Australian Government

Department of Health and Ageing

Therapeutic Goods Administration

Australian Public Assessment Report for Fingolimod

Proprietary Product Name Gilenya, Fynefta & Filosir

Submission No: PM-2010-00401-3-1

Sponsor: Novartis Pharmaceuticals Australia Pty Limited

March 2011

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	New Chemical Entity
Decision:	Approved
Date of Decision:	19 January 2011
Active ingredient(s):	Fingolimod
Product Name(s):	Gilenya, Fynefta & Filosir
Sponsor's Name and Address:	Novartis Pharmaceuticals Australia Pty Limited, 54 Waterloo Rd, North Ryde NSW 2113
Dose form(s):	Capsule
Strength(s):	0.5 mg
Container(s):	Blister packs
Pack size(s):	7, 28 and 84
Approved Therapeutic use:	The treatment of Relapsing Remitting Multiple Sclerosis and Secondary Progressive Multiple Sclerosis with superimposed relapses to delay the progression of physical disability and reduce the frequency of relapse. Safety and efficacy of Gilenya/Fynefta/Filosir beyond 2 years are unknown.
Route(s) of administration:	Oral
Dosage:	One 0.5 mg capsule per day
ARTG Number (s)	169890, 169896, 169897

Product Background

Novartis Pharmaceuticals Australia Pty Limited has applied to register the new chemical entity, fingolimod (Gilenya and its alternative tradenames Fynefta and Filosir) as an oral agent for the treatment of patients with relapsing multiple sclerosis (MS), to reduce the frequency of relapses and to delay the progression of disability.

With the current Australian submission the sponsor proposes to register fingolimod, a sphingosine-1-phosphate (S1P) receptor modulator which can be taken orally for the treatment of relapsing forms of MS.

MS is an inflammatory condition that damages the myelin of the CNS causing neurological impairment. It's generally assumed to be mediated by an autoimmune process. As many as 80 to 85 % of all patients present with a form of disease known as relapsing-remitting MS (RRMS), characterised by unpredictable acute episodes of neurological dysfunction, followed by variable recovery and periods of clinical stability. Within ten years more than 50% of patients who presented with a RR form develop sustained deterioration with or without relapses superimposed; this form is called the secondary progressive MS (SPMS).

The term relapsing MS includes: 1) patients with RRMS, 2) patients with SPMS and superimposed relapses and 3) patients with a single demyelinating clinical event who show lesion dissemination on subsequent MRI scans according to McDonald's criteria. Relapses are considered the clinical expression of acute inflammatory focal lesions whereas progression is considered to reflect the occurrence of demyelination, axonal loss and gliosis. Relapsing remitting multiple sclerosis and

secondary progressive multiple sclerosis are probably different stages of the same disease while primary progressive multiple sclerosis may imply different processes.

At the time of submission there were no oral treatments indicated for the treatment of MS. Subsequently Movectro (cladribine) was approved in August 2010 for RRMS only and only for up to 2 years. Other treatments for MS include: interferon β -1a, interferon β -1b, glatiramer and natalizumab. All these products require parenteral administration. The interferons and glatiramer have indications that include treatment after a single demyelinating event with associated brain MRI abnormalities characteristic of MS. Natalizumab is indicated only for treatment of RRMS. Interferon β-1b and natalizumab have indications which include delaying progression of disease/ disability and reduction in frequency of relapse. To date, only the interferons have indications that include treatment of all forms of RMS. No product specifically states it is a "disease modifying therapy" as is proposed for inclusion in the indication for fingolimod, although all the above products modify the disease process.

The TGA has adopted the 2007 version of the EU *Guideline on clinical investigation of Medicinal Products for the Treatment of Multiple Sclerosis*. An important point to consider in that guideline with respect to RMS is that although the effect on relapse rate may be investigated in patients with any form of relapsing MS, it is advised to assess the effect on disability only in patients with RRMS. It is therefore accepted that the indication in RMS will mainly rely on the effects shown in patients with RRMS and that an effect on relapses in RRMS may be extrapolated to an effect on relapses in SPMS (Section 3.2.1 of the guideline).

The guideline provides the following advice on primary efficacy parameters in clinical trials for RRMS:

- The most relevant parameter in MS, the accumulation of disability, usually takes place over many years.
- Changes in progression of disability in a few years, which can be shown in clinical trials, could be accepted as a proof of efficacy, although it would be highly desirable to evaluate if the effect is maintained on a long-term basis.
- Changes in progression of disability should be distinguished between accumulation of disability in relation to relapses in Relapsing Remitting Multiple Sclerosis (RRMS) and progression of disability in Secondary Progressive Multiple Sclerosis (SPMS) or in Primary Progressive Multiple Sclerosis (PPMS).
- In patients with RRMS or SPMS with superimposed relapses (RMS), the primary efficacy parameter may also be the relapse rate although the number, duration or severity of relapses cannot be taken as a surrogate for disease progression and this would be expressed accordingly in the SPC[1] (equivalent to the Product Information in Australia).
- Progression of disability should be evaluated and worsening of disability should be reasonably excluded by means of adequately powered long-term studies.

Regulatory Status

Fingolimod was submitted to the FDA and European medicines Agency (EMA) in December 2009.
Gilenya was approved by the FDA on the 21 September 2010 with the indication:

> *"For the treatment of patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability."*

Gilenya was also approved in Russia (17 August 2010) for the indication:

> *Relapsing-remitting multiple sclerosis (RMS)-to reduce the frequency of clinical relapses of disease and to decrease the risk of disability progression."*

Gilenya was also approved in Switzerland (3 January 2011) for the indication:

[1] European Summary of Product Characteristics

Gilenya is indicated for the treatment of patients with relapsing remitting multiple sclerosis (MS) to reduce the frequency of relapses and delay the progression of disability.

The registration processes are ongoing in the European Union (EU), Canada and New Zealand.

Product Information

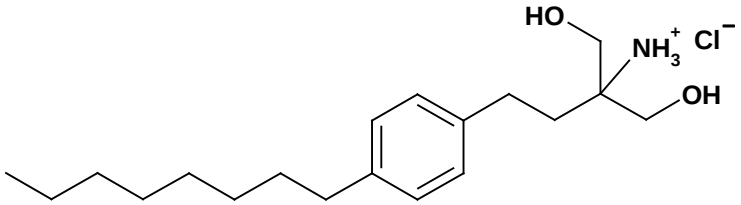
The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

Fingolimod hydrochloride is manufactured by chemical synthesis and has the following structure:

Figure 1. Chemical structure.



It has no chiral centres. It is a crystalline solid that exists in at least five polymorphic forms.

Fingolimod hydrochloride is freely soluble in water and hydrochloric acid (HCl). It has a pKa of 7.8.

The particle size of fingolimod hydrochloride is controlled. The drug substance specifications include limits for specified impurities and also for unspecified impurities. The proposed limits have been adequately qualified.

The drug substance exhibits good stability, and a retest period of 5 years with storage below 30°C has been satisfactorily established.

Drug Product

Apart from the active ingredient, the capsules contain mannitol and magnesium stearate.

The specifications include a dissolution limit and the dissolution method has been shown to be stability indicating.

Specified degradants are controlled in the finished product. All proposed limits have been adequately qualified.

Stability studies on the capsules showed significant decreases in assay values during storage, although there were minimal increases in detected degradants. A shelf life of 18 months below 30°C is approvable at this stage.

Biopharmaceutics

Fingolimod is a prodrug. It is reversibly phosphorylated by sphingosine kinase to the active (S)-fingolimod phosphate. Phosphorylation is stereospecific, producing only the (S)-enantiomer.

Five bioavailability studies were submitted. Two involved an early clinical trial formulation, which is not relevant because all Phase II and Phase III MS clinical trials used the 0.5 mg capsule formulation proposed for registration or a directly scaled 1.25 mg capsule. Another study assessed bioequivalence of two strengths, 1.25 mg and 2.5 mg, which are not proposed for registration.

Study 0108 was a single dose comparison in eleven healthy male and female subjects of one 1.25 mg fingolimod capsule with a 1 mg intravenous (IV) infusion over a two hour period. The dose-adjusted oral/IV geometric mean ratio for fingolimod area under the plasma concentration time curve (AUC) in whole blood was determined to be 0.94 (95% CI 0.78-1.12), suggesting that fingolimod is completely

absorbed via the oral route. Fingolimod phosphate was quantifiable in only one subject after IV administration and in eight subjects after oral administration. For a prodrug, absolute bioavailability would normally be determined by comparing oral administration with IV administration of the active metabolite. However, the issue is complicated in this case by the fact that the phosphorylation of fingolimod is reversible. In addition, IV administration of fingolimod phosphate was claimed to be precluded because of its toxicity.

Study 2107 was a single dose study in 29 healthy male subjects; one 1.25 mg capsule was administered in the fasting state and immediately after a standard high fat meal. The high fat meal had no significant effect on fingolimod AUC or the maximal plasma concentration (C_{max}), and no significant effect on fingolimod phosphate AUC. Fingolimod phosphate C_{max} was reduced by 34% after the high fat meal. The sponsor argued that this is not clinically relevant, and recommends in the PI that the capsules may be taken without regard to meals. This has been referred to the Clinical Delegate.

No bioavailability studies were conducted on the 0.5 mg capsule proposed for registration. The studies discussed above used a 1.25 mg capsule that is a direct scale of the 0.5 mg capsule, differing only in fill weight. Fingolimod hydrochloride is highly soluble under acidic conditions, the two strengths of capsule show similar dissolution profiles, and fingolimod and fingolimod phosphate blood concentrations increase in an apparently dose proportional manner after multiple once-daily doses of 0.5 mg or 1.25 mg. Therefore, the studies conducted on the 1.25 mg capsule are considered applicable to the 0.5 mg capsule.

Quality Summary and Conclusions

Consideration by the Pharmaceutical Subcommittee

This application was considered by the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM) at its 134th meeting in September 2010. The subcommittee supported registration of the product but made the following additional comments:

1. The subcommittee reiterated its objection to the use of multiple trade names for products containing the same drug substance.

2. The subcommittee considered that the 34% decrease in C_{max} caused by a high fat meal is unlikely to be clinically relevant given the mechanism of action (related to exposure) and the very long half-life of fingolimod phosphate, the active metabolite.

Conclusion

There are no objections with regard to Chemistry, Manufacturing and Controls to registration of fingolimod 0.5 mg capsules. A shelf life of 18 months below 30°C should be applied.

III. Nonclinical Findings

Introduction

The overall quality of the submitted dossier was high, with all pivotal toxicity studies conducted under Good Laboratory Practice (GLP) conditions using the proposed clinical route (PO).

Pharmacology

Primary pharmacology

Rationale and mechanism of action

Sphingosine 1-phosphate (S1P) is a bioactive sphingolipid with various functions. The effects of S1P are mediated by 5 G-protein coupled receptors (S1P1-5) that have different spatial expression patterns and mediate signals through different G-protein signalling pathways (see ***Table 1***; reviewed

in Brinkmann, 2007[2]). Fingolimod is intended as an immunosuppressant that, when phosphorylated, modulates the activity of S1P1, in particular, which is located on lymphocytes or on the lymph node endothelium, leading to a down-regulation of S1P1 receptors and prevention of the egress of lymphocytes from secondary lymphatic tissues (Sanna *et al.*, 2006[3]; Matloubian *et al.*, 2004[4]). A reduction in inflammation may also occur *via* S1P1 receptors expressed in neural tissue. The reduction in circulating lymphocytes and reduced T cell infiltration of the central nervous system (CNS) should lead to reduced autoimmune damage to myelin sheaths and axons, ameliorating MS disease pathology.

Table 1. S1P receptors, signalling and function (adapted from Brinkmann, 2007)

S1P receptor	Site of expression	G_{α} subunit	Function
S1P1	cardiovascular system lymphocytes endothelial cells brain (widespread)	$G_{i/o}$	angiogenesis & neurogenesis; regulation of immune cell trafficking; endothelial barrier function & vascular tone
S1P2	cardiovascular system brain auditory & vestibular systems (widespread)	$G_{i/o}$ G_q $G_{12/13}$	development and/or mediation of neuronal excitability; hearing & vestibular systems
S1P3	cardiovascular system brain spleen kidney certain cartilaginous regions	$G_{i/o}$ G_q $G_{12/13}$	fine tunes cardiovascular functions
S1P4	immune compartments leukocytes airway smooth muscle	$G_{i/o}$ $G_{12/13}$	fine tunes T cell cytokine production
S1P5	white matter of CNS	$G_{i/o}$ $G_{12/13}$	unknown

[2] Brinkmann, V. (2007) Sphingosine 1-phosphate receptors in health and disease: mechanistic insights from gene deletion studies and reverse pharmacology. *Pharmacol. Ther.* **115:** 84-105.

[3] Sanna, M.G., S.-K. Wang, P.J. Gonzalez-Cabrera, A. Don, D. Marsolais, M.P. Matheu, S.H. Wei, I. Parker, E. Jo, W.-C. Cheng, M.D. Cahalan, C.-H. Wong & H. Rosen. (2006) Enhancement of capillary leakage and restoration of lymphocyte egress by a chiral $S1P_1$ antagonist *in vivo*. *Nature Chem. Biol.* **2:** 434-441.

[4] Matloubian, M., C.G. Lo, G. Cinamon, M.J. Lesneski, Y. Xu, V. Brinkmann, M.L. Allende, R.L. Proia & J.G. Cyster. (2004) Lymphocyte egress from thymus and peripheral lymphoid organs is dependent on S1P receptor 1. *Nature* **427:** 355-359.

Efficacy

Fingolimod could be converted to fingolimod phosphate in various murine and human tissues *via* the sphingosine kinase enzymes (SPHK1 and SPHK2) (Billich *et al.*, 2003[5]). While SPHK1 could phosphorylate fingolimod, SPHK2 (both murine and human) was quantitatively more efficient than the SPHK1 (K_m18.5 μM for the human isozyme) (Billich *et al.*, 2003) and is likely to be the predominant enzyme involved in the *in vivo* conversion (Zemann *et al.*, 2006[6]). The fingolimod phosphate formed was almost exclusively the *S* isomer (Albert *et al.*, 2005[7]). Racemic fingolimod phosphate was an agonist at the human S1P1, S1P3, S1P4 and S1P5 receptors. The 50% effective dose (EC_{50}) value at the S1P1 receptor was 2.7 times lower than the estimated steady state plasma levels (C_{ss}) of fingolimod phosphate (0.39 ng/mL compared to 1.064 ng/mL[8]), while the EC_{50} values at the S1P3, S1P4 and S1P5 receptors were 16, 211 and 13 times higher than the C_{ss} of fingolimod phosphate, respectively, confirming a preference for the S1P1 receptor. Fingolimod phosphate showed no agonistic or antagonistic activity at the S1P2 receptor (EC_{50} >3600 times the C_{ss} for fingolimod phosphate) (Mandala *et al.*, 2002[9]). In the absence of phosphorylation, fingolimod was not an agonist at the S1P receptors (EC_{50} >308 ng/mL, 150 times the estimated fingolimod C_{ss}).

Fingolimod was a non-competitive inhibitor of recombinant human S1P1 and S1P5 receptors (nanomolar potency) and to a lower extent (circa 10-fold less) the S1P2 receptor. Significant inhibition at the S1P1 and S1P5 receptors was seen at concentrations approximately equivalent to the C_{ss} of fingolimod (3.08 ng/mL [or 10 nM] compared to 2.036 ng/mL), while some inhibition was seen at the S1P2 receptor at 3 times this concentration. No significant inhibition was seen at the S1P3 or S1P4 receptors (Gräler & Goetzel, 2004[10]). Taken together, some inhibition of S1P receptors may occur clinically, but may in part contribute to the desired physiological effects.

Experimental allergic encephalomyelitis (EAE) was used as the rodent model for MS. The disease course is similar to MS, with an acute phase and, depending on the method of EAE induction, a relapsing-remitting phase. Fingolimod was examined for amelioration of clinical disease during both the acute and chronic phases. Rats treated with 0.3 mg/kg/day PO for 2 weeks immediately following EAE induction, delayed the time of acute disease onset by 2 weeks. Disease severity was also reduced with a maximum clinical disease score of 0.9 compared to 2.0 in control animals. The total exposure at this dose is circa 27 times the anticipated clinical AUC[11]. Fingolimod appeared to

[5] Billich, A., F. Bornancin, P. Dévay, D. Mechtcheriakova, N. Urtz & T. Baumruker. (2003) Phosphorylation of the immunomodulatory drug FTY720 by sphingosine kinases. *J. Biol. Chem.* **278:** 47408-47415.

[6] Zemann, B., B. Kinzel, M. Müller, R. Reuschel, D. Mechtcheriakova, N. Urtz, F. Bornancin, T. Baumruker & A. Billich. (2006) Sphingosine kinase type 2 is essential for lymphopenia induced by the immunomodulatory drug FTY720. *Blood* **107:** 1454-1458.

[7] Albert, R., K. Hinterding, V. Brinkmann, D. Guerini, C. Müller-Hartwieg, H. Knecht, C. Simeon, M. Streiff, T. Wagner, K. Welzenbach, F. Zécri, M. Zollinger, N. Cooke & E. Francotte. (2005) Novel immunomodulator FTY720 is phosphorylated in rats and humans to form a single stereoisomer. Identification, chemical proof, and biological characterisation of the biologically active species and its enantiomer. *J. Med. Chem.* **48:** 5373-5377.

[8] The C_{ss} of fingolimod phosphate following a 0.5 mg human dose was estimated from the C_{ss} following a 1.25 mg dose (2.66 ng/mL) shown in Table 3.2.5. Using the same rationale, the C_{ss} for fingolimod (0.5 mg dose) is estimated to be 2.036 ng/mL.

[9] Mandala, S., R. Hadju, J. Bergstrom, E. Quackenbush *et al.* (2002) Alteration of lymphocyte trafficking by sphingosine-1-phosphate receptor agonists. *Science* **296:** 346-349.

[10] Gräler, M.H. and E.J. Goetzel. (2004) The immunosuppressant FTY720 down-regulates sphingosine 1-phosphate G-protein-coupled receptors. *FASEB J.* **18:** 551-553.

[11] Rat $AUC_{0-\infty}$ 2397 ng•h/mL for fingolimod phosphate, with treatment for 2 weeks in a 6 week period. Clinical AUC_{0-24h} 30 ng•h/mL fingolimod phosphate, with treatment daily for a 6 week period.

be efficacious in the relapsing-remitting phase of the disease with a dose of 0.1 mg/kg/day administered orally for 2 weeks after or during the acute phase of the disease, significantly inhibited disease development with disease onset delayed and severity reduced (clinical score 0.75 compared to 1.9 in controls). Fingolimod treatment inhibited neo-angiogenesis in the lumbar region of the spinal cord, with both vascular casting and histological analysis indicating fingolimod-treated rats were similar to naive rats. The minimal effective dose in rats (0.1 mg/kg/day) is estimated to result in an exposure 8 times the clinical AUC. The nonclinical pharmacology studies support the proposed indication for relapsing MS, to reduce the frequency of relapses and delay progression of disability.

Pharmacodynamic drug interactions

The combination of cyclosporine A with fingolimod suppressed EAE disease in rats, but a rebound of disease was evident after treatment, with a clinical score greater than or equivalent to untreated EAE-induced animals, suggesting fingolimod should not be used in combination with cyclosporine A for the proposed indication. The combination of fingolimod with interferon-β to mice had similar efficacy to fingolimod monotherapy in the chronic phase, suggesting no significant pharmacodynamic interactions with this combination.

Secondary pharmacodynamics

At concentrations up to 10 μM *S*-fingolimod phosphate (*ca* 3000 times the clinical C_{ss}), no significant affinity/inhibitory activity was observed for circa 66 G-protein-coupled receptors (GPCRs), transporters, ion channels and enzymes. In a similar screen, as well as in published papers, fingolimod had some inhibitory activity for the histamine H_2 receptor (K_i 0.50 μM or 154 ng/mL), sphingosine phosphate lyase (inhibition at 0.3 μM or 92 ng/mL) (Bandhuvula *et al.*, 2005[12]) and the cannabinoid receptor type 1 (CB_1) receptor (K_i 1 μM or 308 ng/mL) (Paugh *et al.*, 2006[13]). As inhibitory activity at these sites was only detectable at concentrations ≥45 times the clinical C_{ss} for fingolimod, it is unlikely to be of clinical concern at the proposed dose level. *In vitro*, fingolimod at concentrations marginally above the clinical C_{ss} inhibited cytosolic phospholipases A_2 ($cPLA_2$) (but not the secretory or intracellular forms; $sPLA_2$ or $iPLA_2$) and reduced prostaglandin D_2 (PGD_2) secretion by mast cells (Payne *et al.*, 2007[14]). As the major anti-inflammatory effects of fingolimod treatment, in particular, lymphopaenia, are best explained by activity at the S1P1 receptor (Zemann *et al.*, 2006), fingolimod inhibition of $cPLA_2$ with subsequent reduction in the release of the pro-inflammatory, arachidonic acid, may contribute only slightly to the anti-inflammatory activity seen with fingolimod treatment,

Safety pharmacology

Specialised safety pharmacology studies investigated the central and autonomic nervous systems, the cardiovascular, respiratory, renal and gastrointestinal (GI) systems. The majority of the studies were GLP-compliant, while the design, the conduct and reporting of the other studies were adequate to reveal any treatment-related effects.

[12] Bandhuvula, P., Y.Y.Tam, B. Oskouian & J.D. Saba. (2005) The immune modulator FTY720 inhibits sphingosine-1-phosphate lyase activity. *J. Biol. Chem.* **280:** 33697-33700.

[13] Paugh, S.W., M.P. Cassidy, H. He, S. Milstien, L.J. Sim-Selley, S. Spiegel and D.E. Selley. (2006) Sphingosine and its analog, the immunosuppressant 2-amino-2-(2-[4-octylphenyl]ethyl)-1,3-propanediol, interact with the CB_1 cannabinoid receptor. *Mol. Pharmacol.* **70:** 41-50.

[14] Payne, S.G., C.A. Oskertzian, R. Griffiths, P. Subramanian, S.E., Barbour, C.E. Chalfant, S. Milstien and S. Spiegel. (2007) The immunosuppressant drug FTY720 inhibits cytosolic phospholipase A2 independently of sphingosine-1-phosphate receptors. *Blood* **109:** 1077-1085.

Neurological studies examined behaviour, neuromuscular function, locomotor activity, seizure potentiation, effects on sleeping time and autonomic function in mice, rats, rabbits and/or cats. While a slight reduction in motor coordination was seen in mice treated with 10 mg/kg PO fingolimod and a mild CNS depressive activity seen in rats treated with ≥4 mg/kg/day PO fingolimod, there were no remarkable central or autonomic nervous system effects seen at doses resulting in C_{max} values ≤95 ng/mL, or up to 47 times the clinical C_{ss}. Therefore there are no particular CNS concerns at the proposed dose level.

Fingolimod (≥154 ng/mL) and *S*-fingolimod phosphate (387 ng/mL) inhibited hERG K^+ tail current (25-49% and 18%, respectively), however, the No Observable Effect Levels (NOELs) were 49 and 110 times, respectively, the clinical C_{ss}, suggesting no clinically relevant interactions at the hERG K^+ channel would be expected. There was no effect on QT_c prolongation[15] *in vitro* (isolated porcine heart) with fingolimod and fingolimod phosphate concentrations at least 75 times the clinical C_{ss}, or *in vivo* in dogs (5 mg/kg PO; ratio of estimated C_{max} to clinical C_{ss} [$ER_{Cmax/Css}$], 75) and monkeys (10 mg/kg PO; $ER_{Cmax/Css}$, 85). Effects on QT prolongation during clinical use are not predicted to occur based on animal data.

While no effect on QT prolongation was observed in electrocardiogram (ECG) analyses, prolongation of the PR interval, disappearance of P wave, 2nd to 3rd degree atrioventricular (AV) block and ventricular premature complexes were commonly seen. *In vivo*, consistent negative chronotropic effects were seen in animals, with bradycardia, increased blood pressure and sinus arrhythmias seen. These occurred in rats at oral doses ≥1 mg/kg (NOEL 0.1 mg/kg PO; $ER_{Cmax/Css}$, 9). The sinus arrhythmias consisted of sinus arrest for 2-3 beats, occasionally associated with AV junctional escape beats. In isolated Langendorff-perfused rabbit hearts, acting at the sinus node, a significant increase in cycle length was seen with ≥100 nM fingolimod (NOEL 30 nM; 4 times the clinical C_{ss}). The effect was more pronounced with fingolimod phosphate (≥10 nM; 4 times the clinical C_{ss}), was similar with sphingosine 1-phosphate and could be inhibited with pertussis toxin. These effects are consistent with a pharmacological effect on S1P3 receptors activating G-protein activated inwardly rectifying potassium (GIRK; I_{KACh}) channels in atrial tissues (Koyrakh *et al.*, 2005[16]; Jan and Jan, 2000[17]). Reports of bradycardia and AV conduction block in clinical studies with fingolimod (Product Information) confirm the relevance of animal findings. In animals, bradycardia and sinus arrhythmias were most prominent at initial dosing, but lasted for several hr, even up to 17 hr in one study. A trend to tolerance was evident with repeat dosing. However, as the effects were similar in intensity after a washout period, in animals which still had low lymphocyte levels, caution would be necessary with intermittent dosing or at times when patients may neglect their medication.

The most notable respiratory effect was dyspnoea that occurred at a similar time and dose as the ECG changes and observed bradycardia in most animals. As with the cardiovascular findings the dyspnoea is likely to be pharmacologically mediated, being associated with bronchoconstriction, and occurred at clinically relevant exposures. Other minor findings included a modest decrease in respiratory minute volume and respiratory tidal volume in rats at 3 mg/kg IV fingolimod. However, no effect was seen on respiratory rate in rats and monkeys that had received 10 mg/kg PO

[15] QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death. The QT interval is dependent on the heart rate (the faster the heart rate, the shorter the QT interval). To correct for changes in heart rate and thereby improve the detection of patients at increased risk of ventricular arrhythmia, a heart rate-corrected QT interval *QTc* is often calculated.

[16] Koyrakh, L., M.I. Roman, V. Brinkmann and K. Wickman. (2005) The heart rate decrease caused by acute FTY720 administration is mediated by the G protein-gated potassium channel I_{KACh}. *Am. J. Transplant.* **5:** 529-536.

[17] Jan, L.Y. and Y.N. Jan. (2000) Heartfelt crosstalk: desensitisation of the GIRK current. *Nat. Cell Biol.* **2:** E165-E167.

fingolimod. It is noted that coughs and dyspnoea are described as common adverse drug reactions (ADRs) in the Product Information.

In rats, fingolimod (10 mg/kg PO; estimated $ER_{Cmax/Css}$, 186) induced a reduction in urinary volume while creatinine clearance and sodium excretion were transiently affected in treated dogs (10 mg/kg PO; estimated ER_{AUC}, 248). Given the nature of these findings, the high exposure ratios and the lack of any consistent renal toxicity signals in repeat dose toxicity studies, there are no obvious renal toxicity concerns with the proposed dose.

No significant effects on the GI system were seen with fingolimod. Fingolimod (up to 1 μM; ~150 times the clinical C_{ss}), had no significant effects on agonist-induced contractions of isolated guinea pig ileum strips. There was no effect on GI motility in mice that had received 10 mg/kg PO fingolimod ($ER_{Cmax/Css}$, 186), no effect on gastric acid output in rats (up to 10 mg/kg intraduodenal; 1000 times the clinical mg/kg dose) and no effect on gastric emptying in rats with repeat dosing (relative exposure based on AUC [ER_{AUC}], 74).

No significant effect on platelet aggregation or plasma corticosterone levels was seen with fingolimod and/or *S*-fingolimod phosphate.

Pharmacokinetics

There were no apparent gender differences in pharmacokinetic parameters. Fingolimod was slowly absorbed in all species (8-12 hr in animals and 8-16 hr in humans). The half-life of fingolimod in blood was relatively long in animals; 25-38 hr in mice, 14-30 hr in rats, 25-43 hr in dogs and 30-44 hr in monkeys, but much longer in humans; 147 h. The volume of distribution was greater than total body water and clearance was roughly similar in all species. Oral bioavailability was moderate in animals (40-87%) and much higher in humans (95%). Lymphatic absorption of fingolimod in rats was negligible.

Fingolimod was rapidly converted to the pharmacologically-active *S*-fingolimod phosphate, following IV administration to rats, suggesting rapid phosphorylation. Likewise a rapid dephosphorylation was detectable following IV administration of fingolimod phosphate. The interconversion of fingolimod and fingolimod phosphate was evident in the blood from all species but clearly different rates were quantified. Phosphorylation and dephosphorylation were lowest in human blood, while the fastest phosphorylation was in rodent blood and dephosphorylation in mouse blood. The differing interconversion rates of fingolimod phosphate and fingolimod probably accounts for the different molar exposure (AUC) ratios of these across species (fingolimod phosphate/fingolimod); 1.5 in mice, 1.9 in rats, 1.3 in dogs, 0.8 in monkeys and 0.41 in humans.

Fingolimod largely distributed to red blood cells from animals (80-90% in blood from rats, dogs and monkeys) and to a lesser extent to human blood cells (65%). *S*-fingolimod had a smaller uptake in red blood cells (33-54% in mice, rats and monkeys, and 13-17% in dogs and humans). Protein binding of both fingolimod and *S*-fingolimod phosphate was high (≥99.5%) and independent of concentration in plasma from mice, rats, dogs, monkeys and humans. The high protein binding in human plasma was mainly attributable to serum albumin binding and, in the case of fingolimod, various lipoproteins. Slow migration into the systemic circulation was observed with the time of maximal plasma concentration (T_{max}) in most tissues ≥12 h. Aside from organs of excretion (liver and kidneys), the adrenal, Harderian (in mice), lachrymal and pituitary glands, glandular stomach, lungs, spleen, spinal cord and brain had high levels of radioactivity after radioactive carbon (^{14}C) labelled-fingolimod administration. Reversible melanin-binding was evident in pigmented rats.

Dose-dependent uptake into the brain was evident, with a slow clearance from the cerebrum, cerebellum and spinal cord in rats and dogs; elimination half-lives were ~10 times that from blood. It is unknown what, if any, transporters are involved in fingolimod and/or fingolimod phosphate uptake into or efflux from the brain. Delayed elimination from the brain was not caused by irreversible binding of the compound to brain tissues. Steady-state calculations suggested

brain:blood concentration ratios of 41-346 in mice, rats, dogs and monkeys, depending on dose. Fingolimod appeared to localise to the cerebellum white matter and, in particular, the myelin sheaths. There was no apparent binding to neurons. After repeated daily dosing to rats, the highest accumulation was seen in the cerebellum white matter, spinal cord, and brain and eye lens.

Fingolimod was extensively metabolised in all species with >21 drug-related entities detected. All metabolites in humans were found in animal species. Fingolimod phosphate was the major metabolite in the plasma/blood of all species. Only a low level of absorbed fingolimod was excreted intact. Besides phosphorylation, metabolism involved oxidation with chain shortening *via* β-oxidation, conjugation with taurine or glucuronide, or the formation of ceramide analogues. Fingolimod and its phosphate were the only significant drug-related entities detected in the CNS of rats. *In vitro* studies with recombinant human cytochrome p450 (CYPs) enzymes and hepatic microsomes indicated a major role of CYP4F2 in the initial ω-hydroxylation of fingolimod with a subsequent oxidation by alcohol dehydrogenase to the corresponding carboxylic acid.

Drug-related material was excreted in both the urine and the faeces in animals. Predominantly urinary excretion was observed following ^{14}C-fingolimod to human subjects. Enterohepatic recycling of drug related material was seen in rats but this constituted largely non-pharmacologically active metabolites. Overall, the pharmacokinetic profile of fingolimod was qualitatively similar across the tested animals and humans.

Pharmacokinetic drug interactions

CYP4F2 is the major CYP involved in fingolimod metabolism and it is possible that inhibitors of this isozyme, such as ketoconazole, could alter the exposure of fingolimod clinically. No significant inhibition of human CYPs[18] or transporters[19] was seen with fingolimod or fingolimod phosphate at clinically-relevant concentrations (50% inhibitory concentration (IC_{50}) values >1500 times the clinical C_{ss}). No significant induction of CYP1A2, 3A4 or 4F2 or ABCB1[20] (P-glycoprotein) messenger ribonucleic acid (mRNA) or effect on CYP1A2, 3A4, 4F2, 2B6 or CYP2C8/9/19 activity was seen with fingolimod at concentrations 150 times the clinical C_{ss}. Due to technical difficulties with *in vitro* studies, no conclusions could be made with regard to P-glycoprotein transport, though pharmacokinetic studies following co-administration of fingolimod with cyclosporine A (CsA) suggest fingolimod does not interact with this transporter. Based on these data, fingolimod is not expected to significantly alter the exposure of co-medications.

Toxicology

Acute toxicity

The acute toxicity of fingolimod was investigated in mice, rats and dogs, with studies using animals of both sexes, the clinical (PO) and, in mice, the IV route, and an observation period of 14 days, in accordance with the EU guideline for single-dose toxicity[21]. All doses tested would be expected to generate maximum plasma concentrations in excess of that attained clinically. All animals were subjected to gross examination. The maximum non-lethal dose of fingolimod by the oral route was 2000 mg/kg in dogs and by the IV route 25 mg/kg and 10 mg/kg in mice and rats, respectively.

[18] CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4/5 and 4A9/11

[19](OATP1B1, OATP1B3, NTCP, MXR, MRP2 or BSEP

[20] The membrane-associated protein encoded by this gene is a member of the superfamily of ATP-binding cassette (ABC) transporters. ABC proteins transport various molecules across extra- and intra-cellular membranes. ABC genes are divided into seven distinct subfamilies (ABC1, MDR/TAP, MRP, ALD, OABP, GCN20, White). The protein encoded by this gene is an ATP-dependent drug efflux pump for xenobiotic compounds with broad substrate specificity. It is responsible for decreased drug accumulation in multidrug-resistant cells and often mediates the development of resistance to anticancer drugs. This protein also functions as a transporter in the blood-brain barrier.

[21] Single dose Toxicity 3BS1a (1987). http://www.tga.gov.au/docs/pdf/euguide/vol3b/3bs1aen.pdf

These doses are estimated to result in exposures at least 260 times that anticipated clinically, indicating a low order of acute toxicity for the drugs. Similar findings were seen across the studies with the lymphoid tissue and, in rodents, the lungs as target organs. Clinical signs were seen in all species, and included ruffled fur, sedation, dyspnoea, hunched posture, uncoordinated movements and convulsions in rodents following IV administration and high oral doses (rats). Vomiting was also seen in dogs at high oral doses. Gross examinations indicated lymphoid atrophy of the spleen, thymus and lymph nodes of rats and dogs. Medullary enlargement was also evident in the thymus. Dark-red discolouration, haemorrhage and bronchial foamy fluid release were evident in the lungs of rodents.

Repeat dose toxicity

Studies by the oral route of up to 3 months were conducted in mice, 6 months in rats and in dogs and 52 weeks in cynomolgus monkeys. No marked differences were noted in the toxicity profiles across the species. The duration of the pivotal studies, the species used, group sizes and the use of both sexes were consistent with ICH guidelines. Dose selection in the pivotal studies was appropriate.

Relative exposure

Relative exposure levels achieved in repeat dose toxicity studies have been calculated as the ratio of the AUC for fingolimod in animals to that of humans at the recommended dose (0.5 mg/day). Though fingolimod phosphate is the pharmacologically active metabolite, only exposure data for fingolimod were available. As the molar ratio of fingolimod phosphate and fingolimod is higher in the blood of animals than that in humans, calculating exposure margins on the basis of fingolimod is a conservative measure. The human AUC and C_{max} were extrapolated from data for a 1.25 mg PO dose. High relative exposures (≥25) were obtained at the highest doses in all pivotal studies (***Table 2***).

Lymphoid organ toxicity

Lymphopaenia, with associated lymphoid atrophy of the splenic white pulp, mesenteric and submandibular lymph nodes, and thymic cortical atrophy with medullary enlargement were seen in all species; mice ≥0.1 mg/kg/day PO (relative exposure based on AUC [ER_{AUC}], 2.3), rats ≥0.01 mg/kg/day PO (ER_{AUC}, 0.15), dogs ≥0.01 mg/kg/day PO (ER_{AUC}, 0.2) and monkeys ≥0.5 mg/kg/day PO (ER_{AUC}, 7). A NOEL could not be established in mice, rats or monkeys. These can all be attributed to pharmacological activity of fingolimod phosphate on the S1P1 receptor, reducing T cell egress into the periphery (Matloubian *et al.*, 2004[22]). These findings are consistent with the anti-inflammatory activity of fingolimod, were reversible after cessation of treatment and are not considered adverse. The increased haemopoiesis in the spleen seen in mice at ≥0.1 mg/kg/day and rats at ≥0.3 mg/kg/day and apparent increase in granulocyte production in the bone marrow (increased metamyelocyte ratio in rats at 30 mg/kg/day, increased number of neutrophilic granulocytes in mice at 5 mg/kg/day and myeloid hyperplasia in monkeys at ≥1 mg/kg/day) are secondary to the reduced lymphocyte release from the thymus.

