg, Fingolimod 0.5 mg, and placebo respectively. A diagnosis of macular edema was made by the local ophthalmologist for 7 (2.0%) patients on Fingolimod 1.25 mg, 5 (1.4%) patients on Fingolimod 0.5 mg, and 2 (0.6%) patients on placebo. The retinal expert on the Data and Safety Monitoring Board (DSMB) confirmed the macular edema diagnosis in only 3 (0.8%) patients on Fingolimod 1.25 mg, 3 (0.9%) patients on Fingolimod 0.5 mg, and 1 (0.3%) patient on placebo, with one case (on Fingolimod 1.25 mg) listed as pending. Of the 7 cases confirmed as macular edema by the DMSB ophthalmologist, 5 had central foveal thickness >300 microns. For the 6 cases not considered as macular edema by the DMSB ophthalmologist, the maximal central foveal thickness was 262 microns; central foveal thickness in the 5 other non-confirmed cases was <210 microns. Central foveal thickness in the case pending DSMB confirmation was >300 microns.

Reviewer's Comments: *The findings above are consistent with a dose dependent increase in macular edema.*

Summary Comments:

There are a variety of known causes of macular edema. They include ocular surgery, central or branch vein occlusions, diabetes, uveitis, and topical ocular application of prostaglandin analogs.

In the case of ocular surgery, surgery leads to a break (leakage) in the blood-retinal barrier. Multiple studies have demonstrated that five-six weeks after surgery, approximately 35% of patients have leakage demonstrated on fluorescein angiograms, however only 10-20% have decreased visual acuity. By four-six months, decreased visual acuity is at a 1% incidence where it may remain for years.

Topical ocular administration of prostaglandin analogs in patients without an intact posterior lens capsule can result in the development of macular edema. These cases almost always resolve following discontinuation of the prostaglandin analog.

Central or branch vein occlusions can cause the development of macular edema. Without treatment, visual acuity improves in only about 30% of patients in the first year following the development of macular edema. Treatment with intravitreal steroids or anti-VEGF products has been demonstrated to increase the improvement in visual acuity.

Patients with non-proliferative or proliferative diabetic retinopathy may develop macular edema. Approximately 30% resolve without treatment over the span of approximately 6 months.

While a thickened macula will lead to decreased visual acuity, there is no direct correlation between visual acuity and retinal thickness. Among the principal unanswered questions about macular edema is how thick the retina must get and for how long must it be at that thickness to result in permanent visual acuity loss.

Fingolimod causes macular edema is a dose dependent manner. The frequency of macular edema events following administration of fingolimod appears to be not only related to dose but to predisposing conditions for macular edema, such as diabetes mellitus. At the dose currently proposed for the treatment of multiple sclerosis, 0.5 mg, there have been a limited number of cases of macular edema. To date, these cases have been completely reversible following cessation of fingolimod; however, the number of cases is limited and complete resolution cannot be assured in future cases.

Recommendations:

1. The visual acuity scores are not reported in a manner that permits adequate comparisons between groups. Letter size is being divided by the distance to the target, the decimal value needs to be transformed to a log value before averaging or reporting a difference between scores. It would be preferable to report the visual acuity as LogMAR scores.

2. Patients with multiple sclerosis are often recommended to be followed with a full ophthalmic examination including dilated funduscopy (and ocular coherence tomography as needed) every six months. The ocular findings in the new drug application for Fingolimod do not suggest that ophthalmologic follow-up needs to be more frequent than routine ophthalmic monitoring for multiple sclerosis unless an ocular adverse event is identified by history or routine monitoring.

Wiley A. Chambers, M.D.
Supervisory Medical Officer, Ophthalmology

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22527	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	FINGOLIMOD HCL ORAL CAPSULES

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WILEY A CHAMBERS
05/25/2010

Medical Officer Review of Consult
Division of Drug Oncology Products

NDA #:	22527
Drug:	Fingolimod
Drug Class:	Sphingosine-1-phosphate (S1P) modulator
Sponsor:	Novartis
Consulting Division:	Division of Neurology Products
Consulting Reviewer:	Lourdes Villalba, MD
Primary Reviewer:	Gwynn Ison, MD
Team Leader:	V. Ellen Maher, MD
Consult Due Date:	4/30/10

Reason for consult: DNP requests DDOP input on the safety of fingolimod in multiple sclerosis patients, due to a possible case of lymphoma in a patient treated with fingolimod.

Background:
The Division of Neurology Products requests DDOP input on a safety aspect of NDA 22-572 (fingolimod, a sphingosine-1- phosphate (S1P) modulator). The drug works to reduce circulating lymphocytes, and was initially developed in the renal transplant population. That indication is no longer pursued, and it is notable that there were 3 cases of lymphoma (one T cell, one B cell, and one lymphoproliferative disorder) identified in the renal transplant setting.

Per DNP input, regarding the renal transplant population, there were an excess number of cardiovascular deaths, as well as cases of macular edema and lung edema in the fingolimod groups (2.5 mg and 5 mg doses) when compared to mycophenolate mofetil (MMF). In addition, the efficacy for fingolimod was not superior to MMF and the 5 mg dose of fingolimod was associated with a higher risk of transplant rejection than MMF. Also noted in that study was the occurrence of 3 cases of lymphoma (out of 456 patients) in the 2.5 mg arm (one B cell, one T cell, and one lymphoproliferative disorder), compared to one case of CNS lymphoma in the MMF arm. However, there were no cases of lymphoma seen in the 5 mg fingolimod dose group.

The current indication for approval is for use in patients with multiple sclerosis. DNP has provided a patient narrative on a case suspicious for lymphoma and requests evaluation by DDOP (including what to request from the Sponsor in order to evaluate future cases that may arise). In addition, DNP would like input on what kind of malignancies are generally associated with long-term immunosuppression (associated with lymphopenia), as well as the relevance of an increased number of cases of melanocytic nevi and fibrous histiocytoma seen in the current NDA.

Brief patient synopsis for Question 1: (patientD1201E1-0005-00001), 42 y/o Japanese male with relapsing multiple sclerosis in the core study from 2/26/08 to 8/25/08, and the extension study from 8/26/08 to 11/12/08, where he received fingolimod 0.5 mg daily. The patient was originally diagnosed with MS in January 2003, with 6 relapses from

diagnosis till study entry (5 of which were treated with steroids). He had never received any disease modifying agents to treat his MS. In December 2008 (one month after last study drug dose, and after his 5th course of steroids since study entry), he underwent an MRI (presumably of the brain) that was read to be "suspicious for lymphoma". An LP was performed, but was inconclusive and no other biopsies were performed. In May 2009, the patient was found to have new lung lesions on CT scan, although he was also suffering from aspiration pneumonia and was febrile at the time. He was noted to have small scattered lymph nodes in the hilum, mediastinum, neck, axillae, abdominal, and para-aortic regions on that CT. His blood work revealed pancytopenia and abnormal coagulation parameters. A kidney biopsy was performed and "an Epstein-Barr (EB) virus related lymphoproliferative disorder was possible", however the biopsy specimen was too small for any additional staining and a definitive diagnosis could not be made. Another CT was performed later in May 2009 because the patient was having persistent fevers and it revealed worsening of the lung nodules, with no notable changes in the kidney lesions or the abdominal lymph nodes. Hepatosplenomegaly was noted on that scan, as well. On May 26, 2009, an upper endoscopy identified tumor or lipomas in the esophagus and gastric polyps, but biopsy of the stomach was negative for malignancy and positive for H. pylori. In June 2009, gallium scan was performed and revealed uptake in the upper left abdomen and both kidneys. (at that point, his MRSA pneumonia had resolved, although unclear when it began).

In September 2009, the patient's general condition had deteriorated, requiring gastric tube insertion. A bone marrow biopsy was suggested, however it was not done due to thrombocytopenia. A skin biopsy was performed due to the onset of invasive erythematous eruptions, and the pathology was read as "highly suspicious of a T cell lymphoma of the skin", based upon immunostaining and gene rearrangements. Another CT in September 2009 showed increasing lung and kidney nodules. At that point, the report states that the study investigator consulted a lymphoma expert for a second opinion. The investigator stated that if a diagnosis could not be made, the patient would be sent to another hospital for further workup. No additional information is available.

Question 1: DNP is interested in the evaluation of the case described above. Also, could DDOP discuss special staining or analyses that would be helpful to make a definitive diagnosis of lymphoma (in case they could be requested from the Sponsor for other patients)?

DDOP comments: Although lymphoma is a possibility, as speculated in the history, there is no definitive biopsy-proven evidence to support this suspicion. The reported skin biopsy was read as "suspicious", but it is impossible to make a determination without an official pathology report, including special immunostains for B and T lymphocyte markers in the specimen. It is equally possible that this patient had an infectious process, as suggested by the fevers and lung infiltrates. A lymph node biopsy would likely have been the most helpful diagnostic aid in determining a diagnosis in this case, but an infection should have been ruled out, as well.

Also, it would be worthwhile to suggest that the Sponsor obtain tissue biopsies and immunostaining, as mentioned, for all future cases that are similar in nature.

Question 2: Could you briefly discuss what kinds of malignancies one could expect from long term immunosuppression caused by decreased peripheral lymphocytes? We note that there seems to be an increase in the risk of basal cell carcinoma in controlled studies, but the numbers are very small and do not seem to be dose-related. Also, when looking at serious and non-serious neoplasias, there is an increased risk of melanocytic nevus and fibrous histiocytoma in the fingolimod and interferon groups. Can DDOP comment on this?

DDOP comments: **When discussing malignancies that have an association with prolonged immunosuppression (specifically lymphopenia), the classic examples are cancers commonly diagnosed in HIV patients (usually in patients with low CD4 counts, but this may vary) and transplant recipients. The malignancies that occur most commonly in these patients include: skin cancers (basal and squamous cell carcinomas), lymphomas (EBV-associated B cell lymphomas, diffuse large B cell lymphoma, Burkitt's lymphoma, Hodgkin's lymphoma, primary CNS lymphoma, post-transplant lymphoproliferative disease), cervical cancer (HPV associated), and Kaposi's sarcoma (associated with Human Herpes Virus-8). Although others tumors do occur, these are the classic examples. It is notable, that B cell lymphomas tend to be more common than T cell lymphomas in immunosuppressed patients. Both melanocytic nevi and cutaneous fibrous histiocytomas have been described in immunosuppressed patients.**

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22527	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	FINGOLIMOD HCL ORAL CAPSULES

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/s/

GWYNN C Ison
04/29/2010

VIRGINIA E MAHER
04/29/2010

Shari L. Targum, M.D.
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, Maryland 20993
Tel (301) 796-1151

Memorandum

DATE: April 10, 2010

FROM: Shari L. Targum, MD, Team Leader
Division of Cardiovascular and Renal Products, HFD-110

THROUGH: Norman Stockbridge, MD, PhD, Director
Division of Cardiovascular and Renal Products, HFD-110

TO: Eric Bastings, M.D., Deputy Director, Division of Neurology

SUBJECT: NDA 022527

NAME OF DRUG: Fingolimod
TRADE NAME: Gilenia
FORMULATION: Oral
RELATED APPLICATIONS: IND #70,139; IND #70,407 (treatment of hepatitis C virus); IND #57,293 (organ rejection in transplantation).
APPROVED INDICATIONS: N/A

SPONSOR: Novartis

DOCUMENTS AVAILABLE FOR REVIEW: 1. Consultation request; 2. edr; 3. prior Cardio-Renal consultations (Desai; 2005, 2006)
DATE CONSULT RECEIVED: February 2, 2010
DESIRED COMPLETION DATE: March 12, 2010 (postponed per discussion with Dr. Villalba)
DATE CONSULT COMPLETED: April 10, 2010

REASON FOR CONSULTATION:
The Division of Neurology Products has asked for an evaluation of cardiovascular safety of fingolimod, an oral agent for the treatment of multiple sclerosis (MS), including an evaluation of echocardiography data submitted in this application.

This is a rolling NDA. The clinical data in the MS population were submitted on December 18, 2009 (SN 003 and 004); the clinical data in the transplant population were submitted on October 5, 2009 (SN 002). This application has a priority review (PDUFA goal data June 21, 2010) and will go to an advisory committee (AC) on June 10, 2010. The Neurology division has asked for a reviewer to represent this Division. In addition, the review division asked us to suggest three outside experts for participation in the advisory committee panel (done via email).

BACKGROUND:
Fingolimod is a sphingosine-1-phosphate (S1P) receptor agonist that has been developed as an oral disease-modifying agent for patients with relapsing, remitting multiple sclerosis (MS). Fingolimod induces immunosuppression by reduction of circulating lymphocytes.

Cardiac effects:

1. Conduction system effects:
    a. Heart rate reduction was observed in the first human study (B101) and in all subsequent clinical studies as an effect related to initial stimulation of S1P receptors in the heart. FTY720 induces a dose-dependent reduction in heart rate that is maximal within hours after the first dose, and then attenuates over days-weeks despite increasing blood levels with continued dosing.
    b. From the investigator's brochure:
        i. "Using telemetric devices in rats, dogs, or monkeys, it could be shown that FTY720 induced a moderate decrease in heart rate and an increase in blood pressure after a single p.o. dose.
        ii. "Short periods of sinus arrest were seen in rats or dogs." (Source: Investigator's Brochure, 2007: IRT-QT review).
    c. In a previous consultation to the Cardio-Renal Division (Desai, 12/9/2005), several cases of 2nd degree AV block (Mobitz I) and 2:1 AV block were observed
2. Cardiovascular effects of S1P have been described in preclinical studies in the literature, including reduced cardiac function (via alteration of intracellular calcium release, altered conductance of various ion channels in the plasma membrane, and/or mediators of the negative inotropic effects of tumor necrosis factor) and angiogenesis with extended exposure.[1, 2]
3. In nonclinical oral toxicity studies in the dog, microscopic examination showed vascular wall thickening and perivascular and focal perimysial fibrosis of the left ventricular papilla in the heart. Additionally, several cases of heart failure, pulmonary edema, pulmonary congestion and fluid overload were observed in the transplant trials, at doses above the dose currently recommended for approval. As a result, the Division of Neurology Products requested HRCT and echocardiographic monitoring in phase 3 studies in MS (Hold letter #3, 3/19/2006). The clinical hold was lifted on 5/19/2006.

Other Development Programs:

1. The drug was initially developed in the renal transplant population (IND filed 1998) at doses up to 5 mg/day but that indication is no longer pursued. [3] A clinical pharmacology review (Meyer, 2002) noted a negative chronotropic effect related to the first dose, with the nadir of heart rate decline 4-12 hours post-dose, typically resolving within the first 48 hours and not recurring despite continued daily drug administration. In an End-of Phase 2 meeting (2002), the sponsor stated that approximately 200 subjects were treated with drug for 6 months; about 25% of these patients developed bradycardia in which half required atropine (or beta-agonist) to ameliorate this effect. The overall serious adverse event rate of bradycardia was 4%. The sponsor reviewed a single case of cardiac arrest in a 54 year-old male with an extensive cardiac history (including stent placements, LVH on echo, positive tilt-table) and bradycardia

[1] Alewijnse AE et. Al. Cardiovascular effects of sphingosine-1-phosphate and other sphingomyelin metabolites. *Br J Pharmacol* 2004 Nov; 143 (6): 666-84.
[2] Landeen LK et. Al. Mechanisms of the negative inotropic effects of sphingosine-1-phosphate on adult mouse ventricular myocytes. *Am J Physiol Heart Circ Physiol* 2008 Feb; 294 (2): H736-9.
[3] According to a prior Cardio-Renal consultation (Desai, 2006), the sponsor "apparently terminated the development of FTY720 in renal transplant patients due to an unfavorable benefit to risk profile."

on Day 7 after drug discontinuation. In 2005, the development program was placed on partial clinical hold, after 1600 subjects received drug, because of cases of macular edema. Because of the macular edema (and one Phase III trial missing its non-inferiority endpoint), the sponsor decided to not move forward with the development program (2005) and withdrew the IND (2008).

2. The sponsor also filed an IND for the treatment of hepatitis C (2004); however, because of cases of bradycardia in clinical trials and insufficient monitoring plan for outpatients in the original protocol, the drug was place on hold and the IND was withdrawn (2005).

Multiple sclerosis indication: The proposed dose in MS is 0.5 mg/day, lower than the doses studied in the two pivotal Phase 3 trials in the renal transplant program (2.5 mg/day and 5 mg/day).

MS phase 2/3 clinical program:

The Phase III program in relapsing MS included 3 studies (D2301, D2302, D2309) evaluating efficacy and safety of once daily oral doses of fingolimod 0.5 mg and 1.25 mg. Of these studies, D2301 and D2302 are completed.

Table 1. MS phase 2/3 double-blind clinical studies

Study Number	Design	Control	Patients Randomized	Treatment/dose	Treatment duration	Patient population
Phase III studies (completed)						
D2301	Double-blind	Placebo	1272	0.5 mg/day, 1.25 mg/day, placebo	24 months	Relapsing-remitting MS
D2302	Double-blind, double-dummy	Active (Avonex)	1292	0.5 mg/day, 1.25 mg/day, Avonex 30 mcg im once/week	12 months	Relapsing-remitting MS
Phase II study (completed)						
D2201	Double-blind	Placebo	281	5.0 mg/day, 1.25 mg/day, placebo	6 months	Relapsing MS
Ongoing clinical studies						
D2309	Double-blind	Placebo	1089	0.5 mg/day, 1.25 mg/day, placebo	24 months	Relapsing-remitting MS
D1201	Double-blind, efficacy/safety in Japan	Placebo	165 planned	0.5 mg/day, 1.25 mg/day, placebo	6 months	Relapsing MS
D2306	Double-blind, efficacy/safety	Placebo	650 planned	1.25 mg/day, placebo	Up to 4-5 years	Progressive MS

This consultation will focus on studies 2302 and 2309 and echocardiographic data performed at selected sites. "Avonex" and "interferon" will be used interchangeably.

Study populations in 2301, 2302 and 2309:

Subject 18-55 years with relapsing-remitting MS were eligible for enrollment.

Relevant Exclusions: Any of the following conditions:

- Myocardial infarction within the 6 months prior to enrollment or current unstable ischemic heart disease
- Cardiac failure at time of screening (Class III according to New York Heart Association Classification or any severe cardiac disease as determined by the investigator)
- History of cardiac arrest, symptomatic bradycardia, sino-atrial heart block, or positive tilt test from workup for vasovagal syncope
- Resting pulse rate <55 bpm prior to randomization
- History or presence of a second degree or third degree atrioventricular (AV) block or an increased QTc interval >440 ms on screening ECG
- Arrhythmia requiring current treatment with Class III anti-arrhythmic drugs
- Renal impairment: serum creatinine > 1.7 mg/dL
- Uncontrolled hypertension
- History of angina pectoris due to coronary spasm or history of Raynaud's phenomenon
- Any medically unstable condition, as assessed by the primary treating physician
- Sick sinus syndrome
- Diabetes

Echocardiography:

2D and Doppler echocardiography were performed at selected sites in D2302 and in ongoing study D2309. The sponsor submitted a pooled analysis of 183 patients from studies D2309 (152 patients) and D2302 (31 patients), in which a total of 64 were on FTY 1.25 mg, 60 were on FTY 0.5 mg, 48 on placebo and 11 on interferon. Echocardiograms were performed at screening, Month 3, Month 12, and in the case of D2309, Month 24. (D2309 Special Safety Interim report).

Reviewer: Most of the echocardiography data were obtained from ongoing study D2309.

Methods:

Echocardiography data were collected and analyzed by a central reader. The reader was blinded to subject name, treatment arm, site identifiers, exam date, reason for exam. The echocardiograms were reviewed independent of other imaging or clinical data, and each time point was assessed independently, without comparison to previous time points. A subset of echocardiograms were re-read by the primary reader to determine intra-observer variability. It is not clear from the D2302 Echocardiogram Independent Review Charter (April 8, 2008) or corresponding D2309 Charter (September 19, 2008) whether inter-observer variability was assessed.

Table 2 Echo Views Obtained in D2302 at Screening, visit 7 (month 3) and visit 10 (month 12)

	Schedule	Assessments
Screening	Within 45 days of randomization to treatment arm	• Parasternal Views o Parasternal Long axis (PLA) of Left Ventricle: 2-D imaging o RV inflow view of Tricuspid Valve: 2-D imaging, color flow and continuous wave Doppler o Parasternal Short Axis (PSA) View at the mid-ventricular level (papillary level): 2-D imaging • Apical 2-chamber (A2C) View o 2-D imaging • Apical 3-chamber (A3C) View o 2-D imaging, color wave Doppler • Apical 4-chamber (A4C) View o Left ventricle: 2-D imaging o Tricuspid Valve: color flow Doppler, continuous wave Doppler o Mitral valve:, color flow Doppler, continuous and pulse waveDoppler

	Schedule	Assessments
Follow up images during treatment	Visit 7, month 3 (+60 days/-10 days) Visit 10, month 12 (± 14 days)	• Parasternal Views o Parasternal Long axis (PLA) of Left Ventricle: 2-D imaging o RV inflow view of Tricuspid Valve: 2-D imaging, color flow and continuous wave Doppler o Parasternal Short Axis (PSA) View at the mid-ventricular level (papillary level): 2-D imaging • Apical 2-chamber (A2C) View o 2-D imaging • Apical 3-chamber (A3C) View o 2-D imaging, color wave Doppler • Apical 4-chamber (A4C) View o Left ventricle: 2-D imaging o Tricuspid Valve:color flow Doppler, continuous wave Doppler o Mitral valve:, color flow Doppler, continuous and pulse waveDoppler
Additional Imaging Studies	Unscheduled echos will be tracked and reviewed.	

Anatomy	Results
Left ventricular end-diastolic volume	ml
Left ventricular end-systolic volume	ml
LV internal dimension diastole (LVIDd)	cm
LV internal dimension systole (LVIDs)	cm
LV posterior wall thickness	cm
IV septum thickness	cm
Left atrial volume	ml

Table 2. Quantitative Assessments

The following measurements will then be calculated by the independent reviewer using the data obtained from the echocardiogram:

Stroke Volume (SV)	ml
Cardiac Output (CO)	L/min
Cardiac Index (CI)	$L/min/m^2$
Systemic Vascular Resistance (SVR)	$Dyn{\cdot}s/cm^5$
Systemic Vascular Resistance Index (SVRI)	$Dyn{\cdot}s/cm^5/m^2$
Fractional shortening	%
Left Ventricular Ejection Fraction (LVEF)	%
Left Ventricular Mass (LVM)	g
Left Ventricular Mass Index (LVMI)	g/m^2
Estimated pulmonary artery pressure	mmHg

Table 3. Study 2309: Echocardiographic assessments:

	Schedule	Assessments
Screening	Within 45 days of randomization to treatment arm	• Parasternal Views o Parasternal Long axis (PLA) of Left Ventricle: 2-D imaging o RV inflow view of Tricuspid Valve: 2-D imaging, color flow and continuous wave Doppler o Parasternal Short Axis (PSA) View at the mid-ventricular level (papillary level): 2-D imaging • Apical 2-chamber (A2C) View o 2-D imaging • Apical 3-chamber (A3C) View o 2-D imaging, color wave Doppler • Apical 4-chamber (A4C) View o Left ventricle: 2-D imaging o Tricuspid Valve: color flow Doppler, continuous wave Doppler o Mitral valve:, color flow Doppler, continuous and pulse wave Doppler

Assessments	Results
Left ventricular end-diastolic volume	ml
Left ventricular end-systolic volume	ml
LV internal dimension diastole (LVIDd)	cm
LV internal dimension systole (LVIDs)	cm
LV posterior wall thickness	cm
IV septum thickness	cm
Left atrial volume	ml
Stroke Volume (SV)	ml
Cardiac Output (CO)	L/min
Cardiac Index (CI)	$L/min/m^2$
Fractional Shortening	%
Left Ventricular Ejection Fraction (LVEF)	%
RA-RV Systolic Gradient	mmHg

The following measurements will then be calculated by the Perceptive validated export using the reviewer's results listed above:

Assessments	Results
Systemic Vascular Resistance (SVR)	$Dyn{\cdot}s/cm^5$
Systemic Vascular Resistance Index (SVRI)	$Dyn{\cdot}s/cm^5/m^2$
Left Ventricular Mass (LVM)	g
Left Ventricular Mass Index (LVMI)	g/m^2
Estimated Pulmonary Artery Pressure	mmHg

Results:

The baseline characteristics of the 183 patients in the pooled echo analysis (D2302 + D2309) were similar to D2309; the mean age, 39-42 years, was slightly older than in 2301 and 2302, where the mean age was about 37-38 years. The population was majority female (about 75%) and Caucasian (86%). Diabetics were excluded.

