NOVARTIS

Fingolimod (NDA 22-527)

# Briefing Document

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## List of abbreviations

| | |
|---|---|
| ADR | Adverse drug reaction |
| AE | Adverse event |
| AJ | Adherens junction |
| ALT | Alanine aminotransferase |
| ARR | Annualized relapse rate |
| AST | Aspartate aminotransferase |
| AUC | Area under the curve |
| AV | Atrio-ventricular |
| BBB | Blood-brain barrier |
| bpm | Beats per minute |
| BRB | Blood-retinal barrier |
| BP | Blood pressure |
| CFT | Central foveal thickness |
| $C_{max}$ | Maximum concentration of drug |
| CI | confidence interval |
| CIS | Clinically isolated syndrome |
| CMV | Cytomegalovirus |
| CNS | Central nervous system |
| CsA | Cyclosporine A |
| CYP3A | Cytochrome P450 3A |
| CYP4F | Cytochrome P450 4F |
| DBP | Diastolic blood pressure |
| $D_LCO$ | Diffusion capacity for carbon monoxide |
| DMT | Disease-modifying treatment |
| DSMB | Data and Safety Monitoring Board |
| EAE | Experimental autoimmune encephalomyelitis |
| EC | Endothelial cell |
| ECG | Electrocardiogram |
| EDSS | Expanded disability status scale |
| eNOS | Endothelial nitric oxide synthase |
| FDA | Food and Drug Administration |

| | |
|---|---|
| $FEF_{25-75}$ | Forced Expiratory Flow 25-75% |
| $FEV_1$ | Forced expiratory volume in 1 second |
| FVC | Forced vital capacity |
| FS | Functional systems |
| GA | Glatiramer acetate |
| GIRK | G protein-coupled inwardly-rectifying potassium channel |
| GGT | Gamma-glutamyl transferase |
| HCP | Health Care Practitioner |
| hERG | Human Ether-a-go-go Related Gene |
| HR | Hazard Ratio |
| HRCT | High resolution computed tomography |
| IFN | Interferon |
| i.m. | Intramuscular |
| IND | Investigational New Drug |
| ITT | Intent-to-treat |
| IV | Intravenous |
| KAB | Knowledge, Attitude and Behavior survey |
| MAdCAM | Mucosal Addressin Cell Adhesion Molecule |
| ME | Macular edema |
| MLCK | Myosin light chain kinase |
| MMF | Mycophenolate mofetil |
| MRI | Magnetic resonance imaging |
| MS | Multiple sclerosis |
| MSFC | Multiple Sclerosis Functional Composite |
| NO | Nitric oxide |
| OCT | Optical coherence tomography |
| PASS | Post-authorization safety study |
| PFT | Pulmonary function testing |
| PI | package insert |
| PML | Progressive multifocal leukoencephalopathy |
| PP | Per-protocol |
| PRES | Posterior reversible encephalopathy syndrome |

| | |
|---|---|
| QTc/QTcI | QT interval corrected |
| REMS | Risk Evaluation and Mitigation Strategy |
| RRMS | Relapsing remitting MS |
| S1P | Sphingosine-1-phosphate (Receptor) |
| SAE | Serious adverse event |
| SBP | Systolic blood pressure |
| SC | Subcutaneous |
| SD | standard deviation |
| SIENA | Structural Image Evaluation, using Normalisation of Atrophy |
| SMC | smooth muscle cells |
| SMH | Smooth muscle cell hypertrophy |
| SOC | System organ class |
| SPMS | Secondary progressive MS |
| TJ | Tight junction |
| ULN | Upper limit of the normal range |
| VCAM-1 | Vascular Cell Adhesion Molecule-1 |
| VLA-4 | very late anitgen-4; also known as α4β1 |
| VPC | Ventricular premature contractions |
| $V_{z,b}$ | Volume of distribution |
| WBC | White blood cell |

# EXECUTIVE SUMMARY

This document is prepared for members of the Food and Drug Administration (FDA) P&CNS Advisory Committee for the purpose of outlining the medical need for new therapies for patients with multiple sclerosis (MS), the rationale for the use of fingolimod in MS, the efficacy and safety data supporting the use of fingolimod in relapsing MS and an overall assessment of the benefit-risk profile of the drug in MS, including risk mitigation proposals.

## MS Background

Multiple sclerosis (MS) is a chronic, autoimmune and neurodegenerative disorder of the central nervous system (CNS), characterized by inflammation, demyelination, oligodendrocyte and neuronal loss. MS represents the leading cause of non-traumatic neurologic disability in young and middle-aged adults, affecting an estimated 2.5 million individuals worldwide, of whom approximately 400,000 live in the USA. The prevalence is greatest in Caucasians, with higher prevalence rates reported in Europe, Canada, USA, Australia, New Zealand and northern Asia (Rosati 2001; Noseworthy et al 2000).

Relapsing MS is the most frequent clinical presentation of the disease. The majority of patients are diagnosed in the prime of life, between the ages of 20 and 40, affecting women twice as commonly as men. At diagnosis, approximately 85% of patients have relapsing remitting MS (RRMS), characterized by recurrent acute exacerbations (relapses) of neurological dysfunction, including paralysis, numbness, incoordination, visual loss and loss of bladder control, followed by varying degrees of recovery. As many as half of relapses may be associated with incomplete recovery (Lublin et al 2003). The median time at which patients with RRMS have evolved to secondary progressive MS (SPMS), a stage of disease in which a less inflammatory and more neurodegenerative course predominates, is about 10 years. Ultimately >80% of RRMS patients evolve to SPMS, with 50% of patients requiring aids for walking within 15 years of disease onset. MS itself is associated with a life-span shortened by 6 to 7 years (Sadovnik et al 1991; Bronnum-Hansen et al 2004).

The disease is immune-mediated, directed against auto-antigens, with inflammatory damage in the CNS and resultant loss of myelin and axons, leading to the symptoms of the disease and progressive tissue destruction. Therapies to treat the disease target this auto-immune, lymphocyte-mediated etiology.

## Unmet Need in Multiple Sclerosis

Treatment strategies for MS make use of disease-modifying therapies to reduce the frequency of exacerbations (relapses) and to slow the accumulation of neurological impairment that affects the ability of affected individuals to function normally. First-line disease-modifying therapy consists primarily of (i) interferon (IFN) β (50-60% of treated patients), a cytokine that has antiviral, antiproliferative, and immunomodulatory activities and (ii) glatiramer acetate (30% of treated patients), a polypeptide copolymer. These products have moderate efficacy, providing about a 30-35% reduction in the relapse rate compared to placebo over 2 years. (IFNB MS Study Group 1993; Jacobs et al 1996; PRISMS Study Group 1998; Johnson et al 1995). Interferon β-1a has also been shown to reduce disability accumulation in patients with RRMS (Goodin et al 2002; Jacobs et al 1996; PRISMS Study Group 1998). A

number of comparative studies have been conducted with these agents that suggest thrice weekly IFN is modestly superior to weekly IFN (15% relative effect size on relapses over 1 year) (Panitch et al 2002) and that high frequency IFN appears comparable to glatiramer acetate (Mikol et al 2008; O'Connor et al 2009) These agents are administered by frequent injections (daily subcutaneous (SC) to once weekly by intramuscular (i.m.) route) and have known side-effects such as flu-like symptoms and injection site reactions which are frequent and reduce tolerability and adherence to therapy. Less commonly reported adverse events with IFNs involve liver dysfunction and cytopenias.

A more recently approved therapy, natalizumab, administered via monthly intravenous (IV) infusions, offers enhanced efficacy with a reduction in relapse rate by 68% and a reduced risk of sustained progression of disability by 42% compared to placebo (Polman et al 2006). However, natalizumab has been associated with hypersensitivity reactions, and a rare but usually fatal demyelinating disease of the brain - progressive multifocal leukoencephalopathy (PML). An additional IV product, the chemotherapeutic agent mitoxantrone, has been approved for use in MS. However, cumulative dose-related cardiac toxicity and risk for secondary leukemia limits its use. Due to their safety profiles, natalizumab and mitoxantrone are currently primarily used as second and third-line treatments respectively.

All of the current products are given by injection, presenting challenges both from the perspective of injection-related adverse effects but also regarding convenience and compliance. Given the therapeutic and logistical limitations of currently available therapies, i.e. modest efficacy, potentially serious, albeit rare risks plus convenience issues, there is a need for an MS treatment that can be safely used, is more effective and more convenient than the current first-line therapies and safer than second- and third-line therapies.

## Scientific Rationale for S1P Receptor Modulators in MS

The key pharmacodynamic effect of fingolimod is a dose-dependent, reversible reduction of the peripheral lymphocyte count mediated by down-modulation of the sphingosine-1-phosphate (S1P1) receptor on lymphocytes. This results in a reduced egress of lymphocytes from the lymph nodes. In particular, auto-reactive T-cells that play a central role in the inflammatory process that is the hallmark of MS are prevented from re-circulating to the CNS. Based on animal data, but not shown yet in humans, fingolimod may also provide a second effect relevant to MS via modulation of S1P receptors in the CNS, that may further inhibit inflammation but also potentially reduce astrogliosis and neurodegeneration while promoting repair, as has been shown in mouse models of MS (Brinkmann et al 2009).

The clinical development program of fingolimod in MS was pursued based on both (1) the hypothesis that restricting lymphocytes to peripheral lymphoid tissue could be of benefit and (2) data from experimental models of MS in animal showing efficacy.

## Development Program

Fingolimod was first developed for the prevention of acute rejection after renal transplantation in adult *de novo* renal transplant patients at daily doses of 2.5 mg and 5.0 mg in combination with cyclosporine A and corticosteroids. The renal transplantation clinical program (in nearly 2,300 patients, including two Phase 3 studies) was discontinued, as fingolimod did not confer advantages over the standard of care.

Based on pre-clinical data showing efficacy in animal models of MS, a clinical program in MS was initiated in 2003. A 6-month Phase 2 clinical study in MS showed efficacy of fingolimod on magnetic resonance imaging (MRI) measures as well as relapse endpoints with fingolimod, 1.25 and 5.0 mg, but with no difference in efficacy between the two doses. The 5.0 mg dose was thus discontinued.

The Phase 3 clinical development program of fingolimod in MS was then pursued with once-daily oral doses of 0.5 and 1.25 mg. In the Phase 3 program, involving over 2,800 patients, fingolimod has demonstrated a reduction in the frequency of relapses and a reduction in the risk of disability progression relative to placebo in a 2-year Study in patients with RRMS. Fingolimod has also reduced relapse and MRI activity measures compared to an approved therapy for MS, IFN β-1a (Avonex®) in a 1-year study.

This document provides an overview of the efficacy and safety outcomes and considers the overall benefit-risk profile of fingolimod 0.5 mg capsules as a disease-modifying therapy for the treatment of patients with relapsing MS to reduce the frequency of clinical exacerbations (relapses) and to delay the accumulation of physical disability. This document will also convey the sponsor's high level thoughts on the Risk Evaluation and Mitigation Strategy (REMS) for fingolimod.

## Regulatory History

The original Investigational New Drug (IND) for renal transplantation was submitted to the FDA in November 1998. As stated above, the renal transplant program was discontinued and the IND was subsequently closed in February, 2008.

The MS clinical development program commenced in Europe and Canada in March 2003 with Study 2201 and subsequently moved to Phase 3, both globally and in the USA. The MS IND was submitted in May 2005.

U.S. participation in the Global Phase 3 program was delayed, relative to other countries due to ongoing discussions regarding FDA-proposed additional safety data collection in Phase 3 (Holter monitoring, echocardiograms, ocular testing). After agreement with the FDA in June 2006 regarding safety data collection, U.S. sites began enrolling in the Phase 3 program.

In March 2007, the FDA granted fast-track status to the fingolimod development program in MS, based on the fact that MS is a serious condition and that fingolimod is an oral product. FDA indicated that all approved treatments for MS involve some type of injection and that fingolimod has the potential to address an unmet medical need in patients who can not tolerate injections.

Upon completion of the first Phase 3 study D2302, the FDA agreed that the fingolimod NDA was eligible for a rolling NDA submission. A rolling NDA, one of the fast-track designated programs, provides for the submission and review of portions of the NDA before the complete NDA is submitted. The rolling submission began in June, 2009 with subsequent submissions in July, September and the final documents in December, 2009.

After submission of the last components of the NDA, the FDA subsequently granted priority review (review within 6 months) in February, 2010. FDA grants priority review when one of

several criteria are met, such as when a preliminary review indicates that the drug may offer a significant advance beyond current treatments or in the case where no adequate therapy exists.

## Summary of Major Efficacy Findings

Study D2301 was a 2-year Phase 3 study, involving 1,272 RRMS patients, evaluating the efficacy and safety of two doses of fingolimod (0.5 and 1.25 mg given orally once daily) compared to placebo. The study demonstrated that both doses of fingolimod were effective compared to placebo over 2 years duration of treatment on multiple outcomes in a relapsing MS patients. For the 0.5 mg dose, compared to placebo over 2 years there was a:

- 54% relative reduction in annualized relapse rate (primary efficacy measure) compared to placebo over 24 months ($p<0.001$) including benefit in both treatment-naïve patients and those previously treated with approved MS therapies.
- 30% reduction in the risk of 3-month confirmed disability progression (key secondary efficacy measure) ($p=0.02$) and 37% reduction in risk of 6-month confirmed disability progression ($p\leq0.01$) compared to placebo.
- 74% relative reduction in the number of new and enlarging T2 lesions (key MRI secondary endpoint) as well as reduction in change of T2 lesion volume compared to placebo ($p<0.001$).
- 82% relative reduction in the mean number of Gd-enhancing lesions ($p<0.001$) as well as reduction in Gd-enhancing lesion volume ($p<0.001$) at Months 6, 12 and 24.
- 30% reduction in the mean loss of brain volume over 24 months compared to placebo ($p<0.001$).

Study D2302 was a 1-year Phase 3 study, involving 1,280 RRMS patients, evaluating the efficacy and safety of two doses of fingolimod (0.5 and 1.25 mg given orally once daily) compared to IFN β-1a, 30 mcg IM once weekly (Avonex®). The study demonstrated that fingolimod at both doses was more effective than a currently approved MS therapy on multiple outcomes across a spectrum of severity of relapsing MS patients. For the 0.5 mg dose, compared to IFN β-1a over 12 months there was:

- 52% relative reduction in annualized relapse rate (primary efficacy measure, $p<0.001$), including benefit in both treatment-naïve patients and those previously exposed to MS therapies.
- 31% relative reduction in the mean number of new and enlarging T2-weighted MRI lesions (key MRI secondary efficacy measure) ($p<0.01$).
- No significant difference in risk of 3-month confirmed disability progression (key secondary efficacy measure).
- 55% relative reduction in the mean number of Gd-enhancing lesions ($p<0.001$) as well as reduction in Gd-enhancing lesion volume compared to IFN ($p<0.001$) on T1-weighted MRI scans at Month 12.
- 30% relative reduction in loss of brain volume ($p<0.001$).

## Summary of Major Safety Findings

Comprehensive safety data are derived from over 2,600 MS patients exposed to fingolimod (providing approximately 4,500 patient-years of exposure), of whom ~ 1,800 patients have had >1 year and 1,200 patients > 2 years exposure to drug. Additionally, serious adverse event data and special safety assessment data are available on an additional 1,000 patients in ongoing blinded clinical trials. The review of integrated data has provided the following profile of safety for fingolimod in MS:

- Adverse event (AE) discontinuations and serious adverse events (SAEs) were of comparable frequency in the 0.5 mg and placebo groups but higher with 1.25 mg dosing.
- The incidence of common and serious adverse events were similar across treatment groups.
- Increased incidence of specific adverse drug reactions, frequently dose-dependent, predominantly felt to be related to the mechanism of action of fingolimod.
    - On treatment initiation, transient bradycardia and infrequent, low-grade atrio-ventricular (AV) conduction block.
    - Mild elevation of blood pressure (1-3 mmHg) that is reversible when drug is stopped.
    - Slightly increased incidence of lower respiratory tract infections, mainly bronchitis.
    - Macular edema.
    - Hepatic enzyme elevation (unclear if related to mechanism of action).
    - Lymphopenia, an expected outcome.

Based on the evaluation of safety data, specific information regarding identified and potential risks will be included in the label, including the Warnings and Precautions section. In addition, a risk evaluation and mitigation strategy has been developed for the product.

## Summary of Risk Evaluation and Mitigation Strategy (REMS)

The proposed REMS for fingolimod includes a Medication Guide and a Communication Plan to reinforce key risk messages to patients and prescribers. The goal of the REMS is to educate patients and prescribers about the potential serious risks of fingolimod, primarily bradycardia/bradyarrhythmia on treatment initiation, infections, macular edema, and reproductive toxicity.

In addition, Novartis proposes to perform a world-wide post-authorization safety study (PASS) the primary objective of which will be to investigate the incidence of selected safety-related outcomes in patients with MS receiving fingolimod under conditions of routine clinical practice. This will be a 5-year, multi-national, observational study including approximately 5,000 patients with relapsing MS. In addition to the primary objective, this study will enable Novartis to further explore the overall safety of fingolimod in patients with relapsing MS under conditions of routine practical care.

As part of the post-marketing safety surveillance, a pregnancy registry will also be established to collect information about the effect of fingolimod on the fetus.

### Conclusions

Data presented in this briefing book support the assertion that fingolimod is indicated as a first-line disease-modifying therapy for the treatment of patients with relapsing MS to reduce the frequency of relapses and to delay the accumulation of physical disability. Fingolimod addresses the above-mentioned need for an oral therapy that is highly effective and provides a favorable benefit-to-risk ratio in patients who have a chronic neurological disorder associated with severe, permanent damage to the CNS with resultant physical and cognitive impairment.

Prescribing recommendations as proposed in the package insert, along with the proposed evaluation and mitigation strategy (REMS) will facilitate the safe use of fingolimod in the treatment of MS patients.

# 1 Introduction and Background

This Briefing Document has been prepared for members of the Peripheral and Central Nervous System Drugs Advisory Committee to provide clinical and MRI data describing the benefits and risks of fingolimod as a treatment for patients with relapsing forms of MS. The data that is provided will help demonstrate that fingolimod has shown efficacy over placebo and over a currently approved MS therapy and provides a risk-benefit profile that supports its use as a first-line therapy for the treatment of a serious neurological disorder.

Based upon data obtained during clinical development, Novartis believes that fingolimod has a benefit-risk profile that supports approval for the following indication:

*"Gilenia is indicated as a disease-modifying therapy for the treatment of patients with relapsing multiple sclerosis to reduce the frequency of relapses and to delay the progression of disability."*

## 1.1 Multiple Sclerosis

Multiple sclerosis (MS) is a chronic disorder of the central nervous system (CNS), involving brain, spinal cord and optic nerves and is characterized clinically by recurring episodes of neurological symptoms (relapses). The disease is characterized pathologically by inflammatory infiltration of the CNS with resultant edema, demyelination, oligodendrocyte and neuronal loss, including axonal transection. MS represents the leading cause of neurologic disability in young and middle-aged adults, affecting an estimated 2.5 million individuals worldwide, of which 400,000 reside in the United States. The prevalence is greatest in Caucasians, with rates of >100/100,000 in regions of highest prevalence (e.g. Northern Europe, Canada) with incidence rates in the USA of 30-100/100,000 and prevalence of approximately 1/1,000. (Rosati 2001; Noseworthy et al 2000).

Relapsing MS is the most frequent clinical presentation of the disease. The majority of patients are diagnosed between the ages of 20 and 40, with a peak at age 29-30. There is a consistent, and strong, 2:1 female to male ratio. Diagnosis is uncommon at less than 18 years of age (<5%) and rare below the age of 10. Likewise, onset is uncommon beyond age 50. At onset, approximately 85% of patients have relapsing remitting MS (RRMS), characterized by recurrent acute exacerbations (relapses) of neurological dysfunction followed by variable degrees of recovery with clinical stability between relapses. The first clinical manifestations

of MS usually take the form of a clinically isolated syndrome (CIS) affecting the optic nerve (optic neuritis), spinal cord (transverse myelitis), or brainstem/cerebellum (Runmarker and Anderson 1993). Typical symptoms include numbness in the legs, difficulty walking, visual loss, incoordination and muscle weakness. These lesion-driven symptoms are also associated with considerable anxiety and distress to patients. Almost half of relapses may result in incomplete recovery of function and leave permanent disability and impairment (Lublin et al 2003) that accumulates over time. RRMS evolves to SPMS, a stage of disease in which disability accumulation continues either in the absence of relapses or between relapses. The median time at which patients with RRMS have progressed to SPMS is approximately 10 years, a stage of disease in which a less inflammatory and more neurodegenerative course appears to take precedence. Ultimately >80% of RRMS patients evolve to SPMS, with 50% of patients requiring assistance to ambulate within 15 years of disease onset (Weinshenker et al 1989; Runmarker and Anderson 1993). Life-span is shortened by 6 to 7 years in MS, either due to complications of chronic disability or the recognized increase in suicide rate in MS patients (Sadovnik et al 1991; Bronnum-Hansen et al 2004).

A typical MS patient at presentation is a woman in her 20's, just beginning a career and married life. She goes on to experience approximately one relapse every year or two with increasing problems with ambulation, co-ordination, dexterity, vision and other neurological symptoms. This accumulating disability leads to the need for a cane to walk on average by age 40-45, and limits her ability to work or care for family. Disease progression requires assistance of family to carry out daily activities. As the SPMS phase of disease takes over, disability increases leading to wheelchair dependence by age 50-60, frequently accompanied by other problems such as spasticity, pain and recurrent urinary infections. With a greater than average frequency, marriage breakdown occurs, leading to social isolation or the need for chronic institutional care and ultimately a premature death due to complications of advanced disease.

The pathological changes leading to these symptoms and signs are thought to begin with the migration of activated T lymphocytes across the blood-brain barrier (BBB) into the CNS where engagement of target antigens (presumably myelin proteins) leads to release of pro-inflammatory cytokines. This results in recruitment of additional lymphocytes into the CNS where inflammation leads to demyelination and axonal dysfunction/destruction. The initiating event of the inflammatory cascade remains unknown, but may involve antigen mimicry to viral proteins that results in generation of activated T-cells with CNS antigen specificity. Such cells home to the CNS, via attachment to brain endothelial receptors.

All of the pathological features of MS lesions can lead to the clinical symptoms experienced by patients. Inflammation and edema may result in short-lasting events that resolve completely whereas regions of demyelination may require longer to recover (if at all), depending on the severity. Oligodendrocyte death reduces the potential for remyelination, while axonal transaction is permanent, leads to neuronal death and is associated with persistent deficits if neuronal plasticity or redundancy is unable to overcome the tissue loss.

### 1.1.1 Current Therapy for Multiple Sclerosis

Therapy in MS consists of symptomatic therapies and disease-modifying treatments (DMTs). Symptomatic therapies include corticosteroids for acute relapses, as well as medications for spasticity, depression, urinary dysfunction, pain, and other MS-related symptoms.

Currently seven products, representing four distinct drug classes are approved in the US as disease-modifying agents for the treatment of relapsing forms of MS. These include IFN β (4 marketed products), glatiramer acetate, natalizumab and mitoxantrone.

The IFN group consists of four products using one of two forms of IFN β; Betaseron® and Extavia® (IFN β-1b 250 µg given by SC route on alternate days), Avonex® (IFN β-1a 30 µg given by intramuscular route given once weekly and Rebif® (IFN β-1a given by SC route 3 times per week at 22 or 44 µg dose). These therapies reduce relapse rates by about one-third (IFNB MS Study Group 1993; Jacobs et al 1996; PRISMS Study Group 1998; Johnson et al 1995). Although registration studies have been 2 years in duration, an impact on relapses is demonstrable in each of these studies, and others (Panitch et al 2002), within 6-12 months. In addition to relapse effect, the IFN β-1a products have shown an impact on MRI outcomes within weeks to months of initiating therapy and on delaying progression of disability in 2-year studies.

The most frequent side effects from IFN β are flu-like symptoms and injection site reactions. Although not serious or life-threatening, such side effects negatively impact patient quality of life and consequently, reduce compliance with therapy. Serious side effects include rare reports of hypersensitivity reactions, depression and suicide, decreased peripheral blood counts, hepatic injury, cardiomyopathy, and various autoimmune disorders (Betaseron Package Insert [PI] 2008; Rebif PI 2009; Avonex PI 2008). Neutralizing antibodies develop in 5-40% of patients receiving IFN, particularly those administered SC and such antibodies abrogate efficacy. (IFNB MS Study Group 1996; PRISMS Study Group 2001; Francis et al 2005; Pachner et al 2009).

The other first-line therapy is glatiramer acetate (GA, Copaxone® 20 mg) given SC daily. Copaxone is a random mixture of peptides composed of 4 amino acids that are over-represented in the encephalitogenic region of myelin basic protein, a protein deemed an important target of immune attack in MS. GA decreases relapse rate by approximately 30%, but has not shown an effect on preventing disability progression (Johnson et al 1995). The most notable side effects with GA are injection site reactions and acute systemic reactions of uncertain etiology (Copaxone PI 2009).

Although serious events are infrequent, the common adverse events of these first-line products impact tolerability and convenience for patients, ultimately affecting compliance or even willingness to initiate therapy. It is estimated that 20% to 25% of treated patients discontinue therapy annually (over 200,000 are being treated in US currently) leaving a large pool of patients who cycle between products or discontinue therapy entirely.

Natalizumab is the most recently approved therapy for treating MS. This product is a monoclonal antibody that binds to α4-integrins, α4β1 (also called VLA-4), and α4β7 leading to inhibition of binding of these integrins with the vascular cell adhesion molecule-1 (VCAM-1) and mucosal addressin cell adhesion molecule (MAdCAM-1) receptors respectively on endothelial cells. This blocks migration of leukocytes into sites of

inflammation. In Phase 3 studies, natalizumab (Tysabri®) reduced relapses by two-thirds, delaying disability progression and reducing MRI lesion activity (Polman et al 2006; Rudick et al 2006). However, in addition to an approximate 5% rate of neutralizing antibodies (loss of efficacy and hypersensitivity reactions), in approximately 0.1% of natalizumab patients, a fatal, or seriously disabling CNS infection, progressive multifocal leukoencepalopathy (PML) has been reported (Kleinschmidt-DeMasters et al 2005; Langer-Gould et al 2005). This overall rate appears to be higher in those on therapy for > 2 years and virtually not seen with therapy of < 1year. The product is thus recommended predominantly as a second-line therapy.

Mitoxantrone (Novantrone®), a chemotherapeutic agent, is also approved for patients with MS based on data from a single, relatively small clinical trial (Hartung et al 2002). Due to safety concerns, mitoxantrone is used predominantly as a third-line agent for those with severe RRMS or SPMS who have failed other therapies (Goodin et al 2003). Side effects include nausea, amenorrhea, mild alopecia, liver dysfunction, and leucopenia, but of more concern is the occurrence of acute myelogenous leukemia in 0.25 to 2.8% of MS patients (Novantrone PI 2009; Pascual et al 2009) and dose-related cardiotoxicity that limits lifetime exposure.

## 1.2 The Unmet Medical Need in Multiple Sclerosis

MS is a serious and disabling disease affecting individuals at a time of life when they are beginning careers and families. The disease inexorably leads to increasing levels of disability that limit employment (opportunities and productivity), place a strain on personal relationships, impact the lives of loved ones and culminate in a reduced life expectancy, a cascade of events mandating better therapies.

MS patients are faced with difficult therapeutic choices. Usually therapy starts with a first-line therapy that has modest relapse efficacy, limited if any disability benefit, and is associated with side-effects that are more irritants than major safety issues, but which affect patient quality of life and adherence to therapy. Additionally, many patients (up to two-thirds over 2 years in clinical trials) will continue to have relapses and disability accumulation despite therapy, prompting patients to seek other therapies. This can lead to cycling between first-line therapies, quitting therapy or moving to more potent, at times unapproved, therapies. Additionally, many patients fear injections sufficiently that they never begin therapy. Natalizumab, a second-line therapy, offers enhanced efficacy compared to first-line products. However, as experience with natalizumab increases, the rate of PML, particularly with more than 2 years of therapy, is steadily increasing and may limit use or lead to “drug holidays”.

Given the limitations of currently available therapies, there is a strong medical need for an MS treatment that can be safely used and is more effective and convenient than the current first-line therapies, without having physicians resort to potent, but riskier second-line therapies or toxic, unproven and unapproved therapies. Early intervention with the most effective, yet safe product, is the therapeutic ideal and the importance of this is highlighted by the occurrence of irreversible changes (i.e. axonal transaction) that accompany even the earliest relapses, changes that might be prevented with effective products used early in the course of disease.

## 1.3 Sphingosine 1-Phosphate Receptor Modulators

Fingolimod (FTY720) is the first sphingosine-1-phosphate (S1P) receptor modulator, in development for the treatment of MS. After oral dosing, fingolimod is phosphorylated *in vivo* by sphingosine kinase to form the active moiety fingolimod-phosphate (fingolimod-P). Fingolimod-P acts as an agonist at four of five G protein-coupled S1P receptors, namely $S1P_1$, $S1P_3$, $S1P_4$ and $S1P_5$, but not $S1P_2$. Depending on the cell type, the concentration, and the time following administration, fingolimod-P agonism at these receptors leads to receptor down-modulation, so that the end result is functional antagonism. Therefore, fingolimod-P may act as both an "agonist" and a "functional antagonist" at S1P receptors.

A brief summary of fingolimod effects on $S1P_1$ and $S1P_3$ in animal models is presented in Table 1-1. $S1P_4$ is specifically expressed in lymphoid tissue while $S1P_5$ is present in white matter tracts of the CNS (primarily on oligodendrocytes) and has been shown to modulate process outgrowth *in vitro*, in both neurons and oligodendroglia. The dynamic effects of agonism or functional antagonism of $S1P_4$ or $S1P_5$ *in vivo* are not currently known.

**Table 1-1 Sphingosine-1-phosphate biology and fingolimod effects in animal models**

| Physiologic effect | S1P receptor | Mechanism |
|---|---|---|
| Inhibition of lymphocyte egress from lymph node | $S1P_1$ | Internalization of $S1P_1$ on lymphocytes, prevents lymphocyte egress from LN, prevention of lymphocyte recirculation to peripheral tissues |
| Reduction of heart rate | $S1P_3$ & $S1P_1$ | Activation of S1P receptors and GIRK/IKACh channels in atrial myocytes, prior to down-modulation and/or desensitization of S1P receptors |
| Increased airway hyper-reactivity, airways constriction | $S1P_3$ & $S1P_1$ | At low fingolimod exposure, increase of lung hyper-reactivity to bronchospasmogens. At higher fingolimod exposure, direct constrictor effects. |
| Inhibition of astrogliosis, demyelination and neurodegeneration | $S1P_1$ | Functional antagonism of $S1P_1$ on astrocytes or neural cells in the CNS. |

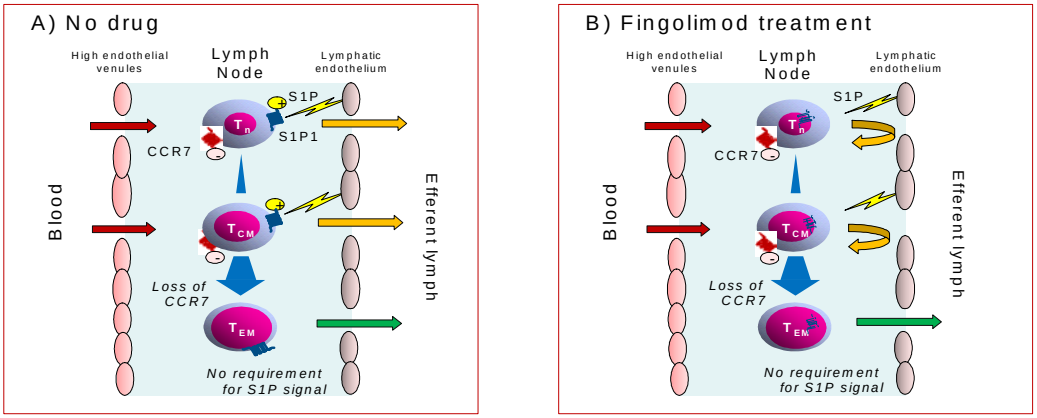
The key pharmacodynamic effect of fingolimod relates to a retention of selected lymphocyte subsets in lymph nodes (LNs). It was shown that the egress of lymphocytes from lymphoid organs is regulated by S1P and the lymphocytic $S1P_1$ receptor (Matloubian 2004, Brinkmann 2004, Pham 2008), and that treatment with fingolimod caused effective internalization of cell-membrane-expressed $S1P_1$ in LN T-cells (Pham 2008). This reduced S1P- dependent egress into the efferent lymph and blood and, as a consequence, reduced the peripheral blood lymphocyte count (Matloubian 2004, Brinkmann 2004).

Importantly, fingolimod retained only the $CCR7^+$ naive and central memory T cells (TCM) in LNs (the latter subset being key to central inflammation in MS), but did not retain CCR7-effector memory T cells (TEM) (a key subset in anti-infective immunity) (Figure 1-1). (Pham 2008, Mehling 2008). This is explained by the fact that $CCR7^+$ naive and TCM cells require the $S1P_1$ signal to override CCR7-mediated retention to allow egress from LNs. In contrast, terminally differentiated TEM cells have irreversibly lost CCR7 expression (and related retention signals) and egress independent of $S1P_1$ (Pham 2008). A similar regulation

may occur in B-cells where loss of CCR7 in plasmablasts coincided with accelerated egress from LNs. Collectively these findings support a model where $S1P_1$-signalling in naive and TCM cells overrides CCR7-mediated retention to promote egress from LNs, and that functional antagonism of S1P1 by fingolimod favours retention of $CCR7^+$ subsets in the nodes. In contrast, $CCR7^-$ TEM cells would not require S1P1 for egress and, thus, not be affected by fingolimod. In line with this model, blood lymphocytes of fingolimod-treated MS patients almost exclusively expressed a functional TEM cell phenotype (Mehling 2008). Such TEM cells could be key to the maintenance of protective immunity (Sallusto 2004).

**Figure 1-1 Mechanism of action of Fingolimod**

**Egress of T cells from lymph nodes is regulated by S1P1 and CCR7** 2




- S1P1-signaling in lymphocytes overrides CCR7-mediated retention to promote egress from LNs
- Fingolimod functionally antagonizes S1P1, thereby favoring CCR7-mediated retention of naive and TCM cells, but not of TEM cells

Matloubian et al., *Nature* 2004; Brinkmann et al., *Am J Transplant* 2004; Pham et al., *Immunity* 2008; Metzler et al., *Int Immunol* 2008, Mehling & Brinkmann et al., *Neurology* 2008, Brinkmann et al., *Brit J Pharmacol* 2009

S1P receptors are also expressed on neural tissues. Conditional $S1P_1$ gene deletion from neural cells, particularly astrocytes, showed reduced experimental allergic encephalomyelitis (EAE) disease and attenuated astrogliosis, demyelination, and axonal damage compared with wild-type counterparts. The CNS histopathologic phenotype in these animals was very similar to that observed in fingolimod-treated wild type mice EAE models. Therefore, fingolimod may display additional activities relevant to MS via down-modulation of CNS $S1P_1$ receptors, either via local downstream anti-inflammatory effects or potentially by an ability to inhibit astrogliosis, reduce neurodegeneration, and promote repair.

