CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
22-527

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	August 13, 2010
From	Eric Bastings, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	22,527
Applicant	Novartis
Date of Submission	December 18, 2009
PDUFA Goal Date	September 21, 2010
Proprietary Name / Established (USAN) names	GILENYA/ fingolimod
Dosage forms / Strength	Oral capsule/0.5mg daily
Proposed Indication(s)	Treatment of patients with relapsing forms of MS to reduce the frequency of relapses and delay the accumulation of physical disability
Recommended:	Approval

1. Introduction

Novartis submitted a new drug application (NDA) to support the marketing of fingolimod (Gilenya), the first oral drug to be indicated 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.

Fingolimod is a new molecular entity, and a first in class sphingosine 1 phosphate (S1P) receptor modulator. The proposed mechanism of action in MS is that fingolimod induces a reversible retention of CD4 and CD8 T-cells and B-cells into lymph nodes and Peyer's patches, which in turn reduces the number of these cells that may have access to sites of MS related inflammation in the brain.

The fingolimod review team included the following FDA staff:

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2. Background

Fingolimod was initially developed for the prevention of acute rejection after renal transplantation in adults at doses of 2.5 mg and 5 mg/day. After evaluation of the risks and benefits of fingolimod, the renal transplant development program was stopped. The clinical development program in MS focused on a lower dose range than the renal transplant program: 1.25 mg and 0.5 mg/day.

The Phase III clinical development program of fingolimod for the treatment of MS includes three pivotal efficacy studies (2301, 2302, 2309), all evaluating once daily oral doses of 0.5 mg and 1.25 mg. Studies 2301 and 2302 are completed and were submitted in this NDA. Study 2309 was still ongoing at time of NDA submission, but interim safety data were submitted. In addition, the safety of the product was also evaluated in long term extensions of the efficacy studies.

As discussed below, the pivotal efficacy studies provide robust evidence of the efficacy of fingolimod to reduce the frequency of clinical exacerbations in patients with relapsing remitting MS (RRMS). The clinical development program also uncovered a number of safety issues, which will be discussed below:

- Cardiac effects
- Risk of infections
- Macular edema
- Pulmonary effects
- Liver effects

It is important for the reader to know that after evaluation of the results of clinical studies in MS, and because of similar efficacy for both doses, but greater toxicity for the 1.25 mg/day dose, Novartis is proposing to market only the 0.5 mg/day dose for the treatment of MS.

3. CMC

There are no unresolved CMC issues.

The Office of Compliance found the facilities acceptable.

4. Nonclinical Pharmacology/Toxicology

Dr. Richard Siarey, nonclinical reviewer, recommends against approving fingolimod. Dr. Siarey's supervisor, Dr. Lois Freed, disagrees with that recommendation.

I refer to Dr. Freed's and Dr. Katz's supervisory memoranda for a discussion of the reasons why the arguments presented by Dr. Siarey do not support his recommendation.

I agree with Dr. Freed that the nonclinical studies are adequate to support approval of fingolimod.

5. Clinical Pharmacology/Biopharmaceutics

Pharmacokinetics
OCPB notes that fingolimod is phosphorylated to the active moiety, S-enantiomer fingolimod-P. In addition, fingolimod-P is dephosphorylated back to fingolimod. At steady state, fingolimod and fingolimod-P are in dynamic equilibrium. Absorption of fingolimod is slow (about 12 hours) but complete (>85 % of drug recovered in urine). Fingolimod-P reaches Cmax after about 8 hours. Fingolimod is extensively distributed (volume of distribution about 1200 L). Fingolimod is believed to be metabolized mainly via cytochrome P450 4F2. The apparent terminal half-life for both fingolimod and fingolimod-P is 6 to 9 days. Steady-state exposure is reached after 1 to 2 months, 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%.

Food effect
Food has no clinically significant effect on fingolimod pharmacokinetics.

Pharmacodynamics

The key pharmacodynamic effect of fingolimod is a dose dependent reduction of the peripheral lymphocyte count, which reaches 30-40% of baseline values with fingolimod 0.5mg or 1.25 mg.

Intrinsic factors

Age, gender, or weight: No clinically significant pharmacokinetic differences were noted. No dose adjustment is recommended.

Race: Data are inconclusive. No dose adjustment is recommended.

PK and PD in MS patients: Based on population analysis, the PK/PDs of fingolimod and fingolimod-P are similar between MS patients and healthy subjects.

Hepatic impairment: Moderate and severe hepatic impairment increased fingolimod AUC by 44% and 103%. The apparent elimination half-life is prolonged by about 50% in patients with moderate or severe hepatic impairment. Fingolimod-P Cmax and AUC were increased by 22% and 29% in patients with severe hepatic impairment. OCPB recommends that the fingolimod dose does not need to be adjusted in patients with mild or moderate hepatic impairment, but recommends decreasing the dose by 50% in patients with severe hepatic impairment. As there is no lower strength (0.25 mg) formulation available, OCPB recommends that labeling states that "the use of fingolimod is not recommended in severe hepatic impaired patients". As the exposure in patients with severe hepatic impairment is similar to that observed with the 1.25 mg dose in patients with normal function (and the safety profile with that dose, while being worse than 0.5mg, is not unacceptable), the review team reached alignment for use of the following language in fingolimod labeling: "Monitor patients with severe hepatic impairment closely, as GILENYA exposure is doubled, and risk of adverse reactions is greater."

Renal impairment: OCPB notes that severe renal impairment increases fingolimod Cmax and AUC by 32% and 43%, and fingolimod-P Cmax and AUC by 25% and 14%. The apparent elimination half-life is unchanged. OCPB further notes that exposure to fingolimod inactive metabolites is also increased with patients with severe renal impairment (>300% for M2 and > 1300% for M3). OCPB observes that the clinical impact of such an increase is unknown. OCPB recommends that the use of fingolimod be contraindicated in patients with renal impairment due to uncertainty of the safety profiles of M2 and M3. I disagree. As discussed by Dr. Freed in her memo, "the available nonclinical TK data … indicate that M2 and M3 have been adequately assessed in most of the definitive nonclinical studies, with the clear exceptions being the pre- and post-natal development and carcinogenicity studies in rat." Dr. Freed further notes that "based on the acute-dose PK data, it is likely that plasma AUCs achieved for these metabolites in the mouse carcinogenicity study would have been at least similar to those in seen in humans with severe renal impairment". Considering the available nonclinical toxicology data, the fact that these metabolites are inactive (in term of the fingolimod main pharmacodynamic effect on lymphocytes), and the robust efficacy of this product, the review team reached alignment for the use of the following statement in fingolimod labeling: “The blood level of some GILENYA metabolites is increased (up to 13-fold) in patients with severe renal impairment. The toxicity of these metabolites has not been fully explored. The blood level of these metabolites has not been assessed in patients with mild or moderate renal impairment.”

Drug-drug interactions

Ketoconazole: Coadministration of a single 5 mg dose of fingolimod with steady state ketoconazole 200 mg twice-daily increased fingolimod Cmax by 1.2 fold and AUC by 1.7 fold. Fingolimod-phosphate AUC was increased to a similar extent. OCPB recommends decreasing the dose of fingolimod by 50% when it is coadministered with ketoconazole. As there is no lower strength (0.25 mg) formulation available, OCPB recommends that fingolimod should not be coadministered with ketoconazole. The situation here is similar to that discussed above for patients with severe hepatic impairment: the exposure in patients using ketoconazole and fingolimod is similar to that observed with the 1.25 mg dose in patients with normal function, and the safety profile with that dose, while being worse than 0.5mg, is not unacceptable. Therefore, the review team reached alignment for the use of the following statement in fingolimod labeling: “Patients who use GILENYA and systemic ketoconazole concomitantly should be closely monitored, as the risk of adverse reactions is greater”.

Isoproterenol: Isoproterenol was effective in reversing the negative chronotropic effect of fingolimod. The exposure of fingolimod or fingolimod-P was not altered by isoproterenol.

Salmeterol: Salmeterol had a mild, positive chronotropic effect on heart rate of approximately six beats per minute. The fingolimod and fingolimod-P blood exposure are not altered by salmeterol.

Atropine: Intravenous atropine (≤2 mg) reversed fingolimod induced negative chronotropic effect by approximately 10 BPM. Fingolimod and fingolimod-P exposure were not influenced by atropine.

Diltiazem: Diltiazem had no additional negative chronotropic effect over fingolimod alone. The pharmacokinetics of diltiazem (a moderate CYP3A inhibitor), fingolimod, and fingolimod-P were not altered when coadministered.

Atenolol: Atenolol combined with fingolimod had an approximately 15% additional negative chronotropic effect over fingolimod alone.

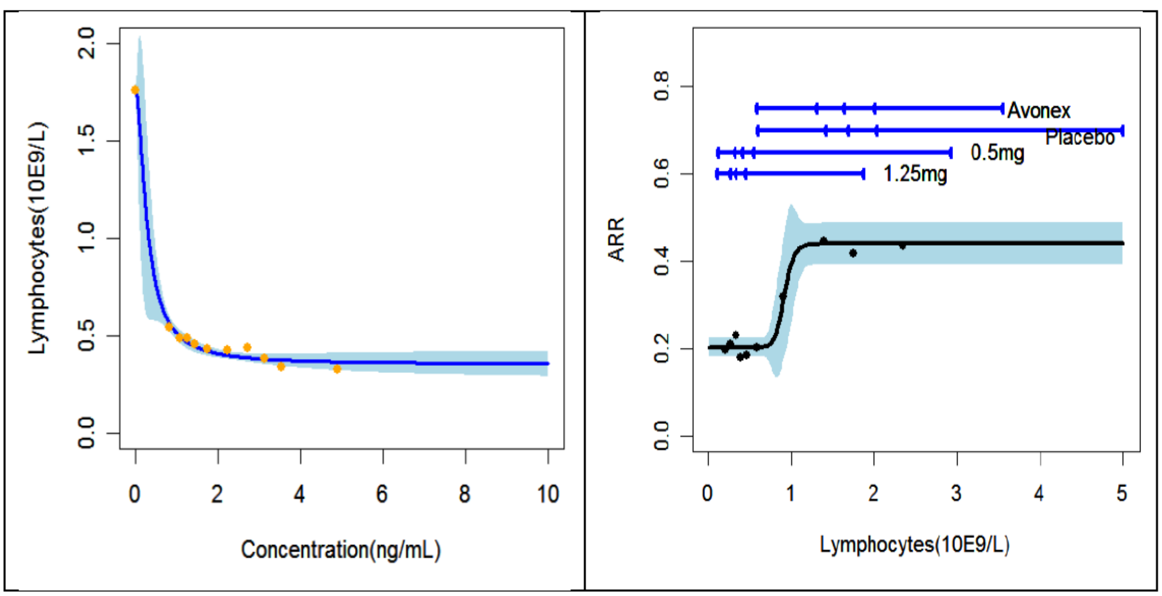
Thorough QT study

The QT study was conducted with a 1.25 mg and 2.5 mg dose of fingolimod. In that study, 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 QT prolongation for moxifloxacin was about 10.5 ms and occurred at 6 and 8 hours post-dose. Despite a 2-fold increase in the exposure to fingolimod plasma concentrations, there was no dose-response relationship for QT prolongation for fingolimod or fingolimod-P. The study could not exclude a 10 ms prolongation of the QT interval for both doses of fingolimod, as at 6 hours post-dosing on Day 7, the maximum mean QTc prolongation for both fingolimod doses was 10 ms, with an upper one-sided 95% confidence interval of 14 ms. In fingolimod clinical trials, there was no signal for a treatment related increased incidence of QTc outliers, and no clinically relevant prolongation of QT interval. However, patients at risk for QT prolongation were not included in clinical studies.