In contrast, the renal transplant population (key safety population) was majority male (about 64%) and Caucasian (76-79%), with mean age about 44-45 years. About 12-14% had a history of diabetes.

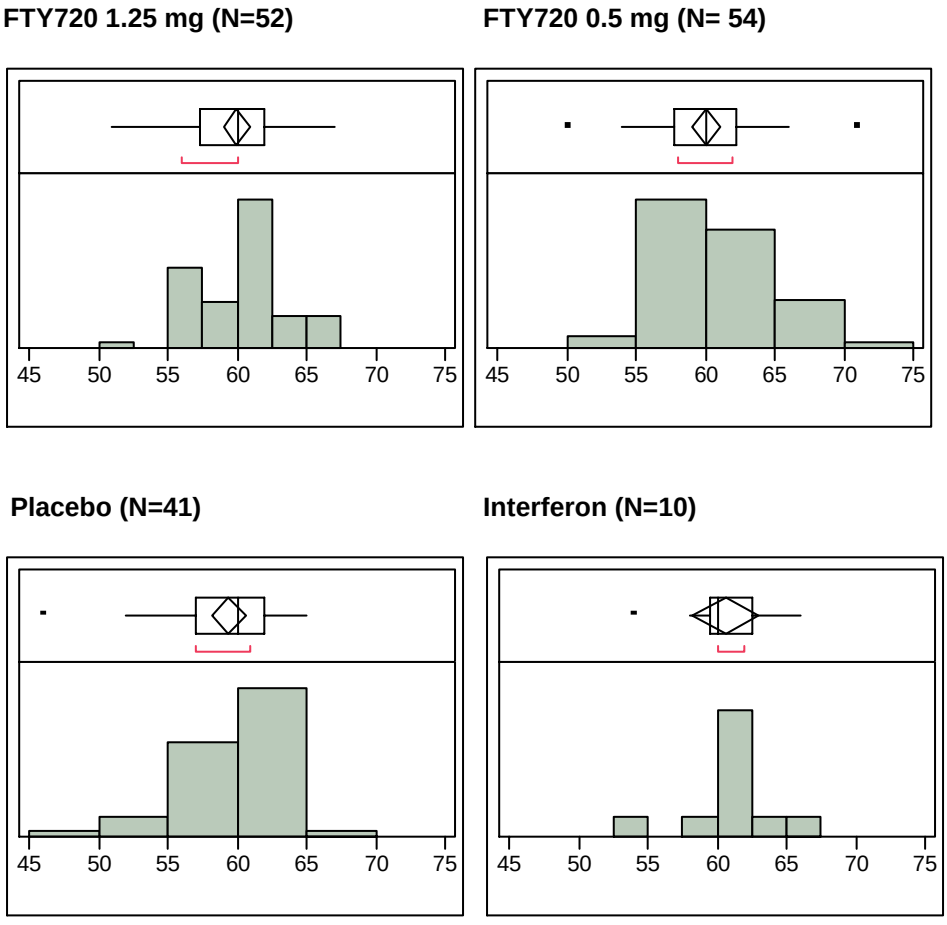
A total of 33 patients from D2302 and 173 patients from D2309 contributed baseline echocardiograms in the interim safety analysis (source: echo dataset, interim safety analysis). Of these, 176 echos were included in the echo population (46 on placebo, 11 on interferon, 58 on FTY0.5 mg and 61 on FTY 1.25 mg).

The figures below focus on Month 12 and last-available post-baseline echocardiogram data, as there are few 24 month data.

Ejection Fraction (EF):

Except for one echocardiogram in the placebo group (baseline ejection EF 46%), the baseline ejection fractions were $\geq$ 50%. Ejection fraction values between 50-70% are considered to be within the normal (or "preserved") range, and no subject with baseline moderate or severe reduction in left ventricular (LV) systolic function was included in this subpopulation.

Figure 1. Distribution of baseline left ventricular ejection fractions (%): echo population (N=176)



Source: echo dataset

Reviewer Note: Ejection fraction, cardiac output and ventricular volume measurements may be influenced by ventricular loading conditions (e.g., preload or afterload).

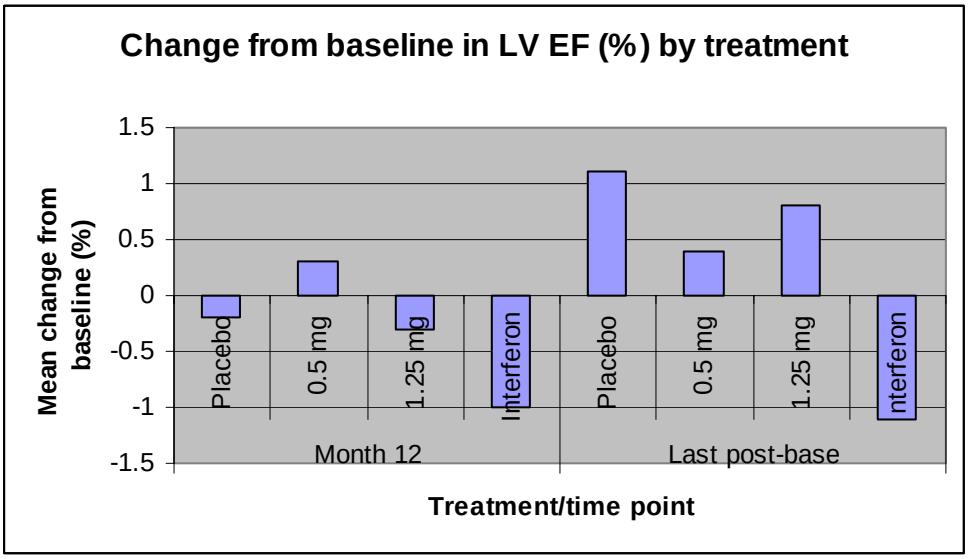


Figure 2. Mean change from baseline in left ventricular ejection fraction (LVEF) by treatment (Source: sponsor)

Largest EF decreases on FTY720: One patient on FTY720 1.25 mg (D2309_0578_00010) with the largest decrease in EF (12% decrease) had a baseline EF of 67% and follow-up EF of 55%.
One patient (D2309_0523_00006) on FTY720 0.5 mg, with baseline EF 62%, had an 8% decrease in EF.

Fractional Shortening:
Mean baseline fractional shortening was about 29-30% in all treatment groups. There was a mean increase from baseline (about 1-4%) in fractional shortening in all treatment groups (not shown).

LV End-systolic volume (ESV)/LV End-diastolic volume (LV EDV)/stroke volume (SV):

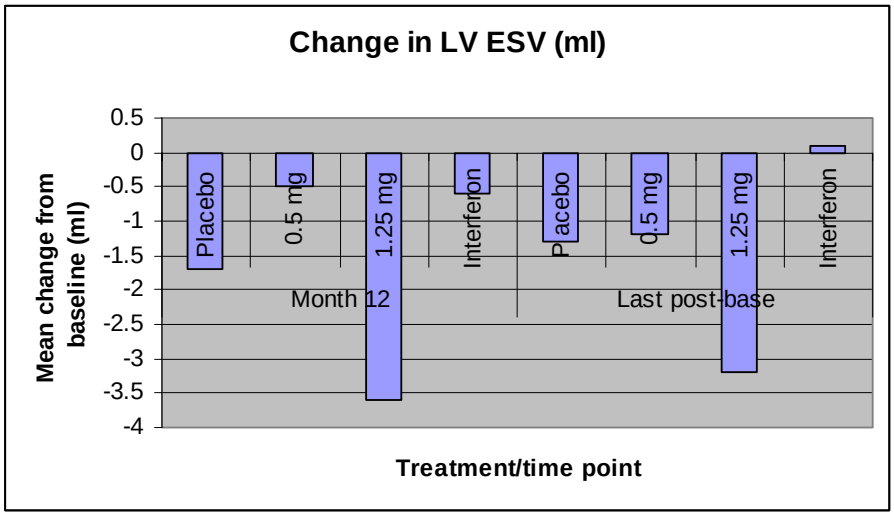


Figure 3. Change in left ventricular end-systolic volume (LV ESV) (ml) by treatment (source: sponsor)

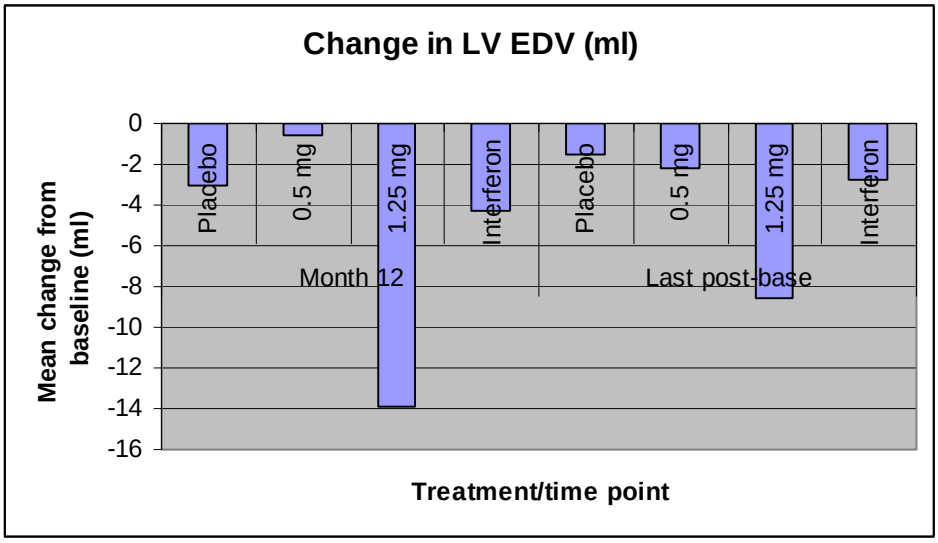


Figure 4. Change in left ventricular end-diastolic volume (LV EDV) (ml) by treatment (source: sponsor)

Stroke Volume:

Reviewer Note: Mean baseline stroke volume was 51.13 (placebo) to 54.6 (interferon) ml, with baseline values as low as 29 ml (placebo).

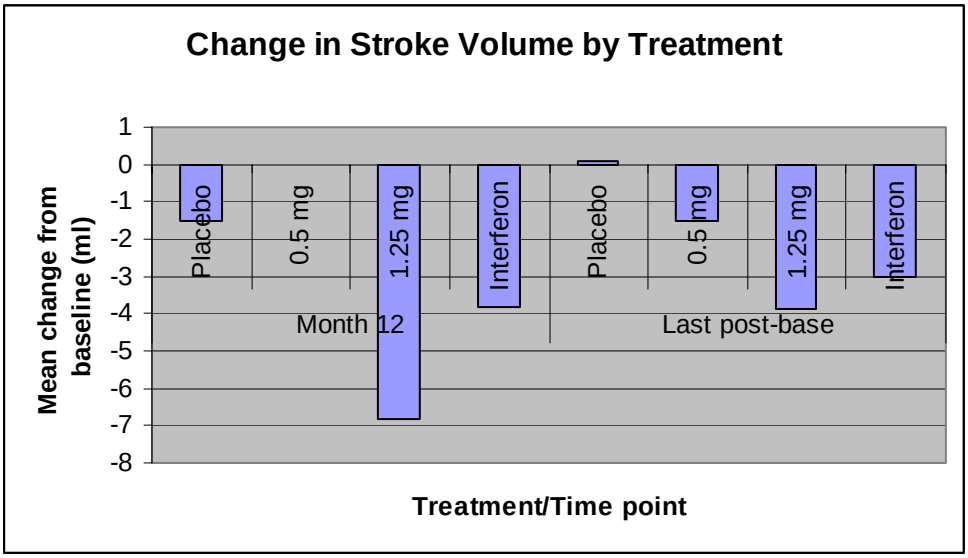
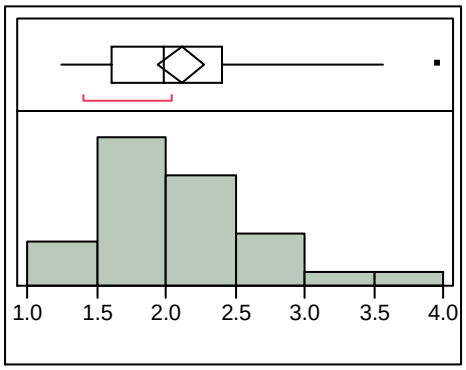


Figure 5. Change in stroke volume (ml) by treatment (source: sponsor)

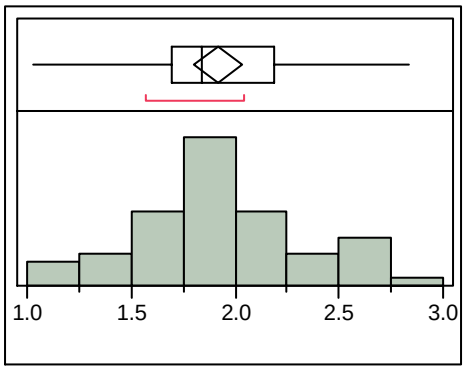
Cardiac Index (L/min/m^2):

Figure 6. Histograms of baseline cardiac index by treatment

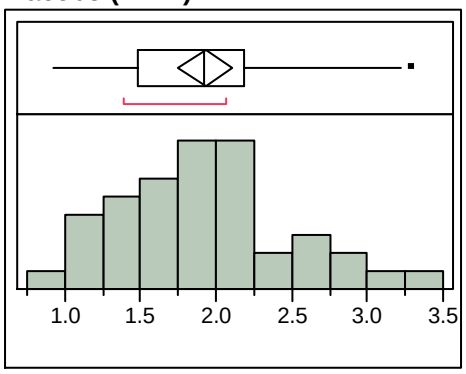
FTY720 1.25 mg (N= 52)



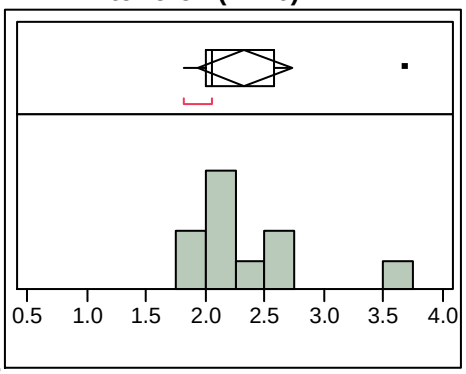
FTY720 0.5 mg (N=54)



Placebo (N=41)



Interferon (N=10)



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Reviewer Note: . According to Hurst's The Heart (12th Edition: 2008), a normal cardiac index is defined as > 2.5 L/min/square meter, and a cardiac index of 1.4 L/min/square meter would be considered low. All treatment groups included some patients with baseline cardiac index < 2.0. However, severe heart failure patients would not have met enrollment criteria.
The submission did not include an algorithm for cardiac index or stroke volume measurement.

The lowest baseline cardiac index was observed in placebo patient (D2309_0524_00008), with baseline cardiac index 0.92 l/min/m^2, stroke volume 39 ml and ejection fraction of 64%. This patient had an echocardiogram about 3 months later (repeat cardiac index 1.04 l/min/m^2, stroke volume 36 ml, ejection fraction 62%); a third "end of study" echocardiogram at 9 months showed a cardiac index of 1.68 l/min/m^2, stroke volume of 54 ml and ejection fraction 66%.

One patient (D2309_0524_00007) on FTY 720 1.25 mg QD with baseline EF 56% had a calculated baseline cardiac output of 2.47 and cardiac index of 1.4. At the end of study (3 months after screening), the ejection fraction was essentially unchanged (57%) and the cardiac index was 1.64.

LV end-diastolic and end-systolic dimensions (cm):

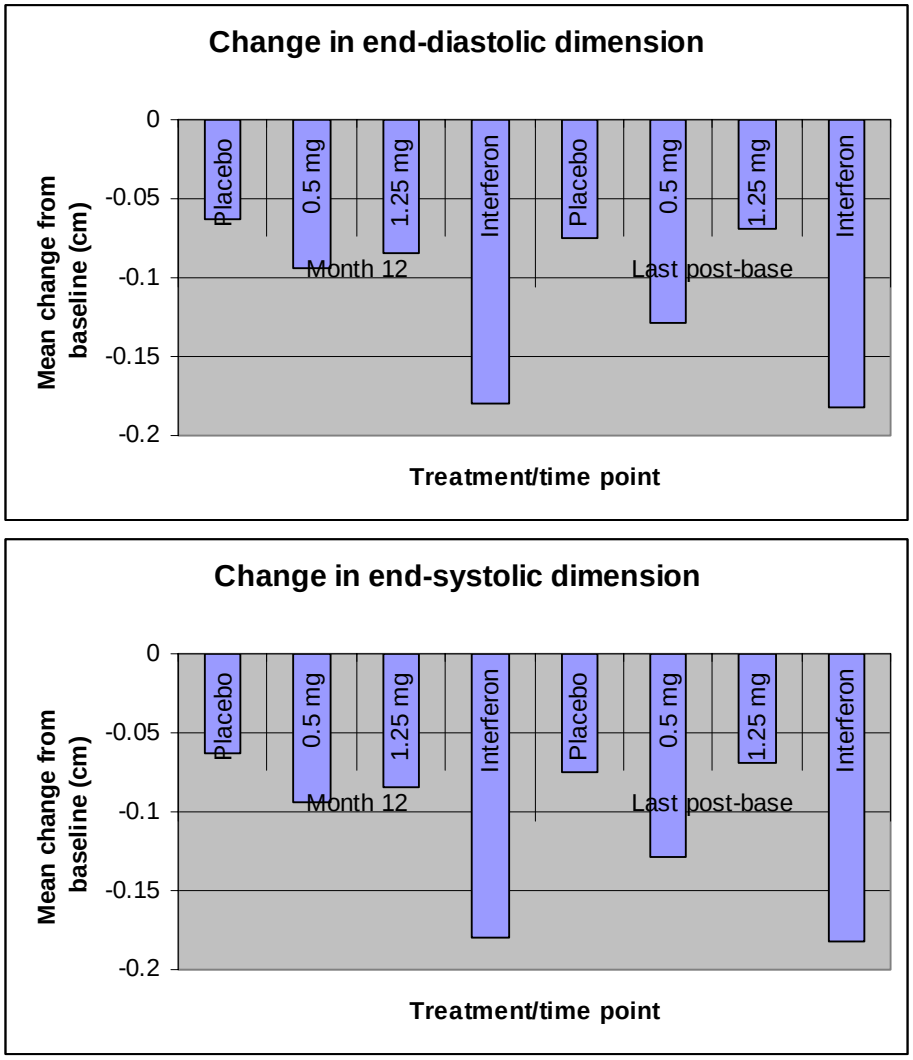


Figure 7. Mean change from baseline in LV end-diastolic and end-systolic dimensions (cm) (source: sponsor)

In severe chronic mitral regurgitation, for example, one would have expected an increase in end-diastolic dimension consistent with volume overload. In this case, end-diastolic and end-systolic dimensions decreased from baseline in all groups.

Estimated pulmonary artery pressure (PAP):

The method of estimating PAP was not explicitly stated. The apparent mean increase in PAP in the 1.25 mg group appears due to a single outlier (see below). Also, the available PAP measurements were available in a small subset of the echo population (FTY720 1.25 mg, N=10 for month 12).

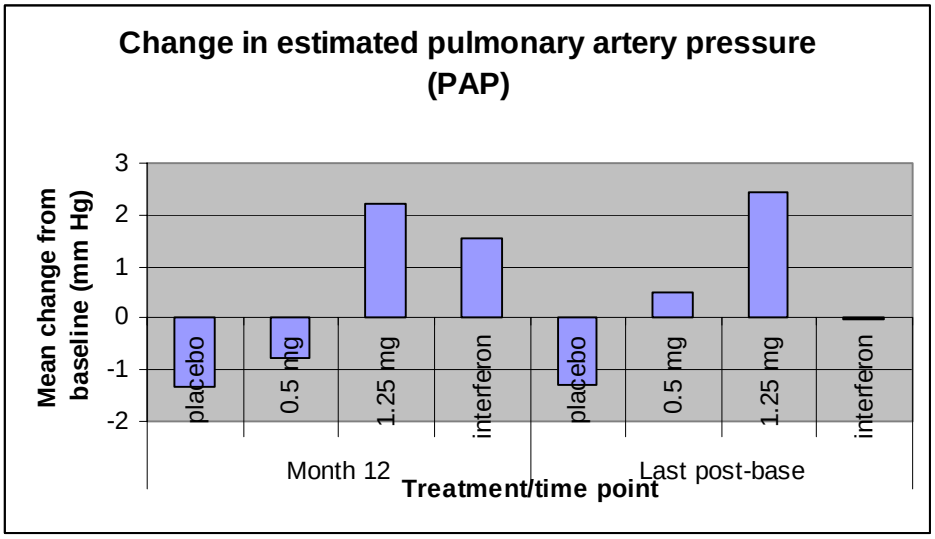


Figure 8. Change from baseline in estimated pulmonary artery pressure (source: sponsor)

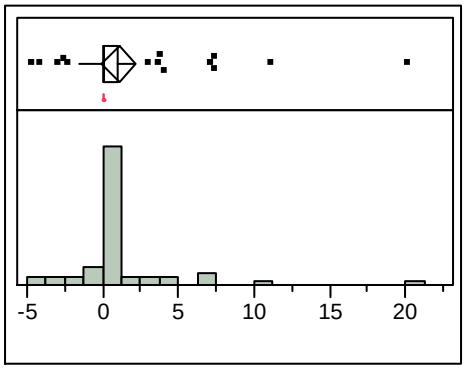


Figure 9. Histogram of the change from baseline in estimated pulmonary artery pressure (FTY 1.25 mg; N= 51) (source: AE echo dataset)

There was one outlier in the FTY720 mg 1.25 mg group with an increase in PAP of 20 mm Hg at 12 months; the median change from baseline was 0 and the mean change was < 1 mm Hg.

Wall thickness/LV mass index:
Interventricular septum thickness: The mean change in IVS thickness in patients treated with FTY720 was less than the change seen in patients treated with placebo (not shown).

