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Fingolimod

A Review of its Use in the Management of Relapsing-Remitting Multiple Sclerosis

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Data Selection

Sources: Medical literature (including published and unpublished data) on 'fingolimod' was identified by searching databases since 1996 (including MEDLINE and EMBASE and in-house AdisBase), bibliographies from published literature, clinical trial registries/databases and websites (including those of regional regulatory agencies and the manufacturer). Additional information (including contributory unpublished data) was also requested from the company developing the drug.

Search strategy: MEDLINE, EMBASE and AdisBase search terms were 'fingolimod' and ('multiple sclerosis' or 'relapsing remitting multiple sclerosis' or 'multiple sclerosis relapsing remitting'). Searches were last updated 6 July 2011.

Selection: Studies in patients with relapsing remitting multiple sclerosis who received fingolimod. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Fingolimod, sphingosine 1-phosphate receptor agonists, multiple sclerosis, relapsing-remitting multiple sclerosis, immunosuppressants, immunomodulators, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability.

Contents

Abstract

Oral fingolimod (Gilenya™), a sphingosine 1-phosphate (S1P) receptor agonist, is the first oral agent and the first in a novel class of disease-modifying therapies (DMTs) to be approved for use in the US for the treatment of relapsing forms of multiple sclerosis (MS). In the EU, fingolimod is approved for use as a single-agent DMT in selected patients with highly-active, relapsing-remitting (RR) MS. This article reviews the pharmacological properties and clinical use of the drug in patients with RRMS.

Fingolimod is rapidly converted *in vivo* to the active moiety *S*-fingolimod-phosphate, which binds with high affinity to S1P receptors, thereby sequestering lymphocytes in the lymph nodes and preventing their egress into the peripheral circulation. As a consequence, there is a reduction in the infiltration of autoaggressive lymphocytes into the CNS. Fingolimod-phosphate also acts as a functional antagonist, as its binding to S1P receptors results in their internalization and degradation, thereby downregulating S1P receptors on the lymphocyte cell surface. Since fingolimod crosses the blood : brain barrier, it also potentially acts at S1P receptors on neural cells in the CNS to mitigate neuropathological processes associated with MS.

In large multinational trials in adult patients with RRMS, oral fingolimod 0.5 mg/day was more effective than oral placebo (FREEDOMS) and recommended dosages of intramuscular interferon-β (IFNβ)-1a (TRANSFORMS) in reducing the annualized relapse rate and was also generally more effective at slowing progression of neurological disability and at reducing the burden and activity of disease. Fingolimod was generally well tolerated in these trials of up to 2 years' duration, with most adverse events being manageable and of mild to moderate severity; there were two deaths from opportunistic infections, albeit these occurred with fingolimod 1.25 mg/day (higher than the recommended dosage). Limited long-term data indicated that no new safety concerns had arisen after 5 years of fingolimod treatment. However, further clinical experience is required to fully determine the long-term safety profile of fingolimod, particularly with regard to any potentially serious or life-threatening adverse events. In the absence of robust pharmacoeconomic studies and of head-to-head trials comparing fingolimod with other formulations of IFNβ and glatiramer acetate, the relative position of fingolimod with respect to other DMTs remains to be fully determined. In the meantime, given its convenient once-daily oral treatment regimen and better efficacy than intramuscular IFNβ-1a, fingolimod is a valuable emerging option for the treatment of adult patients with relapsing forms of MS.

1. Introduction

Multiple sclerosis (MS) is a common, usually progressive, neurological disease that affects the CNS.[1-3] Globally, it is estimated that the total number of people affected with MS is approximately 2.5 million, with MS being one of the most common neurological disorders and causes of disability in young adults, especially in Europe and North America.[1,4] Worldwide, the disease is

approximately twice as common in women as it is in men, with the average age of onset being approximately 30 years.[1,4] Most patients with MS have a normal or near-normal life expectancy.[4]

The exact aetiology of MS is unknown; it is generally considered to be an organ-specific autoimmune disease that occurs in genetically susceptible young adults, although multiple pathogenic mechanisms are likely to be involved.[5] The disease is characterized histologically by the presence of demyelinated, sclerotic lesions in the CNS. Localized areas of inflammation lead to a loss of oligodendrocytes and the development of demyelination that subsequently interferes with nerve conduction, resulting in progressive neurological impairment.[5] Clinical signs and symptoms of MS show considerable variations between individuals, with the exact symptoms dependent on the site and extent of MS lesions.[4,5] Clinical signs and symptoms commonly include paraesthesia or numbness, motor weakness, visual disturbances and lack of co-ordination.[5] Approximately 60% of patients with MS are no longer ambulatory within 20 years of disease onset.[4]

The exact course of the disease for any given individual shows a high degree of heterogeneity in terms of clinical, immunological and pathomorphological changes.[3,4,6] The various subtypes of the disease are classified according to the most common clinical course of the disease, with the majority of patients (≈80–85%) having relapsing-remitting (RR) MS at onset. RRMS is characterized by episodes of acute worsening (i.e. a relapse) with recovery and a stable disease course between relapses. It progresses in approximately 50% and 80% of patients within 10 and 20 years of disease onset, with relapses becoming more severe and being associated with less complete recovery such that patients develop more progressive disease.[4,6]

MS is a treatable, but as yet incurable, disease for which there are a limited number of licensed disease-modifying therapies (DMTs) available.[2,4] Since the disease is primarily considered an autoimmune disease, the mainstay of treatment has been the immunomodulatory agents interferon-β (IFNβ)-1a, IFNβ-1b and glatiramer acetate, all of which have modest efficacy and good safety profiles.[2] However, all of these agents are administered either intramuscularly or subcutaneously, which may significantly impact on adherence (e.g. many patients have an aversion to injections).[3,7] Hence, the availability of effective oral formulations would potentially improve the patient's quality of life and increase adherence to therapy.[3,7-9] An improved understanding of the immunopathogenesis of MS, including the cellular and molecular mechanisms involved in immune cell migration and activation, along with better technology, has led to the development of new targeted therapies for the management of MS.[2,3]

One potential therapeutic target for the treatment of MS is sphingosine 1-phosphate (S1P) and its receptors, which play a pivotal role in normal physiological processes and in pathogenic processes, particularly those associated with the immune, central nervous and cardiovascular systems.[10-12] S1P is a member of the lysophospholipid family of plieotropic mediators and is involved in several cellular responses associated with the pathogenesis of MS, including proliferation, migration, adherence, tight junction assembly, and neural cell communication and survival. Signalling by S1P is mediated by five related plasma membrane G-protein-coupled receptors ($S1P_1$, $S1P_2$, $S1P_3$, $S1P_4$ and $S1P_5$) that are differentially expressed on several cell types throughout the body, including cells of the immune system and CNS. Each receptor triggers different, but overlapping, signalling pathways that elicit diverse cellular responses. Potential targets whereby an S1P receptor agonist may act to mitigate the pathological processes associated with MS include $S1P_1$ receptors expressed on lymphocytes and S1P receptors expressed on neural cells in the CNS.[10-12]

Fingolimod (Gilenya™) is a novel S1P receptor agonist derived from myriocin, which is a metabolite of the fungus ascomycete *Isaria sinclairii*.[11] The drug is the first oral agent and the first in its class to be approved in the US for the treatment of adult patients with relapsing forms of MS (section 6).[13] In the EU, fingolimod is approved for use as a single-agent DMT in selected patients with highly active RRMS (section 6).[14] This article reviews the use of oral fingolimod in

the management of RRMS, providing an overview of its pharmacological properties and discussing its efficacy and tolerability in this patient population.

2. Pharmacodynamic Properties

The pharmacological properties of fingolimod (figure 1) have been extensively reviewed[11,12,15-19] and, for the most part, are summarized in this section.

Fingolimod is phosphorylated by sphingosine kinase 2 to the pharmacologically active moiety *S*-fingolimod-phosphate (section 3), which is a close structural analogue of endogenous S1P.[20] *S*-fingolimod-phosphate (the enantiomer being referred to in all subsequent discussion), but not *R*-fingolimod-phosphate or fingolimod, is a potent agonist at four of the five S1P receptors (figure 2).[11,16-18,20] Respective binding affinity constants (K_i) of fingolimod-phosphate at $S1P_1$, $S1P_3$, $S1P_4$ and $S1P_5$ receptors were 0.3, 3.1, 0.6 and 0.3 nmol/L.[16,18,20,21] Fingolimod-phosphate has no affinity for $S1P_2$ receptors (K_i >10 000 nmol/L).[16,18,20,21]

By binding with high affinity at S1P receptors, fingolimod-phosphate mediates lymphocyte trafficking, sequestering lymphocytes, including potentially encephalitogenic T cells and their naive progenitors, in the lymph nodes and preventing their egress into the peripheral circulation.[15,17,18] As a consequence, there is a reduction in the number of peripheral blood lymphocytes and in the infiltration of autoaggressive lymphocytes into the CNS. Fingolimod-phosphate also acts as a functional antagonist, as its binding to the $S1P_1$ receptor results in their internalization and degradation, thereby down-regulating $S1P_1$ receptors on the lymphocyte cell surface and removing the signalling pathway that would allow their egress from lymphoid tissues into the circulation.[17] In patients with MS, fingolimod most likely exerts its key pharmacological effects via these S1P receptor-mediated actions on the immune system (section 2.1) and its potential actions in the CNS (section 2.2), with proposed/potential mechanisms summarized in figure 2.[15-17]

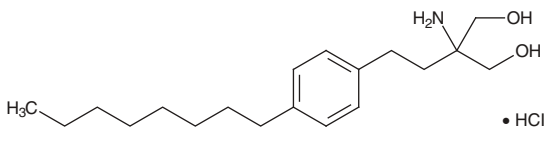


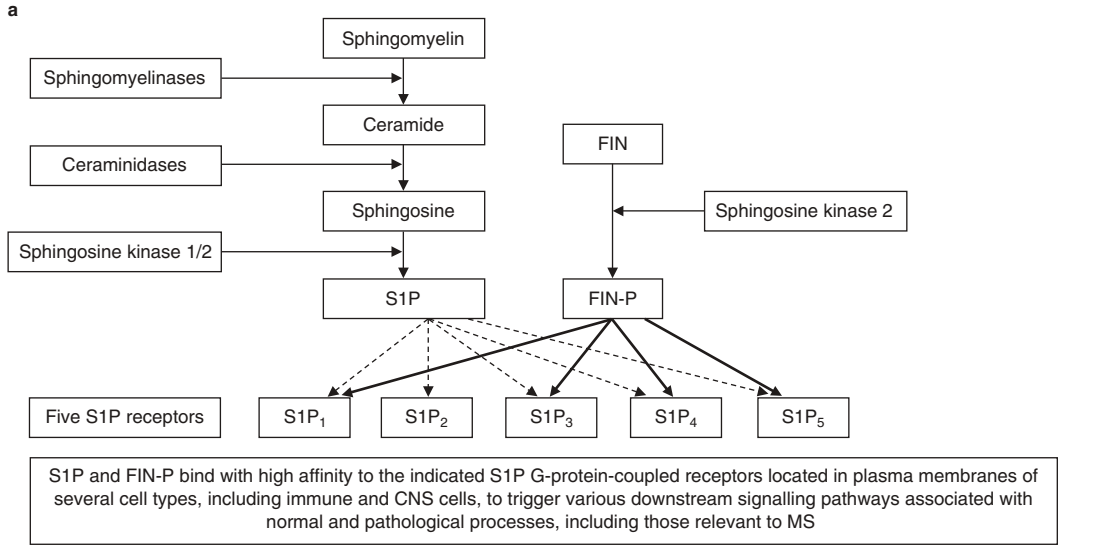
Fig. 1. Chemical structure of fingolimod hydrochloride.