[22] Matloubian, M., C.G. Lo, G. Cinamon, M.J. Lesneski, Y. Xu, V. Brinkmann, M.L. Allende, R.L. Proia & J.G. Cyster. (2004) Lymphocyte egress from thymus and peripheral lymphoid organs is dependent on S1P receptor 1. *Nature* **427:** 355-359.

Table 2. Relative exposure of fingolimod in repeat dose toxicity studies.

Species (Strain)	Study	Treatment duration		Dose (mg/kg/day) PO	AUC_{0-24h} (ng·h/mL)	C_{max} (ng/mL)	Exposure ratio based on[a]	
							AUC	C_{max}
Mouse (CD-1)	DMPK(CH) R98-2057	13 weeks		0.1	126	6	2.3	2.2
				0.5	588	33	11	12
				5	6252	328	112	121
	PCS(EU) R00-0479 [carcinogenicity]	104 weeks		0.025	31	1.6	0.6	0.6
				0.25	288	17	5	6
				2.5	3167	171	57	63
Rat (Han:Wist)	DMPK(CH) R98-2058	13 weeks		0.1	140	7.4	2.5	2.7
				0.5	566	29	10	11
				5	5283	272	94	101
	DMPK(CH) R99-2083	6 months		0.3	437	23	8	9
				1.5	2295	127	41	47
				7.5	9557	509	171	189
	PCS(EU) R00-0478 [carcinogenicity]	104 weeks		0.05	58	3	1.0	1.1
				0.15	171	9	3	3
				0.5	603	32	11	12
				2.5	3027	157	54	58
Rat (SD)	R-7219	6 months		0.01 [b]	8.6	0.49	0.15	0.18
				0.03 [b]	26	1.5	0.5	0.6
				0.3 [b]	258	15	5	6
				10	8589	493	153	183
	PCS(EU) R0300286 [*juveniles*]	9 weeks	Day 7 pp	0.5	321	6	2.2	2.2
				5	3250	58	21	21
			Day 27 pp	0.5	208	4	1.5	1.5
				5	1915	34	13	13
Dog (Beagle)	R-7393	6 months		0.001 [b]	1	0.06	0.02	0.02
				0.01 [b]	10	0.6	0.18	0.2
				1 [b]	1022	55	18	20
				10	10224	548	183	203
	R-7010 [c]	1 month		0.01	13	–	0.2	–
				0.1	119	–	2	–
				1	1086	–	19	–
	R-7148 [c]	1 month		3	3822	–	68	–
				10	11136	–	199	–
				30	38616	–	690	–

Table continued on next page.

Table 2 continued.

Monkey (Cynomolgus)	R-7456	2 weeks	3	2946	180	53	67
			10	10322	646	184	239
			30	36027	1894	643	701
	R-7767	13 weeks	1	835	43	15	16
			3	2199	115	39	43
			10	12511	674	223	250
	DMPK(CH) R99-1761	39 weeks	0.5	402	20	7	7
			3	2761	142	49	53
	971546 [d]	52 weeks	1	648	–	12	–
			3	1800	–	32	–
			10	6648	–	119	–
Human	D2101	multiple dose	[0.5 mg]	56	2.7	–	–

[a]calculated as animal:human AUC from 0 to 24 h ($_{0–24h}$); [b]extrapolated from data for 10 mg/kg/day dose; [c]AUC=(C_{8h} +C_{24h})×12; [d]AUC= C_{24h}×24; data are for the sexes combined (except in rats), and averages across sampling days (excluding Day 1)

Pulmonary toxicity

Pulmonary changes were evident in all species following fingolimod treatment. Increased levels of alveolar macrophages were seen in mice treated with ≥0.025 for 104 weeks (ER_{AUC}, 0.6), dogs with ≥1 mg/kg/day for 6 months (NOEL 0.01 mg/kg/day; ER_{AUC}, 0.2) and monkeys with ≥3 mg/kg/day for 52 weeks (NOEL 1 mg/kg/day; ER_{AUC}, 12). Pneumonia and congestion were also evident in dogs at ≥0.1 mg/kg/day (ER_{AUC}, 2). Increased interstitial collagenisation in the walls of bronchioles and alveolar ducts were seen in mice (≥0.25 mg/kg/day for 104 weeks; ER_{AUC}, 5), rats (≥0.1 mg/kg/day for 13 weeks; ER_{AUC}, 2.5) and monkeys (≥3 mg/kg/day for 39 weeks; ER_{AUC}, 49). Osseous metaplasia, probably as a result of chronic collagenisation and inflammation, was evident in both mice and rats treated for a prolonged period with fingolimod (ER_{AUC} at the NOEL, 0.6 and 3, respectively). Subpleural fibrosis and scarring were still evident after a 4 week treatment-free period in dogs and had only partially resolved after a 26 week treatment-free period in monkeys. Microarrays and gene expression analyses in mice, rats and monkeys indicated fingolimod treatment induced extracellular matrix (ECM) remodelling, endothelial cell activation and macrophage infiltration. The use of S1P3 knockout mice, an S1P1/S1P5 dual agonist and structural analogues, suggested the effects were pharmacologically-mediated *via* the S1P1 receptor. Given the nature of the effects, the low exposures and the poor reversibility of the effects, some concern with pulmonary function and pulmonary tissue damage exists with chronic administration.

Smooth muscle hypertrophy in the lungs was also seen in treated rats (≥0.05 mg/kg/day for 104 weeks; ER_{AUC} 1) and monkeys (≥0.5 mg/kg/day for 39/52 weeks; ER_{AUC} 7). The mechanism of hypertrophy is unclear but it is likely to be mechanistically similar to the hypertrophy observed in cardiac tissue (see below) and involve pharmacological action on S1P1 receptors on smooth muscle cells (Means and Brown, 2009[23]). The clinical relevance of this pulmonary hypertrophy is unclear. At higher exposures, pulmonary oedema was evident in mice (≥5 mg/kg/day for 2 weeks; estimated ER_{AUC}, 112) and dogs (≥1 mg/kg/day for 6 months; ER_{AUC}, 18). This is likely associated with S1P3

[23] Means, C.K. and J. Heller Brown. (2009) Sphingosine 1-phosphate receptor signalling in the heart. *Cardiovasc. Res.***82:** 193-200.

receptor signalling in epithelial cells affecting lung barrier function (Gon *et al.*, 2005[24]). Given the high exposures with no oedematous effect seen in rats or monkeys, pulmonary oedema is unlikely to be a clinical concern.

In summary, the pulmonary effects of most concern are the persistent inflammation and collagenisation with scarring and pulmonary remodelling which were seen in all species after chronic administration. These effects were not completely reversible, occurred at clinically-relevant exposures and were only evident after long-term administration. An irreversible or only partially reversible deterioration in pulmonary function may occur with long term clinical use. Given the intended chronic dosing, monitoring of pulmonary function would be recommended with fingolimod.

Cardiovascular toxicity

Increased heart weights were seen in mice treated with 5 mg/kg/day for 3 months (ER_{AUC}, 112) and rats treated with ≥1.5 mg/kg/day for 6 months (ER_{AUC}, 41). No effect on heart weight was seen in dogs and monkeys. Myocardial hypertrophy was seen in mice (20 mg/kg/day; estimated ER_{AUC} at the NOEL, 112) and monkeys (males only, 3 mg/kg/day for 52 weeks; ER_{AUC} 32). Myocardial hypertrophic responses have previously been attributed to S1P1 signalling in smooth muscle cells (Means and Brown, 2009). While myocardial inflammation and degeneration were evident in rats treated with 2.5 mg/kg/day for 104 weeks (ER_{AUC}, 54), this dose was also associated with excessive mortality. Generalised vasculopathy (in the thymus, mesentery, spleen and/or kidneys) was seen in mice treated with 20 mg/kg/day (ER_{AUC} at the NOEL, 112) and rats with 1.5 mg/kg/day for 6 months (ER_{AUC}, 41), while vascular thickening, subendocardial haemorrhage and/or endocardial fibrosis were restricted to the heart in both dogs (≥1 mg/kg/day for 6 months; ER_{AUC}, 18) and monkeys (≥1 mg/kg/day for 52 weeks; ER_{AUC}, 12). While these cardiovascular effects are either associated with fingolimod pharmacology (myocardial hypertrophy) or are secondary to haemodynamic effects (vasculopathy), the exposures at the NOEL in all species suggest they are unlikely to be of clinical concern at the proposed dose level.

Renal effects

Kidney changes included basophilic tubules and hyaline casts in rats treated for 6 months with ≥0.3 mg/kg/day (ER_{AUC}, 8) and nephropathy in female mice treated for 104 weeks with 0.25 mg/kg/day (ER_{AUC} at the NOEL, 0.6). No kidney findings were seen in dogs or monkeys treated with up to 10 mg/kg/day (ER_{AUC} >110), suggesting the renal effects are likely to be restricted to rodents.

Ophthalmological effects

An increase in the incidence of posterior subcapsular lens opacity, slight to moderate in severity, was seen in mice treated with ≥0.25 mg/kg/day for 104 weeks (ER_{AUC}, 5). The exposure at the NOEL was below that expected clinically. The relevance of this to clinical use is unclear as no ophthalmological findings were seen in rats or monkeys at high exposures and/or chronic administration and the only significant ophthalmological finding in dogs at high exposures (10 mg/kg/day PO for 6 months; ER_{AUC}, 183) was retinal vacuolation. Furthermore the increased lens opacity in mice is not relevant to the ophthalmic findings in the clinical studies. No consistent effects on blood-retina barrier integrity were seen in rats treated orally with up to 10 mg/kg/day fingolimod for 35 days even though eye levels of fingolimod were 7-12 times blood levels.

[24] Gon, Y., M.R. Wood, W.B. Kiosses, E. Jo, M.G. Sanna, J. Chun and H. Rosen. (2005) $S1P_3$ receptor-induced reorganisation of epithelial tight junctions comprises lung barrier integrity and is potentiated by TNF. *Proc. Natl. Acad. Sci. USA* **102:** 9270-9275.

Other toxicities

Single cell necrosis of hepatocytes was only seen at high doses in rats (≥10 mg/kg/day for 6 months; ER_{AUC}, 171) and dogs (30 mg/kg/day for 1 month; ER_{AUC}, 690). There was no evidence of hepatotoxicity in mice or monkeys (ER_{AUC}, 110). Vacuolation of the adrenal medulla, with reduced medullary cells and fibrosis was seen in dogs treated for 6 months with 10 mg/kg/day PO fingolimod (ER_{AUC}, 183). There were no meaningful adrenal findings in any other species. Mononuclear cell infiltration into the brain and GFAP[25] positive astrocytes were seen in dogs and monkeys, respectively, treated with 10 mg/kg/day PO fingolimod (ER_{AUC}, >110). As these findings occurred at exposures far exceeding that expected clinically, they are not of particular concern.

Genotoxicity

The potential genotoxicity of fingolimod was investigated in the standard battery of tests and in an assay for mammalian gene mutation. A suitable set of *S. typhimurium* and *E. coli* strains were used in bacterial mutagenicity assays and animals of both sexes were used in at least one of the micronucleus assays. Doses used in *in vivo* studies were appropriate. While the conduct of the studies was in accordance with ICH guidelines[26], concentrations achievable in *in vitro* assays were limited due to excessive cytotoxicity, with concentrations ≤100 mg/plate and ≤40 mg/mL achievable in bacterial mutagenicity and mammalian mutagenicity/clastogenicity assays, respectively, limiting the predictive value of the negative findings[27]. The only significant finding was an increase in numerical aberrations (polyploidy) in a strain of Chinese hamster lung cells (V79) at fingolimod concentrations ≥3.7 µg/mL (3 hr incubation) in the absence of metabolic activation. The relevance of polyploidy as a genotoxic lesion is uncertain, and suggested to only be relevant if it occurs at or below therapeutic concentrations (Mitchell *et al.*, 1995[28]). As polyploidy only occurred at concentrations >1800 times the clinical C_{ss} for fingolimod and it did not appear to occur in another cell line (human peripheral blood lymphocytes) at similar concentrations, and it is therefore not likely to be toxicologically important. An absence of chromosomal aberration findings in both mouse and rat clastogenicity assays with IP and PO doses, respectively, resulting in exposures (AUC and C_{max}) at least 500 times that expected clinically, further confirms the *in vitro* polyploidy findings are not clinically-relevant.

Carcinogenicity

The carcinogenic potential of fingolimod by the oral route was investigated in 2-year studies in mice and rats (GLP-compliant). Group sizes were appropriate and dual control groups were used, as recommended in the EU guideline on carcinogenic potential (3BS7a). The highest doses used in both studies (2.5 mg/kg/day) produced excessive mortality in male mice and both sexes in rats, necessitating early termination of dosing (in Week 92 for male mice, Week 99 for male rats and Week 75 for female rats). Given the late stage of termination of the male groups, this is not considered to have adversely affected the adequacy of the studies to reveal potential carcinogenic effects. For the rat study, the next highest dose given to females (0.5 mg/kg/day) is considered to be the highest one adequately tested for carcinogenic potential in females due to the early termination of this group. No treatment-related increases in tumour incidence were observed in rats; exposure ratios at the highest adequate doses are 54 in males and 11 in females. In mice at doses ≥0.25

[25] glial fibrillary acidic protein

[26] ICH Topic S2b. Genotoxicity: A standard battery for genotoxcicity testing of pharmaceuticals. http://www.tga.gov.au/docs/pdf/euguide/ich/017495en.pdf. Testing of Medicinal Products for Their Mutagenic Potentia 3bS5 l http://www.tga.gov.au/docs/pdf/euguide/vol3b/3bs5aen.pdf.

[27] Guideline ICH 3BS6a indicates that desired concentrations are 5 mg/plate for bacteria and 5 mg/mL or 10 mM (whichever is lower) for mammalian cells.

[28] Mitchell, I. de G., T.R. Lambert, M. Burden, J. Sunderland, R.L. Porter and J.B. Carlton. (1995) Is polyploidy an important genotoxic lesion? *Mutagen.* **10:** 79-83.

mg/kg/day, there was a trend to increased incidences of systemic tumours. The incidences of histiocytic sarcomas, haemangiomas and haemangiosarcomas were all within historical control data for this strain[29]. However, in both males and females treated with ≥0.25 mg/kg/day (ER_{AUC}, 5), there was a dose-dependent increase in malignant lymphomas, most likely secondary to immunosuppression. As the exposure at the NOEL was below the anticipated clinical exposure (ER_{AUC}, 0.6), and lymphoproliferative disorders are known to be associated with chronic immunosuppressive therapy in humans (Andreone *et al.*, 2003[30]), these tumours are likely to be clinically-relevant.

Reproductive toxicity

A standard set of GLP-compliant reproductive toxicity studies was submitted and examined fertility (in rats), embryofetal toxicity (rats and rabbits) and pre/postnatal development (rats). Adequate animal numbers were used and treatment periods were appropriate. Unfortunately, supportive toxicokinetic data submitted for the reproductive toxicity studies were limited. Where necessary, exposure values have been estimated by extrapolation from data obtained in other appropriate studies (***Table 3***). Estimated exposures achieved in the reproductive studies were adequate

There was no apparent effect on fertility in rats up to 10 mg/kg/day (ER_{AUC}, 153) in a study in which both male and female animals were treated and mated. However, testicular epididymal, prostate and seminal vesicle atrophy was evident in 1-2 males/dose at ≥1 mg/kg/day (ER_{AUC}, 15) but with no apparent effect on sperm count. Reduced prostatic secretion in rats was seen in only one repeat dose toxicity study at doses ≥0.1 mg/kg/day, while hypospermatogenesis in dogs was only seen at high doses (30 mg/kg/day; ER_{AUC}, 690). There were no apparent effects on female reproductive organs. As the effects in males only occurred at high exposures, they are unlikely to be of clinical concern.

[29] Charles River (March 2005) Spontaneous lesions in the Crl:CD-1(ICR) mouse in control groups from 18 month to 2 year studies.

[30] Andreone, P., A. Gramenzi, S. Lorenzini, M. Biselli, C. Cursaro, S. Pileri and M. Bernardi. (2003) Posttransplantation lymphoproliferative disorders. *Arch. Intern. Med.* **163:** 1997-2004.

Table 3. Relative exposure in reproductive toxicity studies.

Study	Species & strain	Dose (mg/kg/day); PO	AUC_{0-24h} (ng·h/mL)	C_{max} (ng/mL)	Exposure ratio based on	
					AUC	C_{max}
Fertility; R-7027[a]	**Rat** (SD) *[nonpregnant males and females]*	1	859	49	15	18
		3	2577	148	46	55
		10	8589	493	153	183
Embryofetal; R-7763, R-7797[a]	**Rat** (SD) *[pregnant females]*	0.03	26	1.5	0.46	0.6
		0.1	86	5	1.5	2
		0.3	258	15	4.6	6
		1	859	49	15	18
		3	2577	148	46	55
		10	8589	493	153	183
Pre/Postnatal; 997110[a]	**Rat** (SD) *[pregnant females]*	0.05	43	2.5	0.77	1
		0.15	129	7.5	2.3	3
		0.5	430	25	8	9
Embryofetal; R-7873, R-7912[b]	**Rabbit** (Kbl:JW(SPF)) *[pregnant females]*	0.01	0.32	0.062	0.006	0.023
		0.03	1	0.19	0.02	0.070
		0.3	9.6	1.9	0.17	0.7
		3	114	11	2	4
		10	546	85	10	31
		30	1638	255	29	94
Embryofetal; 987117	**Rabbit** (NZW) *[pregnant females]*	0.5	16	3.1	0.29	1
		1.5	57	5.5	1	2
		5	273	42.6	5	16
D2101	**Human**	[0.5 mg]	56	2.7	–	–

[a]*Estimated from data in another study, Study R-7219;* [b]*Estimated from data in Study 987117, assuming no significant strain differences in pharmacokinetics*

Fingolimod and/or its metabolites (S-fingolimod phosphate, M3 and M4) readily crossed the placenta in rats and rabbits with fetal fingolimod and fingolimod phosphate exposures, at least in rats, equivalent to those in maternal blood. Fingolimod was teratogenic in both rats and rabbits, with evidence of defects in the thymus (rats, rabbits[31]) and the cardiovascular system (rats only). The cardiovascular malformations included persistent truncus arteriosis, ventricular septal defect, left umbilical artery and supernumerary artery. The estimated exposures[32] were similar to clinical exposures (ER_{AUC} 2 (rabbits) and 0.5 (rats)) for teratogenicity, and less than clinical exposure at the NOEL. In New Zealand White (NZW) rabbits at clinical exposures (≥1.5 mg/kg/day; ER_{AUC} 1), there was an increase in skeletal variations (incomplete/no ossification, misshapen or bent bones

[31] The thymic defect seen in Kbl:JW(SPF) rabbits at 3 mg/kg/day was not observed in NZW rabbits at doses up to 5 mg/kg/day, but as this finding also occurred in rats, it is likely to be treatment-related; the differing rabbit results may represent a strain difference in susceptibility.

[32] Direct systemic exposures were not measured in these studies and have been estimated from similar studies. For comparison, the teratogenic doses on a body surface area basis (mg/m^2) were: rabbits 33 mg/m^2/day (100x clinical) with NOEL 3.3 mg/m^2/day (10x clinical); rats 0.18 mg/m^2/day (0.5x clinical) with NOEL not established.

and supernumerary vertebrae or ribs), effects not seen in Kbl:JW(SPF) rabbits. All of the findings in the embryofetal studies are consistent with a role of the S1P1 receptor in vascular maturation (Liu *et al.*, 2000[33]) and limb development (chondrocyte deposition and digit morphogenesis) (Chae *et al.*, 2004[34]), suggesting they are associated with a pharmacological effect. The increased incidence of post-implantation loss and resorptions seen in rats (≥1 mg/kg/day, ER_{AUC}, 15) and rabbits (≥5 mg/kg/day; ER_{AUC}, 5) are consistent with the embryolethality reported for a murine S1P1 mutant, which is assumed to occur as a result of severe smooth muscle and vascular developmental impairment (Liu *et al.*, 2000). The sponsor's Clinical Overview reported that 18 fingolimod-treated women chose to take their pregnancies to term. In this small number, three women spontaneously aborted while a fourth delivered a baby with unilateral congenital posteromedial bowing of the tibia. Unfortunately the size of the placebo group was too small for comparison purposes (one pregnancy for one spontaneous abortion). Abortions and skeletal deformities are consistent with animal findings with fingolimod. Although this would require clinical comment, an association with fingolimod treatment cannot be dismissed. Given the evidence of fetal damage at clinically-relevant exposures in two species, fingolimod should not be used in pregnancy.

In a pre/postnatal study in rats, in which dams were treated from gestation day (GD) 6 and throughout lactation, an increased incidence of total litter loss and increased number of stillbirths were seen at 0.5 mg/kg/day (ER_{AUC}, 8), while reduced postnatal viability was evident at all doses (≥0.05 mg/kg/day; ER_{AUC}, 0.8). The reduced perinatal survival (to Day 4) could not be attributed to maternal neglect and although no septal defects were seen in pups, a contribution of vascular defects (see above) to pup demise cannot be ruled out. Fingolimod and *S*-fingolimod phosphate were detected in excreted milk with exposures similar to that in maternal blood. While no effect on pup developmental parameters was evident in breast-fed pups, given its pharmacological action, fingolimod should not be used by women who are breast-feeding.

Pregnancy classification

The sponsor has proposed pregnancy Category C, which is for drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful, potentially reversible effects on the fetus or neonate without causing malformations. As there was clear evidence of malformations in rats and rabbits at clinical exposures, the effects of which are unlikely to be reversible, and perinatal deaths attributed to *in utero* exposure were seen in a pre/postnatal rat study, Category D would be more appropriate. Category D also includes the potential for adverse pharmacological effects.

Use in children

Fingolimod is not indicated for use in children. The toxicity profile of fingolimod (up to 5 mg/kg/day for 9 weeks) in juvenile rats (7 days old at commencement) was not significantly different from that seen in adults, with the secondary lymphatic tissue and thymus as target organs. A reduced level of monocytes, basophils and lymphocytes (B and T cells) with a correspondingly diminished immune capacity was evident in treated animals (≥0.5 mg/kg/day; ER_{AUC}, *ca* 2).

[33] Liu, Y., R. Wada, T. Yamashita, Y. Mi, C.-X. Deng, J.P. Hobson, H.M. Rosenfekdt, V.E. Nava, S.-S. Chae, M.-J. Lee, C.H. Liu, T. Hla, S. Spiegel and R.L. Proia. (2000). Edg-1, the G-protein-coupled receptor for sphingsine-1-phosphate, is essential for vascular maturation *J. Clin. Invest.* **106:** 951-961.

[34] C hae, S.-S., J.H. Paik, M.L. Allende, R.L. Proia and T. Hla. (2004) Regulation of limb development by the sphingosine 1-phosphate receptor *S1p$_1$/EDG-1* occurs via the hypoxia/VEGF axis. *Develop. Biol.* **268:** 441-447

Local tolerance

Phlebitis and perivascular inflammation at the injection site were seen in dogs after IV administration of ≥4.5 mg/kg/day fingolimod (0.2 mg/mL in 5% dextrose with or without 1% hydroxypropyl dextrin). Anti-fingolimod antibodies could not be detected in mice or guinea pigs and no systemic anaphylactic reactions were evident in guinea pigs.

Immunotoxicity

The effects of fingolimod on the immune system and immunocompetence were assessed in repeat dose toxicity studies and dedicated immunotoxicity studies as outlined in the EU guideline[35]. Lymphopaenia with associated effects on lymphoid tissue were a feature in toxicity studies. The reduction in circulating lymphocytes is intended to reduce the autoimmune damage associated with MS. Based on studies in rats and monkeys, B cell populations in the spleen were largely unaffected, while T cell populations (helper T cells, cytotoxic T cells, natural killer T cells and memory T cells) were reduced in the spleen, as well as in the circulation. A decrease in cortical proliferating cells (undifferentiated T cells and thymocytes) with an increase in differentiated T cells in the thymic medulla was also evident. Similar effects were seen in mice lacking the haemopoietic S1P1 receptor, where mature T cells were unable to exit the thymus and though B cells were present in peripheral lymphoid organs, they were extremely low in the blood (Matloubian *et al.*, 2004). Consistent with the reduced level of T cells in the periphery, a reduction in the T cell dependent antibody response was seen in rats (KLH and sheep red blood cell tests) and monkeys (tetanus toxoid test), while a diminished cellular mediated response (lymphoid hyperplasia) was observed in a mouse contact allergy model. There was no apparent effect on T cell function (cytokine release) in mice or on the boost immunoglobulin G (IgG) response to tetanus toxoid in monkeys, consistent with published reports that fingolimod depletes naive T cells and not peripheral effector/memory T cells that lack the lymph node homing ligand (Hofmann *et al.*, 2006[36]; Pinschewer *et al.*, 2000[37]). An increase in protozoan infections in the gastric glands of monkeys treated orally with ≥0.5 mg/kg/day fingolimod for 39 weeks (ER_{AUC}, 7) and the increased incidence of lymphomas in mice treated for 104 weeks with ≥0.25 mg/kg/day (ER_{AUC}, 5) (see **Carcinogenicity**), are consistent with an impaired T cell immune function. Clinical fingolimod use may be associated with an increased risk of infection, as listed in the ADRs of the PI.

Impurities

The proposed specifications for a number of impurities and the shelf-life limit of a degradant, require toxicological qualification according to ICH Guidelines Q3A(R) and Q3B(R)[38]. The Sponsor submitted *in vitro* genotoxicity and repeat dose toxicity studies using batches of fingolimod containing higher levels of these compounds. The degradant is a human and animal metabolite and, according to ICH Q3B(R) (Impurities in New Drug Products) can be considered to be qualified.

[35] ICHS8; Immunotoxicity studies for human pharmaceuticals. http://www.fda.gov/RegulatoryInformation/Guidances/ucm129118.htm

[36] Hofmann, M., V. Brinkmann and H.-G. Zerwes. (2006) FTY720 preferentially depletes naive T cells from peripheral and lymphoid organs. *Int. Immunopharm.* **6:** 1902-1910.

[37] Pinschewer, D.D., A.F. Ochsenbein, B. Odermatt, V. Brinkmann, H. Hengartner and R.M. Zinkernagel. (2000) FTY720 immunosuppression impairs effector T cell peripheral homing without affecting induction, expansion, and memory. *J. Immunol.* **164:** 5761-5770.

[38] Impurities in new drug products/Impurities in new drug substances: http://private.ich.org/cache/compo/363-272-1.html

Although no significant mutagenicity/clastogenicity findings were evident in the submitted genotoxicity studies, as with other *in vitro* genotoxicity studies with fingolimod, the concentrations achievable in these assays were too low to adequately ascertain the genotoxic potential of either fingolimod or the above-mentioned impurities. Unfortunately, batches used in the mouse and rat micronucleus assays had no detectable levels of the impurities of interest. In the absence of adequate *in vitro* genotoxicity assays, the carcinogenicity studies, which used a batch containing detectable levels of impurities, were used to assess the carcinogenic risk of these compounds. An increase in lymphoma incidence in mice was the only significant treatment-related tumour finding observed in 2 year mouse and rat studies. As these tumours are believed to arise as a result of a non-genotoxic mechanism (due to immunosuppression), no carcinogenic risk appears to exist at doses (based on body surface area) greater than twice the expected maximum of these impurities. The impurities are structural homologues of fingolimod, containing different C side chains compared to that of fingolimod. Based on this structural similarity, they are not expected to pose a genotoxic risk.

Toxicity studies in rats using batches of fingolimod with appreciable levels of these impurities (as well as three others), revealed no novel toxicities that could be attributed to the impurities. The level of impurities in these studies are ≥64 times the maximum expected exposure to patients (Table 4).Therefore, the proposed limits of these impurities in the drug substance and the shelf-life limit of another, can be considered to be toxicologically qualified.

Table 4. Dose comparisons for impurities in relevant toxicity studies (NOAELs shown in bold-face)

Study[a]	**Fingolimod dose (mg/kg/day)**	**Impurity level (%)**	**Impurity dose**		**Maximum human dose (µg/m²/day)**[b]	**Animal/human dose ratio by BSA**
			µg/kg/day	**µg/m²/day**[b]		
017020	1, 10	0.47%	4.7, 47	28.2, 282	1.65	**17**, 171
017020	1, 10	0.65%	6.5, 65	39, 390	1.65	**24**, 236
001039 *[carc.]*	0.025, 0.25, 2.5	0.05%	0.0125,0.125, 1.25	0.375, 0.375, 3.75		0.023, 0.23, **2.3**
001040 *[carc.]*	0.05, 0.15, 0.5, 2.5	0.05%	0.025, 0.075, 0.25, 1.25	0.15, 0.45, 1.5, 7.5		0.1, 0.3, 0.9, **5**
017020	1, 10	0.88%	8.8, 88	52.8, 528	1.65	**32**, 320
001039 *[carc.]*	0.025, 0.25, 2.5	0.11%	0.0275, 0.275, 2.75	0.0825, 0.825, 8.25		0.05, 0.5, **5**
001040 *[carc.]*	0.05, 0.15, 0.5, 2.5	0.11%	0.055, 0.165, 0.55, 2.75	0.33, 0.99, 3.3, 16.5		0.2, 0.6, 2, **10**
017020	1, 10	0.72%	7.2, 72	43.2, 432	1.65	**26**, 262
017020	1, 10	0.07%	0.7, 7	4.2, 42	0.66	**6**, 64
001039 *[carc.]*	0.025, 0.25, 2.5	0.05%	0.0125,0.125, 1.25	0.375, 0.375, 3.75		0.06, 0.6, **6**
001040 *[carc.]*	0.05, 0.15, 0.5, 2.5	0.05%	0.025, 0.075, 0.25, 1.25	0.15, 0.45, 1.5, 7.5		0.23, 0.7, 2, **11**
017020	1, 10	0.07%	0.7, 7	4.2, 42	0.66	**6**, 64
001039 *[carc.]*	0.025, 0.25, 2.5	0.07%	0.0175, 0.175, 1.75	0.0525, 0.525, 5.25		0.08, 0.8, **8**
001040 *[carc.]*	0.05, 0.15, 0.5, 2.5	0.07%	0.035, 0.105, 0.35, 1.75	0.21, 0.63, 2.1, 10.5		0.3, 1, 3, **16**
03220066	3, 10	4.6%	138, 460	828, 2760	4.95	167, **558**

[a]*Studies 017020 and 0320066, 4 week toxicity studies in rats; Studies 001039 and 001040, 2-year carcinogenicity studies in mice and rats, respectively;* [b] *µg/kg data converted to µg/m² using conversion factors of 3, 6 and 33 for mice, rats and humans (assuming a 50 kg individual), respectively*

Nonclinical Summary

- The overall quality of the submitted nonclinical data was high, with all pivotal toxicity studies conducted under GLP conditions using the proposed clinical route (PO).

- *In vitro*, fingolimod was converted to the active metabolite *S*-fingolimod phosphate by sphingosine kinase. Fingolimod phosphate was an agonist at the sphingosine 1-phosphate receptors (S1P1, S1P3, S1P4 and S1P5) with nanomolar potency. *In vivo*, fingolimod treatment in the relapsing-remitting phase of appropriate rodent models of MS reduced clinical disease and inhibited neo-angiogenesis in the spinal cord.

- Disease rebound, greater in severity than in untreated animals, was evident after cessation of a fingolimod-cyclosporine A combination treatment to diseased rats. No significant pharmacodynamic interactions were observed with fingolimod and interferon-β.

- There was no clinically significant inhibition of or affinity for circa 66 GPCRs, transporters, ion channels or enzymes with either fingolimod or *S*-fingolimod phosphate. While fingolimod had some inhibitory activity on $cPLA_2$, this is not considered adverse.

- Safety pharmacology studies covered the central and autonomic nervous systems, the cardiovascular, respiratory, renal and gastrointestinal (GI) systems. There were no remarkable central or autonomic nervous system effects at doses resulting in C_{max} values up to 47 times the clinical C_{ss}. No inhibition of hERG K^+ channels was seen at fingolimod and *S*-fingolimod phosphate concentrations up to 49 and 110 times, respectively, the clinical C_{ss}. However, consistent negative chronotropic effects were seen in animals, with bradycardia, increased blood pressure, sinus arrhythmias and 2^{nd} to 3^{rd} degree atrioventricular (AV) conduction blockage. The effect lasted for several hr and was more pronounced with *S*-fingolimod phosphate. The NOEL was 4 times the clinical C_{ss} for fingolimod and <4 times the clinical C_{ss} for *S*-fingolimod phosphate. Bradycardia and sinus arrhythmias were most prominent at initial dosing with a trend to tolerance evident with repeat dosing. The most notable respiratory effect was dyspnoea, which occurred at a similar time and dose as ECG changes and observed the bradycardia. No clinically-relevant effects on the renal or GI systems were seen.

- Pharmacokinetic studies indicated slow absorption of fingolimod in all species. The plasma half-life was shorter in laboratory animal species (14-44 h) than humans (147 h). Interconversion of fingolimod and fingolimod phosphate was evident in the blood from all species. The molar ratio of fingolimod phosphate to fingolimod was higher in the blood of animals than that in humans. Fingolimod largely distributed to red blood cells from animals and to a lesser extent to human blood cells. Protein binding of both fingolimod and *S*-fingolimod phosphate was high. Migration into the systemic circulation was slow and tissue distribution wide. Dose-dependent uptake into the brain was evident, with a slow clearance. Fingolimod was extensively metabolised in all species with fingolimod phosphate the major circulating metabolite. Drug-related material was excreted in both the urine and the faeces in animals, while predominantly urinary excretion was observed in human subjects.

- *In vitro* studies indicated a major role of CYP4F2 in fingolimod metabolism. Inhibitors of this isozyme, such as ketoconazole, could theoretically alter the exposure of fingolimod clinically. No significant inhibition of human CYPs (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4/5 and 4A9/11) or transporters (OATP1B1, OATP1B3, NTCP, MXR, MRP2 or BSEP) was seen with fingolimod or fingolimod phosphate at clinically-relevant concentrations. No significant induction of CYP1A2, 3A4 or 4F2 or ABCB1 (P-glycoprotein) was seen with

fingolimod at concentrations 150 times the clinical C_{ss}. No adequate information regarding P-glycoprotein interactions was provided.

- Fingolimod had a low order of acute toxicity in tested animal species.
- Repeat dose toxicity studies were performed in mice (up to 3 months), rats (6 months), dogs (6 months) and cynomolgus monkeys (52 weeks), using the clinical route (oral). High relative exposures (≥25) were obtained at the highest doses in all pivotal studies. Lymphopaenia, with associated lymphoid atrophy of the spleen, lymph nodes, and thymic cortical atrophy with medullary enlargement were seen in all species at exposures less than or equivalent to the clinical AUC. These findings are consistent with the anti-inflammatory activity of fingolimod, were reversible after cessation of treatment and are not considered adverse. Myocardial hypertrophy was seen in mice and monkeys with vascular thickening, subendocardial haemorrhage and/or endocardial fibrosis seen in dogs and monkeys. Generalised vasculopathy was restricted to mice and rats. Exposures at the NOEL suggest these cardiovascular findings are unlikely to be of clinical concern at the proposed dose. Renal, ophthalmological, adrenal and hepatic findings only occurred in isolated species and/or at high relative exposures.
- Pulmonary changes, seen in all species, included increased alveolar macrophage levels, pneumonia, congestion and/or interstitial collagenisation. This chronic inflammation and collagenisation led to metaplastic ossification in the bronchi of rats and mice following long term treatment. Exposures at the NOEL were subclinical in mice, rats and dogs. Scarring was still evident after a 4 week treatment-free period in dogs and had only partially resolved after a 26 week treatment free period in monkeys. Smooth muscle hypertrophy was seen in lungs of rats at the clinical exposure and monkeys at all doses (exposures ≥7 the clinical AUC). The clinical relevance of the hypertrophy is unclear.
- Fingolimod was not clastogenic in rodent micronucleus assays. In 2 year oral carcinogenicity studies, no treatment-related increase in tumour incidence was observed in rats, while an increase in malignant lymphomas, secondary to immunosuppression, was seen in mice. The exposure at the NOEL was below the anticipated clinical AUC.
- There was no apparent effect on fertility in rats at estimated exposures up to 150 times the clinical AUC. Placental transfer of fingolimod and/or its metabolites was demonstrated in rats and rabbits. Fingolimod was teratogenic in both species with increased incidences of defects in the thymus (rats and rabbits) and cardiovascular system (rats only). Increased incidences of skeletal variations (incomplete or no ossification, misshapen or bent bones) were evident in rabbits. Embryolethality was indicated in both species. Exposures at the NOEL for adverse embryofetal effects were subclinical. An increased incidence of abortions and an increased number of stillbirths was seen in rats at estimated exposures 8 times the clinical AUC, while reduced perinatal survival was evident at all doses (estimated exposures less than the clinical AUC). Fingolimod and *S*-fingolimod phosphate were readily excreted in milk with exposures similar to that in maternal blood. Reduced immunocompetence was evident in juvenile rats following oral administration.
- Consistent with the reduced level of T cells in the periphery, a reduction in the T cell-dependent antibody response and a diminished cellular mediated response were evident in treated animals. There was no apparent effect on T cell function or peripheral effector/memory T cell responses. An increase in gastric protozoan infections was seen in monkeys.