LV posterior wall thickness:

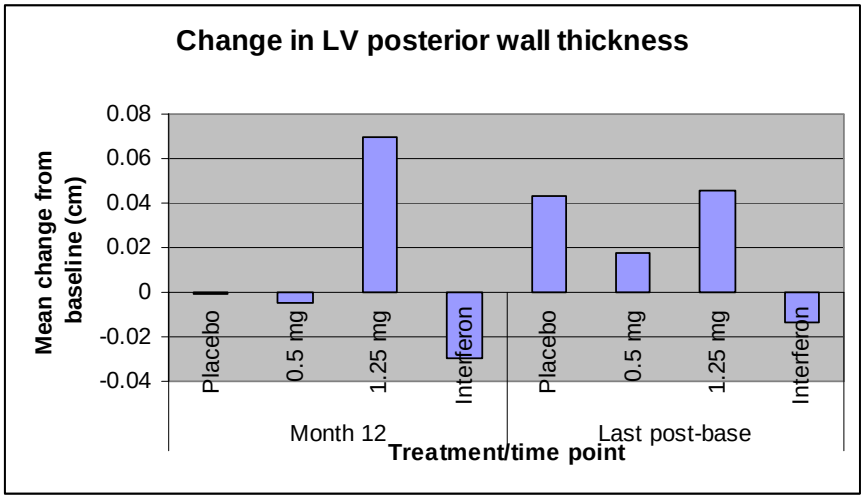


Figure 10. Mean change from baseline in LV posterior wall thickness (cm) (source: sponsor)

LV mass index (reference range: 50-102 g/m^2 (M), 44-88 g/m^2 (F):

Mean baseline LV mass index was 68.0 to 69.5 (g/m^2). There were 1-2 outliers in the placebo, 0.5 mg and 1.25 mg groups with baseline LV mass index > 100 g/m^2. However, in the FTY720 0.5 mg and 1.25 mg groups, the patients with the highest baseline LV mass index (100-130 g/m^2 range) showed decreases from baseline in the last available follow-up echocardiograms.

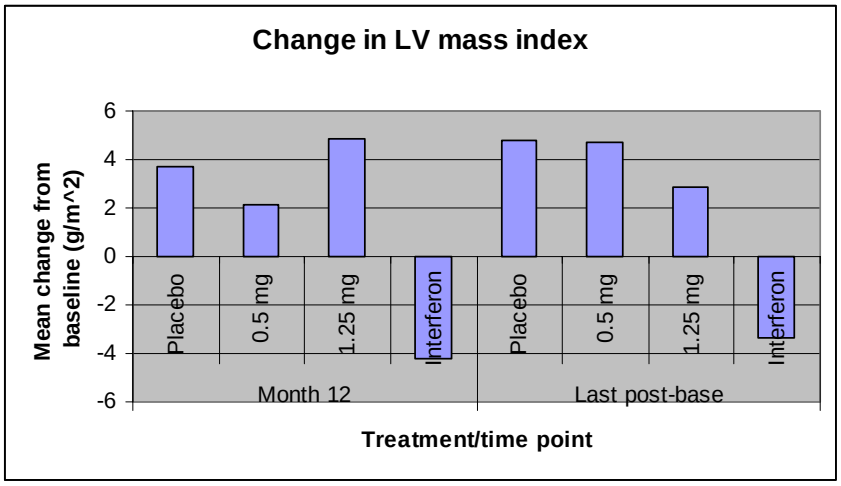


Figure 11. Mean change from baseline in LV mass index (source: sponsor)

Reviewer Note: It is not clear whether the small increases in LV posterior wall thickness or LV mass index in the 1.25 mg group are of clinical significance. There was no increase in interventricular septum thickness compared with placebo.

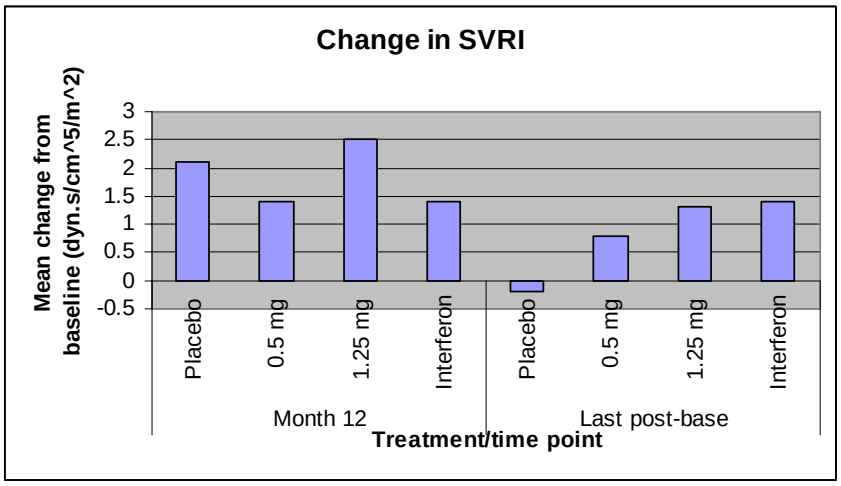


Figure 12. Mean change from baseline in SVRI (source: sponsor)

Reviewer Note: There is a small increase in SVRI in the 1.25 mg compared to placebo, of uncertain clinical significance.

The change from baseline in left atrial volume was similar between FTY720 groups and placebo (not shown). If there were significant mitral regurgitation, one would have expected an increase in left atrial size and volume due to the increased volume load.

COMMENTS:

In summary, the available echocardiographic data do not reveal a large safety signal. Despite the preclinical signal of myocardial fibrosis, depressed left ventricular systolic function is not observed in this sample.

However, the available echocardiographic evaluations are limited. The application did not include the actual echocardiograms. This reviewer is unable to comment on image quality of the images, or methods of calculation. We were not given the extent of intra-reader or inter-reader variability. In addition, no Doppler results or any evaluations of valve morphology were submitted. If one were concerned about papillary muscle fibrosis, one would have evaluated the mitral and tricuspid valves, including an assessment of regurgitation. Those examinations were not part of this application.

If there were a large signal—for example, an imbalance in severe chronic mitral regurgitation in the FTY720 group--one would have expected consequences of chronic volume overload such as left ventricular and left atrial dilatation, in addition to a holosystolic murmur heard best at the apex. It is therefore somewhat reassuring that the 12 month left atrial volume, end-diastolic and end-systolic dimensions are not increased from baseline. However, one cannot exclude a smaller signal, or a signal appearing over a longer time period. Finally, since the study population excluded diabetics and subjects with significant heart disease, one cannot exclude safety signals that might surface in a more vulnerable population.

Thank you. If you have any further questions, please feel free to contact me or the Division.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22527	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	FINGOLIMOD HCL ORAL CAPSULES

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHARI L TARGUM
04/12/2010

NORMAN L STOCKBRIDGE
04/13/2010

DIVISION OF SPECIAL PATHOGEN AND TRANSPLANT PRODUCTS
MEDICAL OFFICER CONSULTATION

Date:	April 8, 2010
To:	Eric P. Bastings, M.D. Deputy Director Division of Neurology
From:	Marc W. Cavaillé-Coll, M.D., Ph.D. Lead Medical Officer, DSPTP
Through:	Renata Albrecht, M.D. Director, DSPTP
Subject:	NDA Safety Consultation

General Information:

Application:	NDA 22-527
Sponsor:	Novartis Pharmaceutical Corporation
Drug Product:	Gilenia® (fingolimod HCL) FTY720 0.5 and 1.25 mg capsules
Request From:	Lourdes Villalba, M.D. Medical Officer, Division of Neurology
Date of Request:	February 18, 2010
Date Received:	February 23, 2010
Materials Reviewed:	Request for Consultation, NDA 22-527; (\\CDSUB1\EVSPROD\NDA022527); CTD 2.5 Clinical Overview; CTD 2.7.4 Summary of Clinical Safety; CTD2.7.2 Summary of Clinical Pharmacology; Annotated Package Insert; Summary of Clinical Safety (renal transplantation) SN002, October 5, 2009.

Introduction:

We are asked to evaluate the risk for opportunistic infections with fingolimod treatment and provide advice on how to adequately identify, monitor, treat early and/or prevent opportunistic infections in this population.

Gilenia® (fingolimod HCL), also known as FTY720, an orally active synthetic sphingosine 1-phosphate (SIP) receptor modulator, is submitted under NDA 22-527 for approval as monotherapy for the treatment of patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability. The dose proposed for approval in MS is 0.5 mg/day.

Background:

FTY720 was initially developed for the prevention of rejection in renal transplantation under IND 57,293; however, development in renal transplantation was discontinued after Phase III studies showed that FTY720 (2.5 mg/day and 5.0 mg/day) in combination with cyclosporine A (CsA) did not offer advantage over standard of care. In particular, FTY720 at a daily dose of 5.0 mg/day in combination with reduced dose Neoral® (cyclosporine USP) Modified and corticosteroids, was associated with an unacceptable increased rate of acute rejection in *de novo* renal transplantation recipients compared to the control regimen of full dose Neoral® plus mycophenolate mofetil (MMF) and corticosteroids. FTY720 at a daily dose of 2.5 mg, in combination with full dose Neoral® and corticosteroids, resulted in similar efficacy in *de novo* renal transplant recipients compared to the control regimen of full dose Neoral® plus MMF and corticosteroids, with respect to a combined endpoint of prevention of graft rejection, graft loss or death at 12 months after transplantation; however, creatinine clearance was decreased in the FTY720 group compared to the control group.

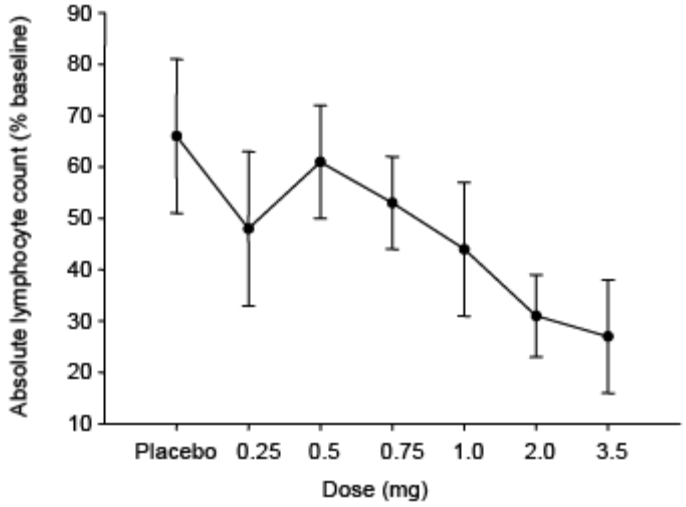
While the key pharmacodynamic effect of FTY720 is a dose-dependent reduction of peripheral lymphocyte counts mediated by down-modulation of SIP1 receptor on lymphocytes a number of other off-target biologic effects were observed in clinical studies of FY720 in renal transplant patients, including but not limited to transient dose-dependent reduction in heart rate (negative chronotropic effect) and atrioventricular conduction, as well as an increased incidence of macular edema compared to mycophenolate mofetil in combination with CsA.

FTY702 is phosphorylated *in vivo* by sphingosine kinase to form the active moiety FTY720 phosphate, which acts as an agonist at four of five G protein-coupled sphingosine 1-phosphate receptors (SIP), namely SIP1, SIP3, SIP4 and SIP5. Thus, depending on the cell type, the concentration, and the time following administration, FTY720 may act as an "agonist" or "functional antagonist" at SIP receptors.

By acting as a functional antagonist of S1PR on lymphocytes, fingolimod-phosphate blocks the capacity of lymphocytes to egress from lymph nodes, causing a redistribution, rather than depletion, of lymphocytes. Thus, fingolimod causes a reversible retention of a proportion of CD4+ and CD8+ T-cells from the peripheral blood into lymph nodes and other lymphoid tissues without affecting many of the functional properties of these cells. This must be taken into consideration when interpreting the relationship between peripheral blood lymphocyte counts, including subset counts, and the relative risk for opportunistic infections.

The dose-response relationship of single dose of fingolimod and peripheral blood lymphocyte count was measured by the Applicant in two studies, FTY720AB101, in which doses of 0.25 to 3.5 mg were used in stable renal transplant patients on cyclosporine based immunosuppression, and FTY720A2215, in which doses of 5 to 40 mg were used in healthy volunteers (Section 4.1.2 Effects of single doses of fingolimod on lymphocyte count, in CTD 2.7.2 Summary of Clinical Pharmacology). The effect is still modest at the proposed recommended dose of 0.5 mg per day compared to placebo in stable renal transplant recipients as shown in the Applicant's Figure 4.2 (Section 4.2.2 in CTD 2.7.2) below, and a little more pronounced at the doses of 1 mg and greater.

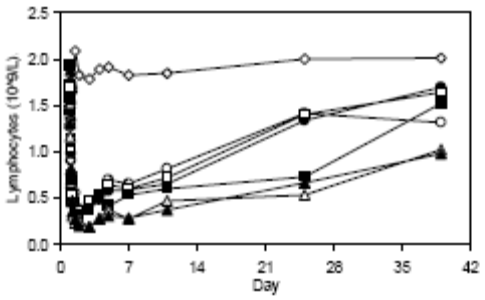
Figure 4-2 **Mean (± SD) percent of baseline of nadir absolute lymphocyte count after single dose**



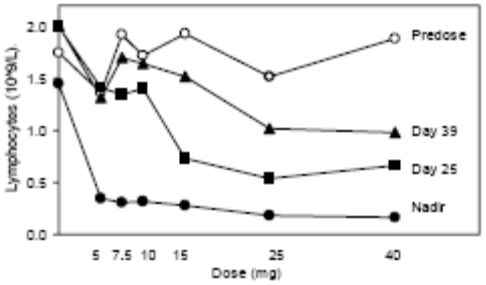
Source: [Study FTY720AB101 FSR, Table 7.5-1]

Single doses of fingolimod (5 to 40 mg in healthy volunteers) cause a rapid dose dependent decrease in peripheral lymphocyte count which reverses as the blood concentration of fingolimod is disposed, as shown the Applicant's Figure 4.3 below (Section 4.2.2 in CTD 2.7.2). However, the range of doses evaluated begins only at ten times the proposed recommended daily dose of 0.5 mg.

Figure 4-3 **Lymphocyte dose-response plots**



Lymphocyte trajectories after placebo (*open diamonds*) and fingolimod doses of 5mg (*open circles*), 7.5mg (*filled circles*), 10mg (*open squares*), 15mg (*filled squares*), 25mg (*open triangles*) and 40mg (*filled triangles*).

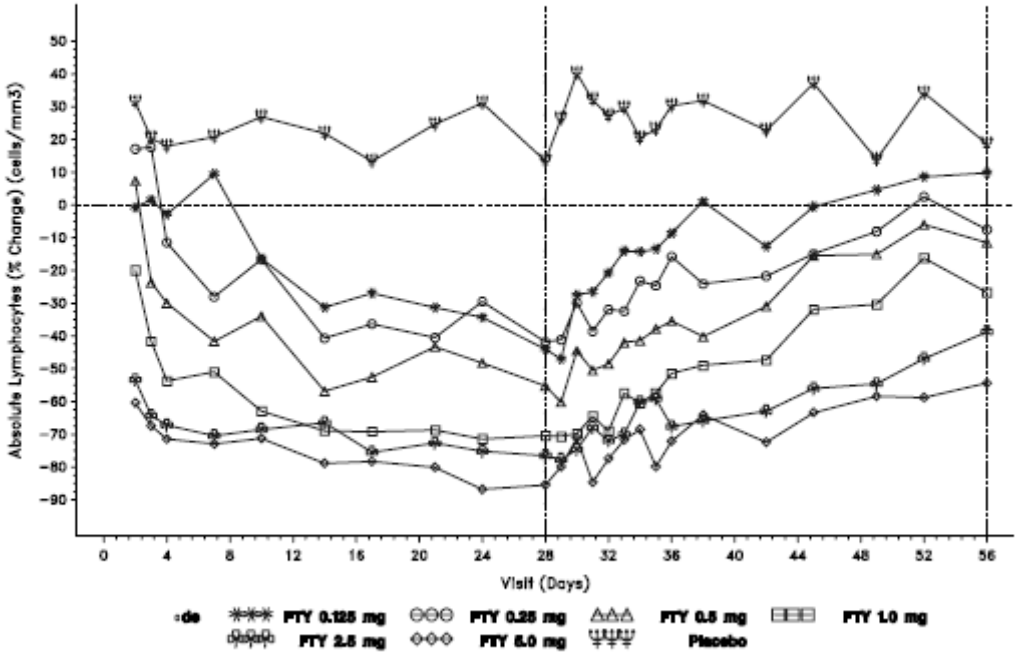


Mean predose, nadir, day 11, and day 39 lymphocyte counts with respect to fingolimod dose.

Source: [FTY720A2215] FSR

The effect of multiple doses of fingolimod on peripheral blood lymphocyte count was assessed in a multiple ascending dose study, FTY720AB102 in stable renal transplant patients on cyclosporine based immunosuppression who received daily fingolmod doses of 0.125 to 5 mg for twenty-eight days. Shown in the Applicant's figure 4.5 below, as fingolimod concentrations approach steady state, a persistent, dose dependent decrease in lymphocyte count is observed over the dosing interval. With discontinuation of fingolimod dosing the lymphocyte count slowly increases as fingolimod concentration decreases (Section 4.1.3 Effects of multiple doses of fingolimod on lymphocyte count, in CTD 2.7.2 Summary of Clinical Pharmacology).

Figure 4-5 Mean percent change from baseline for absolute lymphocytes by visit (safety population)



Source: [FTY720AB102 Section 10.3.1] FSR

Reviewer's Comment: *While peripheral blood lymphocyte counts, including CD4+ lymphocyte subset counts, represent a potential pharmacodynamic (PD) marker for fingolimod, that follows a pattern consistent with the long pharmacokinetic half life of fingolimod, such counts, unlike their use in HIV infected patients, should not be interpreted as reflections of the net state of immunosuppression in patients dosed with fingolimod. The effect of fingolimod on peripheral blood lymphocyte counts reflects lymphocyte distribution and inhibition of circulation, but not lymphocyte depletion.*

The effect of multiple doses of fingolimod on lymphocyte counts was not evaluated in this study at the proposed recommended daily dose of 0.5 mg, but is detectible at the dose of 1.25 mg per day. The absolute clinical significance of a mean percent change of absolute lymphocyte count of about 30% is not certain; however, its persistence can be interpreted as reflecting the persistence of whatever effect fingolimod may have on the immune system and other targets of this molecule. This should be taken into consideration if fingolimod is discontinued in the setting of the occurrence of an infection.

Evaluation of risk for opportunistic infections with fingolimod treatment:

This request is prompted by the observation of the deaths of two young patients (ID# D2302-0212-00021 and D2302-0821-00007) from disseminated herpes infections (one herpes simplex

encephalitis and one disseminated herpes zoster) among approximately 3000 subjects with MS exposed to fingolimod. Both deaths occurred in the 1.25mg/day dose group.

Narratives of these cases were provided in the consult request, and are reproduced below:

Patient [D2302-0212-00021] – Herpes zoster disseminated
Treatment Group: FTY720 1.25mg
Treatment Period: Active Treatment Phase
ARGUS Case No: PHHO2008IT06575
Event(s): Immunosuppression, multiple sclerosis relapse, abdominal pain upper, viremia, asthenia, transaminases increased, hepatic necrosis, hepatitis, renal haemorrhage, disseminated intravascular coagulation, blister, fatigue, disseminated intravascular coagulation, hepatic function abnormal, endotracheal intubation, hematuria, bradycardia, acute hepatic failure, muscular weakness, hypoaesthesia, paraesthesia, gait disturbance, tension headache, alopecia, depression, presyncope

Narrative Text
The first symptoms probably related to MS occurred in August 2004. The patient was diagnosed with multiple sclerosis in August-2006. No previous MS disease-modifying therapies were given and last corticosteroid use was in August-2006. Prior to study entry the patient also experienced two MS relapses in 2007; in January 2007 a mild event for which no treatment was administered and in May 2007 for which only diazepam was administered. During the study, the patient had a relapse in February 2008, which was treated with 5 mg iv methylprednisolone.
Based on information which the patient provided to a Gastroenterologist in Siena in May 2008, she did not have a history of Varicella as a child and also was not vaccinated against varicella. Serology tests for neurotropic viruses were believed to have been performed at the time of diagnosis of MS in August 2006. It was later determined that the patient was negative for VZV IgG from the August 2006 serology and stored sera collected during study visits in Jan/April 2008.
On 12-July-2007 patient commenced FTY720 1.25 mg daily.
On 8-Feb-2008 (Friday) patient was seen by the investigator complaining of a 6 day history of progressive weakness in the right lower limb. Clinical examination confirmed right lower limb weakness. No other investigations were performed – MRI was not performed. She had been able to continue to work as a teacher in a local Nursery (for children aged 0 – 3 years) up to 7-Feb. There was no mention of specific infections in the Nursery at this time.
On (b) (4) (Monday) commenced methylprednisolone 1g i.v. daily for MS relapse. Treatment administered as an out-patient at the (b) (4) (investigational site). Continued for 5 days up to Friday (b) (4). Patient was off work during this time period. Routine hematology and biochemistry was performed at the (b) (4). [In the week of (b) (4), investigator learned that the lymphocyte count was 434/mm3 at this time; LFTs were normal.]
On 27-Feb-2008 complete recovery from the MS relapse documented.
On 8-Apr-2008 the patient was seen by the neurologist for their month 9 visit and reported no symptoms.
On 6-May-2008, approximately 10 months after receiving study medication the patient was seen for a suspected MS relapse. Symptoms consisted of intermittent paresthesia in both lower limbs. On physical examination, plantar hypoesthesia was noted in both feet. There was no muscle weakness noted in the lower limbs but her gait was affected by the paresthesia and hypothesia. Despite the relapse, the patient continued to work because she did not wish her work colleagues to think that MS was affecting her working ability. It was decided to wait before starting corticosteroid treatment.
On 12-May-2008, the patient reported deterioration in symptoms and it was decided to start corticosteroid treatment. Apart from the neurological symptomatology the patient was feeling well. [The patient subsequently reported that there was a Varicella outbreak in the Nursery at

this time.]
On (b) (6) patient commenced methylprednisolone 1g i.v. daily for MS relapse. Treatment administered as an out-patient by an Ambulatory service where she lived. Continued for 5 days up to (b) (6). She also received omeprazole therapy. Despite being advised by the investigator to rest, she continued to work at the Nursery during the course of this therapy.
On (b) (6) without the knowledge of the investigator, the patient continued on oral steroid therapy with medication which she had at home. From (b) (6) she took Medrol 48 mg daily (16 mg t.i.d.). She planned to reduce this to 32 mg daily (16 mg b.i.d.) on (b) (6)
On (b) (5) in the early morning (i.e. during the night), the patient called the local physician on-call because of epigastric pain. He recommended to double the omeprazole dosage. At 8:30 AM, she called the investigator because of continuing epigastric pain. The investigator instructed her to stop the Medrol therapy – she may have taken 16 mg that morning although this is not certain. In the late afternoon, she went to the Emergency dept. at a hospital in (b) (6). The investigator was contacted by the ED physician at 7:30 PM. He informed her that the liver transaminases were approx. 300. Abdominal ultrasound was normal and drug-induced liver toxicity was suspected. The investigator recommended to stop the study medication. The investigator also spoke with the patient on the phone who complained only of epigastric pain and general weakness. The patient was admitted to the hospital and then sent to the gastroenterology department.
On (b) (6) the investigator was contacted by the Gastroenterologist at approx. 5:30 PM. Liver transaminases had increased to 1200. [Lymphocytes were 2.5% of approx. 10,000 leucocytes] He also noted vesicles in the throat, compatible with herpes (did not look like candida). At 6:30 PM the investigator was contacted again. The Gastroenterologist now also noted a vesicular eruption on the trunk. Consultations with an Infectious Disease specialist and a hematologist were organized. Acyclovir therapy i.v. was now commenced. At 8:00 PM, the investigator spoke with the patient on the phone. Although speaking with a weak voice, she was fully orientated. She complained of epigastric pain and was extremely tired. Later that evening, coagulation tests were reported to have worsened, DIC was suspected and the patient was transferred to the ICU. A request was made to the Transplantation center in Pisa concerning a possible hepatic transplantation, which was felt to be contraindicated due to the suspicion of viremia. The patient was conscious and breathing well. [On this date, the patient informed the Gastroenterologist, on direct questioning, about a Varicella outbreak at the Nursery where she worked, approx. 14 days earlier.]
Serology tests for hepatitis viruses A, B, C were all negative. Herpes virus serology and aspiration of skin lesions for microbiological tests also performed (Reported by gastroenterologist to investigator later that skin vesicles positive for VZV). Blood cultures and throat swabs were probably not performed.
On (b) (6) the patient was in the ICU. The investigator was called by the Anesthesiologist in the evening. The patient was conscious and able to speak but, because of the rules of the ICU, was not permitted to speak with the investigator on the phone. The Anesthesiologist stated that hepatic function was “extremely poor” [no LFT figures mentioned]. Other organs were functioning, the patient was not intubated and was passing urine. The patient received platelet transfusions and coagulation factors.
On (b) (6) a dramatic deterioration in the patient’s condition during the early morning hours was noted. She was intubated, had massive hematuria and renal dialysis considered which didn't occur due to bradycardia..The patient died at 10:00 AM.
On (b) (6) an autopsy was performed. Cause of death stated to be acute hepatic failure. Initial autopsy report to be provided on (b) (6).
During the study the patient had the following adverse events suspected to be related to study drug:.tension headache (Jul-Oct-2007) and alopecia (Aug-2007 to Jan-2008) and the following adverse events not suspected to be related to study drug.presyncope (3-Sep-2007), depression (Aug-Sep-2007. Concomitant medications taken during the study included: fluribiprofen (Jan-2008), clarithromycin (Jan-2008), ibuprophen (Aug-2007-current), paracetamol (Oct-08), sertraline hydrochloride (Aug-Sep-2007). The patient had one

confirmed relapse (EDSS value increased from score of 1.0 to 3.5) from 2-Feb-2008 to 27-Feb-2008..The patient was treated with steroids.and completely recovered..The patient did not have any notable vital sign values and all PFT values were within expected ranges..The patients laboratory values were generally within normal ranges without any pattern of change observed. The investigator suspected a relationship between the event (herpes zoster disseminated) and the study medication.