Beside lymphocytes and neural cells, S1P receptors are found in multiple tissues, including other blood cells, cardiac myocytes, vascular endothelium, smooth muscle cells of the vasculature, and bronchial smooth muscle. This broad distribution can lead to clinical effects, both desired and unwanted, in different organ systems, as will be further discussed.

# 2 MS Clinical Development Program of Fingolimod

Fingolimod was first developed for the prevention of acute rejection after renal transplantation in adult *de novo* renal transplant patients in combination with cyclosporine A and corticosteroids. The renal transplantation clinical program (in approximately 2,300 patients, including two Phase 3 studies) was discontinued, as fingolimod did not confer advantages over the standard of care.

However, fingolimod also demonstrated strong anti-inflammatory activity in EAE, and was subsequently developed as a treatment for relapsing MS patients.

The Phase 2 clinical study investigated two doses of fingolimod, 1.25 and 5.0 mg. Based on equal efficacy of the two doses seen in the Phase 2 study, the 1.25 mg dose was selected for further development. The Phase 3 clinical development program of fingolimod in MS was then pursued with once-daily oral doses of 0.5 and 1.25 mg and includes three Phase 3 studies (D2301, D2302, D2309) all evaluating the efficacy and safety of fingolimod.

## Target Population

The fingolimod Phase 2 and 3 program has demonstrated efficacy in patients with relapsing MS. Based on these results, the proposed labeled indication is:

*"Gilenia is indicated as a disease-modifying therapy for the treatment of patients with relapsing multiple sclerosis to reduce the frequency of clinical exacerbations and to delay accumulation of physical of disability"*

The program assessed efficacy and safety in patients who were either naïve to approved MS therapies or in those who were previously treated with such medications. Patients were predominantly female, < 55 years of age, had evidence of recent disease activity (MRI or clinical) and had a broad range of fixed neurological disability (Expanded disability status scale (EDSS) 0 to 5.0). Importantly, efficacy was compared not solely against placebo but also an approved MS therapy, IFN β. MS was defined according to the modified McDonald criteria (Polman et al 2005).

## Clinical Studies

Two studies that constituted the pivotal program are completed (D2301, D2302) and are included in the current submission in support of the proposed claims.

- D2301: a 2-year, double-blind, placebo-controlled study in 1272 patients with RRMS conducted globally (outside of the USA). Primary endpoint: annualized relapse rate; Key secondary endpoint: time to 3-month confirmed disability progression; Other secondary endpoints: various relapse- and disability-related endpoints, MRI measures of inflammation, disease burden, and brain volume.
- D2302: a 1-year, double-blind, double-dummy, active-controlled (once weekly 30 μg intramuscular IFN β-1a, Avonex®) study in 1292 patients with RRMS conducted globally. Primary endpoint: annualized relapse rate; Key secondary endpoints: number of new/newly enlarging T2 MRI lesions, time to 3-month confirmed disability progression; Other secondary endpoints: various relapse-related endpoints, other MRI measures of inflammation, and disease burden.

The third, fully enrolled, ongoing study (D2309), is a 2-year, double-blind, placebo-controlled study in 1,083 patients with RRMS, conducted mainly in the USA. This study includes specialized assessments to further characterize the safety profile of fingolimod in areas of interest based on previous clinical experience (heart, lung and eye). As requested by the FDA, interim safety data from these specialized safety assessments, corresponding to 1273 patient-years of exposure, are included in the NDA submission. The design of D2309 is otherwise identical to D2301 and therefore will provide information supportive to that seen in D2301. Filing with the two completed studies (D2301 and D2302) was deemed sufficient for regulatory consideration of approval without waiting for completion of study D2309.

The Phase 3 studies include long-term extensions (D2301E1, D2302E1, D2309E1) all of which are ongoing. Patients completing the core studies had the option to enter the extension where they either continued on their fingolimod dose from the core study (0.5 mg or 1.25 mg) or, if they had been in the control group, were re-randomized (from placebo or IFN β-1a) to receive either fingolimod 0.5 mg or 1.25 mg in the extension. Based on data obtained during the Phase 3 program, a decision was made to convert all patients to the 0.5 mg dose and discontinue development of 1.25 mg dosing in MS.

An earlier Phase 2 study consisted of a 6-month, placebo-controlled MRI study (core study D2201) in 281 patients with relapsing MS, which fed into a long-term ongoing extension study, D2201E1. Study D2201 evaluated once-daily fingolimod doses of 1.25 mg and 5.0 mg. The extension included 250 patients who either continued on their fingolimod dose from the core study or, if they had been in the placebo group, were re-randomized to receive either the fingolimod 1.25 mg or the 5.0 mg dose in the extension. The core study demonstrated superior efficacy versus placebo on MRI and relapse outcomes with no difference in efficacy between the two doses. The 5.0 mg dose was discontinued and the patients were switched to the 1.25 mg dose during the extension, and ultimately to 0.5 mg based on Phase 3 findings. This extension is now in its 7th year, with 140 patients having completed at least 5 years in the study. Data from patients treated for up to 60 months (6 months core study + 54 months extension) are included in this submission.

A large clinical pharmacology program was performed, comprising 30 clinical pharmacology studies that included 1,069 subjects in total (including healthy volunteers and renal transplant patients), of which 856 were exposed to at least one dose of fingolimod. The clinical pharmacology studies evaluated single doses up to 40 mg and multiple doses of 0.125 to 5 mg daily for up to 28 days. Relevant results from these studies are summarized in Section 3.

# 3 Clinical Pharmacology

## 3.1 Absorption, Distribution, Metabolism, Excretion

### 3.1.1 Absorption and distribution

Fingolimod absorption is slow ($t_{max}$ of 12-16 hours) and extensive, with measured absolute oral bioavailability of 93%. Fingolimod has dose-linear pharmacokinetics at single doses from 0.25 to 40 mg and at multiple once daily doses from 0.125 to 5 mg. A high-fat meal has no significant effect on fingolimod pharmacokinetics. Fingolimod and fingolimod-P pharmacokinetics after multiple once-daily doses are consistent with those after single dose

and are time-independent. Steady-state exposure is reached between 1 to 2 months during once-daily dosing with an estimated 12-fold accumulation of blood levels from first dose to steady state. Both fingolimod and fingolimod-P are highly protein bound (>99.7%). Fingolimod is extensively distributed to body tissues with volume of distribution ($V_{z,b}$) of about 1200±260 L. Fingolimod and fingolimod-P protein binding is not altered by renal or hepatic impairment. No drug interaction is expected from displacement from plasma proteins due to the low fingolimod concentration versus protein binding capacity.

### 3.1.2 Metabolism

The biotransformation of fingolimod in humans occurs by three main pathways: (i) by reversible phosphorylation to fingolimod-P, (ii) by oxidative biotransformation mainly via the cytochrome P450 4F2 isoenzyme and subsequent fatty acid-like degradation to inactive metabolites, (iii) by formation of inactive, non-polar ceramide analogs of fingolimod. Fingolimod-P can be converted back to fingolimod and the non-polar ceramide metabolites of fingolimod may also be converted back to fingolimod. Therefore, it is assumed that fingolimod, fingolimod-P and the non-polar ceramide analogs of fingolimod are in dynamic equilibrium at steady-state. At steady-state, the ratio of fingolimod-P to fingolimod area under the curve (AUC) is dose-independent and is approximately 0.4.

### 3.1.3 Excretion

Fingolimod blood clearance is low, 6.3±2.3 L/h, and the average apparent terminal half-life is 6-9 days. Blood levels of fingolimod-P decline in parallel with fingolimod in the terminal phase yielding similar half-lives for both. After an oral administration, about 81% of the dose is slowly excreted in the urine as inactive metabolites. Fingolimod and fingolimod-P are not excreted intact in urine but are the major components in the feces with amounts representing less than 2.5% of the dose each. As expected based on high protein binding and high volume of distribution, hemodialysis results in only a minor, 14% decrease in fingolimod blood concentration.

### 3.1.4 Drug and substance interactions

*In vitro* studies demonstrated that fingolimod and fingolimod-P are unlikely to reduce the clearance of drugs metabolized by the major cytochrome P450 isoenzymes, induce the major cytochrome P450 isoenzymes and P-gp or inhibit major drug transporters. No clinically relevant drug interaction (≤ 2-fold effect) was observed when fingolimod was co-administered with cyclosporine A (a CYP3A substrate and potent transporter inhibitor), diltiazem (a moderate CYP3A inhibitor) and ketoconazole (a CYP4F inhibitor and strong CYP3A inhibitor). Based on both *in vitro* and *in vivo* drug interaction data, it is assumed that fingolimod has i) a very low probability of a relevant pharmacokinetic drug interaction with any known drug in clinical use and 2) a very low probability that any known drug will have a clinically relevant pharmacokinetic drug interaction with fingolimod.

### 3.1.5 Pharmacokinetics in special patient populations

In a combined population pharmacokinetics analysis from the fingolimod transplant program, ethnicity differences (Black n=52, Asian n=55, Hispanic n=36) had little effect on fingolimod

pharmacokinetics. Similarly, neither age, weight nor gender have a clinically relevant effect on the pharmacokinetics of fingolimod and fingolimod-P.

Mild, moderate and severe hepatic impairments have no influence on fingolimod maximum concentration of drug ($C_{max}$) but fingolimod AUC is increased by 12%, 44% and 103%, respectively. Fingolimod-P was measured in severe hepatic impairment only, and $C_{max}$ and AUC were increased by 22% and 29%. The fingolimod dose does not need to be adjusted in mild or moderate hepatic impaired patients. Fingolimod should be used with caution in severe hepatic impairment subjects.

Severe renal impairment increases fingolimod $C_{max}$ and AUC by 32% and 43%, respectively, and fingolimod-P $C_{max}$ and AUC by 25% and 14%, respectively. The fingolimod dose does not need to be adjusted in mild, moderate or severe renal impaired patients.

## 3.2 Pharmacokinetic assessments in clinical studies

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

### 3.2.1 Pharmacodynamics

#### 3.2.1.1 Lymphocyte and leukocyte counts

Single doses of fingolimod from 0.5 to 5.0 mg result in a rapid (3-4 hours), dose-dependent decrease in lymphocyte count with minimal additional effect on the lymphocyte count above 5mg. Multiple doses of fingolimod from 0.125 mg to 5 mg result in counts reduced by 40% for 0.125 mg and 85-90% for 5 mg relative to baseline count. Maximal reduction takes up to 6 weeks.

All main lymphocyte subsets measured, including B cells, CD4+ T cells, CD8+ T cells, decrease in the setting of fingolimod treatment. In a study of 16 MS patients, there was reduced numbers of both CD4+ and CD8+ T lymphocytes, with a predominant reduction in the CD4+ T cell subset. In these MS patients, the memory effector sub-subset of T cells, appears not to be affected by fingolimod treatment (Mehling et al 2008; Brinkmann 2009). These cells are important in immune surveillance and upon re-stimulation by antigen, differentiate locally into effector cells that can provide first-line defense against recall infection.

Fingolimod may inhibit antibody responses to localized antigens which require T-/B-cell trafficking to the local draining lymph nodes, as such cells would be trapped within the lymph tissue. In contrast, the drug would not impair humoral immunity to systemic infection where the antigen is widely distributed to most lymphoid organs. Importantly, fingolimod would not reduce serum antibody levels maintained by long-lived plasma (memory) B-cells residing in the bone marrow.

Importantly for the presumed mechanism of action in MS, pro-inflammatory Th17 cells reside predominantly within the $CCR7^+$ re-circulating central memory T cell subset, and fingolimod traps >90% of phenotypic Th17 cells in lymph nodes.

Because of the contribution of the lymphocyte count to the total white blood cell count, the latter also decreases on fingolimod treatment. The monocyte count is not affected by fingolimod.

Recovery of lymphocyte count begins within days of discontinuing fingolimod therapy and counts have reached the normal range within 4-6 weeks in pharmacology studies.

#### 3.2.1.2 Heart

Over ten years ago, S1P was identified as a normal constituent of human blood that had heart rate lowering effects. Similar to S1P, fingolimod-P also manifests this dynamic effect through its capacity to signal S1P receptors in the atria of the heart. In pre-clinical studies, the heart rate lowering effect of S1P and fingolimod-P is mediated by the same ion channel (G protein coupled inwardly rectifying potassium channel (GIRK)) that is also used by the parasympathetic nervous system to lower heart rate.

Fingolimod 0.5 and 1.25 mg doses induce a mean negative chronotropic effect of approximately 7-8 and 10-15 beats per minute, respectively. This effect is seen within 3 hours of the first dose, has a nadir approximately 4-5 hours post single dose and with single doses, the negative chronotropic effect attenuates over 24 hours post-dose. With multiple dose administration of fingolimod 0.5, 1.25 or 5 mg, the majority (70%) of the negative chronotropic effect is manifest on the first day of dosing. After continued, chronic dosing for four weeks, the negative chronotropic effect of fingolimod is no longer observed. This return to baseline over time is believed to be due to functional antagonism of S1P receptors with continued dosing of fingolimod or auto-regulation of the heart or a combination of the two. Single or multiple doses of fingolimod >1.25 mg have little incremental negative chronotropic effect on heart rate. Patients who stop chronic fingolimod treatment but then restart treatment within two weeks will have no recurrence of the negative chronotropic effect associated with treatment initiation.

The circadian rhythm of heart rate is maintained during fingolimod dosing, although mildly blunted on the first day. This finding supports the conclusion that the capacity of the heart to respond to autonomic inputs is intact on fingolimod treatment. Subjects treated with multiple doses of fingolimod manifest an intact capacity to increase heart rate in response to exercise and drugs including atropine, isoprenaline and salmeterol. Fingolimod treatment can be used in combination with heart rate lowering drugs such as atenolol and diltiazem. The acute administration of the combination of fingolimod with atenolol, but not with diltiazem, results in an additional 15% reduction of heart rate when compared to fingolimod treatment alone.

Fingolimod 0.5 and 1.25 mg have no detectable effect on ventricular function as measured by cardiac output or stroke volume.

In clinical pharmacology studies, fingolimod treatment is not associated with an increased rate of atrial fibrillation or ventricular ectopy. A higher rate of benign atrial ectopy may be seen in fingolimod treated subjects on the first day of fingolimod dosing, however this treatment effect appears to attenuate by day 7 of treatment. Treatment initiation with fingolimod does not increase the rate of clinically significant, high grade (>3 sec) sinus pauses. The rate of “low grade sinus pauses” (2-3 sec) as detected by Holter monitor, may increase on day 1 of fingolimod dosing, however no sinus pauses are detectable after seven days of fingolimod treatment. Close inspection of these “low grade sinus pauses” reveal that most, if not all, are

not classical sinus pauses, but rather sinus arrhythmia superimposed on low heart rate. With fingolimod doses ≤1.25 mg the incidence rate of second degree atrioventricular block (7%) is approximately twice the incidence rate measured in placebo treated healthy subjects (3%). The duration of these blocks is also longer with fingolimod. These blocks are typically asymptomatic, do not require treatment and resolve within twenty-four hours of starting fingolimod treatment. There were no second-degree Mobitz type II or wide complex third-degree heart blocks in the clinical pharmacology studies.

After seven days of dosing to pharmacokinetic steady state, when a negative chronotropic effect of fingolimod was still present, fingolimod treatment resulted in a significant prolongation of QTcI, with the upper bound of the 90% confidence interval (CI) being an increase of ≤13.0 ms. There was no dose or exposure-response relationship of fingolimod and QTcI prolongation. There was no consistent signal of increased incidence of QTcI outliers, either absolute change or as percentage change from baseline, associated with fingolimod treatment.

#### 3.2.1.3 Lung

Fingolimod treatment with single or multiple doses of 0.5 and 1.25 mg for two weeks is not associated with a detectable increase in airway resistance as measured by forced expiratory volume in 1 second ($FEV_1$) and forced expiratory flow 25-75% ($FEF_{25-75}$). However, single fingolimod doses ≥5 mg are associated with a dose dependent increase in airway resistance. Single doses of fingolimod ≥20 mg are associated with symptoms of increased airway resistance including chest tightness and chest discomfort.

Fingolimod treatment with multiple doses of 0.5, 1.25, or 5 mg is not associated with impaired oxygenation or oxygen desaturation with exercise or an increase in airway responsiveness to methacholine. Subjects on fingolimod treatment have a normal bronchodilator response to inhaled β-agonists. Patients with mild or moderate asthma may be safely started on fingolimod treatment.

#### 3.2.1.4 Other

Overdose: Patients who received the highest, single fingolimod dose tested of 40 mg (80 capsules of the target 0.5mg dose for MS patients) complained of symptoms consistent with mild, acute reactive airways lasting for several hours. No medical intervention was needed and this effect was self-limited. No cases of macular edema were seen but the numbers of patients with sufficiently long exposure may have been too limited to detect this uncommon side effect. Liver enzyme elevation, an event not clearly related to drug mechanism of action, was seen in the pharmacology program.

## 3.3 Clinical Pharmacology Conclusions

Fingolimod is a well-absorbed drug with a long half-life and linear pharmacokinetics. Once absorbed, both fingolimod and the active metabolite, fingolimod-P are in dynamic equilibrium in the systemic circulation with a fingolimod to fingolimod-P ratio of approximately 2:1. At steady state, fingolimod 0.5 mg taken daily results in stable fingolimod and fingolimod-P concentrations over the dosing interval. In part due to its novel pathway of metabolism, CYP450 4F, clinically relevant drug-drug interactions are not expected in patients on

fingolimod treatment. Other than fingolimod-P, there are no other active metabolites of fingolimod. Neither intrinsic nor extrinsic factors have an appreciable effect on fingolimod pharmacokinetics. Even in patients with severe renal or hepatic impairment, there is little change (≤ 2-fold) in fingolimod or fingolimod pharmacokinetics.

Once daily dosing of fingolimod is supported by the long half-life of the drug and the low fluctuation of drug concentration over the dosing interval.

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

# 4 Design of Phase 3 Studies

The pivotal studies D2301 (a 2-year, double-blind, placebo-controlled study), and D2302 (a 1-year double-blind, double-dummy, active-controlled study) compared the efficacy and safety of the target dose of fingolimod 0.5 mg/day and the 1.25 mg/day dose with placebo (D2301) and IFN β-1a, (Avonex®) (D2302) in patients with RRMS.

The fingolimod Phase 3 program included patients with a diagnosis of MS, according to the 2005 revisions to the McDonald diagnostic criteria (Polman et al 2005), with a relapsing-remitting course and an EDSS score between 0 and 5.5.

The efficacy measures included in the fingolimod clinical development program are those widely used and accepted by regulatory authorities for the demonstration of efficacy in patients with relapsing forms of MS.

## 4.1 Outcome Measures for Multiple Sclerosis

### 4.1.1 Relapses

Relapses (exacerbations) are a cardinal feature of MS, being both the heralding events but also a feature that recurs until later stages of the disease. In addition to the physical impact, both acute, impairment that resolves but also permanent disability, patients experience considerable anxiety and distress with resultant impact on quality of life as a result of relapses. The importance of prevention of clinical relapses is highlighted by the fact that 42% to 57% of relapses are associated with residual neurological deficits (Lublin et al 2003).

Relapses are an accepted indicator of disease activity and reduction of relapse rate is recognized as providing therapeutic benefit to patients by regulatory agencies and qualifies as a clinically meaningful endpoint in studies of potential MS therapies.

All previous Phase 3 studies of disease-modifying therapies in MS have included relapse rates as an efficacy endpoint, playing a significant role in approval for all, and in the case of IFN β-1b (Betaseron® and Extavia®) and glatiramer acetate (Copaxone®) relapse effect was the only clinical criterion used. Annualized relapse rate was the primary outcome measure used in the fingolimod Phase 3 program studies.

*MS relapse definition:* MS relapse in the fingolimod program was defined as the appearance of a new neurological abnormality or worsening of previously stable or improving pre-existing neurological abnormality, separated by at least 30 days from onset of a preceding clinical demyelinating event. The abnormality must have been present for at least 24 hours and occurred in the absence of fever or known infection.

*Diagnosing MS relapses during the study*: In case of new neurological symptoms or worsening of previous symptoms, patients were instructed to immediately contact the treating physician. The treating physician was then requested to assess whether the new/worsening neurological abnormality met the definition of MS relapse as per protocol. If the treating physician assessed the new/worsening neurological abnormality as a MS relapse, then a neurological examination by a second physician not involved in the clinical care and management of the study patients (the Independent Evaluating Physician) was performed as soon as possible.

*Confirmation of MS relapse:* An MS relapse was considered confirmed when accompanied by a clinically relevant change in Expanded Disability Status Scale (EDSS) obtained by the Evaluating Physician, compared to the previous rating. This was defined as an increase of at least 0.5 on the EDSS score or an increase of 1 point in two Functional Systems (FS) or 2 points in one FS, excluding Bowel/Bladder or Cerebral FS.

Based on the results of the FS and EDSS scores obtained by the Evaluating Physician, the MS relapses was considered "confirmed" or "not confirmed".

*Assessment of MS relapse severity:* all MS relapses during the study were assessed as mild, moderate or severe based on change in the EDSS score and/or its Functional Systems (Panitch et al 2002) (Table 4-1).

**Table 4-1 Severity of MS relapse**

| Mild relapse | Moderate relapse | Severe relapse |
|---|---|---|
| EDSS increase of 0.5 point | EDSS increase of 1 or 2 points | Exceeding Moderate criteria |
| or | or | or |
| 1 point FS change in one to three systems | 2-point FS change in one or two systems | Exceeding Moderate criteria |
| | or | or |
| | 1-point change in four or more systems | Exceeding Moderate criteria |

### 4.1.2 Disability

#### 4.1.2.1 Kurtzke's expanded disability status scale (EDSS)

The EDSS is an ordinal scale widely used for impairment and disability rating in MS (Kurtzke 1983). It remains the accepted 'gold standard' primary disability endpoint for MS clinical trials. The EDSS is based on a standardized neurological examination, but focuses on the signs/symptoms that occur frequently in MS. Seven functional scales (FS) are assessed: Visual, Brain Stem, Pyramidal, Cerebellum, Sensory, Bowel & Bladder, and Cerebral. Based on the FS scores and ambulation ability, an EDSS score is determined.

The range of the EDSS includes 20 half-point steps from 0 to 10 (no 0.5), with 0 corresponding to a completely normal neurological examination and 10 to death due to MS. Between 0 and 4, the scale relies predominantly on the scores of the individual FS, whereas between 4.5 and 6.5 it relies on the ability and range of walking, and between 7.0 and 9.5 on the dependence on help.

Many factors can affect a patient's clinical status (e.g. fatigue, illness, time of day) as well as the reproducibility of physician performance/interpretation of neurological examinations. Thus a minimum threshold of 1-point change in EDSS is typically required in order to exceed change due to factors other than true neurological change. Additionally, to obviate temporal instability in assessments, confirmation of the change in EDSS is required at a subsequent visit, generally 3 months later, but also 6 months later as a more stringent definition of progression. Finally, to avoid attributing relapse-related temporary change in EDSS, confirmation of progression cannot occur if a relapse is ongoing.

EDSS assessments were scheduled at Screening, Baseline and then every 3 months. In the case of MS attack/relapse, EDSS assessment was also required at an unscheduled visit for confirmation of relapse.

EDSS progression was the key disability measure in the fingolimod program and was defined as a 1-point increase in EDSS (0.5 points for those with baseline EDSS of 5.5 given the magnitude of clinical change required to move from 5.5 to 6.0), confirmed 3 months later. The more rigorous requirement of 6-month confirmation was also evaluated.

#### 4.1.2.2 Multiple sclerosis functional composite (MSFC)

The Multiple Sclerosis Functional Composite (MSFC) was developed (Whitaker et al 1995) with the aim to identify an alternative outcome measure to the EDSS that captures aspects of the MS clinical profile not well reflected in the EDSS and to try and improve the sensitivity to change in disability (Miller et al 2000). This composite scale has been included in several clinical MS studies conducted in past decade.

The MSFC includes three well-known, objective, quantitative, continuous subscales that evaluate ambulation, arm dexterity, and cognition:

- 25-foot timed walking test (25'TWT): ambulation measurement, time (in seconds) that patients takes to walk 25 feet as quickly as possible without running.
- Nine hole peg test (9HPT): arm dexterity measurement, mean time (in seconds) to insert and remove 9 pegs with right and left arm scores.
- Paced Auditory Serial Addition Test-3 minute version (PASAT-3): cognitive function measurement, number of correct answers by adding 60 serial single digit numbers each provided every 3 seconds.

The scores for these 3 components are combined to create a single composite score by creating z-scores for each component and averaging them to create the overall z-score. The baseline population was used as the reference population for the calculation of the MSFC z-scores.

The MSFC was considered as a secondary disability measure in the fingolimod program and was evaluated by the Independent Evaluating Physician or other trained and experienced site personnel not involved in the treatment of the patient.

MSFC assessments were scheduled at Screening, Baseline and then every 6 months. Two MSFC training sessions had to be performed at Screening. The third MSFC assessment, performed prior to randomization, was considered as the baseline for the study.

### 4.1.3 Magnetic resonance imaging (MRI)

Magnetic resonance techniques were introduced 20-25 years ago and have had a major impact in diagnosis of MS and evaluating putative MS therapies (McFarland et al 2002). In a disease with a high degree of variability of clinical signs and symptoms over time and between individuals, and with no other adequate biological markers of disease activity or progression, MR techniques provide a highly sensitive, quantitative and objective indication of disease activity and pathology.

Lesions detected on T2-weighted sequences in MS patients are pathologically non-specific, as they can represent edema, inflammation, demyelination or gliosis. However, this non-specificity means that this measure detects many aspects of histopathology related to disease, particularly as it changes and accumulates over time, making T2-weighted images a good representation of the accumulation of disease burden over time. These lesions are typically reported as lesion count per scan, or per scan interval as an indication of activity but also reported as a change in the total volume of such lesions (lesion burden) over time to give a more global perspective of MRI-detected disease.

T1-weighted images can provide two sets of information. Infusion of gadolinium will reveal brain lesions with increased signal on T1-weighted images in the presence of inflammation or BBB breakdown, features typical of acute MS lesions (Bruck et al 1997). Such lesions persist only for 2-8 weeks and thus serve as a cross-sectional look at MRI disease activity at that time. In general, the presence of Gadolinium (Gd)-enhancing lesions predicts a higher rate of subsequent clinical disease activity than the absence of such lesions (Kappos et al 1999; McFarland et al 2002).

In the absence of contrast infusion, T1-weighted sequences often reveal hypointense lesions, which may be recent (acute T1-hypointense lesions) reflecting active lesions or more remote (chronic T1-hypointense lesions or so-called “black holes”) representing more severe MS lesions corresponding to demyelination with significant axonal loss. Approximately half of the acute T1 hypointensities on MRI will evolve into chronic “T1 black holes,” which correlates with disability progression (Simon et al 2000).

Another feature of MRI scanning is the ability to measure total brain volume allowing for an estimate of loss of brain tissue (atrophy) over time. Cerebral atrophy is a normal aging phenomenon but is increased in certain disease states, including MS (Anderson et al 2007). In the fingolimod program, this was assessed using the SIENA methodology (Structural Image Evaluation, using Normalisation, of Atrophy), a technique that is validated and commonly used in multi-center MS studies (Smith et al 2004; Sormani et al 2004). This outcome might best reflect the end result of repeated insults to the CNS by inflammation and the associated demyelination, loss of oligodendroglia, axons and other neural elements.

In the fingolimod Phase 3 program, each of the above MRI measures, commonly used in pivotal MS studies, were performed. Processes were in place to standardize the MRI scanning sequences and acquisition activities to ensure uniformity of data collection, followed by centralized review and analysis of scans for the endpoints of interest.

### 4.1.4 Phase 3 Outcome Measures

The annualized relapse rate (ARR) was the primary outcome measure for both pivotal studies, and disability progression, defined as time to a 3-month confirmed increase in the Expanded Disability Status Scale (EDSS), constituted a key secondary outcome measure. Other secondary efficacy outcome measures included MRI evaluation of inflammatory activity, burden of disease, and brain volume, as well as other relapse and disability-related outcomes, all widely used in MS clinical studies.

Blinding of outcome assessments is important in Phase 3 programs, and extensive measures were implemented to avoid inadvertent unblinding of physicians and patients. Such measures included double-dummy design in D2302, use of separate assessing and treating physicians, use of separate Day 1 clinicians to avoid unblinding by the initial effect of fingolimod on heart rate, non-disclosure of potentially unblinding laboratory results (e.g. lymphocyte counts) as well as other measures to maintain the masking of dose allocation. No assessment of the success of blinding, either at patient or study site personnel level, was conducted.

The 2-year, placebo-controlled study design, used in study D2301, has remained the standard, accepted design for Phase 3 studies in RRMS aimed at demonstrating efficacy on disability progression, in addition to annualized relapse rate, as well as characterizing safety. The currently available treatment options for patients with relapsing MS have known limitations (require injections, at times frequent, have moderate efficacy and/or are associated with serious safety concerns). Therefore, despite the availability of these treatments, the use of placebo as a control has remained acceptable, as long as ethical considerations are appropriately addressed.

In order to provide data on the efficacy of fingolimod versus a current standard of care, study D2302, a 1-year study of fingolimod vs. IFN β-1a (Avonex®) was included in the program. A 1-year study duration was chosen as a sufficient time interval in which to demonstrate superior efficacy vs. an active comparator for relapse- and MRI-related outcomes, as has been previously demonstrated in an active comparator study (Panitch et al 2002). The selection of Avonex® as the comparator for study D2302 was based on two major considerations. Firstly, the efficacy of currently available first-line therapies is roughly comparable (Goodin et al 2002). Secondly, Avonex® is injected less frequently (once-weekly i.m. rather than daily to three-times weekly s.c.) and therefore represents a better choice for patients participating in a double-blind, double-dummy study.

### 4.1.4.1 Statistical methods

#### 4.1.4.1.1 Statistical methods for pivotal studies D2301 and D2302

**Analysis populations**

The main analysis population was ITT in both studies, defined as patients who were randomized and received treatment (in D2301, the randomized and ITT populations were identical).

**Endpoints**

The primary efficacy endpoint was the aggregate annualized relapse rate (ARR). Only confirmed relapses were used for the primary analyses.

Key secondary efficacy endpoints were the following:

- Time to 3-month confirmed disability progression based on EDSS at Month 12 (D2302) and Month 24 (D2301).
- Number of new or newly enlarging T2 lesions at Month 12 (D2302)

**Annualized relapse rate and risk of relapses**

The primary efficacy endpoint, ARR, was analyzed using a negative binomial regression model adjusting for treatment, country, number of relapses in the previous 2 years, and baseline EDSS. The response variable was the number of relapses for each patient and a quadratic variance estimate was used. Log of time on study was used as an offset variable to adjust for different patient follow-up durations.

For patients who withdrew from the study completely, the number of relapses occurring during the double-blind phase was used in the primary analysis model and no imputation was applied to the uncompleted study duration. Patients who discontinued study medication were encouraged to remain in the study; for such patients, all available data was used.

In a sensitivity analysis using the Per-Protocol (PP) population, for patients who discontinued treatment, only relapses starting prior to study drug withdrawal were used in the negative binomial regression model and no imputation was applied.

An additional sensitivity analysis was performed using a rank ANCOVA model with an imputation scheme for patients prematurely withdrawn from the study. Monthly mean relapses of all patients contributing data to particular months were determined to impute data for patients with "missing" months. "Relapses" in this analysis used the actual observed events prior to study withdrawal, and imputed events based on these monthly means after dropout.

**Disability progression**

For the time to 3-month (and 6-month) confirmed disability progression endpoint, time-to-event curves for each treatment group were generated by the Kaplan–Meier method and compared using the log-rank test. As a supportive analysis, the Cox proportional hazards

model adjusting for treatment, country, baseline EDSS and age was used, and hazard ratios were obtained.

### Inflammatory disease activity as measured by MRI

The number of new and newly enlarged T2 lesions was compared between treatment groups using a negative binomial regression model adjusting for treatment and country. For other MRI measurements, treatment comparisons used a Rank ANCOVA model adjusting for treatment, country, and the corresponding baseline measurement. For the proportion type of MRI endpoints, treatment comparisons used a logistic regression model adjusting for treatment, country, and the baseline number of lesions when applicable.

### Multiplicity scheme

Because of the multiplicity of doses and key endpoints to be tested, a hierarchical multiplicity scheme was prospectively planned to control the overall Type I error rate and enable reliable conclusions. All statistical tests would use a significance level of 0.05; however, the tests within each study would be ordered. Within this scheme significance for an analysis could only be claimed if every higher-ordered analysis was statistically significant.

For study D2301, the hierarchical order of tests versus placebo was: fingolimod 1.25 mg ARR, followed by fingolimod 0.5 mg ARR; then fingolimod 1.25 mg disability progression, and fingolimod 0.5 mg disability progression.

For D2302, the hierarchical order for testing against IFN β-1a in a similar manner ordered the endpoints as: ARR, number of new and newly enlarging T2 lesions at Month 12, and disability progression; for each of endpoints, similarly as in D2301, the 1.25 mg dose was ordered higher than the 0.5 mg dose.

### Power and sample size

For Study D2301, the sample size was determined to provide adequate power for both the ARR and disability progression endpoints. Using a two-sided 0.05 significance level and a hypothesis of a 30% progression rate during 2 years for placebo and 18% for fingolimod 1.25 mg, a log-rank test would have a power of 93% for a design with 312 patients per arm. Allowing for a 25% drop-out rate would increase this to 416 patients per arm. A simulation study confirmed that this sample size would provide 95% power for the primary endpoint (ARR) using the negative binomial regression analysis, under the hypothesis that the ARR at 24 months is 0.7 for placebo and 0.42 for fingolimod 1.25 mg.

For Study D2302, the sample size calculation was based on the Wilcoxon rank sum test to achieve 90% power using a 2-sided 0.05 significance level. Under a hypothesis of ARRs of 0.33 and 0.55 for the fingolimod 1.25 mg arm and the IFN β-1a arm, respectively, assuming a standard deviation of 0.9, and allowing a dropout rate of approximately 15% per year, yielded a sample size of 425 patients per arm.

## 4.1.5 Phase 3 Population

Certain patient groups were excluded from the Phase 3 clinical studies because, without efficacy and safety having been first studied in a broader MS population, it was felt that the

risk/benefit of testing an experimental therapy in these patients could not yet be determined. Based on the known transient pharmacological effects occurring after the first dose of fingolimod, patients with relevant cardiac conditions (symptomatic bradycardia, sino-atrial heart block, second- or third-degree AV block or vasovagal syncope, treatment with Class III antiarrhythmic drugs) were excluded. Whether these patients will have a greater risk of events on drug is unknown and the proposed label recommends caution in the use of fingolimod in such patients until experience is gained in those settings.

Based on previous clinical experience, primarily from the renal transplantation program, patients with relevant pulmonary conditions, macular edema, diabetes mellitus and low white blood cell or lymphocyte counts were also excluded. The largest cohort not studied in MS patients in Phase 3 was diabetics. Such patients were excluded to remove a potential confounder for the development of macular edema. However, the low rate of macular edema in the non-diabetic MS patients on 0.5 mg dose suggests that diabetes not be viewed as a contraindication but may require closer monitoring for development of macular edema. Other exclusion criteria were in line with those in Phase 3 studies with other MS immunomodulatory therapies. In the Phase 3 program, patients having used other MS therapies were allowed into the study, either directly after stopping prior therapy, or within a specified timeframe.