Data from animal models of MS (i.e. experimental autoimmune encephalomyelitis [EAE] models) support the concept that fingolimod exerts its effects via inhibition of encephalitogenic T-cell responses and preventing the migration of these cells into the CNS.[16,17] In these animal models, development of the clinical features of EAE was prevented by the prophylactic use of fingolimod and, in animals with different stages of established EAE, fingolimod treatment improved and/or reversed clinical symptoms.[22-26] In addition, fingolimod treatment appeared to provide some degree of neuroprotection, with improvements in clinical symptoms, normalization of expression of myelin proteins and reductions in inflammatory infiltrates, axonal loss and demyelination (section 2.2).[16,17]

2.1 Effects on Immune System

Fingolimod-induced decreases in levels of peripheral lymphocytes were dose dependent in studies in healthy volunteers, with a near maximal effect observed with fingolimod 5 mg/day (i.e. typically an 81% decrease in lymphocyte levels from baseline).[15,27,28] Decreases in peripheral lymphocyte levels reached a nadir during the first day and remained at this level with once-daily fingolimod treatment. After discontinuation of treatment, lymphocyte counts returned to normal levels in a dose-dependent manner (i.e. the effects on lymphocyte egress into the peripheral circulation were reversible).[15,27,28]

Autoaggressive interleukin-17 (IL-17)-producing T (Th17) lymphocytes are thought to play a central role in the pathogenesis of MS by migrating across the blood : brain barrier (BBB), disrupting BBB tight-junctions and promoting CNS inflammation.[17,29] Levels of Th17 cells are elevated in the blood and CSF of patients with MS and, in EAE animal models of MS, Th17 cells have been shown to induce inflammation.[17,29]



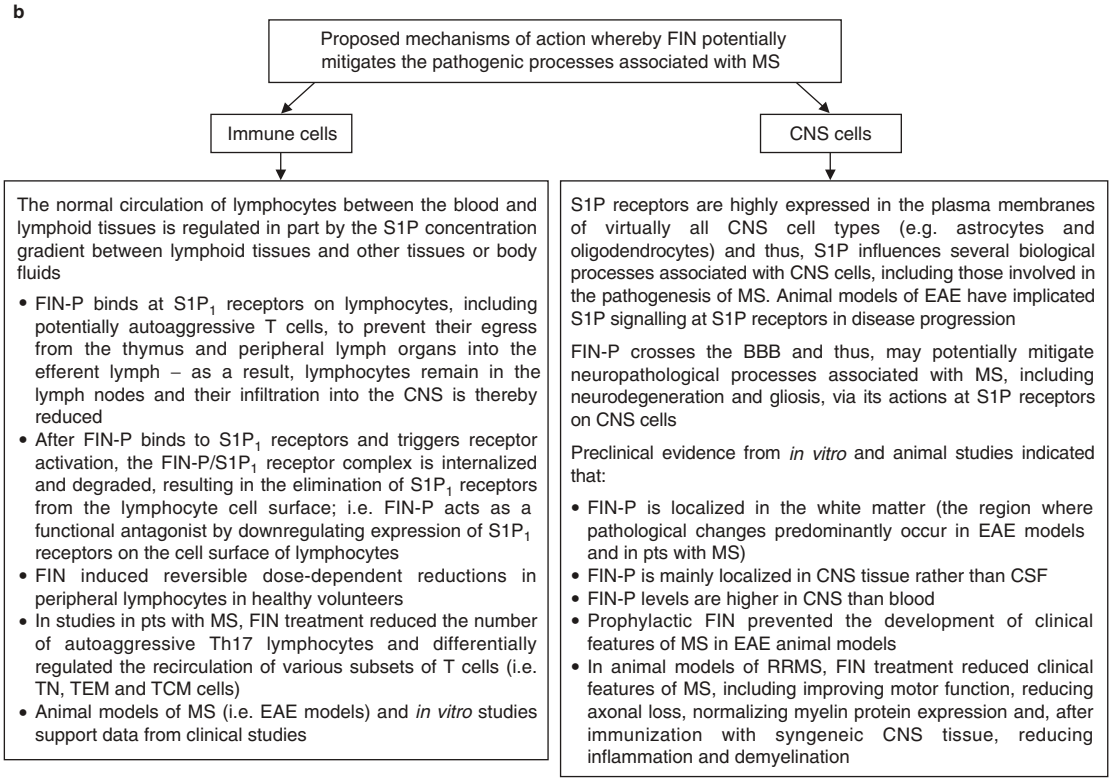


Fig. 2. Schematic summary of (**a**) the biosynthetic pathway of sphingosine 1-phosphate (S1P) and (**b**) the proposed/potential mechanisms of action of oral fingolimod (FIN).[11,12,16-19] **BBB** = blood : brain barrier; **EAE** = experimental autoimmune encephalomyelitis; **FIN-P** = *S*-FIN-phosphate; **MS** = multiple sclerosis; **pts** = patients; **RRMS** = relapsing-remitting MS; **S1P$_{1-5}$** = S1P receptor types 1–5; **TCM** = central memory T; **TEM** = effector memory T; **Th17** = interleukin-17-producing T; **TN** = naive-T.

Th17 cells also co-express C-C chemokine-receptor (CCR) type 4 (CCR4) and CCR6.[29] Fingolimod treatment reduced the number of Th17 cells in the blood by >90% in patients with MS, with this decrease relating to the reduction of CCR7-expressing naive-T (TN) cells and effector memory T (TEM) cells in an observational study.[29] There was no direct effect of fingolimod or its active metabolite fingolimod-phosphate on the secretion of IL-17 in *in vitro* studies of anti-CD3/CD28-stimulated CD3+ T cells derived from healthy individuals.[29]

The recirculation of various subsets of T cells (i.e. TN, TEM and central memory T [TCM] cells) was differentially regulated by fingolimod treatment in patients with MS.[30] In 16 patients with RRMS receiving fingolimod, there was a marked reduction in levels of peripheral blood CD4+ T cells (by ≈80%) and CD8+ T cells (by ≈60%) compared with patients receiving IFNβ (n = 7) or untreated individuals (i.e. patients with MS [n = 5] or healthy adults [n = 10]).[30] This reflected a reduction in TN (CCR7+ CD45RA+) and TCM (CCR7+ CD45RA−) cells and a relative increase in TEM cells (CCR7− CD45RA− and CCR7− CD45RA+).

The marked reduction in peripheral blood lymphocyte levels associated with fingolimod treatment appears to reflect the redistribution rather than the destruction of these cells.[31] In *in vitro* studies of peripheral blood from patients with MS, the predominant population of T cells in the peripheral circulation was CD8+ CCR7− cells; this subset forms a minority of the peripheral lymphocyte population in untreated individuals.[31] Furthermore, T cells from fingolimod-treated patients showed less migration towards CXCL12 and CCL2 (chemokines that regulate lymphocyte migration into tissues, including the CNS) than those from untreated patients with MS or healthy adult donors.

T-lymphocyte induction, proliferation and memory functions were not affected by fingolimod treatment in *in vitro* and preclinical studies.[15,30]

Since fingolimod is an immunosuppressant, it may potentially slow and/or impair the development of immunity to systemic viral infections.[11,18,32,33] In a prospective, open-label, observational study, cellular and humoral immune responses following administration of influenza virus vaccine were similar in 14 patients with MS treated with fingolimod to those in 18 untreated healthy adult volunteers.[32] Although this study had several limitations, including a lack of power to evaluate clinical endpoints such as protection from influenza virus infection, it suggests that fingolimod-treated patients, despite having CD4+ and CD8+ T-cell lymphopenia, have the ability to mount immune responses to specific viral antigens.[32] These data are supported by a prospective, 4-week, double-blind study that evaluated T-cell responses to vaccination with keyhole limpet haemocyanin (KLH) and humoral responses to pneumococcal polysaccharide vaccine (PPV-23) in 72 healthy volunteers receiving fingolimod 0.5 or 1.25 mg or placebo once daily (abstract plus poster presentation).[33] In this study, antibody responses to both of these antigens were attenuated and/or delayed in fingolimod recipients compared with those in placebo recipients; however, responder rates (i.e. >4-fold increase in IgG levels from pre-immunization levels) at 4 weeks in the fingolimod 0.5 mg/day group did not differ significantly from those in the placebo group for both KLH (91% vs 91%) and PPV-23 antigens (41% vs 55%).[33]

2.2 Effects in the CNS

The lipophilic nature of fingolimod means that it readily crosses the BBB into the CNS.[16,17] Since virtually all neural cell types, including neurons, oligodendrocytes, microglia and astrocytes, express S1P receptors, fingolimod-phosphate may potentially act at S1P receptors on these CNS cells to mitigate neuropathological processes associated with MS such as neurodegeneration and gliosis.[11,16,17] Specific cellular responses to S1P are dependent on the ratio of expression of the individual S1P receptors and on the stage of differentiation of the neural cells. S1P activity is pivotal for numerous aspects of normal neural function, including regulation of microglial proliferation and activation, maintenance of the integrity of the BBB, migration of neuronal progenitor cells towards areas of damage, migration of astrocytes and their communication with other

CNS cells, and regulation of oligodendrocyte survival, function and modulation of myelination following injury.[10-12,17]

In preclinical studies, fingolimod has been shown to act in a differentiation-, time- and dose-dependent manner to impact on several CNS processes, including improving clinical symptoms, reducing inflammatory responses, axonal loss and demyelination, and normalizing the expression of myelin proteins.[16,17] In *in vitro* studies, fingolimod reduced cytokine-induced cell death, increased the number of progenitor and mature oligodendrocytes, and modulated the outgrowth of oligodendrocytes, which at least in part may reflect the relative expression of each individual S1P receptor.[16,17,34-36] For instance, in an *in vitro* model using mouse organotypic cerebellar slices, fingolimod treatment enhanced remyelination and process extension by oligodendrocyte progenitor cells and mature oligodendrocytes after lysolecithin-induced demyelination.[36] These effects correlated with a significant fingolimod-induced increase in microglia and in astrocytic reactivity and were postulated to be mediated via fingolimod-phosphate activity at $S1P_3$ and $S1P_5$ receptors.[36]

Astrocytes play a pivotal role in pro- and anti-inflammatory processes in the CNS and are a potential target for fingolimod since they express $S1P_1$, $S1P_2$, $S1P_3$ and $S1P_5$ receptors.[11,17] Activities associated with astrocytes include enhancement of immune responses associated with the inhibition of myelin repair, neuroprotective effects, reduced secretion of proinflammatory cytokines and promotion of oligodendrocyte and axonal regeneration.[11,17] Autopsy material from patients who had MS indicated that there were increased levels of $S1P_1$ and $S1P_3$ receptors in both active and inactive MS lesions, with the highest immunohistochemical staining for both of these receptors being associated with astrocytes.[37] In primary cultures of human astrocytes derived from white matter of autopsied brains from individuals without neurological disease, fingolimod treatment reduced the synthesis of proinflammatory cytokines, including a dose-dependent decrease in monocyte chemotactic protein-1.[37]

In patients with MS, fingolimod treatment ($n = 12$) significantly ($p < 0.001$) reduced T-cell counts in the CSF relative to levels in 20 treatment-naive patients and to baseline levels ($p < 0.05$), with T-cell counts in the CSF returning to normal levels in fingolimod-treated patients.[38] Fingolimod treatment had no significant effects on IgG levels in the CSF or on intrathecal IgG synthesis. There was also no significant difference in terms of reductions in monocyte counts between fingolimod-treated patients and natalizumab-treated ($n = 9$) patients with MS. Fingolimod had no significant effects on B-cell counts in the CSF, whereas B-cell counts in blood were significantly decreased. In addition, there was a reduction in the percentage of CD4+ T cells and an increase in the percentage of CD8+ T cells, natural killer cells and monocytes in fingolimod-treated patients versus treatment-naive patients, with a reversal of the CD4+ : CD8+ ratio in most patients receiving fingolimod.[38]

2.3 Effects on Heart Rate and Rhythm

As might be predicted since S1P receptors are expressed on myocytes of the atrial sinus node, fingolimod treatment is associated with a negative chronotropic effect in man.[15] In healthy adults, the circadian rhythm in supine heart rate remained unchanged after single 1 mg doses of fingolimod, although the overall heart rate-versus-time curve was reduced by 10% during the first 24 hours post-dose and returned to baseline levels by 3–5 days post-dose. These effects on heart rate were asymptomatic.[28]

Similarly, a normal daytime circadian rhythm was observed after single intravenous (1 mg) or oral (1.25 mg) doses of fingolimod in a crossover study in healthy adult volunteers.[39] The mean heart rate nadir was 11% lower after oral administration than after intravenous administration (47 vs 53 beats/minute [bpm]; respective baseline values were 67 and 66 bpm). Mean heart rates were returning to baseline levels by the end of day 2 after both oral (62 bpm) and intravenous (61 bpm) fingolimod.[39]

After 4 weeks' treatment, the mean heart rate in healthy adult volunteers receiving fingolimod 0.5 ($n = 30$) or 1.25 mg/day ($n = 29$) was similar to that in volunteers receiving placebo ($n = 29$) in a

double-blind study (abstract plus poster presentation; no quantitative data reported).[40] In the initial 4-day treatment period, there were asymptomatic reductions in mean heart rates in the fingolimod groups relative to the placebo group.