Conclusions and recommendations

Overall, the submitted nonclinical dossier supports the proposed indication with the only major concerns involving: (i) infection risk and a risk of lymphomas, (ii) sinus arrhythmias, bradycardia and dyspnoea at treatment initiation, (iii) pneumonia, congestion and bronchial collagenisation, with

long term scarring and a subsequent deterioration of pulmonary function, which may not be completely reversible, and (iv) adverse fetal effects during pregnancy.

With the exception of potential pulmonary remodelling and deterioration with long term exposure, the above toxicity concerns have been identified and adequately described in the Safety Specification in the Risk Management Plan.

There are no objections on nonclinical grounds to the submission.

Factors to consider in a benefit risk assessment

Fingolimod is a first-in-class immunosuppressant intended for the treatment of RRMS. Significant efficacy of fingolimod (based on clinical disease scores and histopathological analyses) was demonstrated in the relapsing-remitting phase of an appropriate rodent model of MS, while efficacy on the acute phase was less significant. Based on data in the rodent disease model, a fingolimod-cyclosporine A combination should be avoided. Although the combination reduced the clinical disease, cessation of treatment resulted in a rebound of disease, greater in severity than in untreated, diseased animals.

As with other immunosuppressants, concerns exist with the risk of infections and lymphomas. However, these concerns are somewhat lessened as fingolimod affects the primary (naive) T cell response and is not likely to affect a booster response, mediated by peripheral T cells.

The toxicity profile of fingolimod included effects on the lymphoid tissues (as expected for an immunosuppressant), and the pulmonary and cardiovascular systems. The latter two systems appear to be unique targets to fingolimod, compared with currently-registered MS drugs and other immunosuppressants. Animal studies indicated AV conduction blockage, sinus arrhythmias, bradycardia and dyspnoea upon initiation of fingolimod treatment. This occurred at exposures marginally greater than that expected clinically, and lasted for several hr after treatment initiation. While a trend to tolerance was evident with repeat dosing, caution would be warranted with intermittent or disruptions in dosing. These effects are likely manageable and are not anticipated to have any long term adverse effects. Other cardiovascular effects observed in toxicity studies (myocardial hypertrophy and vasculopathy) are unlikely to be a clinical concern at the proposed dose level.

Pulmonary changes, seen in all species, included increased alveolar macrophage levels, pneumonia, congestion and/or interstitial collagenisation. This chronic inflammation and collagenisation led to metaplastic ossification in the bronchi of rats and mice following long term treatment. Scarring was still evident after a 4 week treatment-free period in dogs and had only partially resolved after a 26 week treatment free period in monkeys. Given the nature of the effects, the low exposures (compared to clinical) and the poor reversibility of the effects, some concern with pulmonary function and pulmonary tissue damage exists with chronic administration of fingolimod, even if adequate monitoring were available. The current human safety database, limited by low patient numbers with >5 years exposure, may not be adequate to eliminate this as a clinical concern.

In embryofetal studies, fingolimod, at or below the clinical exposure, was embryolethal in rats and rabbits, teratogenic in rats (malformations of the cardiovascular system) and produced fetal skeletal variations in rabbits (incomplete or no ossification and misshapen or bent bones). The spontaneous abortions and abnormal offspring noted in clinical trials are consistent with findings in animal studies, and thus a relationship with treatment cannot be dismissed.

With the exception of potential pulmonary changes, the above toxicity concerns have been identified and adequately described in the Safety Specification in the Risk Management Plan. The Safety Specification states that, in women of child-bearing potential, concomitant contraception is recommended prior to treatment initiation, throughout the treatment course, and for at least 2 months following discontinuation of therapy. The washout period represents more than nine half-

lives, and is therefore considered adequate. Appropriate statements have been included in the relevant section of the Product Information document.

Overall, the submitted nonclinical dossier supports the proposed indication with the only major concerns involving: (i) infection risk, (ii) sinus arrhythmias, bradycardia and dyspnoea at treatment initiation, (iii) pneumonia, congestion and bronchial collagenisation, with long term scarring and a subsequent deterioration of pulmonary function, which may not be completely reversible, and (iv) adverse fetal effects during pregnancy.

IV. Clinical Findings

Introduction

Aspects of development

The clinical development programme of fingolimod consisted of pharmacokinetic studies (distribution, excretion, metabolism, dose proportionality, special populations, drug-drug interactions and safety/interaction studies), pharmacodynamic studies, and efficacy and safety clinical studies.

Product development rationale

Multiple sclerosis (MS) is a chronic, autoimmune and neurodegenerative disorder of the central nervous system (CNS), characterised by inflammation, demyelination, oligodendrocyte and neuronal loss. MS is a leading cause of neurologic disability in young and middle-aged adults. Relapsing MS is the most frequent clinical presentation of the disease. The majority of patients are diagnosed between the ages of 20 and 40 (2:1 female to male ratio). At diagnosis, approximately 85% of patients have relapsing remitting MS (RRMS), characterised by recurrent acute exacerbations (relapses) of neurological dysfunction followed by recovery. A significant proportion of relapses may result in incomplete recovery of function and leave permanent disability and impairment. After 6–10 years, 30–40% of patients with RRMS have progressed to secondary progressive MS (SPMS), in which a less inflammatory and more neurodegenerative course of disease appears to take precedence. SPMS presents with steady progression in disability with or without superimposed relapses.

Treatment strategies in MS usually involve management of symptoms and use of disease modifying therapies to reduce the frequency of exacerbations (relapses) and to slow the progress of disability. Currently available first-line therapies such as interferon have moderate efficacy, providing about a 30-35% reduction in the relapse rate compared to placebo over 2 years. Interferon (IFN) β-1a has been shown to reduce disability accumulation in patients with RRMS (Goodin *et al* 2002). IFN is administered by frequent injections and has known side effects such as flu-like symptoms and injection site reactions which are frequent and affect tolerability and compliance. Less commonly reported adverse events involve liver dysfunction and cytopaenias.

A more recently approved therapy, natalizumab (Tysabri), administered via monthly 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 in a 2-year study of patients with RRMS (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 product, the chemotherapeutic agent mitoxantrone, has been approved for use in relapsing forms of MS. However, cumulative dose-related cardiac toxicity and risk for secondary leukaemia limits the total amount that can be administered. Due to their safety profiles, natalizumab and mitoxantrone are currently used as second and third-line treatment.

Given the limitations of currently available therapies, there is a strong medical need for an oral MS treatment that is more effective and convenient than the current first line therapies and associated with an acceptable safety profile.

Fingolimod (referred to as FTY720 in the clinical trials) 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 metabolite fingolimod-phosphate (fingolimod-P). Fingolimod-P acts as an agonist at four of five G protein-coupled sphingosine 1-phosphate receptors (S1P), namely S1P1, S1P3, S1P4 and S1P5, but not S1P2. Depending on the cell type, the concentration, and the time following administration, fingolimod-P may act as an "agonist" or "functional antagonist" at S1P receptors.

The key pharmacodynamic effect of fingolimod is a dose-dependent reduction of the peripheral lymphocyte count mediated by down-modulation of the S1P1 receptor on lymphocytes. This results in a reduced egress of lymphocytes from the lymph nodes; in particular auto-aggressive T-cells that perform a central role in the MS inflammatory disease process are prevented from recirculating to the CNS. Fingolimod may display additional activities relevant to MS via down modulation of S1P1 receptors in the central nervous system, since conditional S1P1 gene deletion from astrocytes, or fingolimod treatment, both inhibit astrogliosis, reduce neurodegeneration and promote repair in mouse preclinical models of MS.

Due to the presence of S1P receptors in multiple tissues, fingolimod manifests a number of other biological effects in addition to the reduction in circulating lymphocytes. These include a transient reduction in heart rate and atrio-ventricular conduction on treatment initiation, a dose-dependent mild increase in airway resistance, macular oedema, a mild increase in blood pressure, and asymptomatic elevation in serum levels of hepatic transaminases.

Clinical development program

The clinical development programme 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.

A large clinical pharmacology programme was performed, comprising 29 clinical pharmacology studies that included 1069 subjects in total (including healthy volunteers and renal transplant patients), and of which 856 were exposed to at least one dose of fingolimod to characterise the pharmacokinetic, pharmacodynamic and biopharmaceutical effects of fingolimod in man. The clinical pharmacology studies have evaluated single doses up to 40 mg and multiple doses of 0.125 to 5 mg daily for up to 28 days.

The Phase III clinical development programme of fingolimod in relapsing MS is the largest programme conducted to date in this population, and includes 3 Phase III studies (Studies FTY720D2301, FTY720D2302, FTY720D2309) all evaluating the efficacy and safety of fingolimod at once daily oral doses of 0.5 mg and 1.25 mg. Two of these studies are completed and are nominated by the sponsors as pivotal (Studies FTY720D2301, FTY720D2302) in the current submission in support of the proposed indication:

• ***Study FTY720D2301***: a 2-year, double-blind, placebo-controlled study in 1272 patients with RRMS conducted globally (outside of the USA). Primary endpoint: annualised relapse rate; Key secondary endpoint: time to 3-month confirmed disability progression; Other secondary endpoints: other relapse- and disability-related endpoints, MRI measures of inflammation, disease burden, and brain volume.

• ***Study FTY720D2302***: a 1-year, double-blind, double-dummy, active-controlled (once weekly 30μg intramuscular IFN β-1a, Avonex) study in 1292 patients with RRMS conducted globally. Primary endpoint: annualised relapse rate; Key secondary endpoints: number of new/newly enlarging T2 MRI lesions, time to 3-month confirmed disability progression; Other secondary endpoints: other relapse-related endpoints, other MRI measures of inflammation, and disease burden.

In this evaluation report the studies will be referred to by the full title or abbreviated, for example Study FTY720D2301 may be referred to as study D2301. Fingolimod will be referred to by the full name or as FTY720), as it was named during the clinical trial program.

The third, still ongoing study (Stud***y FTY720D2309***), is a 2-year, double-blind, placebo-controlled study in approximately 1080 patients with RRMS, conducted mainly in the USA (completed recruitment). This study includes specialised safety assessments to further support the characterisation of the safety profile of fingolimod in areas of special interest based on previous clinical experience (heart, lung and eye). Interim safety data from these specialised safety assessments are included in the submission. To protect the integrity of this ongoing study, these interim data were analysed and reported by an independent (unblinded) team not otherwise involved in the study. The report was named as the Special Safety Interim Report (SSIR). Summary conclusions of the findings were provided in the Summary of Clinical Safety (SCS). The design of D2309 was identical to D2301 and therefore will provide information supportive to that seen in D2301.

The Phase III studies include long-term extensions (D2301E1, D2302E1 and 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-randomised (from placebo or IFN β-1a) to receive either fingolimod 0.5 mg or 1.25 mg in the extension. The original treatment allocation in the core study and the fingolimod dose in the extension remained blinded to investigators and patients. Interim safety data (up to 1 year or 1 June 2009) from extension Study D2302E1 were included in this submission. Serious adverse events (SAEs) (blinded to treatment) were provided from the D2301E1, D2302E1, and D2309E1 extensions up to September 30, 2009.

An earlier Phase II 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-randomised 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 with no difference in efficacy between the two doses, and being associated with more adverse effects, the 5.0 mg dose was discontinued and the patients were switched between their study Months 15 and 24 (after 9 to 18 months in the extension), to treatment at the lower 1.25 mg dose. This extension is now ongoing in its 6th year, with 140 patients having completed at least 5 years (60 months) in the study. Interim data from patients treated for up to 60 months (6 months core study + 54 months extension) were included in this submission.

An additional Phase II study is being conducted in Japan in patients with relapsing MS with the aim to support the submission of fingolimod in Japan. Study D1201 is a 6-month, placebo-controlled, study with a long-term extension (D1201E1). This study evaluates the efficacy and safety of fingolimod in approximately 165 relapsing (RRMS or relapsing SPMS) MS patients. The primary outcome is MRI – based. SAEs (blinded) were provided in this submission.

In addition to the clinical studies in patients with relapsing MS, a Phase III study (D2306) in patients with primary progressive MS (PPMS) is also currently being conducted. This double-blind study is evaluating the efficacy and safety of fingolimod in approximately 650 patients with PPMS treated for up to 3-5 years (double-blind treatment continues until all patients have completed 3-year double-blind treatment phase). The primary outcome is time to disability progression. The study is being conducted globally. SAEs (blinded) were provided in this submission.

Guidance

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 design of the fingolimod Phase III studies was in line with the requirements of the CHMP guideline on clinical investigation of medicinal products for the treatment of MS (CPMP/EWP/561/98 Rev.1, Nov 2006[39]) and incorporates requirements of the U.S. Food and Drug Administration (FDA) as well as scientific advice received from the EMEA (CHMP), FDA and other health authorities during the development in MS. The sponsor provided detailed information on Health Authority interactions in a document entitled "FTY720D Health Authority Interactions Summary." Given the results of D2301, filing with the two completed studies was deemed sufficient for regulatory consideration of approval without waiting for further data from D2309.

The proposed indication is as disease-modifying therapy for treatment of patients with relapsing MS to reduce the frequency of relapses and to delay the progression of disability. The population included in the fingolimod Phase III program were patients with a diagnosis of MS, according to the 2005 revisions to the McDonald diagnostic criteria[40] (Polman *et al* 2005), with a relapsing-remitting course and an EDSS score between 0 to 5.5. Of the populations with relapsing MS (RRMS, SPMS with superimposed relapses, patients with a clinically isolated syndrome), the RRMS population is typically the population studied in Phase III studies aimed at demonstrating the efficacy of a new potential disease-modifying therapy to reduce the frequency of relapses and delay the progression of disability.

Bioequivalence of market and development forms

Over the course of development of fingolimod, three Final Market Image (FMI) formulations have been used: 0.5, 1.25 and 2.5 mg capsules. The 0.5 and 1.25 mg FMIs were used in the MS pivotal Phase III trials. The 1.25 and 2.5 mg FMIs were used in the pivotal Phase III trials of the previous transplant indication of fingolimod. In addition, several fingolimod oral, capsule Clinical Service Form (CSF) formulations were used in Phase I and Phase II studies. At the two fingolimod doses studied in formal biopharmaceutic studies, 1.25 and 2.5 mg, the CSF and FMI were shown to be bioequivalent. In addition, the 1.25 and 2.5 mg FMIs were also found to be bioequivalent.

The two dosage strengths used in the pivotal, Phase III multiple sclerosis studies, 0.5 and 1.25 mg are compositionally proportional. The CSF and FMI formulations used in the clinical programme have similar dissolution profiles or *in vitro* release behaviour. Once the gelatin capsule is dissolved in the dissolution medium, the drug substance is immediately released (more than 80% in 10 minutes) independently of the formulation. Furthermore, clinical studies have shown that the onset of absorption of fingolimod is rapid (less than 30 minutes) confirming the quick release of the drug

[39] http://www.tga.gov.au/docs/pdf/euguide/ewp/056198en.pdf

[40] The McDonald criteria are diagnostic criteria for MS. In April 2001 an international panel in association with the National Multiple Sclerosis Society (NMSS) of America recommended revised diagnostic criteria for MS. They make use of advances in MRI imaging techniques. The McDonald criteria for the diagnosis of multiple sclerosis were revised in 2005 to clarify exactly what is meant by an "attack," "dissemination," a "positive MRI," and so on.

McDonald WI, Compston A, Edan G, *et al.* (2001). "Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis [1]". *Ann. Neurol.* **50** (1): 121–7. and

Polman CH, Reingold SC, Edan G, *et al.* (2005). "Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria"". *Ann. Neurol.* **58** (6): 840–6.

substance from the capsule. Finally, in the relative bioavailability study described above, it was shown that the CSF and FMI formulations had similar pharmacokinetic behaviour, and it was concluded that the CSF and FMI formulations were bioequivalent. It was considered that there was no need to establish an *in vitro-in vivo* correlation.

GCP aspects

The sponsor stated that the clinical trials submitted for evaluation were performed in accordance with Good Clinical Practice (GCP).

Pharmacokinetics

Introduction

A total of twenty-nine clinical pharmacology studies were completed and reported at the time of submission of this dossier. Study numbers beginning with "FTY720A" were conducted during the initial development of fingolimod. Those study numbers beginning with "FTY720D" were conducted during the development of fingolimod for the multiple sclerosis indication. The first in-human study, Study FTY720AB101, was initiated in August 1998. Almost all of the clinical pharmacology studies since then have included both pharmacokinetic and pharmacodynamic measures. The main pharmacodynamic measures have been lymphocyte count, heart rate and pulmonary function. From the first-in-human study, to the current time, fingolimod has been dosed as a capsule formulation. Both the CSF used in the early clinical pharmacology studies and the FMI were shown to be bioequivalent (Study FTY720A0116).

Methods

The assay validations for fingolimod and its metabolites, fingolimod-P, M2 and M3, are acceptable. Concentrations of fingolimod and fingolimod-P in whole blood were determined using specific l(LC-MS) methods with lower limit of quantification (LLOQ) of 0.08 ng/mL for fingolimod and 0.1 ng/mL for fingolimod-P (1-1.5 ng/mL in early studies). Blood concentrations of the metabolites M2 and M3 were determined using a LC-MS method with a LLOQ set at 0.1 ng/mL. Urine fingolimod together with metabolite M2 and M3 concentrations were determined using a LC-MS/MS method with a LLOQ set at 1 ng/mL for all three analytes.

Absorption

Study FTY720A2217 was an open-label study in four healthy volunteers using a radiolabelled single 4.47 mg dose of fingolimod to examine the pharmacokinetics of fingolimod. Fingolimod was slowly absorbed ($C_{max,b}$ between 10 to 12 hr for fingolimod and total compound-related radioactivity) with a fraction of the dose absorbed estimated to be greater than or equal to 85% (based on the amount of radioactivity excreted in urine and the amount of metabolites in faeces extrapolated to infinity). The apparent volume of distribution ($V_{z,b}/F$) of fingolimod was large (1509 L) and the apparent clearance (CL_b/F) was low (8.7 L/h). Fingolimod and its metabolites disappeared slowly from the blood with mean terminal half-lives of 137 hr (5.7 days) for fingolimod, 166 hr (6.9 days) for fingolimod-P and 382 hr (15.9 days) for radioactivity. The biotransformation of fingolimod involved (i) reversible phosphorylation to fingolimod-P, (ii) hydroxylation at the terminal methyl group of the octyl chain, followed by rapid further oxidation (M1) and subsequent β-oxidation (M2, M3, M4) and (iii) formation of nonpolar ceramide analogs (M27-M30). Fingolimod-P was observed in blood only in the form of its (*S*)-enantiomer. The AUC_b values of the metabolites, relative to that of fingolimod, amounted to 36% for M3, 44% for fingolimod-P, 53% for M29 and 41% for M30. Elimination of fingolimod occurred predominantly by oxidative metabolism. Fingolimod-P was eliminated mainly by dephosphorylation back to fingolimod. The similar apparent elimination half-life between fingolimod-P and fingolimod supports these two molecules being in equilibrium in the terminal phase. Fingolimod-related radioactivity was excreted very slowly, predominantly *via* the kidney (81%) in the form of metabolites. M3 was the major metabolite in urine (38% of dose). Fingolimod and fingolimod-P

were not detected in urine. Average faecal excretion of total fingolimod-related radioactivity amounted to 11% of the radioactive dose with fingolimod and fingolimod-P accounting for 2.4% and 1.7% of dose, respectively.

Study FTY720A0108 was an open-label, two period, crossover single-dose study which measured the absolute bioavailability of fingolimod using a 1 mg IV infusion over 2 hr and a 1.25 mg oral dose in twelve subjects (eleven completed). The apparent absolute oral bioavailability of fingolimod, was estimated to be 93% (95% CI: 79% - 111%). Fingolimod calculated volume of distribution was high (1199±260 L), clearance was low (6.3±2.3 L/h), and the terminal half-life was about 6 days. Fingolimod-P could be quantified in only a few subjects' blood samples after oral administration but no pharmacokinetic parameters could be derived. Both IV and oral doses resulted in a similar decrease in heart rate of approximately 10-15 beats per minute at several hr post-dose.

Study FTY720AB101 was a first in human, ascending single-dose placebo-controlled safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) study (0.125 – 3.5 mg) in twenty stable renal transplant patients on Neoral cyclosporin based immunosuppression. Twelve of these subjects re-enrolled in later dose cohorts. The onset of fingolimod absorption was fast with measurable concentration in blood 0.5 hr post-dose for the two highest doses. The maximum concentration was reached between 8 and 36 hr post-dose (overall median was 24 hr). The $C_{max,b}$ was generally embedded in a broad plateau region between 8 to 36 hr post-dose. Both $C_{max,b}$ and AUC_b rose in an apparent dose-proportional manner over the full range 0.25 mg to 3.5 mg. The apparent elimination half-life was similar across all dose levels and averaged 4.5 ± 1.4 days or 108 ± 32 hr. As the last sample was collected 96 hr post-dose, the elimination half-life may not have been assessed accurately. Oral clearance (CL_b/F) and apparent distribution volume ($V_{z,b}/F$) were independent of the doses and averaged 9.5±2.3 L/h and 1407±324 L, respectively. Fingolimod-P was not measured in this early study.

Study FTY720AB102 was an ascending multiple-dose placebo-controlled safety, tolerability, PK and PD study (0.125 – 5 mg) in sixty-five stable renal transplant patients on Neoral cyclosporin based immunosuppression. Eleven of these subjects re-enrolled in later dose cohorts. Each subject received fingolimod once-daily for 28 days. After the first dose on study Day 1, fingolimod blood concentrations rose over the first 12 hr post-dose and thereafter entered a plateau-like region up to 24 hr before the next dose was administered. $C_{max,b}$ and $AUC_{\tau,b}$ after the first dose rose in an apparent dose proportional manner over the full dose range. On Day 28, fingolimod blood concentration profiles over the 24-hour dose interval were very flat giving rise to a shallow peak-trough fluctuation averaging 20 %. Although not strictly in a dose-proportional manner, the exposure parameters increased with the dose. The variability was about 35% for $C_{max\ ss,b}$ and $AUC_{\tau,b}$. The apparent clearance averaged 9.2 ± 5.2 L/h. The elimination half-life appeared dose-independent and, when averaged across all dose levels, was 8.4 ± 2.6 days corresponding to 202 ± 62 hr. Consistent with this value, the accumulation index based on the $AUC_{\tau,b}$ on Day 1 versus Day 28 appeared dose-independent and averaged 11.4 ± 3.7 across doses. Accumulation based on $C_{24,b}$ on Days 1 and 29 was comparable averaging 9.4 ± 3.1. $C_{0ss\ b}$ was well correlated with $AUC_{\tau,b}$ on Day 28 with a coefficient of determination (r^2) of 0.974. Fingolimod-P was not measured in this early study. Compared to the pre-treatment baseline, steady-state cyclosporin pharmacokinetics were unchanged after 28 days of coadministration with fingolimod.

Study FTY720D2101 was a multiple dose, seven day, randomised, placebo- controlled, parallel designed Thorough QT[41] study which, by using a 4-day loading dose regimen (maintenance dose on Day 1, doubled on Day 2, tripled on Day 3 and quadrupled on Day 4) followed by a 3-day once daily maintenance dose period, maintained subjects at steady state fingolimod 1.25 and 2.5 mg

[41] Note for guidance on the clinical evaluation of qt/qtc interval prolongation and proarrhythmic potential for nonantiarrhythmic drugs. CHMP/ICH/2/04. www.tga.gov.au/docs/pdf/euguide/ich/000204entga.pdf

dosing at time of QT measurements. In this study, 199 subjects were enrolled and 189 subjects completed it. On Day 7, fingolimod and fingolimod-P $C_{0ss,b}$ and $C_{24ss,b}$ were similar suggesting that steady state blood concentration values were reached. Fingolimod blood concentration profiles were relatively flat with peak to trough fluctuation (PTF) around 30%, and a median t_{max} of 8 hr for both doses. Fingolimod- P blood concentration profiles peaked between 6 and 8 hr post-dose in all subjects (median 6 hr for both dose groups). The geometric mean molar ratios of fingolimod-P/fingolimod $AUC_{\tau,b}$ were 0.43 and 0.42 for 1.25 and 2.5 mg doses, respectively. Although subjects achieved steady-state concentrations of fingolimod by Day 5, a negative chronotropic effect of fingolimod of approximately 10-15 beats per minute was still detected on Day 7. Fingolimod treatment resulted in a significant prolongation of the double-delta QTcI, with the upper bound of the 90% CI ≤13.0 ms. There was no dose response relationship of fingolimod and QTcI prolongation. There was no consistent signal of increased incidence of QTcI outliers, either absolute or change from baseline, associated with fingolimod treatment. Over a fingolimod exposure range of approximately one log, no exposure-response relationship between fingolimod or fingolimod-P and QTcI was detected.

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. T_{max} is variable, occurring at a median time of 12 hr. Fingolimod-P reaches $C_{max,b}$ at a median time of 8 hr, and the peak to trough fluctuation is approximately 45% (Studies FTY720AB102 and FTY720D2101).

Bioavailability

Study FTY720A0108 assessed the absolute oral bioavailability of fingolimod (1.25 mg FMI hard gelatin capsule). Eleven healthy subjects were randomly assigned to receive in a sequential manner, with an interval between treatment periods of at least 30 days, a 1.25 mg capsule and a 1 mg IV infusion over 2 hr (1 mg/mL solution for infusion). Because of the reversible metabolism between fingolimod and fingolimod-P, an exact estimate of the absolute oral bioavailability of fingolimod could not be determined. A four-way crossover study (parent and metabolite administered separately by oral and IV routes) would have been necessary to precisely measure the absolute bioavailability of fingolimod. However, a conventional two-way crossover study to compare the pharmacokinetics of fingolimod after oral and IV administration was conducted since IV administration of the fingolimod-P metabolite was determined from a rat single dose toxicity study to be inappropriate for the clinic due to signs related to sinus arrest, marked respiratory complications, and arrhythmias other than sinus block. This two-way cross-over approach, however, while unable to provide an exact estimate of absolute oral bioavailability, did yield the fingolimod oral/IV AUC ratio, or “apparent absolute oral bioavailability”. Table 5 below summarises the PK of fingolimod after oral and IV administration.

Table 5: Fingolimod pharmacokinetic parameters after oral and IV Administration

Parameter	Intravenous	Oral
Dose (mg)	1	1.25
t_{lag} (h)	--	0.5 (0 – 1)
t_{max} (h)	2 (1.5 – 2.0)	12 (8 – 36)
$C_{max,b}$ (ng/mL)	4.9 ± 0.8	1.1 ± 0.2
$AUC_{(0\text{-}tz)b}$ (ng.h/mL)	149 ± 44	174 ± 32
AUC_b (ng.h/mL)	175 ± 50	201 ± 31
AUC_b/Dose (ng.h/Ml/mg)	175 ± 50	161 ± 25
CL_b (L/h)	6.3 ± 2.3	--
$V_{z,b}$ (L)	1199 ± 260	--
$t_{1/2}$ (days)	6.0 ± 1.9	6.1 ± 1.0

Values are mean ± SD except for temporal parameters which are median (range).

A conventional evaluation of the pharmacokinetic data yielded an overall average apparent absolute oral bioavailability of 0.93 (95% CI: 0.79 – 1.11). Of the eleven subjects, three had a higher dose-adjusted AUC after oral versus IV administration yielding AUC-ratios greater than 100 percent.

Effect of food

The effect of food on the pharmacokinetics of fingolimod was determined using 1 mg CSF capsules (Study FTY720A0106) and 1.25 mg FMI capsules (Study FTY720D2107), in fourteen and twenty-nine healthy subjects, respectively. Both studies were of a randomised crossover design in which healthy subjects received a single dose of 1 mg CSF or a single dose of 1.25 mg FMI capsule, respectively, under fasting conditions and after a high fat breakfast (FDA recommended high fat meal). A high fat meal did not alter the pharmacokinetics of fingolimod from a CSF capsule or a FMI capsule. The 90% confidence intervals for the ratio of parameter values between the fed and the fasted state were 0.86-1.11 for AUC_b and 0.86-1.17 for $C_{max,b}$ for the CSF capsule and 0.92-1.06 for AUC_b and 0.88-0.96 for $C_{max,b}$ for the FMI capsule, respectively. These intervals were within the predefined bioequivalence range of 0.8-1.25. Additionally, the effect of food on the pharmacokinetics of fingolimod-P was assessed using the 1.25 mg FMI capsules only (Study FTY720D2107). Although fingolimod-P total exposure (AUC_b) was not influenced by the high fat meal, $C_{max,b}$ was decreased by 34%. This decrease of $C_{max,b}$ in fed state compared to fasted state is considered small and of no clinical impact.

Distribution

Fingolimod highly distributes in red blood cells, with the fraction in blood of 86%, but fingolimod-P has a smaller uptake in blood of <17%. 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 (Study FTY720A0108).

Elimination

The biotransformation of fingolimod in humans occurs by three main pathways: (i) by reversible stereoselective phosphorylation to the (S)-enantiomer of 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 nonpolar ceramide analogs of fingolimod (Study FTY720A2217). Fingolimod-P can be converted back to fingolimod and the nonpolar ceramide metabolites of fingolimod may also be converted back to fingolimod. Therefore, it is assumed that fingolimod, fingolimod-P and the nonpolar ceramide analogs of fingolimod are in

dynamic equilibrium at steady-state. At steady-state, the ratio of fingolimod-P to fingolimod $AUC_{\tau,b}$ is dose-independent and is approximately 0.4 (Studies FTY720A2215, FTY720D2107, and FTY720D210).

Study FTY720A2215 was a randomised, placebo controlled parallel design, single ascending dose study which measured the PK, safety, tolerability and PD of high doses fingolimod (5 – 40 mg). Fifty-six subjects were enrolled in this study. The onset of fingolimod absorption was fast with measurable concentration in blood 0.5 hr post-dose. The absolute maximum concentration was reached generally at 12 hr post-dose and was embedded in a broad plateau region between 8 to 36 hr post-dose, especially for the lower doses. Both $C_{max,b}$ and AUC_b rose in an apparent dose-proportional manner over the range of 5 mg to 40 mg, with some deviations from dose proportionality. The elimination half-life was similar across all dose levels and averaged 7.7±2.2 days or 185±52 hr. Oral blood clearance (CL_b/F) averaged 8.0±3.0 L/h and the apparent volume of distribution ($V_{z,b}/F$) averaged 1973±558 L. Fingolimod-P generally became quantifiable in blood later than fingolimod. The maximum concentration generally occurred at 8 hr post-dose (range, 6-24 h). The increase in $C_{max,b}$ with dose was underproportional over the range of 5 mg to 40 mg, whereas the $AUC_{(0-144)b}$ (the AUC portion measurable at all dose levels) satisfied dose-proportionality over the full dose range.

The elimination half-life across dose levels in which it could be derived (15 mg to 40 mg) averaged 7.9±3.1 days or 189±75 hr. Fingolimod-P $C_{max,b}$ was greater than that of fingolimod at doses <7.5 mg; whereas, the fingolimod $C_{max,b}$ was greater than that of fingolimod-P at doses >10 mg. After 24 hr post-dose, the mean concentration profiles of these two analytes declined in parallel with fingolimod-P always at lower ng/mL concentrations compared with fingolimod. The fingolimod-P/fingolimod $AUC_{(0-144)b}$ molar ratios were relatively dose independent over the range 5 mg to 40 mg and averaged 0.38.

Following single oral administration of [^{14}C]fingolimod, the major fingolimod-related components in blood, as judged from their contribution to the $AUC_{(0-816)b}$ of total radiolabelled components, are fingolimod itself (23.3%), fingolimod-P (10.3%), M3 (8.3%), M29 (8.9%) and M30 (7.3%) (Study FTY720A2217).

Fingolimod blood clearance is low, 6.3±2.3 L/h, and the average apparent terminal half-life ($t_{1/2}$) is long, 6-9 days. Blood levels of fingolimod-P decline in parallel with fingolimod in the terminal phase yielding similar half-lives for both (Studies FTY720A0108 and FTY720D2107).

After 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 faeces with amounts representing less than 2.5% of the dose each. After 34 days, the recovery of the administered dose is 89% (Study FTY720A2217).

Dose proportionality and time dependency

Single dose

In Study FTY720AB101, stable renal transplant patients on Neoral cyclosporin based immunosuppression, received single fingolimod doses of 0.25, 0.5, 0.75, 1, 2 and 3.5 mg. In Study FTY720A2304, healthy volunteers received single fingolimod doses of 1.25, 2.5 and 5 mg. In Study FTY720A2215 healthy volunteers received single fingolimod doses of 5, 7.5, 10, 15, 25, and 40 mg. In the three studies, both fingolimod $C_{max,b}$ and AUC_b rose in an apparent dose-proportional manner over the investigated dose range; however there were some deviations from dose proportionality.

Table 6 below displays, for the three studies, the estimate and 90% confidence interval (CI) for the exponent parameter of the statistical power model ($Y = \alpha * Dose^{\beta}$, where Y, α and β correspond to fingolimod PK parameter ($C_{max,b}$ and AUC_b), proportionality constant and an exponent,

respectively). The values are comparable between the studies with a substantial overlap of the 90% CI and the deviations from dose-proportionality are small.

Table 6: Estimate and 90% CI of the exponent (slope) of the power model for Fingolimod

Study	AUC_b	$C_{max,b}$
Study FTY720AB101	1.11 (1.01- 1.21)	1.08 (1.01- 1.15)
Study FTY720A2304	1.16 (0.99- 1.32)	0.98 (0.86- 1.11)
Study FTY720A2215	1.05 (0.91- 1.19)	1.04 (0.96- 1.12)

Fingolimod-P was measured in Study FTY720A2304 and in study FTY720A2215 (discussed in section 2.1.5 of this report). AUC was truncated at a common end time-point (96 hr) up to which concentration-time profiles were measurable at all dose levels in study FTY720A2215. Fingolimod-P could not be measured accurately in Study FTY720A2304, especially for the two smallest doses. Table 7 displays the estimate and 90% confidence interval (CI) for the exponent parameter of the power model ($Y = \alpha * Dose^{\beta}$, where Y, α and β correspond to PK parameter ($C_{max,b}$ and $AUC_{(0-96)b}$), proportionality constant and an exponent, respectively).

Table 7: Estimate and 90% CI of the exponent (slope) of the power model for fingolimod-P

Study	$AUC_{(0-96)b}$	$C_{max,b}$
[CP Study FTY720A2304]	NA	0.68 (0.57- 0.79)
[CP Study FTY720A2215]	0.99 (0.87- 1.12)	0.75 (0.64- 0.86)

There is a clear under-proportional increase in fingolimod-P $C_{max,b}$ with the dose in both studies; based on the slope (90% CI) estimated from the results of Study FTY720A2304, a dose increased by a factor 2 results in a $C_{max,b}$ increased by a factor 1.60 (CI1.48, 1.73).

Steady-state

In study FTY720AB102, stable renal transplant patients on Neoral cyclosporin based immunosuppression, received fingolimod doses of 0.125, 0.25, 0.5, 1, 2.5 and 5 mg once daily for 28 days. Fingolimod $C_{0ss,b}$, $C_{max\ ss,b}$ and $AUC_{\tau,b}$ rose over the investigated dose range, although the statistical power model showed some slight deviations from dose proportionality. The estimate (90% CI) of the exponent (slope) of the power model were 0.89 (0.80-0.98), 0.89 (0.81-0.96) and 0.88 (0.80-0.96) for $C_{0ss,b}$, $C_{max\ ss,b}$ and $AUC_{\tau,b}$ respectively.