Pharmacometrics
A pharmacometric analysis looked at fingolimod dose-response. OCPB notes that there was a flat exposure-response relationship within the observed exposure range. OCPB tried to quantify the relationship between annualized relapse rate (ARR) and fingolimod-P concentration directly. However, the lack of data at lower exposure range made it impossible to predict ARR at doses lower than 0.5mg. Therefore, OCPB used lymphocyte counts (a pharmacodynamic biomarker) as a bridge to link ARR and fingolimod-P concentration.

Figure 1 below shows the pharmacometric modeling:

Figure 1: Modeling of predicted relationship between lymphocyte counts and fingolimod-P concentration (left) and between ARR and lymphocyte counts (right), with 95% prediction interval (blue shaded area). Orange dots on the left are observed absolute number of lymphocyte at deciles of exposure range. Black dots on the right panel indicate the observed ARR at deciles of lymphocyte counts. Blue vertical bars on the right panel show the distribution of lymphocyte counts for each treatment group (adapted from Figure 6 of OCPB review, page 355).



Based on this modeling, the average ARR for fingolimod 0.25 mg is predicted at 0.26 (95%CI: 0.22-0.30), which is close to the rate observed with fingolimod 0.5 mg (about 0.21) and lower than the rate observed in the placebo group (0.47).

OCPB proposed several post-marketing requirements (PMRs) or commitments (PMCs), described in their review. These were discussed internally, and alignment for the list described at the end of this document was reached between the review disciplines.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Novartis conducted two adequate and well-controlled pivotal efficacy studies. Study 2301 was a 2-year, double-blind, placebo-controlled study in 1272 RRMS patients; Study 2302 was a 1-year, double-blind, double-dummy, active-controlled (once weekly 30μg intramuscular IFN β-1a [Avonex]) study in 1292 RRMS patients.

The primary endpoint in both studies was the annualized relapse rate (ARR). The key secondary endpoints were however different: in Study 2301, the single key secondary endpoint was the time to 3-month confirmed disability progression up to month 24; in Study 2302, the two key secondary endpoints were the number of new or newly enlarged T2 lesions on MRI scan at month 12 and the time to 3-month confirmed disability progression at month 12.

To control the overall type-I error rate, a multiplicity adjustment was applied to the primary and key secondary endpoints in both studies, with significant level set at 0.05 for each comparison, and lower-rank testing to be performed only if higher-rank testing was statistically significant.

In Study 2301, testing was made in the following order:
1. 24-month relapse rate of fingolimod 1.25 mg vs. placebo
2. 24-month relapse rate of fingolimod 0.5 mg vs. placebo
3. Time to 3-month confirmed disability progression of fingolimod 1.25 mg vs. placebo
4. Time to 3-month confirmed disability progression of fingolimod 0.5 mg vs. placebo

In Study 2302, testing was made in the following order:
1. 12-month relapse rate of fingolimod 1.25 mg vs. Avonex
2. 12-month relapse rate of fingolimod 0.5 mg vs. Avonex
3. New and newly enlarged T2 lesions of fingolimod 1.25 mg vs. Avonex at 12 months
4. New and newly enlarged T2 lesions of fingolimod 0.5 mg vs. Avonex at 12 months
5. Time to 3-month confirmed disability progression of fingolimod 1.25 mg vs. Avonex
6. Time to 3-month confirmed disability progression of fingolimod 0.5 mg vs. Avonex

Fingolimod effect on relapse rate

The pivotal studies clearly provide substantial evidence for an effect of both doses of fingolimod on relapse rate, as the contrasts between fingolimod and placebo for the primary endpoints and for various sensitivity analyses of the relapse rate showed robust clinical and statistical significance.

Study 2301
As discussed by Dr. Yan, treatment with fingolimod 1.25 mg and 0.5 mg resulted in a significantly lower annualized relapse rate compared to placebo (ARR estimates of 0.16 and 0.18 vs. 0.40, respectively). This corresponds to a relative relapse rate reduction of 60% with fingolimod 1.25 mg and of 54% with fingolimod 0.5 mg. The difference between the two fingolimod doses was not statistically significant (p=0.238) (see table 1).

Table 1: Annualized relapse rate in Study 2301 (adapted from table 5 of Dr. Yan's review)

Annualized Relapse Rate (ARR)	**Fingolimod 1.25 mg N=429**	**Fingolimod 0.5 mg N=425**	**Placebo N=418**
Confirmed relapses during Study			
Unadjusted (observed)	0.19	0.21	0.47
Adjusted (estimated from model)	0.16	0.18	0.40
95% CI	(0.13, 0.19)	(0.15, 0.22)	(0.34, 0.47)
p-value	<.001	<.001	
Hazard ratio* from Cox model	0.38	0.48	
% free of confirmed relapse	76	71	48

* Hazard ratio measures the relative risk of having a relapse over the duration of the study

Study 2302
For Study 2302, Dr. Yan reports that treatment with both fingolimod doses resulted in a significantly lower annualized relapse rate compared to Avonex (ARR estimates of 0.20 and 0.16 vs. 0.33, respectively). This corresponds to a relative relapse rate reduction of 38% with fingolimod 1.25 mg and of 52% with fingolimod 0.5 mg.

Table 2: Annualized relapse rate in Study 2302 (adapted from table 11 of Dr. Yan's review)

Annualized Relapse Rate (ARR)	**Fingolimod 1.25 mg N=420**	**Fingolimod 0.5 mg N=429**	**IFN β-1a N=431**
Confirmed relapses during Study			
Unadjusted (observed)	.26	.21	.43
Adjusted	.20	.16	.33
95% CI	(.16, .26)	(.12, .21)	(.26, .41)
p-value	<.001	<.0001	
Hazard ratio from Cox model	.63	.52	
% free of confirmed relapse	80	82	70

It is noteworthy that in that study, fingolimod 0.5 mg was numerically (but not statistically) better than fingolimod 1.25 mg for the annualized relapse rare, hazard ratio, and percentage of patients free of confirmed relapse.

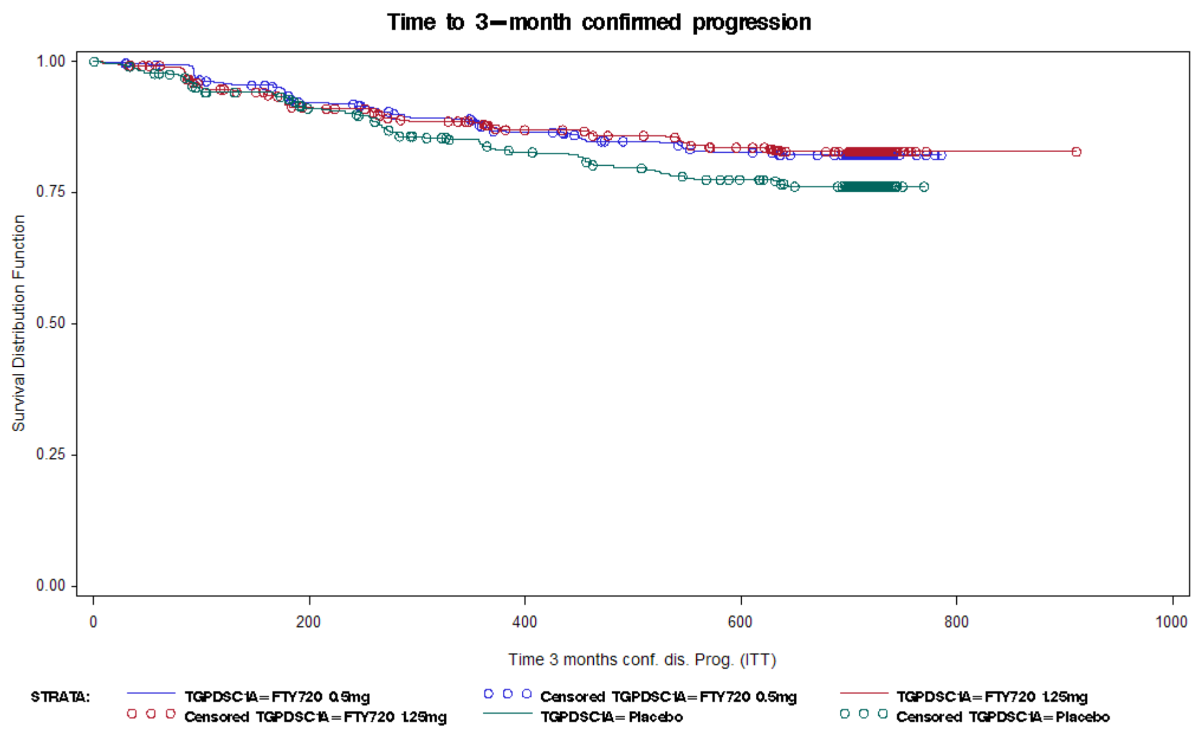
Fingolimod effect on disability progression

Time to 3-month confirmed disability progression (measured by the EDSS scale) was the only key secondary endpoint in Study 2301, and the second key secondary endpoint in Study 2302 (T2 MRI lesions was the first key secondary endpoint in Study 2302). As discussed by Dr. Fitter and by Dr. Yan, both doses of fingolimod delayed the time to 3-month confirmed disability progression compared to placebo in Study 2301, but no significant difference between either dose of fingolimod and Avonex was found in Study 2302.

Study 2301

Fingolimod 1.25 mg and 0.5 mg significantly delayed the time to 3-month confirmed disability progression compared to placebo (p=0.012 and p=0.026, respectively) (Figure 2). The two fingolimod dose groups were not significantly different (p=0.7427). In a sensitivity analysis of the time to 6-month confirmed disability, results were very similar (nominal p-values of 0.0044 and 0.0112 for fingolimod 1.25 mg and 0.5 mg versus placebo). The percentage of patients without 3-month confirmed disability progression at Month 24 was higher in both fingolimod treatment groups (85% and 83% for 1.25 mg and 0.5 mg) compared with placebo (78%). The pairwise comparisons yielded nominal p-values of 0.008 and 0.043 for fingolimod 1.25 mg and 0.5 mg versus placebo, respectively.