In healthy volunteers who had received atenolol (50 mg once daily) or diltiazem (240 mg extended release once daily) for 5 days, concomitant administration of a single 5 mg dose of fingolimod had minimal effects on heart rate (abstract presentation).[41]

In a thorough QT interval study of multiple doses of fingolimod 1.25 or 5 mg/day (i.e. at steady state), when a negative chronotropic effect of fingolimod was still present, fingolimod treatment resulted in a prolongation of the corrected QT interval, with the upper bound of the 90% confidence interval being 14 milliseconds.[13] In clinical studies in patients with MS, there were no clinically relevant cases of prolongation of the QT interval; patients at risk of QT prolongation were excluded from these studies.[13]

3. Pharmacokinetic Properties

Fingolimod exhibits linear, dose-dependent absorption across a dose range of 0.125–5 mg.[42] Absorption of fingolimod is slow (maximum plasma concentrations [C_{max}] are attained in 12–16 hours), but almost complete, with an apparent absolute oral bioavailability of 93%.[13,14] After single intravenous or oral doses of fingolimod 1.25 mg in healthy volunteers, the oral : intravenous ratio for the dose-normalized area under the plasma concentration-time curve (AUC) was 0.94, indicating that average systemic exposure was similar after oral or intravenous administration.[39] Steady-state plasma concentrations are attained within 1–2 months following fingolimod once daily, with these levels being approximately 10-fold higher than those attained after the initial dose.[13,14]

After fingolimod enters the systemic circulation it undergoes reversible, stereoselective phosphorylation by sphingosine kinase 2 to the pharmacologically active *S*-enantiomer of fingolimod-phosphate.[20] After a single oral 5 mg dose in a typical healthy volunteer, although plasma concentrations of fingolimod and fingolimod-phosphate were similar at 4 hours post-dose, the concentration of fingolimod-phosphate exceeded the parent compound during the remainder of the 24-hour post-dose period.[15] With multiple doses, the ratio of parent compound to fingolimod-phosphate appeared to plateau after 7 days.[15]

Fingolimod is extensively distributed throughout the body, with a volume of distribution of approximately 1200 L.[13,14] Fingolimod is predominately distributed into red blood cells (86%), whereas there is markedly less distribution of fingolimod-phosphate into red blood cells (<17%). Both the parent compound and fingolimod-phosphate are highly bound to protein (>99.7%); this binding is not altered by renal or hepatic impairment.[13,14]

In healthy volunteers, there were no clinically relevant differences in absorption pharmacokinetics between the fed and fasted state after a single dose of fingolimod 1 mg, with fed-fasting ratios for mean C_{max} and AUC values of 1.0 and 0.98.[28]

Fingolimod is rapidly metabolized via three main pathways: phosphorylation to *S*-fingolimod-phosphate; oxidative transformation via cytochrome P450 (CYP) isoenzymes and subsequent fatty acid-like degradation to inactive metabolites; and formation of pharmacologically inactive non-polar ceramide analogues of fingolimod.[13,43] Fingolimod is primarily metabolized by the CYP4F2 isoenzyme, with minor metabolism occurring via CYP2D6, CYP2E1, CYP3A4 and CYP4F12 isoenzymes. Since multiple CYP isoenzymes are involved in its metabolism, it appears unlikely that the metabolism of fingolimod will be substantially affected by an inhibitor of a single CYP isoenzyme.[13]

In healthy volunteers, after a single oral radioactive fingolimod 4.5 mg dose, based on the AUC up to 816 hours, the main fingolimod-related components in the blood were fingolimod (23.3%), fingolimod-phosphate (10.3%), the inactive M3 carboxylic acid metabolite (8.3%) and the inactive M29 (8.9%) and M30 (7.3%) ceramide metabolites.[13,43]

The elimination of fingolimod is mostly via metabolism to inactive metabolites.[43] Approximately 81% of a single dose of radioactive fingolimod was slowly eliminated via the urine as inactive

metabolites.[13,14,43] There was no elimination of fingolimod and fingolimod-phosphate via the urine, with relatively low concentrations eliminated in the faeces (<2.5% of the dose).[13,14]

Clearance of fingolimod from the blood is 6.3 L/h, with blood levels of fingolimod-phosphate declining in parallel with those of the parent compound.[13,14] The apparent terminal elimination half-life ($t_{½}$) of fingolimod is 6–9 days, which is similar to that of fingolimod-phosphate.[13,14]

3.1 In Special Patient Populations

There were no clinically significant effects of gender on the pharmacokinetics of fingolimod or fingolimod-phosphate.[13,14] The effects of race on the pharmacokinetics of fingolimod and fingolimod-phosphate cannot be adequately assessed due to the low number of non-White patients in the clinical programme.[13] A pharmacokinetic study in healthy adult Caucasian and Asian volunteers indicated that there were no marked differences in the pharmacokinetics of fingolimod or fingolimod-phosphate between these populations (abstract presentation).[44]

Relative to healthy adult volunteers, there were no clinically relevant changes in mean C_{max} values for fingolimod in patients with mild (Child-Pugh class A),[45] moderate (Child-Pugh class B)[45] or severe (Child-Pugh class C)[46] hepatic impairment, although AUC values increased by 12%,[45] 44%[45] and 103%,[46] respectively. In patients with severe hepatic impairment, compared with healthy volunteers, the time to attain C_{max} was delayed by 24 hours, apparent clearance was reduced by 50% and $t_{½}$ was prolonged by 50%.[46] For fingolimod-phosphate, C_{max} and AUC values were reduced by 22% and 29% in patients with severe hepatic impairment.[46] In the US, patients with severe hepatic impairment should be closely monitored as the risk of adverse events is increased; no dosage adjustment is required in patients with mild or moderate hepatic impairment.[13] In the EU, fingolimod is contraindicated in patients with hepatic impairment.[14]

There are no clinically relevant effects of renal impairment on the pharmacokinetics of fingolimod or its active metabolite.[13,14]

3.2 Potential for Drug-Drug Interactions

Fingolimod and its active metabolite fingolimod-phosphate appear to have a low potential for pharmacokinetic drug-drug interactions, based on *in vitro* and human studies.[13]

Based on *in vitro* studies, therapeutic concentrations of fingolimod and fingolimod-phosphate have no or limited inhibitory activity at several CYP isoenzymes and fingolimod does not induce evaluated CYP isoenzymes.[13] The potential of fingolimod-phosphate to induce CYP isoenzymes is unknown. At concentrations up to 3-fold higher than therapeutic concentrations, fingolimod and its active metabolite have no or limited potential to inhibit the activity of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6 and CYP2E1.[13] Fingolimod also has limited or no inhibitory activity for CYP3A4/5 and CYP4A9/11 isoenzymes; its potential to inhibit the isoenzyme CYP2C8 is unknown. Fingolimod-phosphate also has limited or no inhibitory activity for CYP2C8 and CYP3A4 isoenzymes; its potential to inhibit CYP2B6 isoenzyme is unknown. As a consequence, fingolimod and its active metabolite are unlikely to reduce the clearance of drugs that are primarily metabolized by these major CYP isoenzymes.[13]

A population pharmacokinetic study in MS patients indicated that the strong CYP2D6 inhibitors fluoxetine and paroxetine, and carbamazepine (a strong inducer of CYP isoenzymes, including CYP3A4) had no clinically relevant effects on fingolimod or fingolimod-phosphate pre-dose concentrations.[13] There were also no clinically relevant effects on fingolimod and fingolimod-phosphate pre-dose concentrations when it was coadministered with other medications, including ciclosporin (or vice versa), atenolol (or vice versa), diltiazem (or vice versa), gabapentin, modafinil, amitriptyline, pregabalin and corticosteroids.[13]

4. Therapeutic Efficacy

The efficacy of oral fingolimod in the treatment of adult patients with RRMS has been evaluated in large (n = 281–1272), randomized, double-blind, placebo-controlled[47,48] (section 4.1) or active comparator-controlled[49] (section 4.2),

Table I. Summary of patient characteristics and clinical efficacy endpoints in randomized, double-blind, multinational trials in patients (pts) with relapsing-remitting (RR) multiple sclerosis (MS)

Parameter	FTY720 D2201 Study Group[48] (proof-of-concept; phase II)	FREEDOMS[47] (phase III)	TRANSFORMS[49] (phase III; dd)
Duration of trial (mo)	6	24	12
Comparator arm	Placebo	Placebo	Interferon-β-1a
Key inclusion criteria	Aged 18–60 y; a diagnosis of MS; had had ≥1 documented relapse during the prior 12 mo or ≥2 during prior 24 mo and/or had ≥1 Gd-enhanced lesion detected on MRI at screening; EDSS score of 0–6	Aged 18–55 y; met MS diagnosis according to revised McDonald criteria;[56] a RR disease course; had had ≥1 documented relapse during the prior 12 mo or ≥2 during prior 24 mo; had an EDSS score of 0–5.5	
Key exclusion criteria	Documented relapse or CS treatment in prior 30 d; immunomodulatory therapy in prior 3 mo; immunosuppressive treatment (e.g. AZA or MET within 6 mo; CYC within 12 mo; MIT or CLA within 24 mo)	Documented relapse or CS treatment within 30 d before randomization; active infection; macular oedema; drug- or disease-induced immunosuppression; clinically significant coexisting systemic disease; use of interferon-β-1a or glatiramer acetate within 3 mo of randomization (the latter was not an exclusion criterion in the TRANSFORMS trial)	
Mean MS duration (y)	8.4–9.5	8.0–8.4	7.3–7.5
Course of disease	87–90% of pts in individual treatment arms had RRMS; remainder had SPMS	100% of pts had RRMS	100% of pts had RRMS
Primary endpoint	Total no. of Gd-enhanced lesions/pt on T1W MRI at 1 mo intervals for 6 mo	Annualized relapse rate (defined as the number of confirmed relapses during a 12 mo period)	
Key secondary endpoints	Other MRI variables and clinical endpoints such as the annualized relapse rate; % of pts free of relapse; time to first relapse	Time to confirmed disability progression	No. of new or enlarged lesions on T2W MRI scans at 12 mo; time to confirmed disability progression

AZA = azathioprine; **CLA** = cladribine; **CS** = corticosteroid; **CYC** = cyclophosphamide; **dd** = double-dummy; **EDSS** = Expanded Disability Status Scale; **FREEDOMS** = FTY720 Research Evaluating Effects of Daily Oral therapy in Multiple Sclerosis; **Gd** = gadolinium; **MET** = methotrexate; **MIT** = mitoxantrone; **SPMS** = secondary-progressive MS; **TRANSFORMS** = Trial Assessing Injectable Interferon versus FTY720 Oral in Relapsing-Remitting Multiple Sclerosis; **TxW** = Tx-weighted.

multinational trials of 6–24 months' duration. Definitions of clinical trial acronyms, key design details and characteristics of patients enrolled in these trials are summarized in table I. Long-term data are available after 1,[48] 2,[50] 3,[51] 4[52] and 5[53] years (4- and 5-year data available as abstract and/or poster presentations) of fingolimod treatment from the extension study of the phase II trial (section 4.1) and from the 2-year extension study[54] of the TRANSFORMS trial (section 4.2). In addition, health-related quality of life (HR-QOL) data are available from the TRANSFORMS[55] trial (abstract presentation) [section 4.2].

The prespecified populations for primary endpoint (see table I for endpoints) analyses were the per-protocol (PP) population in the phase II trial,[48] the intent-to-treat population (ITT; i.e. all randomized patients) in the phase III FREEDOMS[47] trial and the modified ITT population (mITT; i.e. all patients who received at least one dose of study drug) in the phase III TRANSFORMS[49] trial. All study drugs were given orally, except for IFNβ-1a which was administered as an intramuscular injection.

At baseline, there were no significant between-group differences in baseline demographics and MS disease history within each trial.[47-49] There were also no significant between-group differences in these characteristics at the beginning of the single-blind, extension phase of the FTY720 D2201 Study Group trial[51] or the extension phase of the TRANSFORMS trial.[54]

4.1 Placebo-Controlled Trials

4.1.1 FTY720 D2201 Study Group Trial

At the end of the 6-month core study, the total cumulative number of T1-weighted (T1) gadolinium (Gd)-enhanced lesions/patient was significantly lower in fingolimod recipients than in

placebo recipients in the PP population (primary endpoint) [table II], with the benefits of fingolimod treatment evident from 2 months onwards.[48] Secondary MRI endpoints, as assessed in the PP population, also generally favoured fingolimod 1.25 or 5 mg/day relative to placebo treatment at 6 months, including the mean number of T1 Gd-enhanced lesions/patient and the percentage of patients free of T1 Gd-enhanced lesions (table II).[48] Sensitivity analyses in the ITT population, with and without imputation for missing data, indicated that all MRI results were similar to those reported for the PP population.

Clinical outcomes, as assessed in the ITT population, also favoured fingolimod treatment at the end of the core study (secondary outcomes) [table II], albeit the study was not powered to detect a treatment effect.[48] The annualized relapse rate (ARR) was significantly lower (reduced by approximately one-half) in the fingolimod groups than in the placebo group (table II) and a significantly greater percentage of fingolimod recipients were free of relapses (table II). Fingolimod treatment also prolonged the estimated time to a first confirmed relapse, as assessed using Kaplan-Meier methods. There were no significant differences for mean changes from baseline in Expanded Disability Status Scale (EDSS) scores between the fingolimod 1.25 or 5 mg/day groups and the placebo group (table II).[48]

Extension Phase

In the single-blind, extension phase of the core study, patients who had received fingolimod during the core study continued with the same treatment regimen and those who had received placebo during the core study were randomly assigned to fingolimod 1.25 or 5 mg once daily.[48] During months 15–24 of the extension phase, all patients receiving fingolimod 5 mg once daily were switched to the lower dosage of fingolimod.[51] Of the 255 patients who completed the core study, 250 entered the extension study, with 227 (91%), 189 (76%), 173 (69%), 155 (62%) and 140 (56%) completing 1,[48] 2,[50] 3,[51] 4[52] and 5[53] years of treatment, respectively.