Repeated administration

In study FTY720D2101, healthy subjects received a loading dose regimen such that escalating doses of fingolimod were administered over a 4 day period in order to achieve steady-state concentrations at the end of this time period. On Day 7 (after the 4 day loading dose regimen and a 3 day period with administration of the once-daily maintenance dose) fingolimod and fingolimod-P $AUC_{\tau,b}$ and $C_{maxss,b}$ were dose-dependently higher (2x) for the 2.5 mg dose compared with the 1.25 mg dose (see Table 8 below).

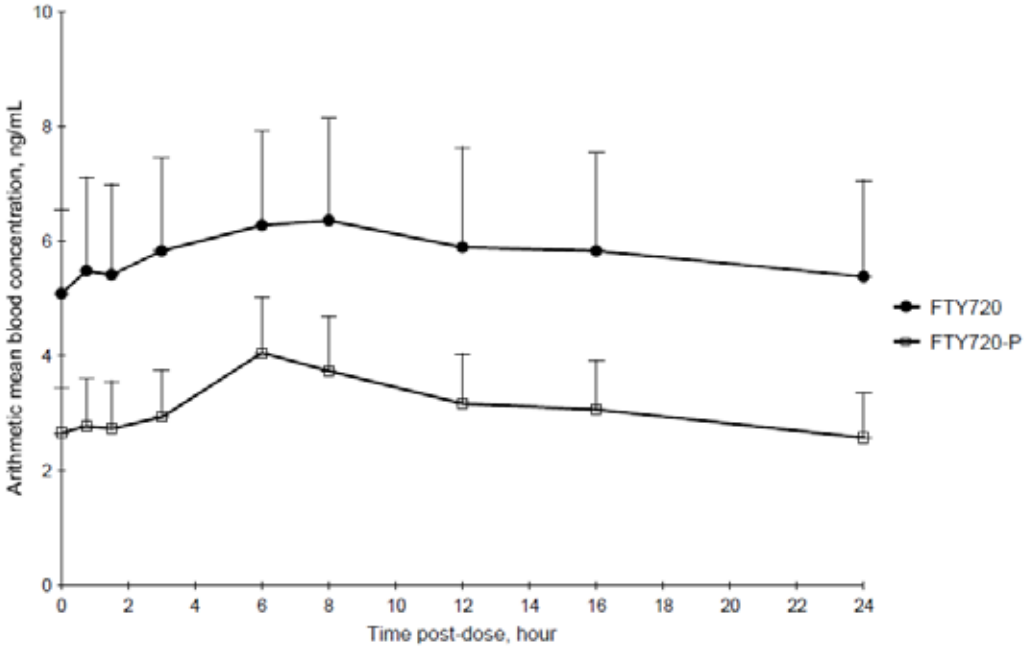
Table 8: Fingolimod and fingolimod-P pharmacokinetics on Day 7 after a four day loading dose regimen and a three-day once-daily maintenance dose administration in healthy subjects

PK parameters	Fingolimod		Fingolimod-P	
	1.25 mg	2.5 mg	1.25 mg	2.5 mg
N	52	61	52	61
$C_0^{ss}{}_{,b}$ (ng/mL)	5.09 ± 1.46	10.1 ± 2.93	2.66 ± 0.781	5.18 ± 1.45
t_{max} (h)	8.00	8.00	6.00	6.00
	(0.75- 16.0)	(3.00- 24.0)	(6.00- 8.08)	(5.92- 8.02)
$C_{max}{}^{ss}{}_{,b}$ (ng/mL)	6.73 ± 1.82	13.4 ± 3.87	4.11 ± 0.951	7.94 ± 1.79
$AUC_{\tau,b}$(ng/mL.h)	140 ± 39.1	280 ± 81.7	75.1 ± 20.0	147 ± 38.2
PTF (%)	28 ± 10	28 ± 11	48 ± 14	47 ± 13
R	7.0 ± 1.5	6.8 ± 2.1	5.0 ± 1.0	5.2 ± 1.3 *

Values are mean ± SD except for t_{max} which is median (range). Subscript *b* is for measurement in blood; *: n=60

As shown in Figure 2 below, fingolimod-P blood concentration profiles were not as flat as those of fingolimod with a peak between 6 and 8 hr post-dose and peak-to-trough fluctuations greater than for fingolimod (about 47% for both dose groups). The variability as measured by the CV%, was smaller than 30% for $AUC_{\tau,b}$ and $C_{maxss,b}$.

Figure 2: Fingolimod and fingolimod-P arithmetic mean (+ SD) 24-hour blood concentration- time profile (ng/mL) on Day 7, after a four-day loading dose regimen and a three-day once-daily 1.25 mg maintenance dose administration; n= 52 healthy subjects



Evaluator's Comment: *Overall the pharmacokinetics of fingolimod was dose-proportional after single dose administration in the dose range of 0.125 to 40 mg and multiple doses at doses at 0.5 mg once a day (QD) and lower. There was less than dose-proportional increase in C_{max} and AUC with increasing doses higher than 0.5 mg QD. For fingolimod-P, fingolimod-P C_{max} displays an under-proportional increase with the dose, over the range 1.25-40 mg.*

Intra- and inter-individual variability

The inter- and intra-subject variability of fingolimod and fingolimod-P pharmacokinetics after single dose administration was determined from a bioequivalence Study FTY720A2309 and from the food effect Study FTY720D2107 (discussed earlier). Study FTY720A2309 was an open-label, two period, crossover, single-dose study evaluating the bioequivalence of the fingolimod 1.25 mg x

2 and fingolimod 2.5 mg FMI. Thirty-five subjects were enrolled. The period of time between fingolimod doses was at least 36 days. Study FTY720D2107 was an open- label, two period, crossover single-dose study which measured the effect of food on the PK of a 1.25 mg FMI of fingolimod. Thirty-four subjects were enrolled.

Study FTY720A2309

Fingolimod. After a lag-time ranging from 0.25 to 4 hr until fingolimod was quantifiable in blood, the time to reach the maximum fingolimod concentration (t_{max}) ranged from 8 to 48 hr postdose with a median of 12 hr from both capsule strengths. The mean peak concentration was similar between capsule strengths and exhibited moderate inter-individual variability with coefficients of variation of 20% and 22%. A supplemental descriptive metric for peak exposure was generated around the concept of an apical concentration (Pollack, Freeman, Carruthers 1988). For this metric, concentrations within 20% of $C_{max,b}$ were identified along with their sampling time-points. Across all profiles, concentrations contributing to the apex region occurred as early as 8 hr post-dose and as delayed as 54 hr post-dose in individual subjects.

The AUC_b was similar between capsule strengths and exhibited high inter-individual variability of 32% and 34%. The estimated elimination half life averaged 4.4 days (range, 2.2 – 7.9).

Fingolimod-P. Lag-times until fingolimod-P became quantifiable in blood were longer than for fingolimod which was likely a consequence of the higher assay quantification limit for this analyte rather than a delay in its formation. Peak exposure for fingolimod-P generally occurred earlier and at slightly higher concentrations than for fingolimod. Fingolimod-P $C_{max,b}$ was similar between capsule strengths and exhibited moderate inter-subject variability of 20% and 24%.

The mean truncated $AUC(0\text{-}t_z)_b$ was numerically higher from the 2.5 mg versus the 1.25 mg capsule strengths with high inter-subject variability of 60% from both.

Study FTY720D2107

Fingolimod $C_{max,b}$ exhibited small inter-individual variability with coefficients of variation of geometric mean of 16% and 19%, in fasted and fed state, respectively.

On average, AUC from 0 h to infinity ($_{0\text{-}\infty,b}$) and AUC from time zero to the last quantifiable concentration ($AUC_{last,b}$) were similar in fasted and fed state with a 90% CI for the geometric mean ratio (fed/fasted) lying entirely within 0.8-1.25 range. $AUC_{last,b}$ represented approximately 90% of $AUC_{0\text{-}\infty,b}$. Both AUC exhibited moderate to high inter-individual variability with coefficients of variation of geometric mean ranging from 32% to 39%. The geometric mean $t_{1/2}$ was similar in fasted and fed state (about 132 hr) with the same high inter-individual variability (about 45%). In both states, there was a large mean apparent distribution volume close to 1000 L and small mean apparent clearance of about 5 L/h.

At steady-state, the variability of fingolimod and fingolimod-P pharmacokinetics was determined from Study FTY720D2101 where healthy subjects received a loading dose regimen such that escalating doses of fingolimod were administered over a 4 day period in order to achieve pharmacokinetic steady state concentrations at the end of this time period. The exposure parameters were determined only once per subject, hence precise estimates of intra and inter-subject variability. Variability was expressed as the coefficient of variation. For both fingolimod and fingolimod-P inter-individual variability for $AUC_{,b}$ and $C_{maxss,b}$ was moderate with a coefficient of variation smaller than 30%.

Pharmacokinetics in the target population

No dedicated clinical pharmacology studies have been conducted in patients with multiple sclerosis but in the three clinical studies conducted in patients (Study FTY720D2201, Study FTY720D2301 and Study FTY720D2302**)**, blood samples were collected for pharmacokinetic purposes. As a

consequence, the comparison between healthy subjects and patients was carried out using fingolimod $C_{max,b}$ and $AUC_{,b}$ for the transplantation patients and using fingolimod and fingolimod-P predose concentrations for the multiple sclerosis patients.

Table 9 displays the mean (± SD) (except D2301, geometric mean, [CV% geometric mean]) predose steady state concentrations for fingolimod and fingolimod-P in healthy subjects (Studies FTY720D2101 and FTY720A2305) and in multiple sclerosis patients (Studies FTY720D2201, FTY720D2301 and FTY720D2302). Fingolimod and fingolimod-P mean predose concentrations are consistent across all the studies suggesting that there is no difference in the pharmacokinetics of fingolimod between multiple sclerosis patients and healthy subjects.

Table 9: Fingolimod and fingolimod-P arithmetic mean (± SD) (except D2301, geometric mean, (CV% geometric mean)) observed and dose-normalised (DN) blood steady state predose concentrations (ng/mL and ng/mL/mg, respectively), using once-daily administration, from different fingolimod studies

Study	Population	Dose (mg)	fingolimod Predose	fingolimod-P Predose	fingolimod DN predose	fingolimod-P DN predose
D2101 (n=52)	HS	1.25	5.09 ± 1.46	2.66 ± 0.781	4.07±1.17	2.13±0.625
D2101 (n=61)	HS	2.5	10.1 ± 2.93	5.18 ± 1.45	4.04±1.17	2.07±0.58
A2305 (group A) (n=6)	HS	5	26.1 ± 3.3	8.9 ± 0.9	5.22±0.66	1.78±0.18
A2305 (group B) (n=6)	HS	5	29.8 ± 8.2	9.7 ± 2.0	5.96±1.64	1.94±0.4
D2201 (n=72)	MS	1.25	7.3 ± 4.3	Not measured	5.84±3.44	Not measured
D2201 (n=61)	MS	5	30.2 ± 19.1	Not measured	6.04±3.82	Not measured
D2301 (fingo.: n=411; fingo.-P: n=405)	MS	0.5	2.51 (56%)	1.35 (53%)	3.02 (56%)	2.70 (53%)
D2301 (fingo.: n=407; fingo.-P: n=404)	MS	1.25	5.91 (65%)	3.29 (57%)	4.73 (65%)	2.63 (57%)
D2302 (fingo.: n=281; fingo.-P: n=255)	MS	0.5	2.31 ± 1.35	1.28 ± 0.71	4.62 ± 2.70	2.56 ± 1.42
D2302 (fingo.: n=267; fingo.-P: n=239)	MS	1.25	5.35 ± 2.93	2.97 ± 1.46	4.28 ± 2.34	2.38 ± 1.17

Study FTY720D2101 and study FTY720A2305: predose sample collected on day 7 after a 4-day loading dose regimen followed by a 3-day once daily maintenance dose period

Study FTY720D2201: predose samples collected after 3 and 6 months of start of treatment

Study FTY720D2301: predose samples collected after 2, 3, 6, 9, 12, 15, 18, 21, and 24 months of start of treatment

Study FTY720D2302: predose samples collected after 6 and 12 months of start of treatment

Special populations

Gender

The influence of gender on fingolimod and fingolimod-P pre-dose concentrations (as markers of $AUC_{\tau,b}$) was investigated in four population pharmacokinetics evaluations. In kidney transplant patients from Phase IIb and Phase III clinical studies (Studies FTY720A2218, FTY720A124 and FTY720A125), based on data from 321 women and 540 men, it was shown that fingolimod and fingolimod-P apparent clearance (CL_b/F) was not gender dependent. This is consistent with the results from the population pharmacokinetics evaluation in kidney transplant patients from Phase IIa (Study FTY720AB201) based on 72 women and 91 men (only fingolimod was measured).

Similarly, in multiple sclerosis patients from the Phase III clinical study (FTY720D2302 Exposure-response analysis), based on data from 340 women and 150 men, it was found that fingolimod and fingolimod-P blood concentrations were not statistically different between men and women. Finally, the population pharmacokinetics evaluation combining data from the two Phase III clinical studies in multiple sclerosis patients, Study FTY720D2301 and Study FTY720D2302, based on data from 881 women and 371 men, revealed that the differences in fingolimod-P concentrations (10% smaller in men than in women) were deemed not to be clinically significant.

Ethnic origin

The single-dose (1.25, 2.5, 5 mg) and multiple-dose (5 mg once a day for 7 days) pharmacokinetics of fingolimod and fingolimod-P were compared between Asian (Japanese) and demographically matched Caucasian healthy subjects in Study FTY720A2304. There were no apparent differences in fingolimod and fingolimod-P peak concentration, total exposure and elimination half-life (estimated for fingolimod, only) between the ethnic groups. There were no apparent interethnic differences in fingolimod or fingolimod-P accumulation, exposure, or elimination during multiple-dosing (mean Asian/Caucasian ratio close to 1 and 90% CI including 1 for all pharmacokinetic parameters). On the basis of this study, Asian patients do not appear to need a fingolimod dose regimen different from Caucasian patients.

In addition, the impact of ethnicities on the steady-state pharmacokinetics of fingolimod and fingolimod-P (pre-dose concentrations as markers of $AUC_{\tau,b}$) was also assessed in four population pharmacokinetics evaluations. In 861 kidney transplant patients from Phase IIb and Phase III clinical studies (Studies FTY720A2218, FTY720A124 and FTY720A125), the data consisted of Caucasian (78.51%), Black (6.1%), Hispanic (4.18%), Japanese (4%), Oriental (2.44%), and Others (4.65%). Small ethnicity differences in apparent clearance were seen but they were all of a similar size as the inter-subject variability, and hence are unlikely to be of clinical relevance.

In multiple sclerosis patients from the Phase III clinical Study FTY720D2302, the pharmacokinetic information was derived from Caucasian (92.4%), Asian (2.9%), Black (1.4%), Native American (0.2%) and Others (3.1%). No effect of ethnicity on fingolimod-P was observed except for the Asian patients having significantly higher concentrations (expected average fingolimod and fingolimod-P concentrations 81% greater in Asian compared to Caucasian patients). However, as there were only 12 Asian patients in the population (versus 517 Caucasian patients), no firm conclusions can be drawn.

In Study FTY720D2301 (Phase III clinical study in multiple sclerosis patients), the percentage of Black and Asian patients was small (0.1% and 0.4%, respectively) compared to that of Caucasian (95.3%), making it difficult to draw conclusions on effect of ethnic origin on fingolimod/fingolimod-P pharmacokinetics.

Elderly (≥65 years old)

In study FTY720A0121 de novo renal transplant patients on Neoral cyclosporin based immunosuppression received fingolimod 2.5 or 5 mg once a day for 1 year. The pharmacokinetic study population included 5 elderly patients aged 65 to 70 years (versus 193 non-elderly patients). Exposure in the elderly was similar to that in the non-elderly: mean (range) 4.0 (1.0 - 7.5) ng/ml versus 3.6 (0.2 – 11.2) ng/ml, respectively. A population pharmacokinetics evaluation, performed on the Phase IIb and Phase III clinical studies (Studies FTY720A2218, FTY720A124 and FTY720A125) in 861 kidney transplant patients, explored the effect of age on fingolimod and fingolimod-P pre-dose concentrations (as markers of $AUC_{\tau,b}$). There were 19 patients aged ≥65 years old in the analysis (with fingolimod samples in all of them but a fingolimod-P sample in only nine of them). The population pharmacokinetics analysis revealed that a patient aged 66 years old would have a lower (by 10.7%) apparent clearance and apparent volume (8.5%) for both fingolimod and fingolimod-P than a typical patient of 44 years of age. Table 10 displays the statistics on

apparent clearance from elderly patients (≥65 years) and the other patients (<65 years). Overall, this analysis shows that the effect of age on fingolimod and fingolimod-P pharmacokinetics, is small and not likely to be clinically relevant.

Table 10: Statistics on fingolimod and fingolimod-P apparent clearance, CLb/F (L/h), in elderly kidney transplant patients (age ≥65 years) compared to the rest of the kidney transplant patients population (<65 years)

	Fingolimod		fingolimod-P	
	≥65 years	<65 years	≥65 years	<65 years
N	19	842	9	463
Mean	10.32	12.14	12.87	14.28
SD	3.44	6.27	5.24	6.16
Minimum	4.44	1.52	6.83	2.59
Maximum	15.55	40.5	20.69	38.38

Children (<17 years old)

There is limited information on the pharmacokinetics of fingolimod and fingolimod-P in children. In Study FTY720A0115 fingolimod was administered as a single 0.07 mg/kg dose to seven stable paediatric renal transplant patients, aged 11 to 16 years, on Neoral cyclosporin based immunosuppression. The pharmacokinetics observed in paediatric patients were comparable to those of adults receiving a 5 mg dose (see Table 11).

Table 11: Comparison of the pharmacokinetic parameters between adolescents

(n=7) and adults (n=6) (M2.7.2, v4, p59)

Parameter	Fingolimod		fingolimod-P	
	Adolescents	Adults	Adolescents	Adults
Dose (mg/kg)	0.07	0.07 ± 0.02	--	--
t_{lag} (h)	0	0	2 (0-4)	2 (1-4)
t_{max} (h)	8 (4-24)	12 (12-16)	6 (4-24)	12 (6-12)
$C_{max,b}$ (ng/mL)	3.6 ± 0.6	4.4 ± 0.9	3.2 ± 1.4	3.6 ± 0.8
$AUC_{(0\text{-}tz)b}$ (ng.h/mL)	675 ± 194	794 ± 250	100 ± 69	142 ± 72
AUC_b (ng.h/mL)	731 ± 240	861 ± 302	--	--
CL_b/F (L/h)	5.3 ± 1.2	6.4 ± 1.9	--	--
CL_b/F (L/h/kg)	0.10 ± 0.02	0.09 ± 0.03	--	--
$V_{z,b}/F$ (L)	1122 ± 172	1354 ± 373	--	--
$V_{z,b}/F$ (L/kg)	22 ± 6	20 ± 5	--	--
$t_{1/2}$ (days)	6.5 ± 1.9	6.7 ± 2.8	--	--

Data are mean ± SD except for temporal parameters which are median (range).
Adults received a fixed 5 mg dose; dose per kg back-calculated from individual weights.

Weight

Based on data from the two pivotal studies, no dosage adjustment is recommended based on weight.

Impaired renal function

The effect of renal impairment on the pharmacokinetics of fingolimod, fingolimod-P and inactive metabolites M2 and M3, was studied in nine subjects with severe renal impairment (creatinine clearance (CLcr)<30 mL/min) compared to nine demographically-matched healthy subjects (Study FTY720D2108) after administration of a single 1.25 mg oral dose of fingolimod. In severe renal impaired subjects, , fingolimod $C_{max,b}$ and AUC_b were increased by 32% and 43%, respectively, and fingolimod-P $C_{max,b}$ and AUC_b were increased by 25% and 14%, respectively (compared to control subjects; see Table 12).

Table 12: Study FTY720D2108 - Geometric mean ratio (test/reference) and 90% confidence intervals for FTY720 PK parameters in blood

	Adjusted geo-mean*		Geo-mean ratio*		
Parameter (Unit)	**Impaired**	**Control**	**Estimate**	**Lower 90% CL**	**Upper 90% CL**
$C_{max,b}$ (ng/mL)	0.844	0.639	1.32	1.06	1.65
$AUC_{(0\text{-}tz),b}$ (h*ng/mL)	91.226	61.576	1.48	0.94	2.33
AUC_b (h*ng/mL)	109.440	76.723	1.43	0.94	2.18
$AUC_{(0\text{-}72),b}$ (h*ng/mL)	45.638	34.379	1.33	1.04	1.69

* back-transformed from log scale; geo-mean=geometric mean.

Fingolimod and fingolimod-P protein binding was not altered by severe renal impairment. As M2 pharmacokinetics could not be defined in healthy controls (all M2 blood concentrations being below the LLOQ), the assessment of the effect of severe renal impairment on this metabolite pharmacokinetics was not possible. However, by comparing the mean $C_{max,b}$ observed in severe renal subjects to the LLOQ for this analyte, it can be hypothesised that the increase in concentration in these subjects be at least three-fold compared to control subjects. M3 $C_{max,b}$ and AUC_b were greatly increased in severe renal impaired subjects compared with control subjects by 805% and 1356%, respectively (see Table 13). The apparent elimination half-life for M3, was greater than in healthy controls. Recovery of M3 in urine to Day 3 was reduced in severe renal impaired subjects to one-third the corresponding recovery in control subjects in line with the increased blood exposure.

Table 13: Study FTY720D2108 - Geometric mean ratio (test/reference) and 90% confidence intervals for M3 PK parameters in blood

	Adjusted geo-mean*		Geo-mean ratio*		
Parameter (Unit)	**Impaired**	**Control**	**Estimate**	**Lower 90% CL**	**Upper 90% CL**
$C_{max,b}$ (ng/mL)	5.082	0.631	8.05	5.53	11.72
$AUC_{(0\text{-}tz),b}$ (h*ng/mL)	905.959	40.928	22.14	13.43	36.49
AUC_b (h*ng/mL)	1002.995	73.979	13.56	7.95	23.14
$AUC_{(0\text{-}72),b}$ (h*ng/mL)	267.001	29.060	9.19	6.50	12.99

* back-transformed from log scale; geo-mean=geometric mean.

In study FTY720A2202, the effect of renal impairment and haemodialysis on fingolimod steady state blood levels was assessed. This one-year, single-arm study, was conducted in fifty-two de novo adult renal transplant recipients at increased risk of delayed graft function receiving an immunosuppressive regimen of fingolimod (2.5 mg, once a day), therapeutically monitored everolimus and corticosteroids. Of this total, forty-nine patients were evaluable for fingolimod pharmacokinetics. Blood samples were obtained regularly for fingolimod trough concentrations ($C_{0,b}$) and were also requested before and after each haemodialysis run for analysis of fingolimod. The results showed that patients with mild and moderate renal impairment (30 to 80 ml/min creatinine clearance) had similar exposure as patients with normal renal function. The mean post/pre haemodialysis concentration ratio (based on 207 paired blood samples) was 0.86 ± 0.39 (95% CI, 0.80 – 0.91) indicating an average 14% decrease in blood concentrations. Haemodialysis leads to a 14% reduction in fingolimod blood concentrations.

Evaluator's comment: *The sponsor argues that fingolimod dose does not need to be adjusted in mild, moderate or severe renal impaired patients as M2 and M3 are two inactive metabolites. The sponsor believes that the magnitude of the changes in fingolimod and fingolimod-P disposition support no adjustment of fingolimod dose in severe renal impaired patients or patients with mild or moderate renal impairment.*

The clinical evaluator pointed out that the safety profiles of M2 and M3 are unknown. In addition, there were no data submitted on patients with severe renal failure undergoing dialysis. The clinical evaluator agreed that dose modification need not be recommended for patients with mild to moderate renal impairment. However, fingolimod should be contraindicated for patients with severe renal impairment.

Impaired hepatic function

The effect of hepatic impairment on the pharmacokinetics of fingolimod, fingolimod-P, M2 and M3 was studied in subjects with mild and moderate (Study FTY720A0112) and severe (Study FTY720A22040 hepatic impairment compared to demographically-matched healthy subjects. Both studies were of an open-label parallel group design in which the classification of the degree of hepatic impairment was based on the Child-Pugh score. A single oral dose of fingolimod was administered to mild (1 mg, n=8), moderate (1mg, n=8) and severe (5mg, n=6) hepatic impaired subjects and matched healthy subjects (the number of patients was similar to the hepatic impairment group).

Mild, moderate and severe hepatic impairment had no influence on fingolimod C_{max}, however fingolimod AUC is increased by 12%, 44% and 103%, respectively (see Table 14). The apparent elimination half-life is unchanged in mild hepatic impairment but is prolonged by 49 to 50% in moderate and severe hepatic impairment.

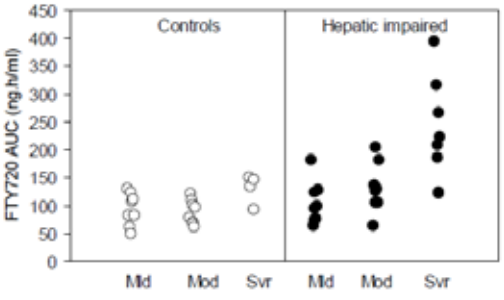
Fingolimod-P was measured in severe hepatic impairment only, and C_{max} and $AUC_{(0-96)}$ were reduced by 22% and 29%, respectively. AUC_b was increased by 12%, 44% and 103 % in mild, moderate and severe hepatic impaired subjects, respectively, compared to the control subjects (oral clearance was decreased by 10%, 31% and 51%, respectively). The estimated elimination half-life was similar in mild hepatic impaired subjects and control subjects, but was prolonged by 49% and 50% in moderate and severe hepatic impaired subjects, respectively.

Table 14: Ratios of geometric mean (90% CI) fingolimod pharmacokinetic parameters in hepatic impaired subjects relative to demographically matched healthy subjects

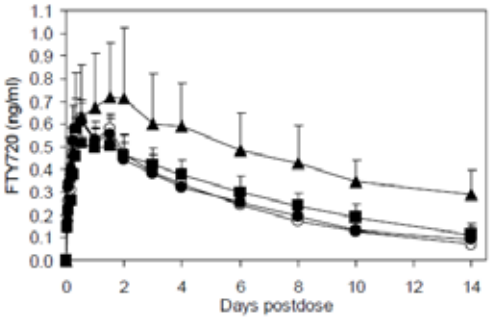
Analyte	Parameter	Mild	Moderate	Severe
Fingolimod	$C_{max,b}$	0.95 (0.83- 1.09)	1.01 (0.87- 1.16)	1.07 (0.81- 1.42)
Fingolimod	AUC_b	1.12 (0.85- 1.47)	1.44 (1.10- 1.90)	2.03 (1.62- 2.54)
Fingolimod-P	$C_{max,b}$	not determined	not determined	0.78 (0.53- 1.15)
Fingolimod-P	$AUC_{(0-96)b}$	not determined	not determined	0.71 (0.28- 1.76)

Patterns are shown for fingolimod AUC_b in the left panel of Figure 2. The mean concentration profiles are shown in the right panel of Figure 2.

Figure 3: Fingolimod exposure across hepatic impairment categories



Comparison of individual fingolimod AUC values in mild (Mld), moderate (Mod) and severe (Svr) hepatic impaired subjects (*filled circles*) and matched healthy controls (*open circles*). Data adjusted for a 1-mg dose.



Mean fingolimod concentration profiles in healthy subjects (*open circles*) and subjects with mild (*filled circles*), moderate (*filled squares*), and severe (*filled triangles*) hepatic impairment. *Bars* represent 95% confidence intervals. Data adjusted to a 1-mg dose.

Fingolimod-P was not measured in the mild-moderate hepatic impairment study. In severe hepatic impaired subjects, compared to the matched healthy volunteers, $C_{max,b}$ and $AUC_{(0-96)b}$ were 22% and 29% smaller, respectively (see Table 14). Elimination half-life could not be assessed but was likely prolonged in severe hepatic impaired subjects compared to the control subjects.

Blood concentrations of the inactive metabolites, M2 and M3, were measured in the mild-moderate hepatic impairment study only (but with no reliable estimation of M2 pharmacokinetic parameters due to the sporadically quantifiable concentrations). The urine recovery of these metabolites was assessed in mild, moderate and severe hepatic impairment. Peak and total exposure of M3 were not different between control and mild-moderate hepatic impaired subjects due, in part, to high inter-subject variability. Recovery of M2 in urine over the first 4 days post-dose was not affected by mild hepatic impairment but was reduced by an average of 70% and 53% in moderate and severe hepatic impairment, respectively. M3 urine recovery was reduced on average by 47%, 68% and 65% in mild, moderate and severe hepatic impairment, respectively.

Evaluator's comment: *The sponsor has stated that although hepatic impairment elicited changes in the disposition of fingolimod and fingolimod-P, the magnitude of these changes suggests that the fingolimod dose does not need to be adjusted in mild or moderate hepatic impaired patients, and that fingolimod should be used with caution in severe hepatic impaired subjects.*

The data submitted for evaluation indicate that the pharmacokinetics of fingolimod is substantially different in patients with severe hepatic impairment compared to controls. Therefore the clinical evaluator's recommendation for use in patients with hepatic impairment is as follows:

> *"The fingolimod dose does not need to be adjusted in mild or moderate hepatic impaired patients. Use of fingolimod is not recommended in patients with severe hepatic impairment."*

Interactions

Fingolimod is primarily metabolised via human CYP4F2 with significant turnover also observed for CYP2D6*1, 2E1, 3A4, and 4F12 (Study R0301153). The involvement of multiple CYP isoenzymes in the oxidation of fingolimod suggests that the metabolism of fingolimod may not be the subject of substantial inhibition in the presence of a single specific CYP inhibitor. *In vitro* inhibition studies in pooled human liver microsomes and specific metabolic probe substrates demonstrated that fingolimod and the pharmacologically active S-enantiomer of fingolimod-P (AML629) have little or no capacity to inhibit the activity of CYP450 enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, or CYP4A9/11).

Fingolimod was examined for its potential to induce human CYP3A4, CYP1A2, CYP4F2, and ABCB1 (P-gp) mRNA and CYP3A, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP4F2 activity in primary human hepatocytes of three individual donors after 72 hr of treatment (Study R0500157). Fingolimod (0.01-1 μmol/L) did not induce mRNA or activity of the different CYP450 enzymes and ABCB1 with respect to the vehicle control suggesting that there would be no clinically relevant induction of the tested CYP450 enzymes or ABCB1 (P-gp) by fingolimod at therapeutic concentrations.

The biotransformation of [^{14}C] fingolimod was investigated *in vitro* in primary human hepatocytes in order to test whether it can be induced by 72-hr pre-treatment with the known drug metabolizing enzymes inducers rifampicin, phenytoin, phenobarbital, or carbamazepine (Study R0500655). All four inducers affected the biotransformation of fingolimod only moderately with maximum increase of 4.12-fold with rifampicin (25 μmol/L). The increase in fingolimod metabolism by these inducers was likely due to induction of CYP4F activity.

Cyclosporin

The effect of co-administration of cyclosporin at steady-state (200 mg twice daily) and a single dose of fingolimod (1 mg) was investigated in an open-label, cross-over study in psoriatic patients (Study FTY720A0107). Compared to the administration alone, the pharmacokinetics of fingolimod were not altered during the coadministration with cyclosporin at steady-state. Similarly, compared to the administration alone, cyclosporin steady-state pharmacokinetics was not altered during the coadministration with the single dose fingolimod.

In Study FTY720AB102, steady state cyclosporin pharmacokinetics were unchanged after 28 days of coadministration with fingolimod (once daily doses ranging from 0.125 to 5 mg) compared with the pre-treatment baseline. These data indicate that fingolimod is unlikely to reduce the clearance of drugs mainly cleared by CYP3A4.

Ketoconazole

The effects of co-administration of ketoconazole at steady-state (200 mg twice daily over a 9 day period) and a single dose of fingolimod (5 mg) was investigated in an open-label, crossover study in healthy subjects (Study FTY720A2311). In Period 1 (Days 1-35) subjects received a single 5 mg dose of FTY720 on Day 1 with pharmacokinetic blood sampling and clinical assessments up to Day 35. In period 2 (Days 36-73) subjects received ketoconazole 200 mg twice-daily for 9 days (Days 36-44) and a single 5 mg dose of FTY720 coadministered on the fourth day of ketoconazole treatment (Day 39).

Co-administration increased fingolimod peak exposure, C_{max} by 1.22-fold and overall exposure AUC by 1.71-fold. Fingolimod-P $AUC_{(0-tz)}$ was increased to a similar extent (1.7-fold) as the parent fingolimod, however C_{max} was unaffected by ketoconazole. Table 15 represents pharmacokinetic profiles of fingolimod and fingolimod-P when fingolimod was administered alone and in the presence of ketoconazole.

Evaluator's comment: *Given the pharmacokinetic results from Study FTY720A2311 the clinical evaluator believed that coadministration of fingolimod with ketoconazole is not recommended. This should be reflected in the Australian Product Information (PI).*

Table 15: Study FTY720A2311 - Fingolimod and fingolimod-phosphate pharmacokinetics

Parameter	Fingolimod alone	Fingolimod with ketoconazole	Ratio of geometric means (90%CI)
Fingolimod:			
t_{lag} (h)	0.25 (0.25-0.5)	0.25 (0-0.25)	--
t_{max} (h)	12 (8-36)	12 (3-48)	--
$C_{max,b}$ (ng/ml)	3.9 ± 0.7	4.8 ± 1.1	1.22 (1.15 – 1.30)
$AUC(0\text{-}120)_b$ (ng.h/ml)	312 ± 67	439 ± 98	1.40 (1.31 – 1.50)
$AUC(0\text{-}t_z)_b$ (ng.h/ml)	635 ± 201	1087 ± 277	1.74 (1.56 – 1.94)
AUC_b (ng.h/ml)	665 ± 202	1124 ± 293	1.71 (1.53 – 1.91)
CL_b/F (L/h)	8.2 ± 2.4	4.7 ± 1.2	0.58 (0.52 – 0.65)
$V_{z,b}/F$ (L)	1361 ± 305	936 ± 291	0.68 (0.63 – 0.73)
$t_{1/2}$ (days)	5.1 ± 1.6	5.8 ± 1.6	1.15 (1.06 – 1.26)
Fingolimod-phosphate:			
t_{lag} (h)	2 (1-4)	2 (1.5-4)	--
t_{max} (h)	8 (6-12)	8 (6-12)	--
$C_{max,b}$ (ng/ml)	4.5 ± 1.3	4.4 ± 1.1	0.99 (0.92 – 1.06)
$AUC(0\text{-}t_z)_b$ (ng.h/ml)	128 ± 49	217 ± 99	1.67 (1.50 – 1.85)

Values are mean ± sd except for temporal parameters which are median (range).

Isoproterenol

Supportive pharmacokinetic data for fingolimod and fingolimod-P were generated in a pharmacodynamic study investigating the influence of IV isoproterenol ≤5 µg/min on the negative chronotropic effect of a single 5 mg fingolimod dose in healthy subjects (Study FTY720A0119). Compared to placebo administration, the exposure to both analytes was not altered in presence of isoproterenol.

Atropine

Supportive pharmacokinetic data for fingolimod and fingolimod-P were generated in a pharmacodynamic study investigating the influence of IV atropine ≤2 mg on the negative chronotropic effect of a single 5 mg fingolimod dose in healthy subjects (Study FTY720A0118). Fingolimod and fingolimod-P exposure ($C_{max,b}$ and $AUC_{(0\text{-}24)b}$) were not influenced by atropine, either co-administered with fingolimod or administered 4 hr after fingolimod.

Calcium channel blocker and beta-blocker

The single dose pharmacokinetics of fingolimod (5 mg) and fingolimod-P and the steady-state pharmacokinetics of atenolol (50 mg/day for 5 days) and extended-release diltiazem (240 mg/day for 5 days) were assessed in a study in healthy subjects investigating the negative chronotropic effect of a single-dose of fingolimod when coadministered with a beta-blocker and calcium channel blocker at steady state (Study FTY720A0114). Compared to the administration of atenolol alone and fingolimod alone, the pharmacokinetics of atenolol, fingolimod, and fingolimod-P appeared not to be altered during the coadministration of the two drugs. Similar results were obtained with diltiazem (a moderate CYP3A inhibitor).