Demographics and baseline disease characteristics of the included patients are shown in Table 4-2.

**Table 4-2 Demographic and baseline disease characteristics – Study D2031 and D2302**

| Study D2301 | FTY720 1.25mg N = 429 | FTY720 0.5mg N = 425 | Placebo N = 418 | Total N = 1272 |
|---|---|---|---|---|
| | | **Age (years)** | | |
| Mean (SD) | 37.4 (8.91) | 36.6 (8.77) | 37.2 (8.60) | 37.1 (8.76) |
| Median | 38.0 | 36.0 | 37.0 | 37.0 |
| Range | 17 - 55 | 18 - 55 | 18 - 55 | 17 – 55 |
| | | **Number of relapses in the last 2 years** | | |
| Median (range) | 2 (1-10) | 2 (1-11) | 2 (1-10) | 2 (1-11) |
| | | **Baseline EDSS score** | | |
| EDSS, median (range) | 2 (0-5.5) | 2 (0-5.5) | 2 (0-5.5) | 2 (0-5.5) |
| | | **Gender n (%)** | | |
| Female | 295 (68.8) | 296 (69.6) | 298 (71.3) | 889 (69.9) |
| | | **Race - n (%)** | | |
| Caucasian | 408 (95.1) | 406 (95.5) | 399 (95.5) | 1213 (95.4) |

| Study D2302 | FTY720 1.25 mg (N = 426) | FTY720 0.5 mg (N = 431) | IFN β-1a i.m. (N = 435) | Total (N = 1292) |
|---|---|---|---|---|
| | | **Age (years)** | | |
| Mean (SD) | 35.8 (8.39) | 36.7 (8.81) | 36.0 (8.29) | 36.2 (8.50) |
| Median | 36.0 | 37.0 | 36.0 | 36.0 |
| Range | 18 - 54 | 18 - 55 | 18 - 55 | 18 – 55 |
| | | **Number of relapses in the last 2 years** | | |
| Median (range) | 2 (1-8) | 2 (1-40) | 2 (1-12) | 2 (1-40) |
| | | **Baseline EDSS score** | | |
| EDSS, median (range) | 2 (0-5.5) | 2 (0-5.5) | 2 (0-5.5) | 2 (0-5.5) |
| | | **Gender- n (%)** | | |
| Female | 293 (68.8) | 282 (65.4) | 295 (67.8) | 870 (67.3) |
| | | **Race - n (%)** | | |
| Caucasian | 404 (94.8) | 404 (93.7) | 408 (93.8) | 1216 (94.1) |

Abbreviation: IFN = interferon, SD = standard deviation

# 5 Overview of Efficacy

Two large adequate and well-controlled Phase 3 studies contributed the bulk of the efficacy data in this submission; a 2-year, placebo-controlled study, and a 1-year, active-controlled study employing one of the current approved therapies, IFN β-1a (Avonex®), as the active comparator. A 6-month, Phase 2 placebo-controlled study and its long-term open-label extension up to 5 years provide additional information in support of the efficacy of fingolimod in the target population. The studies contributing efficacy data are summarized in Table 5-1.

**Table 5-1 Summary of studies providing data**

| Study No. | Study Objective, Population | No. of patients Design | Treatment Duration | Medication dose/day | Primary Efficacy Endpoint |
|---|---|---|---|---|---|
| Phase 3 | | | | | |
| D2301 | Efficacy and safety in RRMS | 1272 randomized, double-blind | 2 years | fingolimod 1.25mg/day fingolimod 0.5mg/day Placebo | Annualized relapse rate |
| D2302 | Efficacy and safety in RRMS | 1292 randomized, double-blind, double-dummy | 1 year | fingolimod 1.25mg/day fingolimod 0.5mg/day IFN β-1a i.m. 30µg once weekly | Annualized relapse rate |
| Phase 2 | | | | | |
| D2201 | Efficacy and safety in relapsing MS | 281 randomized, double-blind | 6 months | fingolimod 5.0mg/day fingolimod 1.25mg/day Placebo | Total number of Gd-enhancing lesions on 6 monthly post-baseline MRI scans |
| D2201E1 | Long-term efficacy and safety, extension of study D2201 | 250 Initially double-blind, then open-label | Open (interim data up to Month 60 included) | fingolimod initially 1.25 mg or 5.0 mg orally o.d., between months 15 and 24, 5.0 mg patients switched to open label 1.25 mg orally o.d. | None. MRI and clinical endpoints evaluated |

## 5.1 Dose Selection Rationale

Clinical studies in MS have evaluated the efficacy and safety of fingolimod at once-daily doses of 0.5 mg, 1.25 mg and 5.0 mg.

Reduction in the number of circulating lymphocytes is believed to be relevant to the efficacy of fingolimod in MS. Reduction in lymphocyte counts exhibited a clear dose-response over the dose range 0.125, 0.25, 0.5, 2.5 and 5.0 mg in an early transplant study, with near maximal effect achieved at the 2.5 mg dose. In the transplant program, the 5.0 mg dose was more efficacious than lower doses. Based on these observations, two doses of fingolimod were selected for evaluation in the initial 6-month, Phase 2 study (D2201) in relapsing MS; a 5.0 mg dose (highest dose studied in the Phase 3 renal transplant program), and a 4-fold lower dose, 1.25 mg (a dose expected to achieve sub-maximal effect on lymphocyte count reduction). Both doses were shown to be highly effective in reducing inflammatory disease activity on both MRI and relapse-related parameters with no clear difference between the two doses.

Given comparable efficacy of doses in Phase 2, the 5.0 mg dose was not carried forward but a lower dose, 0.5 mg, was selected for inclusion in the Phase 3 program, along with 1.25 mg, based on adequate separation of doses in terms of pharmacokinetic exposure, and demonstration of a relevant pharmacodynamic effect with 0.5 mg (reduction in lymphocyte counts of about 70%) in the earlier renal transplant program.

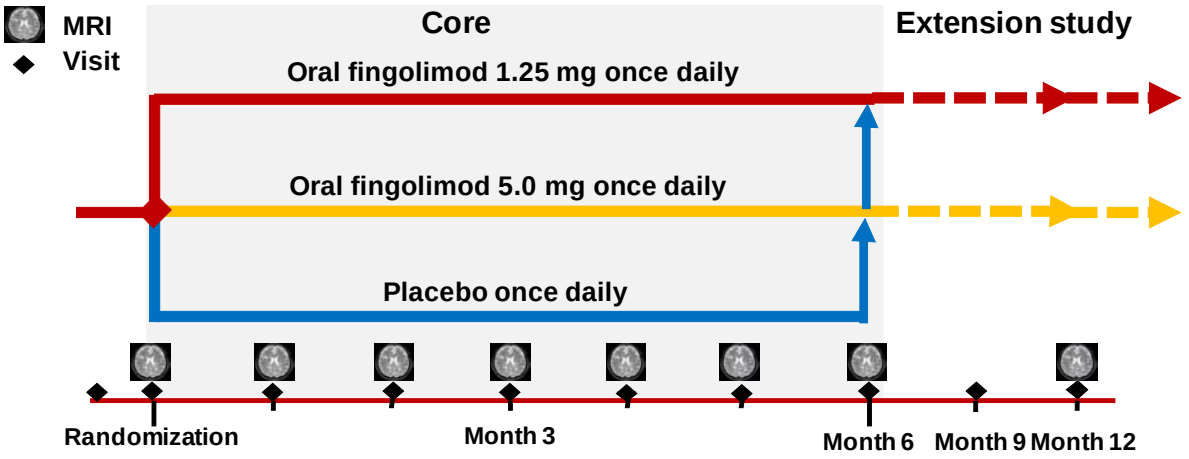
All fingolimod clinical studies have been conducted with once-daily oral administration. The half-life of fingolimod (approximately 6-9 days) fully supports once-a-day administration. Although less frequent dosing might have been possible, once-a-day was seen as the dosing frequency that would be the most reliable for patient compliance based on ease of remembering and limited impact of a missed dose versus risk for re-occurrence of the initial negative chronotropic effect. Once-a-day dosing also offers a PK profile with minimal fluctuations between peaks and troughs.

## 5.2 Efficacy Results

### 5.2.1 Phase 2 placebo-controlled study

Study D2201 was a 6-month multi-center, multinational, randomized, double-blind, parallel-group, placebo-controlled study comparing the efficacy of fingolimod 1.25 mg and 5.0 mg once daily with placebo in patients with relapsing MS (Figure 5-1). Patients who completed the 6-month study could enter an optional long-term extension of the study during which all patients received fingolimod.

**Figure 5-1 Design of Study D2201**




The study enrolled 281 patients, 18 to 60 years old with relapsing MS, either relapsing-remitting (89%) or secondary progressive (11%) with a diagnosis based on McDonald et al 2001 criteria. Eligible patients were those with at least two documented relapses during the 2 years before enrollment or at least one documented relapse during the last year before enrollment or a positive Gd-enhancing MRI scan at screening and with an EDSS score of 0-6.

The primary objectives of the study were to evaluate the effect of fingolimod on the total number of monthly MRI Gd-enhancing T1 lesions seen on post-baseline scans during 6 months of treatment and to evaluate the safety and tolerability of the two different doses of fingolimod.

Secondary MRI objectives included:

- Effect on other MRI measures of inflammatory activity (volume of Gd-enhancing MRI lesions, number of T2 lesions) and of disease burden (volume of T2 lesions, brain volume) over 6 months of treatment.

Secondary clinical efficacy parameters included:

- Number of relapses observed during 6 months of treatment, time to first relapse, % of relapse-free patients at month 6.

This study showed a statistically significant effect of both doses of fingolimod on both MRI and clinical relapse-related endpoints in patients with MS over a treatment period of 6 months with the 1.25 mg dose being as effective as the 5.0 mg dose.

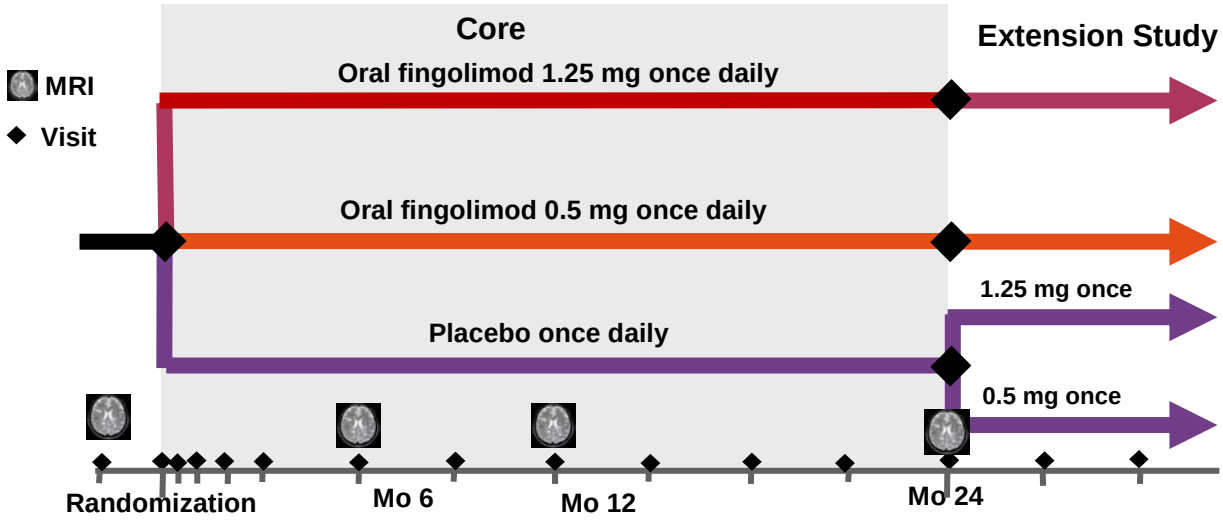
- There was a statistically significant reduction of the total number of monthly MRI Gd-enhanced lesions seen on post-baseline scans for patients treated with fingolimod 5.0 mg ($p= 0.006$) or fingolimod 1.25 mg ($p<0.001$) compared to placebo.
- Other MRI endpoints including number of new T2 lesions, volume of Gd-enhancing lesions and proportions of patients free of inflammatory lesions at Month 6 showed a consistent improvement for both fingolimod groups compared to placebo.
- Although the study was not powered to demonstrate a clinical effect of fingolimod, all clinical relapse-related parameters (including ARR) showed a statistically significant reduction for both fingolimod treatment groups compared to placebo (ARR 0.36 for fingolimod 5.0 mg ($p=0.014$) and 0.35 for fingolimod 1.25 mg ($p=0.009$) respectively vs. 0.77 for placebo).
- In the small subgroup of SPMS patients (11%), the effect of fingolimod on MRI lesion activity and relapses were of similar direction and magnitude to that in the overall population.

### 5.2.2 2-year Placebo-Controlled Study – D2301

Study D2301 was a 24-month multi-center, placebo-controlled study comparing the efficacy and safety of once daily fingolimod 0.5 mg and 1.25 mg with placebo in 1,272 patients with RRMS randomized in equal proportions (Figure 5-2).

The intent-to-treat (ITT) population, used for primary efficacy analyses, consisted of all patients who were randomized and received at least one dose of study drug. All randomized patients were treated. The safety population consisted of all patients that received at least one dose of study drug. Patients stopping treatment early were encouraged to continue with scheduled visits until study end. After completion of the 24-month study, patients were allowed to enter the extension, where all patients received fingolimod.

**Figure 5-2 Design of Study 2301**




The primary objective of the study was to evaluate if fingolimod (1.25 mg and 0.5mg) was superior to placebo in terms of ARR in patients with RRMS treated for up to 24 months.

The key secondary objective was to evaluate the effect of fingolimod relative to placebo on disability progression as measured by the time to 3-month confirmed disability progression.

Other secondary objectives included:

- An evaluation of the safety and tolerability of fingolimod in patients with RRMS.
- An evaluation of the effect of fingolimod in patients with respect to other relapse- and disability progression-related outcomes.
- An evaluation of the effect of fingolimod in patients with respect to MRI measures of inflammatory disease activity, burden of disease and brain volume.

Treatment groups were generally well balanced for baseline demographic and disease characteristics (see Table 4-2).

Over the 2-year duration of the study, discontinuation of study drug occurred in 31% of the fingolimod 1.25 mg group, 19% of the 0.5 mg dose group, and 28% of the placebo group. Patients discontinuing therapy were encouraged to remain in the study. The percentages of patients who completed the study were 77%, 87%, and 79% in the fingolimod 1.25 mg, fingolimod 0.5 mg, and placebo, groups, respectively (Table 5-2). Many patients discontinuing the study actually did so quite late during the study. The mean times on study for the 1.25 mg, 0.5 mg, and placebo groups were 675, 700, and 673 days, respectively.

**Table 5-2 Study Completion - 2-year Study D2301**

| | FTY720D 1.25mg N=429 | FTY720D 0.5mg N=425 | Placebo N=418 |
|---|---|---|---|
| Completed study, n (%) | 332 (77%) | 369 (87%) | 332 (79%) |
| Completed study on treatment, n (%) | 297 (69%) | 345 (81%) | 303 (72%) |

The most common reasons for discontinuing therapy were for the combination of adverse events or abnormal laboratory tests (15% for fingolimod 1.25 mg, 8.0% for fingolimod 0.5 mg and 7.0% for placebo).

#### 5.2.2.1 Annualized relapse rate and risk of relapse

The ARR up to Month 24 (primary efficacy endpoint) is summarized in Table 5-3. The ARR was reduced by 60% in the 1.25mg group and 54% in the 0.5 mg group relative to placebo.

**Table 5-3 ARR up to Month 24 (confirmed relapses) – study D2301 (ITT population)**

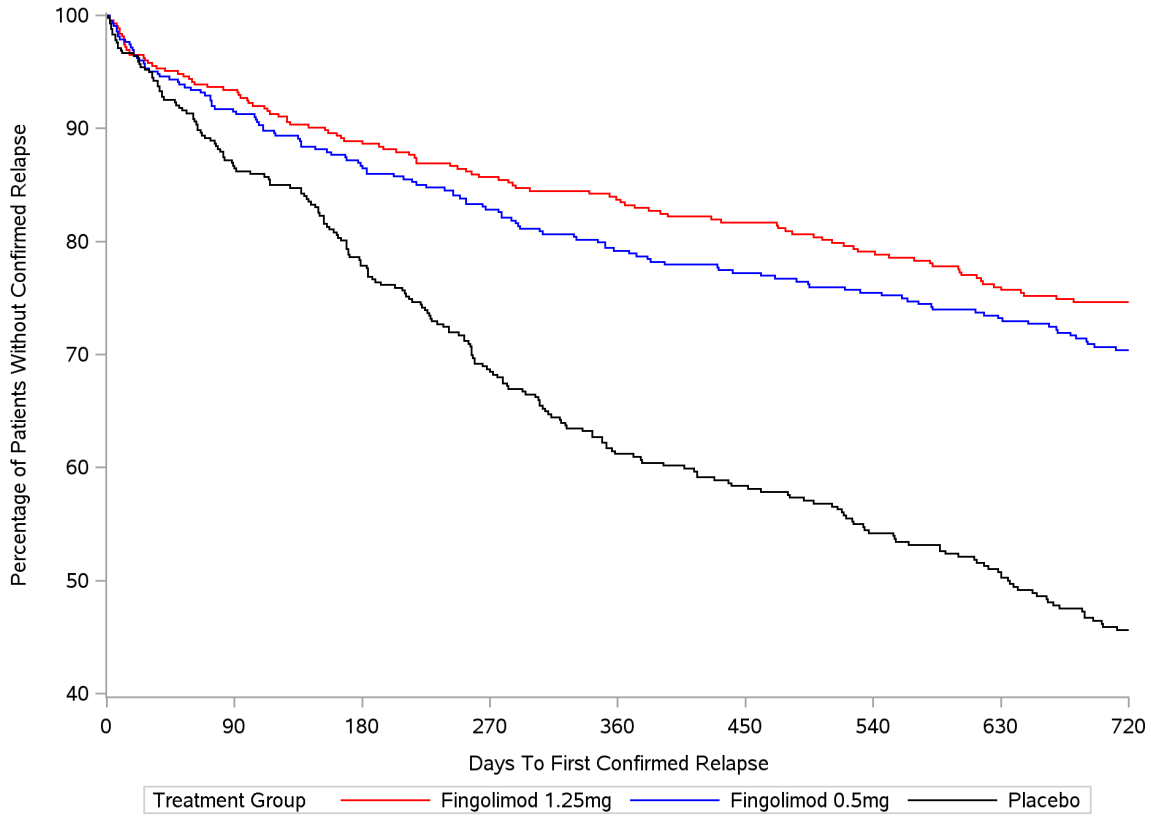
| | FTY720D 1.25mg N=429 | FTY720D 0.5mg N=425 | Placebo N=418 |
|---|---|---|---|
| ARR estimate (95% CI) | 0.16 (0.13, 0.19) | 0.18 (0.15, 0.22) | 0.40 (0.34, 0.47) |
| ARR ratio (95% CI) vs. placebo | 0.40 (0.32, 0.50) | 0.46 (0.37, 0.57) | -- |
| P-value vs. placebo | <0.001 | <0.001 | -- |
| P-value fingolimod 1.25mg vs. 0.5mg | | 0 226 | -- |

ARR estimate (95% CI), ARR ratio, and p-value are calculated using negative binomial regression adjusted by treatment, pooled country, number of relapses in the previous 2 years, and baseline EDSS.
Log (time of study) is the offset variable.

Sensitivity analyses included ARR in the per protocol population (defined as all patients in the ITT population without any major protocol deviations) as well as analyses using all relapses (confirmed and not confirmed) in the ITT and PP populations. These sensitivity analyses support the primary efficacy result for both doses by showing a significant effect of fingolimod with effect sizes of 53 - 66% relative to placebo. Additionally, benefit with fingolimod 0.5 mg was seen both in patients who were naïve to MS therapy (65% reduction compared to placebo) and in those who had previously used one of the approved MS therapies (42% reduction).

Additional relapse measures including time to first relapse (Figure 5-3), proportion of patients free of relapse at 24 months (75% for 1.25mg, 70% for 0.5 mg and 46% for placebo), and risk of relapse (HR = 0.38, 95%CI:0.30-0.48 for 1.25mg and 0.48 (95%CI:0.39-0.61 for fingolimod 0.5 mg) supported the findings of the primary endpoint ($p<0.001$ for all comparisons vs. placebo).

**Figure 5-3 Kaplan-Meier plot of time to first confirmed MS relapse - Study D2301 (ITT population)**

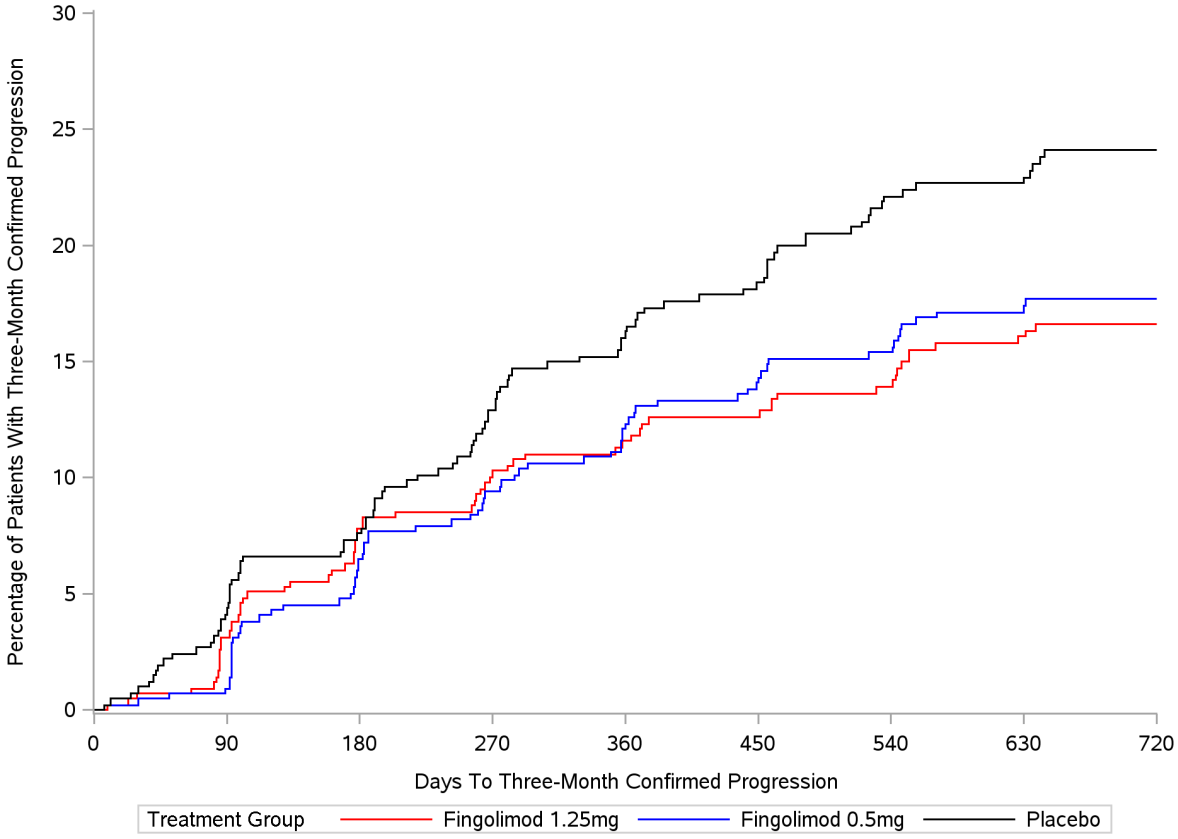



Other aspects of relapse were also investigated, including relapse severity, use of steroids, and hospitalizations due to relapse. Consistent with the above results, both doses of fingolimod had fewer patients, compared to placebo, with severe relapses, relapses that required steroid treatment, or relapses that led to hospitalization.

### 5.2.2.2 Disability progression

As shown in Figure 5-4 and Table 5-4, the time to 3-month confirmed disability progression based on the EDSS was significantly delayed with fingolimod compared to placebo.

**Figure 5-4 Cumulative plot of time to 3-month confirmed disability progression – Study D2301 (ITT population)**




Disability progression had to occur at least 3 months prior to the end-of-study visit to be confirmed

**Table 5-4 Time to 3-month confirmed disability progression up to Month 24 – Study D2301 (ITT population)**

| | FTY720D 1.25 mg N = 429 | FTY720D 0.5 mg N = 425 | Placebo N = 418 |
|---|---|---|---|
| P-value vs. placebo | 0.012 | 0.026 | -- |
| Hazard ratio (95% CI) | 0.68 (0.50, 0.93) | 0.70 (0.52, 0.96) | -- |
| P-value vs. placebo** | 0.017 | 0.024 | -- |
| Proportion of patients with progression at 720 days by Kaplan Meier | 17% | 18% | 24% |

*log-rank test (main analysis)**Cox's proportional hazards model adjusted for treatment, country, baseline EDSS & age (supportive analysis).

The time to 6-month confirmed disability progression based on EDSS is a more rigorous assessment of disability progression as the longer timeframe reduces the effect of transient worsening from relapses or patient/evaluator variance on disability progression. By this measure, disability progression was reduced in favor of both doses of fingolimod compared to placebo. This reduction (HR=0.60, 95% CI: 0.41-0.86 and HR=0.63, 95%CI: 0.44-0.90, for fingolimod 1.25mg and 0.5mg respectively; $p \leq 0.01$ for both) was greater than the 3-month

confirmed progression and equates to 40% and 37% reductions in risk of 6-month confirmed progression compared to placebo, supporting the finding on the principal disability outcome. Additional support for disability effect came from significant benefit on change in the MSFC z-score, an alternate MS disability measure.

#### 5.2.2.3 Inflammatory disease activity as measured by MRI

Treatment with both fingolimod doses resulted in a statistically significant reduction in the number of new or newly-enlarged T2 lesions up to Month 24 compared to placebo (Table 5-5). Also, a significantly greater proportion of patients were free of new or newly-enlarged T2 lesions at Month 24. The same outcomes were also observed for Gd-enhancing lesion count and for the proportion of patients free of such lesions at Month 24. The effect of fingolimod on reducing MRI inflammatory lesions was apparent by Month 6.

**Table 5-5 MRI inflammatory activity – study D2301 (ITT population)**

| Number of new/newly enlarging T2 lesions up to Month 24 | FTY720D 1.25mg N=429 | FTY720D 0.5mg N=425 | Placebo N=418 |
|---|---|---|---|
| n | 337 | 370 | 339 |
| Median (mean) | 0.0 (2.5) | 0.0 (2.5) | 5.0 (9.8) |
| P-value vs. placebo* | <0.001 | <0.001 | --- |
| Proportion (%) of patients free of lesions | 51.9 | 50.5 | 21.2 |
| P-value vs. placebo** | <0.001 | <0.001 | --- |
| **Number of Gd-enhancing lesions at Month 24** | | | |
| n | 343 | 369 | 332 |
| Median (mean) | 0.0 (0.2) | 0.0 (0.2) | 0.0 (1.1) |
| P-value vs. placebo# | <0.001 | <0.001 | --- |
| Proportion (%) of patients free of lesions | 89.8 | 89.7 | 65.1 |
| P-value vs. placebo¶ | <0.001 | <0.001 | --- |

n=the number of ITT patients with evaluable MRI for the assessment and timepoints.
Any Gd-enhancing data obtained less than 30 days after the steroid used to treat MS relapses were excluded from the analysis.
*Negative binomial model adjusted for treatment and country.
**logistic regression model adjusted for treatment, country, and baseline T2 lesion volume.
# Rank ANCOVA model adjusted for treatment country, and baseline number of Gd-enhancing T1 lesions.
Logistic regression model adjusting for treatment, country, and baseline number of Gd-enhancing T1 lesions.

#### 5.2.2.4 Burden of disease as measured by MRI

The changes from baseline in total volume of T2 lesions and total volume of T1 hypointense lesions at Month 24 in the fingolimod group were small, while greater increases in lesion volume were seen in the placebo group, leading to a significant difference in favor of fingolimod treatment compared to placebo (T2 lesion volume: $p<0.001$ in both comparisons, T1 hypointense lesion volume: $p<0.02$ in both comparisons, using rank ANCOVA adjusting for treatment, country and baseline lesion volume).

### 5.2.2.5 Brain volume change

There was statistically significantly less reduction in brain volume (i.e. less atrophy) with fingolimod treatment compared to placebo over 24 months (Table 5-6). The effect (median reduction 30%) was seen as early as Month 6, and sustained through to Month 24.

**Table 5-6 Percent brain volume change from baseline to Month 24 – study D2301 (ITT population)**

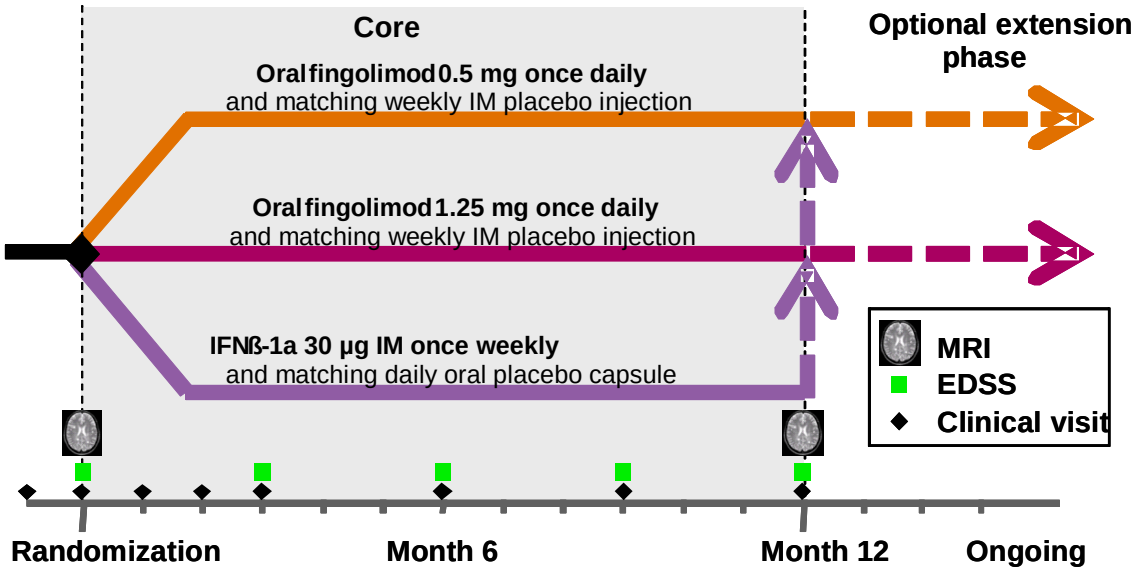
| | FTY720D 1.25 mg N = 429 | FTY720D 0.5 mg N = 425 | Placebo N = 418 |
|---|---|---|---|
| n | 334 | 357 | 331 |
| Median (mean) | -0.7 (-0.9) | -0.7 (-0.8) | -1.0 (-1.3) |
| p-value vs. placebo* | <0.001 | <0.001 | |

n= number of ITT patients who had evaluable SIENA assessments at baseline and Month 24.
* Rank ANCOVA with treatment, country and baseline normalized brain volume.

### 5.2.3 1-Year Active Comparator Study – D2302

Study D2302 was a 12-month, multi-center double-blind, double-dummy, randomized, three-armed trial comparing the efficacy and safety of oral fingolimod 0.5 mg and 1.25 mg administered once daily with intramuscular (i.m.) IFN β-1a, 30 µg administered once weekly, (Avonex®) in 1292 patients with RRMS randomized in equal ratios (Figure 5-5).

**Figure 5-5 Design of Study D2302**




The ITT population, used for primary efficacy analyses, consisted of all patients who were randomized and received at least one dose of study drug. The safety population consisted of all patients that received at least one dose of study drug. Patients stopping treatment early were encouraged to attend the scheduled visits (with limited assessments) until study end.

The primary efficacy endpoint was the annualized relapse rate (ARR) up to 12 months.

Key secondary efficacy endpoints were the following:

- Number of new or newly enlarging T2 lesions at Month 12.
- Time to 3-month confirmed disability progression at Month 12.

Other secondary endpoints were the same as for D2301, except for the 6-month confirmed disability progression which was not included given the shorter study duration.

Treatment groups were generally well balanced for baseline demographics and disease characteristics (see Table 4-2), and in exposure to study therapy. Over the 1-year duration of the study, discontinuation of study drug occurred in 16% of the fingolimod 1.25 mg group, 11% of the 0.5 mg dose group, and 13% of the placebo group. Patients discontinuing therapy were encouraged to remain in the study. The percentages of patients who completed the study were 87%, 92%, and 89% in the fingolimod 1.25 mg, fingolimod 0.5 mg, and placebo, groups, respectively (Table 5-7). Many patients discontinuing the study actually did so quite late during the study. The mean times on study for the 1.25 mg, 0.5 mg, and placebo groups were 352, 362, and 352 days, respectively.

**Table 5-7 Study completion – study D2302**

| | FTY720D 1.25mg N=426 | FTY720D 0.5mg N=431 | IFN-β-1a N=435 |
|---|---|---|---|
| Completed study, n (%) | 369 (87%) | 398 (92%) | 386 (89%) |
| Completed study on treatment, n (%) | 358 (84%) | 385 (89%) | 380 (87%) |

### 5.2.3.1 Annualized relapse rate and risk of relapse

The ARR was significantly lower in both fingolimod groups compared with the IFN β-1a group (Table 5-8), resulting in a relative reduction in the ARR of 38% for 1.25mg and 52% for 0.5 mg, with no significant difference between the two fingolimod doses.

**Table 5-8 Aggregate annualized relapse rate up to Month 12 (confirmed relapses only) – Study D2302 (ITT population)**

| | FTY720D 1.25 mg N=420 | FTY720D 0.5 mg N=429 | IFN-β-1a N=431 |
|---|---|---|---|
| ARR estimate (95% CI) | 0.20 (0.16, 0.26) | 0.16 (0.12, 0.21) | 0.33 (0.26, 0.42) |
| ARR ratio (95%CI) vs. IFN beta-1a | 0.62 (0.47-0.84) | 0.48 (0.37-0.64) | -- |
| P-value vs. IFN beta-1a | <0.001* | <0.001* | -- |
| P-value FTY720D 1.25mg vs. 0.5mg | | 0.159 | |

* Indicates two-sided statistical significance at the 0.05 level.