The beneficial effects of fingolimod treatment on MRI-assessed and clinical endpoints that were

Table II. Efficacy of once-daily oral fingolimod (FIN) in adult patients (pts) with relapsing-remitting multiple sclerosis. Results at study end from a 6-month, randomized, double-blind, multinational, phase II trial (FTY720 D2201 Study Group).[48] All values are means

Endpoint	Regimen		
	FIN 1.25 mg	FIN 5 mg	placebo
MRI-related endpoints	(n = 83; PP[a])	(n = 77; PP[a])	(n = 81; PP[a])
Total cumulative no. of T1 Gd-lesions/pt[b]	8.4**	5.7*	14.8
No. of T1 Gd-enhanced lesions/pt [BL]	1.29** [3.4]	0.27** [2.8]	2.21 [2.8]
% of pts free of T1 Gd-enhanced lesions [BL]	77** [53]	82** [43]	47 [49]
Clinical endpoints	(n = 93; ITT[c])	(n = 92; ITT[c])	(n = 92; ITT[c])
ARR	0.35*	0.36*	0.77
% of pts free of relapses[d]	86*	86*	66
EDSS score[e] [BL]	2.6 [2.7]	2.6 [2.5]	2.7 [2.6]

a All pts who received 6 mo treatment, had no major protocol violations and had MRI data for BL and ≥3 other 1-mo visits.

b Primary endpoint.

c All randomized pts who received ≥1 dose of study drug and had ≥1 post-BL MRI.

d Based on Kaplan-Meier estimates. A confirmed relapse was defined as the occurrence of new symptoms or worsening of previously stable or improving symptoms and signs not associated with a fever, lasting more than 24 h and accompanied by an increase of ≥½ a point in the EDSS score or 1 point in the score for at least one of the EDSS functional systems (excluding scores for the bowel, bladder or cerebral functional systems).

e Scores range from 0 to 10, with higher scores indicating a higher degree of disability.

ARR = annualized relapse rate; **BL** = baseline; **EDSS** = Expanded Disability Status Scale; **Gd** = gadolinium; **ITT** = intent-to-treat population; **PP** = per-protocol population; * $p \leq 0.01$, ** $p < 0.001$ vs placebo.

observed in the 6-month core study (table II) were sustained during the extension phase of the study (up to 60 months total study time) at all timepoints evaluated.[48,50-53] Furthermore, in the first 6 months of the extension phase, patients who were switched from placebo to fingolimod 1.25 (n = 28 evaluable) or 5 mg/day (n = 32) showed rapid improvements in inflammatory activity, as assessed by MRI, and in clinical endpoints, including a reduction in the frequency of relapses.[48] At the latest assessment timepoint (5 years),[53] the ARR was 0.17 in those who received continuous fingolimod 1.25 mg/day, 0.19 in those who received continuous fingolimod 5 mg/day for up to 2 years and then fingolimod 1.25 mg/day, and 0.23 in those switched from placebo to fingolimod treatment at the start of the extension phase. Kaplan-Meier estimates indicated that 61–68% of patients who received fingolimod throughout the study and 51% of patients who were initially randomized to placebo then switched to fingolimod remained relapse free at 5 years. MRI showed that, for all groups, the majority (91–93%) of patients remained free of T1 Gd-enhanced lesions at 5 years, 83–89% of patients were free of active T2 lesions and 83–89% were free of any inflammatory activity.[53]

4.1.2 FREEDOMS Trial

In the 2-year, multinational FREEDOMS trial, 24 months of treatment with fingolimod 0.5 or 1.25 mg/day was significantly better than placebo treatment in terms of the ARR (primary endpoint) [table III].[47] Compared with placebo, the ARR was reduced by 55% in the fingolimod 0.5 mg/day group and by 60% in the fingolimod 1.25 mg/day group (table III). Moreover, the ARRs in the fingolimod groups were significantly ($p < 0.01$) lower than placebo, irrespective of whether patients were antimyeloma treatment-naive or -experienced.

A *post hoc* analysis indicated that treatment with fingolimod 0.5 or 1.25 mg/day was associated with significantly better ARRs than placebo treatment when relapses were categorized according to severity, steroid use, requirement for hospitalization and impact on a patient's daily activities (abstract plus poster presentation).[57] For example, fingolimod 0.5 mg/day significantly (all $p \leq 0.001$) reduced ARRs for severe relapses (0.012 vs 0.044 in the placebo group), relapses requiring steroid use (0.167 vs 0.384), relapses requiring hospitalization (0.072 vs 0.178), relapses affecting daily activities (0.151 vs 0.314) and relapses with incomplete recovery (0.069 vs 0.155). Severe relapse was defined as exceeding the criteria for a moderate relapse; criteria for a moderate relapse were an EDSS score increase of 1 or 2 points or a 2-point Functional System (FS) change in one or two systems or a 1-point change in four or more FS.[57]

Secondary clinical endpoints also favoured fingolimod treatment over placebo treatment at 24 months, including the proportion of patients who were relapse free, the risk of disability progression and mean change in EDSS score (table III).[47] The risk of relapse with fingolimod 0.5 and 1.25 mg/day was significantly reduced by 52% and 62% compared with placebo, with the risk of 3-month confirmed disability progression also significantly reduced over the 24-month period by approximately 30% in both fingolimod groups. The estimated median time to first relapse was also prolonged in the fingolimod groups versus the placebo group, as determined using Kaplan-Meier methods. There was very little change in mean EDSS score at 24 months in the fingolimod groups, whereas patients in the placebo group showed a deterioration in EDSS scores (table III). The same trend was seen for mean changes in z scores on the Multiple Sclerosis Functional Composite (MSFC) scale (mean increases in the fingolimod 0.5 and 1.25 mg/day groups of 0.03 and 0.01 vs a reduction of 0.06 in the placebo group; $p \leq 0.02$ for both groups vs placebo; higher MSFC z scores represent an improvement).[47]

Both dosages of fingolimod were significantly better than placebo in terms of all MRI outcomes (secondary endpoints), including measures of inflammatory markers or scar formation such as the mean number of T1 Gd-enhanced lesions/patient, the percentage of patients without T1 Gd-enhanced lesions, the mean number of new or enlarged T2 lesions/patient and the percentage of patients without new or enlarged T2 lesions (table III).[47] In addition to having significantly

Table III. Efficacy of once-daily oral fingolimod (FIN) in adult patients (pts) with relapsing-remitting multiple sclerosis. Results at study end from the 2-year, randomized, double-blind, multinational FREEDOMS trial.[47] Analyses were conducted using various statistical methods (including analysis of covariance and negative-binomial regression models with adjustment according to specified criteria such as study group, country, baseline [BL] value for a given endpoint and/or age)

Endpoint	Regimen		
	FIN 0.5 mg	FIN 1.25 mg	placebo
Clinical endpoints	(n = 425)[a]	(n = 429)[a]	(n = 418)[a]
ARR[b]	0.18***	0.16***	0.40
Absence of relapse (% of pts) [HR; 95% CI]	70*** [0.48; 0.39, 0.61]***	75*** [0.38; 0.30, 0.48]***	46
Absence of disability progression[c] (% of pts) [HR; 95% CI]	82* [0.70; 0.52, 0.96]*	83** [0.68; 0.50, 0.93]*	76
Mean change in EDSS score[d] [mean BL score]	0.00** [2.3]	–0.03** [2.4]	+0.13 [2.5]
MRI-related endpoints	(n = 346–395)[e]	(n = 317–384)[e]	(n = 305–383)[e]
Mean no. of T1 Gd-enhanced lesions/pt	0.2***	0.2***	1.1
Absence of T1 Gd-enhanced lesions (% of pts)	90***	90***	65
Mean no. of new or enlarged T2 lesions/pt	2.5***	2.5***	9.8
Absence of new or enlarged T2 lesions (% of pts)	51***	52***	21

a Intent-to-treat population (i.e. all pts who were randomized).

b Primary endpoint. No. of confirmed relapses over 24 mo. Confirmed relapse was defined as symptoms accompanied by an increase of ≥½ a point in EDSS score, or of 1 point in each of two EDSS functional systems scores or of 2 points in one EDSS functional system score (excluding scores for the bowel, bladder or cerebral functional systems).

c Disability progression was defined as an increase of 1 point in EDSS score (increase of ½ a point if the BL EDSS score was 5.5), confirmed at 3 mo, with an absence of relapse at the time of assessment and with all EDSS scores measured during that time meeting the criteria for disease progression.

d Scores range from 0 to 10, with higher scores indicating a higher degree of disability.

e No. of pts with data.

ARR = annualized relapse rates; **EDSS** = Expanded Disability Status Scale; **Gd** = gadolinium; **HR** = hazard ratio; * $p < 0.05$, ** $p \leq 0.01$, *** $p < 0.001$ vs placebo.

fewer Gd-enhanced lesions at 24 months (table III), patients receiving fingolimod 0.5 or 1.25 mg/day also had significantly fewer Gd-enhanced lesions at 6 and 12 months (no data reported).

MRI-assessed measures of tissue damage or loss also favoured treatment with fingolimod 0.5 and 1.25 mg/day over placebo at 24 months and, where assessed, at interim 6- and 12-month timepoints.[47] Over the entire 24-month study period, the mean percentage changes in brain volume in fingolimod 0.5 and 1.25 mg/day recipients were –0.84% and –0.89% versus –1.31% in the placebo recipients (both $p < 0.001$). The respective mean percentage changes in the volume of hypointense T1 lesions were 8.8% ($p = 0.01$ vs placebo), 12.2% ($p = 0.02$) versus 50.7%. Analyses were conducted using an analysis of covariance, with adjustment for study group, country and normalized brain volume at baseline (for brain volume data) or lesion volume at baseline (for hypointense T1 lesion volume).[47]

4.2 Active Comparator-Controlled Trial

4.2.1 TRANSFORMS Trial

After 1 year of treatment, the ARR was significantly lower with fingolimod 0.5 or 1.25 mg/day than with intramuscular IFNβ-1a 30 μg once weekly (primary endpoint), with a reduction in the ARR of approximately 40–50% in the fingolimod groups relative to the IFNβ-1a group (table IV).[49] Secondary clinical outcomes also generally favoured fingolimod treatment, including the proportion of patients who were relapse free at 1 year (table IV) and the median time to first relapse ($p < 0.001$ vs IFNβ-1a for both fingolimod groups; assessed using Kaplan-Meier estimates).

Based on *post hoc* analyses, fingolimod 0.5 or 1.25 mg/day was also associated with significantly better ARRs than IFNβ-1a treatment when relapses were categorized according to severity, corticosteroid use, requirement for hospitalization

and impact on a patient's daily activities.[57] For example, treatment with fingolimod 0.5 mg/day significantly ($p < 0.01$ vs IFNβ-1a) reduced ARRs for severe relapses (0.022 vs 0.068 in the IFNβ-1a group), relapses requiring corticosteroid use (0.141 vs 0.334), relapses requiring hospitalization (0.022 vs 0.077), relapses affecting daily activities (0.101 vs 0.256) and relapses with incomplete recovery (0.039 vs 0.102).

Confirmed disability progression was uncommon in all treatment groups, with no significant differences between the fingolimod groups and the IFNβ-1a group in the percentage of patients who had no disability progression (table IV) and the median time to disability progression.[49] Nonetheless, patients receiving fingolimod 1.25 mg/day, but not those receiving fingolimod 0.5 mg/day, had significantly greater improvements in mean EDSS scores at study end than patients treated with IFNβ-1a (table IV). At 1 year, mean changes in MSFC z scores from baseline were significantly ($p \leq 0.02$) greater in the fingolimod 0.5 and 1.25 mg/day groups than in the IFNβ-1a group, with fingolimod recipients showing improvements in these scores versus a slight deterioration in scores in IFNβ-1a recipients (+0.04 and +0.08 vs −0.03).

MRI-related outcomes at 1 year were also generally better with fingolimod treatment than with IFNβ-1a treatment (table IV).[49] In addition, the mean percentage reduction in brain volume from baseline was significantly lower in the fingolimod 0.5 and 1.25 mg/day groups than in the IFNβ-1a group (0.31% and 0.30% vs 0.45%), although there were no significant between-group differences for percentage changes from baseline in the volume of T2 hyperintense lesions or T1 hypointense lesions.[49]

Fingolimod-treated patients experienced significantly less deterioration in HR-QOL than patients receiving IFNβ-1a, based on a *post hoc* analysis using the Patient-Reported Indices for

Table IV. Efficacy of once-daily oral fingolimod (FIN) in adult patients (pts) with relapsing-remitting multiple sclerosis. Results at study end from the 1-year, randomized, double-blind, double-dummy, multinational TRANSFORMS trial.[49] Analysis were conducted using various statistical methods (including analysis of covariance and negative-binomial regression models with adjustment according to specified criteria such as study group, country, baseline [BL] value for a given endpoint and/or age)

Endpoint	Regimen		
	FIN 0.5 mg	FIN 1.25 mg	IM IFNβ-1a 30 μg q1w
Clinical endpoints	(n = 429)[a]	(n = 420)[a]	(n = 431)[a]
ARR[b]	0.16***	0.20***	0.33
Absence of relapse (% of pts)	83***	80***	69
Absence of disability progression[c] (% of pts)	94	93	92
Mean change in EDSS score[d] [mean BL score]	−0.08 [2.24]	−0.11* [2.21]	+0.01 [2.19]
MRI-related endpoints	(n = 372–374)[e]	(n = 350–352)[e]	(n = 354–361)[e]
Mean no. of T1 Gd-enhanced lesions/pt	0.23***	0.14***	0.51
Absence of TI Gd-enhanced lesions (% of pts)	90***	91***	81
Mean no. of new or enlarged T2 lesions/pt	1.7***	1.5**	2.6
Absence of new or enlarged T2 lesions (% of pts)	55**	48	46

a Modified intent-to-treat population (i.e. all pts who were randomized and received ≥1 dose of study drug).

b Primary endpoint. No. of confirmed relapses over 12 mo. Confirmed relapse was defined as new, worsening or recurrent symptoms that occurred ≥30 days after the onset of a preceding relapse, that lasted ≥24 h without fever or infection and that was accompanied by an increase of ≥½ a point in EDSS score, or of ≥1 point in each of two EDSS functional systems scores or of ≥2 points in one EDSS functional system score (excluding scores for the bowel, bladder or cerebral functional systems).

c Disability progression was defined as an increase of 1 point in EDSS score (increase of ½ a point if the BL EDSS score was ≥5.5), confirmed 3 mo later.

d Scores range from 0 to 10, with higher scores indicating a higher degree of disability.

e No. of pts with data.