Population pharmacokinetic analysis for co-medications influencing fingolimod and fingolimod-P pharmacokinetics

A population pharmacokinetics evaluation, performed on the Phase IIb and Phase III clinical studies (Studies FTY720A2218, FTY720A124 and FTY720A125) in 861 kidney transplant patients, explored the effect of CYP3A and CYP2D6 inhibitors on fingolimod and fingolimod-P pre-dose concentrations (FTY720_0124_0125_2218_PopPK). Based on the data from the 342 patients having

received a CYP3A inhibitor (fluconazole, diltiazem, verapamil, azithromycine, ketoconazole, cimetidine, clarithromycin, erythromycin, itraconazole, roxythromycin, voriconazole) and having fingolimod concentration measured (101 having fingolimod-P concentration measured) and from the 61 patients having received a CYP2D6 inhibitor (sertraline, paroxetine, fluoxetine, amiodarone, quinidine, terbinafine) and having fingolimod concentration measured (12 having fingolimod-P concentration measured), it was found that these co-medications have a no or a weak effect (less than 20% change) on fingolimod and fingolimod-P steady-state pharmacokinetics.

This population pharmacokinetics evaluation also explored the effect of CYP3A inducers on fingolimod and fingolimod-P pharmacokinetics. Based on the data from the 29 patients having received a CYP3A inducer (rifampicin, phenytoin, phenobarbital, carbamazepine, and oxcarbazepine) and having fingolimod concentration measured (11 having fingolimod-P concentration measured) there was no evidence for an increase in apparent clearance or reduction in fingolimod and fingolimod-P pre-dose concentrations.

A population pharmacokinetics evaluation, combining the data from more than 1200 multiple sclerosis patients from the two Phase III clinical studies (Studies FTY720D2301 and FTY720D2302), also explored the effect of strong CYP2D6 inhibitors (paroxetine and fluoxetine), and a potent CYP3A inducer (carbamazepine) on fingolimod and fingolimod-P pre-dose concentrations (FTY720D2301-CFTY720D2302 Exposure response analysis). The fingolimod and fingolimod-P concentrations measured in samples from patients on the co-medication were compared to those from samples drawn from patients not receiving the co-medication (total number of fingolimod-P samples was about 7000). Based on nearly 250 samples, it was found that the effect of the strong CYP2D6 inhibitors on fingolimod-P concentration is minor (less than 12% decrease). Similarly, based on more than 100 samples, carbamazepine had no significant effect (less than 30% decrease) on fingolimod-P concentration. In addition, the following, commonly prescribed substances had no clinically relevant effect (<30% and even $\leq$20% for the 0.5 mg dose group) on fingolimod-P pre-dose concentrations: baclofen, gabapentin, oxybutynin, amantidine, modafinil, amitriptyline, pregabalin, corticosteroids and oral contraceptives (with number of samples greater than 100 in most cases).

Exposure relevant for safety evaluation

See previous sections for expected exposure in the target population.

Evaluator's overall conclusions on pharmacokinetics

Absorption

Fingolimod absorption is slow (t_{max} of 12-16 hr) and extensive ($\geq$85%, based on the amount of radioactivity excreted in urine and the amount of metabolites in faeces extrapolated to infinity). The apparent absolute oral bioavailability is high (93%).

Fingolimod $C_{max,b}$ and AUC_b rise in an apparent dose proportional manner at single doses from 0.25 to 40 mg and at multiple once daily doses from 0.125 to 5 mg. Fingolimod-P $C_{max,b}$ increases in an under-proportional manner with increasing single doses (a dose increase by a factor 2 results in a $C_{max,b}$ increase by a factor 1.60). A high-fat meal does not alter fingolimod $C_{max,b}$ or AUC_b. Fingolimod-P AUC_b is also unchanged when given with a high fat meal whereas $C_{max,b}$ decreases by 34%. This is considered small and of no clinical impact.

Steady-state exposure is reached after 1 to 2 months during once-daily dosing with an estimated 12-fold accumulation in blood from the first dose to steady state. The fingolimod blood concentration profile at steady-state shows a peak to trough fluctuation (PTF) of approximately 20%. T_{max} is variable, occurring at a median time of 12 hr. Fingolimod-P reaches $C_{max,b}$ at a median time of 8 hr, and the peak to trough fluctuation is approximately 45%.

Distribution

Fingolimod highly distributes in red blood cells, with the fraction in blood of 86%, but fingolimod-P has a smaller uptake in blood of <17%. 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 (Study FTY720A0108).

Metabolism

The biotransformation of fingolimod in humans occurs by three main pathways: (i) by reversible stereoselective phosphorylation to the (S)-enantiomer of fingolimod-P (AML629, the active metabolite), (ii) by oxidative biotransformation mainly via the cytochrome P450 4F2 isoenzyme and subsequent fatty acid-like degradation to inactive metabolites and (iii) by formation of nonpolar ceramide analogs of fingolimod. Fingolimod-P can be converted back to fingolimod and the nonpolar ceramide metabolites of fingolimod may also be converted back to fingolimod.

Following single oral administration of [^{14}C]fingolimod, the major fingolimod-related components in blood, as judged from their contribution to the $AUC_{(0\text{-}816)b}$ of total radiolabelled components, are fingolimod itself (23.3%), fingolimod-P (10.3%), M3 (8.3%), M29 (8.9%) and M30 (7.3%).

Excretion

Fingolimod blood clearance is low, 6.3±2.3 L/h, and the average apparent terminal half-life is long, 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 faeces with amounts representing less than 2.5% of the dose each. After 34 days, the recovery of the administered dose is 89%. **Drug interactions**

In vitro studies with human liver microsomes demonstrated that fingolimod and fingolimod-P are unlikely to reduce the clearance of drugs metabolised by the major cytochrome P450 isoenzymes. Similarly, based on *in vitro* human hepatocytes studies, fingolimod and fingolimod-P are not likely to induce the major cytochrome P450 isoenzymes and P-gp.

No clinically relevant drug interaction has been observed when fingolimod was coadministered with cyclosporin (a CYP3A substrate and potent transporter inhibitor), and diltiazem (a moderate CYP3A inhibitor). However, an interaction was observed with ketoconazole (a CYP4F and strong CYP3Ainhibitor) and it should be recommended that fingolimod should not be coadministered with ketoconazole.

Special populations

Intrinsic Factors

Age: No age effect was noticed in the population model. No dose adjustments are therefore recommended based on age.

Gender: A slight lower concentration (10.4%) was observed in males than in females, however, the magnitude of the effect was deemed to be not clinically relevant. No dose adjustments are therefore recommended based on gender.

Weight: No dose adjustments are therefore recommended based on weight.

Race: No dose adjustments are recommended based on race.

PK in MS patients: Based on population analysis, the PK of fingolimod and fingolimod-P following oral administration of FTY720 capsules were similar between MS patients and healthy subjects.

Hepatic impairment patients: Moderate and severe hepatic impairments increased fingolimod AUC by 44% and 103%, respectively. The apparent elimination half-life is prolonged by 49-50% in moderate and severe hepatic impairment. Fingolimod-P C_{max} and $AUC_{(0\text{-}96)}$ were increased by 22%

and 29%, respectively, in severe hepatic impaired patients. The fingolimod dose does not need to be adjusted in mild or moderate hepatic impaired patients. This evaluator recommends that fingolimod should not be used in patients with severe hepatic impairment. Renal impairment patients: 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 apparent elimination half-life is unchanged for both analytes.

Exposure to the inactive metabolites is also increased with severe renal impairment, by at least 300% for M2, and by 805% and 1356% for the C_{max} and AUC, respectively, for M3. The clinical impact of this increase has not been determined. The use of fingolimod should be contraindicated in renal impaired patients due to uncertainty in relation to the safety profiles of M2 and M3.

Pharmacodynamics

Introduction

The clinical pharmacology programme has focused on measuring the following three pharmacologic effects of fingolimod; decrease in the peripheral lymphocyte count, decrease in heart rate and increase of airway resistance. The three main clinical pharmacology studies which highlight the effect of fingolimod on peripheral lymphocyte count are Studies FTY720AB101, FTY720AB102 and FTY720A2215. In addition to these three main studies, most of the other human clinical pharmacology studies conducted during the development of fingolimod also collected lymphocyte data.

Mechanism of action

Fingolimod (FTY720), a synthetic sphingosine 1-phosphate (S1P) receptor modulator (MW: 307.47). Under normal circumstances, T-cells selectively require S1P1 activation for emigration from the thymus, and both T- and B-cells require this receptor for egress from peripheral lymphoid organs. Fingolimod-P acts as a functional antagonist of the S1P1 receptor on lymphocytes, inducing its uncoupling/internalisation. The internalisation of S1P1 renders these cells unresponsive to S1P, depriving them of the obligatory signal to egress from lymphoid organs and recirculate to peripheral inflammatory tissues. Fingolimod-P may also act on other cells and, depending on the cell type, may act as an “agonist” or “functional antagonist” at S1P receptors. Fingolimod-P causes a reversible retention of a proportion of CD4 and CD8 positive T-cells and B-cells from blood and spleen into lymph nodes (LNs) and Peyer’s patches, apparently without affecting many of the functional properties of these cells. The retention of CD4 and CD8 cells in peripheral LNs and Peyer’s patches reduces the number of these immune cells that have access to sites of MS-related inflammation in the brain and therefore decreases the inflammatory component of this disease. At steady state in both animals and humans fingolimod and fingolimod-P are in dynamic equilibrium.

Primary pharmacology

Single doses

The dose - response relationship of single doses of fingolimod and lymphocyte count was measured in two studies; Study FTY720AB101, in which doses of 0.25 to 3.5 mg were used and Study FTY720A2215, in which doses of 5 to 40 mg were used.

In Study FTY720AB101, the first-in-human study, the dynamic effect of a single dose of fingolimod on lymphocyte count was first quantified. This study was conducted in stable renal transplant patients on cyclosporin-based immunosuppression. The onset of a decrease in lymphocyte count occurred 2-3 hr post single dose and the lowest point (nadir) of this effect was seen at 4-6 hr post-dose In this study, there was a decrease of lymphocyte count in the placebo treatment group to approximately 65% of baseline which was due to circadian rhythm. With the low single fingolimod doses of 0.25 and 0.5 mg it was not possible to clearly distinguish a fingolimod effect from circadian rhythm. At fingolimod doses of 1 mg to 3.5 mg, a dose dependent decrease of

lymphocyte count was clearly noted. At the maximal fingolimod dose used in this study, 3.5 mg, average lymphocyte count was approximately 700 cells/μL, or 27% of baseline. Finally, even at this highest, single fingolimod dose tested, there was a nadir lymphocyte count >400 cells/μL in all subjects. After nadir, the lymphocyte count slowly increased back to normal limits over the next 24-48 hr. All subjects had normal lymphocyte count by 96 hr post-dose.

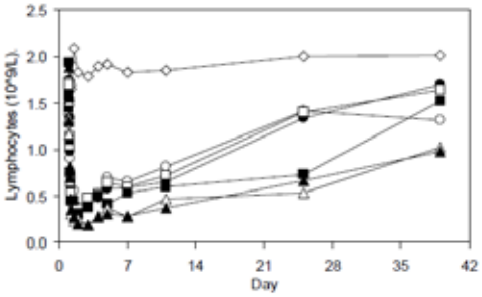
In Study FTY720A2215, the lymphocyte count after single, supra-therapeutic doses of fingolimod from 5 to 40 mg were studied in healthy volunteers. Lymphocyte data from this study are shown in Table 16 and Figure 4 below. At fingolimod single doses of ≥5 mg, there is little incremental decrease in lymphocyte count. In other words, the pharmacodynamic effect of fingolimod on lymphocyte count appeared to reach a plateau. Even at maximal single doses of fingolimod of 40 mg, there was still a residual number of lymphocytes present, approximately 10% of baseline at nadir.

Table 16: Study FTY720A2215 - Lymphocyte dose-response parameters

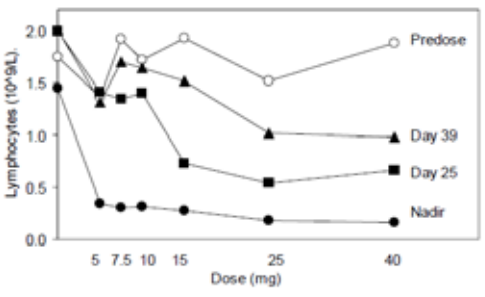
Parameter	Placebo	5mg	7.5mg	10mg	15mg	25mg	40mg
N	14	6	12	5	6	6	6
Acute effect:							
Predose count (10^9/L)	1.8 ± 0.5	1.4 ± 0.3	1.9 ± 0.2	1.7 ± 0.4	1.9 ± 0.5	1.5 ± 0.4	1.9 ± 0.6
t_{nadir} (day)	1.1 (1-11)	1.5 (1-2)	2 (1-3)	2 (1-2)	2 (1-5)	1.8 (1-3)	2 (2-3)
Nadir count (10^9/L)	1.5 ± 0.4	0.4 ± 0.1	0.3 ± 0.1	0.3 ± 0.2	0.3 ± 0.1	0.2 ± 0	0.2 ± 0.1
Nadir count (% predose)	84 ± 12	26 ± 7	16 ± 4	19 ± 7	15 ± 5	13 ± 4	9 ± 3
Recovery:							
Day 11 count (% predose)	106 ± 16	61 ± 27	34 ± 12	41 ± 9	32 ± 14	33 ± 21	20 ± 8
Day 25 count (% predose)	117 ± 21	107 ± 30	71 ± 25	83 ± 18	41 ± 17	35 ± 20	40 ± 22
Day 39 count (% predose)	114 ± 15	98 ± 30	89 ± 23	98 ± 20	79 ± 27	68 ± 17	58 ± 36
Day 39 count (10^9/L)	2.0 ± 0.7	1.3 ± 0.4	1.7 ± 0.4	1.6 ± 0.3	1.5 ± 0.6	1.0 ± 0.3	1.0 ± 0.4
AUE(1-39) (10^9/L x day)	74 ± 19	42 ± 9	42 ± 11	43 ± 11	31 ± 8	22 ± 6	23 ± 6

Due to the long half-life of fingolimod of approximately 8 days, the recovery of lymphocytes count was increasingly delayed with increasing fingolimod doses as shown in the left panel of Figure 3. At the highest single doses tested it took >1 month for the lymphocyte count to return to normal range (>1x10^9 cells/L).

Figure 4: Study FTY720A2215 - Lymphocyte dose-response plots



Lymphocyte trajectories after placebo (*open diamonds*) and fingolimod doses of 5mg (*open circles*), 7.5mg (*filled circles*), 10mg (*open squares*), 15mg (*filled squares*), 25mg (*open triangles*) and 40mg (*filled triangles*).



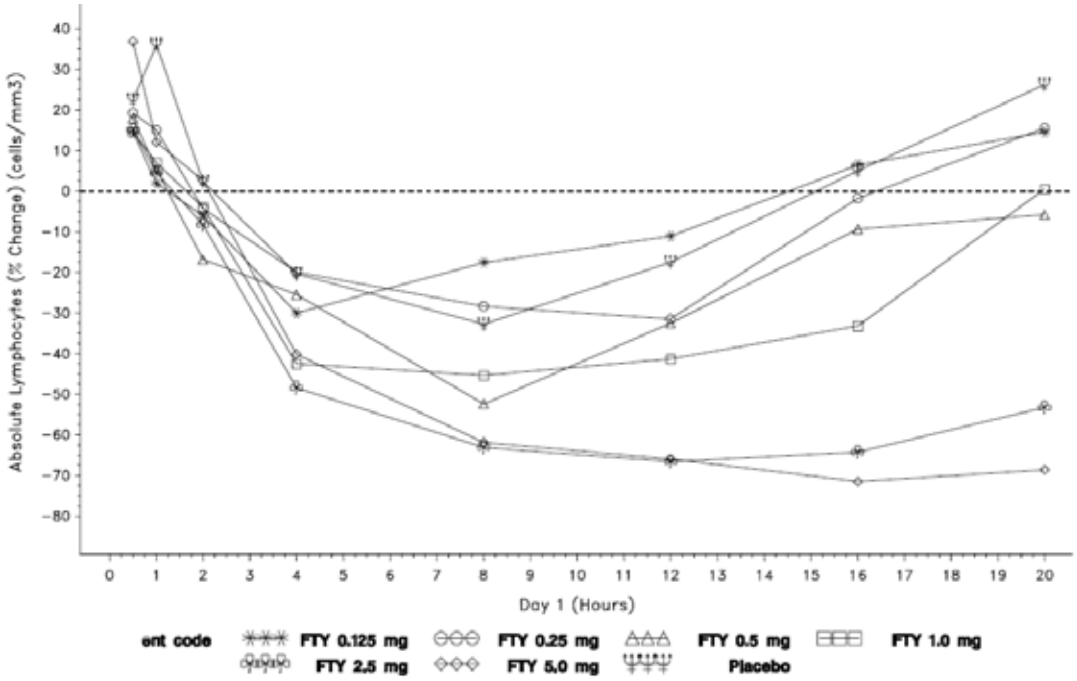
Mean predose, nadir, day 11, and day 39 lymphocyte counts with respect to fingolimod dose.

Multiple doses

In the first multiple ascending dose study, Study FTY720AB102, lymphocyte count was measured in stable renal transplant patients on cyclosporin based immunosuppression who received daily fingolimod doses of 0.125 to 5 mg for twenty-eight days. In Figure 5, lymphocyte count kinetics are shown after the first dose on Day 1. Similar to the results of Study FTY720AB101, it was difficult to discriminate fingolimod treatment from placebo treatment at fingolimod doses <0.5 mg. With

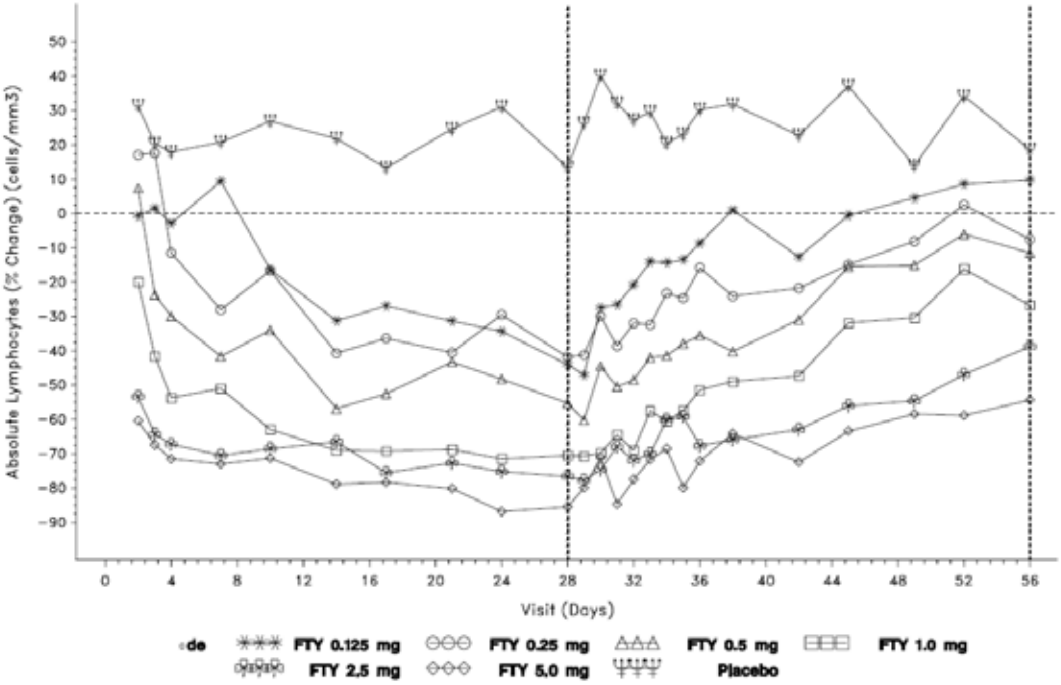
single fingolimod doses ≥0.5 mg, a dose dependent decrease in lymphocyte count was observed. However a plateau of effect was noted at fingolimod doses >2.5 mg. Given the long half-life of fingolimod, both the 2.5 and 5 mg single doses resulted in a persistent fingolimod blood concentration that maintained a nadir lymphocyte count over the 24 hour dosing interval.

Figure 5: Study FTY720AB102 - Mean percent change from baseline for absolute lymphocytes by hr for Day 1 (safety population)



In Figure 6, the time course of lymphocyte count over twenty-eight days of daily dosing and twenty-eight days post dosing are shown. Due to the accumulation of fingolimod, even the lowest fingolimod dose studied, 0.125 mg, had a clear effect on lymphocyte count after the first 4-5 days of daily dosing. After approximately two weeks of dosing, the lymphocyte count reached a dose-dependent plateau which was then maintained for the remaining two weeks of treatment. Even with daily dosing of the highest dose of fingolimod, 5 mg, there was a residual lymphocyte count of approximately 10-15% of baseline. After Day 28, once fingolimod dosing was stopped, all active treatment cohorts manifested an increase of lymphocyte count within one week. The increase in lymphocyte count during the twenty-eight day recovery period inversely approximated the decrease in fingolimod blood concentration during this period.

Figure 6: Study FTY720AB102 - Mean percent change from baseline for absolute lymphocytes by visit (safety population)



Effect of fingolimod on leukocyte subsets

White blood cell flow cytometry was done in Study FTY720AB101 to determine what cell types were affected by fingolimod. The following seven lymphocyte subsets were measured at time -12, 12, 24, 48 and 96 hr post-dose: CD20 (B cell), CD3 (T cell), CD4 (T helper), CD8 (T suppressor), CD16 (Natural killer), CD45RO (T memory), CD45RA (T naïve). In addition, CD14 (Monocyte) and granulocytes were also measured in this assay. The mean cell counts in the placebo group typically ranged from approximately 80% to 120% of baseline over the course of the study. The mean cell count for all seven lymphocytes subtypes decreased in the setting of fingolimod treatment at 12 hr post-dose to approximately 30-65% of baseline. By 24 hr post-dose, all lymphocyte subsets numbers had begun to increase and by 96 hr post-dose all subsets had returned to 80-100% of baseline. At doses higher than 1 mg, the duration of decreased subset number persisted for a longer period of time post-dose.

In contrast, both monocyte and granulocyte counts increased to 150-200% of baseline at Hour 12 post-dose and returned to baseline by 96 hr post-dose. However, after single, supratherapeutic doses of 3.5 mg fingolimod, both monocyte and granulocyte counts decreased to approximately 35% and 65% of baseline, respectively.

The leukocyte subsets listed above were also measured at baseline and at five time points during the one month, multiple dose Study FTY720AB102. All lymphocyte subsets were found to decrease in a dose dependent manner in the setting of multiple doses of fingolimod. The monocyte count was not affected by multiple dose fingolimod treatment.

Secondary pharmacology

Effect of fingolimod on heart rate

A consistent finding in all clinical pharmacology studies of fingolimod was a negative chronotropic effect which is manifested within hr of the first dose.

In Study FTY720AB101, none of the subjects receiving placebo had a bradycardia adverse events (AE). In contrast, approximately one-half of the subjects receiving fingolimod had a bradycardia

AE. Heart rate data over time post fingolimod dose was not collected in this study. Given the bradycardia AEs which occurred in Study FTY720AB101, heart rate data was rigorously collected in the second clinical pharmacology study, FTY720A0106, which was a fingolimod food interaction study. Mean supine heart rate decreased by approximately 8 beats per minute (BPM) at 4 hr post-dose in the fingolimod 1 mg treatment group. This decrease in heart rate persisted over the remaining twenty hr post-dose but then increased over the remainder of the 5-day assessment period.

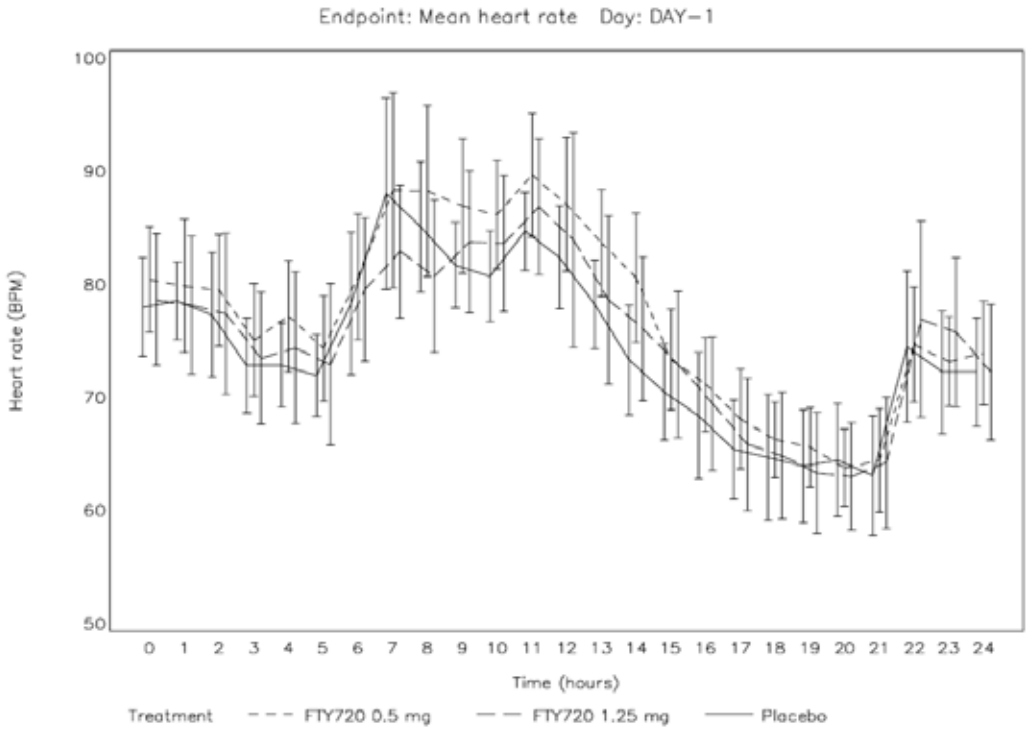
Study FTY720A0108 was an absolute bioavailability study which also profiled heart rate during the day before treatment (Day -1; run-in period) and Day 1 of the treatment period. The study showed there is a circadian rhythm to heart rate with heart rate decreasing from approximately 8AM to 12 noon. Both oral (1.25 mg) and IV (1 mg) doses of fingolimod were associated with a 14 to 20 beat per minute decrease in heart rate occurring 3- 4 hr post-dose.

Study FTY720A2213 was a randomised, double-blind study of heart rate and rhythm. There were three parallel treatment groups: placebo (n=20), fingolimod 1.25 mg (n=20) and fingolimod 5 mg (n=20). Subjects were dosed daily for seven days. This study used 24 hour Holter collection of heart rhythm data on Days -1, 1, 2 and 7 and 24 hour telemetric collection of heart rate data daily from Day -1 to Day 7. On Day –1, all treatment groups manifested an identical and consistent diurnal pattern. Of note, at approximately 8AM on Day –1, all subjects manifested a peak heart rate, with heart rate then decreasing for the next two to three hr. On Day 1 fingolimod resulted in a dose dependent decrease in mean heart rate. This decrease in heart rate was first apparent approximately two hr after the fingolimod dose and reached its nadir at approximately four hr post 1.25 mg and three hr post 5 mg fingolimod. Compared to the placebo group, the mean nadir heart rate decreased by 10 and 18 beats per minute for the fingolimod 1.25 and 5 mg treatment groups, respectively. The acute effect of fingolimod on heart rate that was observed in the first four hr following the dose on Day 1 was no longer observed with dosing on Days 2 through 7 even though fingolimod concentration was increasing by approximately 80% per day due to the long half-life of the drug. From Day 2 to end of study both fingolimod treatment groups had a similar mean heart rate, which was consistently lower than the placebo group by approximately 10 beats per minute. From Day 2 to Day 7, the diurnal pattern of heart rate variation in both fingolimod treatment groups was similar to this pattern in the placebo treatment group. This finding of similar diurnal variation is consistent with intact autonomic regulation of the heart in subjects on fingolimod treatment.

Study FTY720D2105 was a recent study and the first head to head comparison of the two fingolimod doses used in the pivotal, Phase III multiple sclerosis trials; 0.5 and 1.25 mg. There were three parallel, randomised, double blind treatment groups; placebo (n=9), 0.5 mg (n=9) and 1.25 mg (n=9). Treatment duration was 14 days and 24 hour Holter monitor heart rate data was collected on Day -1, 1, 7 and 14. The mean heart rate data from these days are shown in Figure 7, Figure 8, Figure 9 and Figure 10, respectively. The heart rate profiles of the three treatment groups were reasonably well matched on Day -1 (Figure 7). On Day 1 (Figure 7) the 1.25 mg treatment cohort manifested a significant decrease in mean heart rate which started at approximately 3 hr post-dose, reached a nadir at approximately 5 hr post-dose and persisted for the remainder of the dosing interval. The change in mean heart rate from Time 0 to nadir in the 1.25 mg group was approximately -15 beats per minute. Also on Day 1 the 0.5 mg treatment cohort manifested a trend of decrease in mean heart rate which was approximately halfway between the placebo and 1.25 mg cohorts. The difference between placebo and 0.5 mg cohorts started at approximately 5 hr post-dose and persisted for approximately 8 hr, after which the two groups had similar heart rates. In the 0.5 mg dose cohort, the difference in mean heart rate comparing Time 0 and nadir heart rate at time 5 hr was approximately 8-9 beats per minute. On Day 7 (Figure 9) both fingolimod treatment groups had significantly lower heart rates compared to placebo of approximately 10 beats per minutes. On Day 14 (Figure 10) while there was still a trend for lower heart rates in the two fingolimod treatment groups, the negative chronotropic effect of fingolimod began to attenuate. At multiple time points,

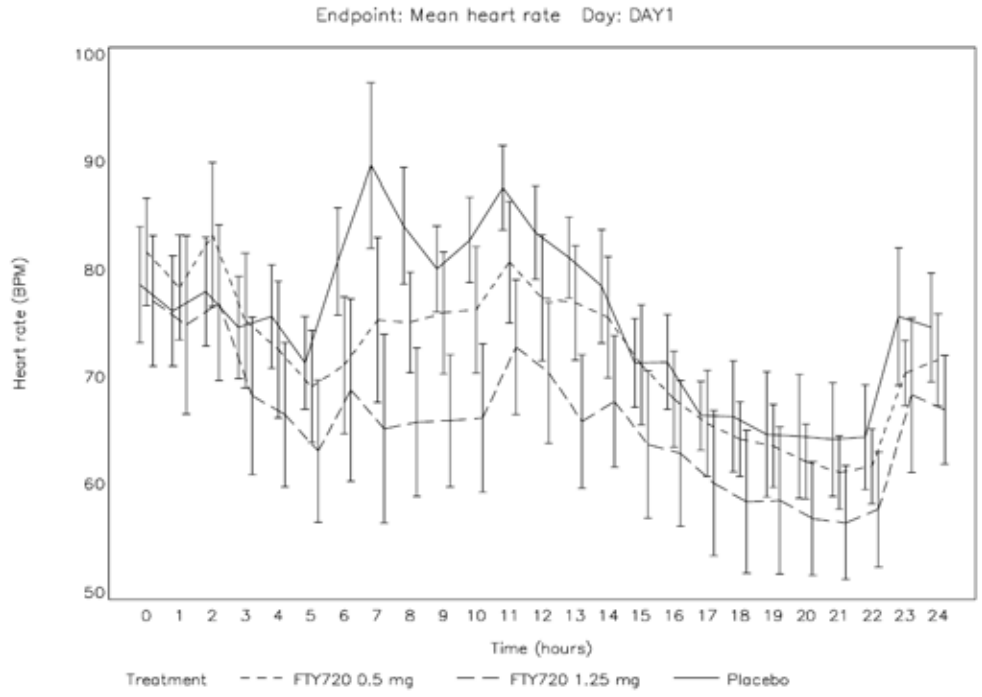
the mean heart rates of the three treatment groups were similar. Over the duration of the study, fingolimod treated cohorts manifested a circadian rhythm of mean heart rate which was similar to placebo

Figure7: Study FTY720D2105 - Mean heart rate by treatment group (placebo and fingolimod 0.5 and 1.25 mg): Day -1



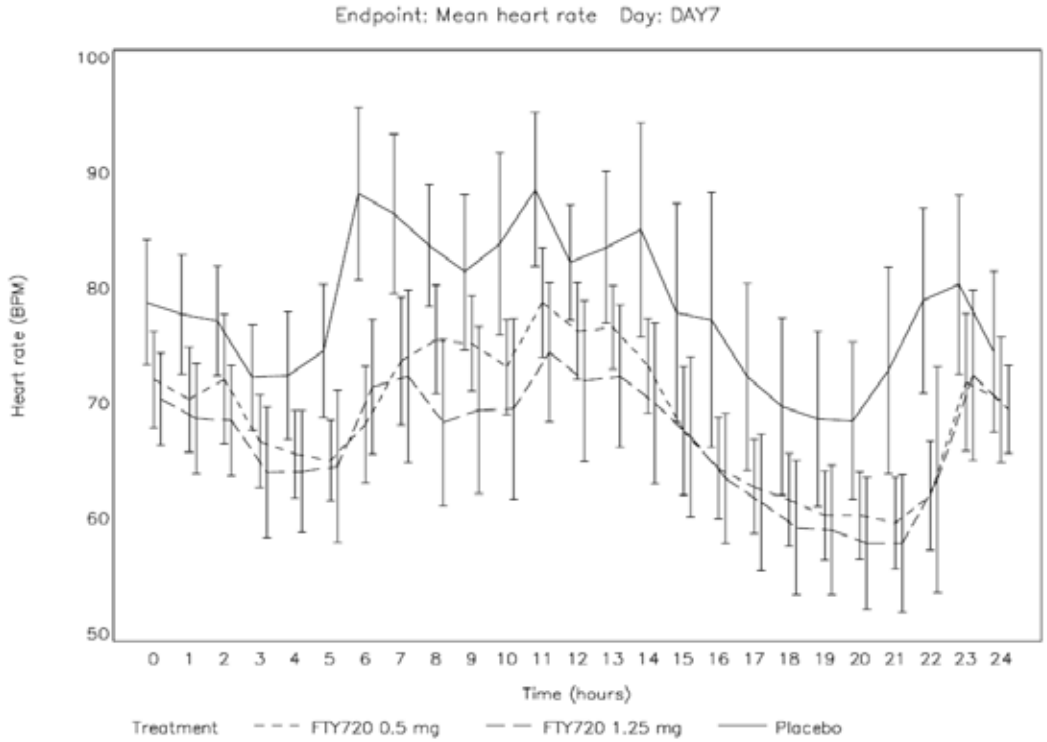
Note: Mean heart rate (±95% CI). Dose occurred at time 0, at approximately 0800-0900 h.

Figure 8 : Study FTY720D2105 - Mean heart rate by treatment group (placebo and fingolimod 0.5 and 1.25 mg): Day 1



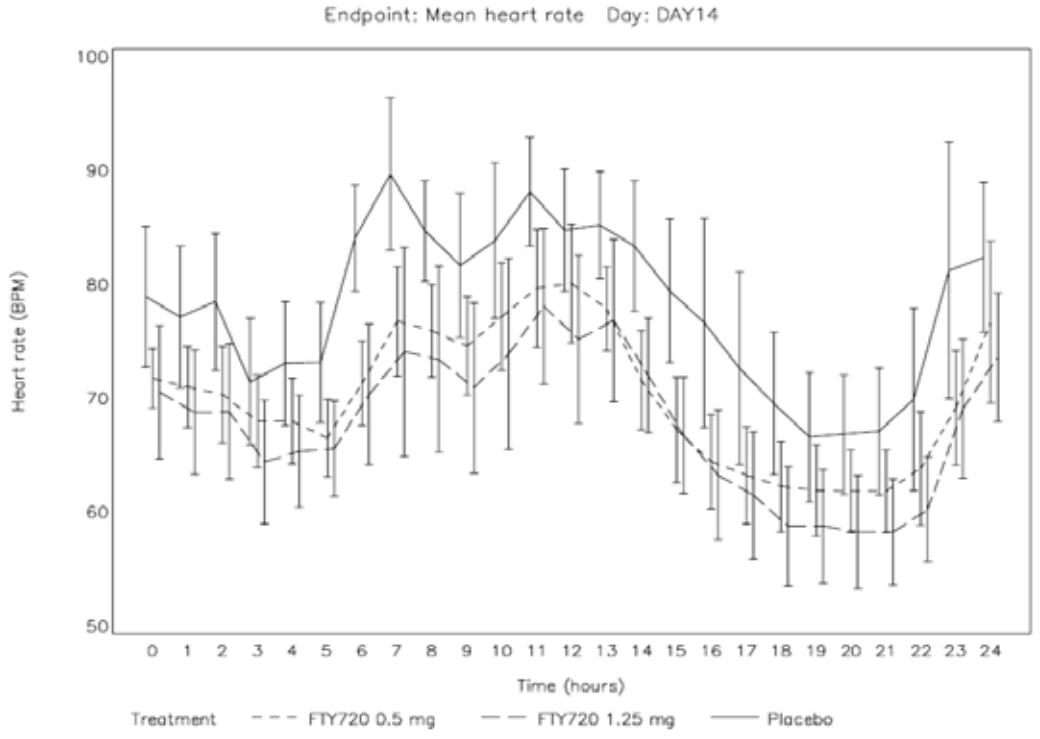
Note: Mean heart rate (±95% CI). Dose occurred at time 0, approximately 0800-0900 h.