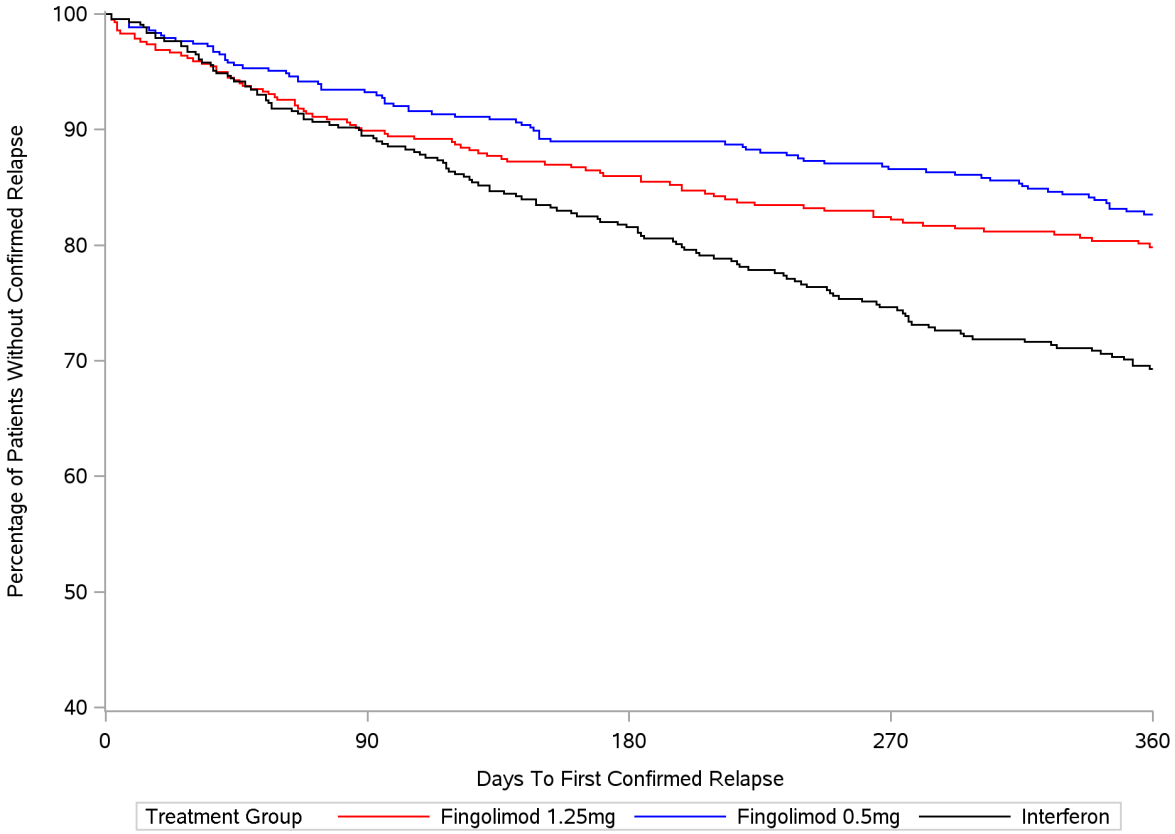
ARR ratio, and p-values are calculated using negative binomial regression adjusted for treatment, pooled country, number of relapses in the previous 2 years, and baseline EDSS. Log (time of study) is the offset variable.

Additionally, it was demonstrated that fingolimod 0.5 mg was effective both in patients who were naïve to MS therapy (52% relative reduction in ARR compared to IFN) and in those who had discontinued one of the approved MS therapies (50% relative reduction).

Sensitivity analyses included ARR in the 'per protocol' population (defined as all patients in the ITT population without any major protocol deviations) as well as analyses using all relapses (confirmed and not confirmed) in the ITT and PP populations. These sensitivity analyses support the primary efficacy result by showing consistent and significant results favoring fingolimod with effect sizes of 40-53% relative to IFN β-1a i.m.

Time to first confirmed relapse (Kaplan-Meier estimate) up to Month 12, was prolonged in both fingolimod groups compared to the IFN β-1a group ($p<0.001$, log-rank test) (Figure 5-6). The proportion of patients who were relapse-free at Month 12 was 83% with fingolimod 0.5 mg compared to 69% for IFN β-1a ($p<0.001$). This was consistent with the results observed in study D2301 at 12 months.

**Figure 5-6 Kaplan-Meier plot for time to first confirmed relapse up to Month 12 – Study D2302 (ITT population)**



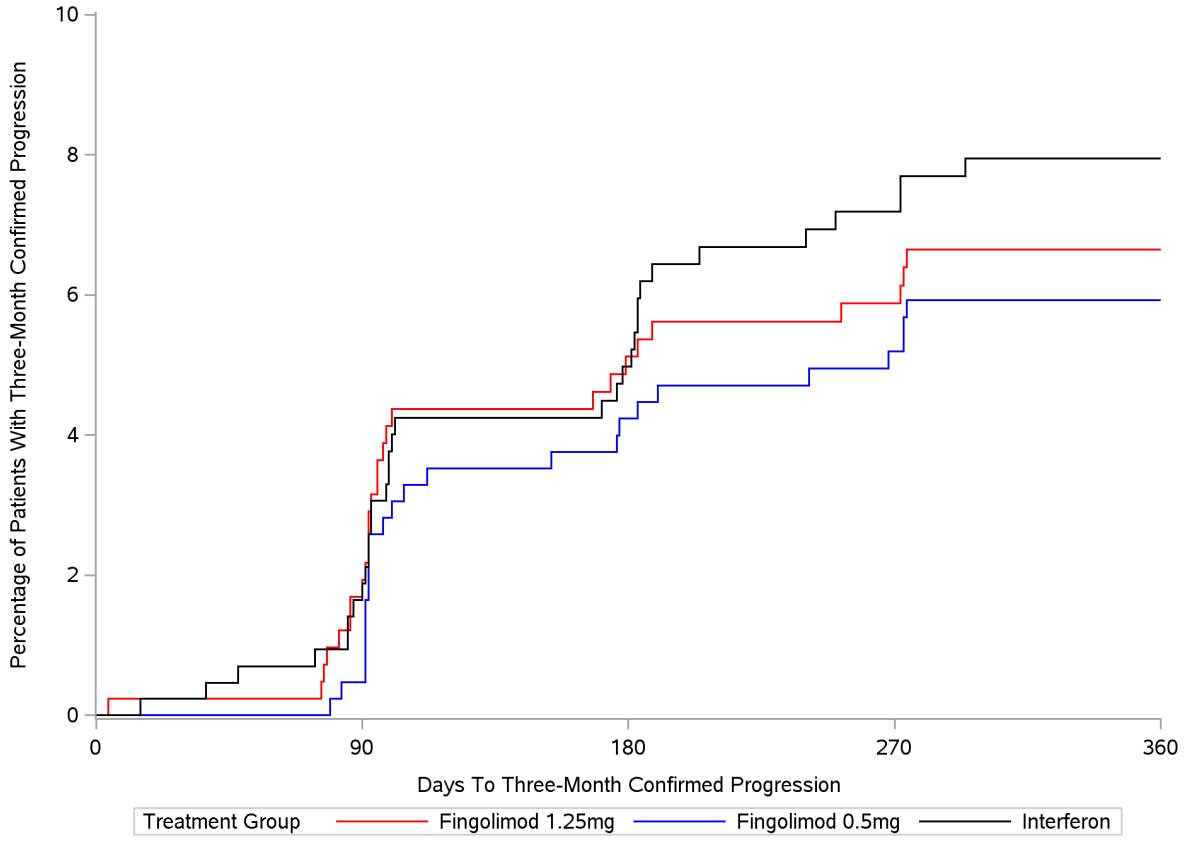

Other aspects of relapse were also investigated during the study, including relapse severity, use of steroids, and hospitalizations due to relapse. Consistent with the above results, fingolimod treatment was effective in reducing the total number of severe relapses, the need for steroid treatment, and the need for hospitalizations compared to IFN β-1a.

No significant dose differences were seen on efficacy measures.

### 5.2.3.2 Disability progression

In study D2302, disability progression rates at 12 months were low in all treatment groups (6-7% in fingolimod groups, 8% in IFN β-1a groups) (Figure 5-7). Although there was no statistically significant difference in the 3-month confirmed disability progression between the fingolimod and IFN β-1a treatment groups, the estimated hazard ratios (0.71; 0.42, 1.21 95% CI for 0.5 mg dose group and 0.85; 0.51, 1.42 95% CI for the 1.25 mg dose group) are directionally consistent with data from D2301. The duration of observation in this study was too short (a patient would have had to progress by Month 9 in order to have a 3-month confirmation by the end of study at Month 12) and the number of events too low in order to reliably evaluate EDSS progression in a RRMS population, particularly when tested against an active comparator with a known effect on disability.

**Figure 5-7 Cumulative plot of time to 3-month confirmed disability progression – Study D2302 (ITT Population)**




### 5.2.3.3 Inflammatory disease activity as measured by MRI

The effect on inflammatory disease activity as measured by the number new or newly-enlarged T2 lesions after up to 12 months of treatment was a key secondary objective of Study D2302. Treatment with fingolimod resulted in a statistically significant reduction of the number of new or newly-enlarged T2 lesions after 12 months compared to treatment with IFN β-1a (Table 5-9). The proportion of patients free of new or newly-enlarged T2 lesions at 12 months was higher in the fingolimod 0.5 mg group than in the IFN β-1a treatment groups

(54.8% vs. 45.7%, p=0.01). The difference versus placebo was not significant for fingolimod 1.25 mg.

Findings were similar for Gd-enhancing lesion outcomes.

**Table 5-9 MRI inflammatory activity – Study D2302 (ITT population)**

| MRI parameter | FTY720D 1.25 mg N=420 | FTY720D 0.5 mg N=429 | IFN β-1 a N=431 |
|---|---|---|---|
| Number of new/newly enlarging T2 lesions up to Month 12 | n=356 | n=380 | n=365 |
| Median (mean) | 1.0 (1.5) | 0.0 (1.7) | 1.0 (2.6) |
| P-value vs. IFN β-1a* | <0.001 | 0.004 | -- |
| Proportion (%) of patients free of lesions | 48.0 | 54.8 | 45.7 |
| P-value vs. IFN β-1a** | 0.372 | 0.01 | |
| Number of Gd-enhancing lesions at Month 12 | n=352 | n=374 | n=354 |
| Median (mean) | 0.0 (0.1) | 0.0 (0.2) | 0.0 (0.5) |
| P-value vs. IFN β-1a# | <0.001 | <0.001 | --- |
| Proportion (%) of patients free of lesions | 91.2 | 90.1 | 80.8 |
| P-value vs. IFN β-1a¶ | | | |

n=the number of ITT patients with evaluable MRI for the assessment and timepoints.
Any Gd-enhancing data obtained less than 30 days after the steroid used to treat MS relapses were excluded from the analysis.
*Negative binomial model adjusted for treatment and country.
**Logistic regression model adjusted for treatment and country.
# Rank ANCOVA model adjusted for treatment country, and baseline no. of Gd-enhancing T1 lesions.
Logistic regression model adjusted for treatment, country, and baseline no. of Gd-enhancing T1 lesions.

### 5.2.3.4 Brain volume change

There was significantly less atrophy with fingolimod compared to IFN β-1a over 12 months in study D2302, similar to what was seen in the D2301 study at the same timepoint (Table 5-10).

**Table 5-10 Brain volume change from baseline to Month 24 – study D2301 (ITT population)**

| | FTY720D 1.25 mg N = 420 | FTY720D 0.5 mg N = 429 | IFN β-1 a N = 431 |
|---|---|---|---|
| n | 345 | 368 | 359 |
| Median (mean) | -0.2 (-0.30) | -0.2 (-0.31) | -0.4 (-0.45) |
| p-value vs. IFN β-1 a * | <0.001 | <0.001 | |

n= number of ITT patients who had evaluable SIENA assessments at baseline and Month 12.
* Wilcoxon rank sum test

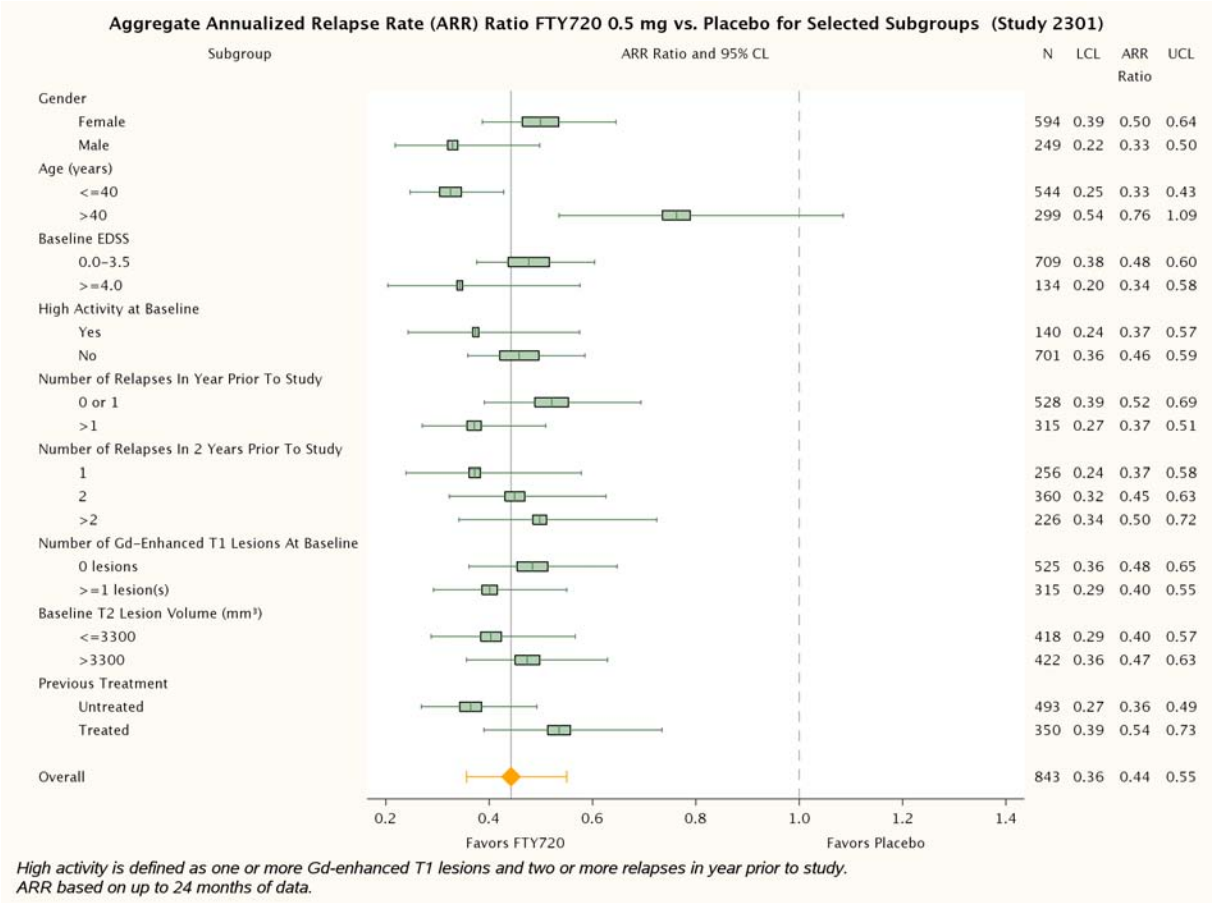
### 5.2.4 Sub-group analyses

The patient population included in the fingolimod Phase 3 studies is representative of the general relapsing MS population in terms of demographics and MS disease characteristics and is consistent with the populations typically included in Phase 3 RRMS studies.

To explore whether demographic or background characteristics of the patient population had an effect on ARR, efficacy outcomes in the following subgroups were examined: age, gender, baseline EDSS, number of relapses in the 2 years prior to study entry, baseline number of Gd-enhancing T1 lesions, and history of previous MS treatment.

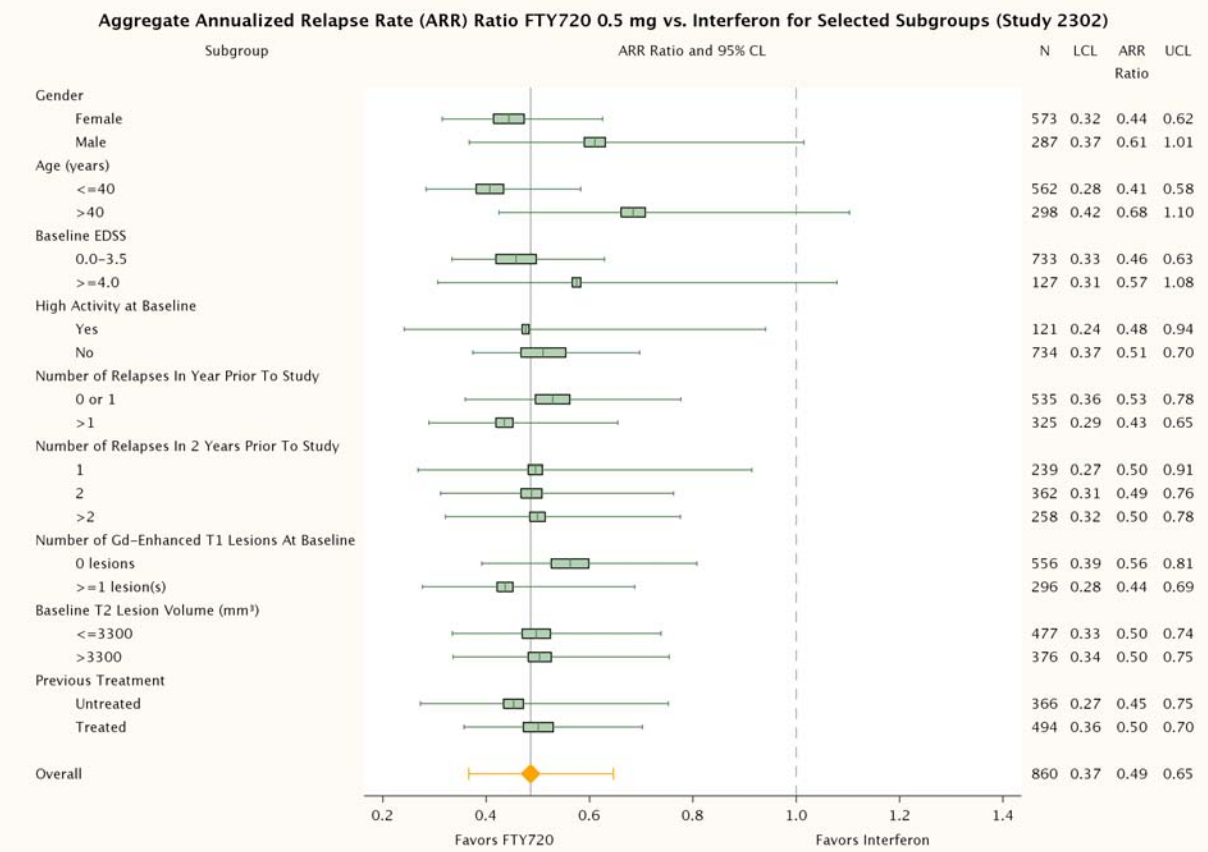
As shown in Figure 5-8 and Figure 5-9 there was a consistent reduction in relapse rate with fingolimod 0.5 mg compared to placebo and to IFN β-1a in the Phase 3 studies for the identified subgroups.

**Figure 5-8 Annualized relapse rate for 0.5mg dose group, relative to placebo, for various subgroups in Study D2301**




*High activity is defined as one or more Gd-enhanced T1 lesions and two or more relapses in year prior to study.*
*ARR based on up to 24 months of data.*

**Figure 5-9 Annualized relapse rate for 0.5mg dose group, relative to interferon beta-1a, for various subgroups in Study D2302**




## 5.2.5 Long-Term Data, Development of Tolerance or Withdrawal Effects

### 5.2.5.1 Long-term use

Study D2201E1 is the ongoing open-label extension to the Phase 2 placebo-controlled, 6-month core study D2201, and provides up to 60 months of data, comprising 6 months core study data and 54 months of extension data.

The objectives of the extension were to collect long-term safety and tolerability data as well as gather information on ongoing relapse activity and disability progression.

Initially during the extension, two doses of fingolimod (1.25 mg and 5.0 mg) continued to be administered in a dose-blind manner. Patients randomized to placebo at the start of the core study were re-randomized to one of the two doses of fingolimod during the extension. Because the 6-month core study demonstrated similar efficacy of the fingolimod 1.25 mg and 5.0 mg doses, with the 1.25 mg dose showing a more favorable safety profile, all patients on the 5.0 mg dose were switched between Months 15 and 24 (Months 9 and 18 of the extension) to receive fingolimod 1.25 mg open-label. Consequently, all patients received fingolimod 1.25 mg at least from Month 24 onwards. The analysis data from 5 years of follow-up

includes data on up to 281 patients of whom 250 entered the extension phase and approximately 140 remained on therapy for 60 months.

Results on clinical and MRI measures from the Month 60 analysis (6 months core study+54 months extension) showed that the reduction in MRI and clinical disease activity observed during the first 6 months of treatment, was sustained throughout the extension study for those remaining on drug. When assessing the efficacy data from this long-term extension, the open label nature, lack of a control group mean that results have to be interpreted with caution. The sample size is also diminished to around 50% of the original study population.

In Summary:

- 140/281 patients originally randomized completed 5 years on study medication.
- > 90% of patients who reached Month 60 were free from Gd-enhancing lesions at Month 60 and >80% of patients did not have new T2 lesions since the prior scan 1 year earlier.
- A majority (~66%) of the patients reaching Month 60 were still free of relapse at that time with an overall annualized relapse rate of 0.20.
- 60% to 71% of the patients originally enrolled were still free of 6-month confirmed disability progression after 5 years of treatment.
- There was no increase in burden of disease on MRI (total volume of T2 lesions) observed over 5 years for those reaching Month 60.
- Brain volume decreased by 2.3% over 5 years, a result comparable to that observed in untreated MS patients after only 3 years (Anderson et al 2007).

#### 5.2.5.2 Tolerance or withdrawal effects

From the 2-year D2301 study and the long-term experience that is available from the Month-60 analysis in study D2201E1, efficacy appeared to be retained throughout the duration of the treatment.

In the follow-up data available from approximately 420 fingolimod-treated patients who discontinued study drug and continued to be followed-up off-drug in studies D2301, D2302 and D2201E1, disease activity on MRI was seen to return within 90 days following treatment discontinuation with no evidence of rebound, where rebound is defined as higher disease activity than present prior to study start or to placebo activity on-study. No new safety issues arose during the 3-month post-dosing interval.

## 5.3 Efficacy Conclusions

Two adequate and well-controlled Phase 3 studies in patients with relapsing MS present evidence that fingolimod, at once daily oral doses of 1.25 mg and 0.5 mg, is efficacious in the target population.

Both Phase 3 studies provide consistent and substantial evidence of efficacy through statistically significant reduction of relapse rate relative to placebo over 2 years and relative to an approved MS therapy over 1 year. The 2-year Study also demonstrates efficacy on disability progression vs. placebo. Clinical efficacy was supported by positive effects on objective MRI measures of inflammation, disease burden, and brain atrophy.

### 5.3.1 Clinical Outcomes

Focusing on the targeted dose (0.5 mg) for the proposed label indication, the Phase 3 studies have shown:

- A 54% reduction in relapse rate relative to placebo over 2 years.
- A 52% reduction in relapse rate relative to an approved first-line MS therapy, IFN β-1a.
- Significant delay in time to first relapse and proportion relapse-free.
- Consistent effect in reduction of relapse rate in subgroups defined by gender, age, prior MS therapy and disease activity prior to study.
- Significant reduction in the risk of disability progression, both 3-month (30%) and 6-month (37%).
- Significant benefit on the MSFC, an alternate disability measure.
- Significant benefit on mean change in EDSS.

### 5.3.2 MRI Outcomes

The above noted clinical findings were supported by results from MRI scan evaluations in both the placebo-controlled and active controlled studies.

- Reduction in inflammatory lesion activity.
  - T2, T1 lesion counts and proportions free of active lesions.
  - Benefit seen at 6 months (1$^{st}$ scan on-study) and at 12 and 24 months.
- Reduction in MRI lesion burden.
  - T2, T1 Gd-enhancing and T1 hypointense lesion volume.

MRI measures provide an *in vivo* assessment of the ability of fingolimod to limit MS disease activity in the brain and accumulation of further total lesion burden. Patients treated with fingolimod had no increase in the total volume of T2 lesions, either after 12 months (study D2301 and D2302) or 24 months (study D2301) while an increase was observed in the control groups. Similar results were observed in the total volume of T1 hypointense lesions, a measure of more destructive MS lesions.

Brain atrophy is an important feature of MS and is correlated with contemporaneous physical disability, with the subsequent development of physical disability and with neurodegeneration at autopsy (Fisher et al 2002; Bermel et al 2006; Mehta et al 2009). Atrophy was over 30% less for patients treated with fingolimod compared both to placebo and to IFN β-1a. The effect was observed within the first 6 months of treatment in study D2301 (versus placebo) and was sustained both at 1 year and at 2 years.

### 5.3.3 Conclusion

Fingolimod 0.5 mg given orally once daily, in patients with relapsing MS, has shown clinically meaningful and statistically significant effects on all aspects of MS disease activity – relapses, disability progression, MRI lesion activity, MRI lesion accumulation and brain atrophy. The strength of the findings are supported by their consistency across both studies and multiple outcomes, including against an approved MS therapy that itself has shown benefit on relapses, disability and MRI lesion activity. The treatment benefit was shown both

in patients who were naïve to MS therapies but also in those who, for various reasons (lack of efficacy, tolerability, adverse events), have stopped using other approved MS drugs. The lack of any relevant efficacy differences between the fingolimod 0.5 mg and 1.25 mg doses, coupled with the evidence of a better overall safety profile with the 0.5 mg dose (see Section 6), supports the 0.5 mg dose as the proposed dose in the label.

# 6 Overview of Safety

The safety profile for MS is based on a large safety database derived from 30 clinical pharmacology studies, one Phase 2 study, three Phase 3 studies (two completed, one ongoing) plus extensions of all the Phase 2 and Phase 3 studies. This data set comprises complete safety data on over 2,600 MS patients exposed to fingolimod with more than 4,500 patient-years of exposure plus selected safety information on an additional 1,000 patients in ongoing blinded studies. The profile seen in Phase 3 is consistent with pre-clinical and clinical pharmacology findings demonstrating that the safety findings are predictable and manageable. Specific areas of interest have been detected during the development program which has allowed careful monitoring and management to enhance patient safety. This section will summarize important safety data which drives product label content and risk management plans and together with efficacy findings will be evaluated for overall benefit-risk in Section 8.3.

Safety data from the renal transplantation studies are not systematically summarized in this overview. However, where this information impacts or informs the understanding of the safety profile in MS, appropriate cross-reference is made.

## 6.1 Safety population in MS

The pre-clinical studies, clinical pharmacology and early clinical studies in the renal transplantation program identified pharmacodynamic effects or safety signals that required particular attention with respect to fingolimod therapy during the MS development program: reduction in heart rate and atrio-ventricular (AV) conduction abnormalities following dosing initiation, a dose-dependent mild increase in airway resistance, asymptomatic elevation of liver enzymes and macular edema. During the early MS program, additional signals which were not clearly seen in the renal transplant program and which were judged to warrant monitoring included a mild increase in blood pressure, infections and possibly skin malignancies.

For the purposes of providing a comprehensive overview of safety data, this report focuses primarily on safety data in 3 groups.

- The first is the 2-year Study group that includes only the placebo-controlled study D2301 patients. This represents the largest controlled safety experience within the program.
- The second group (All Studies Group) includes all data, controlled and uncontrolled, on all patients exposed to fingolimod, including those switched from placebo or IFN during extension phases of the studies but excluding those in ongoing blinded studies. A small portion of the data in this group is safety information on patients with up to 6 years of exposure. The All Studies Group provides an opportunity for observation of dose differences over a long duration.

- Reference will be made to the 1-year IFN β-1a controlled study (study D2302) data in isolation to allow comparison between fingolimod and an approved MS therapy.

The safety population (from all controlled studies) consisted of patients with relapsing-remitting MS, a mean age of 36.8 years (range 17 to 59), a similar demographic profile across treatment groups, and a high proportion of Caucasians (>95%) and females (>68%), features reflective of the MS population as a whole.

As mentioned in Section 2 above, the still ongoing study D2309, a 2-year, double-blind, placebo-controlled study in 1083 patients with RRMS, includes specialized safety assessments to further support the characterization of the safety profile of fingolimod in areas of special interest based on previous clinical experience (heart, lung and eye). As requested by the FDA, interim safety data from these specialized safety assessments are included in the NDA submission. To protect the integrity of this ongoing study, these interim data were analyzed and reported by an independent (unblinded) team not otherwise involved in the study. Summary conclusions of the findings were provided by the independent team for integration in the relevant sections of this Briefing Book.

## 6.2 Safety Evaluations

Based on findings from pre-clinical, pharmacology and transplant studies, in addition to routine safety assessments, all patients in the program underwent mandatory special assessments including monitoring of blood pressure and pulse for at least 6 hours after administration of the first dose; recording of infections (separately from AEs); frequent examinations by an ophthalmologist; frequent pulmonary function tests $FEV_1$, forced vital capacity (FVC), and $D_LCO$ (diffusion capacity for carbon monoxide), high resolution chest computed tomography (HRCT) scans in case of a confirmed decrease in pulmonary function test of 20% or more compared to screening, and an annual examination by a dermatologist.

## 6.3 Patient exposure

Total exposure to fingolimod is presented in Table 6-1. This includes data during the controlled phases of the various clinical trials but also the extension phases, during which all patients who completed the double-blind phase had the option to continue and receive fingolimod treatment. The All Studies Group data provides exposure information only for exposure to fingolimod (excludes control group patients while on control drug but includes these patients once they have converted to fingolimod in the extension phase). Including extension phases, during which an additional 724 patients were exposed to fingolimod beyond those exposed in the control phase, a total of 2,615 patients have received fingolimod at doses of 5 mg, 1.25 mg, or 0.5 mg, accumulating more than 4,500 patient-years of exposure to fingolimod. The table highlights that >1,800 patients have 1-year or more exposure to fingolimod and >1,200 have 2-years or more exposure. Mean (median) exposure is approximately 21 (24) months.

Additional selected safety data from ongoing blinded studies is included from 1,083 patients in D2309 (~722 on fingolimod) and 168 patients in D1201 (~112 on fingolimod), a Phase 2 study in Japanese subjects. As these are ongoing studies, general safety data has not been analyzed or included in this summary. Data from approximately 300 patients (~140 on fingolimod) in the ongoing study in Primary Progressive MS (D2306) are also not included.

**Table 6-1 Duration of exposure to study drug after randomization in All Studies Group (all fingolimod-treated patients safety population)**

| Duration of Exposure (days) | FTY720 5 mg-1.25 mg (N=137) | FTY720 1.25 mg (N=1302) | FTY720 0.5 mg (N=1176) | Total (N=2615) |
|---|---|---|---|---|
| ≥ 7 | 135 (98.5) | 1285 (98.7) | 1173 (99.7) | 2593 (99.2) |
| ≥ 30 | 131 (95.6) | 1259 (96.7) | 1163 (98.9) | 2553 (97.6) |
| ≥ 90 | 126 (92.0) | 1170 (89.9) | 1100 (93.5) | 2396 (91.6) |
| ≥ 180 | 118 (86.1) | 1087 (83.5) | 1025 (87.2) | 2230 (85.3) |
| ≥ 360 | 108 (78.8) | 884 (67.9) | 851 (72.4) | 1843 (70.5) |
| ≥ 540 | 101 (73.7) | 724 (55.6) | 697 (59.3) | 1522 (58.2) |
| ≥ 720 | 96 (70.1) | 561 (43.1) | 567 (48.2) | 1224 (46.8) |
| ≥ 1080 | 85 (62.0) | 114 ( 8.8) | 29 ( 2.5) | 228 ( 8.7) |
| ≥ 1440 | 70 (51.1) | 79 ( 6.1) | 0 ( 0.0) | 149 ( 5.7) |
| ≥ 1800 | 62 (45.3) | 73 ( 5.6) | 0 ( 0.0) | 135 ( 5.2) |
| ≥ 1980 | 45 (32.8) | 47 ( 3.6) | 0 ( 0.0) | 92 ( 3.5) |
| ≥ 2160 | 5 ( 3.6) | 9 ( 0.7) | 0 ( 0.0) | 14 ( 0.5) |
| Patient years | 486.4 | 2218.3 | 1878.0 | 4582.6 |

The duration of exposure is the total actual days patients took the study medication until cut-off date. Patients are cumulatively counted by each level of the duration of exposure intervals.
Patient years is defined as the sum of the number of days on study drug for all patients in each dose group divided by 365.25.
The FTY720D 5 mg–1.25 mg group includes patients who received either FTY720D 5 mg alone or FTY720D 5 mg switched to 1.25 mg.

## 6.4 Adverse events

A summary of deaths, SAEs, and conditions leading to study drug discontinuation in the 2-year Study Group is presented by treatment group in Table 6-2. There were three deaths during this study, one in the fingolimod 1.25 mg group and two in the placebo group. The proportion of patients with AEs leading to study drug discontinuation was higher in the fingolimod 1.25 mg group than for the fingolimod 0.5 mg or placebo groups. Abnormal laboratory values leading to discontinuation were more frequent in fingolimod treatment groups. Further information on AEs leading to drug discontinuations is provided in Section 6.4.6.3 below.

**Table 6-2 Number (%) of patients who died or experienced SAEs or conditions leading to study drug discontinuation in the 2-year Study**

| | FTY720 1.25mg N=429 n (%) | FTY720 0.5mg N=425 n (%) | Placebo N=418 n (%) |
|---|---|---|---|
| Any AE(s) | 404 (94.2) | 401 (94.4) | 387 (92.6) |
| Death | 1 (0.2) | 0 | 2 (0.5) |
| SAE(s) | 51 (11.9) | 43 (10.1) | 56 (13.4) |
| AE(s) leading to study drug discontinuation# | 61 (14.2) | 32 (7.5) | 32 (7.7) |
| Abnormal lab value leading to study drug discontinuation | 32 (7.5) | 20 (4.7) | 5 (1.2) |

The remainder of the Safety section will be presented as follows:

- 2-year Study - adverse events (AEs) by organ systems most frequently affected, by most frequent AEs, and by severity, including details on severe AEs.
- 1-year IFN β-1a controlled study (study D2302) – AEs by organ systems most frequently affected and most frequent AEs for the purpose of comparing rates to an approved MS therapy.
- The All Studies Group – AEs by organ system to permit longer term dose-related comparisons.
- A review of safety areas of special interest.

### 6.4.1 Most frequently affected system organ classes (SOC) among all adverse events – 2-year Study

The number of patients with AEs by system organ class (SOC) is presented in Table 6-3 for the 2-year Study. The overall incidence of AEs was similar across treatment groups. Infection was the most frequent SOC with AEs reported but the rates were comparable between treatment groups. SOCs where the AE profiles differed for the two fingolimod groups compared to the placebo group included **investigations** (explained largely by elevations in liver enzymes that were more frequent with fingolimod than with placebo), **blood and lymphatic disorders** (explained by the impact of fingolimod on lymphocyte counts), and **cardiac disorders** (for which only the fingolimod 1.25 mg group was higher than placebo). The incidence of AEs in most other SOCs was similar across the treatment groups.