ARR = annualized relapse rates; **EDSS** = Expanded Disability Status Scale; **Gd** = gadolinium; **IFNβ-1a** = interferon-β-1a; **IM** = intramuscular; **q1w** = once weekly; * $p < 0.05$, ** $p \leq 0.01$, *** $p < 0.001$ vs IFNβ-1a.

Multiple Sclerosis (PRIMUS)-Activities score (high scores represent a deterioration) [abstract presentation].[55] There were no significant between-group differences in baseline PRIMUS-Activities scores (no data reported). After 12 months, the mean changes from baseline in PRIMUS-Activities scores in the fingolimod 0.5 (n = 280) and 1.25 mg/day (n = 260) groups were significantly ($p < 0.05$) lower than in the IFNβ-1a group (n = 270; mean change 0.08, 0.12 vs 0.43). In addition, an improvement in PRIMUS-Activities score was observed in 17.5–19.6% of patients in the fingolimod groups and by 14% of patients receiving IFNβ-1a; respective percentages of patients experiencing a worsening in PRIMUS-Activities scores were 17.9–19.6% and 24.1%. Odds ratios for an improvement or worsening of PRIMUS-Activities scores indicated that fingolimod treatment was better than IFNβ-1a treatment (no data reported). An improvement or worsening in PRIMUS-Activities scores was defined as a ≥2 point change.[55]

Extension Phase

The longer-term benefits of 2 years of continuous treatment with fingolimod 0.5 or 1.25 mg/day and its relative efficacy versus 1 year of intramuscular IFNβ-1a 30 μg once weekly then switching to 1 year of fingolimod 0.5 or 1.25 mg/day (i.e. the switch group) has been evaluated in an extension phase of the TRANSFORMS trial.[54] Patients in the IFNβ-1a arm of the TRANSFORMS trial were randomized to fingolimod 0.5 or 1.25 mg/day for the extension study; patients in the fingolimod arms of the trial continued with their existing dosage of fingolimod.

The beneficial effects on clinical and MRI-related outcomes that were observed with both dosages of fingolimod at the end of the 1-year TRANSFORMS trial were sustained after a further year of fingolimod treatment in the extension phase.[54] Notably, patients who received continuous fingolimod 0.5 (n = 429) or 1.25 mg/day (n = 420) had significantly ($p < 0.0001$) lower ARRs at 24 months than patients who switched to fingolimod after 1 year of IFNβ-1a treatment (n = 431) [ARR 0.18 and 0.20 vs 0.33]. Relative to the switch group, there was a 42% reduction in the risk of relapse for continuous fingolimod 0.5 mg/day recipients (hazard ratio [HR] 0.58; 95% CI 0.45, 0.74) and a 36% reduction in the risk of relapse for fingolimod 1.25 mg/day recipients (HR 0.64; 95% CI 0.50, 0.82). There were no between-group differences in the proportion of patients who were free from first confirmed relapse or in the time to 3-month confirmed disability progression. Significantly more patients in the continuous fingolimod 0.5 mg/day group (n = 300–316) than in the fingolimod 0.5 mg/day switch group (n = 269–279) had no new or enlarged T2 lesions at 24 months (42% vs 33%; $p = 0.016$) or were free from T1 Gd-enhanced lesions at 24 months (86% vs 77%; $p = 0.001$), with the cumulative number of new or newly enlarged T2 lesions up to 24 months also being lower in the continuous fingolimod group (2.5 vs 3.3; $p < 0.05$).[54]

Switching from IFNβ-1a to fingolimod treatment was associated with significant ($p < 0.05$) improvements in clinical and MRI-related outcomes, irrespective of whether patients were switched to fingolimod 0.5 mg/day or to fingolimod 1.25 mg/day.[54] For example, in those switched to fingolimod 0.5 mg/day at the beginning of the extension phase (n = 167), the estimated ARR was reduced from 0.31 at the start of the extension phase (i.e. after 12 months' IFNβ-1a therapy) to 0.22 during the 1-year extension phase ($p = 0.049$), with a similar improvement in ARR seen in those who switched from IFNβ-1a to fingolimod 1.25 mg/day (n = 1.74; 0.29 reduced to 0.18; $p = 0.024$). Switching to fingolimod treatment also significantly improved MRI measures of inflammatory activity.[54]

5. Tolerability

Oral fingolimod was generally well tolerated in patients with RRMS participating in clinical trials (≤2 years' duration) discussed in section 4 (see section 4 for trial design details),[47-49,54] with most adverse events being of mild to moderate severity and manageable. Discussion focuses on data from the two phase III trials.[47,49] Data concerning the long-term tolerability of fingolimod are more limited, with these data derived from an extension study (≤5 years of treatment) of a phase II trial (see section 4 for trial design

details). Supplemental data are derived from the US manufacturer's prescribing information[13] and from case reports.[58-60]

5.1 General Tolerability

Treatment-emergent adverse events occurring with an incidence of ≥7% in any treatment group in the 2-year FREEDOMS[47] and 1-year TRANSFORMS[49] trials are presented in figure 3. Within each trial, a similar proportion of patients in all treatment groups experienced at least one adverse event (86–94% in fingolimod 0.5 and 1.25 mg/day groups vs 93% in the placebo group[47] and 92% in the IFNβ-1a group[49]), with most adverse events being of mild to moderate severity (77–90%).[47,49] The most common adverse events (i.e. incidence ≥10% and occurring with a ≥2% higher incidence in the fingolimod 0.5 mg/day group than in the placebo group) of any severity were headache, influenza, diarrhoea, back pain and cough (figure 3), and liver enzyme elevations (15.8% vs 5.0%).[47]

In clinical trials, the only adverse event leading to treatment interruption that occurred with an incidence of >1% with fingolimod 0.5 mg/day was elevated serum transaminase levels (incidence 3.8%).[13] In the fingolimod 0.5 mg/day, fingolimod 1.25 mg/day and placebo groups, 7.5%, 14.2% and 7.7% of patients, respectively, discontinued treatment because of adverse event in the FREEDOMS trial.[47] In the active-comparator TRANSFORMS trial, the respective frequencies of treatment discontinuation in the fingolimod 0.5 mg/day, fingolimod 1.25 mg/day and IFNβ-1a groups were 5.6%, 10.0% and 3.7%.[49]

In the placebo-controlled FREEDOMS trial, serious adverse events occurred in 10.1%, 11.9% and 13.4% of patients in the fingolimod 0.5 mg/day, fingolimod 1.25 mg/day and placebo groups, respectively, with no individual serious adverse event occurring with an incidence of >1% in any treatment group.[47] The most common (incidence ≥0.7% in at least one treatment group and numerically higher incidence in either of the fingolimod groups than in the placebo group) serious adverse events were bradycardia (0.9%, 0.7% and 0.2% in the fingolimod 0.5 mg/day, fingolimod 1.25 mg/day and placebo group, respectively), basal-cell carcinoma (0.9%, 0.2% and 0.7%), MS relapse (0.9%, 0.7% and 0.2%), chest pain (0.9%, 0% and 0.5%) and macular oedema (0%, 0.7% and 0%). There were seven episodes of serious bradycardia that occurred in fingolimod-treated patients, six of which were assymptomatic; all episodes occurred after the first dose during the monitoring period and were reported as serious because the protocol-defined discharge criteria were not met. Other serious adverse events occurring with a numerically higher incidence in the fingolimod 0.5 mg/day group than in the placebo group were back pain (0.5% vs 0.2%) and urinary tract infections (0.5% vs 0%). No serious adverse events associated with laboratory parameters occurred in the fingolimod 0.5 mg/day group; however, serious abnormal liver-function tests were reported in 0.5% of patients in the fingolimod 1.25 mg/day group and 0.2% of patients in the placebo group and serious lymphopenia occurred in 0.5% and 0% of patients, respectively. Abnormal liver function tests of any severity occurred in 15.8%, 18.6% and 5.0% of patients in the fingolimod 0.5 mg/day, fingolimod 1.25 mg/day and placebo groups. Corresponding frequencies of leucopenia of any severity were 2.8%, 6.3% and 0.2% and those for lymphopenia of any severity were 3.5%, 5.4% and 0.5%. Of the three deaths that occurred during the trial, one occurred in the fingolimod 1.25 mg/day group (a suicide) and two occurred in the placebo group (a pulmonary embolism and a traffic accident).[47]

In the TRANSFORMS trial, for adverse events of any severity, relative to IFNβ-1a, treatment with fingolimod was associated with a numerically lower (i.e. ≥2% between group difference) incidence of pyrexia (figure 3), flu-like illness (figure 3), myalgia (figure 3), depression (figure 3) and arthralgia (2.8% and 4% in the fingolimod 0.5 mg/day and 1.25 mg/day groups vs 5.6% in the IFNβ-1a group).[49] Conversely, numerically more fingolimod recipients than IFNβ-1a recipients experienced headache (figure 3), nausea (figure 3), diarrhoea (figure 3), fatigue (figure 3) and elevated ALT levels (6.5% and 5.7% in the fingolimod 0.5 mg/day and 1.25 mg/day groups vs 1.9% in the IFNβ-1a group).

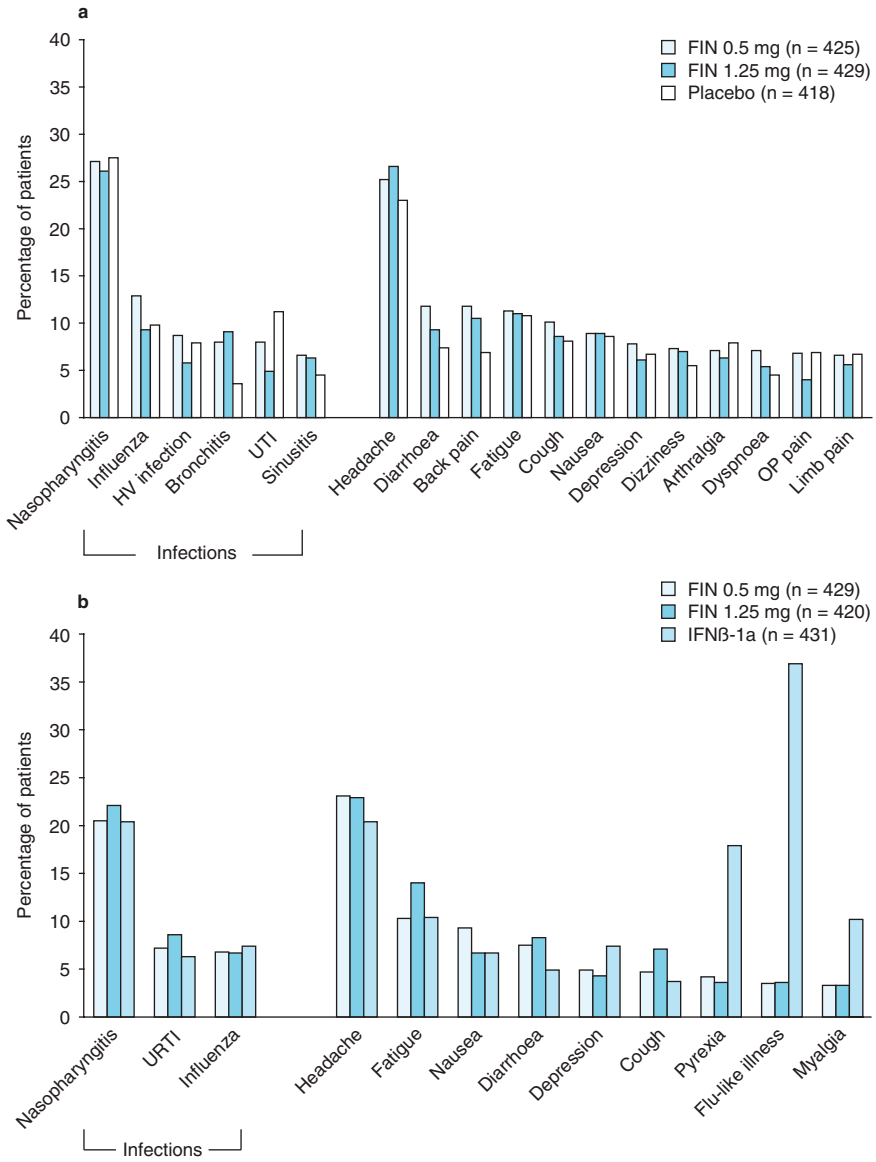


Fig. 3. Tolerability profile of oral fingolimod (FIN) in adult patients with relapsing-remitting multiple sclerosis. Treatment-emergent adverse events that occurred in ≥7% of patients in any treatment group in the randomized, double-blind, multinational (**a**) 2-year FREEDOMS[47] and (**b**) 1-year TRANSFORMS[49] trials. Patients received oral FIN 0.5 or 1.25 mg or placebo once daily, or intramuscular interferon-β-1a (IFNβ-1a) once weekly. See section 4 for further dosage and trial design details. Herpes virus (HV) infections included oral herpes, HV infection, herpes simplex virus infection, herpes zoster, genital herpes and herpes dermatitis. Data are for descriptive analyses. **OP** = oropharyngeal; **URTI** = upper respiratory tract infection; **UTI** = urinary tract infection.