Patient [D2302-0821-00007] – Death, herpes simplex encephalitis, grandmal convulsion, coma, pyrexia,
Treatment Group: FTY720 1.25mg
Treatment Period: Active Treatment Phase
ARGUS Case No: PHHO2008KR06307
Event(s): Encephalitis herpes, pyrexia, grandmal convulsion, partial seizures, partial seizures with secondary generalization, depressed level of consciousness, brain edema, CSF protein increased, CSF
pressure increased, unresponsive to stimuli, intracranial pressure increased, electroencephalogram abnormal, coma, hyperventilation, mechanical
ventilation, areflexia, headache, dizziness

Narrative Text
The patient was diagnosed with multiple sclerosis in Mar-2007. Previous therapy includes interferon-beta-1b from Mar-2007 to May-2007 and the last corticosteroid use was in Apr-2007.
The patient's past medical history included: muscle spasticity (Mar-2007), which was not continuing at start of study. There was no past medical history of seizures.
On 13-May-2008, approximately 11 months after receiving the first dose of study medication, the patient experienced fever, headache and URI symptoms. Most of the symptoms subsided with a common cold medicine. Study drug was permanently discontinued on 13-May-2008.
On (b) (6) the patient developed sudden generalized tonic-clonic seizures and was hospitalized at an outside university hospital close to his place of residence. Initial routine blood testing was unremarkable. CSF tests did not reveal any significant findings (specific details pending), except for an increased opening pressure of 22 cmH20. In the CSF, microbiological analysis was negative for cryptococcal antigen, HSV IgG/IgM and tuberculosis PCR. HSV PCR from this first CSF sample was not performed. A brain MRI scan performed on the same day revealed diffuse low intensity lesion at the left temporal and parietal cortex and subcortical WM on ADC mapping image. No Gd-enhancing lesions were found and there was no significant change in the previously seen multifocal white matter lesions involving both fronto-temporal-parietal PVWM, thalamus, brainstem and cerebellum. No specific diagnosis was made and the patient was treated with the antiepileptic drug, oxcarbazepine. See medication list for medications administered during the hospitalization (update on dosages and timing of administration is pending).
During his hospital course, the patient continued to have intermittent high fevers and partial seizures, but his level of consciousness was not seriously altered until he developed of series of seizures (partial seizures with secondary generalization) on 19-May-2008. Phenytoin and Phenobarbital were administered (unclear start date and duration of treatment), but the seizures did not completely abate. An EEG showed periodic sharp waves on both hemispheres (left > right). The patient's level of consciousness rapidly deteriorated.
On (b) (6), a follow-up MRI revealed a markedly progressed confluent cortex and subcortical white matter lesion with extensive gyral swelling at both cerebral hemispheres mainly in the insula, and temporal and frontal lobes. The patient received antibiotics for aspiration pneumonia, cerol and high dose methylprednisolone (unclear dosage and treatment duration) empirically.
On (b) (6), the patient was transferred to the affiliated hospital of the PI (FTY720 study center hospital). After reviewing the medical records and MRI scans, the patient was tentatively diagnosed with viral encephalitis (most likely herpes simplex). The patient was immediately treated with acyclovir and therapies for cerebral edema were administered. After

admission, the patient had a brief partial seizure on two occasions. Intravenous loading of valproate was done and the dosage of oxcarbazepine was increased..A second CSF sample from (b) (6) supported the diagnosis of a viral encephalitis, showing 22 WBCs (84% of other cells, 16% of mononuclear cells and no granulocytes), 2 RBCs, normal glucose and markedly elevated protein (250 mg/dL), and an elevated opening pressure of 39 cmH2O. HSV PCR from this second CSF sample was positive (qualitative result only, unclear if HSV-1 or HSV-2). Additional CSF from this second sample was sent on 29-May-2008 to the NIH (National Institute of Health) for further analysis (i.e., JC virus PCR, HSV-1 and HSV-2 PCR encephalitis panel).
On (b) (6) the follow-up EEG demonstrated periodic sharp waves in both hemispheres. There was no further seizure activity. However, the patient's condition continuously deteriorated and mechanical ventilation was started.
On (b) (6), the pupillary light response disappeared. In spite of antiviral therapy and massive therapies for increased intracranial pressure, including mannitol, dexamethasone and hyperventilation, his condition continued to deteriorate.
On (b) (6), he only showed only minimal response on endotracheal suction and started having limitation of extraocular movements on Doll's eye maneuver. On EEG, there was no epileptiform discharges, but electrical potentials were markedly decreased (less than 5µV).
On (b) (6), the patient did not show any response to external stimuli and brainstem reflexes had disappeared.
On (b) (6), the patient's vital signs were stable, but his clinical condition had further deteriorated and he was reported as being fully comatose. The apnea test was negative (i.e., the patient showed minimal spontaneous respiratory movements).
The patient had been comatose, with mechanical ventilation, for about 2 months and died on (b) (6). An autopsy was not performed.
The investigator did suspect a relationship between this event and the study drug and considered the event to be life-threatening.

<u>Reviewer's Comment:</u> One patient (ID #D2302-0212-00021) appears to represent a fatal case of acute primary VZV infection, and disseminated herpes zoster, with acute hepatic failure, in a 29 year-old female, without prior immunity to VZV (negative IgG serologies) who was exposed to an outbreak of varicella in the nursery (ages 0-3) where she worked as a teacher, around the time she received 5 days of IV methylprednisolone for MS relapse, followed by self administration of oral methylprednisolone tablets (from medication she had at home) for three days. Although the patient had received FTY720 at a daily dose of 1.25 mg from (b) (6) when she was admitted to the hospital, the chronology of the events and the combination of exposure to the VZV outbreak and acute immunosuppression with high dose steroids make this case highly confounded. The relative contribution of FTY720 to this serious event is difficult to quantify although it cannot be excluded, while that of high dose steroids during primo-infection with VZV may still be considered substantial. The prolonged pharmacokinetic elimination $t_{½}$ of fingolimod (6-9 days) means that there would have been persistence of the immunosuppressive effect after cessation of the drug while high dose steroids were initiated.

The mention of paracetamol (a known hepatotoxin) among other concomitant drugs she had taken during the study (fluribiprophen, ibuprophen, clarithromycin, and sertaline hydrochloride), and of the self-medication with oral Medrol, raise additional questions as to the pathogenesis of the suspected drug-induced liver toxicity mentioned in the case summary.

The second patient (ID#D2302-0821-00007) appears to represent a fatal case of herpes simplex encephalitis in a 23 year old male. Seven days appear to have elapsed between

the onset of the presenting symptoms (sudden tonic-clonic seizures) and the initiation of acyclovir therapy, from which time there was no improvement. Such a delay could have contributed to the poor outcome. The age group is not atypical for primary herpes simplex infection and encephalitis, but the outcome depends on prompt diagnosis and initiation of antiviral therapy, as well as supportive measures to treat convulsions and increased intracranial pressure.

Overall, these two cases out of an approximate total of 3000 subjects with MS exposed to fingolimod do not represent a compelling safety signal supportive of a clinically significant increased risk of opportunistic infections associated with fingolimod at the porposed daily dose of 0.5mg; however, one cannot completely exclude the possible role of fingolimod in the occurrence of these events.

Adverse events related to infections and infestations are summarized in the Summary of Clinical Safety (CTD 2.7.4). Among Safety Group A (double-blind randomized, active and placebo controlled studies, 12 month treatment), herpes viral infections were reported in a slightly higher proportion of patients in the fingolimod 1.25 mg group (33/849 or 3.9%) compared to the fingolimod 0.5 mg (26/854 or 3.0%), placebo (11/418 or 2.6%), and interferon (12/431 or 3.7%) groups (CTD 2.7.4 Summary of Clinical Safety Table 2-43; Source ISS Post Text Table 4.1-15). Overall, the incidence of infections caused by specific pathogens that might be considered opportunistic infections (viruses, fungii, mycobacteria or parasites) was too low in the different subcategories to detect meaningful differences between treatment groups.

Among Safety Group B (double-blind, randomized, controlled study, 24-month treatment), the most common high-level microorganism terms used to report infections as adverse events were influenza infections and herpes viral infections, which occurred in a higher proportion of patients in the fingolimod 0.5 mg (37/425 or 8.7%), followed by the placebo group (33/418 or 7.9%), and a slightly lower proportion in the fingolimod 1.25 mg group (25/429 or 5.8%). Most types of infections identified by microorganism were reported in too few patients to detect meaningful differences between treatment groups (CTD 2.7.4 Summary of Clinical Safety Table 2-48; Source ISS Post Text Table 4.2.7).

<u>Reviewer's Comment:</u> Other opportunistic infections, of the type considered to be AIDS-defining in HIV-infected patients with low peripheral blood CD4+ lymphocyte counts, including, pneumocystis carinii peneumonis, toxoplasmosis, mycobacterium avium intracellulare, tuberculosis, progressive multifocal leukoencephalopathy, cryptococcal meningitis, or aspergillosis were not observed. One case presenting with a left-lower lung lobe mass, described on pathologic examination as a necrotizing granulomatous lesion was observed. Although the diagnosis of tuberculosis was considered there was no bacteriologic confirmation.

In addition, the Applicant did perform some exploratory analyses of the relationship between infection and lymphocyte counts (lymphocyte nadir counts in 12 months or 3 months before infection) but these analyses were not conclusive, and were hindered by the small number of events in the first place. This is consistent with the interpretation of peripheral blood lymphocyte counts and subsets in patients treated with fingolimod which represent sequestration or redistribution and not depletion as seen in advanced HIV infection and AIDS.

Opportunistic infections in the fingolimod renal transplantation program

Approximately 1000 subjects were exposed to fingolimod in the renal transplantation development program. Clinical data on the evaluation of fingolimod in renal transplantation was submitted to the NDA in October 2009 (SN002), and included a Summary of Clinical Safety (SCS) in this population. In the 12-month, phase 3 clinical trials in renal transplantation, fingolomod was administered at daily oral doses of 2.5 mg and 5mg, which are substantially higher than the dose proposed for approval in MS of 0.5 mg per day. In addition, fingolimod was used in combination with cyclosporine and corticosteroids in the renal transplantation studies. Thus, the overall level of immunosuppression in these studies should be considered significantly greater than that achieved in the MS studies.

The key safety population in the renal transplantation program included 461patients treated with fingolimod at 5 mg per day in combination with reduced dose cyclosporine and corticosteroids, 456 treated with fingolimod at 2.5 mg per day in combination with full dose cyclosporine and corticosteroids and a control group consisting of 461 patients treated with mycophenolate mofetil (MMF) in combination with full dose cyclosporine and corticosteroids. Infections and infestations reported as adverse events were common in this population and were observed in about two thirds of the subjects as shown in the Applicant's Table 4-32, reproduced below. Among opportunistic infections of particular clinical interest, oral candidiasis, herpes simplex and herpes zoster occurred with similar incidences in each treatment group. Cytomegalovirus infections, reported as adverse events were more common in the MMF control group.

Table 4-32 Number (percent) of patients with infections occurring in 3 percent or more patients in any treatment group – Key Safety Population

	FTY720 5 mg (N=461) n (%)	FTY720 2.5 mg (N=456) n (%)	MMF (N=461) n (%)
Infections and infestations	281 (61.0)	295 (64.7)	311 (67.5)
Preferred term			
Urinary tract infection	131 (28.4)	136 (29.8)	124 (26.9)
Cytomegalovirus infection	18 (3.9)	22 (4.8)	59 (12.8)
Nasopharyngitis	49 (10.6)	52 (11.4)	56 (12.1)
Upper respiratory tract infection	20 (4.3)	37 (8.1)	33 (7.2)
Herpes simplex	19 (4.1)	29 (6.4)	26 (5.6)
Oral candidiasis	18 (3.9)	14 (3.1)	18 (3.9)
Herpes zoster	15 (3.3)	18 (3.9)	16 (3.5)
Wound infection	5 (1.1)	5 (1.1)	15 (3.3)
Gastroenteritis	9 (2.0)	19 (4.2)	14 (3.0)
Pneumonia	21 (4.6)	16 (3.5)	14 (3.0)
Rhinitis	8 (1.7)	6 (1.3)	14 (3.0)
Sinusitis	9 (2.0)	12 (2.6)	14 (3.0)
Bronchitis	16 (3.5)	16 (3.5)	11 (2.4)
Tinea versicolour	7 (1.5)	15 (3.3)	8 (1.7)

AEs in the Infections and infestations SOC are summarized.
Source: Applicant's Post Text Table 4.2-2.

Table A below summarizes the number and percent of patients with serious opportunistic infections (viral, fungal and other). While the overall incidence of serious infections was higher for the MMF group compared to the fingolimod groups, in general, the incidence of serious opportunistic infections caused by specific pathogens was too low in the different subcategories to detect meaningful differences between treatment groups. No cases of progressive multifocal leukoencephalopathy (PML) were reported.

Table A - Number (percent) of renal transplant patients with serious opportunistic infections – Key Safety Population

Organism Type Micro-organism	FTY720 5 mg (N=461) n (%)	FTY720 2.5 mg (N=456) n (%)	MMF (N=461) n (%)
Viral	14 (3.0)	15 (3.3)	49 (10.6)
Adenovirus	0	0	1 (0.2)
BK virus	0	1 (0.2)	0 2 (0.4)
Cytomegalovirus	12 (2.6)	10 (2.2)	39 (8.5)
Human herpes simplex, NOS	0	1 (0.2)	2 (0.4)
Varicella zoster virus	1 (0.2)	2 (0.4)	3 (0.7)
Polyomavirus, NOS	0	0	2 (0.4)
Respiratory Syncytial Virus	0	0	1 (0.2)
Virus NOS	1 (0.2)	1(0.2)	1 (0.2)
Fungal	7 (1.5)	2 (0.4)	3 (0.7)
Aspergillus, NOS	0	1 (0.2)	0
Candida albicans	2 (0.4)	0	2 (0.4)
Candida, NOS	5 (1.1)	1 (0.2)	2 (0.4)
Other	21 (4.6)	9 (2.0)	16 (3.5)
No living organism identified	14 (3.0)	8 (1.8)	14 (3.0)
Pneumocystis carinii	3 (0.7)	0	1 (0.2)
Trypanozoma cruzi	0	0	1 (0.2)
Unknown living organism	4 (0.9)	1 (0.2)	0

Source: Applicant's Post Text Table 8.5-2

Reviewer's Comment: Compared to the experience in clinical trials of fingolimod in MS patients, opportunistic infections were somewhat more commonly observed in the renal transplantation program, again where fingolimod was used at higher doses and in combination with other immunosuppressants. The higher incidence of serious viral infections in the MMF group was driven by an increased number of cytomegalovirus infections reported as serious infections.

Example of guidelines to monitor, diagnose, document and report infections in solid organ transplantation

Recommendations for screening, monitoring, and reporting of infectious complications in immunosuppression trials in recipients of organ transplantation have been arrived at and published by the American Society of Transplantation[1]. These are based on clinical experience in solid organ transplantation and may not necessarily be extrapolated to MS patients. In particular, the level of immunosuppression, and consequent level of risk, as well as the incidence of opportunistic infections is higher in solid organ transplantation than in MS patients. This raises questions about the relative yield of these approaches and the positive predictive value in MS of monitoring schema, intended to be used in the solid organ transplant population, if they were to be applied to MS patients.

[1] Humar A, Michaels M; AST ID Working Group on Infectious Disease Monitoring. American Society of Transplantation recommendations for screening, monitoring and reporting of infectious complications in immunosuppression trials in recipients of organ transplantation. *Am J Transplant.* 2006 Feb;6(2):262-74.

Supplement 4 of Volume 9 of the American Journal of Transplantation contains the 2nd edition of The American Society of Transplantation Infectious Disease Guidelines. The introduction to the guidelines provides a brief overview of the general principles on the risk of infection after transplantation, including a discussion of the epidemiologic exposures (donor- and recipient-derived infections, and community or nosocomial exposures), and the concept of net state of immunosuppression, which comprises all of the factors that contribute to risk for infection[2]. The introduction also mentions the role of prevention of infection and how antimicrobial prophylaxis has altered the incidence and severity of posttransplant infections. Three general preventive strategies are used, including vaccination, universal prophylaxis (i.e. surgical prophylaxis) and preemptive or presymptomatic therapy. Aside vaccination, these strategies may not be generalized to MS patients. The timeline of post transplant infections which reflects the relationship between the recipient's epidemiologic exposures and immunosuppressive strategy employed may not be generalized to MS patients.

> *Reviewer's Comment: Of the general preventive strategies used to minimize the risk of serious infections in solid organ transplantation, vaccination prior to initiation of long-term immunosuppressant therapy should be recommended. Approved immunosuppressants for prevention of rejection in solid organ transplantation contain class labeling in the PRECAUTIONS section, to the effect that immunosuppressants may affect vaccination, and therefore, vaccination may be less effective during treatment with such immunosuppressants. The labeling further recommends that the use of live vaccines should be avoided; live vaccines may include, but are not limited to measles, mumps, rubella, oral polio, BCG, yellow fever, and Ty21a typhoid*[3].

The 2nd edition of The American Society of Transplantation Infectious Disease Guidelines contains a section on varicella zoster virus (VZV) in solid organ transplantation with recommendations and suggestions that may have some relevance to MS treated with fingolimod [4]. Over 90% of adults are seropositive for VZV. Varicella is rare in adult solid organ transplantation recipients, but can be devastating, with visceral involvement, severe skin disease, and disseminated intravascular coagulation. Thus, pretransplant vaccination is suggested, such that potential transplant patients, who are susceptible to VZV, should be given varicella vaccination provided no contraindications are present. With respect to posttransplant vaccination, live-virus vaccines are generally not recommended in immunocompromised hosts. Thus, available varicella vaccines are currently not routinely recommended posttrasplant.

> *Reviewer's Comment: Similar recommendations should be considered for MS patients who are susceptible to VZV, prior to initiation of fingolimod, provided no contraindications are present, given both that live vaccines are generally not recommended in immunocompromised hosts and that vaccination may be less effective during treatment with immunosuppressants. Specifics as to the type of vaccine and timing of their use with respect to initiation or cessation of fingolimod, are beyond the scope of this consultation. When considering vaccination after cessation of fingolimod,*

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[2] Fishman JA and the AST Infectious Diseases Community of Practice. Introduction: Infection in Solid Organ Transplant Recipients. *Am J Transplant* 2009; 9 (Suppl 4): S3–S6

[3] CDC: Recommendations of the Advisory Committee on Immunization Practices: Use of vaccines and immune globulins in persons with altered immunocompetence. MMWR 1993;42(RR-4):1-18.

[4] Pergama SA, Limaye AP and the AST Infectious Diseases Community of Practice, Varicella Zoster Virus (VZV) in Solid Organ Transplant Recipients *Am J Transplant* 2009; 9 (Suppl 4): S108–S115

the prolonged pharmacokinetic and pharmacodynamic half-life of this immunosuppressant should be taken into account.

With respect to secondary prophylaxis, or postexposure prophylaxis, seronegative transplant recipients are at risk for developing varicella after primary exposure and should, after a significant exposure, receive postexposure prophylaxis. Options for postexposure prophylaxis include passive immunoprophylaxis and/or antiviral therapy. A temporary reduction of immunosuppression may also be suggested.

Reviewer's Comment: A discussion of the specifics of what constitutes a significant exposure is beyond the scope of this consult; however similar recommendations should be considered in MS patients treated with fingolimod, although an immediate temporary reduction of immunosuppression may be difficult to achieve with cessation of fingolimod, due to the long half-life of the drug.

In addition, there remain infection control issues, including but not limited to the potential need for minimization and management of potential household exposure and risks, which are beyond the scope of this consultation. Precautions, generally recommended in populations considered to be at increased risk for infection due to underlying conditions, age or chronic use of immunosuppressants should also be considered in MS patients treated with fingolimod.

Finally, public health authorities recommend treatment of latent tuberculosis in persons who are actively immunosuppressed. Such recommendations should also be considered in MS patients who are treated with fingolimod.

Example of guidelines to monitor, diagnose, document and report opportunistic infections in AIDS/HIV infection

Guidelines to for prevention and treatment of opportunistic infections among adults and adolescents with HIV have been developed by the CDC, NIH and HIV Medicine Association of the Infectious Diseases Society of America[5], and are mentioned here to provide an example of what has been developed for a particular population, whose degree of immunosuppresion may be reflected by decreased peripheral blood lymphocyte counts, specifically the CD4+ subset counts. These guidelines are based on clinical experience in HIV-infected adults and adolescents and may not necessarily be extrapolated to MS patients. In particular, the level of immunosuppression, and consequent level of risk, as well as the incidence of opportunistic infections may be higher in HIV-infected patients. In addition, recommendations and assumptions of risk based on peripheral blood lymphocyte counts in HIV-infected patients may not be generalized to MS patients receiving FTY720, since the mechanism behind decreased lymphocyte counts, especially CD4+ lymphocyte counts, have different significances (redistribution versus depletion). This raises questions about the relative yield of these approaches and the positive predictive value in MS of monitoring schema intended to be used in the HIV-infected population.

[5] Kaplan JE, Benson C, Holmes KH, Brooks JT, Pau A, Masur H; Centers for Disease Control and Prevention (CDC); National Institutes of Health; HIV Medicine Association of the Infectious Diseases Society of America. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR Recomm Rep. 2009 Apr 10;58(RR-4):1-207

Conclusions and Recommendations:

The two cases of fatal viral infections out of an approximate total of 3000 subjects with MS exposed to fingolimod do not represent a compelling safety signal supportive of a clinically significant increased risk of serious opportunistic infections; however, one can not completely exclude a possible role of fingolimod in the occurrence of these events.