Figure 2: Cumulative plot of time to 3-month confirmed disability progression in Study 2301 (copied from Figure 2 of Dr. Yan's review)

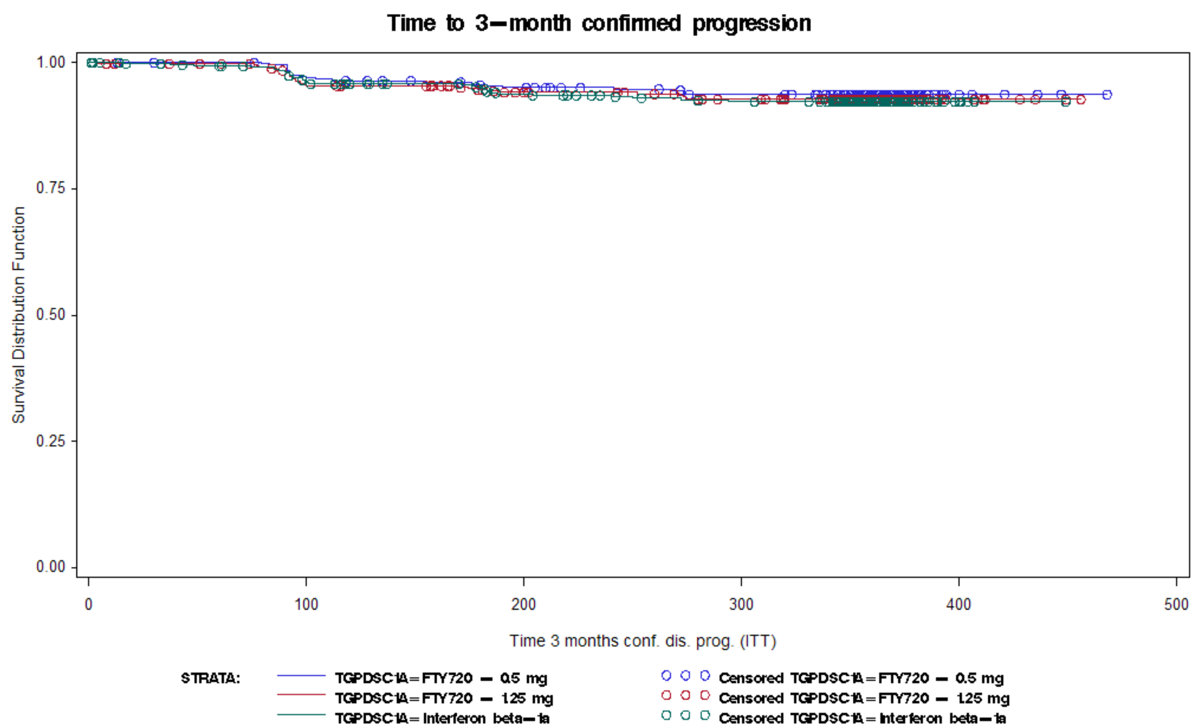


Study 2302

The significant delay in confirmed disability progression seen for both doses for fingolimod in Study 2301 was not independently substantiated in Study 2302, as there was no significant difference between either of the two fingolimod treatment groups and the Avonex group in the time to 3-month confirmed disability progression, based on the log-rank test (p values 0.4979 and .2475 for fingolimod 1.25 mg and 0.5 mg versus Avonex).

Two important factors may account for the lack of drug effect on disability progression in Study 2302: the relatively short duration of the study, and the use of an active comparator. It is important to remember that the lack of significant difference between fingolimod and Avonex on disability progression in Study 2302 should not be inferred to mean than they are "similar" for that endpoint, as the study was not designed to test for non-inferiority of fingolimod to Avonex.

Figure 3: Cumulative plot of time to 3-month confirmed disability progression in Study 2302 (copied from Figure 4 of Dr. Yan's review)



Fingolimod effect on the number of T2 lesions

The number of new or newly enlarged T2 lesions was not identified as a key secondary endpoint in Study 2301, and there was no plan to control the overall type-I error rate of the study for the analysis of that endpoint. The results described below for Study 2301 must be interpreted in that context. The number of new or newly enlarged T2 lesions at Month 12 was the first key secondary endpoint in Study 2302.

Study 2301

In Study 2301, the nominal p value[1] (without multiplicity adjustment) for the contrast between either dose of fingolimod and placebo for the number of new or newly enlarged T2 lesions was under 0.001, with also a rather large effect size (see Table 3).

[1] As reported by Novartis (and not verified by the FDA review team)

Table 3: New or newly enlarged T2 lesions up to month 24- Study 2301 (copied from Figure 25 of Dr. Fitter's review)

	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.

Study 2302

In the original analysis conducted by Novartis (see Table 4), only the 1.25 mg fingolimod dose reached statistical significance for the comparison of the number of new or newly enlarged T2 lesions (p=0.017). The contrast for the 0.5 mg dose trended strongly in favor of fingolimod 0.5 mg, but did not reach significance (p=0.053).

Table 4: Mean number of new or newly enlarged T2 lesions at Month 12 – Study 2302 (copied from Table 12 of Dr. Yan's review)

	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.

As discussed by Dr. Fitter, Novartis proposed a revised (post-hoc) analysis for the number of "new and newly enlarged T2 lesions[2]" in Study 2302, using a different method for counting lesions, and also excluding 18 patients who prematurely discontinued from the study. In that revised analysis, the contrast between fingolimod 0.5 mg and placebo for the number of new and newly enlarged T2 lesions becomes statistically significant. After discussion with Novartis on the methodology used in that recount, and agreement on a different revised analysis (to include the patients who discontinued prematurely), Dr. Yan notes that the difference between

[2] The justification for the change is that that the MRI central reader did not follow the protocol-specified method for counting T2 lesions

fingolimod 0.5mg and placebo reaches statistically significance, according to the sponsor analysis (Table 5).

Table 5: Sponsor reanalysis of T2 MRI results in Study 2302, copied from table 2 of FDA statistical review addendum

Table 2 Number of new or newly enlarged T2 lesions at Month 12 (Study drug endpoint carry-forward, ITT population) (Source: Table 2-2 of Response to FDA Request for Information, 28 June 2010)

	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.
Source: [pt-table-14-2-1-31d-response-20100504-fda]

Dr. Yan also conducted her own analysis, and obtained slightly different results (shown in Table 6). Dr. Yan however confirmed a significantly lower number of new or newly enlarged T2 lesions for fingolimod 0.5 mg compared to active control in Study 2302.

Table 6: FDA reanalysis of T2 MRI results in Study 2302 (copied from Table 3 of FDA statistical review addendum)

Table 3 New or newly enlarged T2 lesions at Month 12 – Study drug endpoint carry forward (Source: 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	.0017	.0007	

The mean number of new or newly enlarged T2 lesions found by the reviewer is slightly larger than the one obtained by the sponsor for all treatment groups.

Dose response

In terms of efficacy, the dose-response between 0.5 mg and 1.25 mg is essentially flat. No significant difference was seen in either pivotal study between fingolimod 1.25 mg and 0.5 mg for relapse rate and time to disability progression. For both of these endpoints, fingolimod 1.25

mg was numerically better than fingolimod 0.5 mg in Study 2301, while the reverse is true in Study 2302. The effect of fingolimod 1.25 mg and 0.5 mg on the number of new or newly enlarging T2 MRI lesions was also very similar. These findings suggest that the fingolimod development program may not have identified the lowest effective dose. In addition, the FDA pharmacometrics team performed modeling analyses that similar efficacy of both doses of fingolimod.

8. Safety

Dr. Villalba conducted the clinical safety review, with Dr. Yasuda as safety clinical team leader.

As discussed by Dr. Villalba, the safety database exceeds ICH guidelines for the standard experience needed to characterize common adverse events. At the time of the 4-month safety update, a total of 2615 patients had been exposed to fingolimod 0.5mg/day or higher, with 1843 patients exposed for 360 days or more, 1224 patients exposed for 720 days or more, and 228 patients exposed for 1080 days or more.

Deaths

Dr. Villalba notes that out of 14 deaths reported in the fingolimod MS development program, nine occurred during or after exposure to fingolimod (plus one still blinded at the time of her review). Dr. Villalba's assessment of causality is shown in Table 7.

Table 7: Summary of deaths in the fingolimod MS program (adapted from Table 11 of Dr. Villalba's review)

During or following fingolimod treatment
Likely Related - 2 herpes viral infections (encephalitis and disseminated VZ)
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 discontinuation) - 1 rapidly deteriorating MS complicated with fatal respiratory infection - 1 MS progression/ADEM (can not rule out CNS infection) – complicated with aspiration pneumonia 6 months after drug discontinuation (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
Blinded – 1 dissecting aortic aneurysm (relationship can not be ruled out)

Serious adverse events (SAEs)

Dr. Villalba notes that in controlled studies, SAEs occurred in 8.5%, 10.6 %, 8.5%, 11.9% and 5.8% of patients in the fingolimod 5 mg, fingolimod 1.25 mg, fingolimod 0.5 mg, placebo and interferon groups, respectively.

Table 8 (adapted from Dr. Villalba's review) shows the most commonly reported SAEs in controlled studies (6 months to 2 years).

Table 8: SAEs with incidence ≥ 3/1000, and with incidence higher with fingolimod 1.25 mg or 0.5 mg than with placebo (adapted from Table 13, Table 16, and Table 21 of Dr. Villalba's review)

	Fingolimod 1.25 mg (N=943) %	**Fingolimod 0.5 mg (N=854) %**	**Placebo (N=511) %**	**Avonex (N=431) %**
Cardiac disorders	**2.4**	**1.2**	**0.8**	**0.2**
Bradycardia^	1.6	0.7	0.2	0
Atrioventricular block first degree	0.4	0.1	0	0
Atrioventricular block second degree	0.4	0.1	0.2	0
Nervous system disorders	**1.9**	**1.4**	**1.0**	**0.7**
Seizure*	0.5	0.1	0	0
Multiple sclerosis/ Multiple sclerosis relapse	0.3	0.5	0.4	0.2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1.0**	**1.6**	**2.3**	**0.5**
Basal cell carcinoma	0.3	0.7	0.4	0
Infections	**1.9**	**0.9**	**1.6**	**1.4**
Herpes infection+	0.4	0.2	0	0.2
Urinary tract infections^	0.3	0.2	0.2	0.2
Investigations	**1.0**	**0.7**	**0.2**	**0.2**
Liver enzymes abnormality or hepatobiliary	0.7	0.5	0.2	0.2
Eye disorders	**0.7**	**0.2**	**0.2**	**0**
Macular edema	0.4	0.1	0	0
Blood and lymphatic system disorders	**0.3**	**0.1**	**0**	**0**
Lymphopenia	0.3	0	0	0

^ Based on FDA analysis
*Pooling of grand mal convulsion, epilepsy, status epilepticus, partial onset seizure
+ Based on FDA analysis; includes one death due to disseminated zoster infection and one death due to herpes simplex encephalitis infection that was coded as Viral infection NEC.