**Table 6-3 Adverse events (>=5% AEs in any group) by system organ class in the 2-year Study**

| Primary system organ class | FTY720 1.25mg N=429 n (%) | FTY720 0.5mg N=425 n (%) | Placebo N=418 n (%) |
|---|---|---|---|
| **Any primary system organ class** | **404 (94.2)** | **401 (94.4)** | **387 (92.6)** |
| Infections and infestations | 294 (68.5) | 304 (71.5) | 301 (72.0) |
| Nervous system disorders | 183 (42.7) | 173 (40.7) | 172 (41.1) |
| Gastrointestinal disorders | 157 (36.6) | 146 (34.4) | 144 (34.4) |
| Investigations | 152 (35.4) | 138 (32.5) | 105 (25.1) |
| Musculoskeletal and connective tissue disorders | 125 (29.1) | 140 (32.9) | 128 (30.6) |
| General disorders and administration site conditions | 110 (25.6) | 108 (25.4) | 107 (25.6) |
| Skin and subcutaneous tissue disorders | 106 (24.7) | 131 (30.8) | 122 (29.2) |
| Respiratory, thoracic and mediastinal disorders | 103 (24.0) | 107 (25.2) | 95 (22.7) |
| Eye disorders | 80 (18.6) | 81 (19.1) | 72 (17.2) |
| Psychiatric disorders | 72 (16.8) | 91 (21.4) | 81 (19.4) |
| Injury, poisoning and procedural complications | 50 (11.7) | 61 (14.4) | 65 (15.6) |
| Neoplasms benign, malignant and unspecified (including cysts and polyps) | 45 (10.5) | 49 (11.5) | 55 (13.2) |
| Reproductive system and breast disorders | 45 (10.5) | 39 (9.2) | 26 (6.2) |
| Vascular disorders | 43 (10.0) | 46 (10.8) | 42 (10.0) |
| Metabolism and nutrition disorders | 41 (9.6) | 43 (10.1) | 44 (10.5) |

| Primary system organ class | FTY720 1.25mg N=429 n (%) | FTY720 0.5mg N=425 n (%) | Placebo N=418 n (%) |
|---|---|---|---|
| Cardiac disorders | 38 (8.9) | 25 (5.9) | 23 (5.5) |
| Blood and lymphatic system disorders | 35 (8.2) | 34 (8.0) | 17 (4.1) |
| Ear and labyrinth disorders | 35 (8.2) | 31 (7.3) | 32 (7.7) |
| Renal and urinary disorders | 31 (7.2) | 20 (4.7) | 40 (9.6) |

A patient with multiple AEs within a primary SOC is counted only once in the SOC. SOCs are sorted in descending frequency for the FTY720 1.25 mg treatment group.

### 6.4.2 Most frequently occurring adverse events – 2-year Study

The most frequently occurring AEs (≥5% patients in any treatment group) by preferred term in the 2-year Study are summarized in Table 6-4. For the three most common AEs (headache, nasopharyngitis, and upper respiratory tract infection) there were no noteworthy differences among dose groups. AEs which occurred at a 2% or higher incidence in both fingolimod groups compared with placebo included preferred terms describing **headache, elevations in liver enzymes** (alanine aminotransferase (ALT) increased, gamma-glutamyl transferase (GGT) increased, and hepatic enzyme increased), **back pain**, **hypertension** and **bronchitis**. Of these AEs, the terms GGT increased, ALT increased and hepatic enzyme increased showed a trend for higher proportion of patients in the fingolimod 1.25 mg group than in the fingolimod 0.5 mg group. Other events of potential clinical relevance occurring more commonly with fingolimod include diarrhea, dizziness, sinusitis, and dyspnea.

**Table 6-4 Number (%) of patients with most frequent AEs by preferred term (>=5% patients in any treatment group) in 2-year Study**

| Preferred term | FTY720 1.25mg N=429 n (%) | FTY720 0.5mg N=425 n (%) | Placebo N=418 n (%) |
|---|---|---|---|
| **Any preferred term** | **404 (94.2)** | **401 (94.4)** | **387 (92.6)** |
| Headache | 114 (26.6) | 107 (25.2) | 96 (23.0) |
| Nasopharyngitis | 112 (26.1) | 115 (27.1) | 115 (27.5) |
| Upper respiratory tract infection | 62 (14.5) | 73 (17.2) | 73 (17.5) |
| **Alanine aminotransferase increased** | 50 (11.7) | 43 (10.1) | 16 (3.8) |
| Fatigue | 47 (11.0) | 48 (11.3) | 45 (10.8) |
| **Back pain** | 45 (10.5) | 50 (11.8) | 29 (6.9) |
| Diarrhoea | 40 (9.3) | 50 (11.8) | 31 (7.4) |
| Influenza | 40 (9.3) | 55 (12.9) | 41 (9.8) |
| **Bronchitis** | 39 (9.1) | 34 (8.0) | 15 (3.6) |
| Nausea | 38 (8.9) | 38 (8.9) | 36 (8.6) |
| Cough | 37 (8.6) | 43 (10.1) | 34 (8.1) |
| **Gamma-glutamyltransferase increased** | 32 (7.5) | 22 (5.2) | 4 (1.0) |
| Dizziness | 30 (7.0) | 31 (7.3) | 23 (5.5) |
| Arthralgia | 27 (6.3) | 30 (7.1) | 33 (7.9) |
| **Hypertension** | 27 (6.3) | 26 (6.1) | 16 (3.8) |
| Sinusitis | 27 (6.3) | 28 (6.6) | 19 (4.5) |
| Depression | 26 (6.1) | 33 (7.8) | 28 (6.7) |
| Hypercholesterolaemia | 26 (6.1) | 24 (5.6) | 26 (6.2) |
| Pharyngitis | 25 (5.8) | 27 (6.4) | 24 (5.7) |
| Pain in extremity | 24 (5.6) | 28 (6.6) | 28 (6.7) |
| Dyspnoea | 23 (5.4) | 30 (7.1) | 19 (4.5) |
| **Hepatic enzyme increased** | 22 (5.1) | 14 (3.3) | 1 (0.2) |
| Urinary tract infection | 21 (4.9) | 34 (8.0) | 47 (11.2) |
| Oropharyngeal pain | 17 (4.0) | 29 (6.8) | 29 (6.9) |
| Paraesthesia | 17 (4.0) | 23 (5.4) | 18 (4.3) |
| Insomnia | 16 (3.7) | 21 (4.9) | 25 (6.0) |
| Weight increased | 14 (3.3) | 14 (3.3) | 22 (5.3) |

Preferred terms are sorted in descending frequency for the FTY720 1.25 mg group. A patient with multiple AEs within a primary SOC is counted only once in the total row.
A patient with multiple occurrences of an AE under one treatment group is counted only once in the AE preferred term for that treatment group.

## Severity

The proportion of patients with mild, moderate, and severe AEs by SOC and preferred term is presented for the 2-year Study in Table 6-5. Most AEs were categorized as mild or moderate. Overall, severe AEs were reported for a similar proportion of patients in the fingolimod 1.25 mg and placebo groups and for a lower proportion of patients in the 0.5 mg group.

**Table 6-5 Number (%) of patients with AEs by maximum severity in 2-year Study**

| Maximum severity | FTY720D 1.25mg N=429 n (%) | FTY720D 0.5mg N=425 n (%) | Placebo N=418 n (%) |
|---|---|---|---|
| Mild | 100 (23.3) | 98 (23.1) | 108 (25.8) |
| Moderate | 231 (53.8) | 252 (59.3) | 212 (50.7) |
| Severe | 73 (17.0) | 50 (11.8) | 67 (16.0) |

For the most frequently reported SOC, infections, the proportion of patients with severe AEs was similar across the treatment groups, although slightly lower in the fingolimod 0.5 mg group compared to the other two treatment groups.

A higher proportion of patients with AEs considered severe was seen for fingolimod groups compared to placebo for investigations (a difference primarily attributable to the higher incidence of elevated liver enzymes) cardiac and nervous system disorders (Table 6-6). Severe headache was reported at higher frequency in the fingolimod 1.25 mg group than in the fingolimod 0.5 mg and placebo groups.

**Table 6-6 Number (%) of patients with severe AEs by SOC (at least 4 patients in any treatment group) and preferred term (at least 2 patients in any treatment group) in 2-year Study**

| System organ class<br>Preferred term | FTY720D 1.25 mg (N=429) n (%) | FTY720D 0.5 mg (N=425) n (%) | Placebo (N=418) n (%) |
|---|---|---|---|
| **Any severe AE** | 73 (17.0) | 50 (11.8) | 67 (16.0) |
| **Blood and lymphatic system disorders** | 4 (0.9) | 5 (1.2) | 0 |
| Lymphopenia | 4 (0.9) | 4 (0.9) | 0 |
| **Cardiac disorders** | 6 (1.4) | 4 (0.9) | 1 (0.2) |
| Bradycardia | 2 (0.5) | 2 (0.5) | 0 |
| **Eye disorders** | 4 (0.9) | 0 | 2 (0.5) |
| Macular oedema | 2 (0.5) | 0 | 0 |
| **Gastrointestinal disorders** | 6 (1.4) | 7 (1.6) | 3 (0.7) |
| Abdominal pain | 0 | 3 (0.7) | 0 |
| **General disorders and administration site conditions** | 3 (0.7) | 4 (0.9) | 6 (1.4) |
| Fatigue | 3 (0.7) | 2 (0.5) | 4 (1.0) |
| **Infections and infestations** | 15 (3.5) | 12 (2.8) | 13 (3.1) |
| Nasopharyngitis | 2 (0.5) | 1 (0.2) | 2 (0.5) |
| Influenza | 1 (0.2) | 4 (0.9) | 1 (0.2) |
| Rhinitis | 0 | 0 | 2 (0.5) |
| Upper respiratory tract infection | 0 | 2 (0.5) | 1 (0.2) |

| System organ class<br>Preferred term | FTY720D 1.25 mg (N=429) n (%) | FTY720D 0.5 mg (N=425) n (%) | Placebo (N=418) n (%) |
|---|---|---|---|
| **Investigations** | 16 (3.7) | 7 (1.6) | 1 (0.2) |
| Hepatic enzyme increased | 4 (0.9) | 1 (0.2) | 0 |
| Alanine aminotransferase increased | 3 (0.7) | 4 (0.9) | 1 (0.2) |
| Gamma-glutamyltransferase increased | 2 (0.5) | 2 (0.5) | 0 |
| Lymphocyte count decreased | 2 (0.5) | 0 | 0 |
| Aspartate aminotransferase increased | 0 | 2 (0.5) | 0 |
| **Musculoskeletal and connective tissue disorders** | 6 (1.4) | 4 (0.9) | 4 (1.0) |
| Pain in jaw | 0 | 0 | 2 (0.5) |
| **Neoplasms benign, malignant and unspecified (incl. cysts and polyps)** | 3 (0.7) | 0 | 8 (1.9) |
| Basal cell carcinoma | 1 (0.2) | 0 | 2 (0.5) |
| **Nervous system disorders** | 21 (4.9) | 14 (3.8) | 11 (2.6) |
| Headache | 9 (2.1) | 3 (0.7) | 4 (1.0) |
| Migraine | 3 (0.7) | 1 (0.2) | 1 (0.2) |
| Multiple sclerosis relapse | 3 (0.7) | 2 (0.5) | 1 (0.2) |
| Epilepsy | 2 (0.5) | 0 | 0 |
| **Psychiatric disorders** | 3 (0.7) | 1 (0.2) | 5 (1.2) |
| Depression | 2 (0.5) | 1 (0.2) | 1 (0.2) |
| Anxiety | 1 (0.2) | 0 | 2 (0.5) |
| **Respiratory, thoracic and mediastinal disorders** | 3 (0.7) | 1 (0.2) | 4 (1.0) |

Primary SOCs are presented alphabetically; preferred terms are sorted within primary SOC in descending frequency for the FTY720 1.25 mg group.
A patient with multiple AEs within a primary SOC is counted only once in the total row.
A patient with multiple occurrences of an AE under one treatment group is counted only once in the AE preferred term for that treatment group.

Adverse events were also assessed for any relationship to time on drug in the 2-year Study. AEs were examined over the following time intervals: for Months 0-6, Months 6-12, Months 12-18, and > Month 18. In all treatment groups, AEs tended to occur more frequently during the first six months than during the later intervals. Differences between treatment groups in the proportion of patients experiencing AEs mostly remained stable or decreased over time. Macular edema occurred primarily in the first six months, while the majority of cardiac events were reported on the first day of treatment. Leucopenia, lymphopenia, and infections did not increase in frequency over time. There were no AEs that increased over time relative to placebo, with the possible exception of lymphopenia, the reporting of which increased in year 2. However, this was probably driven by the fact that the 'notable' alert level (at which point investigators would receive notification of a laboratory finding) for lymphocytes was increased from 100 to 200 cells/mL, thus artificially leading to increased reporting.

### 6.4.3 Adverse events in 1-year Interferon β-1a controlled Study

The findings in the large 1-year IFN β-1a controlled study, D2302, are similar to those of the 2-year Study.

The number of patients with AEs by system organ class (SOC) is presented in Table 6-7 for the 1-year Study. The overall incidence of AEs was similar across the treatment groups. However, the AE profiles differed for the two fingolimod (FTY720) groups compared to the IFN β-1a i.m. group. In the IFN β-1a i.m. group, the system organ class with the highest incidence of AEs was general disorders and administration site conditions, with an incidence more than twice as high as in the two fingolimod treatment groups. The incidence of musculoskeletal and connective tissue disorders was also higher in the IFN β-1a i.m. group than in the fingolimod treatment groups.

In the two fingolimod treatment groups, incidence of AEs was notably higher than in the IFN β-1a i.m. group for the SOC of investigations, gastrointestinal disorders, and neoplasms benign, malignant and unspecified.

**Table 6-7 Adverse events (>=5% AEs in any group) by system organ class in the 1-year Study D2302**

| Primary system organ class | FTY720 1.25mg N=420 n (%) | FTY720 0.5mg N=429 n (%) | Interferon beta-1a i.m. N=431 n (%) |
|---|---|---|---|
| **Any primary system organ class** | **380 (90.5)** | **369 (86.0)** | **395 (91.6)** |
| Infections and infestations | 221 (52.6) | 222 (51.7) | 219 (50.8) |
| Nervous system disorders | 166 (39.5) | 157 (36.6) | 145 (33.6) |
| Gastrointestinal disorders | 135 (32.1) | 127 (29.6) | 105 (24.4) |
| General disorders and administration site conditions | 109 (26.0) | 108 (25.2) | 270 (62.6) |
| Musculoskeletal and connective tissue disorders | 108 (25.7) | 118 (27.5) | 137 (31.8) |
| Skin and subcutaneous tissue disorders | 89 (21.2) | 69 (16.1) | 82 (19.0) |
| Respiratory, thoracic and mediastinal disorders | 82 (19.5) | 61 (14.2) | 63 (14.6) |
| Investigations | 77 (18.3) | 86 (20.0) | 37 (8.6) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 66 (15.7) | 62 (14.5) | 42 (9.7) |
| Psychiatric disorders | 57 (13.6) | 68 (15.9) | 75 (17.4) |
| Eye disorders | 52 (12.4) | 54 (12.6) | 52 (12.1) |
| Cardiac disorders | 35 (8.3) | 18 (4.2) | 23 (5.3) |
| Reproductive system and breast disorders | 34 (8.1) | 29 (6.8) | 31 (7.2) |
| Metabolism and nutrition disorders | 31 (7.4) | 21 (4.9) | 17 (3.9) |
| Ear and labyrinth disorders | 30 (7.1) | 16 (3.7) | 21 (4.9) |
| Injury, poisoning and procedural complications | 28 (6.7) | 45 (10.5) | 43 (10.0) |
| Vascular disorders | 27 (6.4) | 28 (6.5) | 21 (4.9) |

Sorted in descending frequency in the FTY720 1.25 mg group.

The most frequently occurring AEs (≥5% patients in any treatment group) by preferred term in the 1-year Study are summarized in Table 6-8. For the fingolimod groups, the most commonly reported AEs were headache and nasopharyngitis; both showing no meaningful differences between treatment groups. AEs which occurred at 2% higher incidence in both fingolimod groups compared with IFN β-1a included headache, ALT increased, and diarrhea. AEs characteristic of the adverse drug reaction profile for IFN β-1a (influenza-like illness, pyrexia and myalgia) were observed with much lower incidence in the fingolimod groups.

**Table 6-8 Number (%) of patients with most frequent AEs by preferred term (>=5% patients in any treatment group) in the 1-year Study D2302**

| | FTY720 1.25mg N=420 n (%) | FTY720 0.5mg N=429 n (%) | Interferon beta-1a i.m. N=431 n (%) |
|---|---|---|---|
| Any preferred term(s) | 380 (90.5) | 369 (86.0) | 395 (91.6) |
| Headache | 96 (22.9) | 99 (23.1) | 88 (20.4) |
| Nasopharyngitis | 93 (22.1) | 88 (20.5) | 88 (20.4) |
| Fatigue | 59 (14.0) | 44 (10.3) | 45 (10.4) |
| Melanocytic nevus | 42 (10.0) | 28 (6.5) | 24 (5.6) |
| Upper respiratory tract infection | 36 (8.6) | 31 (7.2) | 27 (6.3) |
| Diarrhea | 35 (8.3) | 32 (7.5) | 21 (4.9) |
| Cough | 30 (7.1) | 20 (4.7) | 16 (3.7) |
| Influenza | 28 (6.7) | 29 (6.8) | 32 (7.4) |
| Nausea | 28 (6.7) | 40 (9.3) | 29 (6.7) |
| Back pain | 27 (6.4) | 26 (6.1) | 23 (5.3) |
| Alanine aminotransferase increased | 24 (5.7) | 28 (6.5) | 8 (1.9) |
| Urinary tract infection | 24 (5.7) | 26 (6.1) | 22 (5.1) |
| Dizziness | 23 (5.5) | 24 (5.6) | 21 (4.9) |
| Dyspnea | 22 (5.2) | 8 (1.9) | 7 (1.6) |
| Hypertension | 21 (5.0) | 16 (3.7) | 8 (1.9) |
| Pain in extremity | 20 (4.8) | 21 (4.9) | 28 (6.5) |
| Depression | 18 (4.3) | 21 (4.9) | 32 (7.4) |
| Arthralgia | 17 (4.0) | 12 (2.8) | 24 (5.6) |
| Influenza like illness | 15 (3.6) | 15 (3.5) | 159 (36.9) |
| Pyrexia | 15 (3.6) | 18 (4.2) | 77 (17.9) |
| Myalgia | 14 (3.3) | 14 (3.3) | 44 (10.2) |

A patient with multiple occurrences of an AE under one treatment group is counted only once in the AE preferred term for that treatment group.
Preferred terms are sorted in descending frequency in the FTY720 1.25 mg treatment group.

### 6.4.4 Adverse events in all studies group

The incidence of the most common AEs is presented by primary SOC for the All Studies Group in Table 6-9. Although differences are small, the incidence of AEs in the fingolimod 1.25 mg group is slightly higher compared to the fingolimod 0.5 mg dose group for many of the items but only lymphopenia and lymphocyte decreased are ≥2% higher for 1.25mg than 0.5mg. No AE meets this criterion for 0.5 mg relative to 1.25mg.

**Table 6-9 Number (%) of patients with AEs by preferred term (>=5% patients in any dose group) in Group E (FTY720-treated safety population)**

| Preferred term | FTY720 1.25 mg N=1302 n (%) | FTY720 0.5 mg N=1176 n (%) |
|---|---|---|
| Any preferred term | 1203 (92.4) | 1054 (89.6) |
| Nasopharyngitis | 358 (27.5) | 308 (26.2) |
| Headache | 322 (24.7) | 278 (23.6) |
| Upper respiratory tract infection | 184 (14.1) | 154 (13.1) |
| Lymphopenia | 165 (12.7) | 105 ( 8.9) |
| Fatigue | 163 (12.5) | 126 (10.7) |
| Diarrhoea | 138 (10.6) | 121 (10.3) |
| Back pain | 133 (10.2) | 109 ( 9.3) |
| Influenza | 129 ( 9.9) | 122 (10.4) |
| Alanine aminotransferase increased | 126 ( 9.7) | 92 ( 7.8) |
| Cough | 125 ( 9.6) | 97 ( 8.2) |
| Nausea | 104 ( 8.0) | 110 ( 9.4) |
| Bronchitis | 102 ( 7.8) | 77 ( 6.5) |
| Hypertension | 100 ( 7.7) | 74 ( 6.3) |
| Lymphocyte count decreased | 91 ( 7.0) | 56 ( 4.8) |
| Arthralgia | 89 ( 6.8) | 71 ( 6.0) |
| Depression | 87 ( 6.7) | 74 ( 6.3) |
| Pain in extremity | 87 ( 6.7) | 72 ( 6.1) |
| Urinary tract infection | 83 ( 6.4) | 90 ( 7.7) |
| Sinusitis | 82 ( 6.3) | 59 ( 5.0) |
| Melanocytic naevus | 81 ( 6.2) | 61 ( 5.2) |
| Dyspnoea | 76 ( 5.8) | 56 ( 4.8) |
| Dizziness | 75 ( 5.8) | 76 ( 6.5) |
| Gamma-glutamyltransferase increased | 75 ( 5.8) | 51 ( 4.3) |
| Oropharyngeal pain | 73 ( 5.6) | 70 ( 6.0) |
| Pharyngitis | 73 ( 5.6) | 60 ( 5.1) |
| Insomnia | 67 ( 5.1) | 59 ( 5.0) |
| Gastroenteritis | 65 ( 5.0) | 51 ( 4.3) |
| Abdominal pain upper | 63( 4.8) | 43( 3.7) |
| Hypercholesterolaemia | 61 ( 4.7) | 61 ( 5.2) |
| Leukopenia | 57 ( 4.4) | 30 ( 2.6) |
| Paraesthesia | 57 ( 4.4) | 57 ( 4.8) |
| Pyrexia | 57 ( 4.4) | 42 ( 3.6) |
| Hypoaesthesia | 54 ( 4.1) | 38 ( 3.2) |
| Migraine | 48 ( 3.7) | 42 ( 3.6) |
| Abdominal pain | 47 ( 3.6) | 33 ( 2.8) |
| Rash | 47 ( 3.6) | 25 ( 2.1) |

| Preferred term | FTY720 1.25 mg N=1302 n (%) | FTY720 0.5 mg N=1176 n (%) |
|---|---|---|
| Toothache | 46 ( 3.5) | 52 ( 4.4) |
| Vomiting | 44 ( 3.4) | 34 ( 2.9) |
| White blood cell count decreased | 44 ( 3.4) | 21 ( 1.8) |
| Eczema | 43 ( 3.3) | 27 ( 2.3) |
| Constipation | 42 ( 3.2) | 41 ( 3.5) |
| Alopecia | 40 ( 3.1) | 32 ( 2.7) |
| Anxiety | 40 ( 3.1) | 49 ( 4.2) |
| Muscle spasms | 40 ( 3.1) | 31 ( 2.6) |
| Cystitis | 32 ( 2.5) | 40 ( 3.4) |
| Musculoskeletal pain | 32 ( 2.5) | 25 ( 2.1) |
| Herpes zoster | 29 ( 2.2) | 18 ( 1.5) |
| Fall | 28 ( 2.2) | 32 ( 2.7) |
| Oedema peripheral | 28( 2.2) | 14( 1.2) |
| Tooth infection | 22 ( 1.7) | 16 ( 1.4) |
| Asthma | 15 ( 1.2) | 9 ( 0.8) |
| Chest pain | 14 ( 1.1) | 12 ( 1.0) |

A patient with multiple occurrences of an AE under 1 dose group is counted only once in the AE preferred term for that treatment group.
Preferred terms are sorted in descending frequency in the FTY720 1.25 mg dose group.
Subgroup evaluation of adverse events

Subgroup evaluations of adverse events (by gender, age, previous MS treatment status) indicated that the only difference of note between subgroups was for gender where a larger proportion of male patients had AEs in the investigational SOC compared to the female patients in the fingolimod treatment groups. This difference was driven by a higher proportion of male patients with AEs of elevated liver enzymes compared to females, a trend that repeated across the datasets and which was mirrored when looking at laboratory results irrespective of AE reporting. No explanation for this finding is available at present, although similar gender differences have been reported for interferon therapy in MS (Francis et al, 2003).

### 6.4.5 Safety areas of special interest

Safety areas of special interest were defined based on knowledge of the biology of S1P receptors, the known pharmacodynamic effects of fingolimod and the emerging clinical experience in the clinical development program. Safety data were evaluated in the following areas:

Cardiac, Blood pressure, Eye, Liver, Neoplasms, Infections, Vascular, Nervous system, and Respiratory.

For completeness, as relevant, reference is also made in this section to data from animal studies and renal transplantation studies.

### 6.4.5.1 Cardiac disorders

This section will present the clinical experience including Pulse, BP, electrocardiogram (ECG), and Holter monitoring data on Treatment Initiation, and will also present adverse event, ECG and echocardiography data on Chronic Therapy.

#### 6.4.5.1.1 Treatment initiation

**Preclinical pharmacology**

In short-term studies in animals it was shown that fingolimod causes a transient decrease in heart rate which may be combined with sinus arrhythmia, and an acute increase in blood pressure. In repeated-dose toxicology studies of sub-chronic or chronic nature, no sustained effects on heart rate and blood pressure were found.

The mechanism of fingolimod's effect on heart rate and atrio-ventricular conduction is linked to an activation of G-protein-coupled inwardly rectifying $K^+$ channels (GIRK channels) in atrial myocytes and a hyperpolarization of cell membranes that transiently reduces the excitability of the cells (Brinkmann 2007). Although experiments with $S1P_3$-deficient mice suggested a dominant role of $S1P_3$ in this process (Forrest et al 2004), data in humans suggest indicated that $S1P_1$ (rather than $S1P_3$) plays the dominant role in the regulation of atrial myocyte function, AV conduction and heart rate (Brinkmann 2007).

**Clinical trials**

In the clinical trials, fingolimod was introduced in an outpatient setting in which patients were observed in the clinic for at least the first 6 hours after taking the first dose of study drug with hourly heart rate and blood pressure measurements. Extended observation was mandated per protocol for any patient who did not meet protocol pre-defined discharge criteria (i.e. patients could only be discharged if maximal lowering effect on heart rate had already been observed in the first 6 hours, the heart rate was at least 51 beats per minute (bpm), the patient was asymptomatic, and the 6-hour ECG did not show any new relevant abnormality). In addition, patients with a heart rate decrease of more than 30% or the presence of symptomatic bradycardia, had to return to the clinic for the same 6-hour monitoring for the second dose of study drug.

**Pulse and Blood Pressure**

Initiation of fingolimod treatment was associated with dose-dependent reductions in sitting pulse, starting as early as 1 hour after dosing. The decrease in sitting pulse on Day 1 was maximal at 4-5 hours after the first-dose administration, with declines in mean heart rate of 11 bpm for fingolimod 1.25 mg and 8 bpm for fingolimod 0.5 mg. There were no relevant changes in mean sitting pulse in the placebo group while an 8 bpm increase was seen in the IFN β-1a group, potentially related to systemic effects seen with IFN. The reduction in sitting pulse seen at the initiation of fingolimod treatment attenuated with chronic treatment, returning to baseline levels by Month 1, after which heart rate remained stable throughout the duration of treatment.

Systolic and diastolic blood pressure (BP) were slightly decreased in both fingolimod groups during the 6-hour monitoring period after first dose, with a somewhat more pronounced effect in the 1.25 mg group compared to the 0.5 mg group.

### Clinical experience

The majority of patients in all treatment groups were discharged after 6 hours observation (Table 6-10). In the All Studies Group extended observation after 6 hours was more frequently required in patients receiving fingolimod 1.25 mg than in patients receiving fingolimod 0.5 mg. The number of patients required to return for Day 2 second-dose observation was also higher for fingolimod 1.25 mg than for the fingolimod 0.5 mg group. Study drug was permanently discontinued after the first dose for 16 patients (1.4%) receiving fingolimod 1.25 mg and 2 patients (0.2%) receiving fingolimod 0.5 mg.

**Table 6-10 First dose administration experience in All Studies Group**

| | **FTY720 1.25 mg (N=1168) n (%)** | **FTY720 0.5 mg (N=1176) n (%)** |
|---|---|---|
| Discharged at 6 hours | 918 (78.6) | 991 (84.3) |
| Required extended monitoring after 6 hours | 200 (17.1) | 136 (11.6) |
| Hospitalized | 29 (2.5) | 18 (1.5) |
| Required Day 2 monitoring | 78 (6.7) | 23 (2.0) |
| Study drug permanently discontinued | 16 (1.4 ) | 2 (0.2) |
| Symptomatic bradycardia events, total | 15 (1.3) | 4 (0.3) |
| Mild symptoms | 9 (0.8) | 3 (0.3) |
| Moderate symptoms | 4 (0.3) | 1 (0.1) |
| Severe symptoms | 2 (0.2) | 0 (0.0) |
| Treated events | 5 (0.4) | 1 (0.1) |

Study D2201 and Study D2201E1 data are not included in this table as this information was not collected in those studies.

In the vast majority of cases, the changes seen in vital signs following treatment initiation were not associated with symptoms. First- and second-degree AV conduction blocks were infrequently symptomatic and all blocks recovered spontaneously. Symptomatic events were observed in 15 patients (1.3%) administered fingolimod 1.25 mg and four patients (0.3%) on fingolimod 0.5 mg. Most symptomatic events occurred on Day 1, were mild or moderate in severity and resolved spontaneously without requiring treatment. The most common symptoms associated with bradycardia were dizziness, chest discomfort, and palpitations. Severe symptoms were reported only in the fingolimod 1.25 mg group: a severe event of syncope in the context of a transient third-degree AV block as described below, and another patient with severe dizziness. In the fingolimod 0.5 mg group, the symptoms reported were mild dizziness in three patients, and moderate somnolence in the evening in one patient. Symptomatic events on Day 2 occurred in three patients on fingolimod 1.25 mg and no patient on fingolimod 0.5 mg. It should be noted that study drug was also permanently discontinued after the first dose for one (0.2%) patient receiving placebo in the 2-year placebo controlled study.

Medications for bradycardia were administered to six (0.3%) patients during first dose administration monitoring. In the fingolimod 1.25 mg group four patients (two with symptomatic events) received atropine and one asymptomatic patient received a saline infusion. In the fingolimod 0.5 mg dose group, only one patient received isoprenaline (isoproterenol) in the context of an asymptomatic second degree AV block Mobitz I from which she made a complete recovery. This patient's heart rate before the first dose of the study medication was 65 bpm and during the 6 hours monitoring it was 46 bpm.

One case of transient, narrow complex, third-degree AV block was reported in a 40-year-old female patient participating in Study D2302E1. Two hours after the first dose of fingolimod 1.25 mg, her pulse was irregular and ECG showed second-degree Type I AV block with a heart rate of 55 bpm. At 3 hours post-dose, she was noted to have pallor and apparent loss of consciousness for approximately 30 seconds. At the time of the event, cardiac monitoring showed third-degree AV block which lasted for 30 seconds. The patient recovered spontaneously and then was treated with a single dose of atropine (0.125 mg, IV). She made a complete recovery with normal sinus rhythm (61 bpm) within 24 hours of onset of this event.

## ECG Findings

In the Phase III clinical trials, initiation of fingolimod was associated with a dose-dependent delay of AV conduction, with prolongations in mean PR interval of 11.3 ms for fingolimod 1.25 mg and 4.5 ms for fingolimod 0.5 mg on the 6-hours post-dose ECG. There were no relevant changes in PR interval in the placebo group while a 3.2 ms decrease was seen in the IFN β-1a group. No differences in AV conduction were observed on ECG at 1 month of treatment or during chronic treatment.

In the All Studies Group the majority of patients in the fingolimod 1.25 mg and fingolimod 0.5 mg groups had normal ECGs at 6 hours after the first dose (Table 6-11). Conduction and rhythm abnormalities were the most frequently observed findings in the 6 hours after the first dose ECG, with a higher incidence in the fingolimod 1.25 mg group compared to the fingolimod 0.5 mg group. The most frequently observed conduction finding was first-degree AV block, which was seen more frequently in the fingolimod 1.25 mg group. A small number of patients had Mobitz I or 2:1 AV block findings, with a higher percentage in the fingolimod 1.25 mg group versus the fingolimod 0.5 mg group. No patient had a Mobitz I or 2:1 AV block on ECGs at Month 1 or during chronic treatment.

**Table 6-11 Incidence of abnormal ECGs by type of abnormality and time-point after first FTY720 dose administration for All Studies Group**

| Day 1 pre-dose | FTY720 1.25 mg (N=1302) n (%) | FTY720 0.5 mg (N=1176) n (%) | Day 1 post-dose (6 hours) | FTY720 1.25 mg (N=1302) n (%) | FTY720 0.5 mg (N=1176) n (%) |
|---|---|---|---|---|---|
| **Number of patients with ECG** | **1301** | **1174** | **Number of patients with ECG** | **1282** | **1156** |
| **Any abnormality** | **89 (6.8)** | **92 (7.8)** | **Any abnormality** | **193 (15.1)** | **115 (9.9)** |
| **Conduction** | **54 (4.2)** | **53 (4.5)** | **Conduction** | **152 (11.9)** | **82 (7.1)** |
| First degree AV Block | 25 (1.9) | 29 (2.5) | First degree AV Block | 113 (8.8) | 55 (4.8) |
| LAH | 17 (1.3) | 20 (1.7) | LAH | 18 (1.4) | 20 (1.7) |
| IVCD | 7 (0.5) | 2 (0.2) | AV Mobitz I | 10 (0.8) | 2 (0.2) |
| RBBB | 7 (0.5) | 6 (0.5) | RBBB | 5 (0.4) | 5 (0.4) |
| IRBBB | 2 (0.2) | 0 (0.0) | IVCD | 4 (0.3) | 3 (0.3) |
| ILBBB | 0 (0.0) | 1 (0.1) | 2:1 AV block | 3 (0.2) | 1 (0.1) |
| | | | IRBBB | 2 (0.2) | 2 (0.2) |
| | | | ILBBB | 0 (0.0) | 1 (0.1) |
| | | | Other conduction | 0 (0.0) | 1 (0.1) |
| **Rhythm** | **14 (1.1)** | **8 (0.7)** | **Rhythm** | **35 (2.7)** | **8 (0.7)** |
| Ectopic Supraventricular Rhythm | 8 (0.6) | 2 (0.2) | Ectopic Supraventricular Rhythm | 6 (0.5) | 0 (0.0) |
| Sinus tachycardia | 3 (0.2) | 3 (0.3) | Junctional tachycardia | 0 (0.0) | 1 (0.1) |
| Junctional rhythm | 1 (0.1) | 0 (0.0) | Junctional rhythm | 1 (0.1) | 0 (0.0) |
| Other Rhythm | 1 (0.1) | 2 (0.2) | Other rhythm | 3 (0.2) | 2 (0.2) |
| Sinus bradycardia | 1 (0.1) | 1 (0.1) | SInus bradycardia | 25 (2.0) | 5 (0.4) |

Abnormality types are presented alphabetically; findings are sorted within abnormality type by frequency from highest to lowest in the FTY720 1.25 mg group for the pre-dose time-point.
A patient with multiple occurrences of an abnormality is counted only once in the corresponding category.
A patient with multiple findings within an abnormality type is counted only once in the total row of this abnormality type.