Figure 9: Study FTY720D2105 - Mean heart rate by treatment group (placebo and fingolimod 0.5 and 1.25 mg): Day 7



Note: Mean heart rate (±95% CI). Dose occurred at time 0, approximately 0800-0900 h.

Figure 10: Study FTY720D2105 - Mean heart rate by treatment group (placebo and fingolimod 0.5 and 1.25 mg): Day14



Note: Mean heart rate (±95% CI). Dose occurred at time 0, approximately 0800-0900 h.

The attenuation of negative chronotropic effect with continued dosing was also explored in a pooled modelling and simulation analysis of multiple clinical pharmacology studies, including study FTY720D2105. The report of this analysis is titled “Model-based characterization of the effect of fingolimod on heart rate in healthy subjects” One of the conclusions of this report is that over weeks of fingolimod dosing, there should be a further loss of negative chronotropic effect. This has been confirmed in two recent studies. In Study FTY720D2113 healthy volunteers were brought to fingolimod pharmacokinetic steady-state using a four day loading regimen and then maintained at steady state with fingolimod doses of either 0.5 or 1.25 mg daily for an additional 24 days. While a clear, negative chronotropic effect of fingolimod was noted at the beginning of the study, by the end of treatment (Day 28) it was not possible to observe a difference in heart rate comparing placebo and the fingolimod treatment groups.

In Study FTY720D2302, the first completed Phase III pivotal trial in multiple sclerosis, it was shown that by Month 3 the average heart rate in both the fingolimod treatment groups and the active comparator group were similar.

Effect of fingolimod on AV blocks

Early in the clinical development of fingolimod a signal of atrioventricular block was detected. For this reason, a number of fingolimod clinical pharmacology studies measured heart rhythm during treatment initiation by Holter monitor. The studies in which Holter monitoring was used were: Studies FTY720A0108, FTY720A0115, FTY720A2213, FTY720A2215, FTY720A2304, FTY720A2305, FTY720A2306, FTY720D2105 and FTY720D2110. The rate of first degree atrioventricular block as defined by a PR interval >200 ms in a single ECG was approximately 18% in placebo treated subjects. The rate of new onset first degree atrioventricular block on day 1 of fingolimod treatment is approximately 12%. The rate of new onset first degree atrioventricular block in subjects after one week of fingolimod treatment is <1%.

With fingolimod doses ≤1.25 mg the incidence rate of second degree atrioventricular block (7%) was approximately twice the incidence rate measured in placebo treated subjects (3%). These blocks were typically asymptomatic and did not require treatment. There were no second degree Mobitz Type 2 atrioventricular blocks or “classical” wide complex, third degree atrioventricular blocks in any clinical pharmacology study.

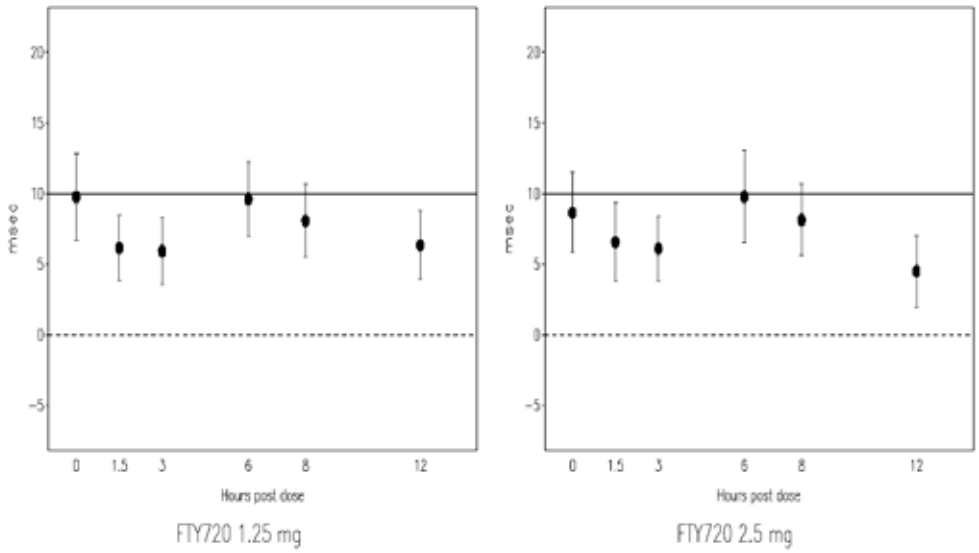
Effect of fingolimod on QT interval

Study FTY720D2101 was a pivotal, randomised, placebo-controlled, multiple oral dose “Thorough QT” study conducted in parallel groups of healthy volunteers. Moxifloxacin was administered under open-label conditions. Fingolimod and matching placebo were administered under double-blind conditions. Subjects were randomised to one of the four treatment groups below: moxifloxacin hydrochloride 400 mg, fingolimod matched-placebo, fingolimod 1.25 mg loading regimen, fingolimod 2.5 mg loading regimen. The primary comparison of QT data was between Day -1 and Day 7. On Day 7 the mean heart rate of both fingolimod treatment groups was approximately 10 BPM lower than either placebo or moxifloxicin treatment groups.

In Figure 10, the double delta QTcI data from the two fingolimod treatment groups are shown. A line is placed at +10 ms to represent a “threshold of interest” typically set by health authorities. The point estimates for both fingolimod treatment groups are net positive changes which range from approximately 5 to 10 ms. For both of these treatment groups, at 3 out of the 6 time points the upper limit of the 90% confidence interval is ≥10 ms. These data are consistent with a positive effect of fingolimod on the QTcI. Two additional features are noted. First, there is no dose effect of fingolimod on QTcI. Second, both fingolimod treatment groups manifest an almost identical time profile.

The positive control, a single oral dose of 400 mg moxifloxacin, failed to have the expected effect on QTcI (change from baseline and placebo corrected); the largest QTcI for moxifloxacin was about 10.5 ms and occurred at 6 and 8 hr post-dose.

Figure 11: Study FTY720D2101 - Double delta corrected QTcI



Note: Mean QTcI change in fingolimod treatment groups corrected by mean baseline and placebo group (with 90% confidence interval)

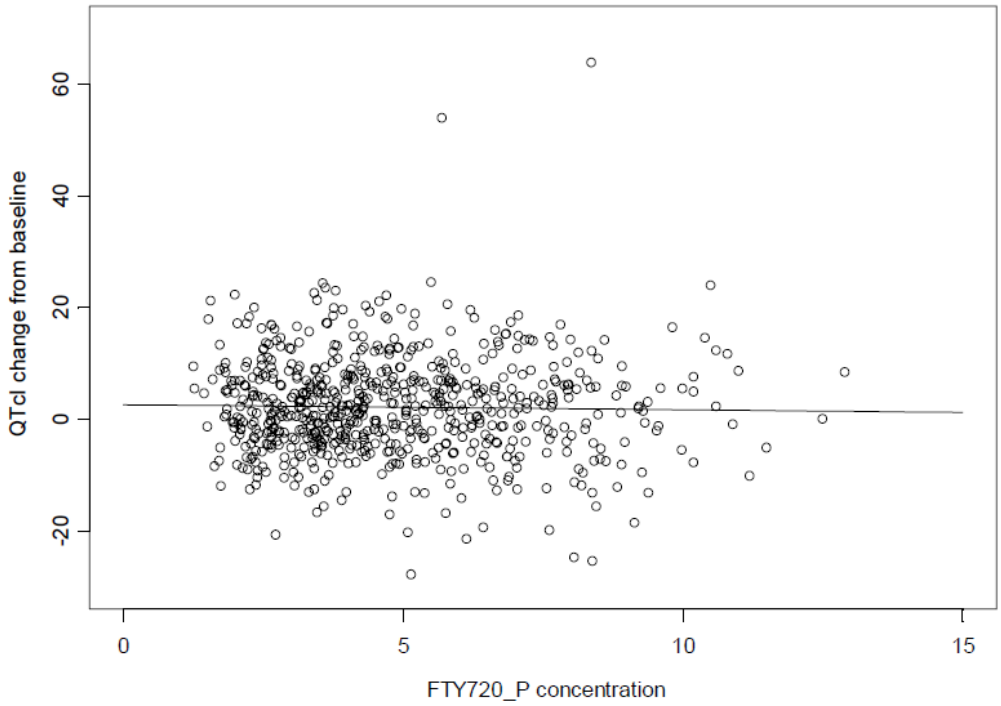
*Exposure – Response Analysis on Day 7***.** In Figure 12 below, the placebo treatment group has been removed from the analysis. This figure shows the relationship of between the concentration of the active metabolite, fingolimod-P, and QTcI. A best fit linear regression line is provided. Based on these data, it is not possible to detect an effect of an approximately one log range in fingolimod-P concentration on QTcI. Similar results were also seen with fingolimod concentration.

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% CI ≤13.0 ms. There was no dose or exposure - response relationship of fingolimod and QTcI prolongation.

Evaluator's comment: *This study failed to exclude a 10 ms prolongation of the QT interval for both doses of FTY720 (1.25 and 2.5 mg). The positive control failed to have the expected effect on QTcI (change from baseline and placebo corrected). In addition, despite a 2-fold increase in the exposure to FTY720 plasma concentrations, there was no dose-response relationship for QT prolongation. There was also not a concentration-QTc relationship for FTY720 and its metabolite FTY720-P. This raises concerns about the validity of the results.*

It is not possible to rule out the existence of a positive exposure-response relationship. The clinical evaluator believed that it should be recommended that baseline and periodic on-therapy ECGs are collected for safety assessments when fingolimod is used in clinical practice.

Figure 12: Study FTY720D2101 - QTcI change from baseline versus fingolimod-P blood concentration on Day 7



Note: Fingolimod-P blood concentration in ng/mL

Effect of fingolimod on ventricular function and blood pressure

Doppler echocardiography was used to measure the effect of fingolimod treatment on ventricular function in two clinical pharmacology studies, Studies FTY720A2306 and FTY720D2105. Daily dosing of fingolimod 0.5 and 1.25 mg for fourteen days had no effect on ventricular function.

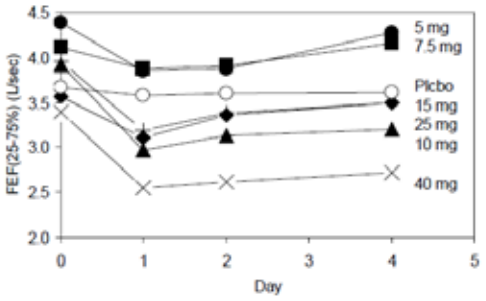
Blood pressure on both Day 1 and during two weeks of fingolimod dosing was profiled in Studies FTY720A2213 and FTY720D2105. Daily dosing of fingolimod 0.5 and 1.25 mg for fourteen days had no effect on blood pressure.

Effect of fingolimod on pulmonary function

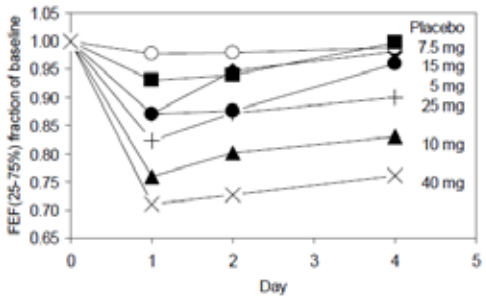
The following three studies of fingolimod's effect on pulmonary function were conducted in healthy volunteers; Studies FTY720A2215 (single high dose from 5 to 40 mg), FTY720A2306 (multiple supratherapeutic dose 5 mg daily for two weeks) and FTY720D2105 (clinical doses of 0.5 and 1.25 mg daily for two weeks).

The effects of high, single doses of fingolimod (5 mg to 40 mg) on the first day of treatment were studied in study FTY720A2215. The left panel of Figure 13 shows the temporal course for mean mid-expiratory flow (FEF_{25-75}) in each dose cohort. No change was noted over four days in the placebo group. Dose dependent decreases of FEF_{25-75} from Time 0 were noted in all fingolimod groups with a nadir reached on Day 1 (6 hr post-dose). The right panel of Figure 13 shows the values as fraction of baseline. By Day 4, mean values had recovered back to baseline except in the 10 mg, 25 mg, and 40 mg groups. Similar results were also seen for FEV1. The FVC was not affected by fingolimod 5-25 mg treatment, however it decreased by 6% from baseline with fingolimod 40 mg treatment ($p<0.05$).

Figure 13: Study FTY720A2215 - Mid-expiratory flow (FEF_{25-75}) trajectories after single high doses of fingolimod: 5 to 40 mg



Mean $FEF_{25-75\%}$ over 4 days post-dose in subjects receiving placebo (*open circles*) or fingolimod 5mg (*circles*), 7.5mg (*squares*), 10mg (*triangles*), 15mg (*diamonds*), 25mg (+), or 40mg (*X*). (day 1: p<0.05 for 5, 10, 25 and 40 mg groups)



As in left panel for $FEF_{25-75\%}$ expressed as the fraction of the baseline value.

Pulmonary effects of multiple sclerosis clinical doses of fingolimod, 0.5 and 1.25 mg given daily for fourteen days were measured in Study FTY720D2105. Pulmonary function, FEV_1, FEF_{25-75} and FVC was measured on Days -1, 1, 7, 14 and 28. Neither dose of fingolimod had an effect on FEV_1, FVC or FEF_{25-75} when compared to the placebo treatment group.

Relationship between plasma concentration and effect

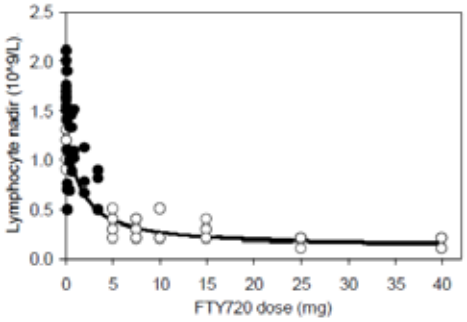
For both lymphocyte count and negative chronotropic effect a pooled analysis was done, combining data from both the low single dose study, Study FTY720AB101 and the high single dose study, Study FTY720A2215. Because fingolimod-P, the active moiety, was not measured in Study FTY720AB101, dose was used as the measure of exposure over a pooled dose range of 0.25 to 40 mg. Given the high correlation of dose to fingolimod systemic exposure, this pooled analysis using dose as a measure of systemic exposure is justified.

Dose-lymphocyte relationship

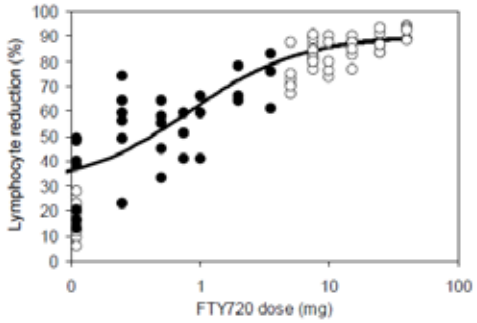
As shown in Figure 14, the relationships between fingolimod dose and lymphocyte nadir were adequately described by an inhibitory effect E_{max} model[42]. When the lymphocyte nadir was expressed as the measured values (cells x 10^9/L), the model-estimated nadir in the absence of fingolimod (placebo) was 1.39 x 10^9/L (CV 5%), the half-maximal dose was 1.4 mg (CV 24%), and the minimal nadir was 0.11 x 10^9/L (CV 35%). When the lymphocyte nadir was expressed as percent reduction from the predose count, the model-estimated reduction (that is, temporal fluctuation) in the absence of fingolimod (placebo) was 30% (CV 4%), the half-maximal dose was 0.8 mg (CV 22%), and the maximal reduction was 90% (CV 14%) as shown in the right panel of Figure 14. Single doses of fingolimod >2.5 to 5 mg have little additional effect on lymphocyte count.

[42] E_{max} model:A three-parameter logistic equation or sigmoid E_{max} model (four-parameter if inhibitory sigmoid) or modified Hill equation.

Figure 14: Study FTY720A2215 - Fingolimod dose-lymphocyte response



Fingolimod dose vs. lymphocyte nadir relationship. Shown are the individual values from renal transplant patients (*filled circles*) and healthy subjects (*open circles*) and the fit of an inhibitory effect E_{max} model to the data.

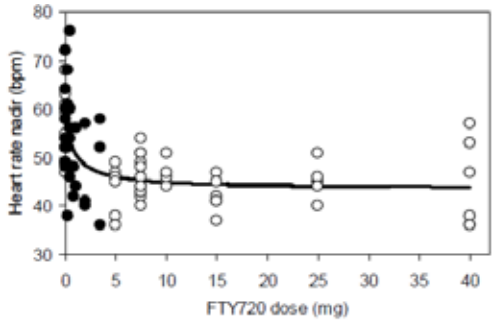


As in left panel for lymphocyte nadir expressed as percent reduction from predose count with a logarithmic dose scale (x-axis).

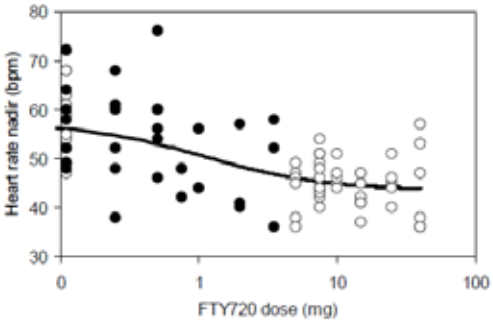
Dose-heart rate relationship

As shown in Figure 15, the relationships between fingolimod dose and nadir heart rate from vital signs recordings (pulse) were adequately described by an inhibitory effect E_{max} model. The model-estimated nadir in the absence of fingolimod (placebo) was 57 BPM (CV 4%), the half-maximal dose was 1.1 mg (CV 70%), and the minimal nadir was 44 BPM (CV 4%). When a similar evaluation was performed on area under the effect curve from 0 to 4 h ($AUE_{(0-4)}$) as the response parameter, the model-estimated AUE(0-4) in the absence of fingolimod (placebo) was 245 BPM.h (CV 3%), the half-maximal dose was 2.2 mg (CV 114%), and the minimal AUE(0-4) was 205 BPM.h (CV 5%). There is a plateau of fingolimod effect on heart rate.

Figure 15: Study FTY720A2215 - Fingolimod dose-heart rate response



Fingolimod dose vs. heart rate nadir relationship. Shown are the individual values from renal transplant patients (*filled circles*) and healthy subjects (*open circles*) and the fit of an inhibitory effect E_{max} model to the data.



As in left panel with a logarithmic dose scale.

Pharmacodynamic interactions with other medicinal products or substances

Atenolol

Study FTY720A0114 was a cross-over designed study in which healthy volunteers (n=14) received fingolimod 5 mg single dose or atenolol 50 mg daily for four days or both treatments together.

Fingolimod versus atenolol. The mean heart rate nadir was significantly lower by 8% for fingolimod compared with atenolol (p = 0.03), but the fingolimod/atenolol ratio and 90% confidence interval remained in the equivalence bounds: 0.92 (0.86-0.98). None of the other cardiovascular responses were different between treatments with fingolimod/atenolol ratios for heart rate $AUE_{(0-12)}$ of 0.97 (0.92-1.03); for mean arterial pressure nadir of 1.02 (1.00- 1.04); and for mean arterial pressure $AUE_{(0-12)}$ of 1.02 (1.00-1.04).

Fingolimod versus fingolimod+ atenolol. Fingolimod 5 mg + atenolol decreased heart rate responses by 15% and mean arterial pressure responses by 7-8% compared with fingolimod 5 mg alone. Ratios and 90% confidence intervals were as follows: heart rate nadir 0.85 (0.79-0.92); heart rate $AUE_{(0-12)}$ 0.85 (0.81-0.89); mean arterial pressure nadir 0.93 (0.91-0.96); and mean arterial pressure $AUE_{(0-12)}$ 0.92 (0.90-0.95). Although the heart rate and mean arterial pressure trajectories were shifted downward on the measurement scale after fingolimod 5 mg + atenolol, they retained their normal circadian patterns.

Overall, starting fingolimod treatment in the setting of ongoing β-blocker treatment had no synergistic negative chronotropic effect. There was however there was a mild additive effect for heart rate (decreased an additional 15%).

Diltiazem

Study FTY720A0114 was a cross-over study in which healthy volunteers (n=14) received fingolimod 5 mg single dose or diltiazem extended release 240 mg daily for four days or both treatments together. Starting fingolimod treatment in the setting of ongoing calcium channel treatment had neither an additive nor a synergistic negative chronotropic effect.

Atropine

In study FTY720A0118, two different interventions of atropine on the negative chronotropic effect of fingolimod were measured in healthy volunteers (n=14). The first intervention, the use of atropine given prophylactically at the time of the fingolimod 5 mg dose (Time 0), did not have any effect on heart rate. In the second intervention strategy, IV atropine was given therapeutically and titrated up to a maximal dose of 2 mg starting four hr after a single dose of fingolimod 5 mg or placebo. Four hr post fingolimod dose is the usual time of maximal negative chronotropic effect.

Atropine increased mean heart rate in the placebo treatment group by approximately 30 BPM. In the fingolimod treatment group, atropine increased mean heart rate by approximately 10 BPM within minutes of initiation of atropine dosing. The increase in mean heart rate during and after the atropine titration persisted for several hr after atropine dosing ended at Hour 5. These data are consistent with atropine having a moderate, positive chronotropic effect in the setting of fingolimod treatment.

Isoproterenol

In Study FTY720A0119 the effect of therapeutic IV isoproterenol on fingolimod 5 mg induced negative chronotropic was measured in healthy volunteers (n=14). Subjects received a 5 mg dose of fingolimod at Time 0 and then the effect of repeated, 30 minute infusions of either placebo or isoproterenol ≤5 μg/min on heart rate was measured. Placebo infusions 2, 3, 4, and 5 had no effect on average heart rate which remained at the nadir of 52 ± 7 BPM. In contrast, isoproterenol infusions consistently increased mean heart rate to ≥100 BPM. The study showed that isoproterenol had a strong, positive chronotropic effect, increasing mean heart rate to ≥100 BPM in the setting of fingolimod treatment.

Salmeterol

In study FTY720D2106 the effect of inhaled salmeterol 250 micrograms (mcg) on fingolimod 1.25 mg induced negative chronotropic was measured in healthy volunteers (n=14). Immediately after the fingolimod 1.25 mg dose, from 08.00 to 11.00 AM, the change in heart rate from baseline ranged from -1.2 to -7.1 BPM. However, at 11.30 AM and 12.00 PM, the change in heart rate from baseline was -18.4 and -16.1, respectively. This further negative inflection of the change in heart rate from baseline is consistent with a significant fingolimod-induced negative chronotropic effect ($p<0.02$, comparing hr 08.00 AM and 12.00 PM). At 12.00 PM, 4 hr post fingolimod 1.25 mg dose,

salmeterol dosing commenced. With salmeterol dosing, the negative chronotropic effect of fingolimod 1.25 mg began to attenuate, with the change in heart rate from baseline significantly increasing from -16.1 at 12.00 PM to - 6.0 BPM at 16.00 PM, a difference of approximately 10 BPM ($p<0.003$). Salmeterol dosing ended at 1600 and the positive chronotropic effect of salmeterol diminished substantially by 16.30 PM and appeared to be gone by 17.30 PM. The study showed that salmeterol had a moderate, positive chronotropic effect of approximately 10 BPM in the setting of fingolimod treatment.

Genetic differences in pharmacodynamic response

No studies were submitted.

Evaluator's overall conclusions on pharmacodynamics

Lymphocyte count

Single doses of fingolimod ≥0.5 mg result in a dose dependent decrease in lymphocyte count. This decrease occurs rapidly, within 3-4 hr of the oral dose. With single doses from 5 to 40 mg, there is minimal additional dynamic effect on the lymphocyte count. With multiple dosing of fingolimod from 0.125 mg to 5 mg there is a dose dependent decrease in lymphocyte count. Even at the lowest dose of fingolimod tested, 0.125 mg, a decrease in lymphocyte count can be detected within several days after the start of treatment. With low daily doses of fingolimod, 0.125 and 0.25 mg, after one month the mean lymphocyte count is maintained constantly at approximately 60% of baseline count. With supratherapeutic daily dosing of fingolimod, 5 mg, after one month the mean lymphocyte count is maintained constantly at approximately 10 - 15% of baseline count. Intermediate doses of fingolimod result in dose dependent, mean lymphocyte counts between 20% to 50% of the baseline count.

Within the first week after stopping chronic treatment of fingolimod, there is a clear increase in lymphocyte count. With termination of chronic dosing of 0.5 and 1.25 mg the time to a lymphocyte count of 80% of baseline is approximately one month. With a supratherapeutic, chronic dose of 5 mg fingolimod, it is estimated to take approximately two months for lymphocyte count to return to 80% of baseline. Given that the normal mean lymphocyte count is approximately 2500 cells/μL and the low normal range is approximately 1000 cells/μL, the majority of subjects on 0.5 and 1.25 mg would be expected to have a normal lymphocyte count (≥1000 cells/μL) within 1-2 weeks of termination of treatment.

Heart

Single doses of 0.5 and 1.25 mg fingolimod have a mean negative chronotropic effect of approximately 7-8 and 10-15 beats per minute, respectively. This effect is seen within 3 hr of the first dose, with a nadir of heart rate occurring approximately 4-5 hr post single dose. The negative chronotropic effect persists but attenuates over the remainder of the 24 hr post dose. With continued, chronic dosing, the negative chronotropic effect of fingolimod is attenuated. With multiple dose administration of fingolimod 0.5, 1.25 or 5 mg, the majority of the negative chronotropic effect (>70%) is manifested on the first day of dosing.

Interactions with other drugs

Atropine, isoproterenol and salmeterol treatment increases heart rate in the setting of fingolimod treatment. Data suggest that fingolimod treatment can be used in combination with heart rate lowering drugs such as atenolol and diltiazem. When fingolimod is used with diltiazem, there is no additional effect on heart rate compared with fingolimod treatment alone. When fingolimod is used with atenolol, there is an additional 15% reduction of heart rate when compared to fingolimod treatment alone.

Efficacy

Introduction

The main efficacy data were provided from two large Phase III trials in this submission; a single two year placebo controlled trial (Study FTY720D2301) and a single one year active controlled study using IFN β-1a as the active comparator (Study FTY720 D2302). The sponsor also presented efficacy data from a 6 month Phase II placebo controlled study (Study FTY720D2201) and its long term open label extension (Study FTY720D2201E1). A tabular summary of the studies is provided in Table 17 below.

Table 17: Summary of studies providing efficacy data

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

Dose-response studies and main clinical studies

Refer also to Clinical Pharmacology above.

Main (pivotal) studies

Study FTY720D2301

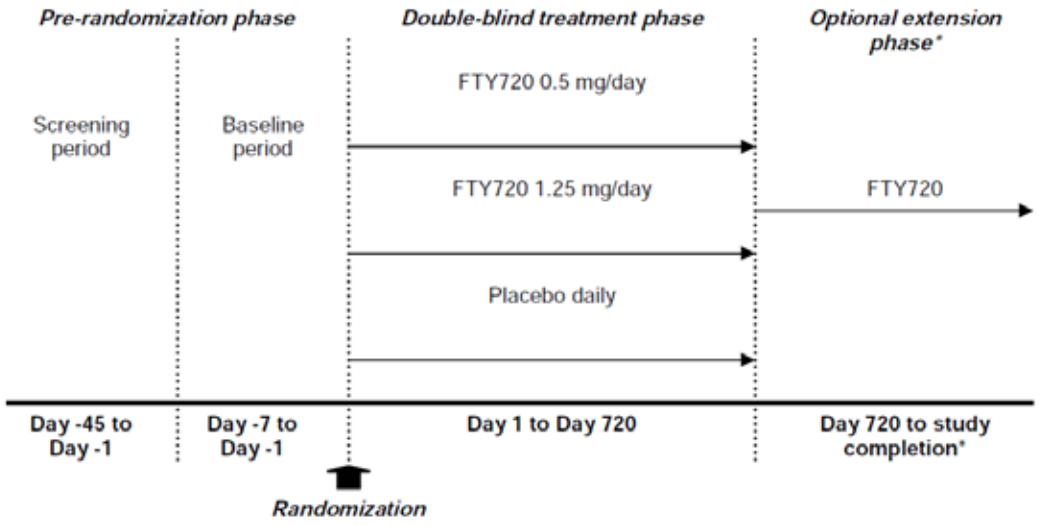
Study design: This was a 24-month, double-blind, randomised, multicentre, placebo-controlled, parallel-group study comparing efficacy and safety of fingolimod (referred to as FTY720 in the clinical development program) 1.25 mg and 0.5 mg administered orally once daily versus placebo in patients with RRMS. Patients were randomised in a 1:1:1 fashion to receive FTY720 0.5 mg/day, FTY720 1.25 mg/day, or placebo for up to 24 months. The study was conducted in 138 centres across 22 countries. The first patient was enrolled on 26 January 2006 and the last patient completed the study on 30 July 2009.

The study consisted of two phases: a pre-randomisation phase (lasting for up to 45 days) and a double-blind treatment phase (see Figure 16). The pre-randomisation phase consisted of two periods, Screening and Baseline. The core phase of the study was considered completed for an individual patient when he/she completed the double-blind treatment phase. The core phase of the study as a whole was considered completed when all randomised patients remaining in the core

phase had completed the double-blind treatment phase. Patients who completed the 24-month double-blind treatment phase, if eligible, could enter an optional long-term extension study under a separate protocol (FTY720D2301E1).

The data presented in this evaluation report are the efficacy and safety results from the core phase of the study. An external Data and Safety Monitoring Board (DSMB) provided an independent assessment of safety and risk/benefit for the duration of the study. Regular safety updates were provided to the DSMB to monitor drug safety. No formal interim efficacy analyses were planned for the study.

Figure 16: Study FTY720D2301 - Study outline



*The optional extension phase (under a separate protocol, FTY720D2301E1) was expected to last until FTY720 was commercially available or development was stopped.

Objectives

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

Secondary objectives: The key secondary objective was to evaluate the effect of FTY720 1.25 mg and 0.5 mg relative to placebo on disability progression as measured by the time to 3-month confirmed disability progression as measured by EDSS in patients treated for up to 24 months.

Other secondary objectives were:

- To evaluate the safety and tolerability of FTY720 compared to placebo in patients with RRMS treated up to 24 months
- To evaluate the effect of FTY720 1.25 mg and 0.5 mg compared to placebo in patients treated for up to 24 months with respect to magnetic resonance imaging (MRI) parameters of inflammatory disease activity, burden of disease and brain volume (atrophy)
- To evaluate the effect of FTY720 1.25 mg and 0.5 mg compared to placebo in patients treated for up to 24 months with respect to relapse-related parameters:
    - time to the first relapse
    - proportion of relapse-free patients

- To evaluate the effect of FTY720 1.25 mg and 0.5 mg compared to placebo in patients treated for up to 24 months on disability progression with respect to:
    - time to 6-month confirmed disability progression as measured by Expanded Disability Status Scale (EDSS)
    - proportion of patients with confirmed disability progression
    - change from baseline to the end of the study on the MS Functional Composite (MSFC) z-score
- To evaluate the effect of FTY720 1.25 mg and 0.5 mg compared to placebo on multidimensional health status as measured by the Patient Utility Index derived from patient responses on the EuroQoL (EQ-5D)[43]
- To evaluate the pharmacokinetics of FTY720
- To evaluate the pharmacokinetic/pharmacodynamic relationship of FTY720 1.25 mg and 0.5 mg for main efficacy and safety outcomes in patients with RRMS.

Study participants

Inclusion criteria

Patients who m*et al*l of the following inclusion criteria during the pre-randomisation phase were eligible for enrolment in the study:

General inclusion criteria

1. Males or females aged 18 to 55 years inclusive

2. Females of childbearing potential must have had a negative pregnancy test prior to entry into the double-blind treatment phase and were required to use simultaneously two forms of effective contraception (either partner) during treatment and for 3 months after discontinuation of the study medication. Females that were either post-menopausal for 12 months prior to randomisation or were surgically sterile (through hysterectomy or bilateral oophorectomy) were not required to use birth control.

3. Provided written informed consent prior to participating in the study

Multiple sclerosis

1. Diagnosis of MS as defined by the 2005 revised McDonald criteria.

2. A relapsing-remitting course with at least one documented relapse during the previous year or two documented relapses during the previous 2 years, prior to randomisation.

3. Expanded Disability Status Scale (EDSS) score of 0 to 5.5 inclusive.

4. Patients who explicitly declined initiation or continuation of treatment with available disease-modifying drugs for whatever reason after having been informed about their respective benefits and possible adverse events by the investigator.

5. Neurologically stable with no evidence of relapse or corticosteroid treatment within 30 days prior to randomisation.

Exclusion criteria

[43] EQ-5D™ is a standardised instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status.

Patients who met any of the following exclusion criteria during the pre-randomisation phase were not eligible for enrolment in the study:

1. Manifestation of MS other than RRMS.

2. History of chronic disease of the immune system other than MS or a known

immunodeficiency syndrome.

3. History or presence of malignancy (except for successfully treated basal or squamous cell carcinoma of skin).

4. Known or 'new' diagnosis of diabetes mellitus (if screening blood glucose was suspicious for diabetes (≥ 126 mg/dayL or ≥ 7 mmol/L if fasting; ≥ 200 mg/dayL or 11.1 mmol/L if random testing) the patient was to be further evaluated for diabetes mellitus).

5. Diagnosis of macular oedema during the pre-randomization phase (patients with a history of macular oedema were allowed to enter the study provided that they did not have macular oedema at the ophthalmic screening visit).

6. Active systemic bacterial, viral, or fungal infections, or diagnosis of Acquired Immunodeficiency Syndrome (AIDS), hepatitis B, or hepatitis C infection (defined as a positive HIV antibody, hepatitis B surface antigen, or hepatitis C antibody test, respectively).

7. Received total lymphoid irradiation or bone marrow transplantation.

8. Had been treated with systemic corticosteroids or adrenocorticotropic hormones (ACTH) within 1 month prior to randomisation; immunosuppressive medications such as azathioprine or methotrexate within 6 months prior to randomisation; immunoglobulins and/or monoclonal antibodies (including natalizumab) within 6 months prior to randomisation; IFN-β or glatiramer acetate within 3 months prior to randomisation; or cladribine, cyclophosphamide, or mitoxantrone at any time.

9. Any medically unstable condition, as assessed by the primary treating physician.

10. Any of the following cardiovascular conditions:

- Myocardial infarction within the 6 months prior to enrolment or current unstable ischemic heart disease.
- History of angina pectoris due to coronary spasm or history of Raynaud's phenomenon.
- Cardiac failure at time of screening (Class III according to New York Heart Association Classification) or any severe cardiac disease as determined by the investigator.
- History of cardiac arrest, symptomatic bradycardia, sick sinus syndrome or sino-atrial heart block, or positive tilt test from workup for vasovagal syncope
- Resting pulse rate < 55 BPM prior to randomisation
- History or presence of a second degree AV block or a third degree AV block or an increased QTc interval > 440 ms on screening ECG
- Arrhythmia requiring current treatment with Class III anti-arrhythmic drugs (like amiodarone, bretylium, sotalol, ibulitide, azimilide, dofelitide)
- Hypertension uncontrolled by medication

11. Any of the following pulmonary conditions:

- Severe respiratory disease or pulmonary fibrosis

- Tuberculosis, except for history of successfully treated tuberculosis or history of prophylactic treatment after positive PPD skin reaction
- Abnormal chest x-ray or High Resolution Computer Tomography (HRCT) (at selected sites) suggestive of active pulmonary disease
- Abnormal pulmonary function tests: FEV_1, FVC[44] values lower than 70% of predicted value, D_LCO[45] values lower than 60% of predicted value
- Asthma requiring daily (chronic) therapies

12. Any of the following hepatic conditions:

- Known history of alcohol abuse, chronic liver or biliary disease
- Total bilirubin greater than the upper limit of the normal (ULN) range, unless in

context of Gilbert's syndrome

- Conjugated bilirubin greater than ULN range
- Alkaline phosphatase greater than 1.5 times ULN range
- Aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT) greater than 2 times ULN (Canada only: ALT/SGPT greater than 1.5 times ULN)
- Gamma-glutamyl-transferase (GGT) greater than 3 times ULN range

13. Any of the following abnormal laboratory values:

- Serum creatinine > 1.7 mg/dayL (150 μmol/L)
- White blood cell (WBC) count < 3,500/mm^3 (< 3.5 x 10^9/ L)
- Lymphocyte count < 800/mm^3 (< 0.8 x 10^9/ L).