The following serious adverse events are further discussed under "Safety issues of possible concern with fingolimod":

- Bradycardia- and atrioventricular block
- Seizure
- Neoplasm
- Infections
- Eye disorders

- Hepatobiliary disorders (including liver enzyme abnormalities)
- Blood and Lymphatic system disorders

AEs leading to study discontinuation

Dr. Villalba notes that overall, the risk of AEs leading to study drug discontinuation ("adverse dropouts") was higher for fingolimod 1.25 mg (11.9%) than for fingolimod 0.5 mg (7%), placebo (7%) or Avonex (3.9%). Dr. Villalba notes that the difference was driven by dose-related adverse reactions in three system organ classes: Investigations (mostly liver-related), Cardiac, and Eye disorders. Table 9 shows adverse events leading to drug discontinuation that were more common on fingolimod than on placebo in controlled trials.

Table 9: Most frequent (≥ 2/1000 and more frequent with fingolimod than with placebo) discontinuations due to adverse events in controlled MS clinical studies (adapted from Table 37 and 39 of Dr. Villalba's review)

	Fingolimod 1.25 mg (N=943) %	**Fingolimod 0.5 mg (N=854) %**	**Placebo (N=511) %**	**Interferon (N=431) %**
Any AE leading to study drug discontinuation	**11.9**	**7.0**	**7.0**	**3.9**
Investigations	5.0	3.5	1.4	1.6
Liver-related investigations	4.1	3.4	0.6	1.6
Hepatobiliary disorders	0.4	0.2	0.2	0
Eye Disorders	**1.6**	**0.2**	**0.4**	**0.2**
Macular edema	1.1	0.1	0.0	0.2
Cardiac disorders	**1.3**	**0.1**	**0.4**	**0.2**
Bradycardia	0.5	0.0	0.2	0.0
AV block 2nd degree	0.3	0.0	0.0	0.0
AV 1st degree	0.2	0.0	0.0	0.0
Infections and infestations	**0.7**	**0.2**	**0.4**	**0.2**
Respiratory, thoracic and mediastinal disorders	**0.5**	**0.2**	**0.4**	**0.0**
Psychiatric disorders	**0.3**	**0.1**	**0.4**	**0.5**
Depression	0.2	0.1	0	0.2
Vascular disorders	**0.3**	**0.1**	**0.2**	**0**
Gastrointestinal disorders	**0.3**	**0.4**	**0.6**	**0**
Dyspepsia	0.2	0	0	0
Skin and subcutaneous tissue disorders	**0.2**	**0.4**	**0.2**	**0**
Dermatitis allergic	0	0.2	0	0
Musculoskeletal and connective tissue disorders	**0.2**	**0.4**	**0**	**0.2**
Myalgia	0	0.2	0	0
Blood and lymphatic system disorders	**0.2**	**0.4**	**0**	**0**
Thrombocytopenia	0	0.2	0	0
Metabolism and nutrition	**0.2**	**0**	**0**	**0**

The following AEs leading to discontinuation are further discussed under "Safety issues of possible concern with fingolimod":

- Hepatobiliary
- Eye disorders
- Cardiac disorders
- Infections and Infestations disorders.

Common adverse events

Table 10 shows common adverse events in fingolimod controlled trials. The events with the greater difference in risk between fingolimod and placebo were ALT increased, GGT increase, bronchitis, melanocytic nevus, leukopenia (expected based on fingolimod mechanism of action) and influenza like illness (which was also much more frequent with Avonex).

Table 10: Percentage of patients with common AEs in MS controlled trials(>5% in a fingolimod treatment group and ≥1 % higher with fingolimod 1.25mg/day or 0.5mg/day than with placebo; adapted from table 64 of Dr. Villalba's review)*

	Fingolimod 1.25 mg N=943	**Fingolimod 0.5 mg N=854**	**Placebo N=511**	**Avonex N=431**
Headache	25	24	21	20
Nasopharyngitis	23	24	25	20
Fatigue	12	11	11	10
Diarrhea	9	10	7	5
Back pain	8	9	6	5
Nausea	8	9	7	7
ALT increased	**9**	**8**	**4**	**2**
Melanocytic nevus	**6**	**6**	**3**	**6**
Bronchitis	**7**	**6**	**3**	**3**
Hypertension	6	5	3	2
GGT increased	**5**	**4**	**1**	**0**
Dyspnea	5	4	4	2
Upper abdominal pain	4	3	4	3
Pyrexia	4	3	2	18
Leukopenia	**3**	**2**	**0**	**0**
Influenza like illness	**2**	**3**	**1**	**37**

*AEs are listed according to decreasing frequency on fingolimod 0.5mg/day; bolded AEs are those at least twice as frequent with fingolimod 1.25mg/day than with placebo

Dr. Villalba concludes that rates of common adverse events are consistent with the analyses of serious AEs and discontinuations leading to AE, with a signal for increased liver enzymes, but no signal for increased infections, except for bronchitis.

Laboratory data

Hematology

Fingolimod causes lymphopenia. Lymphocyte counts dropped to a mean of about $0.5x10^9$/L for fingolimod 0.5 mg (28% of baseline), and $0.4x10^9$/L for fingolimod 1.25 mg (23% of baseline). The decrease in lymphocyte count was observed after 1 to 2 weeks and was maintained on treatment. After drug discontinuation, lymphocyte counts recovered to within 5% of baseline within 3 months. There were slight decreases in mean neutrophil and platelet counts, of no clinical significance. Analysis of outliers for hematologic parameters did not identify any safety signal, other than the known effect on lymphocyte counts. About 20% of patients who received fingolimod 0.5 mg reached nadir of lymphocytes counts under $0.2x10^9$/L.

Electrolytes
As discussed by Dr. Villalba, electrolytes (sodium, potassium, bicarbonate, calcium, magnesium) were not collected in phase 2 and phase 3 MS studies. This is of concern to Dr. Villalba, particularly for patients who developed adverse events that could be associated with electrolyte disturbances (e.g. bradycardia or extrasystoles). Electrolytes will be included in a new prospective study to evaluate the efficacy of a fingolimod dose lower than 0.5 mg.

Liver enzymes
Liver enzymes are discussed below under "Safety issues of possible concern with fingolimod".

<u>Vital signs</u>

Acute effects
There was an acute hypotensive effect, mostly seen with the 1.25 mg dose (Table 11).

Table 11: Notable blood pressure abnormalities upon first dose administration (adapted from Table 85 of Dr. Villalba's review)

	Systolic BP ≤90mmHg or ≥20mmHg decrease from baseline	**Diastolic BP ≤50mmHg or ≥15mmHg decrease from baseline**
Fingolimod 1.25 mg	23%	29%
Fingolimod 0.5 mg	19%	23%
Placebo	16%	17%
Avonex	13%	14%

There was also a pronounced dose-related bradycardic effect following the initial dose of fingolimod (Table 12). Dr. Villalba notes that of subjects who presented marked vital signs abnormalities upon first dose, 10 to 25% presented vital signs abnormalities following the second dose (on Day 2).

Table 12: Notable pulse rate abnormalities following first dose administration (adapted from Table 85 of Dr. Villalba's review)

	Pulse <50 or ≥15 decrease from baseline
Fingolimod 1.25 mg	48%
Fingolimod 0.5 mg	33%
Placebo	13%
Avonex	8%

Chronic effects

Chronic use of fingolimod causes a dose-dependent increase in systolic and diastolic blood pressure (after a transient decrease after the first dose). That effect was already present after one month, reached a plateau after 6 months, and was maintained throughout the study (Table 13).

Table 13: Changes from baseline (mmHg) in systolic and diastolic blood pressure (BP) in fingolimod controlled studies (adapted from table 81 of Dr. Villalba's review)

	Change (mean) from baseline in systolic BP at month 6*	**Change (mean) from baseline in systolic BP at month 24^**	**Change (mean) from baseline in diastolic BP at month 6***	**Change (mean) from baseline in diastolic BP at month 24^**
Fingolimod 5 mg	7.3	N/A	5.2	N/A
Fingolimod 1.25 mg	3.3	3.6	2.1	2.1
Fingolimod 0.5 mg	1.7	1.9	1.4	0.7
Placebo	-0.4	-0.4	-0.4	-0.5
Avonex	-0.2	N/A	0.3	N/A

*Study 2201, 2301 and 2302 ^Study 2301 only

Outlier analyses of vital signs with chronic use are consistent with the analyses of mean changes, and show that more patients fulfilled "notable criteria" for high blood pressure in the fingolimod groups, particularly for the 1.25 mg and 5 mg doses (Table 14 and Table 15). The difference between fingolimod 0.5 mg and placebo for notable increases in blood pressure was minimal, but hypertension was reported as an adverse reaction more frequently on fingolimod 0.5 mg (5%) than on placebo (3%). Therefore, this finding should be described in labeling.

Table 14: Notable increases in blood pressure (increase in systolic BP from baseline ≥20mmHg or increase in diastolic BP from baseline ≥15 mmHg)

	≥20mmHg increase in systolic BP	**≥15 mmHg increase in diastolic BP**
Fingolimod 5 mg	40%	36%
Fingolimod 1.25 mg	27%	25%
Fingolimod 0.5 mg	22%	22%
Placebo	20%	20%
Avonex	15%	17%

Table 15: Notable increases in blood pressure (systolic ≥160mmHg or diastolic ≥100mmHg)

	Systolic BP ≥160 mmHg	**Diastolic BP ≥ 100 mmHg**
Fingolimod 5 mg	6%	13%
Fingolimod 1.25 mg	5%	8%
Fingolimod 0.5 mg	3%	6%
Placebo	2%	5%
Avonex	2%	4%

5.7 Safety issues of possible concern with fingolimod

A. Cardiac effects
The cardiac toxicity of fingolimod was of particular concern, given the known effect of S1P modulation on heart rate. Also, there was an excess of cardiovascular deaths in renal transplant studies at the 5 mg/day dose, compared to an active control.

Bradycardia- and atrioventricular block-related SAEs
The most common SAEs in the cardiac disorders system organ class (SOC) were dose-related bradycardia and atrioventricular block (AVB). Dr Villalba observes that all SAEs related to bradycardia or AVB had an onset within the first 6 hours after the initial fingolimod dose, and resolved within 24 hours. Some events required a specific treatment, e.g. atropine or isoproterenol, including with fingolimod 0.5 mg. The event led to study discontinuation in approximately half of the cases on fingolimod 1.25 mg, and one case (2nd degree AVB) on fingolimod 0.5 mg. Dr. Villalba also notes that additional cases of bradycardia and AVB occurred upon first fingolimod dosing in extension studies, including one case of 3rd degree AVB in a patient receiving fingolimod 1.25 mg. Some patients who interrupted treatment experienced a similar episode of bradycardia or AV block when the drug was restarted.