The applicant's assessment of opportunistic infections in the clinical summary of safety in MS patients and additional exploratory analyses of relationship between lymphocyte counts and infection appear adequate, and thus no further analyses are deemed necessary.

Among renal transplantation recipients, treated with doses 5 or 10 times the proposed recommended dose for MS in this NDA, no increased risk of serious opportunistic infections was detected in the groups treated with fingolimod compared to the control group treated with MMF.

The risk of opportunistic infections in MS patients treated with fingolimod is not expected to be as great as that in solid organ transplantation patients or HIV-infected patients. Therefore, it is difficult to recommend that guidelines for monitoring, early treatment and prevention of opportunistic infections developed in solid organ transplant recipients or HIV-infected patients, should be systematically applied for MS patients treated with fingolimod. However, vaccination prior to initiation of long-term fingolimod therapy should be considered, as well as wording to the effect that immunosuppressants may affect vaccination, and therefore, vaccination may be less effective during treatment with fingolimod. (Note: this is class labeling for immunosuppressants in solid organ transplantation.)

Class labeling for immunosuppressants for the prevention of rejection in solid organ transplantation recommends that the use of live vaccines should be avoided; live vaccines may include, but are not limited to measles, mumps, rubella, oral polio, BCG, yellow fever, and Ty21a typhoid [6]. A similar recommendation should be considered for fingolimod.

Peripheral blood lymphocyte counts and subsets cannot be used to reliably gauge the net state of immunsuppression in MS patients, treated with the proposed recommended dose of fingolimod, as these counts are used in HIV-infection. While peripheral blood lymphocyte counts may serve as a potential pharmacodynamic marker of fingolimod, to the extent that decreased lymphocyte counts may signify the presence of active drug on board, these counts appear to reflect redistribution and not lymphocyte depletion, and should not be interpreted as a reflection of infectious risk in the way they may be interpreted in HIV-infection.

Due to fingolimod's effect on lymphocyte circulation and distribution, fingolimod has the potential to modify the signs and symptoms of infection. Thus, one should maintain a higher degree of suspicion for infection and atypical presentations in patients treated with fingolimod, as one would with other immunosuppressants or modulators of inflammation.

The question as whether to recommend cessation of fingolimod administration in the event of a new infection and for what type of infections, remains unresolved; however, the prolonged pharmacodynamic and pharmacokinetic half-life of fingolimod (6-9 days) implies that the immunosuppressive effect may persist for as much as 2 months after cessation of the drug.

[6] CDC: Recommendations of the Advisory Committee on Immunization Practices: Use of vaccines and immune globulins in persons with altered immunocompetence. MMWR 1993;42(RR-4):1-18.

Finally, coadministration of immunosuppressants with fingolimod may result in additive immune system effects, and increased risk for serious infection which may persist after cessation of fingolimod, due to its prolonged pharmacodynamic and pharmacokinetic half-life (6-9 days).

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22527	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	FINGOLIMOD HCL ORAL CAPSULES

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARC W CAVAILLE COLL
04/21/2010

RENATA ALBRECHT
04/21/2010

DIVISION OF PULMONARY, ALLERGY, and RHEUMATOLOGY PRODUCTS
MEDICAL OFFICER CONSULTATION

Date:	April 8, 2010
To:	Eric Bastings, M.D., Deputy Director, Division of Neurology Products (DNP)
From:	Brian Oscar Porter, M.D., Ph.D., M.P.H., Medical Reviewer
Through:	Susan Limb, M.D., Medical Team Leader
Through:	Badrul Chowdhury, M.D., Ph.D., Division Director
Subject:	Pulmonary Toxicity Review for Fingolimod (Gilenia®)

General Information

NDA/IND#:	NDA 22-527
Applicant:	Novartis
Drug Product:	Fingolimod (Gilenia®)
Request From:	Eric Bastings, M.D., Deputy Director, DNP
Date of Request:	January 28, 2010
Date Received:	February 1, 2010
Date Due:	April 15, 2010
Materials Reviewed:	Sections of NDA 22-527 (received 12/22/09) related to pulmonary toxicity of drug product, including eCTD Module 1, including proposed labeling and REMS; eCTD Module 2, including Summary of Clinical Safety; eCTD Module 5, including Integrated Safety Summary

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Executive Summary

Fingolimod (Gilenia®) is a sphingosine-1-phosphate (S1P) receptor modulator proposed by Novartis for the chronic treatment of relapsing multiple sclerosis (MS), taken orally at 0.5 mg once daily. Fingolimod causes downregulation of the S1P receptor, which is involved in lymphocyte trafficking from nodal tissue to the peripheral circulation. Thus, fingolimod acts as an immunosuppressant and decreases cell-mediated demyelination in the central nervous system. DPARP provided three prior consultations to the Division of Neurology Products (DNP) during the fingolimod development program, citing deficiencies in the Phase II pulmonary function testing (PFT) data, as well as providing extensive input on pulmonary safety screening in Phase III trials. DPARP has now been asked to review and comment on the safety data related to pulmonary toxicity submitted to NDA 22-527, which is currently under review by DNP.

The safety database consisted of respiratory tract-associated adverse event (AE) data, PFT, and high-resolution CT (HRCT) scans drawn from one Phase II (n = 281) and three Phase III (n = 1089-1292) randomized controlled trials in which relapsing remitting MS patients (predominantly female and Caucasian) were treated for 6 to 24 months with 0.5 mg or 1.25 mg fingolimod versus either placebo or active control (interferon beta-1a). AE and PFT data were

analyzed as pooled safety populations with 12-month, 24-month, or 1-5 year active treatment periods, while one ongoing Phase III trial was analyzed separately at an interim stage. Across trials, the incidence of overall respiratory tract-associated AEs, specifically cough and dyspnea, was higher in fingolimod-recipients versus placebo, although generally with less than a 2% difference in rate. Respiratory tract infections (primarily bronchitis) were also higher in both fingolimod dose groups compared to placebo, which may reflect the immunosuppressive activity of fingolimod. Respiratory tract-associated serious AEs (SAEs) were rare, although more common in fingolimod-treated subjects, with the majority involving infectious causes (11 of 14 cases), while 3 non-infectious SAEs were reported as either dyspnea and/or pleurisy.

Across all trials, PFT measures (changes in percent predicted FEV1, FVC, and DLCO) consistently decreased from baseline to a greater degree in fingolimod-treated subjects versus placebo-control and active-control (interferon beta-1a) subjects in a dose-dependent fashion. In addition, FEV1 decreases generally worsened over time, reflecting a cumulative decline in pulmonary function while on fingolimod treatment. However, it is worth noting that a progressive decline was also observed in the placebo and active-control arms in some of the trials, so that the differences among treatment groups narrowed over time. The reason for the FEV1 decline observed in the placebo arm population is unclear. The changes in percent predicted PFT parameters correlated with changes in absolute values, as the 0.5 mg dose group demonstrated declines in absolute FEV1 of $\geq$100 mL as early as 6 months after starting study drug, which is a greater annual decline in pulmonary function than is typically seen in healthy patients, patients with COPD, or MS patients in general. A review of case narratives revealed that these PFT decreases were not always associated with clinical symptoms, which may have been a function of the high level of baseline pulmonary function in the Phase III trial population, as FEV1 and FVC were consistently greater than 100% of predicted values.

With regard to HRCT scan data, although pooled analyses were not performed, across all 3 trials a greater proportion of patients treated with fingolimod had abnormal HRCT scans at end of treatment, as compared to placebo-recipients. Moreover, a greater percentage of these abnormal scans were read as having new or worsened findings, as compared to baseline. However, the incidence of abnormal findings did not appear to be dose-dependent. Further, from a qualitative perspective, no obvious patterns emerged correlating PFT changes with HRCT scan abnormalities, either at baseline or with those considered new or worsened at follow-up. The HRCT scans were read by local radiologists; no central adjudication of scans was performed, which limits the interpretation of the results.

Based on these findings, DPARP recommends that DNP consider including information about the fingolimod-associated decline in pulmonary lung function and the higher incidence of new or worsened HRCT abnormalities in the fingolimod product label. At the current time, there are insufficient data to support a specific PFT monitoring schedule or to recommend routine HRCT screening of fingolimod recipients. However, providing information on the observed fingolimod-associated PFT and HRCT changes will facilitate the development of individualized monitoring plans by healthcare providers for MS patients on fingolimod. In turn, DPARP recommends that DNP consider inclusion of similar information about pulmonary toxicities in the REMS. Finally, DPARP recommends further study of pulmonary safety to determine the stability and reversibility of pulmonary function deficits with long-term use of fingolimod.

Table of Contents

1. Background Information

1.1 Rationale

Fingolimod is a sphingosine-1-phosphate receptor modulator, which causes rapid downregulation of this receptor on the surface of lymphocytes upon binding. As the sphingosine-1-phosphate receptor is involved in peripheral lymphocyte trafficking from nodal lymphoid tissue to the peripheral blood, fingolimod treatment results in rapid peripheral lymphocytopenia and functional immunosuppression, due to tissue-based sequestration of lymphocytes. Originally developed as an immunosuppressant agent to prevent rejection of renal organ transplants (an indication that is no longer being pursued by the Applicant), fingolimod is being developed for the treatment of multiple sclerosis (MS). T cell-mediated destruction of the outer myelin sheaths of the central nervous system (CNS) is the hallmark pathogenic lesion of this progressive neurological disorder. As fingolimod prevents T lymphocyte trafficking to the blood, these cells cannot enter the CNS via the circulation. As a consequence, the cytopathic process of demyelination would presumably be inhibited, potentially altering the progression of the disease and reducing the propensity for acute attacks in MS.

1.2 Proposed Indication

Fingolimod is proposed for use as a disease-modifying therapy for the treatment of patients with relapsing forms of MS to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.

1.3 Proposed Dosing

The proposed dose of fingolimod is 0.5 mg taken once daily as a single oral capsule, either with or without food.

1.4 Summary of Preclinical Pulmonary Toxicity Data

Nonclinical studies identified the lung as the most sensitive target organ of fingolimod toxicity, as single and multiple-dose studies of intravenous and oral formulations in mice, rats, dogs, and monkeys revealed increased lung weights, smooth muscle hypertrophy/hyperplasia at the bronchoalveolar junction, alveolar macrophage infiltration and inflammatory lesions, development of pneumonia, and subpleural fibrosis.

1.5 Summary of Prior DPARP Consults

DPARP has previously completed 4 prior consults (dated August 29, 2005; November 22, 2005; February 28, 2006; and July 31, 2006) for DNP regarding the assessment of pulmonary toxicity and recommendations for further evaluation of lung-associated adverse effects in Phase III clinical trials for fingolimod under IND #70,139 (FTY720; Novartis).

DPARP consult dated August 25, 2005

Single-dose trials in humans up to 40 mg revealed dose-dependent increases in airway resistance. Moreover, a placebo-controlled Phase II trial (D2201) in patients with relapsing MS demonstrated dose-dependent increases in respiratory complaints, including dyspnea (1.1%, 4.3%, and 12.8% in the placebo, 1.25 mg, and 5.0 mg dose groups, respectively). Pulmonary function tests (PFTs) done over the 6-month study period revealed similar decrements in FEV1 % PRED (decreases of 1.75%, 2.82%, and 8.76%, respectively), FVC (4.35% increase in

placebo and a 0.81% decrease and 3.0% decrease in the 1.25 mg and 5.0 mg groups, respectively), and DLCO (decreases of 4.5%, 12.75%, and 10.91%, respectively).

DPARP noted that decreases of this magnitude in FEV1% PRED were both statistically and clinically relevant, being greater in magnitude than declines associated with the natural history of other pulmonary conditions, such as COPD. The potential for fingolimod to affect the entire airway was reflected in dose-dependent worsening of both FVC and DLCO, as well, although it was noted that DLCO measurements tend to display greater variability than FEV1. As several deficiencies were noted with the quality of the PFT dataset provided in this Phase II trial, DPARP recommended that future Phase III trials should follow a systematic approach to pulmonary function testing, including thorough historical and physical baseline assessments and the reporting of changes in PFT outcomes as both percentage and absolute change. DPARP recommended excluding patients with moderate to severe pulmonary function impairment at baseline (i.e., pre-treatment FEV1% PRED <80%), given that the decreased level of pulmonary reserve in these patients could theoretically potentiate fingolimod-associated pulmonary toxicity. Given the effort-dependent nature of pulmonary function testing and the potential for baseline respiratory muscle weakness due to the primary disease process, DPARP further recommended assessments of respiratory muscle strength in trials of MS patients. Finally, it was stressed that both follow-up guidelines and prospective study withdrawal criteria should be developed for subjects with declining pulmonary function, including an increased frequency of PFTs and more sensitive radiographic assessment such as high-resolution computer tomography (HRCT) of the chest.

DPARP consult dated November 22, 2005
IND #70,139 was placed on full clinical hold (Clinical Hold Letter, dated June 29, 2005) due to multiple toxicities (i.e., ophthalmologic, pulmonary, pancreatic). The Applicant submitted a Complete Response to the clinical hold, which included a more detailed report of pulmonary findings from the D2201 Phase II trial in MS patients, a proposed Phase III protocol in MS that included pulmonary monitoring, and a summary of PFTs data from a fingolimod trial in renal transplant patients (FTY720A 0121). DPARP provided a second consult dated November 22, 2005, regarding the results of Study D2201. A total of 250 of 255 subjects completed not only the initial randomized 6-month treatment phase (placebo, 1.25 mg, or 5.0 mg), but also a 6-month follow-up period in which active treatments were maintained and placebo-recipients were randomized into one of the two fingolimod treatment dose levels. Of these patients, only 211 had PFT data and 78 lacked a baseline assessment. Seven subjects were noted to have baseline FEV1 values reported as larger than FVC values, indicating one or both of the values was invalid. The Applicant also provided revised DLCO data, although details as to these revisions were not provided. Thus, only 100 subjects data available for longitudinal assessment over the first 6 months of treatment, with 84 of these having follow-up PFTs at 12 months, raising concerns for the representative nature of these data.

Based on the information provided, dose-related, clinically significant decrements in FEV1% PRED, FVC, and DLCO were still noted across the first 6 months of the study. Likewise, a higher proportion of MedDRA respiratory system organ class (SOC) adverse events was confirmed in the 5.0 mg (8.8%) and 1.25 mg (5.3%) fingolimod groups versus 5.3% in placebo,

with 24 specific instances of dyspnea in the 5.0 mg fingolimod group, 6 in the 1.25 mg group, and 4 in placebo.

The PFT data reported for Study FTY720A 0121 were also incomplete. In this trial of 84 subjects randomized to either 5.0 mg or 2.5 mg fingolimod (versus active control with mycophenolate mofetil) along with concurrent immunosuppressive therapy (corticosteroids and either high or low dose cyclosporine), only two-thirds of subjects had baseline PFTs. Of these, only 40-76% of subjects in the various fingolimod arms had follow-up testing at 1 year and even fewer (34-53%) had follow-up DLCO testing. Although absolute changes were not as great as in MS patients, a mean decrease in FEV1 of 200 ml was seen in the 5.0 mg fingolimod group in this trial, and dose-dependent decreases in FEV1% PRED were again evident, with the greatest decrements observed in patients with relevant pulmonary histories and impaired pulmonary function at baseline. Although this study was not placebo-controlled, only the fingolimod treatment groups reported adverse events coded as "respiratory failure," "acute respiratory failure," or "acute respiratory distress syndrome," with scattered references to interstitial fibrosis. Finally, HRCT scans were done in a limited number of patients in this trial. Of the 22 subjects with at least 2 scans, 3 in the 5.0 mg fingolimod groups were read as abnormal, with either nodular alveolar opacities, cavitary lesions, or mild bronchiectasis and pulmonary fibrosis. Although the receipt of concurrent immunosuppressive therapy complicated generalization of the findings in renal transplant patients to those in MS patients, based on the findings of these studies, DPARP made the following recommendations for the proposed protocol for Study D2301, a pivotal Phase III trial in MS patients: 1) exclusion of patients with underlying pulmonary disease, 2) standardized PFT procedures reported as both percent predicted and absolute values, 3) independent readings of HRCT scans, 4) inclusion of respiratory muscle strength testing with PFTs, 5) increased frequency of PFTs and HRCT scans in subjects with a demonstrated decline in pulmonary function until decrements resolve or stabilize, with potential discontinuation of study drug in symptomatic patients or those with an unexplained decline over the first 6 months of treatment, and 6) integration of periodic echocardiography to assess cardiac function and pulmonary artery pressure.

DPARP consult dated February 28, 2006

The Applicant subsequently submitted a second response to the Clinical Hold on IND #70,139, which DPARP reviewed in a third consult to DNP dated February 28, 2006. This submission included 2 case descriptions of subjects from the Phase II trial D2201, who were reported as having developed restrictive lung disease: 1) an asymptomatic 36 year-old woman receiving 1.25 mg fingolimod daily whose FEV1 decreased 330 mL and 1680 mL after 6 and 12 months of treatment, with FVC decreases of 520 mL and 1950 mL, respectively (at 18 months, FEV1 remained decreased by 1440 mL from baseline and FVC by 1660 mL); 2) a 19 year-old woman receiving 5.0 mg fingolimod daily whose FEV1 and FVC decreased 450 mL and 620 mL, respectively, after 12 months of treatment (pulmonary function normalized after 5 months off treatment). In addition, a revised version of the protocol for Study D2301 (Phase III trial of relapsing MS patients randomized to either 0.5 or 1.25 mg of fingolimod or placebo treatment for 2 years) was submitted, in response to our prior recommendations. While the design and safety findings of Study D2301 are discussed below, key changes to the protocol included the following: 1) 3 month post-trial PFT follow-up for all subjects, 2) "…longer follow-up for patients who discontinued due to pulmonary issues to evaluate reversibility of abnormalities," 3)

inclusion of respiratory muscle strength testing and detailed baseline pulmonary history, 4) exclusion of subjects with FEV1 or FVC <70% PRED and DLCO <60% PRED, 5) study withdrawal triggered by a fall in FEV1, FVC, or DLCO to <80% of baseline at 3 months or <60% of baseline at any visit, 6) serial HRCT scans to be performed on a subset of 150 subjects (50 per treatment arm) and read at a central facility, and 7) serial echocardiograms to be performed on a subset of 90 subjects (30 per treatment arm).

In response to these modifications, DPARP recommended that the Applicant develop a more rapid follow-up PFT schedule (per ATS/ERS guidelines) in response to decreases in pulmonary function (regardless of accompanying symptomatology), driven in real-time by the site physician, rather than the Applicant. In addition, although conducting HRCT scans on a subset of patients was deemed acceptable, the proposed sample size of 150 subjects was felt to be too small for meaningful analysis. Moreover, the need to perform both baseline and follow-up HRCT scans on all subjects was noted, as well as additional measures to follow-up subjects withdrawn prematurely from the study, such as assessment by a pulmonologist during follow-up.

DPARP consult dated July 31, 2006
The Clinical Hold on IND #70,139 was removed on May 19, 2006, following the submission of a revised protocol for the Phase III trial D2301, which included chest HRCT scans on all subjects at enrollment and end-of-study, as well as follow-up scans on subjects with a prospectively defined decline in pulmonary function. After this trial was initiated, the Applicant submitted a protocol amendment to reduce HRCT scanning to the first 360 subjects enrolled in the study (120 per treatment arm) or just over one-third of the proposed sample size of 960 subjects. However, the management of subjects noted to have declines in pulmonary function, as well as follow-up by the Applicant, was not clearly stated. Thus, in a fourth consult, DPARP recommended that while planned end-of-study HRCT scans may be performed in a randomly sampled subset of 360 subjects selected throughout the duration of the enrollment period (rather than the first 360 enrolled patients), baseline HRCT scans should still be performed on all subjects, to allow for a comparison to follow-up HRCT scans on any subject who experiences a deterioration in pulmonary function but is not within the randomly selected subset of 360 subjects. Follow-up of such patients should also be established prospectively by the Applicant, rather than left to the discretion of the subject's private clinician, although the work-up and outcome of assessments done by private clinicians or specialists should be included in the respective case report form for inclusion in the safety analysis.

2. Overview of pulmonary safety assessments in the fingolimod clinical program

Table 1 summarizes the four key trials in the Phase II and III development program in MS patients from which the fingolimod safety database was obtained: D2201, D2301, D2302, and D2309. In addition, a Phase II trial (D2102) in subjects with moderate asthma but without MS is also described, given its relevance to the potential pulmonary toxicity of fingolimod in a subgroup of patients with underlying pulmonary disease. Results of this trial are discussed separately from pooled trials in MS patients.

Table 1. Key Fingolimod Safety Trials

Phase	Trial	Design	Population	N	Dose Groups	Treatment Period	Pulmonary Endpoints	Comment
Multiple Sclerosis Patients								
II	D2201	R PC DB PG	89% RRMS 11% SPMS	281 (primary) 250 (extension)	***5.0 mg F oral QD** ***1.25 mg F oral QD** ***Placebo oral QD** (Subjects on placebo randomized to either fingolimod dose during extension; 9 to 18 months into extension, subjects on 5.0 mg switched to 1.25 mg)	6 months (primary) + 54 months (open-label extension)	*AE *PFT	Completed
III	D2301	R PC DB PG	RRMS	1272 (primary + extension)	***1.25 mg F oral QD** ***0.5 mg F oral QD** ***Placebo oral QD** (Subjects on placebo randomized to either fingolimod dose during extension)	24 months (primary) + open-ended blinded extension	*AE *PFT-D *HRCT	Completed
III	D2302	R AC DB DD PG	RRMS	1292 (primary) 1030 (extension)	***1.25 mg F oral QD** ***0.5 mg F oral QD** ***30 mcg interferon beta-1a SC QWeek** (Subjects on interferon randomized to either fingolimod dose during extension)	12 months (primary) + 12 months (blinded extension)	*AE *PFT-D *HRCT	Completed
III	D2309	R PC DB PG	RRMS	1089 (primary)	***1.25 mg F oral QD** ***0.5 mg F oral QD** ***Placebo oral QD** (Subjects on placebo randomized to either fingolimod dose during extension)	24 months (primary) + open-ended blinded extension	*PFT-D *HRCT	Ongoing (data not pooled, in order to maintain blinding)
Asthma Patients without Multiple Sclerosis								
II	D2102	R PC DB PG	Moderate Asthma (Diagnosed >6 months; >1 month on ICS+LABA; FEV1 ≥60% at screening; stable ≥3 mon)	36 (18-65 years; BMI=18-33)	***2.5 mg F oral QD** ***1.25 mg F oral QD** ***0.5 mg F oral QD** ***Placebo oral QD**	10 days	*AE *PFT-D	Completed

R = Randomized; PC = Placebo-controlled; AC = Active-controlled; DB = Double-blind; DD = Double-dummy; PG = Parallel-group; RRMS = Relapsing-remitting multiple sclerosis; SPMS = Secondary progressive multiple sclerosis; F = Fingolimod; QD = Once daily; SC = Subcutaneous injection; QWeek = Once weekly; AE = Adverse events; PFT = Spirometry including FEV1, FVC, FEF_{25-75}; PFT-D = Pulmonary function tests including DLCO; HRCT = High-resolution computed tomography of the chest

In addition to the above-listed trials, pulmonary-associated adverse events and toxicity data from a limited number of renal transplant patients treated with fingolimod were discussed previously in the summary of prior DPARP consults.