In this study, serious adverse events occurred in 7.0%, 10.7% and 5.8% of patients in the fingolimod 0.5 mg/day, fingolimod 1.25 mg/day group and IFNβ-1a groups, respectively.[49] Serious adverse events occurring in at least 0.7% of patients in any treatment group were bradycardia or sinus bradycardia (0.5%, 2.4% and 0% in the fingolimod 0.5 mg/day, fingolimod 1.25 mg/day

and IFNβ-1a groups, respectively), atrioventricular block (second degree 0.2%, 0.7% and 0%), herpesvirus infection (0.2%, 0.7% and 0.2%), basal cell carcinoma (0.7%, 0.5% and 0.2%) and melanoma (including in situ; 0.7%, 0% and 0%). All cases of serious bradycardia and atrioventricular block occurred after the first dose of fingolimod and most were asymptomatic but were reported as serious adverse events because protocol-defined discharge criteria at 6 hours post-dose were not met, leading to mandatory hospitalization. No patients in the fingolimod groups experienced elevations in ALT levels of >10 × the upper limit of normal (ULN), with such events occurring in two patients in the IFNβ-1a group. Two deaths occurred during the trial, both in the fingolimod 1.25 mg/day group, with one caused by a disseminated primary varicella zoster virus (VZV) infection and the other due to herpes simplex encephalitis.[49]

In the extension study of the TRANSFORMS trial (total duration of fingolimod treatment was 2 years), the safety profile during the second year (i.e. the extension phase) of fingolimod treatment was consistent with that for the first year.[54] As might be expected, in patients who switched from IFNβ-1a to fingolimod 0.5 or 1.25 mg/day at the end of the 1-year double-blind phase, the nature of adverse events during the extension phase changed from those that are typically observed with IFNβ-1a treatment to those that are typically seen with fingolimod treatment. In patients who switched from IFNβ-1a treatment to fingolimod treatment, the incidence of lymphopenia increased after the switch (from 0% in both groups at the end of 12 months' IFNβ-1a to 12% and 18% in those who switched to fingolimod 0.5 mg/day and 1.25 mg/day); this may in part reflect the more stringent criteria for defining lymphopenia during the second year of treatment (defined as $<0.2 \times 10^3$/mL in the second year vs $<0.1 \times 10^3$/mL for the first year).[54]

A case report of a patient enrolled in the TRANSFORMS trial indicated that they had experienced critical vasospasm affecting the left hand during treatment with fingolimod 1.25 mg/day, with symptoms occurring within 7 days of initiating treatment.[59] This patient was also receiving carbamazepine for paroxysmal brainstem symptoms. After discontinuation of both fingolimod and carbamazepine treatment, the patient was treated with intra-arterial spasmolytic and thrombolytic agents combined with intravenous heparin and piritramide, which improved blood flow. The patient was left with persistent functional deficits of the affected hand.[59]

Fingolimod treatment was associated with dose-dependent reductions in forced expiratory volume over 1 second (FEV_1) and diffusion lung capacity for carbon monoxide (DLCO), which occurred as early as 1 month after initiation of treatment.[13] At 24 months, the reductions from baseline in the percent of predicted values for FEV_1 was 3.1% in the fingolimod 0.5 mg/day group and 2% in the placebo group. Corresponding reductions in DLCO at 24 months were 3.8% and 2.7%. FEV_1 values returned to normal levels upon treatment discontinuation; however, there are insufficient data to determine whether changes in DLCO are reversible with treatment discontinuation. In controlled trials in patients with MS, dyspnoea was reported in 5% of patients treated with fingolimod 0.5 mg/day and 4% of those receiving placebo;[13] also see figure 3. Several patients who participated in the extension studies discontinued treatment because of unexplained dyspnoea.[13]

In clinical trials, 8% of patients treated with fingolimod 0.5 mg/day and 2% of placebo recipients experienced an increase in serum transaminase levels of ≥3 × ULN, with increases of 5 × ULN occurring in 2% and 1% of patients.[13] In these trials, fingolimod treatment was discontinued in patients with liver transaminase levels of >5 × ULN. Some patients showed a recurrence of serum transaminase level elevations upon recommencing treatment, which suggests a causal relationship to fingolimod treatment. Most elevations in serum transaminase levels occurred within 3–4 months of commencing fingolimod treatment and enzyme levels returned to normal within approximately 2 months of discontinuing treatment.[13]

In the FREEDOMS trial, malignant skin neoplasms occurred in four patients in the fingolimod 0.5 mg/day group, three patients in the

fingolimod 1.25 mg/day group and four patients in the placebo group.[47] All of these skin cancers were removed successfully. Similarly, all ten localized skin cancers that were reported in the TRANSFORMS trial were successfully removed; six occurred in the fingolimod 0.5 mg/day group, two in the fingolimod 1.25 mg/day group and two in the IFNβ-1a group.[49] In the fingolimod groups, breast cancer was reported in two patients in each group, with three cases reported within 4 months of commencing treatment and one reported after 11 months of treatment.[49]

5.2 Infections

Infections of any grade that occurred with an incidence of ≥7% in at least one treatment group in the FREEDOMS[47] and TRANSFORMS[49] trials are summarized in figure 3; the vast majority of these were of mild to moderate severity. In the FREEDOMS trial, infections of any grade occurred in 69–72% of patients in the fingolimod and placebo groups (1.6–2.6% were of serious severity).[47] Similarly, in the TRANSFORMS trial, the overall incidence of infections across the fingolimod and IFNβ-1a groups was 51–53%, with only 0.2–1.7% of these considered to be of serious severity. See section 5.1 for discussion of serious infections that occurred in each of these trials.

The overall rate of infections in patients with MS who received fingolimod 0.5 mg/day during clinical trials was 72% (2% were classified as serious infections) and was similar to that in the placebo group.[13] There have been no deaths due to viral infections in patients with MS receiving recommended dosages of fingolimod (0.5 mg/day), with the two deaths that occurred due to serious infections occurring in patients receiving a higher than recommended dosage of fingolimod (1.25 mg/day) [section 5.1]. Both bronchitis and, to a lesser extent pneumonia, were more common in fingolimod-treated patients.[13]

In addition to cases that were reported in the double-blind phase of clinical trials, there have also been two published case reports of infections occurring in patients enrolled in these trials.[58,60] One of these was a case report of a 40-year-old patient enrolled in the extension phase of the TRANSFORMS trial who developed a primary VZV infection after 39 months of fingolimod treatment.[60] This infection was successfully treated with intravenous and then oral aciclovir. The other case was a 28-year-old woman enrolled in the FREEDOMS trial who developed haemorrhagic and centrally necrotic focal encephalitis after 7 months of fingolimod treatment (1.25 mg/day).[58] Follow-up assessment and treatment indicated that the cause of the encephalitis was not likely to be due to a bacterial infection, with an autoimmune or possibly undetected viral aetiology the more likely cause.[58]

5.3 Ophthalmological Events

In clinical trials in patients with MS, macular oedema with or without visual symptoms occurred in 0.4% of the 1204 patients receiving fingolimod 0.5 mg/day compared with 0.1% of 861 patients receiving placebo.[13] It predominantly occurred during the first 3–4 months of therapy, with some patients presenting with blurred vision or decreased visual acuity and others remaining asymptomatic. Macular oedema generally improved or resolved with or without treatment after discontinuation of fingolimod treatment; some patients had residual visual acuity loss even after resolution of macular oedema.[13]

In a pooled analysis of the clinical trials and extension studies discussed in section 4, of the 16 cases of confirmed macular oedema that were reported in 2615 fingolimod-treated patients, most occurred within the first 3–4 months after initiation of fingolimod treatment and resolved upon discontinuation of study drug (abstract plus poster presentation).[61] No patients experienced a further deterioration in vision after discontinuing study treatment. Four (25%) of these 16 patients had a history of uveitis compared with an incidence of uveitis of 1% (25 of 2615 patients) across all fingolimod groups, suggesting that uveitis was a risk factor for macular oedema.

There is an increased risk of macular oedema with fingolimod treatment in MS patients with diabetes mellitus (fingolimod has not been evaluated in this patient population) and in patients

with MS and a history of uveitis.[13] The rate of macular oedema in MS patients with a history of uveitis was 20% compared with 0.6% in those who had no history of uveitis, based on the combined experience across all dosages of fingolimod.[13]

5.4 Long-Term Tolerability

Given that fingolimod has only recently been approved, long-term clinical experience with the drug is limited. After up to 5 years of fingolimod treatment, no new safety concerns had emerged compared with the initial 6-month study,[53] with similar results seen at the 1-,[48] 2-,[50] 3-,[51] 4-[52] and 5-year[53] timepoints. At 5 years, the most commonly (incidence ≥15%) reported adverse events were nasopharyngitis (38.4% of patients), headache (31.7%), influenza (19.9%), fatigue (19.6%), back pain (18.5%), lymphopenia (15.7%), upper respiratory tract infections (15.3%), cough (14.9%), diarrhoea (14.6%) and elevated transaminase levels (14.9%).[53] Fingolimod treatment did not appear to have any chronic effects on heart rate, atrioventricular conduction or heart functioning.[53]

6. Dosage and Administration

In the US,[13] oral fingolimod is indicated for the treatment of adult patients with relapsing forms of MS to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disabilities. In the EU,[14] fingolimod is approved for use as a single-agent DMT in highly active RRMS for the following groups: patients with high disease activity despite treatment with IFNβ or patients with rapidly evolving severe RRMS defined by two or more disabling relapses in 1 year, and with one or more Gd-enhanced lesion on brain MRI or a significant increase in T2 lesion load compared with a previous recent MRI.[14] The recommended dosage is 0.5 mg once daily, which may be taken without regard to food.[13,14]

The manufacturer's prescribing information for the use of fingolimod in the US[13] and EU[14] includes the following precautions/warnings. Fingolimod may potentially cause a decrease in heart rate and/or atrioventricular conduction after the first dose; all patients should be monitored for signs and symptoms of bradycardia for 6 hours after the first dose. As fingolimod may increase the risk of infections, a recent complete blood count should be available before initiating treatment and patients should be monitored for signs and symptoms of infection during treatment and for 2 months after discontinuing treatment. Macular oedema, which may be asymptomatic, may occur during fingolimod treatment; an ophthalmological evaluation should be undertaken before initiating treatment and 3–4 months after initiating treatment. Patients with diabetes mellitus or a history of uveitis are at increased risk and should have regular ophthalmological evaluations. With fingolimod treatment, patients may experience a decrease in pulmonary function tests; when clinically indicated, spirometry and DLCO should be obtained. Fingolimod treatment may increase liver transaminases; liver enzyme tests should be conducted before initiating treatment and re-assessed if symptoms suggestive of hepatic injury develop. Fingolimod treatment should be discontinued if significant liver injury is confirmed. Women of child-bearing potential should use effective contraception during and for 2 months after discontinuing fingolimod treatment, as fingolimod may cause foetal harm. Before initiating fingolimod treatment, in patients who are VZV antibody negative, VZV vaccination should be considered and treatment with fingolimod postponed for 1 month to allow for the full effect of the vaccination to occur.[13,14]

Local prescribing information should be consulted for further details, including precautions, special warnings, contraindications and use in special patient populations.