Cardiac disorders-related adverse events leading to discontinuation
Dr. Villalba notes a dose response in the number of patients who discontinued because of cardiac events. The most common cause of discontinuation was bradycardia, followed by second and first degree AV Block. It is noteworthy that most of these events occurred in the fingolimod 1.25 mg group. The only cardiac adverse dropout in the fingolimod 0.5 mg group, for left ventricular dysfunction, is to be contrasted with a case of adverse dropout for diastolic dysfunction, and a case of adverse dropout for palpitations in the placebo group.

Heart conduction and bradycardia
Patients in Study 2301 and 2302 (as well as in long-term extension studies) were monitored in the clinic for at least 6 hours after taking the first dose of study drug. 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 these criteria had to be observed longer (until criteria were met). 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.

Compared to placebo, more patients who received fingolimod 1.25 mg and 0.5 mg required extended monitoring and hospitalization. The rate of discontinuation was however no higher after the first dose of fingolimod 0.5 mg dose than after the first dose of placebo (Table 16).

Table 16: First dose administration monitoring experience

	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

There is a clear dose-related effect on heart conduction after the first dose of fingolimod. The most frequently observed ECG findings in the 6 hours after the first dose were related to conduction and rhythm disturbances (mostly AV block and sinus bradycardia), and were more frequently reported in the fingolimod 1.25 mg group than in the other groups. ECG data for the fingolimod 0.5mg group are mostly reassuring (Table 17).

Table 17: ECG abnormalities 6 hours after the first fingolimod dose (adapted from Table 87 of Dr. Villalba's review)

Abnormality	Fingolimod 1.25mg N=840	Fingolimod 0.5mg N=837	Placebo N=413	Avonex N=422
First degree AV block	9.8%	4.7%	1.5%	2.8%
AV Mobitz 1	0.7%	0.2%	0	0
2:1 AV block	0.2%	0	0	0

A 24-hour holter monitoring substudy in 129 patients showed that the decline in heart rate was observed as early as 1 hour post-dose, reaching a maximum decrease at 5 hours post-dose in the fingolimod 1.25 mg group (mean drop of approximately 28 bpm), and at 6 hours post-dose in the fingolimod 0.5 mg group (mean drop of approximately 22 bpm). The largest holter database comes from Study 2309 (366 patients on fingolimod 1.25 mg, 356 patients on fingolimod 0.5 mg, and 353 patients on placebo). In Study 2309, second degree AV blocks (Mobitz 1 or 2:1 blocks) were observed in 6.6% of patients on fingolimod 1.25 mg, 3.4% of patients on fingolimod 0.5 mg and 2% of patients on placebo. Bradycardia[3] was observed after the first dose in 1.4% of patients on fingolimod 1.25 mg, 0.3% of patients on fingolimod 0.5 mg and none on placebo. SAEs related to AV block or bradycardia within 6 hours of the first dose were reported in 3 patients on fingolimod 1.25 mg who were symptomatic and hospitalized for observation. They fully recovered by Day 2 and discontinued study drug.

Novartis proposes monitoring for six hours after the first fingolimod dose only in patients on beta blockers and low baseline heart rate. Dr. Villalba notes that labeling is imprecise as to the location for first dose monitoring. Dr. Villalba believes that all patients should be monitored for the first dose in a medical unit capable of immediate treatment for severe cases of bradycardia and heart block. In addition, Dr. Villalba notes that the fingolimod studies excluded patients with pre-existent diseases such as diabetes mellitus, heart conduction

[3] defined as average heart rate of 40 bpm for anyone hour during 24-hour Holter monitoring

disorders, taking antiarrhythmics medications or having pulmonary disease. Dr. Villalba believes that patients with any of these disorders might not tolerate bradycardia or AV block as well as the patients who participated to fingolimod clinical studies. Dr. Villalba also recommends a study in that more vulnerable population. I agree with that recommendation.

Left ventricular function and ischemic heart disease
Because of a signal for vascular wall thickening and perivascular and focal fibrosis of the left ventricular papilla in animal studies, and because cases of heart failure, pulmonary edema, pulmonary congestion and fluid overload were observed on fingolimod in the transplant clinical trials (albeit at doses above that proposed in MS), FDA requested that a subset of MS patients be monitored by echocardiography.

A total of 183 patients were included in the echocardiography substudy (64 patients on fingolimod 1.25 mg, 60 patients on fingolimod 0.5 mg, 48 patients on placebo and 11 patients on Avonex). Unfortunately, available echocardiographic evaluations are limited and incomplete, as at the time of the original submission, only 17 patients had paired echocardiograms for up to 2 years[4]. These limited data did not show evidence for a fingolimod effect on left ventricular function. Of note, there was no excess of congestive heart failure or ischemic heart disease with fingolimod in controlled MS studies.

Division of Cardio-Renal Products (DCRDP) consult
The division consulted Dr. Shari Targum (DCRDP) regarding the echocardiographic data. Dr. Targum believes that available echocardiographic evaluations are limited and incomplete, but did not reveal a large safety signal. Dr. Targum observes that depressed left ventricular systolic function was not observed. As actual echocardiograms were not submitted, Dr. Targum was unable to comment on the quality of the evaluations. Dr Targum notes that no Doppler results or evaluations of valve morphology were submitted. Dr. Targum emphasizes that concerns about papillary muscle fibrosis could be addressed by evaluations of the mitral and tricuspid valves, including an assessment of regurgitation, but those examinations were not done.

Nevertheless, Dr. Targum believes that if there were a large signal, e.g. an imbalance in severe chronic mitral regurgitation, consequences of chronic volume overload such as left ventricular and left atrial dilatation, in addition to a holosystolic murmur heard best at the apex would have been observed. Dr. Targum therefore finds somewhat reassuring that the 12 month left atrial volume, end-diastolic and end-systolic dimensions were not increased from baseline. However, Dr. Targum cannot exclude a smaller signal, or a signal that would appear over a longer time period. Finally, because the study population excluded diabetics and subjects with significant heart disease, Dr. Targum cannot exclude safety signals that might surface in a more vulnerable population.

B. Infections
Fingolimod causes a dose-dependent reduction of lymphocytes count. Therefore, an increased risk of infections had to be examined. There was no excess of infections with fingolimod compared to placebo or Avonex, with the exception of serious herpes infections.

[4] only data on 30 patients exposed for 2 years are expected during the NDA review cycle .

Infection-related deaths and SAEs
Dr. Villalba did not find any major difference in the risk for serious infections between the fingolimod treatment groups and placebo or interferon in controlled studies, with the exception of serious herpes infections, which occurred in 4/1000 patients treated with fingolimod 1.5 mg/day. The rate of serious herpes infection was however the same (1/1000) for fingolimod 0.5 mg and Avonex.

Fatal herpes infections (herpes encephalitis and disseminated zoster) occurred in two young patients on fingolimod 1.25 mg, who also received intravenous steroids for treatment of MS relapse.

In addition to the two fatal cases, four patients on fingolimod in controlled studies experienced an SAE of herpetic infection that required hospitalization (two on fingolimod 1.25 mg and two on fingolimod 0.5 mg), and one patient on fingolimod 1.25 mg presented with an atypical MS relapse that was treated with intravenous acyclovir because viral encephalitis could not be ruled out.

Additionally, six SAE of herpetic infection (one patient who received fingolimod 5 mg in the controlled study, and fingolimod 1.25 mg in the extension study, four patients on fingolimod 1.25 mg, and one patient on fingolimod 0.5 mg) occurred in long-term extension studies. In addition, one patient developed atypical MS and was treated with acyclovir 2 months after the last dose of fingolimod 1.25 mg.

When the entire safety database (controlled and uncontrolled studies) is considered, the percentage of infection-related SAEs suggests a dose response for fingolimod (1.3%, 2.6% and 3.6% respectively for fingolimod 0.5 mg, 1.25 mg, and 1.25-5 mg). The analysis of event rates (events per 100 patient-years) in the controlled and uncontrolled studies database also suggests a higher rate of infection-related SAEs in fingolimod 5 mg (1.4 per 100 patient-years) and 1.25 mg (1.8 per 100 patient-years) compared to fingolimod 0.5 mg (0.9 per 100 patient-years).

Infections-related adverse events leading to discontinuation
There was also a slightly higher rate of infection- and infestation-related adverse events leading to discontinuation for fingolimod 1.25 mg (0.7%), compared with fingolimod 0.5mg (0.1%), placebo (0.4%) or Avonex (0.2%).

Infections-related common adverse events
Bronchitis was the only common adverse event (incidence ≥5%) reported more frequently on fingolimod 1.25 mg (7%) or fingolimod 0.5 mg (6%) than on placebo (3%) or Avonex (3%).

Division of Special Pathogens consult
The division consulted Dr. Marc Cavaille Coll, from the Division of Special Pathogens (DSPTP), regarding the risk for opportunistic infections with fingolimod. Dr. Cavaille Coll notes that fingolimod causes a redistribution (rather than depletion) of lymphocytes, and that lymphocyte count therefore should not be interpreted as reflective of the net state of immunosuppression in patients on fingolimod. Dr. Cavaille Coll does not believe that there is

a compelling signal for a significantly increased risk for opportunistic infections at the proposed fingolimod daily dose of 0.5 mg.

Dr Cavaille Coll also notes that exploratory analyses of the relationship between infections and lymphocyte counts were not conclusive. Dr. Cavaille Coll recommends consideration of vaccination, in particular for varicella zoster virus (VZV), prior to initiation of long-term immunosuppressant therapy. Dr. Cavaille Coll notes that vaccination may be less effective during treatment with immunosuppressants, and that live vaccines should be avoided in that situation[5]. He recommends consideration of post-exposure prophylaxis in patients seronegative for VZV at risk of developing varicella after primary exposure.

C. Macular edema and other ocular toxicity

In the renal transplant safety database, serious macular edema was reported in 4.1%, 3.9% and 1.5% of patients receiving fingolimod 5 mg, fingolimod 2.5 mg or active control, respectively. That finding prompted a requirement for monitoring for macular edema in MS studies, including regular optical coherence tomography testing (OCT) in a subset of patients. The Division consulted Dr. Wiley Chambers, Supervisory Medical Officer in the Division of Anti-Infective and Ophthalmology Products, about fingolimod ocular toxicity.

Eye disorders-related SAEs

In controlled MS studies, there was a dose-related increase of the incidence of macular edema reported as a SAE: 4 cases were reported on fingolimod 1.25 mg (0.4%), and 1 case was reported on fingolimod 0.5 mg (0.1%), versus no case on placebo or Avonex. When the entire (controlled and uncontrolled) MS database is considered, the same dose-response relationship is seen, with a 0.8% incidence of macular edema reported as an SAE for fingolimod 1.25 mg, versus 0.2% for fingolimod 0.5 mg. Four additional cases of macular edema-related SAE were reported in ongoing Study 2309 (2 on fingolimod 1.25 mg, 1 on fingolimod 0.5 mg, and 1 on placebo).