14. Any of the following neurologic/psychiatric disorders:

- History of substance abuse (drug or alcohol) or any other factor (like a serious psychiatric condition) that could interfere with the subject's ability to cooperate and comply with the study procedures.
- Progressive neurological disorder, other than MS, which could affect participation in the study or require the use of medications not allowed by the protocol.

15. Unable to undergo MRI scans, including claustrophobia or history of hypersensitivity to gadolinium-DTPA[46].

16. Participation in any clinical research study evaluating another investigational drug or therapy within 6 months prior to randomisation.

17. Pregnant or nursing (lactating) women, where pregnancy was defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test (> 5 mIU/mL).

18. History of FTY720 therapy.

[44] Forced expiratory volume in 1 second/forced vital capacity
[45] Diffusing capacity of the lung for carbon monoxide.
[46] diethylenetriamine pentaacetic acid

Note: If a patient failed one or more laboratory (or other) assessment criteria as part of the screening process, the assessment(s) were allowed to be repeated at the discretion of the investigator provided the assessments were completed within the screening period.

Treatments administered

Randomised patients were assigned in a ratio of 1:1:1 to receive:

1. FTY720 0.5 mg orally once daily

2. FTY720 1.25 mg orally once daily

3. Matching FTY720 placebo orally once daily

FTY720 study drug and matching FTY720 placebo were to be taken preferably at the same time every day, with or without food. Study medications (FTY720 and FTY720 matching placebo) were dispensed at the randomisation visit (Visit 2). The first dose of study drug was taken in the clinic. After the first dose intake, the patient was monitored in the clinic for at least 6 hr or longer if discharge criteria were not met. Subsequent doses were taken at home. Dose adjustments were not allowed; however drug interruptions were allowed based on the judgment of the investigator.

Concomitant therapy

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

Prohibited medication

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

Immunosuppressive medications (like azothioprine, methotrexate, cyclophosphamide, mitoxantrone, cladribine)

Other concomitant medications: immunoglobulins, monoclonal antibodies (including natalizumab), INF-ß, glatiramer acetate, ACTH.

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

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

Efficacy Outcome Measures

Primary efficacy outcome measure

The primary endpoint was the aggregate annualised relapse rate (ARR) at 24 months, which was defined as the number of relapses per year. For the primary analysis, the ARR of the treatment group was calculated by taking the total number of confirmed relapses for all the patients in the treatment group divided by the total number of days on study for all patients in the group and multiplied by 365.25 to obtain the annual rate (ITT). The sponsor's Clinical Study Report stated that only confirmed relapses were considered for the primary analyses. The report did not state whether analyses were conducted on "Observed Cases at end of study" or "Last Observation Carried Forward".

Key secondary efficacy outcome measure

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

MS relapses

General definition of relapse: 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 hr and have occurred in the absence of fever (< 37.5°C) or infection.

Definition of confirmed relapse: A relapse must have been confirmed by the Independent Evaluating Physician (examining neurologist). It was recommended that this occur within 7 days of the onset of symptoms. A relapse was confirmed when it was accompanied by an increase of at least half a step (0.5) on the EDSS or an increase of 1 point on two different Functional Systems (FS) of the EDSS or 2 points on one of the FS (excluding Bowel/Bladder or Cerebral FS). (Note: Only confirmed relapses were included in the primary efficacy analysis. However the relapse-related analyses were repeated using all relapses to assess the sensitivity of the results.)

Patients may have reported symptoms indicative of a relapse at a scheduled visit or at any other time. Patients were instructed to immediately contact the treating physician if he/she developed new, recurring or worsening neurological symptoms. At each scheduled visit, the patient was also asked whether any such symptoms had occurred.

Upon reporting symptoms indicative of a relapse, the treating physician assessed, in an appropriate manner, whether the symptoms occurred in the presence of fever or infection. If fever or infection was excluded, a neurological examination was arranged as soon as possible. If fever or infection could not be excluded, the neurological examination was postponed until the fever or the infection had ceased (provided that the symptoms indicative of a relapse were still present). Treatment with steroids was not to begin prior to the assessment by the examining neurologist. Based on results of the neurological examination (change in FS and EDSS scores), the relapse was evaluated as to whether or not it met the criteria for “confirmed relapse” as per protocol and also for severity (see Table 18).

Table 18: Study FTY720D2301 - 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

Disability progression

Kurtzke’s Expanded Disability Status Scale (EDSS) is a scale for assessing neurologic impairment in MS (Kurtzke 1983) including 1) a series of scores in each of eight functional systems, and 2) the EDSS steps (ranging from 0 (normal) to 10 [death due to MS]). The functional systems are Visual, Brain Stem, Pyramidal, Cerebellar, Sensory, Bowel & Bladder, Cerebral, and Other Functions. It was recommended that fatigue not be included in the cerebral score of the EDSS. Although EDSS assessments were scheduled at Visit 1, Visit 2, and at each visit from Visit 6 onwards, in the case of MS relapse EDSS assessment was required at every unscheduled visit to confirm relapse.

The Multiple Sclerosis Functional Composite (MSFC) is a composite measure encompassing the major clinical dimensions of arm, leg, and cognitive function. The MSFC consists of three objective quantitative tests of neurological function:

- Nine-hole peg test (arm dimension) measurement: right and left arm scores; metric: time in seconds to insert and remove nine pegs
- Timed 25-foot walk (leg dimension); measurement: a walk of 25 feet; metric: time taken in seconds
- PASAT-3 min (cognitive function); measurement: paced auditory serial addition test, 3 minute version; metric: number of correct answers

The scores for these 3 components are combined to create a single score that is used to detect changes over time. This is done by creating z-scores for each component and averaging them to create the overall z-score. In general, z-scores involve comparing each test result with that found in a reference population (patient baseline data), a process called standardisation. The z-score for each component is calculated by subtracting the mean of the reference population from the test result and then dividing by the standard deviation of the reference population.

The PASAT-3 min auditory test tapes were provided to the sites in the local language. Two MSFC training sessions were performed during Screening (at Visit 1) as rehearsals to the baseline MFSC at Visit 2. Results of MSFC at Visit 2 were used as the baseline value in the MSFC analysis.

The following populations were used for the analyses:

- ***Randomised population (RND)****:* All patients who were assigned randomisation numbers. The patients in this population are called randomised patients. This population was used to summarise patient disposition, demographic and baseline characteristics and protocol deviation information.
- ***Intent-to-treat population (ITT)***: All patients who were randomised and received at least one dose of study medication. Patients were grouped according to the assigned treatment. Efficacy analyses were performed on the ITT population. In this study, the ITT population is the same as the randomised population since all randomised patients took study medications. For MRI analyses, only patients with MRI scans available at the time point under evaluation were included.
- ***Per-protocol population (PP)*****:** All patients in the ITT population without any major protocol deviations. Major protocol deviations were determined before unblinding the treatment according to the pre-defined protocol deviation criteria, which were specified prospectively. Any efficacy data after study drug withdrawal were excluded. Patients were grouped according to the actual treatment received. This population was only used for the supportive analyses of the primary efficacy endpoint and key secondary endpoint.
- ***Safety population (SAF):*** All patients who received at least one dose of study medication. Patients were analysed according to the treatment received. Safety and tolerability analyses were performed on the safety population.
- ***Follow-up population (FU):*** All safety patients who had visit 501 (follow-up safety visit) or at least one safety assessment (AE, laboratory findings, vital, PFT, ophthalmology, ECGs, dermatology, and x-ray/high resolution computed tomography (HRCT)) 46 to 104 days after discontinuing study drug, but before first extension dose (if applicable). Patients were analysed according to the treatment received.

Sample size

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

power calculations for the primary endpoint are based on the Wilcoxon/Mann-Whitney rank sum test to compare the 1.25 mg versus placebo using the hierarchical method to adjust for multiplicity. Assuming that the annualised relapse rate at 24 months is 0.7 for placebo and 0.42 for FTY720 1.25 mg arm, the relative reduction is 40%. Based on data from the Phase II Study FTY720D2201, its extension phase and other historical data for other MS treatment studies, the common standard deviation is assumed to be 1.06. With these assumptions, 416 patients per arm would provide 95% power at the two-sided significance level of 0.05. A simulation study confirmed that the sample size of 416 per arm would provide an adequate power for the primary efficacy analysis.

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

Statistical methods

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

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

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

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

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

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

Primary endpoint analysis

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

If a patient completed study and took extension medication, the number of days on study was calculated as (first extension dose date – first core dose date). If a patient did not take any extension medication, the number of days on study was calculated as the minimum of (max (Visit 778 date, last core dose date) – first core dose date +1) or 734 (720 days defined for 24 months + 14 days for visit window). In case a study phase completion (Visit 778) date was not available, the latest date from VIS panel was used instead (i.e., max [latest date from VIS panel, last core dose date]). This was not the study drug discontinuation (SDD) date (Visit 777 date) because the protocol allowed

the SDD patients to continue in the study until the end of the study. The confirmed relapses within this time period were counted for this patient that was used in the ARR computation.

Key secondary endpoint analysis

Log-rank test was the key secondary efficacy analysis for data up to 24 months for the ITT population. There were two treatment comparisons for the time to 3-month confirmed disability progression: FTY720 1.25 mg versus placebo, and FTY720 0.5 mg versus placebo. Kaplan-Meier estimates at 12 and 24 months, together with their 95% confidence intervals, were calculated and presented. Two-sided 95% confidence intervals of the difference in Kaplan-Meier estimates at 12 and 24 months were also used to visually compare progression rates between the treatment groups. Corresponding Kaplan-Meier plots were provided.

Other secondary efficacy analyses

The ITT population was used for all other secondary efficacy analyses unless otherwise specified.

MRI variables

MRI efficacy variables included the following:

Inflammatory activity up to 24 months:

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

Burden of disease up to 24 months:

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

Brain volume up to 24 months:

- Percent change from baseline in brain volume (atrophy).

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

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

Magnetic resonance imaging (MRI) analysis method

All patients underwent MRI scanning of the brain at Visits 1 (Screening, must have been performed within 30 days prior to randomisation), 7 (Month 6), 9 (Month 12), and 13 (Month 24) according to the MRI protocol. Each MRI scan performed for the study was reviewed by a local neuroradiologist. The Primary Treating Physician was contacted in case of unexpected non-MS-related findings detected on the MRI scan. To avoid potential interference caused by steroids used for the treatment of MS relapses, the following restrictions applied:

- In case of relapse, if an MRI was scheduled within 30 days of the initiation of steroid treatment, this MRI was to be performed before steroid treatment was initiated
- No MRI scan was to be performed while a patient was on IV steroid therapy and within 30 days after termination of steroid therapy. T1-weighted images before and after administration of contrast medium (0.1 mmol/Kg gadolinium-DTPA) as well as T2-weighted (T2 and PD) images were performed. Prior to the start of the study, a radiologist and technician from each centre received an MRI Manual, outlining technical implementation, image quality requirements and MRI administrative procedures. Each site was asked to program the MRI scanner that was designated for evaluation of the study patients and to perform and submit a dummy scan, so-called “dummy or dry run” to assess the image quality and to evaluate the compatibility of the electronic data carrier. Once the dummy run was accepted, all the parameter settings for the study specific MRI sequences were to remain unchanged for the duration of the study.

Numbers of new/newly enlarging T2 lesions, number and volume of Gd-enhancing lesions, total volume of T2 lesions, total volume of T1 hypointense lesions, brain volume at baseline and change over time were obtained according to the protocol.

Lesions were identified as follows:

Gd-enhancing lesions, hyper-intense areas after contrast administration by comparing the pre-contrast T1-weighted images with the post-contrast T1weighted images. Lesions expanding throughout several slices were counted only on the first slice.

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

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

Health-related quality of life (HRQoL)

Generic multidimensional health status was assessed with the EuroQoL (EQ-5D).

Relapse variables

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

- Time to first relapse
- Time to second relapse

- Frequency of corticosteroid use to treat relapses
- Frequency of hospitalisations due to relapses

Additional endpoints were the following:

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

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

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

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

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

Disability progression-related variables.

Other secondary disability progression endpoints included:

Time to 6-month confirmed disability progression as measured by EDSS,

Change from Baseline to the end of study on the EDSS,

and

Change from Baseline to the end of study on the MSFC z-score.

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

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

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

Results

Participant flow

A total of 1564 patients were screened for participation in this study; of these, 1272 (81.3%) were randomised and the remaining 292 (18.7%) patients were screening failures. Patient disposition for the randomised population is presented in Table 19. Of the 1272 patients who were randomised, 1033 (81.2%) completed the study with the highest percentage of patients completing in the

FTY720 0.5 mg group (86.8%) compared with the other treatment groups (77.4% and 79.4% for the FTY720 1.25 mg and placebo groups, respectively). A similar pattern was seen for those who completed the study while on study drug: 81.2% in the FTY720 0.5 mg group compared with 69.2% and 72.5% in the FTY720 1.25 mg and placebo groups, respectively.

Table 19: Study FTY720D2301 - Patient disposition (Study phase completion) (Randomised population)

	FTY720 1.25mg N=429 n (%)	FTY720 0.5mg N=425 n (%)	Placebo N=418 n (%)	Total N=1272 n (%)
Completed study	332 (77.4)	369 (86.8)	332 (79.4)	1033 (81.2)
On study drug [1]	297 (69.2)	345 (81.2)	303 (72.5)	945 (74.3)
Off study drug [2]	35 (8.2)	24 (5.6)	29 (6.9)	88 (6.9)
Discontinued from the study	97 (22.6)	56 13.2)	86 (20.6)	239 (18.8)
Subject withdrew consent	31 (7.2)	17 (4.0)	28 (6.7)	76 (6.0)
Adverse event(s)	22 (5.1)	13 (3.1)	18 (4.3)	53 (4.2)
Unsatisfactory therapeutic effect	13 (3.0)	6 (1.4)	25 (6.0)	44 (3.5)
Abnormal laboratory value(s)	20 (4.7)	9 (2.1)	1 (0.2)	30 (2.4)
Lost to follow-up	3 (0.7)	5 (1.2)	7 (1.7)	15 (1.2)
Protocol violation	5 (1.2)	5 (1.2)	4 (1.0)	14 (1.1)
Abnormal test procedure result(s)	2 (0.5)	1 (0.2)	1 (0.2)	4 (0.3)
Death	1 (0.2)	0 (0.0)	2 (0.5)	3 (0.2)
Discontinued study drug	131 (30.5)	80 (18.8)	115 (27.5)	326 (25.6)
Subject withdrew consent	30 (7.0)	17 (4.0)	31 (7.4)	78 (6.1)
Adverse event(s)	31 (7.2)	15 (3.5)	24 (5.7)	70 (5.5)
Unsatisfactory therapeutic effect	18 (4.2)	8 (1.9)	36 (8.6)	62 (4.9)
Abnormal laboratory value(s)	32 (7.5)	20 (4.7)	5 (1.2)	57 (4.5)
Protocol violation	8 (1.9)	8 (1.9)	5 (1.2)	21 (1.7)
Lost to follow-up	2 (0.5)	6 (1.4)	5 (1.2)	13 (1.0)
Abnormal test procedure result(s)	6 (1.4)	3 (0.7)	3 (0.7)	12 (0.9)
Administrative problems	3 (0.7)	3 (0.7)	4 (1.0)	10 (0.8)
Death	1 (0.2)	0 (0.0)	2 (0.5)	3 (0.2)

[1] 'On study drug': Patients who took study drug until the study completion.
[2] 'Off study drug': Patients who completed the study but discontinued study drug prematurely.
Note: This table displays the number of patients with the primary reason for discontinuation recorded as 'adverse event'; tables in Section 12.3 display patients with AEs with outcome of "discontinuation of study drug" and therefore numbers can be expected to differ.
Reasons for discontinuation are sorted in descending frequency in the Total column.

Discontinuations from study drug were most commonly for safety reasons, that is, due to adverse events and abnormal laboratory values, when taken together. The percentage of patients discontinuing for adverse events was lower in the FTY720 0.5 mg treatment group compared with the FTY720 1.25 mg and placebo treatment groups. The percentage of patients discontinuing for abnormal laboratory values was higher in the FTY720 treatment groups compared with the placebo group; of the two FTY720 groups, the percentage was higher in 1.25 mg group versus the 0.5 mg group.

Of 326 patients who discontinued study drug, 88 patients remained in the study and completed the abbreviated schedule of assessments through the Month 24 visit.

Note that in Table 19, the number of patients in the 1.25 mg FTY720 treatment group who completed the study but were off the study drug is 35 and the number of patients who discontinued from the study is 97, totalling 132 patients. This number differs from the one reported in Table 19, 131. The discrepancy is due to one patient who was marked incorrectly as a non-completer in the database but who did receive study drug for 24 months.

Conduct of the study

The study protocol was amended 10 times. The most important amendments were:

Amendment 1 (17 October 2005) was created in response to the following: (1) recommendations provided by Health Authorities (FDA); (2) completion of ophthalmic examinations for patients involved in FTY720D2201 and FTY720D2201E1 study and evaluation of the data by an external Ophthalmology Advisory Group (OAG); (3) completion and analysis of the 6-month dose-blinded extension Study FTY720D2201E1 (6 months placebo-controlled core phase and 6 month dose-blind extension phase). Key changes are summarised below:

- Monitoring of adverse events for 6 weeks following study drug discontinuation
- Pulmonary function tests assessments performed more frequently
- Ophthalmic screening revised, ophthalmic assessments performed more frequently and ophthalmic monitoring guidelines revised
- Procedure for dermatology exam revised
- Diabetic patients excluded from the study
- Patients who experienced an MS relapse could be re-consented in order to continue taking study drug.

Amendment 2 (04 April 2006) was created following input from regulatory authorities, investigators, new information from the MS Phase II study, and from external experts in the areas of ophthalmology and lung function. Key changes are summarised below:

- Clarification of primary objective to reflect the relative importance of the two FTY720 doses in determining efficacy
- Inclusion criteria clarified to state that the 2005 revised McDonald criteria for MS

diagnosis would be used

- Sample size increased to 1250 to allow for a higher dropout rate (25%) than previously assumed
- Extension of visit windows and duration of screening period
- Modification of notable laboratory criteria
- Primary efficacy endpoint analysis changed from Poisson regression to the rank analysis of covariance
- Changes to safety assessments to collect additional data to better characterize the effects of FTY720 on lung and eye, including:
- maximal inspiratory mouth pressures (PImax) and maximal expiratory pressure (PEmax) added to each PFT assessment
- HRCT added for patients presenting with confirmed 20% reduction of PFTs from

baseline (HRCT replaced chest x-ray at screening and at Visit 13 at selected sites)

- Optical coherence tomography (OCT) to assess retinal thickness at screening and Visit 13

Amendment 5 (25 June 2007) was created following input from regulatory authorities,

investigators and new information from ongoing studies. Key changes are summarised below:

- Criteria and measures to assure the prevention of pregnancy were strengthened.
- Skin examination was to be performed by a dermatologist.
- HRCT scans, echocardiograms and OCT scans were to be analysed by a central reader.

- Following re-start of study drug due to interruption caused by elevated ALT/AST values, further liver safety monitoring and actions to be taken were outlined.
- For patients with symptoms of neurological deterioration inconsistent with MS course a CSF sample could be obtained, if warranted.
- Fatigue was not to be included in the cerebral score assessment of the EDSS.

With Amendment 7 (18 June 2008), measures aimed at reducing the risk of serious infections were added. Investigators were advised to consider the added immunosuppressive effects of corticosteroid therapy and to increase vigilance for infections during and following the use of such treatment. This amendment also included details for the follow-up of patients diagnosed with macular oedema.

Amendment 8 (25 August 2008) was created as a follow-up to Amendment 7, following input from regulatory authorities and infectious disease experts to implement additional safety measures. Additional guidance was provided regarding the risk of infections based on profiling for presence of antibodies against selected viruses, the use of antiviral therapy in the event of primary varicella-zoster virus exposure or herpes-zoster reactivation and prohibition of the use of live or live attenuated vaccines in patients taking study drug. In addition, the criteria for a notably abnormal lymphocyte count was changed from <100 cells/mm^3 to <200 cells/mm^3. A notably low count, if confirmed, was to lead to interruption of study drug. Also, the Guidance for monitoring of patients with elevated liver function tests was modified to add the requirement that for any unscheduled laboratory assessments performed locally to monitor liver function tests, an identical blood sample was also to be sent to the central laboratory for analysis and inclusion in the study database.

Amendment 9 (05 June 2009) was created in response to discussions with the European Medicines Authority (EMA) and the FDA regarding the statistical analysis method for the primary efficacy endpoint (changed from analysis of covariance to negative binomial regression) as well as an FDA recommendation to order the analysis of primary and key secondary endpoints using a multiplicity adjustment. Secondary and additional objectives were also simplified.

These 10 amendments (all of which were implemented before database lock) were not felt to affect the interpretation of study results.

Baseline data

Baseline demographic characteristics are summarised by treatment in Table 20. The study population was consistent with a population of RRMS patients in that approximately two-thirds were female (69.9% female versus 30.1% male), the majority (95.4%) were Caucasian, and the mean (SD) age was 37.1 (8.76) years. The treatment groups were balanced for all baseline demographic characteristics.

Table 20: Study FTY720D2301 - Demographic summary by treatment group (Randomised population)

		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
Age group (years) - n (%)	<18	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)
	18-30	107 (24.9)	120 (28.2)	97 (23.2)	324 (25.5)
	31-40	147 (34.3)	162 (38.1)	165 (39.5)	474 (37.3)
	41-55	174 (40.6)	143 (33.6)	156 (37.3)	473 (37.2)
Sex - n (%)	Male	134 (31.2)	129 (30.4)	120 (28.7)	383 (30.1)
	Female	295 (68.8)	296 (69.6)	298 (71.3)	889 (69.9)
Race - n (%)	Caucasian	408 (95.1)	406 (95.5)	399 (95.5)	1213 (95.4)
	Black	0 (0.0)	1 (0.2)	2 (0.5)	3 (0.2)
	Asian	0 (0.0)	3 (0.7)	3 (0.7)	6 (0.5)
	Other	21 (4.9)	15 (3.5)	14 (3.3)	50 (3.9)
Weight (kg)	Mean (SD)	70.81 (16.296)	71.63 (15.210)	70.70 (14.573)	71.05 (15.377)
	Median	68.00	70.00	69.00	69.00
	Range	40.1-154.3	40.0-128.8	40.0-118.0	40.0-154.3
Height (cm)	Mean (SD)	169.8 (9.05)	169.6 (9.09)	169.0 (8.76)	169.5 (8.97)
	Median	170.0	168.0	168.0	169.0
	Range	148 - 203	144 - 197	148 - 195	144 - 203
BMI (kg/m^2)	Mean (SD)	24.44 (4.748)	24.87 (4.822)	24.67 (4.409)	24.66 (4.664)
	Median	23.53	24.07	23.91	23.83
	Range	16.7- 48.8	17.2- 49.1	15.6- 43.4	15.6- 49.1

Baseline MS disease characteristics were consistent with a RRMS patient population and were adequately balanced across the treatment groups (see Table 21). The median duration of MS since first symptoms was 6.7 years (range 0 to 37 years). The median number of relapses was 2.0 (range 1 to 11) in the previous two years and 1.0 (range 0 to 6) in the previous year. The median baseline EDSS score was 2, identical in all treatment groups (range 0 to 5.5).

In addition to the MS baseline information described in Table 21, a detailed assessment of MS symptoms in the domains of brainstem, motor, sensory, coordination, vegetative, cognitive, and ”other” were collected at screening, prior to randomisation. The most common MS symptom category was sensory (58.4% of all patients), of which numbness (39.9%) and paresthaesia (36.2%) were reported most often. The next most common category was motor (51.7% of all patients), of which lower limb weakness (43.0%) and upper limb weakness (25.2%) were reported most often. The third most common category was “other” (48.2% of all patients), of which fatigue (45.0%) was reported most often. Symptoms were predominantly mild or moderate in severity and occurred in comparable percentages of patients across treatment groups. The most frequently reported severe symptoms (≥1.0% of all patients) were fatigue (2.7%), blurred vision (1.8%), heat intolerance (1.5%), double vision (1.3%) and lower limb weakness (1.3%).

Table 21: Study FTY720D2301 - Table 11-3 Clinical MS baseline characteristics by treatment group (Randomised population)

	FTY720 1.25mg N=429	FTY720 0.5mg N=425	Placebo N=418	Total N=1272
Duration of MS since first symptom, years				
n	429	425	418	1272
Mean (SD)	8.4 (6.86)	8.0 (6.60)	8.1 (6.35)	8.2 (6.60)
Median	6.9	6.6	7.0	6.7
Range	0 - 37	0 - 35	0 - 32	0 - 37
Number of relapses in the last year				
n	429	425	418	1272
Mean (SD)	1.5 (0.81)	1.5 (0.76)	1.4 (0.73)	1.5 (0.77)
Median	1.0	1.0	1.0	1.0
Range	0 - 6	0 - 5	0 - 6	0 - 6
Number of relapses in the last 2 years				
n	429	424	418	1271
Mean (SD)	2.1 (1.25)	2.1 (1.13)	2.2 (1.19)	2.1 (1.19)
Median	2.0	2.0	2.0	2.0
Range	1 - 10	1 - 11	1 - 10	1 - 11
EDSS				
n	429	425	418	1272
Mean (SD)	2.41 (1.36)	2.30 (1.29)	2.49 (1.29)	2.40 (1.32)
Median	2.00	2.00	2.00	2.00
Range	0.0 - 5.5	0.0 - 5.5	0.0 - 5.5	0.0 - 5.5
MSFC z-score				
n	424	422	413	n/a
Mean (SD)	-0.02 (0.75)	0.06 (0.60)	-0.04 (0.76)	n/a
Median	0.13	0.13	0.09	n/a
Range	-5.9 – 1.3	-2.9 – 1.6	-6.4 – 1.9	n/a

n/a=not available.

Baseline MRI characteristics were relatively comparable across the three treatment groups, although the baseline measures for the FTY720 1.25 mg group were slightly worse than for the other two groups, but the difference is not likely meaningful. The MRI features are representative of the broader population with RRMS with approximately 40% of the patients showing active lesions on MRI (see Table 22).

Table 22: Study 720D2301 - MRI baseline characteristics by treatment group (Randomised population)

	FTY720 1.25mg N=429	FTY720 0.5mg N=425	Placebo N=418	Total N=1272
Percentage of patients free of Gd-enhancing T1 lesions - n (%)				
n	424	424	416	1264
	257 (60.6)	263 (62.0)	262 (63.0)	782 (61.9)
Number of Gd enhancing T1 lesions				
n	424	424	416	1264
Mean (SD)	1.8 (4.66)	1.6 (5.57)	1.3 (2.93)	1.6 (4.53)
Median	0.0	0.0	0.0	0.0
Range	0 - 50	0 - 84	0 - 26	0 - 84
Volume of Gd-enhancing T1 lesions (mm^3)				
n	424	424	416	1264
Mean (SD)	197.14 (603.74)	169.87 (601.42)	162.33 (421.21)	176.54 (549.31)
Median	0.00	0.00	0.00	0.00
Range	0.0 - 6852.7	0.0 - 6849.8	0.0 - 2970.0	0.0 - 6852.7
Total volume of T2 lesions (mm^3)				
n	425	424	416	1265
Mean (SD)	6828.70 (8490.54)	6127.71 (7622.97)	6162.40 (7084.84)	6374.63 (7759.71)
Median	3556.50	3303.35	3416.25	3453.30
Range	0.0 - 47734.1	0.0 - 47147.6	0.0 - 37147.8	0.0 - 47734.1
Total volume of T1 hypointense lesions (mm^3)				
n	424	424	416	1264
Mean (SD)	2113.52 (3219.65)	1897.62 (2854.06)	1962.00 (3131.13)	1991.23 (3070.76)
Median	859.55	814.05	811.15	826.90
Range	0.0 - 25885.9	0.0 - 22377.8	0.0 - 20955.9	0.0 - 25885.9
Normalized brain volume (cc)				
n	423	424	414	1261
Mean (SD)	1510.51 (85.94)	1520.84 (83.16)	1512.16 (85.49)	1514.53 (84.92)
Median	1514.69	1528.50	1514.84	1520.22
Range	1217.1 - 1763.8	1143.7 - 1733.7	1229.8 - 1722.6	1143.7 - 1763.8

n=number of patients with an evaluable MRI scan at baseline.

The most commonly reported medical history and continuing medical conditions at baseline (in ≥20% of all patients) by system organ class (SOC) were nervous system disorders (56.5%), psychiatric disorders (22.5%), and infections and infestations (26.9%). In the nervous system disorders SOC, the most common conditions (in ≥10.0% overall) were optic neuritis (41.5%) and headache (10.4%). In the psychiatric disorders SOC, the most common condition (in ≥10.0% overall) was depression (14.9%). In the infections and infestations SOC, the most common conditions (in ≥2.0% overall) were infectious mononucleosis (2.5%), urinary tract infection (2.4%), and nasopharyngitis (2.1%). Other medical conditions of interest to this study include those in the skin and subcutaneous tissue disorders SOC (12.0% overall, the most common of which was eczema, 2.2% overall), the vascular disorders SOC (9.7% overall, the most common of which was hypertension, 5.5% overall), and the respiratory, thoracic and mediastinal disorders SOC (10.5% overall, the most common of which was asthma 2.8%, overall). There were no clinically relevant differences among the treatment groups in the reporting of medical histories.

There were no relevant differences in eye history among the treatment groups. History of optic neuritis was most commonly reported, affecting 41.5%, 38.6% and 44.3% of patients in the FTY720 1.25 mg, FTY720 0.5 mg, and placebo treatment groups, respectively. A history of uveitis was reported in 2.1%, 0.9% and 0.5% of patients in the FTY720 1.25 mg, FTY720 0.5 mg, and placebo treatment groups, respectively. No patient had macular oedema at baseline.

Overall, 28.0% of all patients were active smokers, 3.0% reported a history of other respiratory disorders, 2.7% reported a history of asthma, 1.3% reported a history of exposure to environmental hazards (including asbestos), and 0.2% reported a history of chronic obstructive pulmonary disease. A history of asthma was reported in twice as many patients in the FTY720 0.5 mg treatment group compared to placebo (2.3%, 3.8% and 1.9% in the FTY720 1.25 mg, FTY720 0.5 mg and placebo groups, respectively). There were otherwise no relevant differences among the treatment groups.

Concomitant medications started prior to the start of study medication were taken by 68.9% of all patients. The two most commonly taken prior concomitant medications were ibuprofen (5.6% overall) and paracetamol (5.4% overall). A summary of MS disease-modifying drugs (excluding symptomatic treatments) used at any time prior to the start of study drug treatment is presented by treatment group in Table 23. Slightly more than half of all patients were treatment-naïve (approximately 57-60% across the treatment groups). Of those who had been previously treated, interferon had been used most often (367/520 or 70.6%).

Table 23: Study FTY720D2301 - Prior use of MS disease-modifying drugs (Randomised population)

	FTY720 1.25mg N=429 n (%)	FTY720 0.5mg N=425 n (%)	Placebo N=418 n (%)	Total N=1272 n (%)
Treatment-naïve patients*	259 (60.4)	244 (57.4)	249 (59.6)	752 (59.1)
Previously treated patients	170 (39.6)	181 (42.6)	169 (40.4)	520 (40.9)
Any Interferon beta	125 (29.1)	127 (29.9)	115 (27.5)	367 (28.9)
Interferon beta 1a i.m.	50 (11.7)	65 (15.3)	60 (14.4)	175 (13.8)
Interferon beta 1a s.c.	53 (12.4)	56 (13.2)	49 (11.7)	158 (12.4)
Interferon beta 1b s.c.	44 (10.3)	41 (9.6)	44 (10.5)	129 (10.1)
Glatiramer acetate	52 (12.1)	42 (9.9)	44 (10.5)	138 (10.8)
Natalizumab	1 (0.2)	4 (0.9)	2 (0.5)	7 (0.6)
Other MS medications	43 (10.0)	46 (10.8)	52 (12.4)	141 (11.1)

* Treatment-naïve patients are defined as those not receiving any of the approved 5 MS disease-modifying drugs listed above or any other MS medications.

Data sets analysed

A summary of the study populations for analysis is presented by treatment group in Table 24. In total, 100% of randomised patients were included in the ITT and Safety populations. The PP population included all ITT patients who did not have any major protocol deviations and whose treatment code was not broken. The follow-up population consisted of patients who prematurely discontinued the double-blind phase as well as those who completed the double-blind phase and did not enter the extension phase but returned for follow-up evaluations.

Table 21: Study FTY720D2301 - Analysis populations by treatment group

Population	FTY720 1.25mg n (%)	FTY720 0.5mg n (%)	Placebo n (%)	Total n (%)
Randomized population	429 (100)	425 (100)	418 (100)	1272 (100)
Intent-to-treat (ITT) population	429 (100)	425 (100)	418 (100)	1272 (100)
Per-protocol (PP) population	408 (95.1)	405 (95.3)	397 (95.0)	1210 (95.1)
Safety population	429 (100)	425 (100)	418 (100)	1272 (100)
Follow-up population	114 (26.6)	74 (17.4)	94 (22.5)	282 (22.2)

ITT population includes all the patients who were randomized and received at least one dose of study drug.
Per-protocol population includes all patients in the ITT population without major protocol deviation or whose treatment code was not broken (accidentally or per protocol). Any efficacy data after study drug withdrawal were excluded.
Safety population includes all patients who received at least one dose of study drug.
Follow-up population includes all patients who had follow-up visit 501 or at least one safety assessment 46 to 104 days after discontinuing study drug.

Outcomes

Primary efficacy results

The primary efficacy objective was to compare FTY720 1.25 mg and FTY720 0.5 mg versus placebo on aggregate ARR in patients with RRMS treated for up to 24 months. The results for the primary efficacy analysis are shown in Table 25. Treatment with both FTY720 1.25 mg and FTY720 0.5 mg resulted in lower aggregate ARRs compared to treatment with placebo, with ARR estimates of 0.16 and 0.18 versus 0.40, respectively. This corresponded to reductions of 60% and 54% in ARR estimates, for the 1.25 mg and 0.5 mg doses, respectively. These values were statistically significant relative to placebo (p<0.001 for both comparisons).

Table 25: Study FTY720D2301 - Aggregate annualised relapse rate (ARR) up to Month 24 (confirmed relapses only) (ITT population)

	FTY720 1.25mg N=429	FTY720 0.5mg N=425	Placebo N=418
Aggregate ARR estimate	0.16	0.18	0.40
(95% CI)	(0.13,0.19)	(0.15,0.22)	(0.34,0.47)
Treatment comparison of FTY720 vs. placebo			
ARR ratio	0.40	0.46	---
P-value	<0.001*	<0.001*	---

Aggregate ARR related to group-level annualized relapse rate.
Aggregate ARR estimate (95% CI), ARR ratio, and p-value are calculated using negative binomial regression adjusted by treatment, country, number of relapses in the previous 2 years, and baseline EDSS.
Log (time of study) is the offset variable.
* Indicates two-sided statistical significance at 0.05 level.

Aggregate ARR up to Month 12 results were consistent with those of the Month 24 data, with ARR estimates of 0.17 for FTY720 1.25 mg and 0.21 for FTY720 0.5 mg which can be compared to 0.42 for placebo. This corresponded to reductions of 59% and 50% in ARR estimates, for the 1.25 mg and 0.5 mg doses, respectively, which were statistically significant relative to placebo (p<0.001 for both comparisons). In addition, the effect was maintained in the second 12 months of the study (i.e., from Month 13 to Month 24). ARR estimates were 0.14 for FTY720 1.25 mg and 0.15 for FTY720 0.5 mg compared to 0.34 for placebo. This corresponded to reductions of 60% and 55% in ARR estimates, for the 1.25 mg and 0.5 mg doses, respectively, which were statistically significant relative to placebo (p<0.001 for both comparisons).

Supportive analyses

Two types of supportive analyses were performed for the primary endpoint in the comparison of FTY720 1.25 mg versus placebo and FTY720 0.5 mg versus Placebo.

The aggregate ARRs based on confirmed relapses for the PP population were consistent with the results observed for the ITT population. Both the FTY720 1.25 mg and FTY720 0.5 mg treatment groups had lower aggregate ARRs compared to placebo with ARR estimates of 0.14, 0.18 and 0.41, respectively. This corresponded to 66% and 55% reductions in ARR estimates for the 1.25 mg and 0.5 mg dose groups up to Month 24, respectively, which were statistically significant relative to placebo (p<0.001 for both comparisons).