2.1 Summary Inclusion/Exclusion Criteria in MS Trials

Participation criteria were similar among all trials in MS patients, who primarily had relapsing-remitting MS, other than a small percentage of subjects in Study D2201, who had secondary progressive MS. Studies D2301 and D2302 enrolled men and women aged 18 to 55 years (up to 60 years in D2201). Women in all trials were confirmed as non-pregnant prior to treatment. Key exclusion criteria included the presence of malignancy (other than basal and squamous cell carcinoma), diabetes mellitus, active systemic infection including AIDS and hepatitis, significant cardiovascular disease, hepatic disease or impairment including alcohol abuse, biliary disease, ALK >1.5X ULN (>2X ULN in D2201), and AST/ALT >2X ULN, significant pulmonary disease or impairment including baseline FEV1 <80% PRED, renal impairment (creatinine >1.7 mg/dL), WBC <3500 cells/mcL, lymphocytes <800 cells/mcL, macular edema (in D2301 and D2302), and seizures (in D2302). Subjects were also excluded for certain medication use during variable periods prior to screening or treatment initiation: corticosteroids or ACTH within 30 days, interferon beta or glatiramer within 3 months, other immunosuppressants within 6 months, cyclophosphamide at any time (within 12 months in D2201), mitoxantrone or cladribine at any time (within 24 months in D2201), immunoglobulins within 6 months (within 3 months in D2201), and monoclonal antibodies within 6 months.

2.2 Definition of Pooled Safety Populations

The overall safety population consisted of all patients who received at least one dose of study drug. Serious adverse events (SAEs) were followed in this group up to 45 days after study drug discontinuation. To account for differences in treatment duration, pulmonary function measures and chest HRCT scans were analyzed in several pooled safety populations.

2.2.1 12-Month Safety Population (A)

This population consists of all patients in double-blind, randomized, placebo- and active-controlled trials with at least 12-month treatment data (trials D2301 and D2302). Chest HRCT scans were reported separately for each of these trials, rather than pooled. Mean study drug exposure (fingolimod versus placebo) was comparable in these three groups (0.5 mg = 339 days; 1.25 mg = 321 days; placebo = 329 days; interferon beta-1a = 340 days). The bulk of this population was female and Caucasian, while age groups were more evenly distributed. The demographic breakdown of this population is shown below, reported as n (%):

Table 2. Demographics: 12-Month Safety Population (A)

Treatment	0.5 mg fingolimod N = 856 n (%)	1.25 mg fingolimod N = 855 n (%)	Placebo N = 418 n (%)	Interferon beta-1a N = 435 n (%)
Female	578 (67.5)	588 (68.8)	298 (71.3)	295 (67.8)
Male	278 (32.5)	267 (31.2)	120 (28.7)	140 (32.2)
≤30 years	237 (27.7)	233 (27.3)	97 (23.2)	113 (26.0)
31-40 years	312 (36.2)	307 (35.9)	165 (39.5)	185 (42.5)
≥41 years	307 (35.9)	315 (36.8)	156 (37.3)	137 (31.5)
Age (mean years)	36.6	36.6	37.2	36.0

Caucasian	810 (94.6)	812 (95.0)	399 (95.5)	408 (93.8)
Black	5 (0.6)	6 (0.7)	2 (0.5)	6 (1.4)
Other	41 (4.8)	37 (4.3)	17 (4.0)	21 (4.8)
Chest disorder*	87 (10.2)	99 (11.6)	39 (9.3)	40 (9.2)
Asthma	28 (3.3)	31 (3.6)	11 (2.6)	10 (2.3)

* History of respiratory, thoracic, or mediastinal disorders
[Source: ISS PT-Table 3.1-1; ISS PT-Table 3.6-1]

2.2.2 24-Month Safety Population (B)

This population includes all patients with 24-month treatment data from Study D2301, a double-blind, randomized, placebo-controlled 24-month trial., which provides the greatest long-term comparison of both doses of fingolimod versus placebo. Mean study drug exposure (fingolimod versus placebo) was more variable in these three groups (0.5 mg = 645 days; 1.25 mg = 581 days; placebo = 615 days), due to proportional differences in early withdrawals. Similar to the 12-month population, the bulk of this population was female and Caucasian. History of respiratory disorders and asthma was similar to the 12-month safety population. The demographic breakdown of this population is shown below, reported as n (%):

Table 3. Demographics: 24-Month Safety Population (B)

Treatment	**0.5 mg fingolimod N = 425 n (%)**	**1.25 mg fingolimod N= 429 n (%)**	**Placebo N = 418 n (%)**
Female	296 (69.6)	295 (68.8)	298 (71.3)
Male	129 (30.4)	134 (31.2)	120 (28.7)
≤30 years	120 (28.2)	108 (25.2)	97 (23.2)
31-40 years	162 (38.1)	147 (34.3)	165 (39.5)
≥41 years	143 (33.6)	174 (40.6)	156 (37.3)
Age (mean years)	36.6	37.4	37.2
Caucasian	406 (95.5)	408 (95.1)	399 (95.5)
Black	1 (0.2)	0	2 (0.5)
Other	18 (4.2)	21 (4.9)	17 (4.0)
Chest disorder*	46 (10.8)	49 (11.4)	39 (9.3)
Asthma	16 (3.8)	9 (2.1)	11 (2.6)

[Source: D2301 PT-Table 14.1-3.1; D2301 PT-Table 14.1-3.4]

2.2.3 Total Fingolimod-Recipient Safety Population (E)

All fingolimod-treated subjects from trials D2301 and D2302 (plus the 12-month extension period), and D2201 (plus the 54 month extension period), up to 45 days following study drug discontinuation. This dataset provides information on the long-term safety of the 1.25 mg and 0.5 mg dose levels. HRCT scans were reported for this population. Mean fingolimod exposure was higher in the 1.25 mg (606 days) versus 0.5 mg (566 days) group, given differences in the

dosing schedules across these studies. The demographic breakdown of this population was similar to the 12- and 24-month populations and is shown below, reported as n (%):

Table 4. Demographics: Total Fingolimod-Recipient Safety Population (E)

Treatment	**0.5 mg fingolimod N = 1021 n (%)**	**1.25 mg fingolimod N= 1157 n (%)**
Female	686 (67.2)	794 (68.6)
Male	335 (32.8)	363 (31.4)
≤30 years	284 (27.8)	309 (26.7)
31-40 years	373 (36.5)	437 (37.8)
≥41 years	364 (35.7)	411 (35.5)
Age (mean years)	36.6	36.6
Caucasian	965 (94.5)	1099 (95.0)
Black	10 (1.0)	8 (0.7)
Other	46 (4.5)	50 (4.4)
Chest disorder*	104 (10.2)	126 (10.9)
Asthma	32 (3.1)	37 (3.2)

* History of respiratory, thoracic, or mediastinal disorders
[Source: ISS PT-Table 3.4-1; ISS PT-Table 3.8-1]

The Applicant also conducted safety analyses on a pooled population consisting of all subjects in Studies D2301, D2302, and D2201 during the core randomized active treatment phases of each trial (i.e., 24, 12, and 6 months, respectively). However, the validity of the PFT methodology used in Study D2201, as well as the pulmonary function data generated, were questioned in prior consultations from DPARP. Thus, the 12-Month and 24-Month Safety Populations are drawn from Phase III trials with more reliable PFT data, while data from Study D2201 are still captured in the Total Fingolimod-Recipient Safety Population, which extends the observation period past the primary randomized treatment phase.

As a subset of this same safety population, all fingolimod-treated subjects from trials D2301, D2302, and the 54-month continuation phase of D2201, who received a cumulative dose of at least 3 months of study drug and had follow-up data beyond 14 days post-drug discontinuation were considered a follow-up cohort. Data from post-trial assessments in this population provided information on the reversibility of treatment-emergent safety events in the 1.25 mg and 0.5 mg dose groups. HRCT scans were not reported for this population. Mean fingolimod exposure was comparable between the 0.5 mg and 1.25 mg dose groups. The demographic breakdown of this population is similar to the Total Recipient Safety Population:

Table 5. Demographics: Total Fingolimod-Recipient Follow-Up Safety Population

Treatment	0.5 mg fingolimod N = 194 n (%)	1.25 mg fingolimod N= 297 n (%)
Female	130 (67.0)	198 (66.7)
Male	64 (33.0)	99 (33.3)
≤30 years	47 (24.2)	80 (26.9)
31-40 years	69 (35.6)	108 (36.4)
≥41 years	78 (40.2)	109 (36.7)
Age (mean years)	37.4	37.3
Caucasian	184 (94.8)	276 (92.9)
Black	1 (0.5)	3 (1.0)
Other	9 (4.6)	18 (6.0)

[Source: ISS PT-Table 3.5-1]

2.2.4 Phase II Study D2102 in Moderate Asthma Patients

This trial randomized a total of 36 patients into three fingolimod dose levels: 0.5 mg, 1.25 mg, and 2.5 mg. Each dose cohort of 12 patients was further randomized in a 1:3 ratio to fingolimod versus placebo control, thus resulting in 9 subjects per cohort receiving active treatment and a total of 9 subjects receiving placebo. The demographic breakdown of this population is shown below, reported as n (%).

Table 6. Demographics: Study D2102 Population with Moderate Asthma

Treatment	0.5 mg fingolimod N = 9 n (%)	1.25 mg fingolimod N = 9 n (%)	2.5 mg fingolimod N = 9 n (%)	Placebo N= 9 n (%)
Female	5 (56)	7 (78)	5 (56)	5 (56)
Male	4 (44)	2 (22)	4 (44)	4 (44)
Age (mean years)	43	38	37	38
Caucasian	8 (89)	6 (67)	9 (100)	8 (89)
Black	0	1 (11)	0	0
Other	1 (11)	2 (22)	0	1 (11)

[Source: D2102 PT-Table 14.1-3.1]

2.2.5 Analysis Subgroups

Safety analysis was also conducted post-hoc on the following subgroup populations in the pooled Safety Populations by the following traits: gender (male versus female), age (≤30 years, 31-40 years, versus ≥41 years), and prior asthma history. Subgroup analysis by race was not

conducted, given the predominance of Caucasian subjects in the Phase III program. Numbers of subjects in racial and ethnic minority groups were too low to allow for meaningful analysis.

2.3 Pulmonary Safety Parameters

The pulmonary safety analysis consisted of three primary assessments: respiratory tract-associated adverse events, pulmonary function tests, and high resolution CT scans of the chest.

2.3.1 Respiratory Tract-related Adverse Events

Adverse events were classified at every trial visit using Medical Dictionary for Regulatory Affairs System Organ Class (MedDRA SOC) version 11.0 categories and preferred terms within the different safety populations, comprising a total of 2833 MS patients. Adverse events (AEs) were categorized at the site investigator's discretion by level of intensity (mild, moderate, or severe) and relatedness to study drug (suspected or not suspected). Serious Adverse Events (SAEs) were pre-defined per standard criteria (death, life-threatening event, persistent disability, congenital defect, unplanned hospitalization, or otherwise medically significant). AE data are available from Studies D2102, D2201, D2301, and D2302, but not D2309 in order to maintain the blinding of this ongoing trial.

2.3.2 Pulmonary Function Tests

PFTs were performed per 2005 ATS/ERS criteria in the Phase III development program in MS patients (Studies D2301 and D2302), as well as the Phase II trial in asthmatic patients (D2102). PFTs including FEV1, FVC, and carbon monoxide diffusing capacity (DLCO) corrected for hemoglobin were performed at the following time points for each core safety trial:

- Study D2201: Screening, Month 6, and every 3 months thereafter
- Study D2301: Screening and Months 1, 3, 6, 12, 18, and 24
- Study D2302: Screening and Months 1, 3, 6, 12, 13, 15, 18, and 24

Changes from baseline in PFT parameters were calculated from all subjects with both baseline and follow-up assessments. Either the mean value or the lowest values were used for patients with multiple post-baseline assessments done within the same visit window. The protocol for Study D2201 did not specify that PFTs were performed per ATS/ERS criteria. Data from this trial (including its extension phase) were not included in the 12-Month, 24-Month, and Total Recipient Safety Populations. PFT data from Study D2102 in asthmatic patients without MS did not include DLCO measurements and are reported separately from the MS trials.

2.3.3 Chest High-Resolution Computed Tomography (HRCT) Scans

Scheduled chest HRCT scans were done at selected trial sites (where medical resources and local regulations permitted) in the Phase III program, as follows:

- Study D2301: Screening and Month 24 (n = 360)
- Study D2302: Screening and Month 12 (n = 478)
- Study D2309: Screening and Month 24 (n = 266)

In addition, unscheduled chest HRCT scans were conducted on subjects who demonstrated a progressive decline in lung function, defined as a 20% decrease in PFT parameters from baseline on two consecutive visits. Results of these scans are reported by individual trial, rather than as a pooled analysis. Interim data are presented from Study D2309, as this trial is ongoing. Chest HRCT scans were not done in Studies D2201 or 2102. HRCT scans were read locally by radiologists, with no centralized adjudication. The method of determining clinical significance is not specified in the protocol, although a review of case narratives indicates that in some instances, clinical significance was determined from a combination of both the radiologist's HRCT interpretation and the site investigator's clinical assessment of the patient.

3. Results

3.1 Pulmonary-related Adverse Events (AEs)

Across trials, the incidence of overall respiratory tract-associated AEs (MedDRA Respiratory SOC) was higher in fingolimod dose groups compared to placebo, although generally with less than a 2% difference in rate. Specifically, cough and dyspnea events were consistently seen at higher rates in fingolimod-recipients versus placebo subjects, although with absolute rate differences of less than 3%. Respiratory tract infections were also higher in both fingolimod dose groups compared to placebo, which may reflect the immunosuppressive activity of fingolimod. These AEs were generally mild or moderate, as severe respiratory tract-associated AEs occurred at ≤0.6% within each treatment group, with no consistent differences observed between fingolimod- and placebo-recipients. Respiratory tract-associated AEs led to study drug discontinuation in less than 1% of subjects, again with no pattern of differences among treatment groups. Serious AEs (SAEs) were similarly rare, although they appeared to be more common in fingolimod-treated subjects, as only 1 respiratory tract-associated SAE occurred in placebo recipients in the 12-month safety population (from Study D2301). The majority of respiratory tract-associated SAEs involved infectious causes (11 of 14 cases), while 3 non-infectious SAEs were reported as either dyspnea and/or pleurisy. Post-hoc subgroup analysis revealed no differences in AE distribution by age or gender. Pre-existent asthma, however, conferred a general trend toward increased AEs in subjects both with and without MS, primarily cough and pleurisy.

3.1.1 Major Safety Populations

The incidence of SAEs and AEs leading to discontinuation of study drug was low in fingolimod-treated groups and, for 0.5 mg, was lower than placebo. The proportion of patients who cited early discontinuation due to an AE from the Respiratory SOC was similar among patients treated with fingolimod and placebo. Across trials, the incidence of overall respiratory tract-associated AEs (MedDRA Respiratory SOC) was higher in fingolimod dose groups compared to placebo, although generally with less than a 2% difference in rate. Of note, both dyspnea and bronchitis were reported more commonly in fingolimod- versus placebo-treated patients, with most dyspnea events occurring within the first year of treatment. The incidence of lower respiratory infections (primarily bronchitis) and respiratory AEs were dose-dependent, with the rate of respiratory AEs in the 0.5 mg group being similar to that of placebo. Of note, pulmonary edema (which was seen as a safety signal in trials of renal transplant patients) was not seen in trials of MS patients. Moreover, chest discomfort (all mild cases, predominantly associated with decreases in FEV1 up to 13% and FEF_{25-75} up to 29%) was seen at rates greater than placebo in a pooled safety analysis

of all Phase 2 clinical pharmacology trials (1.0% versus 2.5%), but this was not seen in Phase 3 trials of MS patients.

The following table summarizes the incidence of respiratory tract-associated AEs, including both respiratory tract infections and preferred terms falling under the MedDRA SOC of Respiratory, Thoracic, and Mediastinal Disorders in key safety populations. Overall MedDRA categories are bolded above their respective preferred term subcategories. For the 12-Month and 24-Month Safety Populations, AEs which occurred at rates greater than placebo and greater than 2% are shown. For the Total Recipient Safety Population, respiratory tract-associated AEs occurring at rates greater than 2% are shown. Data from the 12-Month and 24-Month Safety Populations are not directly comparable in terms of tracking changes in AE rates over time in a single patient population, as 24-month safety data are drawn from only one trial (D2301), whereas 12-month data are pooled from both D2301 and D2302. In turn, the Applicant did not report AE data from D2301 (the only trial with a randomized 24-month fingolimod versus placebo treatment period) for Month 12 in comparison to Month 24, but rather as overall AE incidence for each treatment group from the start of study drug until 45 days after the last dose received. With those caveats, the AE profiles at 12- and 24-months appeared similar and did not suggest time-dependence for the more common AEs.

Table 7. Respiratory Tract-associated Adverse Events (AEs)

Safety Population	**Preferred MedDRA Term**	**0.5 mg fingolimod**	**1.25 mg fingolimod**	**Placebo**	**Interferon beta-1a**
12-Month (A)		**N = 854 n (%)**	**N = 849 n (%)**	**N = 418 n (%)**	**N = 431 n (%)**
	Influenza	64 (7.5)	52 (6.1)	30 (7.2)	32 (7.4)
	Nasopharyngitis	166 (19.4)	175 (20.6)	81 (19.4)	88 (20.4)
	Pharyngitis	31 (3.6)	37 (4.4)	16 (3.8)	13 (3.0)
	Sinusitis	27 (3.2)	34 (4.0)	12 (2.9)	11 (2.6)
	Bronchitis	39 (4.6)	46 (5.4)	11 (2.6)	11 (2.6)
	Total in Resp SOC	**148 (17.3)**	**159 (18.7)**	**70 (16.7)**	**63 (14.6)**
	Cough	53 (6.2)	55 (6.5)	23 (5.5)	16 (3.7)
	Dyspnea	36 (4.2)	39 (4.6)	17 (4.1)	7 (1.6)
24-Month (B)		**N = 425 n (%)**	**N = 429 n (%)**	**N = 418 n (%)**	
	Influenza	55 (12.9)	40 (9.3)	41 (9.8)	
	Pharyngitis	27 (6.4)	25 (5.8)	24 (5.7)	
	Sinusitis	28 (6.6)	27 (6.3)	19 (4.5)	
	Bronchitis	34 (8.0)	39 (9.1)	15 (3.6)	
	Total in Resp SOC	**107 (25.2)**	**103 (24.0)**	**95 (22.7)**	
	Cough	43 (10.1)	37 (8.6)	34 (8.1)	
	Dyspnea	30 (7.1)	23 (5.4)	19 (4.5)	
	Nasal congestion	3 (0.7)	9 (2.1)	2 (0.5)	

Total Recipients (E)		**N = 1021 n (%)**	**N = 1157 n (%)**		
	Upper RTI	456 (44.7)	540 (46.7)		
	Influenza	111 (10.9)	115 (9.9)		
	Total in Resp SOC	**229 (22.4)**	**288 (24.9)**		
	Cough	86 (8.4)	109 (9.4)		
	Dyspnea	47 (4.6)	64 (5.5)		
	Oropharyngeal pain	62 (6.1)	64 (5.5)		

RTI = Respiratory Tract Infection; Total in Resp SOC = Total Patients in System Organ Class: Respiratory, Thoracic, and Mediastinal Disorders
12-Month Safety Population (A): Comprised of D2301 and D2302 data through Month 12
24-Month Safety Population (B): Comprised of D2301 data through Month 24
Total Recipients Safety Population (E): Comprised of D2201, D2301, and D2302 data for all fingolimod recipients
[Source: ISS PT-Table 4.1-1; ISS PT-Table 4.1-5; D2301 PT-Table 14.3.1-1.1; ISS PT-Table 4.5-5]

Severe respiratory tract-associated AEs including infections and respiratory SOC disorders, which occurred at a greater rate than placebo, are summarized in the following table. No severe respiratory tract-associated AEs were reported at 0.5% or greater in the Total Recipient Safety Population.

Table 8. Severe Respiratory Tract-associated Adverse Events

Safety Population	**Preferred MedDRA Term**	**0.5 mg fingolimod**	**1.25 mg fingolimod**	**Placebo**	**Interferon beta-1a**
12-Month (A)		**N = 854 n (%)**	**N = 849 n (%)**	**N = 418 n (%)**	**N = 431 n (%)**
	Lower RTI	0	2 (0.2)	0	0
	Bronchitis	2 (0.2)	0	0	1 (0.2)
	Total in Resp SOC	**3 (0.4)**	**5 (0.6)**	**2 (0.5)**	**1 (0.2)**
	Pleurisy	0	2 (0.2)	0	0
24-Month (B)		**N = 425 n (%)**	**N = 429 n (%)**	**N = 418 n (%)**	
	Upper RTI	2 (0.5)	0	1 (0.2)	

RTI = Respiratory Tract Infection; Total in Resp SOC = Total Patients in System Organ Class: Respiratory, Thoracic, and Mediastinal Disorders
[Source: ISS PT-Table 4.1-6; D2301 CSR PT-Table 14.3.1-1.2; ISS PT-Table 4.5-6]

The following table summarizes the respiratory tract-associated AEs, which lead to study drug discontinuation at a greater rate than placebo. For the Total Recipient Safety Population, all respiratory tract-associated AEs that resulted in study drug discontinuation are shown.

Table 9. Respiratory Tract-associated Adverse Events Leading to Drug Discontinuation

Safety Population	Preferred MedDRA Term	0.5 mg fingolimod	1.25 mg fingolimod	Placebo	Interferon beta-1a
12-Month (A)		**N = 854 n (%)**	**N = 849 n (%)**	**N = 418 n (%)**	**N = 431 n (%)**
	Total in Resp SOC	**2 (0.2)**	**5 (0.6)**	**2 (0.5)**	**0**
Total Recipients (E)		**N = 1021 n (%)**	**N = 1157 n (%)**		
	Total in Resp SOC	**4 (0.4)**	**9 (0.8)**		
	Dyspnea	3 (0.3)	5 (0.4)		

Total in Resp SOC = Total Patients in System Organ Class: Respiratory, Thoracic, and Mediastinal Disorders
[Source: ISS PT-Table 4.1-13; D2301 PT-Table 14.3.1-1.17; ISS PT-Table 4.5-13]

The following table summarizes the respiratory tract-associated SAEs, which occurred at a greater rate than placebo. For Total Recipients (E), all lung-associated SAEs are shown.

Table 10. Respiratory Tract-associated Serious Adverse Events (SAEs)

Safety Population	Preferred MedDRA Term	0.5 mg fingolimod	1.25 mg fingolimod	Placebo	Interferon beta-1a
12-Month (A)		**N = 854 n (%)**	**N = 849 n (%)**	**N = 418 n (%)**	**N = 431 n (%)**
	Pneumonia	0	1 (0.1)	0	0
	Total in Resp SOC	**2 (0.2)**	**5 (0.6)**	**1 (0.2)**	**1 (0.2)**
	Dyspnea	0	2 (0.2)	0	0
	Pleurisy	0	2 (0.2)	0	0
24-Month (B)		**N = 425 n (%)**	**N = 429 n (%)**	**N = 418 n (%)**	
	Pneumonia	1 (0.2)	1 (0.2)	0	
Total Recipients (E)		**N = 1021 n (%)**	**N = 1157 n (%)**		
	Pneumonia	1 (0.1)	2 (0.2)		
	Total in Resp SOC	**4 (0.4)**	**9 (0.8)**		
	Dyspnea	0	3 (0.3)		
	Pleurisy	0	2 (0.2)		
	Asthma	0	1 (0.1)		

Total in Resp SOC = Total Patients in System Organ Class: Respiratory, Thoracic, and Mediastinal Disorders
[Source: ISS PT-Table 4.1-12; D2301 PT-Table 14.3.1-1.16; ISS PT-Table 4.5-12]

The following narratives are provided as case summaries of all respiratory tract-associated SAEs, other than deaths, for each individual trial (given the overlap of the different safety populations) and grouped by treatment arm. SAEs are listed for the 0.5 mg and 1.25 mg fingolimod dose groups (the focus of the Phase III clinical program), placebo-control, and active-control (interferon beta-1a) groups during the primary treatment period. No respiratory tract-associated SAEs in the 0.5 mg, 1.25 mg, or placebo groups were reported from the Phase II trial D2201. However, one case of interest is listed of a patient who was initiated on 5.0 mg and later transitioned to 1.25 mg during the extension phase of this trial, given the initial suspicion of pulmonary malignancy (D2201E1-0004-00004). Based on review of the provided case narratives, episodes of dyspnea with chest pain of either cardiac or non-cardiac origin which are not suspected to be of pulmonary etiology are not included in this list. Thus, totals differ from the summary figures reported in Table 10. In further contrast to Table 10, the cases described here include SAEs that occurred in single patients, SAEs that occurred at lower rates than in placebo, and SAEs that occurred throughout the duration of each study (including the extension phases).