Dr. Villalba notes that some patients had symptoms at the time of diagnosis (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 Optical Coherence Tomography[6] (OCT) at protocol scheduled timepoints. In some cases, fluorescein angiography was used to confirm macular edema suspected with OCT. Some cases were bilateral but most cases involved only one eye.

Onset of macular edema was reported as early as 11 days and as late as 932 days after treatment start. Most cases occurred in the first 4 months of treatment (mean 207 days; median 99 days).

All cases of serious macular edema led to study drug discontinuation (one was diagnosed after drug discontinuation). Some patients received additional treatment (NSAIDs, topical steroids).

[5] Live vaccines may include, but are not limited to measles, mumps, rubella, oral polio, BCG, yellow fever, and Ty21a typhoid3.

[6] Optical coherence tomography (OCT) is a noninvasive imaging technology that allows measurements of retinal thickness.

Dr. Villalba notes that most (but not all) patients recovered completely within a few weeks or months after drug discontinuation.

Eye disorders adverse events leading to discontinuation
Dr. Villalba notes that 20 patients had adverse events that led to drug discontinuation in the Eye disorders system organ class in fingolimod controlled studies. Some of them were coded as serious (4 cases of macular edema on fingolimod 1.25 mg and one on fingolimod 0.5 mg described above), but some events of interest were coded as non serious. These include eight cases of macular edema in the fingolimod 1.25 mg group, one in the fingolimod 0.5 mg group and one in a subject who received Avonex (not confirmed by DSMB ophthalmologist). Dr. Villalba also describes a few non-serious cases of retinal hemorrhage and retinal aneurysms, all in the fingolimod treatment groups. There were 4 additional cases in Study 2309 that led to discontinuation of fingolimod 0.5 mg because of macular edema.

Optical coherence tomography monitoring
In controlled studies other than Study 2309, Dr. Chambers notes a higher proportion of patients with a central foveal thickness of >200 but ≤250 microns in the fingolimod treatment groups than in the placebo group (12.5% with fingolimod 1.25 mg, 13% with fingolimod 0.5 mg group, and 9.3% with placebo). Dr. Chambers found no difference between the 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 with 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 patient in the placebo group (Table 18).

Table 18: Change in central foveal thickness (OCT substudy)

	Fingolimod 1.25 mg	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%)

In Study 2309, Dr. Chambers also observed small, dose-dependent effects of fingolimod on central foveal thickness (difference from placebo in mean/median change from baseline 5 microns/4 microns on fingolimod 1.25 mg, and 4 microns/3 microns on 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.

Dr. Chambers notes that 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 a macular edema diagnosis in 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, 5 had central foveal thickness >300 microns. For the 6 cases not considered as macular edema by the DMSB, 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.

Dr. Chambers observes that at the dose proposed for the treatment of MS (0.5 mg), there have been a limited number of cases of macular edema. Dr. Chambers notes that patients with multiple sclerosis are often recommended to be followed with a full ophthalmic examination including dilated fundoscopy (and ocular coherence tomography as needed) every six months. Dr. Chambers believes that ocular findings in the fingolimod NDA 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. Discussion with neurologists at the advisory committee however indicated that neurologists seeing MS patients do not regularly perform dilated fundoscopy, and the need for an ophthalmologic evaluation at baseline and after 3-4 months was emphasized.

D. Pulmonary effects

Nonclinical toxicity studies showed evidence of pulmonary toxicity. In addition, bronchoconstriction was seen in a clinical pharmacology study at single fingolimod doses ≥5 mg/day, and there was an excess of dyspnea and pulmonary edema (of undetermined origin) in fingolimod-treated patients in the renal transplant program. Because of these signals, Novartis was requested to monitor a subset of patients (100 patients each for fingolimod 0.5 mg, fingolimod 1.25 mg and placebo) with chest high resolution CT scans (HRCT) at baseline and at the end of the study. Novartis was also required to monitor pulmonary function tests (PFTs).

Chest HRCTs

In Study 2301, 360 patients (one third of those randomized) had chest HRCT scans at screening. Of these, 259 patients had an assessment at Month 24, and another 34 patients had an end-of-study scan performed outside of the 24-month visit window. At Month 24, the percentage of patients with chest HRCTs showing new or worsened abnormalities was higher in the fingolimod groups than in the placebo group (14.1% on fingolimod 1.25 mg, 4.4% on fingolimod 0.5 mg, and 9.5% on placebo). However, there was no particular pattern of toxicity and no evidence of pulmonary fibrosis.

In Study 2302, chest HRCTs were performed in 478 patients at screening and 421 patients at Month 12. The proportion of patients with chest HRCT showing new or worsening abnormalities compared to baseline was similar across treatment groups (fingolimod 1.25 mg, fingolimod 0.5 mg, and placebo).

Preliminary chest HRCT data from Study 2309 show no significant difference between fingolimod 0.5 mg and placebo, but final data from that study are not yet available.

PFTs
PFTs evaluating FEV1 (Forced expiratory volume in one second), FVC (Forced vital capacity), and carbon monoxide diffusing capacity (DLCO) were performed at 3-6 months intervals during pivotal controlled studies. PFT evaluation over time showed an initial sharp decrease within the first month followed by a progressive decrease in FEV1 (Figure 4 and Figure 5) and DLCO (Figure 6 and Figure 7) over time. There was no correlation of these changes with pulmonary symptoms. There were no significant changes in FVC.

Figure 4: FEV1 change from baseline (pooled data from Study 2301 and 2302; copied from Figure 4 of Dr. Villalba's review)

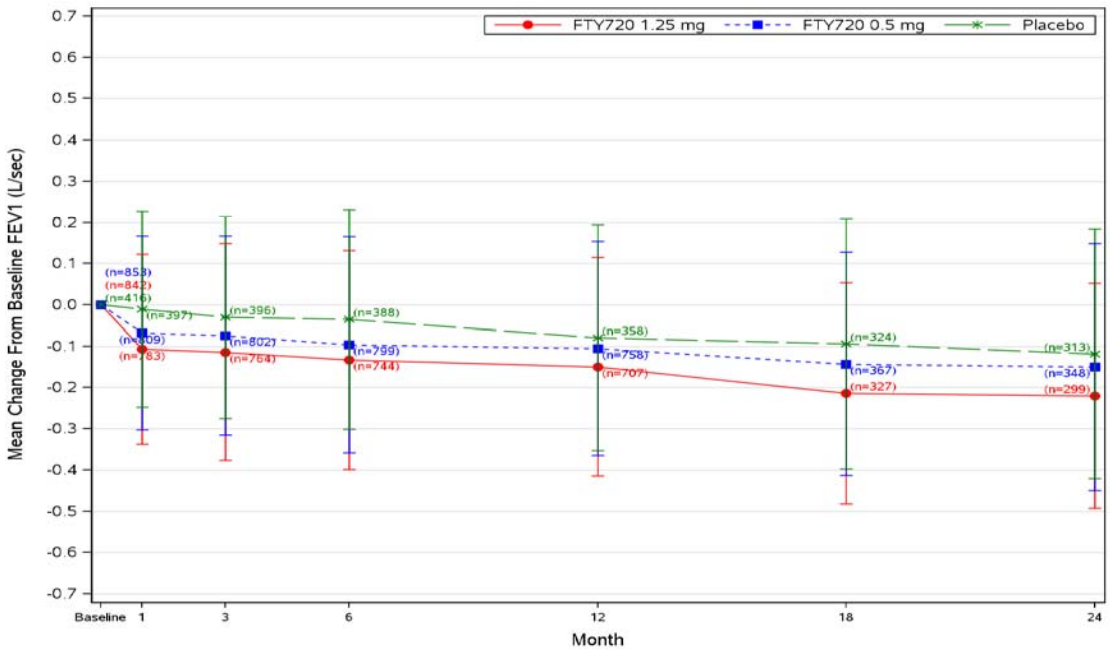


Figure 5: FEV1 change from baseline (Study 2309; copied from Figure 7 of Dr. Villalba's review

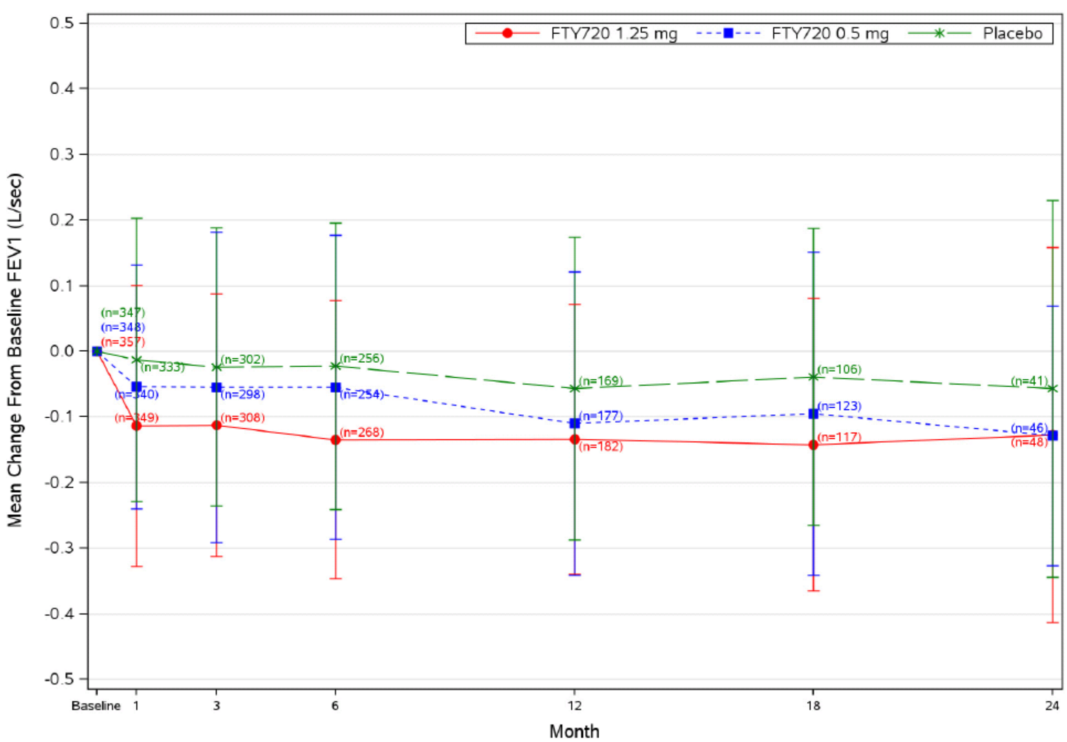


Figure 6: DLCO changes from baseline (pooled data from Study 2301 and 2302; copied from Figure 6 of Dr. Villalba's review)