## Holter Monitor

24-hour Holter ECG data are available from study D2309, at Screening, Day 1 and Month 3, for a total of 1080 patients: 367 on fingolimod 1.25 mg, 358 on fingolimod 0.5 mg and 355 on placebo.

Holter data at screening detected second-degree Mobitz 1 AV block in approximately 1% of patients in all dose groups, including placebo. On Day 1, following drug administration, 2.0% of patients on placebo had Mobitz I (Wenckebach) second degree AV block, compared to 6.6% of patients on fingolimod 1.25 mg and 3.4% on fingolimod 0.5 mg group, indicative of a fingolimod dose-response relationship. 2:1 AV block was observed in 12 patients (3.3%) on fingolimod 1.25 mg, and 6 patients (1.7%) on fingolimod 0.5 mg but in no placebo patient, and no patient in any group at screening. All but one of the 18 patients with 2:1 AV block on Day 1 also had Mobitz I block.

For the majority of patients on fingolimod, the second-degree AV blocks were first seen within 6 hours post-first dose (fingolimod 1.25 mg 18/24 patients, fingolimod 0.5 mg 11/13 patients), whereas for all 7 placebo patients with Mobitz I block, the event occurred >12 hours post dose during the night.

Bradycardia, defined as average heart rate ≤40 bpm for any one hour during 24-hour Holter monitoring, was observed in 5 (1.4%) patients on fingolimod 1.25 mg compared with 1 (0.3%) patient on fingolimod 0.5 mg after the first dose only. One patient on fingolimod 1.25 mg was reported to have a sinus pause >3 seconds during Holter monitoring on Day 1.

One patient on fingolimod 0.5 mg had non-sustained ventricular tachycardia 3-10 beats (1 episode) and frequent VPCs during Holter monitoring on day 1 (frequent VPCs also observed on standard ECG) and day 44 (unscheduled). Ventricular tachycardia was reported as an SAE which was mild in severity. The patient was asymptomatic and not hospitalized, however study drug was discontinued on day 65 due to this event. A repeat Holter 33 days after the last dose of study drug was normal.

At Month 3, neither Mobitz I nor 2:1 AV block was observed in the fingolimod-treated patients, whereas Mobitz I occurred in 5 (1.5%) placebo patients one of whom also had 2:1 AV block.

There was no evidence of newly occurring high-grade AV blocks (Mobitz II, complete heart block), atrial or ventricular fibrillation/flutter, torsades de pointes, non-sustained ventricular tachycardias >10 beats or sustained ventricular tachycardias upon single or multiple dosing of fingolimod.

Thus, both ECG and 24-Holter monitoring indicated that AV conduction block is related to fingolimod treatment initiation and that this effect is dose-related. The increased incidence of conduction block with Holter monitoring compared to AE reporting or ECG results is expected given both the longer duration of observation and the direct ascertainment over the 24-hour interval of what is predominantly an asymptomatic event.

The 24-hour Holter examination at Month 3 in study D2309 confirmed that the effects of fingolimod on heart rate and AV conduction were transient. Neither Mobitz I nor 2:1 AV

block were observed in the fingolimod-treated patients at Month 3, whereas Mobitz I occurred in 4 (1.1%) patients on placebo.

6.4.5.1.2 Chronic therapy

## Adverse Events

The number of patients in the 2-year, placebo-controlled study, D2301, with cardiac disorder AEs (during the study, including first dose administration) by time intervals is summarized in Table 6-12. AEs tended to occur more frequently during the first six months than during the later time intervals. The proportion of patients with cardiac disorder AEs was slightly higher in the fingolimod 1.25 mg group (8.9%) compared to the fingolimod 0.5 mg and placebo treatment groups (5.9% and 5.5%), mainly due to the higher incidence of bradycardia and first degree AV block during the first 6 months.

**Table 6-12 Number (%) of patients with cardiac disorders AEs by preferred term, treatment and time interval (Study D2301) occurring in >1 patient in any group**

| Preferred term | FTY720 1.25mg N=429 n (%) | FTY720 0.5mg N=425 n (%) | Placebo N=418 n (%) |
|---|---|---|---|
| **Total** | **38 (8.9)** | **25 (5.9)** | **23 (5.5)** |
| **Month 0-6, n** | **429** | **425** | **418** |
| Any cardiac AE | 24 (5.6) | 18 (4.2) | 14 (3.3) |
| Bradycardia | 7 (1.6) | 5 (1.2) | 2 (0.5) |
| Palpitations | 6 (1.4) | 3 (0.7) | 6 (1.4) |
| AV block first degree | 3 (0.7) | 1 (0.2) | 0 (0.0) |
| Tachycardia | 2 (0.5) | 2 (0.5) | 2 (0.5) |
| Angina pectoris | 1 (0.2) | 1 (0.2) | 2 (0.5) |
| **Month 6-12, n** | **383** | **406** | **392** |
| Any cardiac AE | 2 (0.5) | 4 (1.0) | 4 (1.0) |
| Palpitations | 1 (0.3) | 2 (0.5) | 1 (0.3) |
| Tachycardia | 0 (0.0) | 0 (0.0) | 2 (0.5) |
| **Month 12-18, n** | **359** | **389** | **367** |
| Any cardiac AE | 10 (2.8) | 0 (0.0) | 1 (0.3) |
| Tachycardia | 4 (1.1) | 0 (0.0) | 0 (0.0) |
| Palpitations | 2 (0.6) | 0 (0.0) | 0 (0.0) |
| **Beyond Month 18, n** | **329** | **371** | **330** |
| Any cardiac AE | 6 (1.8) | 4 (1.1) | 5 (1.5) |
| Tachycardia | 2 (0.6) | 2 (0.5) | 1 (0.3) |

AE preferred terms within MedDRA primary system organ class 'Cardiac disorders' are included in this table.
Preferred terms are sorted by descending frequency in the FTY720 1.25 mg group.

## QT Interval

In the thorough QT study D2101, which included fingolimod doses of 2.5 mg and 1.25 mg and also moxifloxacin and placebo control arms, mild but statistically significant prolongation of mean corrected QT by 5-10 msec on fingolimod treatment was observed. An outlier

analysis revealed no subjects with absolute QTcI >470 msec. There was one subject on fingolimod 2.5 mg and one subject on placebo who had a QTcI >450 msec. The outlier analysis of the study revealed no subjects with a change from baseline of 30-60 msec. There was no dose- or exposure-response indicated by the fact that the systemic fingolimod exposure and QTcI response analysis was flat over one log range of fingolimod exposure (2.5-25 ng/mL). A negative chronotropic effect of fingolimod was still present at the time of the primary QTcI analysis on day 7. QT interval prolongation in this study is believed to be an indirect effect due to compensatory increase in adrenergic tone secondary to fingolimod induced reduction of heart rate. This is supported by the absence of a signal in pre-clinical studies for an effect of fingolimod on cardiac repolarization. Fingolimod had no effect on human Ether-a-go-go Related Gene (hERG) channel currents at concentrations <250 ng/mL and only a slight effect at 500 ng/mL-potentially related to cytotoxicity. In addition, no effects of fingolimod on QT interval was observed in *in vivo* telemetry studies in three species (monkey, dog, guinea pig).

Across all datasets in the clinical studies in MS patients, there were no clear imbalances in QTc across the treatment groups, when adjusted using either Bazett's or Fridericia's formulae, in either maximum increase from baseline or in increase above pre-defined categories for absolute QTc values. No patient in any dataset had QTc interval >500 ms (males) or >520 ms (females). Based on the All Studies Group follow-up population, changes in QTc values appeared to be minor, transient and attenuated within 3 months after study drug discontinuation.

## Echocardiograms

Echocardiography was performed in a subset of patients in studies D2302 and D2309. The echocardiography analysis set submitted with the 120 Day Safety Update comprised a total of 208 patients: 177 from Study D2309 and 31 from Study D2302. Of these 208 patients, 71 were on fingolimod 1.25 mg, 69 were on fingolimod 0.5 mg, 57 were on placebo, and 11 were on IFN β-1a i.m. 198 patients were exposed to study drug for at least 90 days (64 on fingolimod 1.25 mg, 67 on fingolimod 0.5 mg, 56 on placebo, 11 on IFN β-1a i.m.), 113 patients for at least 360 days (39 on fingolimod 1.25 mg, 40 on fingolimod 0.5 mg, 28 on placebo, 6 on IFN β-1a i.m.) and 31 patients for at least 720 days (10 on fingolimod 1.25 mg, 12 on fingolimod 0.5 mg, 9 on placebo).

There was no relevant change in any parameter of left ventricular function, no change suggestive of left ventricular hypertrophic changes, and no relevant change in pulmonary or systemic vascular resistance.

Overall, no difference in distribution of clinically notable echocardiography parameters was observed among the treatment groups at month 3, 12 or at the last post-baseline assessment. Taken together with the summary statistics, no changes were seen which would indicate the development of cardiac valve damage, either significant incompetence or stenosis, since study entry. The number of patients at Month 24 is too small to enable any conclusions.

## Conclusions

A dose-related reduction in heart rate is almost universal with fingolimod therapy, but is mild in degree and transient in duration. Symptomatic events are uncommon, as are AV conduction

blocks (also transient), particularly the more concerning Type II 2nd Degree AV blocks. These events are virtually exclusively seen on Day 1 of dosing and given the limited clinical impact, do not require special monitoring, except in potentially higher risk patients (resting bradycardia, history of bradyarrhythmias, concomitant beta-blocker therapy, evidence of pre-existing AV conduction impairment).

### 6.4.5.2 Blood Pressure

In the Phase 3 clinical trials, blood pressure was measured after the patient had been in the sitting position for 5 minutes. The mean of 3 sitting measurements was used for analysis and reporting. Summary statistics of vital signs by visit showed small mean increases in systolic, diastolic and mean arterial blood pressure in the fingolimod dose groups. This effect was less pronounced with the fingolimod 0.5 mg dose compared to 1.25 mg and was evident by Month 2 without much subsequent change with chronic dosing. At Month 24, the mean increase from baseline in mean arterial blood pressure was 2.6 mmHg for the fingolimod 1.25 mg group, 1.1 mmHg for the fingolimod 0.5 mg group, and -0.5 mmHg for the placebo group. For systolic (diastolic) blood pressure, the mean increases at the Month 24 visit were 3.6 mmHg (2.1 mmHg) for the fingolimod 1.25 mg group, 1.9 mmHg (0.7 mmHg) for the fingolimod 0.5 mg group, and -0.4 mmHg (-0.5 mmHg) for the placebo group.

Notably high or notable increases in systolic or diastolic blood pressure, measured on at least one occasion at any visit during the study, were more frequently observed in the fingolimod groups in the 2-year placebo-controlled study, with some suggestion of a dose-response (Table 6-13).

**Table 6-13 Number (%) of patients with clinically notable BP values (2-year Study)**

| | Criterion | FTY720 1.25mg N=429 n (%) | FTY720 0.5mg N=425 n (%) | Placebo N=418 n (%) |
|---|---|---|---|---|
| Sitting systolic BP (mmHg) | Low: ≤90 | 23 (5.4) | 26 (6.1) | 39 (9.3) |
| | ≥20 decrease from baseline | 76 (17.7) | 79 (18.6) | 94 (22.5) |
| | High: ≥180 | 1 (0.2) | 0 | 0 |
| | ≥160 | 19 (4.4) | 8 (1.9) | 6 (1.4) |
| | ≥20 increase from baseline | 112 (26.1) | 92 (21.6) | 76 (18.2) |
| Sitting diastolic BP (mmHg) | Low: ≤50 | 9 (2.1) | 6 (1.4) | 11 (2.6) |
| | ≥15 decrease from baseline | 70 (16.3) | 76 (17.9) | 98 (23.4) |
| | High: ≥105 | 13 (3.0) | 16 (3.8) | 6 (1.4) |
| | ≥100 | 29 (6.8) | 31 (7.3) | 17 (4.1) |
| | ≥15 increase from baseline | 113 (26.3) | 93 (21.9) | 84 (20.1) |

Rates of hypertension AEs were higher in the fingolimod groups compared to controls. In the 2-year placebo-controlled study, hypertension was reported as an AE in 6.3% and 6.1% of patients in the fingolimod 1.25 mg and 0.5 mg groups respectively, compared with 3.8% of patients in the placebo group. Two cases of “hypertensive crisis” were reported as AEs in the fingolimod 1.25 mg group (study D2302). However, neither patient presented with symptoms or signs suggestive of target-organ damage and neither discontinued study drug due to this event.

At present it is not possible to definitively explain why blood pressure is increased on fingolimod treatment. However, pre-clinical pharmacological data indicate that S1P acts as both a constrictor and a dilator via actions on smooth muscle cells (SMC) and endothelial cells (EC), respectively, to maintain vascular homeostasis (Brinkmann 2007).

#### 6.4.5.3 Eye

Adverse ocular effects were not observed with fingolimod in pre-clinical toxicology studies. However, in the renal transplant studies, fingolimod-treatment at 2.5 mg and 5 mg was associated with a two-fold increase in risk for macular edema (ME) compared to control. The mechanism for the development of ME in patients receiving fingolimod is not fully explained. However, it is known that S1P and its receptors $S1P_1$ and $S1P_3$ play a key role in the regulation of endothelial and epithelial barriers (Brinkmann 2007). The cellular components of the blood retinal barrier (BRB-endothelial cells, epithelial cells, astrocytes) express S1P receptors and these receptors tightly control endothelial and epithelial barriers. The BRB contains both tight junctions (TJ) and adherens junctions (AJ) between its cellular compartments. Pharmacological activation of S1P receptors on the BRB may at the same time increase/protect AJ between cells (via $S1P_1$ receptor agonism), thereby strengthening the barrier, but may also reduce TJ between the cellular components (via $S1P_3$ receptor agonism), thereby reducing barrier function. A reduction of TJ via S1P receptors may lead to macular edema and be of particular concern in cases of previous damage, such as in diabetic retinopathy.

Given the finding of ME in renal transplantation studies, all patients underwent extensive ophthalmic monitoring in the MS clinical program including visual acuity, dilated fundoscopy, and Optical Coherence Tomography (OCT) to determine central foveal thickness (CFT).

Macular edema was reported by the local ophthalmologist in 0.9% of patients (23/2615) in the All Studies Group. The retinal expert on the Data and Safety Monitoring Board (DSMB) reviewed all data on suspected macular edema cases and confirmed the diagnosis of macular edema in 16 cases in the All Studies Group; 14 (1.1%) in the fingolimod 1.25 mg dose group and 2 (0.2%) in the fingolimod 0.5 mg dose group. Most patients (n=12, 75%) with macular edema presented with visual symptoms (blurred vision or decreased visual acuity), while the remainder (n=4, 25%) were asymptomatic and diagnosed on a scheduled ophthalmologic examination. Twelve (75%) cases were diagnosed within 3-4 months of the patient commencing therapy with fingolimod. Of the 4 cases diagnosed later, 1 patient receiving fingolimod 0.5 mg had an alternate cause of macular edema (retinal branch vein occlusion associated with a long-standing history of hypertension diagnosed more than 10 years prior to study entry). Of the remaining 3 cases with later onset of macular edema (all on fingolimod 1.25 mg) 2 had a past history of uveitis. Macular edema improved or resolved after drug discontinuation, and there were no reports of further deterioration in vision after stopping study drug. Visual acuity was comparable across treatment groups and remained stable throughout the study. There were no observed differences due to gender or age.

In the ongoing Phase 3 study D2309 (not included in the All Studies Group because it is an ongoing study), macular edema was confirmed in 4 (1.1%) patients on fingolimod 1.25 mg, 3 (0.9%) patients on fingolimod 0.5 mg and 1 (0.3%) patient on placebo. Combining the

D2309 data with that from the All Studies Group gives a total of 18 cases (1.1%) of confirmed macular edema in patients receiving fingolimod 1.25 mg, five cases (0.3%) on fingolimod 0.5 mg, and one case (0.1%) on placebo.

A history of uveitis appears to be a risk factor for the occurrence of macular edema. Four of the 16 patients (25%) with confirmed macular edema in the All Studies Group had a medical history of uveitis, whereas only 1% (26/2615) of all patients in that Group had a history of uveitis.

Likewise, diabetes is a known risk factor for macular edema, and in the renal transplant program, fingolimod-treated patients had twice the incidence of macular edema both in non-diabetics (4% vs. 2%) and diabetics (30% vs. 15%). Because of this potential confounder, patients with diabetes mellitus were excluded from the MS studies and therefore, data do not exist on the risk of macular edema in diabetic MS patients who receive fingolimod.

### OCT

The mean Central Foveal Thickness (CFT) at baseline in the 2-year placebo-controlled study D2301 was 169 µm. Macular edema usually is associated with CFT of >300 µm. In study D2301, a small increase in mean CFT was seen in the fingolimod groups compared to placebo (5.5 µm for 1.25 mg, 4.1 µm for 0.5 mg vs. 0.9 µm for placebo). Changes of >40 µm also occurred more frequently in the fingolimod groups (8.7% and 6.4% for 1.25 mg and 0.5 mg, respectively) compared to placebo (4.9%).

Frequent, serial OCT measurements of CFT were performed in a total of 1059 patients from Study D2309: 359 on fingolimod 1.25 mg, 350 on fingolimod 0.5 mg and 350 on placebo. The numbers of eyes evaluated for CFT changes from baseline to Months 1 and 12, respectively, were 464 and 392 for fingolimod 1.25 mg, 434 and 388 for fingolimod 0.5 mg, 426 and 384 for placebo. Group descriptive statistics evaluating central tendency in the entire population revealed a very small, possibly dose-dependent effect of fingolimod on CFT. Absolute mean/median CFT changes from baseline to month 1 were 2.24/2.0 µm for fingolimod 1.25 mg, 0.81/0.0 µm for fingolimod 0.5 mg, -0.89/-1.0 µm for placebo; and from baseline to month 12: 4.90/4.0 µm for fingolimod 1.25 mg, 4.63/2.0 µm for fingolimod 0.5 mg, 2.25/0.0 µm for placebo.

The percentage of eyes with CFT changes from baseline >40 µm at month 1 was 4.1%, 3.5% and 2.6% in the fingolimod 1.25 mg, 0.5 mg and placebo groups, respectively. At month 12, the respective percentages of eyes with this CFT change were 6.9%, 8.5% and 6.5%. Absolute CFT >300 µm was observed in a few more patients on fingolimod 1.25 mg or 0.5 mg than on placebo at month 1 (3 vs 3 vs 1 patient) and month 3 (3 vs 1 vs 1 patient).

## 6.4.5.4 Liver

Animal toxicology studies did not provide a signal for liver toxicity, showing only inconsistent and mild liver findings at high dose levels at exposures (based on AUC) more than 50-fold compared to that in patients.

In the MS clinical studies, generally asymptomatic elevation in serum levels of hepatic transaminases (mainly ALT and GGT) was reported at all fingolimod doses with a tendency for a higher rate in the 1.25 mg group. The frequency distribution for abnormal liver function

tests relative to normal ranges at any post-baseline visit are presented for the 2-year Study in Table 6-14. Liver transaminase elevations were seen in a greater proportion of patients on fingolimod than on placebo and were slightly higher for fingolimod 1.25 mg than for the 0.5 mg dose. In patients who experienced ALT elevations ≥3×upper limit of the normal range (ULN), the majority of events were seen within 3-4 months of commencing therapy.

**Table 6-14 Frequency (%) distribution of liver function tests for the 2-year Study**

| Parameters | Criterion | FTY720D 1.25 mg (N=429) n % | FTY720D 0.5 mg (N=425) n % | Placebo (N=418) n % |
|---|---|---|---|---|
| **Patients contributing data n** | | **425** | **424** | **414** |
| **ALT** | No abnormalities | 226 (53.2) | 214 (50.5) | 314 (75.8) |
| | > 1 × ULN | 199 (46.8) | 210 (49.5) | 100 (24.2) |
| | ≥ 2 × ULN | 88 (20.7) | 80 (18.9) | 23 (5.6) |
| | ≥ 3 × ULN | 53 (12.5) | 36 (8.5) | 7 (1.7) |
| | ≥ 5 × ULN | 13 (3.1) | 8 (1.9) | 4 (1.0) |
| | ≥ 10 × ULN | 0 | 1 (0.2) | 0 |
| **AST** | No abnormalities | 292 (68.7) | 299 (70.5) | 369 (89.1) |
| | > 1 × ULN | 133 (31.3) | 125 (29.5) | 45 (10.9) |
| | ≥ 2 × ULN | 30 (7.1) | 14 (3.3) | 8 (1.9) |
| | ≥ 3 × ULN | 6 (1.4) | 8 (1.9) | 5 (1.2) |
| | ≥ 5 × ULN | 1 (0.2) | 2 (0.5) | 1 (0.2) |
| **GGT** | No abnormalities | 267 (62.8) | 273 (64.4) | 378 (91.3) |
| | > 1 × ULN | 158 (37.2) | 151 (35.6) | 36 (8.7) |
| | ≥ 2 × ULN | 81 (19.1) | 70 (16.5) | 10 (2.4) |
| | ≥ 3 × ULN | 44 (10.4) | 29 (6.8) | 3 (0.7) |
| | ≥ 5 × ULN | 11 (2.6) | 6 (1.4) | 0 (0.0) |
| | ≥ 10 × ULN | 0 | 1 (0.2) | 0 |
| | ≥ 20 × ULN | 0 | 1 (0.2) | 0 |
| **Total bilirubin** | No abnormalities | 383 (90.1) | 377 (88.9) | 375 (90.6) |
| | > 1 × ULN | 42 (9.9) | 47 (11.1) | 39 (9.4) |
| | ≥ 2 × ULN | 4 (0.9) | 3 (0.7) | 3 (0.7) |

Abbreviations: ALT=alanine aminotransferase; AST= aspartate aminotransferase;and GGT=gamma-glutamyl transferase

ULN categories are not mutually exclusive. If a patients value is ≥ 20 × ULN, it is also included in the ≥ 10 × ULN category and all the ULN categories above it.

A similar pattern was seen in the All Studies Group where ALT elevations ≥3×ULN were observed in 11.7% of patients on fingolimod 1.25 mg and in 8.0% on fingolimod 0.5 mg. In the All Studies Group, a total of 49 patients treated with fingolimod 1.25 mg (n=32) or 0.5 mg (n=17) had ALT values ≥ 5×ULN during or immediately following treatment. A total of 37 patients (22 in the 1.25 mg group and 15 in the 0.5 mg group) discontinued study drug. After the discontinuation of fingolimod treatment, ALT levels returned to normal or almost normal (>ULN but <2-fold ULN) in most patients within 5 months. The median time to recovery was 57 days in the 1.25 mg group and 64 days in the 0.5 mg group. The remaining

12 patients (10 on 1.25 mg and 2 on 0.5 mg) who did not discontinue fingolimod treatment in spite of ALT values ≥5×ULN, all showed a recovery to normal or almost normal levels on fingolimod treatment, the majority (10/12 patients) within 5 months.

Liver enzyme elevation (particularly ALT elevation) was also the most common event leading to study drug discontinuation. However, it must be kept in mind that elevation to ≥5×ULN, or recurrent elevation to ≥3×ULN were criteria for drug discontinuation, regardless of the presence or absence of symptoms. The proportion of fingolimod-treated patients who experienced ALT elevation leading to study drug discontinuation was 3.7% for fingolimod 1.25 mg and 2.8% for fingolimod 0.5 compared to 0.7% placebo in the 2-year study.

An unexplained finding was the substantial gender difference for liver enzyme elevation, being 3 to 4 times as common in men as in women.

In the All Studies Group, five patients met the biochemical criteria for Hy's law, three on the basis of measurements at the central laboratory and two on the basis of unscheduled evaluations at a local laboratory. Two of the patients who met the criteria on the basis of measurements at the central laboratory had elevated bilirubin at baseline due to Gilbert´s syndrome (a hereditary cause of increased bilirubin). Their liver transaminase elevations were reversible and neither patient was symptomatic. Of these two patients, one continued on fingolimod therapy.

The third patient had previously experienced 5-fold elevation of ALT within 2 months of commencing fingolimod 1.25 mg and drug was discontinued. Approximately 7 months later when liver enzymes were normal, drug was restarted and ALT increased modestly (2-fold), where it remained for the next 10 months. Less than one month after reducing the dose to 0.5 mg (as part of global decision to drop the 1.25 mg dose), he presented (in mid-April 2010) with acute hepatitis associated with jaundice. Maximum ALT level was 2787 U/L (ULN 45) and maximum serum bilirubin was 194 µmol/L (ULN 21). No specific therapy was initiated and within 12 days of discontinuing fingolimod, ALT had decreased to 318 U/L and serum bilirubin to 60 µmol/L. As of early-May 2010, the patient had improved clinically and was being further investigated as an out-patient.

Two further patients also satisfied Hy's law based on local laboratory results, one each in the fingolimod 0.5 mg and placebo groups. The patient in the placebo group was noted to have liver transaminase elevations, in the context of marked dehydration with hypovolemia, 5 days after discontinuing placebo treatment. The patient on fingolimod had been treated for approximately 10 months at the time of the event. This patient, who had been receiving intravenous and oral acetaminophen for several days, experienced significant liver transaminase elevations (aspartate aminotransferase (AST) 9580 U/L; ALT 4332 U/L; serum bilirubin 2.07 mg/dL). These abnormalities started to decrease (more than 10-fold reduction in AST) while still on fingolimod treatment and had resolved within 17 days of stopping therapy, a time when, based on drug half-life, fingolimod would still be detectable in blood. The patient in the placebo group was noted to have liver transaminase elevations 5 days after discontinuing placebo treatment.

#### 6.4.5.5 Vascular

Repeat dose toxicity studies in mice, Sprague-Dawley rats, Wistar rats, dogs and monkeys showed generalized vasculopathy only in Wistar rats (in a life-time assay findings were seen

at doses ≥0.15 mg/kg, i.e. approximately 3.5-fold higher exposure, based on systemic exposure (area under curve, AUC), compared to exposure in patients treated with fingolimod doses of 0.5 mg/day). In dogs, fingolimod-related changes were seen exclusively in the heart (vascular wall thickening and perivascular and focal perimysial fibrosis of the left ventricular papilla in the heart) and were not associated with an inflammatory component. Hemodynamic and immunomodulatory effects of fingolimod and an increased susceptibility of Wistar rats to develop vascular lesions may have contributed to the lesions in comparison to Sprague-Dawley rats. In contrast, hemodynamic effects alone may have led to the development of the lesions seen in the heart of dogs.

In the renal transplantation program, the proportion of patients who experienced ischemic or hemorrhagic cerebrovascular accidents was 1.4% with fingolimod compared to 0.7% in the control group in the overall safety population. The prevalence of cerebrovascular accidents is increased in renal transplant patients compared to the general population and they are the most common neurological problems seen in renal transplant recipients (Adams et al 1986).

The incidence of severe vascular events in the MS program is low. A total of 5 strokes have been reported: two of these occurred while patients were not on study drug (one stroke during the screening period prior to randomization and a transient ischemic attack which occurred 8 months following discontinuation of fingolimod 1.25 mg). The other 3 strokes occurred in patients treated with fingolimod 1.25 mg. Three cases of acute myocardial infarction were reported: 2 cases on placebo and 1 on IFN β-1a. Two peripheral vascular occlusive events were reported in patients treated with fingolimod 1.25 mg. A single case of posterior reversible encephalopathy syndrome (PRES) was reported in a patient treated with the fingolimod 5.0 mg dose. No specific causal mechanism is apparent and the relationship of these events to fingolimod remains uncertain. Longer periods of observation in larger patient numbers, for example in the post-approval safety study will be needed to help clarify this issue.

#### 6.4.5.6 Infections

In the renal transplant program, the rate of infections overall was comparable across the fingolimod and control groups.

Because the immune system effects of fingolimod may increase the risk of infections, particular attention was paid to this potential complication in the clinical trials. In the 2-year placebo controlled study, the rate of infections overall (Table 6-15) was similar in patients treated with fingolimod 1.25 mg (68.5%), fingolimod 0.5 mg (71.5%) or placebo (72%). However, a slight dose-dependent increased risk of lower respiratory tract infections (mainly bronchitis, seven cases of pneumonia on fingolimod 1.25 mg, two on fingolimod 0.5 mg and one on placebo)was noted with fingolimod (11.4%, 9.6% and 6.0% in the fingolimod 1.25 mg, 0.5 mg and placebo groups respectively).

**Table 6-15 Number (%) of patients with infections and infestations AEs in the 2-year Study**

| Infections and infestations System Organ Class | FTY720 1.25mg N=429 n (%) | FTY720 0.5mg N=425 n (%) | Placebo N=418 n (%) |
|---|---|---|---|
| **Total** | 294 (68.5) | 304 (71.5) | 301 (72.0) |
| Influenza viral infections | 40 (9.3) | 55 (12.9) | 41 (9.8) |
| Herpes viral infections | 25 (5.8) | 37 (8.7) | 33 (7.9) |
| Viral infections NEC | 20 (4.7) | 24 (5.6) | 23 (5.5) |
| Upper respiratory tract infections | 206 (48.0) | 212 (49.9) | 211 (50.5) |
| Lower respiratory tract and lung infections | 49 (11.4) | 41 (9.6) | 25 (6.0) |
| Urinary tract infections | 33 (7.7) | 47 (11.1) | 65 (15.6) |
| Abdominal and gastrointestinal infections | 22 (5.1) | 25 (5.9) | 19 (4.5) |

For herpes infections, there was no consistent pattern (i.e. lowest for 1.25 mg, highest for 0.5 mg and placebo in the middle) that would suggest an increased rate of infections in the fingolimod groups compared to placebo. Two fatal herpes virus infections were reported in patients treated with fingolimod 1.25 mg: herpes simplex encephalitis in a patient in whom initiation of acyclovir therapy was delayed by one week, and fulminant primary varicella infection with hepatitis in a sero-negative patient receiving concomitant high dose steroid therapy for a MS relapse. One additional case of note was a patient with disseminated herpes zoster with pulmonary involvement treated with fingolimod 1.25 mg who made a complete recovery after treatment with acyclovir therapy. Opportunistic infections (e.g. systemic fungal or protozoal infections) were not reported. The overall incidence of infections in the All Studies Group was similar to that in the 2-year Study group and did not indicate a difference between the two doses.

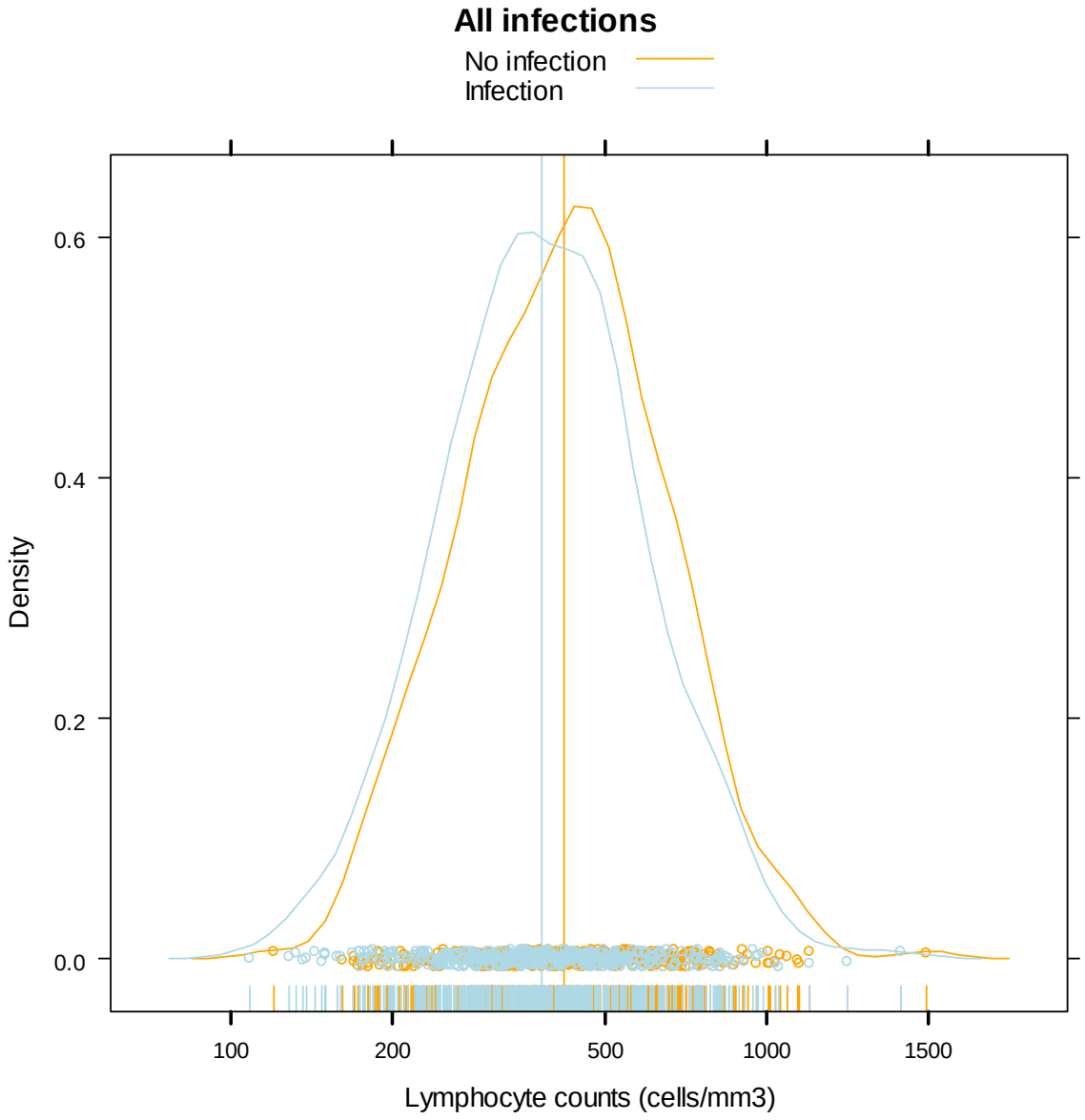
Analyses of the relationship of nadir blood lymphocyte counts and occurrence of infections in the 2-year Study D2301 (Table 6-16) has shown that the proportion of patients with infections for the group with the lowest lymphocyte counts ($<0.2\times10^9$/L) was marginally increased (75.7%) relative to placebo (72.0%). However, the incidence was increased in the low lymphocyte group relative to fingolimod-treated patients with blood lymphocyte counts above $0.4\times10^9$/ (57.7%). This finding of the lower rate of infection (57.7%) in the fingolimod group with blood lymphocyte counts above $0.4\times10^9$/L is unexplained.