Table 11. Respiratory Tract-associated Serious Adverse Events (SAEs) other than Deaths in Fingolimod- and Placebo-recipients: Summaries

Trial	Treatment Group	Subject ID Description of SAE	Relationship to Study Drug*
D2201	5.0 mg to 1.25 mg Fingolimod	**D2201E1-0004-00004** **Necrotizing granulomatous pneumonitis:** 52 yo Caucasian woman who first developed difficulty breathing on Day 1258 and worsened productive cough on Day 1322 of active treatment. CT scan revealed a 3.3 x 4.6 cm mass, for which biopsy was negative for culture and malignancy. Lobectomy of the left lower lobe ultimately revealed necrotizing granulomatous pneumonitis of unknown etiology.	Suspected, due to immunosuppression
D2301	0.5 mg Fingolimod	**D2301-0304-00030** **Sinusitis:** 32 yo Caucasian man who developed fever, rigors, and right-sided nasal purulence on Day 493, which was eventually diagnosed as right frontal and maxillary sinusitis (*Streptococcus sp.* and *Staphylococcus aureus*), with orbital cellulitis and dental abscess as the likely etiology. Patient responded to antibiotics and tooth extraction.	Suspected, due to immunosuppression
D2301	0.5 mg Fingolimod	**D2301-0752-00014** **Sinusitis:** 28 yo man who developed sinusitis on Day 713, which required hospitalization and improved with antibiotics.	Suspected, due to immunosuppression

D2301	0.5 mg Fingolimod	**D2301-0501-00006** **Upper Respiratory Infection (URI):** 35 yo Caucasian woman who developed cough on Day 400, diagnosed as URI of unknown etiology. Patient responded to budesonide, antibiotics, and fluconazole.	Suspected, due to immunosuppression
D2301	0.5 mg Fingolimod	**D2301-0408-00009** **Pulmonary Edema/Pneumonia:** 21 yo Caucasian woman who developed dyspnea and upper respiratory secretions on Day 8, diagnosed as pulmonary edema and pneumonia (beta-hemolytic *Streptococcus* type C via bronchoscopy) with hypotension. Patient required intubation, vasopressors, and responded to antibiotics.	Suspected, due to immunosuppression
D2301	0.5 mg Fingolimod	**D2301-0652-00013** **Pneumonia/Sepsis:** 49 yo woman who developed dyspnea and fever on Day 566, diagnosed as pneumonia, which responded to amoxicillin. Of note, patient further developed pneumonia and pneumococcal sepsis on Day 622, which responded to penicillin and amoxicillin at the time of report.	Suspected, due to immunosuppression
D2302	0.5 mg Fingolimod	**D2302-0145-00003** **Pneumothorax**: 42 yo Caucasian man with a history of pneumothorax 10 years earlier, who developed spontaneous pneumothorax of moderate intensity on Day 85, which required hospitalization. Patient improved with thoracic drainage.	Possible, as no other risk factors reported for spontaneous pneumothorax
D2301	1.25 mg Fingolimod	**D2301-0459-00005** **Bronchitis:** 26 yo Caucasian woman who developed productive cough with severe lymphopenia, diagnosed as non-specific bronchitis, which resulted in a brief hospitalization.	Suspected, due to immunosuppression
D2301	1.25 mg Fingolimod	**D2301-0501-00003** **Respiratory Tract Infection (RTI):** 50 yo Caucasian woman who developed bilateral rales and bronchiectasis with severe leucopenia/lymphopenia on Day 645, diagnosed as RTI. Patient required hospitalization and responded to antibiotics.	Suspected, due to immunosuppression
D2301	1.25 mg Fingolimod	**D2301-0601-00012** **Pneumonic Infiltration/Pleurisy:** 24 yo Caucasian woman who developed chest pain and dyspnea as part of a relapse of MS on Day 65. Further evaluation revealed pleuritis with mild pneumonic infiltration with basal atelectasis. Patient was hospitalized and responded to antibiotics.	Suspected, due to immunosuppression

D2301	1.25 mg Fingolimod	**D2301-0407-00021** **Aspiration Pneumonia:** 34 yo Caucasian man who developed aspiration pneumonia associated with MS relapse on Day 328 (187 days after the last dose of fingolimod), which required ICU care and subsequently responded to antibiotics. He developed a second, albeit milder, episode of aspiration pneumonia on Day 381.	Unrelated to direct pulmonary toxicity, given that patient's neurological impairment leading to aspiration was a likely consequence of MS exacerbation
D2302	1.25 mg Fingolimod	**D2302-0125-00001** **Dyspnea**: 34 yo Caucasian woman who first developed dyspnea on Day 1, which worsened over the next month to become disabling with a fall in DLCO of 13% from baseline. Patient subsequently hospitalized briefly for dyspnea on Day 139 and stopped study drug. Work-up revealed no clear etiology. Although she developed cardiac ischemia 15 days after stopping study drug, dyspnea resolved completely 62 days after her last dose.	Suspected, given time course
D2302	1.25 mg Fingolimod	**D2302-0521-00001** **Pleurisy/Dyspnea**: 51 yo Caucasian woman who developed shortness of breath and chest pain on Day 116 that was diagnosed as severe pleurisy, which resulted in hospitalization and was treated with narcotic analgesia, resolving after 10 days. On Day 198, FEV1 had declined from 2.44 L at baseline to 1.89 L and further to 1.77 L by Day 442. Study drug was stopped on Day 484 and the patient was treated with fluticasone-salmeterol combination therapy. FEV1 was further decreased to 1.58 L on Day 504.	Suspected, given declining FEV1
D2301	Placebo	**D2301-0307-00031** **Asthma Exacerbation:** 53 yo Caucasian woman who developed dyspnea on Day 493, requiring hospitalization and ultimately diagnosed as an asthma exacerbation confirmed by spirometry. Patient improved with bronchodilators, but subsequently developed worsened obstructive PFTs on Day 537 (attributed to COPD and bronchial asthma), which lead to interruption of study treatment but improved with bronchodilators.	Unrelated to fingolimod, given that this patient received placebo
D2301	Placebo	**D2301-0552-00006** **COPD/Chronic Bronchitis/Pneumonia:** 42 yo Caucasian woman who developed cough and dyspnea on Day 230, ultimately diagnosed as COPD, chronic bronchitis, and interstitial pneumonia. She improved after a 4-week hospitalization for treatment with antibiotics and bronchodilators.	Unrelated to fingolimod, given that this patient received placebo

D2302	Interferon beta-1a	**D2302-0142-00004** **Influenza-like Symptoms:** 45 yo Caucasian woman who developed moderate influenza-like symptoms on Day 276, during hospitalization for an upper arm fracture. Study medication was temporarily held for 4 days, but symptoms resolved by Day 294.	Unrelated to fingolimod, given that this patient received interferon beta-1a
D2302	Interferon beta-1a	**D2302-0608-00004** **Pneumothorax secondary to car crash:** 36 yo Caucasian man who developed right-sided pneumothorax secondary to right rib fracture due to a car crash unrelated to study treatment on Day 105. By Day 108, pneumothorax had resolved following placement of a chest tube.	Unrelated to fingolimod, given that this patient received interferon beta-1a

**Determination of DPARP Clinical Reviewer, not the Applicant or Study Investigator*
[Source: D2301 Section 14.3.3; D2301 Narratives for serious adverse events; D2302 CSR Section 14.3.3 ; D2302 Narratives for serious adverse events; D2201 PT Supplement 2; D2201 Patient narratives for serious adverse events]

3.1.2 Patient Deaths

There were 12 deaths of MS patients reported in the fingolimod development program, of which one was due to a lung-associated event: a 42 year-old man in the 1.25 mg dose group died 187 days after his last fingolimod dose. Upon developing a lower respiratory tract infection and acute disseminated encephalomyelitis 11 months after starting study drug, fingolimod was stopped, but he proceeded to develop progressive neurologic decline and, ultimately, an episode of aspiration pneumonia that lead to his death six months later. Although no autopsy was performed, the immediate cause of this patient's death, aspiration pneumonia, appeared to be a consequence of his neurological decline, to which both his episode of encephalomyelitis and his underlying diagnosis of multiple sclerosis may have contributed. While fingolimod is a known immunosuppressant that may have predisposed him to develop acute disseminated encephalomyelitis (an uncommon diagnosis within the context of MS), this patient's death did not appear due to a direct pulmonary toxicity effect of fingolimod.

3.1.3 Subgroup Analysis (Age, Gender, Pre-existent Pulmonary Disease)

No subgroup differences were noted in respiratory tract-associated AEs by age or gender. Although patients with significant pre-existent pulmonary disease were excluded from the Phase III program, a subgroup analysis was conducted on the limited number of multiple sclerosis subjects with a history of asthma.

The following table summarizes the incidence of respiratory tract-associated AEs, which occurred at rates greater than placebo and greater than 2%. For Total Recipients (E), respiratory tract-associated AEs that occurred at rates greater than 2% are shown.

Table 12. Respiratory Tract-associated Adverse Events in MS Patients with a History of Asthma

Safety Population	Preferred MedDRA Term	0.5 mg fingolimod	1.25 mg fingolimod	Placebo	Interferon beta-1a
12-Month (A)		**N = 28 n (%)**	**N = 25 n (%)**	**N = 8 n (%)**	**N = 10 n (%)**
	Cough	3 (10.7)	1 (4.0)	0	1 (10.0)
	Pleurisy	1 (3.6)	0	0	0
24-Month (B)		**N = 16 n (%)**	**N = 10 n (%)**	**N = 8 n (%)**	
	Cough	3 (18.8)	0	1 (12.5)	
	Pleurisy	1 (6.3)	0	0	
Total Recipients (E)		**N = 33 n (%)**	**N = 28 n (%)**		
	Total in Resp SOC	**15 (45.5)**	**8 (28.6)**		
	Asthma	0	2 (7.1)		
	Dyspnea	5 (15.2)	2 (7.1)		
	Cough	6 (18.2)	1 (3.6)		
	Exertional dyspnea	0	1 (3.6)		
	Nasal congestion	1 (3.0)	1 (3.6)		
	Oropharyngeal pain	6 (18.2)	1 (3.6)		
	Sinus Congestion	0	1 (3.6)		
	Epistaxis	1 (3.0)	0		
	Pleurisy	1 (3.0)	0		
	Respiratory tract congestion	1 (3.0)	0		
	Rhinorrhea	1 (3.0)	0		
	Throat irritation	1 (3.0)	0		

Total in Resp SOC = Total Patients in System Organ Class: Respiratory, Thoracic, and Mediastinal Disorders
[Source: ISS PT-Table 4.1-18; ISS PT-Table 4.2-10; ISS PT-Table 4.5-18]

Within an otherwise healthy patient population with moderate asthma but without MS, the AE results of Study D2102 demonstrated a greater number of respiratory tract-associated events in subjects receiving fingolimod in a dose-independent manner, as shown in the following table. No severe respiratory tract-associated AEs, SAEs, or patient deaths were reported in this trial. Given the limited treatment duration (10 days), however, it is difficult to compare these results to the long-term trials in the Phase II and III development program in MS patients. Of note, one subject (ID: 5221) discontinued study drug due to a respiratory tract-associated moderate AE: a 27 year-old Black woman who developed a moderate asthma attack 11 hours after her initial

dose of fingolimod (1.25 mg), which subsequently resolved in 1 hour after treatment with 2 puffs of salbutamol and oxygen.

Table 13. Respiratory Tract-associated Adverse Events in Patients with Moderate Asthma: Study D2102

Preferred MedDRA Term	**0.5 mg fingolimod N = 9 n (%)**	**1.25 mg fingolimod N = 9 n (%)**	**2.5 mg fingolimod N = 9 n (%)**	**Placebo N = 9 n (%)**
Mild URI	1 (11)	1 (11)	1 (11)	0
Moderate URI	0	1 (11)	0	0
Total in Resp SOC	**2 (22)**	**3 (33)**	**1 (11)**	**0**
Mild Epistaxis	1 (11)	1 (11)	0	0
Mild Sore Throat	0	1 (11)	0	0
Mild Dyspnea	0	0	1 (11)	0
Moderate Cough	0	1 (11)	0	0
Moderate Asthma Attack	1 (11)	2 (22)	0	0

Total in Resp SOC = Total Patients in System Organ Class: Respiratory, Thoracic, and Mediastinal Disorders
[Source: D2102 PT-Table 14.3.1-1.1; D2102 PT-Listing 16.2.7-1.1]

3.2 Pulmonary Function Tests:

Across all trials, PFT measures (changes in percent predicted FEV1, FVC, and DLCO) consistently decreased from baseline to a greater degree in fingolimod-treated subjects versus both placebo and active control (interferon beta-1a) subjects in a dose-dependent fashion, with greater declines seen in the 1.25 mg dose group. In addition, for both FEV1 and DLCO, these decreases generally worsened over time, reflecting a cumulative decline in pulmonary function while on fingolimod treatment. A limited analysis of the frequency distribution of FEV1 deficits indicated that a higher percentage of patients presented with decreases in FEV1 < 80% of baseline in the fingolimod 1.25 mg group, followed by the fingolimod 0.5 mg group, compared to patients treated with placebo and interferon beta-1a at both 12-month and 24-month timepoints. For FVC, results were less consistent, as only the 1.25 mg dose group displayed consistently greater declines compared to placebo-recipients at all time points, although this trend did not worsen over time. The changes in percent predicted PFT parameters correlated with changes in absolute values. In particular, subjects in the 0.5 mg dose group demonstrated declines in absolute FEV1 of ≥100 mL as early as 6 months after starting study drug. Changes of this magnitude were evident in subjects in the 1.25 mg dose group by Month 1. However, it is also worth noting that progressive declines in the placebo and active control arms were observed in some of the trials. Although declines in FEV1 remained more marked in the fingolimod arms at all timepoints, the differences among treatment groups diminished over time. This trend was observed in both the 12-month and 24-month safety population, but does not appear to be the case in the ongoing long-term safety trial, D2309. An explanation for this parallel decline in the placebo arm is unclear. Early dropout seems unlikely to have produced this effect, as early discontinuation rates were fairly similar across treatment groups. Review of whisker box-plots

and population distribution histograms of the PFT data indicate a similar distribution of FEV1 values around the presented means, arguing against an effect driven by a few outliers. At the time of this review, an Information Request for more detailed analysis of the frequency distribution changes remains pending. Post-hoc subgroup analysis revealed declines in pulmonary function were greater in women than men, while subjects with pre-existent asthma either with or without MS displayed similar trends.

Changes in FEV1 of this magnitude are clinically meaningful, when one considers the typical rate of FEV1 decline in adults is 25-30 mL/year (Sunyer et al. 2005. AJRCCM. 172:1139), while the rate of decrease in patients with COPD is typically between 50-60 mL/year (Wise. 2006. Am J Med. 119:S4; Lung Health Study Research Group. 2000. NEJM. 343:1902). Although the neurological impairment of multiple sclerosis itself may lead to decreased lung function with prospective studies demonstrating FEV1 % PRED rates of 75-90% depending on underlying MS disease severity (Mutluay et al. 2005. Clin Rehabil. 19:426; Buyse et al. 1997. Eur Respir J. 10:139), these same studies typically demonstrate that decline in pulmonary function does not correlate with duration from initial diagnosis. In addition, except for decreases in DLCO to approximately 80% of predicted values, baseline pulmonary function spirometric indices (FEV1 and FVC) were greater than 100% of predicted values in the pooled safety populations prior to study drug treatment. Thus, the progressive declines observed in the fingolimod treatment groups appear largely due to the extent and duration of study drug exposure. In support of this conclusion, a long-term analysis of the subset of patients who stopped study drug indicated that this impairment in pulmonary function reversed following drug discontinuation. This is notable, as fingolimod is proposed for daily use in the chronic treatment of relapsing MS.

3.2.1 Major Safety Population

Decrements in all three primary PFT measures (FEV1, FVC, and DLCO) greater than those in the placebo group were consistently seen at both fingolimod dose levels in the first 12 months of treatment in Studies D2301 and D2302 (other than for FVC in the 0.5 mg recipients) in a dose-dependent relationship, with greater declines seen in the 1.25 mg dose group. These changes occurred as early as Month 1 post-treatment and became progressively worse. Similar trends were seen when extending these observations to Month 24 in Study D2301. The analysis of total fingolimod recipients confirmed this analysis, with dose-dependent decreases in PFT measures evident at every time point, other than FVC measures in the 0.5 mg dose group. Of note, a review of case narratives for several patients who developed declines in PFT parameters revealed that these decreases were not always associated with clinical symptoms. This may have been a function of the high level of baseline pulmonary function in the Phase III trial population, as FEV1 and FVC were consistently greater than 100% of predicted values. Moreover, although by protocol, study treatment was discontinued in subjects whose PFT parameters fell to <80% of baseline on two consecutive visits, overall the Phase III program does not provide sufficient data to determine a PFT threshold at which to temporarily or permanently discontinue fingolimod in order to reverse trends in pulmonary function.

The following table summarizes the sample sizes of the various safety populations for each PFT measure across all pertinent time points. As shown, sample sizes decline over time, given study withdrawal and losses to follow-up. Of note, DLCO measurements were only performed in a subset of PFTs.

Table 14. Sample Sizes for PFT Analyses: Subject numbers by PFT measure, treatment group, and time point

	Number of patients evaluated											
Timepoint (month)	**FEV1 (L)**				**FVC (L)**				**DLCO** (mL/min/mmHg)			
	0.5	**1.25**	**P**	**I**	**0.5**	**1.25**	**P**	**I**	**0.5**	**1.25**	**P**	**I**
12-Month (A)												
Baseline	854	849	418	431	854	849	418	431	854	849	418	431
3	798	762	396	389	797	761	395	389	777	739	376	376
6	795	742	388	387	794	741	387	387	775	721	371	371
12	753	704	357	360	754	703	356	360	733	679	337	337
24-Month (B)												
Baseline	425	429	418		425	429	418		425	429	418	
6	403	375	388		403	374	387		397	369	377	
12	387	353	358		387	352	357		378	346	351	
24	348	299	313		348	298	312		342	292	303	
Total Recipients (E)												
Baseline	1021	1023			1021	1023			1021	1023		
3	949	913			912	948			924	886		
6	945	895			894	944			922	871		
12	807	750			749	808			787	727		
24	444	391			390	444			434	382		
Study D2309												
Baseline	348	357	347		348	357	347		348	356	344	
3	298	308	302		298	308	302		294	305	299	
6	254	268	256		254	268	256		253	263	254	
12	177	182	169		177	182	169		177	180	168	
24	46	48	41		46	48	41		45	48	41	

0.5 = fingolimod 0.5 mg; 1.25 = fingolimod 1.25 mg; P = Placebo; I = Interferon beta-1a
[Source: ISS PT-Table 8.1-2; D2301 PT-Table 14.3-5.2; ISS PT-Table 8.2-3; Response to Request for Information-Special Safety Interim Report D2309 and D2302 PT-Table 14.3-4.2]

The following table summarizes the percent change from baseline in percent predicted values of key PFT measures, with rounded baseline values shown for reference. No changes in FEV1% PRED were greater than 12%.

Table 15. Change from Baseline in Percent Predicted PFT Values reported as percent

Timepoint (month)	FEV1% PRED				FVC% PRED				DLCO% PRED			
	0.5	**1.25**	**P**	**I**	**0.5**	**1.25**	**P**	**I**	**0.5**	**1.25**	**P**	**I**
12-Month (A)												
Baseline	102	103	105	102	105	105	108	105	85	86	88	85
3	-2.08	-3.25	-0.65	-0.29	0.32	-0.49	0.21	0.27	-1.54	-2.67	-0.57	-2.10
6	-2.56	-3.68	-0.56	-0.49	0.01	-0.59	0.54	0.06	-1.08	-2.71	0.91	-1.27
12	-2.28	-3.79	-1.52	0.31	0.62	-0.20	-0.13	1.09	-1.61	-3.44	1.25	-1.87
24-Month (B)												
Baseline	103	103	105		107	107	108		86	87	88	
6	-2.83	-4.40	-0.56		-0.06	-1.47	0.54		-1.56	-4.02	0.91	
12	-2.36	-4.77	-1.53		0.56	-1.01	-0.17		-2.33	-4.24	1.27	
24	-3.06	-5.30	-1.96		0.54	-0.38	-0.34		-3.83	-7.34	-2.66	
Total Recipients (E)												
Baseline	102	102			105	105			84	86		
3	-2.24	-3.20			0.01	-0.56			-1.21	-2.91		
6	-2.68	-3.70			-0.28	-0.71			-0.80	-2.99		
12	-2.24	-3.79			0.60	-0.29			-1.55	-3.31		
24	-2.74	-4.93			0.84	-0.38			-4.27	-6.74		
Study D2309												
Baseline	101	100	102		108	108	109		84	83	83	
3	-1.54	-3.34	-0.43		0.06	-0.86	-0.04		-1.59	-3.07	0.38	
6	-1.38	-3.87	-0.19		0.56	-0.97	0.02		-1.28	-3.31	0.11	
12	-2.80	-3.53	-0.95		-1.12	-0.19	0.34		-3.02	-4.02	0.04	
24	-2.70	-2.92	-0.16		-0.34	0.67	1.19		-1.40	-6.78	-0.46	

0.5 = fingolimod 0.5 mg; 1.25 = fingolimod 1.25 mg; P = Placebo; I = Interferon beta-1a
[Source: ISS PT-Table 8.1-2; D2301 PT-Table 14.3-5.2; ISS PT-Table 8.2-3]

For Phase 3 protocols, the Applicant defined decreases in PFT parameters to <80% of baseline as clinically significant declines in pulmonary function. No FEV1/FVC ratios fell below this pre-determined safety threshold in the 12- or 24-Month Safety Populations (other than at Month 24 in the 1.25 mg group, for which mean FEV1/FVC% was 79.4%). However. the downward trends in percent predicted PFT values on active treatment corresponded to clinically significant decreases in PFT parameters, e.g., a decrease of ≥100 mL in FEV1 by Month 6 in the 0.5 mg dose group and an even greater decline of ≥200 mL by Month 24 in the 1.25 mg dose group. The following table summarizes the mean changes in absolute PFT values over time in key safety populations, with mean baseline values shown for reference.