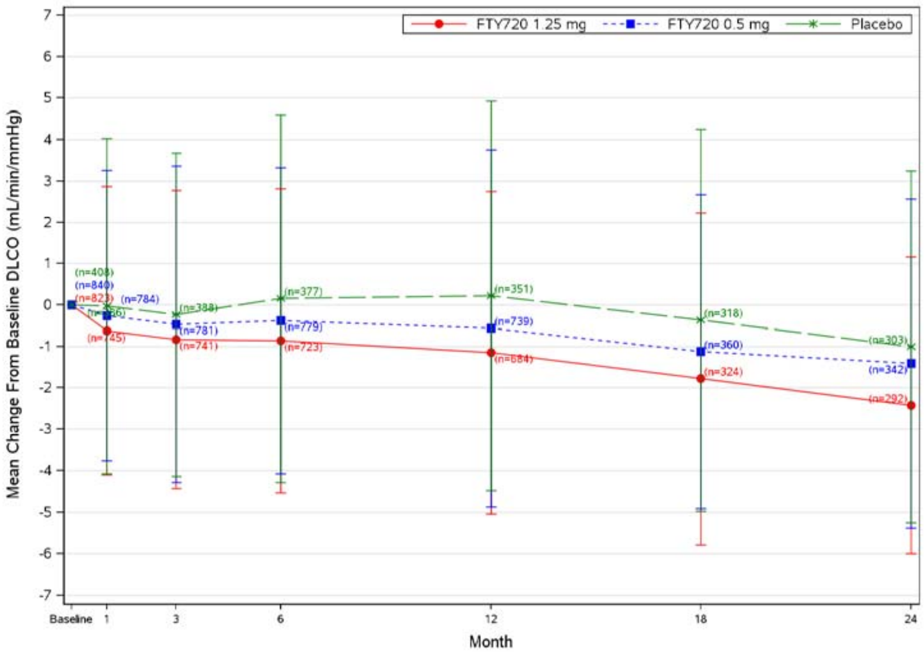
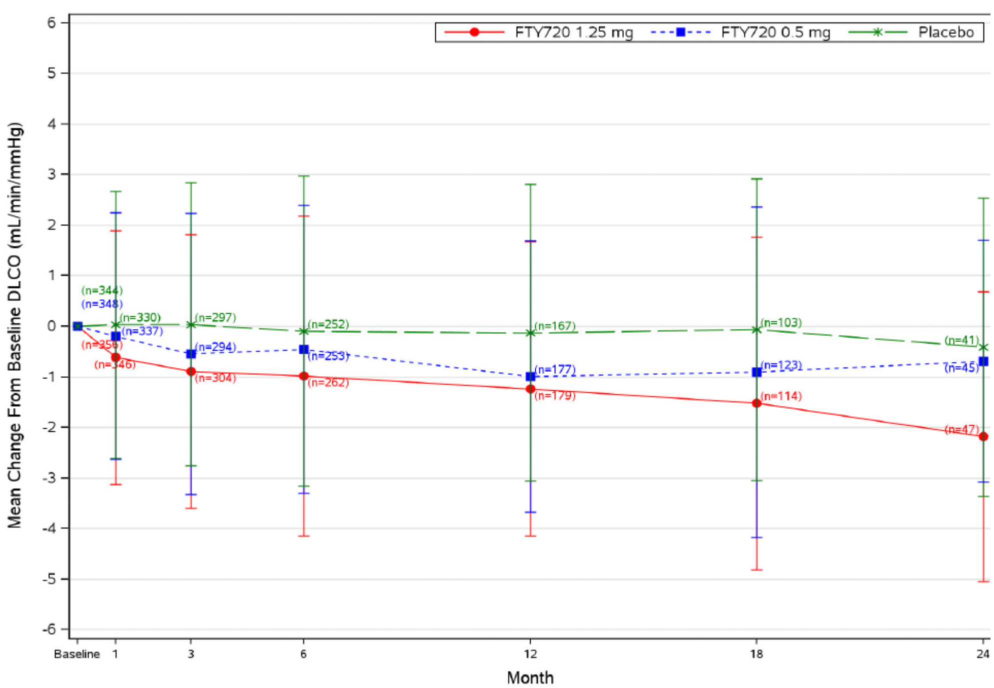


Figure 7: DLCO change from baseline (Study 2309; copied from Figure 8 of Dr. Villalba's review)



On treatment, there was also a dose-response for the proportion of patients with a PFT parameter <80% of baseline (Table 19 and Table 20).

Table 19: PFT outliers (pooled data from Study 2301 or 2302; copied from table 98 of Dr. Villalba's review)

		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%)

Table 20: PFT outliers (Study 2309; copied from table 101 of Dr. Villalba's review)

	FTY720 1.25mg N=358 n (%)	FTY720 0.5mg N=348 n (%)	Placebo N=347 n (%)
<80% of BL PFT absolute values at any post-BL visit			
FEV1	20 (5.6)	11 (3.2)	8 (2.3)
FVC	12 (3.4)	6 (1.7)	5 (1.4)
DLCO	47 (13.1)	41 (11.8)	25 (7.2)

Dr. Villalba believes that the decrease in FEV1 may be in part explained by the known bronchoconstrictive effects of fingolimod, but she finds no explanation for the decreased diffusion capacity.

Importantly, a subset of patients (288 patients on fingolimod 1.25 mg and 211 patients on fingolimod 0.5 mg) was followed up after drug discontinuation. In these patients, the FEV1 changes were largely reversible, but the DLCO changes were not.

Asthma
Subjects with asthma were allowed in fingolimod studies if they did not require active treatment. No adverse event related to asthma occurred on fingolimod 0.5 mg.

Division of Pulmonary, Allergy and Rheumatology Products (DPARP) consult
The division consulted Dr. Brian Porter (DPARP) regarding the pulmonary toxicity of fingolimod. Dr. Porter believes the data do not support requesting routine PFT monitoring or routine HRCT screening of patients treated with fingolimod. However, Dr. Porter recommends a description of the pulmonary findings in labeling and in communications (e.g. Dear Dr. letter). Dr. Porter also recommends further study of the stability and reversibility of pulmonary function deficits with long-term use of fingolimod. After considering the advisory committee recommendations (see below), the review team reached the position that spirometric evaluation of respiratory function and evaluation of DLCO should be performed during therapy with GILENYA if clinically indicated, and that routine monitoring was not justified.

E. Liver effects

Fingolimod causes frequent liver enzymes elevations.

Hepatobiliary-related SAEs (including liver enzyme abnormalities)
There is a clear dose-related increase in SAEs related to hepatobiliary disorders and liver enzyme abnormalities (0.7%, 0.5%, 0.2% and 0.2% respectively for fingolimod 1.25 mg, fingolimod 0.5 mg, placebo and Avonex). Most SAEs related to liver enzyme abnormalities led to study drug discontinuation. In addition, there were many liver-related events that led to study discontinuation but were not coded as serious (these are discussed below). Dr. Villalba notes that patients with hepatobiliary Investigations SAE reported up to the time of the NDA safety update were asymptomatic and the diagnosis was made during protocol scheduled laboratory examinations (mean 162 days after treatment onset; range 19-301 days). Several cases were confounded by the use of concomitant medications, but all cases improved and most fully resolved after fingolimod discontinuation.

Hepatobiliary-related adverse events leading to discontinuation
The majority of hepatobiliary adverse events leading to discontinuation were non serious (i.e. 74/85 cases). Dr. Villalba notes most of the non serious events were associated with increases in ALT or GGT elevation 3 to 5x ULN, without associated increase in bilirubin 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. Dr. Villalba reports cases with positive de-challenge, and several cases of positive re-challenge.

Liver enzymes elevations
Fingolimod is associated with a lasting increase (15-20 IU/L) in mean blood levels of transaminases, mostly ALT and GGT (but not total or direct bilirubin). There was also an excess of patients with liver enzymes abnormalities in fingolimod-treated patients (Table 21). ALT ≥3x the upper limit of normal (ULN) was seen respectively in 9, 10 and 12% of patients in the fingolimod 0.5 mg, 1.25 mg and 5mg group, as compared to only 2% in the placebo or Avonex group. The proportion of patients with ALT ≥5xULN was also slightly higher in the fingolimod treated groups. No case was suggestive of a potential for serious drug-induced hepatotoxicity. A case of ALT elevation and jaundice on GILENYA was reported, but causality was attributed to hepatitis E.

Table 21: Distribution of patients with liver enzyme abnormalities in fingolimod controlled studies (copied from table 62 of Dr. Villalba's review)

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)

F . Blood and Lymphatic system disorders

Fingolimod causes lymphopenia. There were however few serious events related to lymphopenia (0.3% on fingolimod 1.25 mg, and 0.1% on fingolimod 0.5 mg, vs. 0% on placebo). There were also two serious cases of thrombocytopenia (one case of thrombocytopenia on fingolimod 0.5 mg and one case of autoimmune thrombocytopenia on fingolimod 1.25 mg).

G. Neoplasia

There is no signal for an increased incidence of neoplasia in patients treated with fingolimod. Even though there was a higher number of basal cell carcinoma in the fingolimod 0.5 mg group, there was no dose-response, as the rate observed with fingolimod 1.25 mg was lower than that observed with placebo.

As discussed by Dr. Villalba, the long term experience with fingolimod is limited. Given the known effect of fingolimod on circulating lymphocytes and the potential effect on immunosurveillance, Dr. Villalba believes that an increased risk of malignancy with longer exposure can not be ruled out, and she recommends that the sponsor acquire longer term data, e.g. with a registry study. I agree.

H. Seizures

The rate of serious seizure-related events in the renal transplant database was higher for fingolimod 5 mg (1.7%) and 2.5 mg (1.3%) compared to active control (0.2%). A total of 14 patients had seizure related events in the MS safety database. Of those, 10 occurred during controlled studies (9 on fingolimod and one on placebo). Although the numbers are small, the analysis suggests an increase risk of seizure related events in the fingolimod 5 mg and 1.25 mg groups, as compared with placebo. However, the rate seen with fingolimod 0.5 mg (0.1 %) is consistent with the background rate, so the data are inconclusive.

9. Advisory Committee Meeting

The Peripheral and Central Nervous System Drugs Advisory Committee met on June 10, 2010 to discuss fingolimod. The following is a summary of the questions discussed and advisory committee votes and response.