**Table 6-16 Number (%) of patients with infections and infestations AEs by organ-related high level term and nadir lymphocyte count at any time on treatment in 2-year Study in >2% of subjects in any group**

| | FTY720 groups combined | | | |
|---|---|---|---|---|
| **Organ-related high-level term** | **<0.2 × $10^9$/L N=206 n (%)** | **0.2-0.4 × $10^9$/L N=475 n (%)** | **>0.4 × $10^9$/L N=168 n (%)** | **Placebo (N=418) n (%)** |
| **Any high-level term** | 156 (75.7) | 344 (72.4) | 97 (57.7) | **301 (72.0)** |
| Upper respiratory tract infections | 114 (55.3) | 254 (53.5) | 50 (29.8) | 211 (50.5) |
| Lower respiratory tract and lung infections | 25 (12.1) | 53 (11.2) | 12 (7.1) | 25 (6.0) |
| Urinary tract infections | 20 (9.7) | 47 (9.9) | 12 (7.1) | 65 (15.6) |
| Abdominal and gastrointestinal infections | 11 (5.3) | 31 (6.5) | 5 (3.0) | 19 (4.5) |
| Infections NEC | 11 (5.3) | 22 (4.6) | 6 (3.6) | 18 (4.3) |
| Dental and oral soft tissue infections | 8 (3.9) | 17 (3.6) | 0 | 9 (2.2) |
| Ear infections | 5 (2.4) | 15 (3.2) | 1 (0.6) | 4 (1.0) |
| Female reproductive tract infections | 4 (1.9) | 5 (1.1) | 4 (2.4) | 8 (1.9) |
| Skin structures and soft tissue infections | 4 (1.9) | 15 (3.2) | 3 (1.8) | 8 (1.9) |

If one plots infections by lymphocyte count, it is apparent that low lymphocyte counts per se were not predictive of infection, including serious infection, nor were higher counts protective (Figure 6-1). The density curves show a slight shift to lower lymphocyte counts for those with infections compared to those without, but there is considerable overlap.

**Figure 6-1** **Distribution of mean lymphocyte count (month 1 to month 12 or end of study value) in patients with or without infections**




### 6.4.5.7 Neoplasms

Fingolimod does not have mutagenic or clastogenic potential. Pre-clinical data from an animal model pre-disposed to lymphoma, revealed an increase incidence of lymphoma in mice treated with fingolimod but otherwise did not suggest an increased risk for malignancy. In the renal transplant program, the rate of malignancies was comparable across the fingolimod and control groups. Following reports of skin malignancies in the MS Phase 2 study D2201E1, active screening for skin cancers with annual examinations by a dermatologist were implemented in all ongoing studies (including D2301 and D2302). As this screening was implemented after study start, no pre-study assessments were available in Phase 3 to

determine whether newly detected lesions had developed on-study or were present prior to initiation of study medication. Regardless, the point estimates for incidence are low in all groups (Table 6-17) with overlapping CIs.

**Table 6-17 Incidence of skin cancers in studies D2301 and D2302**

| Skin cancer | FTY720D 1.25mg N = 849 n (%) | FTY720D 0.5mg N = 854 n (%) | Placebo N = 418 n (%) | IFN β 1a N = 431 n (%) |
|---|---|---|---|---|
| Basal cell carcinoma | 3 (0.4%) | 7 (0.8%) | 3 (0.7%) | 1 (0.2%) |
| (95% CI) | (0.07%, 1.03%) | (0.33%, 1.68%) | (0.15%, 2.08%) | (0.01%, 1.29%) |
| Squamous cell cancer (including Bowen's dis.) | 1 (0.1%) | 0 | 0 | 1 (0.2%) |
| (95% CI) | (0, 0.65%) | (0, 0.43%) | (0, 0.88%) | (0.01%, 1.29%) |
| Malignant melanoma (including in-situ) | 1 (0.1%) | 3 (0.4%) | 1 (0.2%) | 0 |
| (95% CI) | (0, 0.65%) | (0.07%, 1.02%) | (0.01%, 1.33%) | (0, 0.85%) |

In addition, in study D2201 and its extension, a total of 9 skin malignancies, including 3 cases of melanoma have been reported. However, the absence of a control group impedes an assessment of relationship to drug.

Although a hypothetical mechanism for fingolimod to be associated with skin malignancies would be related to reduced immunosurveillance, the available data do not suggest such a relationship. However, the number of events to date, and the duration of follow-up, are relatively limited and do not permit conclusions on any potential long-term risk.

There is likewise no evidence of an increased risk of non-skin malignancies in patients treated with fingolimod. The incidence of malignancies in the 2-year placebo controlled study was similar in all three treatment groups (Table 6-18) and no change in incidence was seen in the All Studies group.

**Table 6-18 Number (%) of patients with malignant neoplasms in the 2-year Study**

| Preferred term | FTY720 1.25mg N=429 n (%) | FTY720 0.5mg N=425 n (%) | Placebo N=418 n (%) |
|---|---|---|---|
| Total Neoplasms (malignant) | 4 (0.9) | 4 (0.9) | 11 (2.6) |
| Basal cell carcinoma | 1 (0.2) | 4 (0.9) | 3 (0.7) |
| Bowen's disease | 1 (0.2) | 0 | 0 |
| Breast cancer | 1 (0.2) | 0 | 3 (0.7) |
| Malignant melanoma | 1 (0.2) | 0 | 1 (0.2) |
| Cervix carcinoma stage 0 | 0 | 0 | 1 (0.2) |
| Endometrial cancer | 0 | 0 | 1 (0.2) |
| Ovarian adenoma | 0 | 0 | 1 (0.2) |
| Prostate cancer | 0 | 0 | 1 (0.2) |

In study D2201E1, single cases of metastatic ovarian cancer and thyroid cancer were reported in patients in the fingolimod 5.0 mg–1.25 mg group but again, a lack of control group prevents drawing conclusions on causality. Overall there is no evidence of an increased risk of malignancies in patients treated with fingolimod.

### 6.4.5.8 Nervous system

Data from non-clinical studies do not suggest CNS toxicity with fingolimod, with only sporadic CNS findings in studies at high oral doses (≥10 mg/kg). In the 2-year Study headache occurred at a slightly higher incidence in the fingolimod treatment groups (26.6% and 25.2% for the 1.25 mg and 0.5 mg groups respectively) than in the placebo group (23%). A similar pattern, but at a much lower frequency, was found for migraine headaches (3.5-4.7% for fingolimod compared to 1.4% for placebo). There was no clear difference across the groups in any other individual nervous system preferred term.

A higher percentage of renal transplant patients who received fingolimod (1.9%) experienced seizures compared with patients in the control group (0.4%). These events occurred mainly in the first month following surgery, such that a relationship to fingolimod was uncertain. In the MS studies, epilepsy (various preferred terms) occurred in 10 patients in all controlled studies, providing incidence rates (per 100 pt-yr) of 2.3 for 5.0 mg patients, 1.2 for 1.25 mg group, 0.3 for 0.5 mg group and 0.1 for placebo. In the All Studies Group, seizures were reported in 14 patients (0.5%) in total, of whom 3 (2.2%) were in the fingolimod 5.0 – 1.25 mg group, 8 (0.6%) on 1.25 mg and 3 (0.3%) on 0.5 mg. Several of these events had reasons other than fingolimod as plausible explanations, including other medical illnesses, prior history of seizures and seizure occurrence in the setting of an MS relapse. The rate of convulsions for the target dose of 0.5 mg does not appear at variance with that of placebo, although numbers are too small to make definitive conclusions.

Eight relapses were reported as SAEs in the 2-year Study: one (0.2%) in the placebo group, three (0.7%) in the fingolimod 1.25 mg group, and four (0.9%) in the FTY720 0.5 mg group. In the fingolimod groups, four patients were on therapy at relapse onset and three had stopped therapy 1–5 months prior to the relapse. The symptoms observed were generally typical of MS relapses. The data on such relapses is scant, and no conclusions can be drawn regarding whether some relapses are potentially more severe with fingolimod therapy. The overall

number of severe relapses was reduced by treatment with fingolimod to a comparable degree as for relapses in general (i.e. >50% relative reduction compared to placebo).

### 6.4.5.9 Respiratory

#### Adverse Events

Extensive pulmonary testing was included in all clinical studies. Pre-clinical data suggest a direct constrictor effect of S1P on airway smooth muscle, but a release of constrictor molecules from $S1P_1/S1P_3$-activated endothelium is also not excluded. In toxicological studies, there were no morphological changes in bronchi, either at the level of smooth muscle or epithelium, on long-term treatment with fingolimod up to exposure multiples of ≥100 compared to the fingolimod 0.5 mg dose. Minimal to mild smooth muscle cell hypertrophy (SMH) was observed in the terminal bronchioli in rats and monkeys without any sign of progression for up to 1 year in monkeys and 2 years in rats. The SMH showed a clear trend to reversibility after drug discontinuation.

In Clinical Pharmacology and early transplant studies in man, fingolimod was shown to induce a mild, dose-dependent increase in airway resistance (reduction in $FEV_1$) upon treatment initiation (most pronounced at or above the 5.0 mg dose, 10-fold the proposed clinical dose for MS), with no evidence for further progression with chronic treatment. In patients receiving 5.0 mg dosing in the Phase 2 MS clinical program (for which only 6-month control data was available) and comparing with available 6-month data from other studies, respiratory AEs (mainly dyspnea) at 6 months were more than twice as common with the 5.0 mg dose (33%) compared to the lower fingolimod doses (13-15%) or to placebo (14%).

With longer observation in Phase 3 (i.e. 4-fold longer in the 2-year Study) there was no significant difference in respiratory AEs between fingolimod patients (24%, 25%) and placebo (23%). Cough and dyspnea, the most common preferred terms, followed a similar pattern as for overall respiratory AEs. In the small number of patients (approximately 3%) with a history of asthma, there was no increase in the overall number of respiratory AEs associated with fingolimod.

#### Pulmonary Function Testing

In all studies in the MS program extensive pulmonary function (PFT) testing, including $FEV_1$, FVC, and carbon monoxide diffusing capacity ($D_LCO$), was performed at screening and during the study. Data from these tests support the clinical findings above. In summary, minor dose-dependent reductions in $FEV_1$ and $D_LCO$ values were observed with fingolimod treatment starting at Month 1 and remaining stable thereafter. In the 2-year Study, the reduction from baseline values in percent of predicted $FEV_1$ was 5.3% and 3.1% for fingolimod 1.25 mg and 0.5 mg, respectively vs. 2.0% for placebo. For $D_LCO$ the reductions at Month 24 were 7.3% and 3.8% for the two fingolimod groups and 2.7% for placebo. Changes in FVC on chronic dosing were infrequent and not dose-dependent. The majority of patients presenting changes in PFTs at a visit were not confirmed at a second consecutive visit, suggesting that these changes were transient, reversible or not related to study drug. Patients with asthma were not at a higher risk of respiratory AEs, and no further changes in PFTs were seen in patients with a history of asthma. The All Studies Group follow-up

population showed that any changes in PFTs observed during the study resolved within 3 months after treatment cessation.

### High Resolution Chest CT Scanning

Chest HRCT was performed in subsets of patients in studies D2301 (at screening and Month 24) and D2302 (at screening and Month 12), and in ongoing study D2309 (at screening and Month 24). Chest HRCT was also required by the protocols in the event of pre-defined PFT decreases (unscheduled HRCTs).

The percentage of patients showing new or worsening abnormalities compared to baseline was marginally higher in the fingolimod groups than placebo at Month 24. In study D2302, the proportion of patients with chest HRCTs showing new or worsening abnormalities compared to baseline was similar across groups at each visit. There were no reports indicative of drug-induced lung fibrosis in the completed studies (D2301, D2302).

In the ongoing D2309 study, HRCT of the chest was performed in a total of 409 patients: 132 on fingolimod 1.25 mg, 133 on fingolimod 0.5 mg and 144 on placebo. In the analysis set submitted with the 120 Day Safety Update, 249 patients (80 on fingolimod 1.25 mg, 87 on fingolimod 0.5 mg, 82 on placebo) had chest HRCT at the end of the study having completed 24 months of treatment with study drug. None of the radiological findings assessed by the local radiologist were indicative of pulmonary fibrosis.

### Conclusion

Signals that were raised based on pre-clinical and early clinical data were not borne out with larger studies involving lower doses of fingolimod, suggesting a clear dose-effect that has been mitigated with lower doses.

## 6.4.6 Deaths and other serious or clinically significant adverse events

### 6.4.6.1 Deaths

As of 29-Jan-10, including ongoing studies, 14 deaths occurred in the MS program (Table 6-19). Two occurred in placebo patients, two prior to randomization, one which is still dose-blinded and nine deaths in patients exposed to fingolimod – seven on 1.25 mg and one each on the 5.0 mg and 0.5 mg doses. Four of the deaths occurred while still on therapy or having recently discontinued fingolimod. The other five occurred between 2 months and 3 years after drug discontinuation.

Due to the small number of deaths, and the heterogeneity of events leading to death, no assessment can be made regarding any difference between treatment groups in incidence rate, nor the relation to duration of therapy, demographic factors or use of concomitant medication.

**Table 6-19 Deaths in all MS studies, completed and ongoing as of 29-Jan-10**

| PID | Age & gender | Tmt group | Duration of exposure<br>Time since last exposure until patient died | Cause: Preferred term (completed studies) or investigator term (ongoing studies) |
|---|---|---|---|---|
| [D2201E1-0029-00007] | 55 F | Fingolimod 5 mg | 271 days<br>1013 days after last dose | Ovarian adenocarcinoma – initial diagnosis 5 months after stopping study drug |
| [D2301-0708-00011] | 53 M | Fingolimod 1.25 mg | 539 days<br>0 days after last dose | Depression, Suicide |
| [D2302-0212-00021] | 29 F | Fingolimod 1.25 mg | 317 days<br>3 days after last dose | Herpes zoster disseminated |
| [D2302-0821-00007] | 23 M | Fingolimod 1.25 mg | 339 days<br>68 days after last dose | Herpes simplex Encephalitis |
| [D2302-0254-00011] | 42 M | Fingolimod 1.25 mg | Approximately 11 months<br>187 days after last dose | Aspiration pneumonia, acute disseminated encephalomyelitis, lower respiratory tract infection |
| [D2302-0331-00011] | 53 F | Fingolimod 1.25 mg | 11 months<br>305 days after last dose | Breast cancer metastatic |
| [D2201E1-0003-00016] | 35 F | Fingolimod 1.25 mg | 638 days<br>0 days after last dose | Road traffic accident |
| [D2301-0304-00045] | 52 M | Placebo | 651 days<br>6 days after last dose | Pulmonary embolism |
| [D2301-0702-00005] | 37 F | Placebo | 307 days<br>58 days after last dose | Road traffic accident |
| [D2306-0362-00005] | 46 M | Fingolimod 1.25 mg | 103 days<br>0 days after last dose | Rapidly deteriorating MS |
| [D1201E1-0005-00001] | 42 M | Fingolimod 0.5 mg | Died 371 days after last dose<br>Possible malignancy diagnosed 6 months after stopping study drug | Cause unknown. Possible “Malignant kidney and lung tumor, cutaneous T-cell lymphoma, Brain tumor”. Also developed aspiration pneumonia, herpes zoster |
| [D2309-0507-00028] | 55 F | Blinded | 204 days<br>65 days after last dose | Aortic dissection |
| [D1201-0106-00005] | 35 F | – | Died in the screening period, (prior to receiving any study drug) | Sudden death at home |
| [D2306-0461-00006] | 54 M | – | Died in the screening period, (prior to receiving any study drug) | Suicide |

### 6.4.6.2 Serious adverse events

Across the studies, SAEs were reported from the time the patient provided informed consent until up to 3 months after the patient stopped participating in the study. Using all controlled study data, provided rates of non-fatal SAEs for the 5.0 mg, 1.25 mg, 0.5 mg, placebo and IFN β-1a groups of 8.5%, 10.6%, 8.5%, 11.9% and 5.8% respectively.

SAEs occurring in at least two patients in any treatment group in the 2-year Study are presented by primary system organ class, preferred term, and treatment group in Table 6-20.

**Table 6-20 Number (%) of patients with SAEs by primary system organ class (at least 2 patients in any treatment group) and preferred term in the 2-year Study**

| Primary system organ class<br>Preferred term | FTY720D 1.25 mg N=429<br>n (%) | FTY720D 0.5 mg N=425<br>n (%) | Placebo N=418<br>n (%) |
|---|---|---|---|
| **Any serious adverse event** | **51 (11.9)** | **43 (10.1)** | **56 (13.4)** |
| **Infections and infestations** | **11 (2.6)** | **7 (1.6)** | **8 (1.9)** |
| Urinary tract infection | 0 | 2 (0.5) | 0 |
| **Nervous system disorders** | **11 (2.6)** | **10 (2.4)** | **4 (1.0)** |
| Multiple sclerosis relapse | 3 (0.7) | 2 (0.5) | 1 (0.2) |
| Epilepsy | 2 (0.5) | 0 | 0 |
| Headache | 2 (0.5) | 0 | 0 |
| Multiple sclerosis | 0 | 2 (0.5) | 0 |
| **Cardiac disorders** | **7 (1.6)** | **7 (1.6)** | **4 (1.0)** |
| Bradycardia | 3 (0.7) | 4 (0.9) | 1 (0.2) |
| Myocardial infarction | 0 | 0 | 2 (0.5) |
| **Eye disorders** | **6 (1.4)** | **1 (0.2)** | **1 (0.2)** |
| Macular edema | 3 (0.7) | 0 | 0 |
| **Investigations** | **6 (1.4)** | **3 (0.7)** | **1 (0.2)** |
| Liver function test abnormal | 2 (0.5) | 0 | 1 (0.2) |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | **5 (1.2)** | **5 (1.2)** | **11 (2.6)** |
| Basal cell carcinoma | 1 (0.2) | 4 (0.9) | 2 (0.5) |
| Breast cancer | 1 (0.2) | 0 | 3 (0.7) |
| **Gastrointestinal disorders** | **4 (0.9)** | **4 (0.9)** | **4 (1.0)** |
| **Musculoskeletal and connective tissue disorders** | **3 (0.7)** | **2 (0.5)** | **4 (1.0)** |
| Back pain | 0 | 2 (0.5) | 1 (0.2) |
| Intervertebral disc protrusion | 0 | 0 | 2 (0.5) |
| **Respiratory, thoracic and mediastinal disorders** | **3 (0.7)** | **2 (0.5)** | **3 (0.7)** |
| **Blood and lymphatic system disorders** | **2 (0.5)** | **1 (0.2)** | **0** |
| Lymphopenia | 2 (0.5) | 0 | 0 |
| **General disorders and administration site conditions** | **2 (0.5)** | **5 (1.2)** | **2 (0.5)** |
| Chest pain | 0 | 2 (0.5) | 0 |

| Primary system organ class<br>Preferred term | FTY720D 1.25 mg N=429 n (%) | FTY720D 0.5 mg N=425 n (%) | Placebo N=418 n (%) |
|---|---|---|---|
| Non-cardiac chest pain | 0 | 2 (0.5) | 2 (0.5) |
| **Psychiatric disorders** | **2 (0.5)** | **1 (0.2)** | **3 (0.7)** |
| Depression | 2 (0.5) | 0 | 1 (0.2) |
| **Injury, poisoning and procedural complications** | **1 (0.2)** | **3 (0.7)** | **6 (1.4)** |
| **Pregnancy, puerperium and perinatal conditions** | **0** | **0** | **4 (1.0)** |
| Abortion | 0 | 0 | 3 (0.7) |

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency for the FTY720D 1.25 mg group.
A patient with multiple SAEs within a primary system organ class is counted only once in the total row.
A patient with multiple occurrences of an AE under one treatment group is counted only once in the AE preferred term for that treatment group.

The overall proportion of patients with SAEs in the 2-year Study was highest in the placebo group, without evidence of substantial differences between groups.

Infection and infestation SAEs were reported slightly more commonly in the fingolimod 1.25 mg group compared to fingolimod 0.5 mg and placebo. The only infection SAE occurring in >1 patient in any treatment group was urinary tract infection (2 patients in the fingolimod 0.5 mg group). SAEs consistent with the mechanism of action or known safety profile of fingolimod (e.g. bradycardia, macular edema) were reported more commonly in the fingolimod treatment groups compared to placebo. Findings in the All Studies Group were consistent with the 2-year Study data with a dose effect becoming slightly more apparent for events (Table 6-21).

**Table 6-21 Number (%) of patients with SAEs (at least 2 patients in any dose group) by primary SOC and preferred term in Group E (FTY720-treated safety population)**

| Primary system organ class<br>Preferred term | FTY720 1.25 mg (N=1302) n (%) | FTY720 0.5 mg (N=1176) n (%) |
|---|---|---|
| **Any primary system organ class** | **170 (13.1)** | **111 ( 9.4)** |
| **Blood and lymphatic system disorders** | **7 ( 0.5)** | **3 ( 0.3)** |
| Lymphopenia | 5 ( 0.4) | 0 ( 0.0) |
| **Cardiac disorders** | **34 ( 2.6)** | **11 ( 0.9)** |
| Bradycardia | 16 ( 1.2) | 6 ( 0.5) |
| Atrioventricular block second degree | 7 ( 0.5) | 1 ( 0.1) |
| Atrioventricular block first degree | 4 ( 0.3) | 1 ( 0.1) |
| Palpitations | 4 ( 0.3) | 0 ( 0.0) |
| Angina pectoris | 2 ( 0.2) | 1 ( 0.1) |
| Sinus bradycardia | 2 ( 0.2) | 1 ( 0.1) |
| Supraventricular extrasystoles | 2 ( 0.2) | 0 ( 0.0) |
| **Ear and labyrinth disorders** | **3 ( 0.2)** | **1 ( 0.1)** |
| Vertigo | 3 ( 0.2) | 0 ( 0.0) |

| Primary system organ class<br>Preferred term | FTY720<br>1.25 mg<br>(N=1302)<br>n (%) | FTY720<br>0.5 mg<br>(N=1176)<br>n (%) |
|---|---|---|
| **Eye disorders** | **12 ( 0.9)** | **3 ( 0.3)** |
| Macular oedema | 9 ( 0.7) | 2 ( 0.2) |
| **Gastrointestinal disorders** | **13 ( 1.0)** | **5 ( 0.4)** |
| Constipation | 2 ( 0.2) | 0 ( 0.0) |
| **General disorders and administration site conditions** | **8 ( 0.6)** | **6 ( 0.5)** |
| Chest pain | 1 ( 0.1) | 2 ( 0.2) |
| Non-cardiac chest pain | 1 ( 0.1) | 2 ( 0.2) |
| **Hepatobiliary disorders** | **7 ( 0.5)** | **5 ( 0.4)** |
| Biliary colic | 2 ( 0.2) | 2 ( 0.2) |
| Cholelithiasis | 3 ( 0.2) | 2 ( 0.2) |
| **Infections and infestations** | **33 ( 2.5)** | **18 ( 1.5)** |
| Appendicitis | 3 ( 0.2) | 1 ( 0.1) |
| Herpes zoster | 3 ( 0.2) | 0 ( 0.0) |
| Herpes zoster ophthalmic | 2 ( 0.2) | 1 ( 0.1) |
| Pneumonia | 2 ( 0.2) | 1 ( 0.1) |
| **Injury, poisoning and procedural complications** | **4 ( 0.3)** | **11 ( 0.9)** |
| **Investigations** | **10 ( 0.8)** | **6 ( 0.5)** |
| Alanine aminotransferase increased | 2 ( 0.2) | 1 ( 0.1) |
| Hepatic enzyme increased | 2 ( 0.2) | 1 ( 0.1) |
| Liver function test abnormal | 2 ( 0.2) | 0 ( 0.0) |
| **Musculoskeletal and connective tissue disorders** | **9 ( 0.7)** | **7 ( 0.6)** |
| Back pain | 1 ( 0.1) | 2 ( 0.2) |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | **17 ( 1.3)** | **22 ( 1.9)** |
| Basal cell carcinoma | 5 ( 0.4) | 7 ( 0.6) |
| Malignant melanoma | 4 ( 0.3) | 2 ( 0.2) |
| Breast cancer | 3 ( 0.2) | 2 ( 0.2) |
| Uterine leiomyoma | 0 ( 0.0) | 5 ( 0.4) |
| **Nervous system disorders** | **27 ( 2.1)** | **15 ( 1.3)** |
| Multiple sclerosis relapse | 4 ( 0.3) | 4 ( 0.3) |
| Cerebral ischaemia | 2 ( 0.2) | 0 ( 0.0) |
| Epilepsy | 2 ( 0.2) | 1 ( 0.1) |
| Grand mal convulsion | 2 ( 0.2) | 0 ( 0.0) |
| Headache | 2 ( 0.2) | 0 ( 0.0) |
| Paraparesis | 2 ( 0.2) | 0 ( 0.0) |
| Presyncope | 2 ( 0.2) | 0 ( 0.0) |
| **Pregnancy, puerperium and perinatal conditions** | **2 ( 0.2)** | **0 ( 0.0)** |

| Primary system organ class<br>Preferred term | FTY720 1.25 mg (N=1302)<br>n (%) | FTY720 0.5 mg (N=1176)<br>n (%) |
|---|---|---|
| Abortion spontaneous | 2 ( 0.2) | 0 ( 0.0) |
| **Psychiatric disorders** | **9 ( 0.7)** | **2 ( 0.2)** |
| Depression | 5 ( 0.4) | 0 ( 0.0) |
| Anxiety | 2 ( 0.2) | 1 ( 0.1) |
| **Renal and urinary disorders** | **2 ( 0.2)** | **2 ( 0.2)** |
| Nephrolithiasis | 1 ( 0.1) | 2 ( 0.2) |
| **Reproductive system and breast disorders** | **3 ( 0.2)** | **5 ( 0.4)** |
| Cervical dysplasia | 2 ( 0.2) | 0 ( 0.0) |
| **Respiratory, thoracic and mediastinal disorders** | **10 ( 0.8)** | **5 ( 0.4)** |
| Dyspnoea | 4 ( 0.3) | 0 ( 0.0) |
| Pleurisy | 2 ( 0.2) | 0 ( 0.0) |

Primary SOCs are presented alphabetically; preferred terms are sorted within primary SOC in descending frequency for the FTY720 1.25 mg group.
A patient with multiple SAEs within a primary SOC is counted only once in the total row.
A patient with multiple occurrences of an AE under 1 dose group is counted only once in the AE preferred term for that dose group.

### 6.4.6.3 Discontinuation due to AEs

In the 2-year Study, the number of patients with AEs leading to study drug discontinuation was nearly twice as high in the fingolimod 1.25 mg group (14.2%) than in the fingolimod 0.5 mg group (7.5%) and the placebo (7.7%) group (see Table 6-2).

The most common reason for stopping drug was for investigations AEs (primarily due to liver enzyme elevations) with 6.5% in the fingolimod 1.25 mg group, 3.8% in the fingolimod 0.5 mg group, and 1.7% in the placebo group. Note that an increase in ALT or AST ≥5×ULN, or repeat elevation of ≥3×ULN, was a protocol-mandated reason for discontinuation of study drug. Cardiac events also showed an imbalance, being more common in the 1.25 mg group (1.9%) than the 0.5 mg group (0.2%).

For the All Studies Group, where differences in discontinuation rate may become most apparent between fingolimod doses over time, the proportions with AE discontinuations were 14.3% for fingolimod 1.25 mg and 7.8% for 0.5 mg. Patients in the fingolimod 1.25 mg group more frequently experienced bradycardia and AV block leading to study drug discontinuation (discontinuations due to AEs in the SOC Cardiac disorders occurred in 1.5% of patients in the fingolimod 1.25 mg group and 0.1% in the fingolimod 0.5 mg group). Comparable numbers from both fingolimod dose groups stopped study drug due to elevations in liver enzymes.

## 6.5 Hematology

The mechanism of action of fingolimod involves reducing the peripheral lymphocyte count, so abnormalities in lymphocyte count, and to a lesser extent white blood cell (WBC) counts are expected. The frequency (%) distribution of selected hematological parameters by

treatment in the 2-year Study is shown in Table 6-22, where the lowest values recorded over the 24-months treatment are summarized.

The mean lymphocyte counts for the 1.25 mg and 0.5 mg groups in the 2-year Study at 24 months were 0.42 and $0.49\times10^9$/L, respectively representing 76% and 72% reductions compared to baseline levels. The proportion of patients with total WBC ($<2\times10^9$/L) or lymphocyte ($<0.2\times10^9$/L) counts was higher in the fingolimod groups compared with placebo, and showed a relationship to dose (Table 6-22). It is important to note that the investigators were not provided with WBC, lymphocyte and neutrophil results, except in the case of low count alerts, and thus the apparently low rates of reported lymphopenia (as reported in Table 6-6) are a reflection of this protocol-mandated procedure.

Mean neutrophil counts in the 2-year Study were 3.06 and $3.22\times10^9$, respectively representing 29% and 20% reductions from baseline levels for 1.25 mg and 0.5 mg groups. Few patients had clinically notable low ($<1.0\times10^9$/L) neutrophil counts, but the proportions were slightly higher in the fingolimod groups compared with placebo (Table 6-22).

Platelet count and red blood cell abnormalities were infrequent and there were no meaningful differences between the treatment groups.

**Table 6-22 Frequency distribution of selected Hematological parameters by treatment in the 2-year Study**

| Parameter | Criterion | FTY720D 1.25mg N=429 n (%) | FTY720D 0.5mg N=425 n (%) | Placebo N=418 n (%) |
|---|---|---|---|---|
| WBC (x $10^9$/L) | n | 425 | 424 | 414 |
| | > ULN | 1 (0.2) | 0 (0.0) | 3 (0.7) |
| | < 2 x $10^9$/L | 39 (9.2) | 30 (7.1) | 0 (0.0) |
| | < 1.5 x $10^9$/L | 10 (2.4) | 4 (0.9) | 0 (0.0) |
| | < 1 x $10^9$/L | 1 (0.2) | 0 (0.0) | 0 (0.0) |
| Absolute lymphocytes (x $10^9$/L) | n | 425 | 424 | 414 |
| | > ULN | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | < 0.8 x $10^9$/L | 415 (97.6) | 418 (98.6) | 30 (7.2) |
| | < 0.6 x $10^9$/L | 402 (94.6) | 398 (93.9) | 11 (2.7) |
| | < 0.4 x $10^9$/L | 359 (84.5) | 315 (74.3) | 6 (1.4) |
| | < 0.2 x $10^9$/L | 128 (30.1) | 78 (18.4) | 0 (0.0) |
| | < 0.1 x $10^9$/L | 9 (2.1) | 3 (0.7) | 0 (0.0) |
| Absolute neutrophils (x $10^9$/L) | n | 425 | 424 | 414 |
| | > ULN | 1 (0.2) | 0 (0.0) | 1 (0.2) |
| | ≤ 1.5 x $10^9$/L | 63 (14.8) | 64 (15.1) | 16 (3.9) |
| | < 1.0 x $10^9$/L | 12 (2.8) | 5 (1.2) | 4 (1.0) |
| | < 0.5 x $10^9$/L | 1 (0.2) | 0 (0.0) | 0 (0.0) |
| Platelet count (direct) (x $10^9$/L) | n | 425 | 424 | 414 |
| | >ULN | 4 (0.9) | 3 (0.7) | 5 (1.2) |
| | < 125 x $10^9$/L | 5 (1.2) | 7 (1.7) | 5 (1.2) |
| | < 100 x $10^9$/L | 1 (0.2) | 3 (0.7) | 3 (0.7) |
| | < 25 x $10^9$/L | 0 (0.0) | 0 (0.0) | 2 (0.5) |

ULN=upper limit of normal; normal range is specified by study laboratory.
The lowest post-baseline value is used. The results are presented in cumulative form, i.e., the lowest actual laboratory value/upper limit value was used.
Values not classified as abnormal are not included in the table.

Recovery of lymphocyte counts was evaluated in the All Studies Group follow-up population. Fingolimod-treated patients discontinuing from study drug were assessed for peripheral blood lymphocyte count recovery after stopping treatment. Mean lymphocyte counts started to recover in the first 45 days after discontinuation. Mean lymphocyte counts in both fingolimod dose groups were returning to the normal range within 6 weeks after discontinuation. At the 3-month time point, mean values were approximately 80% of the baseline values.

## Subgroup evaluation of hematology parameters

Hematology parameters were evaluated for any differences between subgroups (by gender, age, previous treatment). Males had a lower incidence of clinically notable low lymphocyte counts than females on both fingolimod 1.25 mg and 0.5 mg. There were no clinically

relevant differences between the age groups in incidence of clinically notable hematological abnormalities. There were no clinically relevant differences between patients previously treated with MS therapies and those who were treatment naïve.

## 6.6 Long-term use

Data relating to long-term use of fingolimod in the MS population are available from 2 sources. Phase 2 Study 2201E1 includes patients exposed to fingolimod for up to 60 months, most of that duration being on the fingolimod 1.25 mg dose. Long-term exposure for the All Studies Group is briefly summarized in Table 6-1. No events were seen to emerge as new or unexpected findings, nor were any events seen to increase substantially upon long-term exposure.

## 6.7 Overdose

No cases of overdose of fingolimod have been reported in the clinical trials performed to date. However, fingolimod has been administered to healthy volunteers in doses from 5 mg to 40 mg (80-fold the targeted dose) as a single dose. Lymphocyte count nadirs were dose-dependent with reductions from baseline of 74% at 5 mg to 91% at 40 mg. Recovery of lymphocyte counts back to baseline was dose-dependent ranging from full recovery at day 39 for 5 mg to 58% recovery for subjects given 40 mg. The fingolimod-induced reduction in heart rate was independent of dose over the range 5 mg to 40 mg. Single-dose fingolimod at 25 mg and 40 mg reduced pulmonary function up to 13% for $FEV_1$ and up to 29% for $FEF_{25-75\%}$. At 40 mg, 5 of 6 subjects reported mild chest tightness or discomfort which was clinically consistent with small airway reactivity.

Dialysis or plasma exchange do not result in removal of fingolimod.

## 6.8 Pregnancy, birth and lactation

Fingolimod has been found to have a teratogenic effect (persistent truncus arteriosus, ventricular septal defect) in one animal species. Furthermore, the receptor affected by fingolimod (sphingosine 1-phosphate receptor) is known to be involved in vascular formation during embryogenesis.

Given the demography of the target population (two-thirds female, a significant proportion being of child-bearing age), clear recommendations regarding contraception were included in the protocols. A total of 52 pregnancies have been reported in fingolimod clinical trials in MS, at least some of which have onset while exposed to fingolimod. All pregnancies are summarized in Table 6-23. In addition to the experience in the MS program, 3 pregnancies were also reported in female patients treated with fingolimod in the renal transplant program. All 3 patients had successful delivery of normal offspring through caesarian section.

**Table 6-23 Pregnancies reported in fingolimod studies in MS (Status: 29 January 2010)**

| Treatment | Pregnancy outcome | | | | | Total |
|---|---|---|---|---|---|---|
| | Normal birth | Abnormal offspring | Elective abortion | Spontaneous abortion | Ongoing | |
| FTY720 | 12 [3] † | 1* | 8 | 5 | 4 | 30 |
| Interferon beta-1a | 2 [1] † | 0 | 2 | 0 | 0 | 4 |
| Placebo | 0 | 0 | 6 | 1 | 0 | 7 |
| Still blinded | 1 | 0 | 5 | 0 | 5 | 11 |
| Total | 15 | 1 | 21 | 6 | 9 | 52 |

† [n] = number of patients already discontinued from treatment when pregnancy was detected.
* unilateral congenital posteromedial bowing of the tibia.

The incidence of spontaneous abortion is consistent with expected rates. Only a single malformation has been reported, unilateral congenital posteromedial bowing of the tibia, which is not believed to be related to fingolimod. There were no other abnormalities reported in the baby. The developmental etiology of congenital posteromedial bowing of the tibia is unknown, but most authors believe it occurs secondary to abnormal fetal positioning.