Table 16. Change in Absolute PFT Values over Time reported as Mean

Timepoint (month)	FEV1 (L)				FVC (L)				DLCO (mL/min/mmHg)			
	0.5	**1.25**	**P**	**I**	**0.5**	**1.25**	**P**	**I**	**0.5**	**1.25**	**P**	**I**
12-Month (A)												
Baseline	3.421	3.412	3.472	3.392	4.128	4.107	4.198	4.083	24.67	25.01	25.28	24.59
3	-0.075	-0.144	-0.030	-0.015	0.004	-0.023	-0.002	0.007	-0.46	-0.83	-0.24	-0.668
6	-0.097	-0.133	-0.035	-0.029	-0.015	-0.036	0.002	-0.009	-0.38	-0.86	0.16	-0.505
12	-0.104	-0.151	-0.079	-0.022	-0.006	-0.033	-0.038	0.010	-0.59	-1.19	0.22	-0.774
24-Month (B)												
Baseline	3.46	3.45	3.47		4.20	4.21	4.19		25.10	25.52	25.27	
6	-0.10	-0.16	-0.04		-0.02	-0.07	0		-0.56	-1.26	0.16	
12	-0.10	-0.18	-0.08		-0.01	-0.06	-0.04		-0.84	-1.42	0.22	
24	-0.15	-0.22	-0.12		-0.04	-0.07	-0.07		-1.41	-2.42	-1.01	
Total Recipients (E)												
Baseline	3.418	3.415			4.128	4.127			24.52	24.93		
3	-0.078	-0.113			-0.007	-0.027			-0.38	-0.88		
6	-0.100	-0.133			-0.026	-0.040			-0.30	-0.92		
12	-0.102	-0.151			-0.006	-0.037			-0.57	-1.13		
24	-0.142	-0.211			-0.027	-0.068			-1.52	-2.26		
Study D2309												
Baseline	3.139	3.148	3.169		3.956	3.968	3.962		23.23	23.08	23.01	
3	-0.055	-0.113	-0.024		-0.006	-0.042	-0.012		-0.55	-0.89	0.04	
6	-0.055	-0.135	-0.023		0.005	-0.053	-0.016		-0.46	-0.98	-0.10	
12	-0.110	-0.134	-0.057		-0.066	-0.038	-0.019		-0.10	-1.24	-0.13	
24	-0.129	-0.128	-0.057		-0.068	-0.017	-0.017		-0.70	-2.18	-0.42	

0.5 = fingolimod 0.5 mg; 1.25 = fingolimod 1.25 mg; P = Placebo; I = Interferon beta-1a
[Source: ISS PT-Table 8.1-2; D2301 PT-Table 14.3-5.2; ISS PT-Table 8.2-3]

Despite the progressive decline in PFT parameters in the 24-Month Safety Population, long-term follow-up in a subset of patients from Study D2301 who had PFTs done at 3-months post-study drug termination indicated that the downward trends from baseline in PFT parameters had begun to reverse by this time (i.e., approximately Month 27 post-enrollment). For example, in this subset of patients, the mean change from baseline in FEV1% PRED was -0.49% (absolute value [ABS] = -40 mL) in the 0.5 mg group (n = 50) versus -3.06% (ABS = -150 mL) at Month 24 for the overall trial population. Similarly, the 1.25 mg group went from -5.30% (ABS = -220 mL) for the overall population after 24 months on active treatment to -2.65% (ABS = -130 mL) in this subset by 3 months post-drug termination (n = 79). In contrast, the placebo group continued to decline in FEV1% PRED from -1.96% (ABS = -120 mL) in the overall population at Month 24 to -3.63% (ABS = -160 mL) in the long-term follow-up patient subset (n = 60). Too few subjects were followed beyond 6 months post-drug termination to provide meaningful data. However, given the magnitude of decline in spirometry and DLCO measures observed at Month 24 in this population, the reversal of PFT indices back toward baseline values in this long-term follow-up patient subset suggests declining PFT changes were indeed related to fingolimod treatment. Similar reversals of PFT trends were observed in the Total Recipient Safety Population as in the 24-Month Safety Population. At 3 months post-drug termination, the mean change from baseline in FEV1% PRED in this subset of patients was 0.31% (ABS = -16 mL) in the 0.5 mg group (n = 107) and -1.40% (ABS = -77 mL) in the 1.25 mg group (n = 150), as compared to -2.74% (ABS = -142 mL) and -4.93% (ABS = -211 mL) after 24 months of active treatment at the same respective dose levels in the overall population. Changes in FVC in this subset of patients mirrored the trends described for FEV1 [Source: Table 14.3-5.7 D2301 Study Report, Table 11.4-1 ISS/SCS, and Table 11.4-2 ISS/SCS].

The following table summarizes the number of subjects in each Phase III pivotal trial who discontinued study treatment due to PFT abnormalities, as categorized by treatment group. Decreases in DLCO to < 60% of baseline values accounted for nearly all discontinuations, either with or without concurrent decreases in FEV1 and/or FVC.

Table 17. Subjects Discontinuing Study Treatment due to Pulmonary Function Test Abnormalities by Trial and Treatment Group

Trial	**Reason for Discontinuation**			
D2301		**0.5 mg fingolimod (N = 425)**	**1.25 mg fingolimod (N = 429)**	**Placebo (N = 418)**
	DLCO < 60% of BL	1	3	1
	DLCO < 80% of BL	0	1	1
	FEV1 or FVC < 80% of BL	0	2*	1
	Total	**1**	**5**	**3**

D2302		0.5 mg fingolimod (N = 429)	1.25 mg fingolimod (N = 420)	Interferon beta-1a (N = 431)
	DLCO < 60% of BL	0	3	2
	FEV1 or FVC < 80% of BL	0	1**	0
	Unspecified PFT abnormality	1***	0	0
	Total	**1**	**3**	**2**

*BL = Baseline; *1 of 2 subjects is also represented in category of DLCO < 60% of BL and is only counted once in Total; **Subject is also represented in category of DLCO < 60% of BL and is only counted once in Total; ***Case summary of Subject D2302-0608-00007 does not provide details of abnormal PFTs at time of discontinuation*
[Source: D2301 Narratives for discontinuation due to abnormal test procedure results; D2302 Narratives for discontinuation due to laboratory abnormalities; D2302 PT-Table 14.3-5.3; D2302 Listing 14.3.2-1.3]

3.2.2 Subgroup Analysis (Age, Gender, Pre-existent Pulmonary Disease)

Subgroup analysis by age revealed no significant differences in patterns of reductions in PFT measures, as dose-dependent decreases in all parameters were observed across all age groups. However, some differences emerged when results were examined by gender. Decrements in FVC were greater for women than men. In addition, dose-dependent decreases in FEV1 to less than 80% of baseline were more common in women than men. No differences were seen in the proportion of asthmatic subjects experiencing declines in FEV1 of greater than 80%.

Within an otherwise healthy patient population with moderate asthma but without MS (D2102), spirometric data indicated greater declines in percent predicted FEV1 and FVC occurred in fingolimod- versus placebo-recipients, although these decreases were not clearly dose-dependent. All treatment groups consisted of 9 subjects.

Table 18. Study D2102: Change from Baseline at Day 10 (End of Treatment) in Percent Predicted PFT Values reported as %

FEV1 (L)				FVC (L)			
0.5 mg F (N = 9)	1.25 mg (N = 9)	2.5 mg (N = 9)	Placebo (N = 9)	0.5 mg (N = 9)	1.25 mg (N = 9)	2.5 mg (N = 9)	Placebo (N = 9)
-4.7	-11.8	-9.8	-2.0	-4.1	-8.8	-5.9	-2.6

0.5 = fingolimod 0.5 mg; 1.25 = fingolimod 1.25 mg; 2.5 = fingolimod 2.5 mg
[Source: D2102 Table 14.3-6.1]

3.3 Chest High-Resolution Computed Tomography (HRCT) Scans

In this section, chest HRCT scan results are presented by individual trial for D2301, D2302, and D2309. All scans were read by a local radiologist; there was no central adjudication of scans, which may have impacted these results. Although central reading and pooled analyses were not performed, across all 3 trials a greater proportion of patients treated with fingolimod had abnormal HRCT scans at end of treatment, as compared to placebo-recipients, with a greater percentage of these abnormal scans as having new or worsened findings, as compared to baseline. However, the incidence of abnormal findings did not appear to be dose-dependent. Likewise, from a qualitative perspective, no obvious patterns emerged as to the correlation of

PFT changes with HRCT scan abnormalities either at baseline or with those considered new or worsened at follow-up. Declines in pulmonary function (i.e., decreasing FEV1, FVC, or FEV1/FVC ratio) occurred in approximately half of those subjects with new or worsened abnormalities on follow-up HRCT scans. However, declines in pulmonary function were similarly distributed among subjects with stable HRCT scan abnormalities that did not worsen from baseline. Thus, the pre-existence and/or development of new or worsening chest HRCT findings did not appear to correlate with changes in PFTs. Furthermore, no patterns emerged as to the specific abnormalities noted. Of note, there was no propensity to develop pulmonary fibrosis with fingolimod treatment, as only 1 fingolimod-recipient had a definitive finding of pneumofibrosis that was considered by the study investigator to be clinically significant (Subject ID: D2301-0757-00008). Moreover, while bronchial wall thickening was observed in 1 fingolimod-recipient, this finding was also seen in 1 placebo-recipient. Thus, the Phase III program provide insufficient data to indicate that screening HRCT scans are useful in identifying fingolimod-associated pulmonary pathology.

3.3.1 Study D2301

A total of 360 subjects had HRCT scans performed, which were evenly distributed across the two fingolimod treatment groups and placebo-recipients in Study D2301. Within this group, 259 subjects had scans done at Month 24, while another 34 patients had follow-up scans that fell outside the Month 24 window. The remaining 67 patients had no post-baseline chest HRCT scan and could not be analyzed for comparative purposes. The proportion of subjects with abnormal chest HRCT scans was similar across all treatment groups, the majority of which were related to prior inflammatory events or small nodular changes, per the readings of local radiologists. At Month 24, the proportion of subjects with new or worsening abnormal HRCT findings on scheduled scans was higher in the fingolimod groups versus placebo: 56.5% in 0.5 mg, 50% in 1.25 mg, and 40.9% in placebo.

Findings determined by the Applicant to be clinically significant were observed in 3 subjects in the 0.5 mg dose group (1 with peribronchial pneumofibrosis, 1 with suspected pneumonia, and 1 with a benign cyst with 2 unidentified 4 mm abnormalities), 2 subjects in the 1.25 mg dose group (1 with benign cysts of the lower lobe and 1 with apical scarring and ground glass nodules), and 2 subjects in the placebo group (1 with apical scarring and multiple small nodules and 1 with bullous emphysema). Only the case of pneumofibrosis in the 0.5 mg group was reported as an AE (mild) during the trial; per the case narrative, this subject remained asymptomatic without clinically significant decreases in PFT parameters. Although not considered serious by the Applicant, 4 cases of pulmonary nodules or neoplasms were noted during the primary treatment phase (2 in 0.5 mg, 1 in 1.25 mg, and 1 in placebo), while 2 additional cases in the 0.5 mg group were noted during the extension phase. Although classified as benign, it is unclear how pulmonary nodules were distinguished from neoplasms and whether these lesions were later biopsied for confirmatory diagnosis, as case narratives indicate biopsy was done only rarely.

The following table summarizes the planned chest HRCT scan findings from D2301.

Table 19. Longitudinal Chest HRCT Scan Findings from D2301

Time Point	HRCT Finding	0.5 mg fingolimod n (%)	1.25 mg fingolimod n (%)	Placebo N (%)
Baseline		N = 120	N = 122	N = 118
	Normal	93 (77.5)	87 (71.3)	87 (73.7)
	Abnormal	27 (22.5)	35 (28.7)	31 (26.3)
Month 24*		N = 90	N = 85	N = 95
	Normal	67 (74.4)	61 (71.8)	73 (76.8)
	Abnormal	23 (25.6)	24 (28.2)	22 (23.2)
	New or Worsened**	13 (56.5)	12 (50.0)	9 (40.9)

**N for Month 24 is lower than Baseline due to some patients not receiving follow-up HRCT scans at end of treatment, but also includes 11 subjects who did not have baseline HRCT scans for comparison: 3 in 0.5 mg, 3 in 1.25 mg, and 5 in placebo. **New or Worsened abnormalities were determined by local radiologists, as compared to baseline HRCT scans; percentages are out of the total number of patients with abnormal HRCT scans at Month 24.*
[Source: D2301 PT-Table 14.3-5.8; D2301 PT-Listing 16.2.9-1.5]

A greater proportion of subjects within both fingolimod treatment groups who had normal HRCT scans at baseline developed abnormalities by Month 24, as compared to placebo-recipients. However, across the three treatment groups, approximately 44-47% of subjects with abnormal scans at baseline normalized by Month 24. The Applicant reports that of the 34 subjects with scans performed after Month 24, only 1 patient in the 1.25 mg group had a new or worsened abnormality (atelectasis) compared to baseline. However, review of the individual subject profile for this patient (ID: D2301-0255-00005) indicated the follow-up HRCT scan with this finding was done on Day 128 of the trial, rather than after Month 24. The reason for this discrepancy is unclear.

Table 20. Chest HRCT Scans in D2301: Shift in Interpretation from Baseline to M24

	0.5 mg fingolimod	1.25 mg fingolimod	Placebo
Normal to abnormal shift	13/70 = 18.6%	8/56 = 14.3%	8/67 = 11.9%
Abnormal to normal shift	8/17 = 47.1%	12/26 = 46.2%	10/23 = 43.5%

[Source: D2301 PT-Table 14.3-5.9]

In addition to these planned scans, 29 additional unscheduled HRCT scans were conducted per safety monitoring guidelines in Study D2301: 11 in 0.5 mg, 8 in 1.25 mg, and 10 in placebo. Of these, 6 were judged to be clinically significant by the Applicant: 3 in 0.5 mg (1 with nodal enlargement, 1 with pan-bronchiolitis, and 1 with pneumonic infiltration); 1 in 1.25 mg (pericarditis/focal infiltration/pleuritis), and 2 in placebo (1 with mild bilateral bronchial wall thickening and 1 with bilateral ground glass appearance). The remaining patients in Study D2301 who did not undergo any HRCT scanning had chest X-rays at baseline and Month 24, which were also read by local radiologists. At screening, less than 10% of these subjects across the 3 treatment groups had abnormal chest X-rays, with decreased proportions in all groups at Month 24: 3.3% in 0.5 mg, 8.4% in 1.25 mg, and 6.1% in placebo.

3.3.2 Study D2302

Chest HRCT scans were performed in 478 subjects at baseline and 421 patients at Month 12 in Study D2302. Compared to Study D2301, the proportion of HRCT scans in D2302 that were interpreted as abnormal was lower at both baseline and Month 12 (end of treatment) in both fingolimod groups, without evidence of dose-dependence. However, similar to this earlier trial, at end of treatment, nearly half of the abnormal HRCT scans were read as having new or worsened findings. Of these, a small number were reported as clinically significant by the Applicant: 3 in 0.5 mg (2 with pulmonary nodules and 1 with both pulmonary and hepatic nodules) and 2 in 1.25 mg (1 with bronchopathy/atelectatic strias/tubular bronchiectasis and 1 with bronchiectasis/pulmonary nodules). Of note, in this trial's active control group (interferon beta-1a), 2 worsening HRCT scan findings were also considered clinically significant: 1 with pulmonary nodules and 1 with emphysema. Benign pulmonary nodules and neoplasms were also noted in 4 more cases (2 in 0.5 mg, 1 in 1.25 mg, and 1 in interferon beta-1a active control). Although not considered serious by the Applicant, it is unclear how nodules were distinguished from neoplasms, and whether these lesions were biopsied for confirmatory diagnosis.

A total of 34 unscheduled HRCT scans were performed in 29 subjects whose PFTs declined below 80% on two consecutive visits (a predetermined safety threshold specified in the protocol) or at the investigator's discretion: 15 scans in 14 subjects in 0.5 mg, 10 scans in 9 subjects in 1.25 mg, and 9 scans in 6 patients in the active control group. A total of 5 scans in the two fingolimod groups had abnormal results, as compared to 7 scans in the interferon beta-1a group. Parenchymal changes suggestive of pulmonary fibrosis were not reported for any patient with clinically significant new or worsening findings on chest HRCT scans. One end-of-study HRCT scan (Subject ID: D2302-0723-00003) was initially reported as "mild pulmonary fibrosis," but no baseline scan was available for comparison. This patient was asymptomatic and a follow-up reading by the DSMB pulmonologist was interpreted as normal.

The following table summarizes the planned and unscheduled chest HRCT scan findings in the fingolimod treatment groups and active-control interferon beta-1a recipients from Study D2302.

Table 21. Longitudinal Chest HRCT Scan Findings from D2302

Time Point	HRCT Finding	0.5 mg fingolimod n (%)	1.25 mg fingolimod n (%)	Interferon beta-1a n (%)
Baseline		N = 161	N = 157	N = 160
	Normal	126 (78.3)	133 (84.7)	134 (83.8)
	Abnormal	35 (21.7)	24 (15.3)	26 (16.3)
Month 12		N =139	N = 135	N = 147
	Normal	114 (82.0)	111 (82.2)	122 (83.0)
	Abnormal	25 (18.0)	24 (17.8)	25 (17.0)
	New or Worsened*	11 (44.0)	12 (50.0)	15 (60.0)
	Not Compared*	1 (4.0)	4 (16.7)	2 (8.0)

Unscheduled*		N =14 (15 total scans)	N = 9 (10 total scans)	N = 6 (9 total scans)
	Normal	13 (86.7)	7 (70.0)	2 (22.2)
	Abnormal	2 (13.3)	3 (30.0)	7 (77.8)
	New or Worsened*	1 (50.0)	2 (66.7)	2 (28.6)
	Not Compared*	0	1 (33.3)	5 (71.4)

**New or Worsened abnormalities were determined by local radiologists, as compared to baseline HRCT scans; percentages are either out of the total number of patients with abnormal HRCT scans at Month 12 or out of the total number of abnormal HRCT scans for Unscheduled time points.*
[Source: D2302 PT-Table 14.3-5.6]

3.3.3 Study D2309

Interim results are presented for Study D2309, which is ongoing. The goal for this trial is to have HRCT scans done on 120 subjects in each of the three treatment arms at both baseline and Month 24 (end of treatment). Thus far, as read by local radiologists, the Applicant reports 4 subjects to have developed clinically significant abnormalities on follow-up HRCT scans: 3 in 0.5 mg (1 with mild increased interstitial markings that improved as a right middle lobe opacity and 1 with a right lower lobe ground glass opacity) and 1 in 1.25 mg (1 with bronchial wall thickening). In addition, 3 patients were noted to have new or worsened pulmonary nodules at follow-up (2 in 0.5 mg and 1 in 1.25 mg), which the Applicant felt were not of clinical relevance to fingolimod treatment.

Table 22. Longitudinal Chest HRCT Scan Findings from D2309

Time Point	**HRCT Finding**	**0.5 mg fingolimod n (%)**	**1.25 mg fingolimod n (%)**	**Placebo n (%)**
Baseline		N = 87	N = 87	N = 87
	Normal	49 (56.3)	49 (56.3)	56 (64.4)
	Abnormal	38 (43.7)	38 (43.7)	31 (35.6)
End of study*		N = 64	N = 68	N = 64
	Normal	37 (57.8)	40 (58.8)	38 (59.4)
	Abnormal	27 (42.2)	28 (41.2)	25 (39.1)
	New or Worsened**	16 (59.3)	10 (35.7)	12 (48.0)
	Not Compared**	2 (7.4)	4 (14.3)	4 (16.0)
Unscheduled**		N =10 (14 total scans)	N = 9 (11 total scans)	N = 10 (10 total scans)
	Normal	9 (64.3)	2 (18.2)	7 (70.0)
	Abnormal	5 (35.7)	8 (72.7)	3 (30.0)
	New or Worsened**	2 (40.0)	4 (50.0)	1 (33.3)
	Not Compared**	0	0	0

**End of study includes patients who had HRCT scans at Month 24 (45 in 0.5 mg; 40 in 1.25 mg; 36 in placebo), as well as patients who discontinued study treatment early. **New or Worsened abnormalities were determined by local radiologists, as compared to baseline HRCT scans, and*

percentages are either out of the total number of patients with abnormal HRCT scans at End of study or out of the total number of abnormal HRCT scans for Unscheduled time points.
[Source: D2309 PT-Table 14.3-4.1]

According to readings by local radiologists, none of these scans demonstrated findings indicative of pulmonary fibrosis.

3.3.4 Subgroup Analysis (Age, Gender, Pre-existent Pulmonary Disease)

Formal subgroup analysis was not performed on either scheduled or unscheduled chest HRCT scan results.

4. Proposed product labeling, REMS, and PMRs

4.1 Pulmonary-related Product Labeling

Minimal language regarding pulmonary toxicity is included in the Applicant's proposed labeling for fingolimod. **Section 13.2 Animal toxicology and/or pharmacology** details some of the lung pathology findings noted in the nonclinical program. Section **6.3 Infections** states that lower respiratory infections (bronchitis and pneumonia) were more common in fingolimod recipients, with the incidences from Study D2301 reported in **Table 1** under **14 CLINICAL STUDIES**. This table also details the incidence of cough and dyspnea (falling under the MedDRA Systems Organ Class of *Respiratory, thoracic and mediastinal disorders*) in the fingolimod and placebo groups in D2301. Cough is also listed under **ADVERSE REACTIONS** and section **6.1 Clinical Trials Experience** and as one of the **Common side effects** in the accompanying Medication Guide. Section **10 OVERDOSAGE** describes chest tightness or discomfort consistent with small airway reactivity occurring in 5 out of 6 subjects who received a single 40 mg dose of fingolimod. No other language or data regarding fingolimod-associated pulmonary toxicity, pulmonary function monitoring guidelines, or use restrictions in patients with known pulmonary disease is included in the currently proposed label.

DPARP recommends that DNP consider including information about the fingolimod-associated decline in pulmonary lung function and the higher incidence of new or worsened HRCT abnormalities in the fingolimod product label. PFT declines, in particular, appeared dose-dependent, cumulative, and greater in magnitude than decrements observed in placebo-control and active-control (interferon beta-1a) subjects. Moreover, absolute decreases in pulmonary function were clinically significant by Month 6 in the 0.5 mg dose group, i.e., ≥100 mL decrease in FEV1, which is a greater annual decline in pulmonary function than is typically seen in healthy patients, patients with COPD, or MS patients in general. It is uncertain whether longer courses of treatment would result in greater pulmonary deficits and whether these changes would be reversible after prolonged use. The effects in MS patients with comorbid pulmonary conditions are also not presently known, as patients with these conditions and those with spirometric parameters below pre-specified threshold values were excluded from the trials. At the current time, there are insufficient data to inform recommendations for a specific PFT monitoring schedule. However, providing information on fingolimod-associated PFT changes will facilitate the development of individualized monitoring plans by healthcare providers for MS patients on fingolimod. Similarly, the disparate nature of the HRCT findings in the clinical program limits the clinical utility of routine HRCT monitoring.

4.2 Proposed Pulmonary-related Risk Evaluation and Mitigation Strategy (REMS)

The Applicant's currently proposed REMS includes the citation of cough as one of the **Common side effects** in the proposed **Medication Guide** and a general statement about increased infection risk. The Applicant's Safety Risk Management Plan states that routine pharmacovigilance, including cumulative review in Periodic Safety Update Reports, will be sufficient to address the following potential toxicities: bronchoconstriction, pulmonary edema, infections (which would include those of the lower respiratory tract).

DPARP recommends that DNP consider inclusion of additional information about pulmonary toxicities in the REMS, namely pulmonary function decline and HRCT findings, as discussed above under Product Labeling.

4.3 Pulmonary-related Post-Marketing Requirements (PMRs)

There are currently no post-marketing requirements proposed by the Applicant with respect to specific pulmonary-associated adverse effects, other than infections (which would include those of the lower respiratory tract), for which the Applicant proposes a 5-year post-approval safety trial to monitor this complication. This same trial will also track thromboembolic events and other malignant neoplasms, which could potentially involve the lungs.

DPARP recommends further study of pulmonary safety to evaluate the stability and reversibility of declines in pulmonary function associated with chronic fingolimod treatment..

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22527	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	FINGOLIMOD HCL ORAL CAPSULES

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I concur