1. Has the sponsor demonstrated substantial evidence of effectiveness of fingolimod for the treatment of patients with relapsing remitting multiple sclerosis (M.S.) to reduce the frequency of clinical exacerbations? YES/NO/ABSTAIN

   YES: 25 NO: 0 ABSTAIN: 0

   Committee Discussion: *The committee members unanimously agreed that the efficacy data are robust and that the sponsor has provided substantial evidence of effectiveness of fingolimod in reducing the frequency of clinical exacerbations.*

2. Has the sponsor demonstrated substantial evidence of effectiveness of fingolimod for the treatment of patients with relapsing remitting multiple sclerosis to delay the accumulation of physical disability? YES/NO/ABSTAIN

   YES: 24 NO: 1 ABSTAIN: 0

   Committee Discussion: *The majority of the committee members agreed that the sponsor has provided substantial evidence of effectiveness of fingolimod in delaying the accumulation of physical disability. The one member voting "No" stated that longer studies are needed.*

3. If the answer to question #1 and/or question #2 is yes, should the sponsor be required to evaluate the effects of doses lower than 0.5 mg once daily? YES/NO/ABSTAIN

   YES: 20 NO: 5 ABSTAIN: 0

   Committee Discussion: *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 determine if efficacy would be maintained while reducing the risk of adverse events.*

4. If the answer to question #3 is yes, should this be required prior to approval? YES/NO/ABSTAIN

   YES: 0 NO: 24 ABSTAIN: 0

   Committee Discussion: *Note: one committee member was not present for the vote. The committee agreed that further studies on a lower dose should not be required prior to approval, but should be required as part of the postmarketing commitments from the sponsor.*

5. Does the safety data at 0.5 mg justify approval? YES/NO/ABSTAIN

   YES: 25 NO: 0 ABSTAIN: 0

   Committee Discussion: *Note: the wording of this question was modified to the above during the meeting for clarity. The committee members unanimously agreed that the benefits outweigh the risks and thus agreed that the safety data justify approval.*

6. First-dose effects of fingolimod include bradycardia and heart conduction abnormalities. Based on the data presented to you, should patients be required to receive the first dose in a monitored setting? YES/NO/ABSTAIN

   YES: 25 NO: 0 ABSTAIN: 0

   Committee Discussion: *The committee members unanimously 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, and that a baseline ECG should be obtained before starting therapy.*

7. If the answer to question #6 is yes, should that requirement apply to all patients or to a specific subset?

   Committee Discussion: *The majority of the committee members agreed that all patients should be required to receive the first dose in a monitored setting. 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, and patients taking beta blockers and/or calcium channel blockers concomitantly.*

8. Fingolimod causes macular edema, including at the dose proposed for marketing (0.5 mg). Is routine ophthalmic examination sufficient to monitor patients treated with fingolimod? YES/NO/ABSTAIN

   YES: 4 NO: 20 ABSTAIN: 1

   Committee Discussion: *The majority of the committee believed that routine ophthalmologic assessments of MS patients are not being performed by neurologists, and* *thus recommended that neurologists monitor visual acuity in patients treated with fingolimod. They also recommended a baseline evaluation with dilated ophthalmology before starting the drug.*

9. Fingolimod causes a gradual decline in pulmonary function. Do you believe that routine pharmacovigilance will be sufficient to mitigate the risks associated with the pulmonary toxicity of fingolimod? YES/NO/ABSTAIN

   YES: 7 NO: 17 ABSTAIN: 1

   Committee Discussion: *The majority of the committee agreed that routine pharmacovigilance (spontaneous post-marketing adverse event reporting) is not sufficient to mitigate the risks associated with the pulmonary toxicity of fingolimod.*

10. If the answer to question #9 is no, what additional monitoring or study do you recommend?

    Committee Discussion: *The committee's pulmonologist recommended baseline pulmonary function tests (PFTs).*

11. The sponsor has proposed to conduct a 5-year post-marketing safety study in 5000 patients to further explore the safety of fingolimod 0.5 mg under routine clinical care. Do you believe that such a study would be sufficient to address safety issues observed in this database, or do you believe that other safety studies should be required to assess specific safety concerns? If so, please identify these concerns.

    Committee Discussion: *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, and concomitant therapies.*

12. Considering the risks and benefits, do you believe that fingolimod should be generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate MS therapy? YES/NO/ABSTAIN

    YES: 3 NO: 21 ABSTAIN: 1

    Committee Discussion: *The majority of the committee members agreed that fingolimod should be an option for first-line treatment.*

10. Pediatrics

Fingolimod was discussed at a PeRC/PREA Subcommittee meeting on June 30, 2010. The Division presented a request for partial waiver for patients 0-9 years and deferral for patients 10 to 17 years of age. PeRC agreed with the Division.

The following language was found acceptable by PeRC:

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages birth through nine years of age because necessary studies are impossible or highly impracticable. This is because the number of pediatric patients less than 10 years of age with multiple sclerosis is too small.

Additionally, we are deferring submission of your pediatric study for ages 10 through 17 years for this application because this product is ready for approval for use in adults and the pediatric study have not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

1. Deferred pediatric study under PREA, a 24-month, randomized, active-controlled, parallel group superiority study to evaluate the single and multiple dose pharmacokinetics of fingolimod, 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.

11. Other Relevant Regulatory Issues

Division of Scientific Investigations review

The division requested an inspection of investigators from Study 2301 and 2302, as data from both studies are considered essential to the approval decision. One foreign clinical investigator was selected from Study 2301, and two foreign investigators were selected from Study 2302. These sites were targeted for inspection due to enrollment of a relatively large number of subjects and significant primary efficacy results pertinent to decision making. The inspections of the sites revealed no significant problems that would adversely impact data acceptability.

REMS
Novartis' proposed REMS for Gilenya includes a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS. DRISK/OSE finds the proposed REMS for Gilenya to be acceptable and recommends approval of the REMS.

Kendra Biddick, from the Division of Compliance Risk Management and Surveillance, Office of Compliance also reviewed the REMS. Kendra Biddick recommends that the launch of the communication plan be within 60 days of the approval of the REMS (and not tied to the launch of the drug). She also recommends that the mailing of the introductory letter correspond with the date of the launch of the drug instead of the approval of the REMS. Various editorial changes from the Office of Compliance were also applied to the REMS, REMS supporting documents, and to the action letter.

CSS
Dr. Alicja Lerner notes that the safety profile of fingolimod and the proposed population of use will likely limit its abuse potential. Dr. Lerner notes that no case of overdose has been reported to date, and found no conclusive evidence for an abuse potential of fingolimod. Dr. Lerner believes that collection and analysis of postmarketing safety data are necessary to identify a signal of abuse or misuse of fingolimod. I believe that this can easily be added to the large postmarketing cohort study that the sponsor will be required to conduct.

12. Labeling

The final proposed trade name, GILENYA, was found acceptable by DMEPA. The Medication Guide was reviewed by DRISK.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action
I recommend approval.

Risk Benefit Assessment
Clinical trials show that fingolimod is effective for the treatment of patients with relapsing remitting multiple sclerosis, to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability. The effect on clinical exacerbations was demonstrated not only against placebo, but also against an active control, interferon β-1a i.m. The effect on the accumulation of disability was demonstrated against placebo, but not against the active control. I believe that a disability claim should nevertheless be granted, because it is substantiated by the very robust effect on clinical exacerbations, which is a related endpoint. An effect was also demonstrated on the number of new or newly enlarged T2 lesions, both against placebo and against interferon β-1a i.m. The dose response between the doses tested in pivotal efficacy trials (1.25 mg and 0.5 mg) was essentially flat, and an evaluation of the efficacy of a lower dose, e.g. 0. 25 mg, should be conducted after approval, as recommended by the Peripheral and Central Nervous System Drugs Advisory Committee.

Importantly, as the superiority over interferon β-1a i.m was not independently substantiated, I do not believe that a superiority claim over interferon β-1a i.m should be granted.

Fingolimod benefits, in my opinion, clearly outweighs its risks. These risks are not insignificant, but they are manageable by adequate labeling and a communication plan. The risks include cardiac effects (bradycardia and AV blocks), infections, macular edema, pulmonary effects (decline in pulmonary function), liver effects (frequent elevations of liver transaminases), and fetal toxicity. In particular, as recommended by the PCNS, all patients should be required to receive the first dose in a monitored setting. All patients should also have a baseline ophthalmological evaluation, and a follow-up evaluation after 3-4 months of treatment, and as needed in case of new symptoms. All patients should also have PFTs in case of unexplained pulmonary symptoms.

There are also concerns about the long-term effects of fingolimod, as pre-marketing data beyond two years of treatment are limited. The sponsor has proposed to conduct a 5-year post-marketing safety study in 6000 patients to further explore the safety of fingolimod 0.5 mg under routine clinical care. I agree with the PCNS that this study should be required, with as secondary objectives the collection of data in patients with diabetes and cardiovascular disease.

A pediatric development program in pediatric patients age 10-17 years will also be required.

Recommendation for Postmarketing Risk Evaluation and Management Strategies
A REMS is necessary for fingolimod to ensure that the benefits of the drug outweigh the risks bradyarrhythmia and atrioventricular block at treatment initiation, infections, macular edema, respiratory effects, hepatic effects, and fetal risk. The elements of the REMS will be a Medication Guide and a communication plan.

Recommendation for Postmarketing Requirements and Commitments
I agree with the review team that the following studies should be requested as PMRs:

1) A postmarketing observational prospective, parallel cohort study in relapsing multiple sclerosis patients to assess the potentially serious risk of: eye toxicity, cardiac and vascular toxicity, pulmonary toxicity, seizures, serious and opportunistic infections, malignancies, liver toxicity and atypical multiple sclerosis relapse. Specific outcomes examined should include, but not be limited to, macular edema, symptomatic bradycardia, second and third degree atrioventricular block, and lymphoma. The two observed cohorts should consist of 1) patients newly prescribed fingolimod and 2) patients receiving another disease modifying therapy. The study population should be representative of patients with relapsing multiple sclerosis who take disease modifying therapies and should include patients with a history of diabetes or other cardiovascular risk factors. The study design should minimize differences between the cohorts by defining the populations in both cohorts so that they will be similar, by ensuring that both cohorts have similar clinical assessments, and by ensuring that patients who discontinue treatment have continued follow-up. In addition, the study protocol should account for duration of exposure,

treatment changes, and loss to follow-up. Sample size should be supported by estimates of the rates of the events of interest.

2) 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.

3) An *in vitro* study to evaluate the potential for fingolimod-P to induce CYP450 isoenzymes.

4) An *in vitro* study to evaluate the potential for fingolimod to inhibit CYP2C8 and for fingolimod-P to inhibit CYP2B6.

5) An *in vitro* study to evaluate the potential for statins (e.g. simvastatin, lovastatin) to induce CYP4F2, an enzyme that metabolizes fingolimod.

6) An integrated summary of safety for Studies FTY720D2301, FTY720D2302, and FTY720D2309 (upon completion of Study FTY720D2309). The summary should include updated exposure and analyses of safety following the format of a 4-month NDA safety update report, for the double-blind portion of the studies (Pool D + FTY7202309) and all studies (Pool E + 2309 double blind and extension).

7) A juvenile rat toxicology study. The study should utilize animals of an age range and stage(s) of development that are comparable to the intended pediatric population; the duration of dosing should cover the intended length of treatment in the pediatric population. In addition to the usual toxicological parameters, this study should evaluate effects of fingolimod on growth, reproductive development, and neurological and neurobehavioral development.

8) A drug interaction clinical trial to evaluate the effect of carbamazepine on fingolimod pharmacokinetics.

The sponsor agreed to the following post-marketing commitment:

A prospective, randomized, controlled study of fingolimod 0.5 mg, fingolimod 0.25 mg, and an appropriate control, of at least one year duration, to evaluate the efficacy and safety of the drug.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ERIC P BASTINGS
09/21/2010