7. Place of Fingolimod in the Management of Relapsing-Remitting Multiple Sclerosis

The management of MS involves a multifaceted approach utilizing symptomatic pharmacotherapy and DMTs, and various patient management strategies.[7,62] Apart from treatment to ameliorate symptoms such as spasticity, bladder and bowel symptoms, depression, tremor and ataxia,

pharmacotherapy is primarily focused on the prevention of relapses and progression of the disease. Recent evidence and better knowledge of the pathophysiology of MS have shifted the algorithm for the management of MS, with initial DMTs focusing on modulating the inflammatory processes associated with MS.[7]

Currently, there are several immunomodulatory DMTs available for the treatment of MS, including subcutaneous IFNβ-1a, IFNβ-1b and glatiramer acetate, intramuscular IFNβ-1a, and intravenous mitoxantrone and natalizumab.[7,62-65] However, these are not without their limitations, with the use of natalizumab (increased risk of developing progressive multifocal leukoencephalopathy) and mitoxantrone (cardiotoxicity and myelosuppression) limited to high-risk patients because of safety and tolerability concerns.[63,64,66] Although IFNβ and glatiramer acetate are considered first-line DMTs for patients with RRMS, with both drugs having good long-term safety profiles, their use is limited by parenteral administration, their relatively modest efficacy (relapse rates reduced by ≈30% vs placebo) and, in the case of IFNβ, the development of neutralizing antibodies in some patients.[67] Current treatment guidelines do not have specific formal recommendations for selecting between these first-line therapies.[62-65] However, it is generally recommended that treatment of RRMS with one of these agents should be initiated early in the disease process, including in patients with clinically isolated syndrome (CIS; a syndrome that is indicative of likely progression to clinically definitive MS[7,68]).[62-65] Indeed, IFNβ treatment in patients with CIS reduced the conversion rate to MS to 28–35% over a period of 2–3 years versus 45–50% in untreated patients with CIS.[64]

Given the limitations of current first- and second-line therapies in terms of their modest efficacy, inconvenient routes of administration and/or safety concerns, there is considerable interest in developing novel pharmacotherapies for the treatment of MS, with several agents in development (e.g. oral laquinimod and teriflunomide).[2,7] The recent approval in the US[13] and EU[14] of oral fingolimod, with its convenient once-daily regimen (section 6) and novel mechanism of action (section 2), provides a new option in the treatment algorithm for relapsing forms of MS, albeit its approval is too recent for fingolimod to have been considered in currently available treatment guidelines.

In the large, multinational, 2-year FREEDOMS[47] and 1-year TRANSFORMS[49] trials conducted in adult patients with RRMS, once-daily oral fingolimod was generally significantly more effective than placebo (section 4.1.2) and intramuscular IFNβ-1a (section 4.2.1) at improving clinical outcomes, including reducing relapse rates by approximately 50% compared with the comparator groups, increasing the proportion of patients who were relapse free at study endpoint and slowing progression of neurological disability. Notably, patients who entered the extension phase of the TRANSFORMS trial and were switched from IFNβ-1a treatment to fingolimod treatment experienced significant improvements in clinical and MRI-assessed outcomes at the end of the 1-year extension phase (section 4.2.1).[54] Furthermore, based on data from the extension phase of a 6-month, phase II trial,[48] the beneficial effects of fingolimod treatment were sustained in the long term (≤60 months of treatment with 1.25 and/or 5 mg/day) [section 4.1.1], albeit the dosages given were higher than the recommended dosage of 0.5 mg/day and the number of patients evaluated was relatively small.

MRI technology has provided significant advances in identifying the widespread axonal dysfunction associated with MS and, along with improved diagnostic criteria, has allowed MS to be diagnosed before it becomes clinically definite.[68] Over the past two decades, MRI-assessed outcomes have become surrogate markers of inflammation, scar formation and tissue damage or loss, with typical assessments, including the T2 lesion load, T1 Gd-enhanced lesion load and the number of newly emerging lesions.[2] It remains controversial as to whether these are the optimal surrogate markers of disease.[2] In the pivotal FREEDOMS[47] and TRANSFORMS[49] trials, MRI-assessed outcomes were generally improved to a significantly greater extent with fingolimod treatment than with placebo (section 4.1.2) or IFNβ-1a treatment (section 4.2.1). The beneficial

effects of fingolimod on surrogate MRI-assessed outcomes were sustained after up to 5 years of treatment in an extension study of a phase II trial (section 4.1.1).

MS has a considerable socioeconomic impact on the entire family, including on daily activities such as the ability of the patient and their caregiver to work, transportation and maintaining social and leisure activities.[1,4] With disease progression, there is a well established increase in the emotional and physical burden that is placed on caregivers.[1,4] In the TRANSFORMS trial,[49] fingolimod-treated patients showed significantly less deterioration in HR-QOL than patients receiving IFNβ-1a (section 4.2.1).

Oral fingolimod 0.5 mg/day was generally well tolerated in patients with RRMS participating in shorter-term (≤2 years) clinical trials, with most adverse events being of mild to moderate severity (section 5). The most common treatment-emergent adverse events of any severity occurring during fingolimod treatment were headache, influenza, diarrhoea, back pain, cough and liver enzyme elevations (section 5.1). No individual serious adverse event occurred with an incidence of >1% in any treatment group in the placebo-controlled FREEDOMS trial,[47] with the most common being bradycardia, basal-cell carcinoma, MS relapse, chest pain and macular oedema (section 5.1). Serious adverse events occurring in at least 0.7% of patients in any treatment group in the TRANSFORMS trial[49] were bradycardia or sinus bradycardia, atrioventricular block, herpesvirus infection, basal cell carcinoma and melanoma (section 5.1). Of note, most serious episodes of bradycardia and atrioventricular block that occurred in clinical trials were asymptomatic and all episodes occurred after the first dose during the monitoring period and were reported as serious because the protocol-defined discharge criteria were not met (section 5.1). No serious adverse events associated with laboratory parameters occurred in the fingolimod 0.5 mg/day groups in either of the pivotal trials (section 5.1). In patients with MS, fingolimod treatment was associated with a numerically higher incidence of macular oedema with or without visual symptoms than placebo (0.4% vs 0.1%) [section 5.3]. Most cases occurred during the first 3–4 months of therapy and generally improved or resolved with or without treatment after discontinuation of fingolimod therapy. The risk of macular oedema was increased in patients with a history of diabetes mellitus or uveitis.

In the TRANSFORMS trial,[49] the tolerability profiles of fingolimod and IFNβ-1a were as might be predicted for each individual agent (section 5.1). Hence, fingolimod treatment was associated with a numerically lower incidence of pyrexia, flu-like illness, myalgia, depression and arthralgia than IFNβ-1a treatment and conversely, IFNβ-1a treatment was associated with a numerically lower incidence of headache, nausea, diarrhoea, fatigue and elevated ALT levels than fingolimod (section 5.1).

Fingolimod is an immunosuppressive agent and induces lymphopenia (section 2.1) and thus, there is a potential for it to impact on normal immune responses, including the ability to mount immune responses to specific viral antigens and prevent opportunistic infections. An ongoing multicentre trial[69] should more fully elucidate the effects that fingolimod-induced lymphopenia has on the ability of patients to mount antigen-specific immune responses (section 2.1). The overall rate of infections in patients with MS who received fingolimod 0.5 mg/day during clinical trials was 72% (2% were considered serious infections) and was similar to that in the placebo group (section 5.2). No deaths due to viral infections occurred in patients with MS receiving fingolimod 0.5 mg/day; two deaths resulting from opportunistic infections occurred with fingolimod 1.25 mg/day. It is recommended that patients are monitored for signs and symptoms of infection, since fingolimod treatment may increase the risk of infection (section 6). In clinical trials, the occurrence of serious localized skin cancers was relatively uncommon, with all of these skin cancers successfully removed (section 5.1).

The long-term safety profile of a drug is an important factor when choosing which pharmacotherapy to utilise, with postauthorization safety studies (PASS) being pivotal to ensure that any potentially serious or life-threatening adverse events are identified.[67] Indeed, the manufacturer of oral cladribine (approved in Australia and

Russia for the treatment of RRMS) has recently voluntarily withdrawn the drug from the market worldwide,[70] reflecting issues arising from potential safety concerns raised by the European Medicines Agency[71] and US FDA.[72] Given the limited postmarketing clinical experience with fingolimod treatment, its long-term safety profile remains to be fully determined. After up to 5 years of fingolimod treatment, no new safety concerns had emerged during the extension phase compared with the initial 6-month study and fingolimod treatment had no chronic effects on heart rate, atrioventricular conduction or heart functioning (section 5.4). An ongoing, 5-year, multinational PASS will monitor the incidence of selected safety outcomes in patients with RRMS treated with fingolimod and should help to more definitively establish the long-term safety of the drug.[67]

Pharmacoeconomic considerations play an increasing role in determining the choice of pharmacotherapy,[4,67] with MS posing considerable costs from a societal and healthcare perspective.[4,73] For example, in a US economic analysis of patients with MS receiving DMTs, direct medical and non-medical costs (53%), production losses (37%) and informal care (10%) accounted for most of the estimated total mean costs of $US47 215 per patient per year (2004 costs).[73] To date, a lack of published robust pharmacoeconomic studies precludes any definitive conclusions about the relative costs and benefits of oral fingolimod versus other DMTs, albeit the ease of administration of an oral agent such as fingolimod versus the current parenteral agents should potentially reduce direct costs.

In conclusion, oral fingolimod is the first oral agent and the first agent in a novel class of DMTs to be approved for use in the US for the treatment of relapsing forms of MS. In the EU, fingolimod is approved for use in selected patients with highly active RRMS. In large multinational trials in adult patients with RRMS, oral fingolimod 0.5 mg/day was more effective than oral placebo and recommended dosages of intramuscular IFNβ-1a in reducing the ARR and was also generally more effective at slowing progression of neurological disability and reducing the burden and activity of disease. Fingolimod was generally well tolerated in these shorter-term trials of up to 2 years' duration, with most adverse events being manageable and of mild to moderate severity; there were two deaths from opportunistic infections, albeit these occurred with fingolimod 1.25 mg/day. Limited long-term data indicated that no new safety concerns had arisen after 5 years of fingolimod treatment. However, further clinical experience is required to fully determine the long-term safety profile of fingolimod, particularly with regard to any potentially serious or life-threatening adverse events. In the absence of robust pharmacoeconomic studies and of head-to-head trials comparing fingolimod with other formulations of IFNβ and glatiramer acetate, the relative position of fingolimod with respect to other DMTs remains to be fully determined. In the meantime, given its convenient once-daily oral treatment regimen and better efficacy than intramuscular IFNβ-1a, fingolimod is a valuable emerging option for the treatment of adult patients with relapsing forms of MS.

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References

1. World Health Organization. Atlas: multiple sclerosis resources in the world 2008 [online]. Available from URL: http://www.who.int/mental_health/neurology/Atlas_MS_WEB.pdf [Accessed 2011 May 2]
2. Menge T, Weber MS, Hemmer B, et al. Disease-modifying agents for multiple sclerosis: recent advances and future prospects. Drugs 2008; 68 (17): 2445-68
3. Kieseier BC, Wiendl H. Oral disease-modifying treatments for multiple sclerosis: the story so far. CNS Drugs 2007; 21 (6): 483-502
4. World Health Organization. Neurological disorders: a public health approach [online]. Available from URL: http://www.who.int/mental_health/neurology/chapter_3_a_neuro_disorders_public_h_challenges.pdf [Accessed 2011 May 3]
5. Noseworthy JH, Lucchinetti C, Rodriguez M, et al. Multiple sclerosis. New Engl J Med 2000; 343 (13): 938-52
6. Ryan M, Deno S, Zwibel HL. Review of clinical debate regarding interventions for multiple sclerosis. J Manag Care Pharm 2009; 15 (1 Suppl. S-b): S1-17
7. Lipsy R, Schapiro RT, Prostko CR. Current and future directions in MS management: key considerations for