Available data are too limited to comment on safety of fingolimod during pregnancy. However, given the findings in animals, the use of fingolimod in women who are or may become pregnant should be considered only if benefit is deemed to exceed potential risk to the fetus and women of childbearing potential should be advised to use effective contraception while on fingolimod and for at least 2 months following discontinuation of drug. As part of the post-marketing safety surveillance, a pregnancy registry will be established to collect information about the effect of fingolimod on the fetus.

Given that fingolimod may be secreted in breast milk, breast-feeding should be avoided to reduce risk of drug reactions in the nursing infant.

## 6.9 Safety conclusions

The safety profile of fingolimod has been well characterized with over 2,600 MS patients treated with fingolimod, comprising more than 4,500 patient-years of exposure. Of these patients, >1,700 were exposed to daily doses of 0.5 mg and 1.25 mg in the two completed Phase 3 studies, and 137 exposed to a higher dose of 5.0 mg in the MS Phase 2 study and its extension. Fingolimod is proposed for use at a dose of 0.5 mg daily. Treatment for up to 5 years at the 1.25 mg dose has been used safely, suggesting an acceptable safety margin for the target dose. The safety profile observed in the fingolimod MS development program is as follows:

- The overall incidence of AEs leading to discontinuation of study drug and of SAEs was comparable for the 0.5 mg fingolimod and placebo groups.
- Specific AEs that were reported more commonly in MS patients treated with fingolimod than in placebo-treated patients included:
    - Elevations of liver enzymes (in particular increases in ALT and GGT).

  - Reductions in white blood cell counts (lymphocytes and total WBC) – an expected and desired effect rather than an adverse event.
  - Bradycardia – transient, on treatment initiation (Day 1).
  - Macular edema.
  - Hypertension.
  - Dyspnea.
  - Bronchitis.
  - Diarrhea.
- The AEs most prominently associated with fingolimod treatment, e.g. liver enzyme elevations, bradycardia, and macular edema appeared to show a dose response.
- There were no AEs that appeared to be specifically related to long-term treatment with fingolimod.
- In general, the AE profile of fingolimod in MS patients did not depend on gender (with the exception of liver dysfunction in males), age, or previous treatment with disease-modifying drugs.
- The overall incidence of infections, including serious infections, was similar in the fingolimod treatment groups and the comparator arms (IFN or placebo).
  - Two fatal herpes infections occurred in patients treated with fingolimod 1.25 mg.
  - A slightly higher frequency of lower respiratory tract infections (primarily bronchitis) was observed in fingolimod treated patients, with apparent dose effect.
- The accumulated data from the MS program do not show an association of fingolimod therapy with the development of malignancies, including skin cancer.
- Data on the safe use of fingolimod in pregnancy or with breast-feeding are limited, although pre-clinical data suggest risk to the fetus is possible.

## Dosing in specified subpopulations

**Renal impairment:** No fingolimod dose adjustments are needed in patients with mild, moderate or severe renal impairment.

**Hepatic impairment:** No fingolimod dose adjustments are needed in patients with mild or moderate hepatic impairment. Fingolimod should be used with caution in patients with severe hepatic impairment (Child-Pugh class C).

**Elderly patients:** There are limited data on the use of fingolimod in the elderly (age >65). Population pharmacokinetics data in renal transplant patients did not indicate that dose adjustments were needed in this age group. Nevertheless, fingolimod should be used with caution in patients age 65 years and over.

**Race and ethnicity:** Over 95% of the population in the MS program was Caucasian. Data from intensive PK sampling studies shows that fingolimod has similar pharmacokinetics and pharmacodynamic effects across races and ethnicities including Caucasian, Asian, African and Hispanic, suggesting that no fingolimod dose adjustments are needed based on race or ethnicity.

**Gender:** No fingolimod dose adjustments are needed based on gender, which has no clinically relevant effect on the pharmacokinetics of fingolimod.

# 7 Risk Evaluation and Mitigation Strategy

Communication of the known risks associated with fingolimod therapy to physicians will occur through the prescribing information (package insert). During the development of fingolimod, several risks have been identified that, in addition to warnings in the label warrant additional risk management activities beyond inclusion in the package insert. These include bradycardia/bradyarrhythmia, infections, macular edema, liver toxicity, and reproductive toxicity. Novartis proposes a Risk Evaluation and Mitigation Strategy (REMS) to address these risks.

### Goal

The goal of the REMS is to educate patients and prescribers about the potential serious risks of fingolimod.

## 7.1 Objectives

The specific objectives to be achieved by the fingolimod REMS are to inform and educate patients and prescribers that:

Fingolimod may be associated with serious risks including bradycardia/bradyarrhythmia, infections, macular edema, liver toxicity, and reproductive toxicity:

### Bradycardia/Bradyarrhythmia

- Fingolimod should not be co-administered with Class Ia or Class III antiarrhythmic drugs because of the potential for these drugs to cause torsades de pointes or severe AV block in patients with bradycardia.
- Overall benefit and risk should be considered before initiating fingolimod in patients with high grade atrio-ventricular (AV) block or sick-sinus syndrome and careful observation is required if treatment is initiated in these patients.
- It is recommended that patients with a low resting heart rate (<50) or those taking beta blockers be observed for 6 hours after the first dose of fingolimod to confirm that it is well tolerated.

### Infections

- Fingolimod causes a reversible reduction in the peripheral lymphocyte count.
- Patients should be instructed to report promptly, signs or symptoms of infection to their physician while on fingolimod therapy and be diligent regarding infections for up to two months after discontinuation of fingolimod.

### Macular Edema

- It is recommended that an ophthalmologic examination be performed 3-4 months after starting fingolimod.

- If patients report visual disturbances at any time while on therapy, evaluation of the fundus, including the macula should be carried out.
- Patients who have a history of diabetes or uveitis have an ophthalmologic examination before starting and during fingolimod therapy.

### Liver Toxicity

- Although the risk of liver injury with fingolimod is unknown in patients with a prior history of liver disease, use of fingolimod in this setting should be considered only if benefit is deemed to exceed risk.
- Patients who develop symptoms suggestive of hepatic dysfunction (unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine) should have liver function tests performed. Patients who develop jaundice or other evidence of significant liver injury (e.g. laboratory evidence) should interrupt therapy. If no alternative explanation can be found for the liver dysfunction, patients should not resume therapy with fingolimod unless benefit clearly exceeds the risk of recurrence of liver injury.

### Reproductive toxicity

- Women of childbearing potential should be counseled on the potential risk to the fetus and advised to use effective contraception during, and for at least two months following discontinuation of fingolimod.

## 7.2 Information on proposed REMS elements

The proposed REMS for fingolimod includes a Medication Guide and a Communication Plan to reinforce key risk messages to patients and prescribers.

### 7.2.1 Medication Guide

A Medication Guide will be available for distribution with each fingolimod prescription. The Medication Guide is inserted inside the carton and a statement alerting the dispenser to provide the Medication Guide with the product will be included on the carton. The information included in the Medication Guide will cover information regarding safety events related to fingolimod and how to prevent or identify such events and is presented in easy-to-understand language, appropriate for patients.

### 7.2.2 Communication Plan

The REMS for fingolimod utilizes education and outreach to Health Care Practitioners (HCPs), as well as patient labeling (i.e., the Medication Guide) to inform stakeholders and reinforce important safety information about the product. The content of these materials, described below, is consistent with the prescribing information for the product. The educational materials have been created to concisely convey the most critical information to ensure the safe use of the product. In addition to the PI and Medication Guide, these materials will include:

- Introductory Letter for potential fingolimod prescribers.
- Important Safety Information Brochure for fingolimod prescribers.

After receiving FDA's agreement on the drafted REMS materials, the Sponsor will widely distribute them through a direct mail campaign to HCPs who may potentially prescribe the product. The main prescribers of fingolimod are expected to be neurologists with experience in treating patients with MS. A list of potential prescribers will be compiled using a number of different sources, including the membership lists of professional societies (such as the Consortium of Multiple Sclerosis Centers) and prescription data that identifies prescribers of currently available products indicated for treatment of MS. The letters will also be provided to the leadership of relevant medical societies including the Consortium of Multiple Sclerosis Centers, the American Academy of Neurology and the American Neurology Association.

In addition to the direct mailing approach, email or other technologies may be used to distribute materials.

### 7.2.3 Introductory Letter for Potential Fingolimod Prescribers

An Introductory Letter for prescribers will be distributed via a direct mail campaign shortly after product launch. The letter will include information about the indication for fingolimod and will describe the potential serious risks of the product, including bradycardia/bradyarrhythmia, infections, macular edema, and reproductive toxicity. It will also summarize the specific recommendations related to these risks, based on the relevant information included in the Package Insert. The letter will also include information about the fingolimod Pregnancy Exposure Registry and encourage physicians to register pregnant patients. The Package Insert and Medication Guide will be appended to the letter. The distribution list for the letter will include neurologists who treat MS identified from membership of national medical societies and prescription data that identifies prescribers of currently available products indicated for treatment of MS, as described above.

In order to ensure that HCPs remain informed about the REMS for fingolimod, the Introductory Letter will be updated and provided annually to the HCPs described above. To make certain that all HCPs have the latest information on labeling and patient information, the most current versions of the PI and Medication Guide will also be included. Each packet will have a succinct cover letter highlighting the contents of the mailing with a toll-free number.

### 7.2.4 Important Safety Information Brochure for Fingolimod Prescribers

This brochure will detail the most important product safety information about the risks of bradycardia/bradyarrhythmia, infections, macular edema, liver toxicity, and reproductive toxicity. The areas that will be highlighted in the brochure will include information on:

- Patients who may be at higher risk of cardiac events and thus may require observation after the first dose of fingolimod (e.g. patients with low resting heart rate, concurrent beta-blocker use) and those patients who require further benefit-risk assessment (e.g. patients with high grade atrio-ventricular block or sick sinus syndrome) given that such patients were not studied in the Phase 3 program.
- Risks of avoiding co-administration of fingolimod with Class Ia and III anti-arrhythmic drugs because of the potential for these drugs to cause torsades de pointes in patients with bradycardia.
- The pharmacodynamic effects of fingolimod on lymphocyte count.

- The potential for developing macular edema and recommendations for appropriate monitoring.
- The potential for liver injury and recommendations for minimizing the risk of developing severe liver injury.
- Potential risk to fetus for malformations based on reproductive toxicology studies in animals.
- The fingolimod pregnancy registry.
- The importance of counseling patients about the need for effective contraception during and for two months after discontinuing treatment with fingolimod.
- The importance of counseling patients to report symptoms that could indicate bradycardia, macular edema or infection.

In order to maximize the comprehension of these targeted educational materials, there will be a thorough evaluation performed through qualitative testing with HCPs.

## 7.3 Additional Post-registration and Pediatric Plans

### Post-authorization safety study

Novartis proposes to perform a world-wide post-authorization safety study (PASS) the primary objective of which will be to investigate the incidence of selected safety-related outcomes in patients with MS receiving fingolimod under conditions of routine clinical practice. This will be a 5-year, multi-national, observational study including approximately 5,000 patients with relapsing MS treated with fingolimod in countries where fingolimod is ultimately approved. In addition to the primary objective, this study will enable Novartis to further explore the overall safety of fingolimod in patients with RRMS under conditions of routine practical care.

### Pregnancy exposure registry

As part of the post-marketing safety surveillance, a pregnancy registry will be established to collect information about the effect of fingolimod on the fetus.

### Pediatric plan

In order to comply with Health Authority pediatric regulations, a study in 10 to 17-year old children/adolescents with MS is planned to be initiated once fingolimod in the adult indication has been approved.

## 7.4 Evaluation Plan for REMS

Novartis is committed to evaluating the effectiveness of the REMS for fingolimod and reporting the results to FDA. Assessments of the REMS will be provided to the FDA 18 months after approval of the REMS, with additional reports to be provided 3 and 7 years after approval. The reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment time interval. The assessments will include an evaluation of the effectiveness of the risk minimization program and

recommendations for program improvements or changes, if required. The following sections summarize the sources of information that will be used in conducting the assessments.

### 7.4.1 Knowledge, Attitude, and Behavior Surveys of Patients and Prescribers

Knowledge, Attitude, and Behavior (KAB) surveys will be conducted with a random sample of patients in order to assess their awareness and understanding of the risks of fingolimod as described in the Medication Guide. The surveys will also assess compliance related to distribution of the Medication Guide to patients. In addition, KAB surveys will be conducted to ensure that the informational materials presented to prescribers effectively achieve the REMS educational objectives. The prescriber survey will be administered to a representative sample of known, randomly selected fingolimod prescribers. The sample will be geographically representative and will include prescribers across the predominant medical specialties known to prescribe the product.

- The survey period will begin approximately 13 months after approval of the REMS, and will be repeated prior to each assessment time point. The methodology and protocols for the KAB surveys, and the survey instruments, will be developed after the product labeling and Medication Guide are finalized. These documents will be provided to the FDA at least 90 days before the surveys are administered.

### 7.4.2 Adverse Event Monitoring, Analysis, and Reporting

The activities occurring under the REMS will be integrated with Novartis' pharmacovigilance program to ensure proper surveillance, monitoring, and reporting of adverse events, including reports of events such as bradycardia, syncope or pre-syncope, serious infections, liver toxicity, and macular edema. Reports of pregnancy received through the Pregnancy Exposure Registry (see Section 8.2.8) and as spontaneous reports will be included as well. The Sponsor's pharmacovigilance staff will collect as much information as possible about these events and will collect it in a standardized fashion. Adverse event reports will be individually reviewed and collectively evaluated to determine if changes to the REMS messages could help to further mitigate the risks.

### 7.4.3 Reports from Postmarketing Fingolimod Exposure Registry

Interim results for all cases of symptomatic bradyarrhythmia, serious infections and macular edema reported in the registry will be included as part of the REMS Assessment reports.

### 7.4.4 Reports from Fingolimod Pregnancy Exposure Registry

Interim data from the registry will be included as part of the REMS Assessment reports.

## 7.5 REMS Conclusion

With the implementation of the activities outlined above, Novartis will ensure that important information on the safety profile and effective use of fingolimod is appropriately communicated to healthcare professionals and patients in order to maximize the benefit of fingolimod to those patients with MS in whom it's use is indicated.

# 8 Benefit-Risk Considerations

## 8.1 Summary of benefits

Fingolimod has demonstrated efficacy compared to placebo and to a current first-line MS therapy (IFN β-1a) in patients with RRMS. As a once-daily oral therapy, fingolimod may address some of the unmet medical needs in MS therapeutics by providing an oral disease-modifying treatment that can be safely used and appears to be more effective and convenient than the current first-line therapies.

Fingolimod at the proposed 0.5 mg dose demonstrated efficacy across all clinical and para-clinical measures of disease activity compared to placebo in a 2-year Study and to an active comparator, IFN β-1a in a 1-year study:

- Reduced the frequency of relapses by 54% vs. placebo and by 52% vs. IFN β-1a ($p<0.001$).
- Reduced the risk of relapse by 52% vs. placebo ($p<0.001$) and 48% vs. IFN β-1a ($p<0.001$).
- Reduced the risk for 3-month confirmed disability progression by 30% over two years ($p=0.024$) and the risk of 6-month confirmed progression by 37% over two years ($p=0.012$) compared to placebo. No significant different on disability was seen over 1 year compared to IFN.
- Reduced MRI inflammatory activity (new or newly-enlarged T2 lesions, Gd-enhancing lesions) by 74-82% over two years compared to placebo and by 35-60% over one year vs. IFN β-1a.
- Reduced the accumulation of MRI T2 lesion burden vs. placebo over two years ($p>0.001$).
- Reduced brain volume loss (atrophy) by over 30% vs. placebo over two years ($p<0.001$) and vs. IFN β-1a ($p<0.001$).

Fingolimod also has potential benefits associated with oral dosing compared to injection therapies:

- Oral administration avoids the need for frequent injections that can result in non-compliance, or even avoidance of therapy entirely, due to needle fear or injection site reactions/pain and avoids the issues associated with intravenously infused drugs.
- Lack of IFN-related systemic side effects such as influenza-like symptoms, pyrexia, and myalgia.

Additional benefits related to the pharmacokinetic properties of fingolimod are the lack of a food effect that allows fingolimod to be taken without regards to meals, the very low potential for drug-drug interactions, and with a long half-life, a negligible impact of a missed dose.

## 8.2 Summary of risks and remaining risk questions

In the MS clinical studies, the overall incidence of adverse events and serious adverse events was similar for fingolimod and matched controls (placebo, IFN β-1a). However, specific events associated with the biologic effects of fingolimod, involve cardiac, ocular, infectious, hepatic, and pulmonary systems. Although the safety findings may be multi-faceted, their

impact is relatively modest, both in terms of sequelae and in terms of tolerability. Adverse event related drug discontinuations for the 0.5 mg patients in the 2-year Study were comparable to those of the placebo group and approximately half that of the 1.25 mg group, indicating that despite a number of potential safety concerns, the impact on adherence to therapy is modest, particularly at the target dose of 0.5 mg. Key aspects of the perceived safety issues, assessment of risk and risk management are summarized below.

### 8.2.1 Cardiac

Initiation of fingolimod treatment is associated with a reduction in heart rate in most patients, due to the known stimulation of $S1P_1$ receptors on myocytes. First-dose cardiac adverse events (bradycardia, slowing of AV conduction) are usually asymptomatic, transient and generally of limited clinical consequence and are infrequent with the proposed therapeutic dose. No additional effect on heart rate, atrioventricular conduction, or left ventricular function was observed on chronic fingolimod dosing up to 24 months. Given the low frequency of events with the 0.5 mg dose and the absence of sequelae with first-day dosing, routine monitoring after dose initiation does not appear to be a required condition for use. However, in those identified as potentially at higher risk (use of beta blockers, resting bradycardia, high grade AV blocks or sick-sinus-syndrome), because they were not studied in Phase 3, monitoring is recommended until such time as safety has been confirmed. In these patients, clinical observation for 6 hours following first-dose administration, or after a 2-week or greater dose interruption, is recommended. Fingolimod should either not be co-administered, or administered with caution together with class Ia and III anti-arrhythmics due to the potential risk for Torsades de Pointes or high-grade AV block.

The slight increase in blood pressure (~1 mmHg with 0.5 mg dose) is of uncertain significance. However, more patients on fingolimod 0.5 mg developed hypertension (6%) compared to placebo (4%) and longer observation may be necessary to fully evaluate the impact, if any, of this change in blood pressure. Should hypertension develop, it should be managed as deemed appropriate by the treating physician.

The studies conducted in MS have involved generally young, otherwise healthy individuals, and although any adverse event may increase in incidence with age, the cardiovascular events may require specific consideration if the drug is used in an older population than was studied in the Phase 3 program, e.g. patients aged over 60 years.

### 8.2.2 Ocular

Macular edema occurs infrequently, especially with the 0.5 mg dose (<0.5%), usually occurs within 3-4 months of treatment initiation and is usually symptomatic leading to clinical evaluation. If asymptomatic, macular edema can also be detected based on ophthalmologic evaluation. MS patients often have visual dysfunction and evaluation of visual symptoms could be confounded by optic nerve, rather than retinal problems. Thus, ophthalmologic assessment is recommended in the proposed label for all patients at the 3-4 month time-point after treatment initiation to maximize detection and management.

Patients with a history of uveitis or diabetes mellitus appear to have an increased risk of macular edema and require careful assessment before, and during the initial months of therapy

with fingolimod. Diabetic patients were not included in MS clinical trials and thus the risk in such patients is uncertain.

Whether it is safe to continue dosing with fingolimod during macular edema or to re-challenge after macular edema has resolved is unknown.

### 8.2.3 Infection

Although immune system effects of fingolimod might be anticipated to lead to an increased risk of infection, the overall incidence of infections was similar across treatment groups. Apart from a slight increase in lower respiratory tract infections and two fatal herpes infections, no other infectious signal was seen, including the absence of cases of PML or other opportunistic infections in the MS program.

The lack of a clear infection signal potentially reflects the fact that although the drug dramatically reduces circulating lymphocyte counts (by ~ 70% at the proposed 0.5 mg dose), effector memory T-cells, neutrophils, and antibody responses which are all important in infection surveillance/protection, are not significantly affected by therapy.

Although the infection rate was higher in patients with lower lymphocyte counts, this finding is of unclear significance given that the rates in patients with low lymphocyte counts were not much different than for placebo patients. Inexplicably, the infection rate for patients on fingolimod with higher counts (>400/mL) were *lower* than both placebo and low lymphocyte count patients. No clear relationship between lymphocyte count and the occurrence of severe or serious infections has been shown, such that low cell counts do not reliably predict an increased risk of such infections, nor do higher counts guarantee protection. As such, monitoring of lymphocyte counts is not deemed mandatory as such monitoring will not have utility in predicting more serious infections.

Should clinicians desire to monitor lymphocyte counts, knowing that counts drop quickly (by 1 month) to steady-state levels and that counts remain relatively stable over time, should help in any treatment-related decisions. During clinical trials, 18% of patients taking 0.5 mg dose had a lymphocyte count of <200/mL on at least one occasion while only 5% had this finding on two or more consecutive evaluations. Confirmed lymphocyte counts of <200/mL required dose interruption in clinical trials, but the utility of this is uncertain, based on infection data overall.

However, given the theoretical concern related to the impact of fingolimod on immunity, vigilance on the part of physicians and patients for signs and symptoms of infections is important while on therapy and for up to two months after cessation of treatment. Prompt and effective management of serious infections, should they occur, is warranted to limit sequelae.

If drug is stopped, lymphocyte levels begin to recover within days of stopping therapy, returning to within the normal range within approximately 4-6 weeks and approaching baseline values within 6-12 weeks. Concomitant use of anti-neoplastic, immunosuppressive or immune-modulating therapies should be undertaken with caution due to the risk of additive immune system effects. Discontinuation of fingolimod followed by immediate initiation of a new therapy for MS will result in overlap of exposure of up to 6 weeks due to the 6-9 day half-life of fingolimod.

### 8.2.4 Vaccinations

No data are currently available regarding immunizations in MS patients but based on the drug mechanism of action, pre-clinical and pharmacology data, it is expected that vaccination with recall antigens will be little affected whereas novel antigens will elicit less than optimal responses. Additionally, live attenuated vaccines should not be used in treated patients due to the potential risk of acquiring infection with the agent being used in the vaccine while receiving fingolimod.

### 8.2.5 Hepatic

Elevations of liver transaminases to ≥3×ULN values were seen in 8.0% of patients receiving fingolimod 0.5 mg (All Studies Group). Approximately 50% of occurrence of liver enzyme elevation occurred within the first six months of therapy. These elevations of enzymes were generally asymptomatic but a single recent case fulfilling Hy's Law (without other established etiology to date) with jaundice has occurred in the > 4,000 patients (MS and transplant) exposed to fingolimod. Enzyme elevation improved once therapy was discontinued and no patient developed liver failure. Data, albeit limited, on continued dosing despite elevated enzymes indicated recovery while still receiving fingolimod. An unexplained finding was a substantially greater incidence of liver dysfunction in males compared to females, seen only in the MS population, not in the transplant population.

The mechanism by which fingolimod may cause liver enzyme elevation is unknown. However, given the known low utility of liver enzyme testing to prevent serious liver injury related to drugs, routine testing is not being suggested in the label. Use of fingolimod in patients with prior liver injury or with elevated enzymes prior to starting therapy, should be undertaken cautiously with full consideration of benefit vs. risk. Patients with signs or symptoms of liver disturbance should be promptly evaluated. Suspending, discontinuing or re-initiating therapy should be based on severity of findings and overall assessment of benefit vs. risk.

### 8.2.6 Pulmonary

Fingolimod induces a, dose-dependent increase in airway resistance upon treatment initiation with no evidence of further progression with continuous therapy. In the MS Phase 3 program, no clinically relevant changes in pulmonary function were observed in any treatment group, although reports of dyspnea were more frequent in the fingolimod treatment groups compared to controls. The reduced findings related to pulmonary function in the MS Phase 3 program may reflect the use of lower doses compared to earlier clinical studies. Patients with asthma that did not require chronic therapy could be included in Phase 3 studies and those treated with fingolimod were not at an increased risk of experiencing respiratory symptoms compared to the comparator groups. A clinical pharmacology study in moderate asthmatics requiring chronic therapy (not MS patients) has shown that fingolimod treatment can be safely initiated. Specific pulmonary monitoring, in the absence of symptoms, does not appear warranted and is not suggested in the label.

### 8.2.7 Malignancy

Pre-clinical data did not suggest an increased risk of malignancies with fingolimod, apart from lymphoma in mice at high doses. However, due to reports of skin malignancies during development, active screening was introduced in Phase 3. The incidence estimates for various forms of skin cancer (and indeed other malignancies) from pooled safety data are comparable between treatment groups and placebo with no evidence for a fingolimod dose-effect. These data, from up to 24-month treatment exposure, do not suggest a relationship of fingolimod therapy with the occurrence of cancer. However, the number of events to date and duration of follow-up is too limited to definitively exclude a relationship to low-incidence, late-occurring events. No specific monitoring is recommended in the label while on therapy although physicians should continue to report occurrences of malignancies with use of fingolimod therapy.

### 8.2.8 Pregnancy

There are very limited data from the use of fingolimod in pregnant women. Based on pre-clinical data and knowledge of the role of the $S1P_1$ receptor in vascular embryogenesis, warnings in the label will highlight that fingolimod should not be used during pregnancy unless benefit to the patient is deemed to exceed the potential risk to the fetus. Women of childbearing potential should be counseled as to the potential risk to the fetus and advised to use effective contraception while on fingolimod and for at least 2 months following discontinuation of drug. Likewise, breast-feeding should not be performed in MS patients receiving fingolimod therapy due to the risk of adverse reactions in the nursing infant as a result of fingolimod in breast milk. Given that women of childbearing potential constitute a large proportion of the target population for fingolimod, a pregnancy exposure registry will be established to prospectively collect outcome data on the babies born to women treated with fingolimod and compare it to reference data from general surveillance systems.

### 8.2.9 Other Events of interest

Isolated serious cerebrovascular and peripheral vascular cases were reported in patients treated with the fingolimod 1.25 mg dose (none on fingolimod 0.5 mg). The number of cases is too small and the cases themselves too varied in nature to readily ascertain causality.

An increase in the incidence of seizures/convulsions was reported in the renal transplant program (using doses 5- to 10-fold higher than proposed for MS). In the MS clinical studies, seizures were more common with fingolimod than placebo, but in several instances, causes other than fingolimod were apparent.

### 8.2.10 Risk Management

The risk management strategy related to fingolimod includes use of the Warnings and Precautions section in the label to highlight safety issue, provision of educational materials for prescribers and patients regarding important safety information, conducting a pregnancy registry and initiation of a 5,000 patient post-approval safety registry to capture safety events and further evaluate the long-term safety profile of fingolimod in the MS population.

## 8.3 Overall benefit/risk

The benefit-risk assessment of fingolimod in treating MS has to consider the long-term benefit the patient may receive from the demonstrated reduction in inflammatory disease activity, as manifested by fewer relapses, fewer new brain lesions, a reduction in brain atrophy and ultimately a delay in permanent neurological deterioration contrasted with potential short- and long-term safety risks. The benefit/risk-profile of fingolimod treatment has been characterized within the clinical program for up to 2 years in controlled studies and up to 5 years in a long-term extension study. In addition to efficacy, the oral route of administration will be more convenient for patients than injectable therapies, will avoid the side-effects associated with injections thus enhancing quality of life, and may lead to increased treatment compliance with an associated impact on effectiveness in the target population.

Consistent and robust efficacy of fingolimod has been demonstrated in the clinical development program, involving almost 3,000 MS patients, representative of the relapsing MS population based on demographic characteristics, level of disability, and disease activity, both clinical and MRI-based. Fingolimod 0.5 mg has demonstrated an ability to reduce relapse rate by > 50% relative to placebo while also reducing the risk of disability progression by almost one-third. In addition, fingolimod was superior to one of the currently approved first-line MS therapies (IFN β-1a) in reducing the frequency of relapses over 1 year by over 50%. The benefits seen in the overall population were also seen in multiple subgroups, including those previously treated with, or naïve to, approved MS therapies. The clinical benefits of fingolimod were further supported by the efficacy seen on multiple MRI measures of inflammation and disease burden, including reducing the numbers of new T2 lesions, active lesions, lesion burden and proportions of patients free of new lesion activity. The MRI lesion count and lesion volume findings provide objective, quantitative support to the clinical findings. Importantly, and a unique result for MS therapies, was the impact of fingolimod on reducing brain atrophy. While speculative, this latter finding may support the concept of a tissue protective effect of fingolimod in MS, consistent with pre-clinical data. Fingolimod is the first MS therapy to show such an effect on reducing brain atrophy, a feature of the progression of MS.

As MS therapies become increasingly more effective, the potency may be accompanied by safety risks, as has been exemplified by the heightened efficacy of natalizumab compared to standard of care, but coupled with a risk of a serious CNS infection. The key safety issues identified for fingolimod during clinical development include cardiac, ocular, infectious and hepatic effects. Additionally, consideration was given to safety issues that were previously considered as potential safety risks of note that now appear to be of less concern (pulmonary) or not a signal (malignancy) as well as to issues surrounding lymphocyte dynamics, vaccination and pregnancy.

Thus, there are several aspects of the fingolimod safety profile to consider. However, their overall importance needs to take into consideration both the severity of the events, management options and sequelae. The severity of most events is mild or moderate, the events are either transient, preventable or can be readily managed. The cardiac events are first-day dosing events only, and as described, with the dose proposed, are usually asymptomatic without need for intervention or monitoring. The blood pressure elevation is minor in

population terms, and cases of hypertension that develop can be managed with anti-hypertensive medications. Macular edema is infrequent at the target dose, can be readily detected and reverses with discontinuation of therapy. The incidence can be potentially further decreased by limiting exposure to those at highest risk, but this may be unnecessary and would withhold effective therapy from many to prevent reversible events in a few. Infectious complications do not appear to be increased but merit attention and prompt therapy should they occur. Hepatic dysfunction (seen also with both first- and second-line currently approved MS therapies) can be reduced/mitigated by attention to prior and current history suggestive of liver dysfunction and prompt evaluation in the presence of clinical symptoms or significant increases of liver enzymes.

Due to the potential for teratogenicity, counseling of women on the potential risks to the fetus and the need for effective contraception will be important. Educational material will be provided to give guidance to prescribers on how to appropriately counsel women. The previously suspected relationship between fingolimod exposure and malignancy has not been borne out by more detailed integrated analysis of all safety data, but as discussed above, even with >2,000 MS patients and almost 4,000 patient-years of exposure, data is still too limited to definitively conclude on the risk for low-frequency, late-occurring events such as malignancies.

None of these complications is of sufficient frequency, severity or consequence to limit patient access to this therapy when balanced with clinical and MRI benefit that appears to exceed that of current first-line therapies coupled with a more acceptable safety profile than second-line therapies with their serious, potentially fatal complications.

## 8.4 Medical need

At present, four classes of drugs (and 7 commercial products) are available as therapies for MS – IFN β (IFN β-1a and IFN β-1b – 2 products of each type of IFN are marketed), glatiramer acetate (GA), natalizumab and mitoxantrone. The precise mechanism of action of IFN and GA are unknown but are viewed as immunomodulatory, possibly with pleiotropic actions. Mitoxantrone is a chemotherapeutic agent with strong immunosuppressive properties, while natalizumab blocks alpha-4 integrin receptors preventing interaction with endothelial receptors (VCAM-1, MAdCAM) reducing the ability of inflammatory immune cells to attach to and pass through the blood-brain barrier (and other tissues).

Interferon and GA are viewed as first-line therapies and require systemic injection at frequencies varying from daily to weekly. These products provide about 30% relapse rate reduction and IFN β-1a has demonstrated an effect on disability progression, not shown by IFN β-1b or GA. Side-effects are common, being predominantly related to injection-site reactions or systemic reactions. Rare serious side-effects, including liver failure are reported with IFN, as are varying rates of neutralizing antibody formation (2%-40%) that limits efficacy. Breakthrough clinical activity is common as is cycling between therapies driven by lack of efficacy and/or tolerance.

Natalizumab has shown a 68% relative reduction on relapse rates compared to placebo and 42% reduction in the risk of disability progression and is generally viewed as more efficacious than the first-line therapies but is associated with a risk of PML that approaches approximately 1/800 for patients exposed for at least 24 infusions. The drug is administered

IV once monthly and has approximately 5% incidence of hypersensitivity reactions related to neutralizing antibodies that also abrogate efficacy.

Mitoxantrone is indicated predominantly for worsening cases of MS. The main limitations for this therapy (given monthly or quarterly by IV infusion) are cumulative dose-related cardiac toxicity (leading to a life-time maximal dose) and a rate of drug-induced acute myelogenous leukemia that may approach 1%.

Thus, MS patients are faced with difficult choices. Usually therapy starts with a first-line therapy that has modest relapse efficacy, potentially with no disability benefit but which is associated with side-effects. These are more irritants than major safety issues, but do affect patient quality of life and adherence to therapy. This can lead to cycling between first-line therapies, quitting therapy or moving to more potent, at times unapproved, therapies. Additionally, many patients sufficiently fear injections that they never begin therapy. Natalizumab is used preferentially as a second-line therapy compared to mitoxantrone (both given by IV infusion), given the strength and breadth of clinical data and ultimately a better tolerability profile and arguably better safety. However, as experience with natalizumab increases, the rate of PML, particularly with more than two years of therapy, is steadily increasing and may limit use or lead to “drug holidays”.

Fingolimod will provide a valuable addition to the therapeutic armamentarium of the MS practitioner. While cross-study comparisons can be challenged, the relapse benefit of fingolimod more closely approximates that of natalizumab than that of the first-line therapies. Importantly, in a direct comparative study, fingolimod 0.5 mg dose has demonstrated superiority over one of the first-line IFN products on relapses and MRI measures during a 1-year study. Fingolimod also has a proven effect on disability and is the only product which has shown a benefit in reducing brain atrophy, a prominent feature of MS. Based on efficacy alone, fingolimod merits designation as a first-line therapy. Such a designation must be viewed in the context of the safety profile of the product, but the data available regarding safety does not preclude use of fingolimod as a first-line product.

While of potentially lesser influence than efficacy and safety, convenience, tolerability and adherence to therapy are important features of a successful therapy. The oral administration route provides convenience to the patient and an absence of injection-related side-effects and anxieties. Additionally, infusion-related events and logistics are avoided. Finally, oral therapy may lead to enhanced adherence to therapy due to both convenience and tolerability. Enhanced compliance ultimately translates into better population effectiveness.

## 8.5 Conclusion

Fingolimod has demonstrated convincing efficacy, both with respect to placebo and a current first-line therapy in patients with relapsing MS. At the proposed dose of 0.5 mg, fingolimod has demonstrated an acceptable safety profile which can be further enhanced by the proposed risk management plan. Given the robust efficacy plus the convenience of once-daily oral administration, fingolimod offers significant benefits over current first-line therapies, including direct demonstration of superiority to IFN β-1a.

In considering the totality of fingolimod data and in the context of the current MS therapeutic landscape, the benefit-risk assessment of once daily oral fingolimod 0.5 mg is considered to

be favorable and supports the use of this novel therapeutic option as a first-line therapy in the treatment of patients with relapsing MS.

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