managed care pharmacists. J Manag Care Pharm 2009; 15 (9 Suppl. 9-a): S2-15

8. Lipsy RJ. Will the newer oral MS agents be welcomed by managed care organizations? Am J Manag Care 2010; 16 (8 Suppl.): S227-33
9. Gold R. Oral therapies for multiple sclerosis: a review of agents in phase III development or recently approved. CNS Drugs 2011; 25 (1): 37-52
10. Brinkmann V. Sphingosine 1-phosphate receptors in health and disease: mechanistic insights from gene deletion studies and reverse pharmacology. Pharmacol Ther 2007; 115 (1): 84-105
11. Mehling M, Johnson TA, Antel J, et al. Clinical immunology of the sphingosine 1-phosphate receptor modulator fingolimod (FTY720) in multiple sclerosis. Neurol 2011; 76 Suppl. 3: S20-7
12. Hla T, Brinkmann V. Sphingosine 1-phosphate (S1P): physiology and the effects of S1P receptor modulation. Neurology 2011; 76 (8 Suppl. 3): S3-8
13. Novartis Pharmaceuticals Corporation. US prescribing information: Gilenya™ (fingolimod) capsules [online]. Available from URL: http://www.pharma.us.novartis.com/product/pi/pdf/gilenya.pdf [Accessed 2010 Dec 8]
14. European Medicines Agency. Gilenya: summary of product characteristics [online]. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002202/WC500104528.pdf [Accessed 2011 May 15]
15. Kovarik JM, Schmouder RL, Slade AJ. Overview of FTY720 clinical pharmacokinetics and pharmacology. Ther Drug Monit 2004; 26 (6): 585-7
16. Brinkmann V. FTY720 (fingolimod) in multiple sclerosis: therapeutic effects in the immune and the central nervous system. Br J Pharmacol 2009; 158 (5): 1173-82
17. Chun J, Hartung H-P. Mechanism of action of oral fingolimod (FTY720) in multiple sclerosis. Clin Neuropharmacol 2010; 33 (2): 91-101
18. Brinkmann V, Davis MD, Heise CE, et al. The immune modulator FTY720 targets sphingosine 1-phosphate receptors. J Biol Chem 2002; 277 (24): 21453-7
19. Lee CW, Choi JW, Chun J. Neurological S1P signaling as an emerging mechanism of action of oral FTY720 (fingolimod) in multiple sclerosis. Arch Pharm Res 2010; 33 (10): 1567-74
20. Albert R, Hinterding K, Brinkmann V, et al. Novel immunomodulator FTY720 is phosphorylated in rats and humans to form a single stereoisomer: identification, chemical proof, and biological characterization of the biologically active species and its enantiomer. J Med Chem 2005; 48 (16): 5373-7
21. Mandala S, Hajdu R, Bergstrom J, et al. Alteration of lymphocyte trafficking by sphingosine-1-phosphate receptor agonists. Science 2002; 296 (5566): 346-9
22. Baumruker T, Billich A, Brinkmann V. FTY720, an immunomodulatory sphingolipid mimetic: translation of a novel mechanism into clinical benefit in multiple sclerosis. Expert Opin Investig Drugs 2007; 16 (3): 283-9
23. Webb M, Tham CS, Lin FF, et al. Sphingosine 1-phosphate receptor agonists attenuate relapsing-remitting experimental autoimmune encephalitis in SJL mice. J Neuroimmunol 2004; 153 (1–2): 108-21
24. Fujino M, Funeshima N, Kitazawa Y, et al. Amelioration of experimental autoimmune encephalomyelitis in Lewis rats by FTY720 treatment. J Pharmacol Exp Therap 2003; 305 (1): 70-7
25. Kataoka H, Sugahara K, Shimano K, et al. FTY720, sphingosine 1-phosphate receptor modulator, ameliorates experimental autoimmune encephalomyelitis by inhibition of T cell infiltration. Cell Mol Immunol 2005; 2 (6): 439-48
26. Foster CA, Mechtcheriakova D, Storch MK, et al. FTY720 rescue therapy in the dark agouti rat model of experimental autoimmune encephalomyelitis: expression of central nervous system genes and reversal of blood-brain-barrier damage. Brain Pathol 2009; 19 (2): 254-66
27. Kovarik JM, Schmouder R, Barilla D, et al. Multiple-dose FTY720: tolerability, pharmacokinetics, and lymphocyte responses in healthy subjects. J Clin Pharmacol 2004; 44: 532-7
28. Kovarik JM, Schmouder R, Barilla D, et al. Single-dose FTY720 pharmacokinetics, food effect, and pharmacological responses in healthy subjects. Br J Clin Pharmacol 2004; 57 (5): 586-91
29. Mehling M, Lindberg R, Raulf F, et al. Th17 central memory T cells are reduced by FTY720 in patients with multiple sclerosis. Neurology 2010; 75 (5): 403-10
30. Mehling M, Brinkmann V, Antel J, et al. FTY720 therapy exerts differential effects on T cell subsets in multiple sclerosis. Neurology 2008; 71 (16): 1261-7
31. Johnson TA, Lapierre Y, Bar-Or A, et al. Distinct properties of circulating CD8+ T cells in FTY720-treated patients with multiple sclerosis. Arch Neurol 2010; 67 (12): 1449-55
32. Mehling M, Hilbert P, Fritz S, et al. Antigen-specific adaptive immune responses in fingolimod-treated multiple sclerosis patients. Ann Neurol 2011; 69: 408-13
33. Schmouder R, Boulton C, Wang N, et al. Effects of fingolimod on antibody response following steady-state dosing in healthy volunteers: a 4-week, randomized, placebo-controlled study [abstract plus poster no. P412]. 26th Congress of the European Committee for Treatment and Research in Multiple Sclerosis; 2010 Oct 13-16; Gothenburg
34. Miron VE, Jung CG, Kim HJ, et al. FTY720 modulates human oligodendrocyte progenitor process extension and survival. Ann Neurol 2008; 63 (1): 61-71
35. Coelho RP, Payne SG, Bittman R, et al. The immunomodulator FTY720 has a direct cytoprotective effect in oligodendrocyte progenitors. J Pharm Exp Ther 2007; 323 (2): 626-35
36. Miron VE, Ludwin SK, Darlington PJ, et al. Fingolimod (FTY720) enhances remyelination following demyelination of organotypic cerebellar slices. Am J Pathol 2010; 176 (6): 2682-94
37. Van Doorn R, Van Horssen J, Verzijl D, et al. Sphingosine 1-phosphate receptor 1 and 3 are upregulated in multiple sclerosis lesions. Glia 2010; 58 (12): 1465-76
38. Kowarik MC, Pellkofer H, Cepok S, et al. Differential effects of fingolimod (FTY720) on immune cells in the CSF and blood of patients with MS. Neurology 2011; 76 (14): 1214-21
39. Kovarik JM, Hartmann S, Bartlett M, et al. Oral-intravenous crossover study of fingolimod pharmacokinetics, lymphocyte responses and cardiac effects. Biopharma Drug Dispos 2007; 28 (2): 97-104

40. Burtin P, Ocwieja M, David OJ, et al. Effects of fingolimod on platelet function following steady-state dosing in healthy volunteers: a 4-week, randomized, placebo-controlled study [abstract plus poster no. P445]. 26th Congress of the European Committee for Treatment and Research in Multiple Sclerosis; 2010 Oct 13-16; Gothenburg
41. Schmouder R, Slade A, Kovarik J, et al. Effects on heart rate when oral fingolimod (FTY720) treatment was combined with atenolol, diltiazem, atropine or isoproterenol [abstract no. P 454]. 25th Congress of the European Committee for Treatment and Research in Multiple Sclerosis; 2009 Sep 9-12; Dusseldorf
42. Kahan BD, Karlix JL, Ferguson RM, et al. Pharmacodynamics, pharmacokinetics, and safety of multiple doses of FTY720 in stable renal transplant patients: a multicenter, randomized, placebo-controlled, phase I study. Transplantation 2003; 76 (7): 1079-84
43. Zollinger M, Gschwind H-P, Jin Y, et al. Absorption and disposition of the sphingosine 1-phosphate receptor modulator fingolimod (FTY720) in healthy volunteers: a case of xenobiotic biotransformation following endogenous metabolic pathways. Drug Metab Dispos 2011; 39 (2): 199-207
44. Slade AJ, Schmouder RL, Kovarik JM, et al. Oral fingolimod (FTY720) pharmacokinetics and pharmacodynamics are similar between Caucasian and Asian subjects [abstract no. P515]. Multiple Scler 2008; 14 Suppl.: S179-80
45. Kovarik JM, Schmouder RL, Serra D, et al. FTY720 pharmacokinetics in mild to moderate hepatic impairment. J Clin Pharmacol 2005; 45: 446-52
46. Kovarik JM, Schmouder RL, Hartmann S, et al. Fingolimod (FTY720) in severe hepatic impairment: pharmacokinetics and relationship to markers of liver function. J Clin Pharmacol 2006; 46 (2): 149-56
47. Kappos L, Radue E-W, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med 2010; 362 (5): 387-401
48. Kappos L, Antel J, Comi G, et al. Oral fingolimod (FTY720) for relapsing multiple sclerosis. N Engl J Med 2006; 355 (11): 1124-40
49. Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med 2010; 362 (5): 402-15
50. O'Connor P, Comi G, Montalban X, et al. Oral fingolimod (FTY720) in multiple sclerosis: two-year results of a phase II extension study. Neurology 2009; 72 (1): 73-9
51. Comi G, O'Connor P, Montalban X, et al. Phase II study of oral fingolimod (FTY720) in multiple sclerosis: 3-year results. Mult Scler 2010; 16 (2): 197-207
52. Montalban X, O'Connor P, Antel J, et al. Oral fingolimod (FTY720) shows sustained low rates of clinical and MRI disease activity in patients with relapsing multiple sclerosis: four-year results from a phase II extension [abstract no. P06.128]. 61st Annual Meeting of the American Academy of Neurology; 2009 Apr 25-May 2; Seattle (WA)
53. Izquierdo G, O'Connor P, Montalban X, et al. Long-term fingolimod (FTY720) in relapsing MS: 5 years results from an extension of a phase II, multicenter study show a sustained low level of disease activity [abstract plus poster no. PD6.004]. 63rd Annual Meeting of the American Academy of Neurology (AAN); 2011 Apr 9-16; Honolulu (HI)
54. Khatri B, Barkhof F, Comi G, et al. Comparison of fingolimod with interferon beta-1a in relapsing-remitting multiple sclerosis: a randomised extension of the TRANSFORMS study. Lancet Neurol 2011; 10 (6): 520-9
55. Cohen J, Barkhof F, Comi G, et al. Oral Fingolimod (FTY720) treatment improves the performance of daily activities compared with intramuscular interferon β-1a: Patient-Reported Indices for Multiple Sclerosis (PRIMUS)-Activities results from a phase III Study (TRANSFORMS) [abstract no. P06.137]. 62nd Annual Meeting of the American Academy of Neurology; 2010 Apr 10-17; Toronto (ON)
56. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the Diagnosis of Multiple Sclerosis. Ann Neurol 2001; 50 (1): 121-7
57. Haas J, Hartung HP, Von Rosenstiel P, et al. Effect of fingolimod on severe multiple sclerosis relapses, healthcare utilization and recovery: results from two phase 3 studies, TRANSFORMS and FREEDOMS [abstract plus poster. no P06.049]. 63rd Annual Meeting of the American Academy of Neurology; 2011 Apr 9–16; Honolulu (HI)
58. Leypoldt F, Münchau A, Moeller F, et al. Hemorrhaging focal encephalitis under fingolimod (FTY720) treatment: a case report. Neurology 2009; 72 (11): 1022-4
59. Schwarz A, Korporal M, Hosch W, et al. Critical vasospasm during fingolimod (FTY720) treatment in a patient with multiple sclerosis. Neurology 2010; 74 (24): 2022-4
60. Uccelli A, Ginocchio F, Mancardi GL, et al. Primary varicella zoster infection associated with fingolimod treatment. Neurology 2011; 76: 1023-4
61. Zarbin M, Reder AT, Collins W, et al. Ophthalmic evaluations in clinical studies of fingolimod (FTY720) in multiple sclerosis (MS) [abstract plus poster no. PO3.208]. 63rd Annual Meeting of the American Academy of Neurology; 2011 Apr 9-16; Honolulu (HI)
62. National Institute for Clinical Excellence. Multiple sclerosis: management of multiple sclerosis in primary and secondary care [online]. Available from URL: http://www.nice.org.uk/nicemedia/pdf/cg008guidance.pdf [Accessed 2011 Jun 23]
63. National Clinical Advisory Board of the National Multiple Sclerosis Society. Disease management consensus statement [online]. Available from URL: http://www.nationalmssociety.org/for-professionals/healthcare-professionals/publications/expert-opinion-papers/index.aspx [Accessed 2011 May 10]
64. Association of British Neurologists. Revised (2009) Association of British Neurologists' guidelines for prescribing in multiple sclerosis [online]. Available from URL: http://www.theabn.org/abn/userfiles/file/ABN_MS_Guidelines_2009_Final.pdf [Accessed 2011 May 10]
65. Goodin DS, Frohman EM, Garmany Jr GP, et al. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. Neurology 2002; 58 (2): 169-78
66. Goodin DS, Cohen BA, O'Connor P, et al. Assessment: the use of natalizumab (Tysabri) for treatment of multiple sclerosis (an evidence based review). Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2008; 71 (10): 766-73

67. Hohfeld R, Barkhof F, Polman C. Future clinical challenges in multiple sclerosis: relevance of sphingosine 1-phosphate receptor modulator therapy. Neurology 2011; 76 (8 Suppl. 3): S28-37

68. Coyle PK. Early treatment of multiple sclerosis to prevent neurologic damage. Neurology 2008; 71 (24 Suppl. 3): S3-7

69. Novartis Pharmaceuticals. Effect of treatment with fingolimod on the immune response following seasonal flu vaccination and tetanus booster injection in patients with relapsing multiple sclerosis (MS) [ClinicalTrials.gov identifier NCT01199861]. US National Institutes of Health, ClinicalTrials.gov [online]. Available from URL: http:///www.clinicaltrials.gov [Accessed 2011 Apr 19]

70. Merck KGaA. News release. Merck: regulatory update on cladribine tablets [online]. Available from URL: http://news.merck.de/N/0/DAA395BF12E226E6C12578B6007430DB/$File/CladUpdat_e.pdf [Accessed 2011 Jun 23]

71. European Medicines Agency. Withdrawal of the marketing authorisation application for Movectro (cladribine) [online]. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2011/02/WC500102304.pdf [Accessed 2011 Jun 23]

72. Gandey A. FDA rejects oral cladribine for multiple sclerosis [online]. Available from URL: http://www.medscape.com/viewarticle/738239_print [Accessed 2011 Jun 23]

73. Kobelt G, Berg J, Atherly D, et al. Costs and quality of life in multiple sclerosis: a cross-sectional study in the United States. Neurology 2011; 66 (11): 1696-702

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