The second supportive analysis showed that the patient-level ARRs (confirmed relapses with imputation) in the ITT population were consistent with the results observed for the aggregate ARR estimates in the ITT population. Both the FTY720 1.25 mg and FTY720 0.5 mg treatment groups had significantly lower patient-level ARRs compared to placebo up to Month 24: 0.19 for FTY720 1.25 mg, 0.21 for FTY720 0.5 mg, and 0.45 for placebo, with p<0.001 (rank ANCOVA) for both comparisons. There was no statistically significant difference between the FTY720 1.25 mg and FTY720 0.5 mg treatment groups in the aggregate ARR in the ITT population (corresponding to reduction of 14% in FTY720 1.25 mg versus FTY720 0.5 mg ARR estimates; p=0.226); however the difference reached statistical significance in the PP population (corresponding to reduction of

24% in FTY720 1.25 mg versus FTY720 0.5 mg ARR estimates; p=0.048). There was no statistically significant difference in the patient-level ARR between the FTY720 1.25 mg and FTY720 0.5 mg treatment groups in the ITT population (p=0.441).

Evaluator's comments: *The primary analyses for the study suggest a robust treatment effect of FTY720 over control on the ARR in RRMS. The sensitivity analyses support the findings of the primary analyses, and overall the data do provide support that FTY720 is effective at lowering the relapse rate in RRMS patients.*

Secondary efficacy results

Key secondary efficacy endpoint

The key secondary efficacy endpoint was the time to 3-month confirmed disability progression (as measured by at least a 1-point increase in EDSS, or 0.5 for those with baseline EDSS of 5.5) up to Month 24. FTY720 at doses of 1.25 mg and 0.5 mg significantly delayed the time to 3-month confirmed disability progression compared to placebo in the ITT population (log-rank test; p=0.012 and p=0.026, respectively) (see Figure 17 and Table 26). The percentage of patients free of 3-month confirmed disability progression at Month 24 was higher in both FTY720 treatment groups (83.4% and 82.3% for 1.25 mg and 0.5 mg, respectively) compared with placebo (75.9%). Further analysis using a Cox proportional hazard model (adjusted for treatment, country, baseline EDSS, and age) indicated a risk reduction in 3-month disability progression over 2 years of 32% (hazard ratio (HR) of 0.68) for the FTY720 1.25 mg group and 30% (HR of 0.70) for the FTY720 0.5 mg treatment group relative to the placebo group (p=0.017 and p=0.024, respectively).

Results for the PP population were consistent with those in the ITT population.

Of note is that the point estimate of the HR for FTY720 1.25 mg was 0.57 versus placebo, which was lower than for the corresponding ITT analysis. The point estimate of the HR for FTY720 0.50 mg versus placebo (0.71) was comparable to the corresponding ITT analysis.

Figure 17: Study FTY720D2301 - Cumulative plot of time to 3-month confirmed disability progression (ITT population)

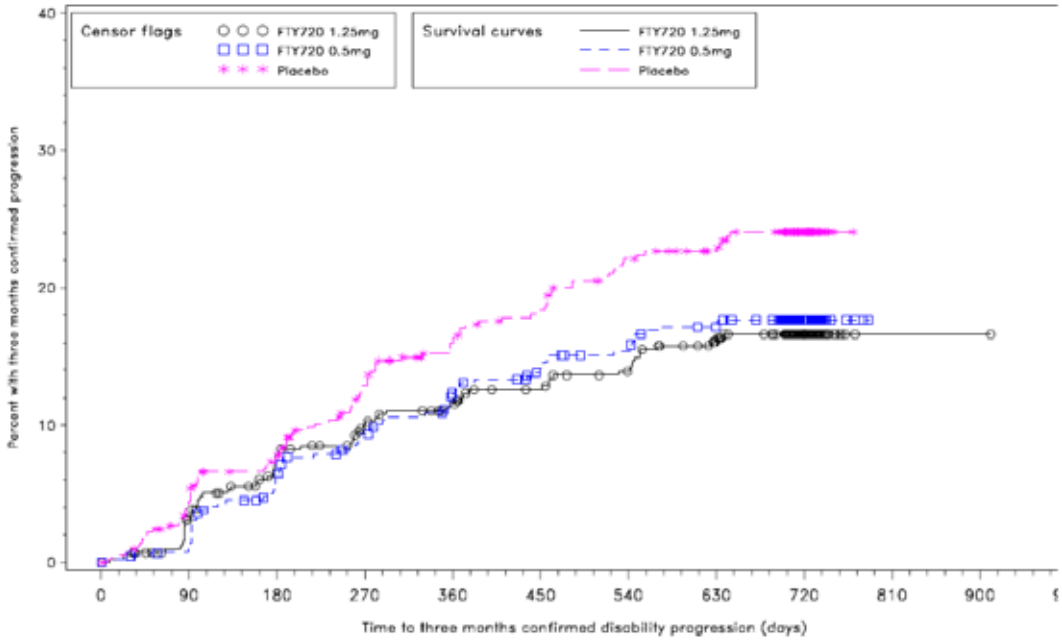


Table 26: Study FTY720D2301- Confirmed 3-month disability progression up to Month 24 based on EDSS (ITT population)

	FTY720 1.25mg N=429	FTY720 0.5mg N=425	Placebo N=418
Kaplan-Meier estimate (SE) of % free of 3-month disability progression at Month 24 (720 days)	83.4 (1.87)	82.3 (1.89)	75.9 (2.17)
(95% CI)	(79.7, 87.1)	(78.6, 86.1)	(71.7, 80.2)
Treatment comparison of FTY720 vs. placebo			
p-value (log-rank test)[1]	0.012*	0.026*	---
Hazard ratio (FTY720 vs. placebo)	0.68	0.70	---
(95% CI)	(0.50, 0.93)	(0.52, 0.96)	---
Cox PH regression p-value[2]	0.017*	0.024*	---

SE = standard error.
[1] Primary analysis method. P-value from log-rank test was used to compare the survival distributions between treatment groups.
[2] P-value from Cox proportional hazard model for time to 3-month confirmed disability progression, adjusted for treatment, country, baseline EDSS, and age.
* Indicates two-sided statistical significance at 0.05 level.

There was no difference between the two FTY720 treatment groups in the time to 3-month confirmed disability progression up to Month 24 as based on the log-rank test using the ITT population (p=0.743) or the PP population (p=0.266).

The time to confirmed 3-month disability progression sustained until last observation was also analysed. Confirmed 3-month disability progression sustained until last observation was defined as a 1 point increase from baseline on EDSS score if baseline EDSS was between 0 and 5.0, or a 0.5 point increase if baseline EDSS was 5.5 or higher. A 3-month confirmed disability progression sustained until last observation required onset EDSS, 3-month confirming EDSS (in absence of relapse), and all EDSS after the onset EDSS to meet the disability progression criteria. The results were consistent with those of the key secondary efficacy endpoint: both FTY720 doses significantly delayed the time to 3-month sustained disability progression up to Month 24 relative to placebo (log-rank test; p=0.006 for each comparison). Further analysis using a Cox proportional hazard model (adjusted for treatment, country, baseline EDSS, and age) indicated a risk reduction over 2 years of 39% (HR of 0.61) for both FTY720 treatment groups relative to the placebo group (p=0.010 and p=0.009, respectively). The percentage of patients free of 3-month confirmed sustained disability progression at Month 24 was higher in both FTY720 treatment groups (88.8% and 88.6% for 1.25 mg and 0.5 mg, respectively) compared with placebo (82.1%).

MRI efficacy endpoints

MRI analyses were conducted only on those patients with available data at the time point under evaluation**.**

T2 lesion activity

The results for new/newly enlarged T2 lesions are summarised by treatment and time point in Table 27. The numbers of new/newly enlarged T2 lesions at Month 24 compared to baseline were statistically significantly lower for both FTY720 treatment groups compared to placebo (negative binomial regression; p<0.001 for both comparisons). Similar results were seen at Month 6 and Month 12 compared to baseline, and at Month 24 compared to Month 12 (p<0.001 for both comparisons at each time point). The baseline to Month 24 data are a summation of the baseline to Month 12 and Month 12 to Month 24 data. A separate analysis of activity was not conducted for Month 24 compared to baseline.

The percentages of patients free of new/newly enlarged T2 lesions at Month 24 compared to baseline were higher in the FTY720 1.25 mg and FTY720 0.5 mg treatment groups (51.9% and

50.5%, respectively) compared to placebo (21.2%); the differences were significant for each of the FTY720 treatment groups versus placebo (logistic regression; $p<0.001$ for both comparisons). Similar results were seen at Month 6 and Month 12 compared to baseline, and at Month 24 compared with Month 12.

T1 Gd-enhancing lesion activity

The results for Gd-enhancing T1 lesion activity are summarised by treatment and visit in Table 28. The numbers of Gd-enhancing T1 lesions at Month 24 were statistically significantly lower for both FTY720 treatment groups compared to placebo (rank ANCOVA; $p<0.001$ for both comparisons). Similar results were seen at Month 6 and Month 12 ($p<0.001$ for both comparisons at each time point). In addition, the percentages of patients free of Gd-enhancing T1 lesions at Month 24 were statistically significantly higher in the FTY720 1.25 mg and FTY720 0.5 mg treatment groups (89.8% and 89.7%, respectively) compared to placebo (65.1%) (logistic regression; $p<0.001$ for both comparisons). Similar results were seen at Months 6 and 12 ($p<0.001$ for both comparisons at each time point).

The total volume of Gd-enhancing T1 lesions at Month 24 was also statistically significantly lower for both FTY720 treatment groups compared to placebo ($p<0.001$ both comparisons). Similar results were seen at Months 6 and 12 ($p<0.001$ for both comparisons at each time point).

The percentages of patients free of new MRI activity (no Gd-enhancing T1 lesions and no new/newly enlarged T2 lesions) at Month 24 were statistically significantly higher in both FTY720 treatment groups (52.0% and 50.7%, respectively) compared to placebo (21.0%) (logistic regression; $p<0.001$ for both comparisons). Similar results were seen at Month 6, Month 12, and at Month 24 compared to Month 12 ($p<0.001$ for both comparisons at each time point).

Table 27: FTY720D2301- Inflammatory activity based on MRI measurement of number of new/newly enlarged T2 lesions (ITT population)

	FTY720 1.25mg N=429	FTY720 0.5mg N=425	Placebo N=418
Month 0 to 6			
n	392	408	394
Mean (SD)	1.1 (2.49)	1.0 (2.63)	3.6 (7.93)
Median	0.0	0.0	1.0
Range	0 to 27	0 to 28	0 to 96
P-value for treatment comparison of FTY720 vs. placebo (negative binomial regression with covariates)	<0.001*	<0.001*	---
Number (%) of patients free of new/newly enlarged T2 lesions	246 (62.76)	264 (64.71)	150 (38.07)
Month 0 to 12			
n	378	401	367
Mean (SD)	1.5 (3.22)	1.6 (4.46)	5.5 (8.00)
Median	0.0	0.0	3.0
Range	0 to 28	0 to 63	0 to 78
P-value for treatment comparison of FTY720 vs. placebo (negative binomial regression with covariates)	<0.001*	<0.001*	---
Number (%) of patients free of new/newly enlarged T2 lesions	222 (58.73)	230 (57.36)	97 (26.43)
Month 0 to 24 [1]			
n	337	370	339
Mean (SD)	2.5 (5.52)	2.5 (7.19)	9.8 (13.17)
Median	0.0	0.0	5.0
Range	0 to 41	0 to 107	0 to 99
P-value for treatment comparison of FTY720 vs. placebo (negative binomial regression with covariates)	<0.001*	<0.001*	---
Number (%) of patients free of new/newly enlarged T2 lesions	175 (51.93)	187 (50.54)	72 (21.24)
Month 12 to 24			
n	338	371	340
Mean (SD)	1.1 (3.61)	0.9 (3.30)	4.3 (7.90)
Median	0.0	0.0	2.0
Range	0 to 32	0 to 44	0 to 69
P-value for treatment comparison of FTY720 vs. placebo (negative binomial regression with covariates)	<0.001*	<0.001*	---
Number (%) of patients free of new/newly enlarged T2 lesions	236 (69.82)	270 (72.78)	113 (33.24)

n=the number of patients who had the specific MRI value at a visit.
[1] For each patient, the number of new or newly-enlarged T2 lesions at Month 0 to 24 was obtained by adding Month 0 to 12 results and Month 12 to 24 results.
P-value is calculated using a negative binomial model adjusted for treatment and country.
* Indicates two-sided statistical significance at 0.05 level.

Table 28: Study FTY720D2301- Inflammatory activity based on MRI measurement of the number of Gd-enhancing T1 lesions (ITT population)

	FTY720 1.25mg N=429	FTY720 0.5mg N=425	Placebo N=418
Month 6 [1]			
n	388	403	373
Mean (SD)	0.3 (1.14)	0.2 (0.84)	1.3 (3.40)
Median	0.0	0.0	0.0
Range	0 to 12	0 to 13	0 to 43
P-value for treatment comparison of FTY720 vs. placebo (rank ANCOVA with covariates)	<0.001*	<0.001*	---
Number (%) of patients free of Gd-enhancing T1 lesions	338 (87.11)	361 (89.58)	232 (62.20)
Month 12 [1]			
n	376	394	356
Mean (SD)	0.3 (0.96)	0.2 (1.35)	1.1 (2.19)
Median	0.0	0.0	0.0
Range	0 to 11	0 to 21	0 to 19
P-value for treatment comparison of FTY720 vs. placebo (rank ANCOVA with covariates)	<0.001*	<0.001*	---
Number (%) of patients free of Gd-enhancing T1 lesions	330 (87.77)	348 (88.32)	229 (64.33)
Month 24 [1]			
n	343	369	332
Mean (SD)	0.2 (1.08)	0.2 (0.84)	1.1 (2.37)
Median	0.0	0.0	0.0
Range	0 to 11	0 to 8	0 to 21
P-value for treatment comparison of FTY720 vs. placebo (rank ANCOVA with covariates)	<0.001*	<0.001*	---
Number (%) of patients free of Gd-enhancing T1 lesions	308 (89.80)	331 (89.70)	216 (65.06)

n=the number of patients who had the specific MRI value at a visit.
[1] Any Gd-enhancing T1 data obtained less than 30 days after the steroid used to treat MS relapses were excluded from the analysis.
P-value is calculated using a rank ANCOVA model adjusted for treatment, country, and baseline number of Gd-enhancing T1 lesions.
* Indicates two-sided statistical significance at 0.05 level.

Lesion volume

Lesion volume as measured by MRI is summarised in Table 29. Given the skewed nature of MRI data, emphasis should be on median values for change in volume measures. The data over 24 months showed that the FTY720 treatment groups both showed a change in the median absolute and percentage change from baseline in total T2 lesion volume compared to placebo patients who accumulated additional T2 lesion volume over the course of 2 years ($p<0.001$ for all comparisons with placebo with no significant dose difference). Data regarding median changes (absolute and percentage change from baseline to Month 24) in total volume of T1 hypointense lesions showed no change with FTY720 but as with T2 lesion volume, an increase was seen for patients receiving placebo ($p<0.02$, all comparisons compared to placebo with no significant dose difference).

Table 29: Study FTY720D2301 - Change from baseline in lesion volume at Month 24 (ITT population)

	FTY720 1.25mg N=429	FTY720 0.5mg N=425	Placebo N=418
Change from baseline in total volume of T2 lesions (mm^3) at Month 24			
n	345	372	342
Mean (SD)	-95.65 (2167.220)	-23.46 (2360.073)	1045.31 (2716.132)
Median	-60.10	-42.40	357.00
Range	-15253.4 to 17508.0	-27656.7 to 22893.0	-5141.7 to 33170.4
P-value for treatment comparison of FTY720 vs. placebo (rank ANCOVA with covariates)	<0.001*	<0.001*	---
Percent change from baseline in total volume of T2 lesions (mm^3) at Month 24			
n	343	368	339
Mean (SD)	1.58 (30.71)	10.61 (103.46)	33.82 (106.90)
Median	-3.10	-1.69	8.61
Range	-68.2 to 221.5	-100.0 to 1828.5	-84.5 to 1378.7
P-value for treatment comparison of FTY720 vs. placebo (rank ANCOVA with covariates)	<0.001*	<0.001*	---
Change from baseline in total volume of T1 hypointense lesions (mm^3) at Month 24			
n	343	372	340
Mean (SD)	30.23 (674.253)	32.93 (536.327)	172.63 (690.229)
Median	0.00	0.00	2.90
Range	-2403.4 to 7811.2	-4912.7 to 3462.1	-3440.4 to 5857.0
P-value for treatment comparison of FTY720 vs. placebo (rank ANCOVA with covariates)	<0.001*	0.008*	---
Percent change from baseline in total volume of T1 hypointense lesions (mm^3) at Month 24			
n	317	346	305
Mean (SD)	12.24 (85.49)	8.80 (76.27)	50.68 (388.26)
Median	-0.20	0.00	1.59
Range	-100 to 888.4	-100.0 to 1037.1	-100.0 to 5285.3
P-value for treatment comparison of FTY720 vs. placebo (rank ANCOVA with covariates)	0.015*	0.012*	---

n = the number of patients with non-missing baseline and post-baseline values.
P-values are from rank ANCOVA with covariates of treatment, country, and the baseline volume of T2 (for total volume of T2 lesions) or T1 hypointensive lesions (for total volume of T1 hypointensive lesions).
* Indicates two-sided statistical significance at 0.05 level.

Brain volume

Percent changes in brain volume are summarised from baseline to Months 6, 12, and 24, as well as from Month 12 to Month 24 in Table 30. Brain volume decreased by a median of 0.98% for patients receiving placebo over 2 years compared to 0.70% for those receiving 1.25 mg FTY720 and 0.67% for the 0.5 mg group ($p<0.001$, both comparisons). Significant differences between FTY720 (both doses) and placebo were observed as early as 6 months and were evident during both Year 1 and Year 2 at both doses.

Table 30: Percent change in brain volume by visit (ITT population)

	FTY720 1.25mg N=429	FTY720 0.5mg N=425	Placebo N=418
Percent change from baseline to Month 6			
n	384	395	383
Mean (SD)	-0.209 (0.8649)	-0.224 (0.8131)	-0.344 (0.7334)
Median	-0.120	-0.140	-0.290
Range	-4.71 to 3.37	-5.62 to 2.25	-4.02 to 2.57
P-value for treatment comparison of FTY720 vs. placebo (rank ANCOVA with covariates)	0.003*	0.006*	---
Percent change from baseline to Month 12			
n	371	383	358
Mean (SD)	-0.438 (1.0792)	-0.500 (1.0509)	-0.647 (1.0527)
Median	-0.300	-0.380	-0.560
Range	-4.91 to 4.34	-8.11 to 2.40	-3.89 to 2.78
P-value for treatment comparison of FTY720 vs. placebo (rank ANCOVA with covariates)	0.001*	0.026*	---
Percent change from baseline to Month 24			
n	334	357	331
Mean (SD)	-0.885 (1.3857)	-0.843 (1.3120)	-1.306 (1.5000)
Median	-0.700	-0.670	-0.980
Range	-6.33 to 3.04	-13.50 to 2.16	-7.58 to 2.38
P-value for treatment comparison of FTY720 vs. placebo (rank ANCOVA with covariates)	<0.001*	<0.001*	---
Percent change from Month 12 to Month 24			
n	327	356	329
Mean (SD)	-0.423 (0.8284)	-0.370 (0.8073)	-0.669 (1.0723)
Median	-0.380	-0.340	-0.570
Range	-5.40 to 2.24	-6.24 to 1.90	-5.60 to 2.43
P-value for treatment comparison of FTY720 vs. placebo (rank ANCOVA with covariates)	0.002*	<0.001*	---

n = the number of patients with non-missing baseline and post-baseline values.
P-values are from rank ANCOVA with covariates of treatment, country, and baseline normalized brain volume.
* Indicates two-sided statistical significance at 0.05 level.

MS relapse-related secondary endpoints

Other MS relapse-related secondary endpoints included:

1. Time to first and second MS relapse

2. Proportion of relapse-free patients at 12 and 24 months

3. Characteristics of the confirmed relapses measured by severity of relapses, recovery status, impact on daily activities, frequency of corticosteroid use for relapse, frequency of hospitalisation due to relapse and duration of relapse.

All relapse-related analyses used confirmed relapses only, however, a sensitivity analysis was done using all relapses (both confirmed and unconfirmed).

Time to first and second MS relapse and percentage of relapse-free patients

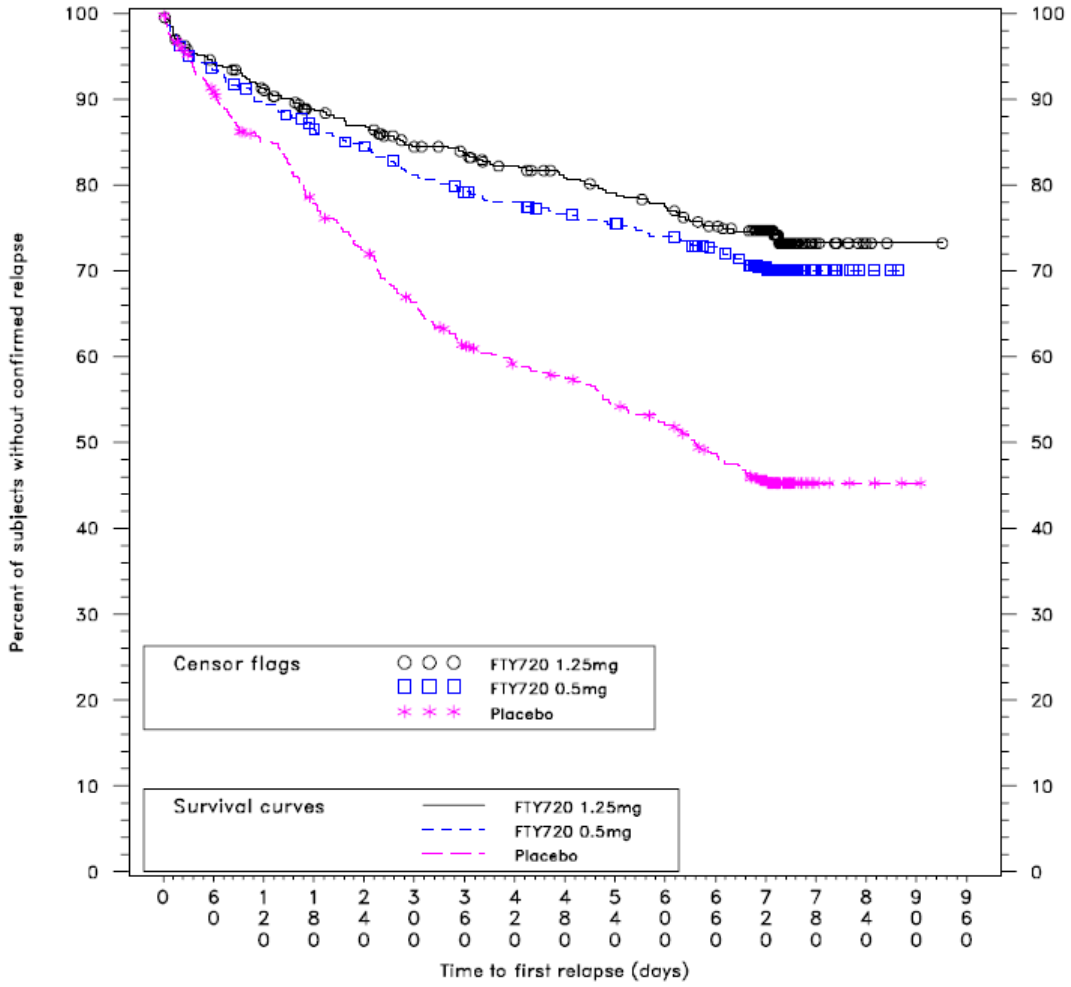
The time to first confirmed MS relapse was significantly delayed in both FTY720 treatment groups compared to placebo (log-rank test; $p<0.001$ for both comparisons) (see Table 31 and Figure 18). The percentage of patients free of MS relapse at Month 24 was higher in both FTY720 treatment groups (74.7% and 70.4% for 1.25 mg and 0.5 mg, respectively) compared with placebo (45.6%). Further analysis using a Cox proportional hazard model (adjusted for treatment, country, number of relapses in previous 2 years and baseline EDSS) indicated a risk reduction in MS relapse over 2 years of 62% for the FTY720 1.25 mg group (HR of 0.38) and 52% for the FTY720 0.5 mg treatment group (HR of 0.48) relative to the placebo group ($p<0.001$ for both comparisons).

Table 31: Study FTY720D2301 - First confirmed MS relapse up to Month 24 (ITT population)

	FTY720 1.25mg N=429	FTY720 0.5mg N=425	Placebo N=418
Kaplan–Meier estimate (SE) of % relapse-free (720 days)	74.7 (2.17)	70.4 (2.26)	45.6 (2.52)
(95% CI)	(70.40, 78.90)	(65.95, 74.80)	(40.70, 50.57)
Treatment comparison of FTY720 vs. placebo			
p-value (log-rank test)[1]	<0.001*	<0.001*	---
Hazard ratio (FTY720 vs. placebo)	0.38	0.48	---
(95% CI)	(0.30, 0.48)	(0.39, 0.61)	---
Cox PH regression p-value[2]	<0.001*	<0.001*	---

SE= standard error .
[1] P-value from log-rank test was used to compare the survival distributions between treatment groups.
[2] Hazard ratio and p-value derived from Cox's proportional hazards model adjusted for treatment, country, number of relapses in previous 2 years, and baseline EDSS.
* Indicates two-sided statistical significance at 0.05 level.

Figure 18: Study FTY720D2301 - Kaplan-Meier plot of time to first confirmed MS relapse (ITT population)



The time to second confirmed MS relapse was also significantly delayed in both FTY720 treatment groups compared to placebo (log-rank test; p<0.001 for both comparisons). The percentage of patients free of a second confirmed MS relapse at Month 24 was higher in both FTY720 treatment groups (92.8% and 91.2% for 1.25 mg and 0.5 mg, respectively) compared with placebo (76.5%). Further analysis using a Cox proportional hazard model (adjusted for treatment, country, number of relapses in previous 2 years and baseline EDSS) indicated a risk reduction in a second confirmed

MS relapse over 2 years of 71% for the FTY720 1.25 mg group (HR of 0.29) and 66% for the FTY720 0.5 mg treatment group (HR of 0.34) relative to the placebo group (p<0.001 for both comparisons).

There was no statistically significant difference between the two FTY720 treatment groups for the time to first confirmed MS relapse (log-rank test; p=0.192) or for the time to second confirmed MS relapse (log-rank test; p=0.635).

Characteristics of confirmed MS relapses

Characteristics of confirmed MS relapses, at the relapse level, are summarised in Table 32.

Table 32: Study FTY720D2301 - Confirmed MS relapse characteristics for 0 to 24 months (ITT population)

MS relapse characteristics	FTY720 1.25mg N=429	FTY720 0.5mg N=425	Placebo N=418
Total number of relapses	148	172	359
Relapse severity			
Mild, n (%)	43 (29.1)	60 (34.9)	119 (33.1)
Moderate, n (%)	86 (58.1)	102 (59.3)	205 (57.1)
Severe, n (%)	19 (12.8)	10 (5.8)	35 (9.7)
Affects daily activities, n (%)	107 (72.3)	130 (75.6)	256 (71.3)
Steroid used, n (%)	120 (81.1)	140 (81.4)	303 (84.4)
Median (range) accumulated steroid dose (mg/kg) [1]	114.53 (6.2 to 1257.9)	117.92 (4.8 to 2528.1)	158.90 (8.4 to 775.0)
Total steroid dose (all patients) (g)	1633	2426	3945
Recovery status			
None, n (%)	13 (8.8)	12 (7.0)	18 (5.0)
Partial, n (%)	56 (37.8)	51 (29.7)	119 (33.1)
Complete, n (%)	78 (52.7)	108 (62.8)	212 (59.1)
Missing, n (%)	1 (0.7)	1 (0.6)	10 (2.8)
Hospitalization due to MS relapse, n (%)	60 (40.5)	63 (36.6)	146 (40.7)
Median (range) duration of relapse (days)	42.0 (5 to 153)	37.0 (4 to 161)	39.0 (3 to 156)

Percentages are calculated using the total number of relapses as the denominator.
[1] Steroid dose for both confirmed and unconfirmed relapses.

The total number of relapses, overall, was more than twice as high in the placebo group compared with either of the two FTY720 treatment groups. The majority of all relapses were characterised as mild or moderate, and of the relapses that were reported, the proportions that were mild or moderate relapses were comparable across the three treatment groups. The percentage of relapses that were severe was lowest in the FTY720 0.5 mg group (5.8%) compared with the FTY720 1.25 mg (12.8%) and placebo (9.7%) groups. However, as with overall relapse count, there was a marked reduction in the total number of severe relapses for FTY720 patients (n=19 for 1.25 mg dose, n=10 for 0.5 mg dose) compared to placebo (n=35).

Of all confirmed relapses, the percentage that required steroid usage was comparable across the treatment groups, however, again the number of relapses requiring steroid therapy was much less for patients receiving FTY720 than for those on placebo. This was accompanied by a higher steroid consumption in the placebo group compared with the two FTY720 treatment groups.

For the majority of relapses in all treatment groups, partial or complete recovery was reported. The total number of relapses for which recovery was incomplete or did not improve was approximately twice as high in the placebo group (n=137) as in the FTY720 dose arms (n=69 and n=63 for 1.25 mg and 0.5 mg dose groups, respectively).

The following MS relapse characteristics were comparable across the treatment groups: the percentage of relapses that affected daily activities, the percentage that required hospitalisation, and the median duration (days) of relapse. Given the effect on total relapses, the number of hospitalisations and number of relapses affecting daily activities were reduced with active therapy

compared to placebo. No statistically significant differences were seen among the treatment groups for the distribution of any confirmed MS relapse characteristic at the relapse level although overall reductions in total number were seen for each characteristic.

The percentage of patients who did not have a confirmed relapse during the study was highest in the FTY720 treatment groups (75.5% and 71.1%, for 1.25 mg and 0.5 mg, respectively) compared to the placebo group (47.8%). The percentage of patients who had 2 or more relapses was highest in the placebo group (21.5%) compared with the FTY720 1.25 mg and 0.5 mg treatment groups (7.0% and 8.2%, respectively). There was no substantial difference between the two FTY720 doses in percentages of patients who had no confirmed relapse, or at least 1 or 2 confirmed relapses. These findings were consistent when taking all relapses (both confirmed and unconfirmed) into consideration.

Annualised relapse rates based on all relapses (confirmed and unconfirmed)

Results for the aggregate ARR based on all relapses (confirmed and unconfirmed) for the 24-month period in the ITT population were consistent with those of the primary efficacy analysis. Lower aggregate ARR estimates were observed for the FTY720 treatment groups (0.24 and 0.29 for the 1.25 mg and 0.5 mg treatment groups, respectively) compared with placebo (0.62). This corresponded to reductions of 61% and 53% in ARR estimates, for the 1.25 mg and 0.5 mg doses, respectively, which were statistically significant relative to placebo (negative binomial regression; $p<0.001$ for both comparisons). There was no statistically significant difference between the two FTY720 treatment groups ($p=0.080$).

The results for the patient-level ARR based on all relapses (confirmed and unconfirmed) with imputation in the ITT population (0.27 for FTY720 1.25 mg, 0.31 for FTY720 0.5 mg, and 0.62 for placebo) were consistent with the results seen for the aggregate ARR estimates. Both the FTY720 1.25 mg and FTY720 0.5 mg treatment groups experienced a significantly lower patient-level ARR compared to placebo (rank ANCOVA; $p<0.001$ for both comparisons). There was no statistically significant difference between the two FTY720 treatment groups ($p=0.319$).

Other disability progression-related secondary endpoints

Time to confirmed 6-month disability progression

FTY720 at doses of 1.25 mg and 0.5 mg significantly delayed the time to 6-month confirmed disability progression up to Month 24 compared to placebo in the ITT population (log-rank test; $p=0.004$ and $p=0.011$, respectively) (see Table 33). The percentage of patients free of 6-month confirmed disability progression at Month 24 was higher in both FTY720 treatment groups (88.5% and 87.5% for 1.25 mg and 0.5 mg, respectively) compared with placebo (81.0%). Further analysis using a Cox proportional hazard model (adjusted for treatment, country, baseline EDSS, and age) indicated a risk reduction in 6-month disability progression over 2 years of 40% for the FTY720 1.25 mg group (HR of 0.60) and 37% for the FTY720 0.5 mg treatment group (HR of 0.63) relative to the placebo group ($p=0.006$ and $p=0.012$, respectively).

Table 33: Study FTY720D2301 - Confirmed 6-month disability progression up to Month 24 based on EDSS (ITT population)

	FTY720 1.25mg N=429	FTY720 0.5mg N=425	Placebo N=418
Kaplan-Meier estimate (SE) of % free of 6-month disability progression at Month 24 (720 days)	88.5 (1.60)	87.5 (1.64)	81.0 (1.99)
(95% CI)	(85.33, 91.61)	(84.26, 90.70)	(77.11, 84.92)
Treatment comparison of FTY720 vs. placebo			
p-value (log-rank test)[1]	0.004*	0.011*	---
Hazard ratio (FTY720 vs. placebo)	0.60	0.63	---
(95% CI)	(0.41, 0.86)	(0.44, 0.90)	---
Cox PH regression p-value[2]	0.006*	0.012*	---

SE = standard error.
[1] P-value from log-rank test is used to compare the survival distributions between treatment groups.
[2] P-value from Cox proportional hazard model for time to 6-month confirmed disability progression, adjusted for treatment, country, baseline EDSS, and age.
* Indicates two-sided statistical significance at 0.05 level.

There was no difference between the two FTY720 treatment groups in the time to 6-month confirmed disability progression up to Month 24 based on log-rank test in the ITT population (log-rank test; p=0.721).

The time to confirmed 6-month disability progression sustained until last observation was also analysed, and the results were consistent with those given in Table 33. Both FTY720 doses significantly delayed the time to 6-month sustained disability progression up to Month 24 relative to placebo (log-rank test; p≤0.01 for both comparisons). Further analysis using a Cox proportional hazard model (adjusted for treatment, country, baseline EDSS, and age) indicated a risk reduction over 2 years of 43% for the FTY720 1.25 mg group (HR of 0.57) and 40% for the FTY720 0.5 mg treatment group (HR of 0.60) relative to the placebo group (p=0.008 and p=0.014, respectively).The percentage of patients free of 6-month sustained disability progression at Month 24 was higher in both FTY720 treatment groups (91.4% and 90.6% for 1.25 mg and 0.5 mg, respectively) compared with placebo (84.9%).

Change from baseline in EDSS score

Changes from baseline in EDSS score at Month 24 are summarised in Table 34. There was a statistically significant difference in the mean change in the EDSS score at Month 24 compared to baseline for the FTY720 groups versus placebo (p=0.002 for both comparisons), with a mean improvement of 0.03 points in the FTY720 1.25 mg group, no changes for the FTY720 0.5 mg group, and a 0.13 point deterioration in the placebo group.

Table 34: Study FTy720D2301 - Change from baseline in EDSS at Month 24 (ITT population)

	FTY720 1.25mg N=429	FTY720 0.5mg N=425	Placebo N=418
Month 24			
n	338	374	332
Mean (SD)	-0.03 (0.875)	0.00 (0.878)	0.13 (0.936)
Median	0.00	0.00	0.00
Range	-3.0 to 4.0	-3.0 to 3.5	-3.0 to 3.5
P-value for treatment comparison of FTY720 vs. placebo	0.002*	0.002*	

n = the number of patients who had EDSS values at both baseline and Month 24.
P-value is calculated using rank ANCOVA with covariates of treatment, country, the corresponding baseline value, and age.
* Indicates two-sided statistical significance at 0.05 level.

Change from baseline in MSFC

The changes from baseline at Month 24 in the MSFC z-score and subscale scores are summarised in Table 35. At Month 24, a slight decrease from baseline was seen in the mean MSFC z-score in the

placebo group, while a slight increase was seen in both FTY720 treatment groups. The differences between the FTY720 treatment groups and placebo were statistically significant ($p<0.05$, both comparisons). For the MSFC subscales, statistically significant differences in favour of the FTY720 groups relative to the placebo group were observed in the 9-hole peg test (both doses) and in the 25-foot timed walking test (0.5 mg dose only) while no statistically significant differences were seen in the PASAT-3.

Table 35: Study FTY 720D2301 - Change from baseline in MSFC at Month 24 (ITT population)

	FTY720 1.25mg N=429	FTY720 0.5mg N=425	Placebo N=418
MSFC z-score			
n	332	361	316
Mean (SD)	0.01 (0.403)	0.03 (0.394)	-0.06 (0.570)
P-value for treatment comparison of FTY720 vs. placebo	0.022*	0.010*	
MSFC subscale: 25-foot timed walking test (seconds)			
n	336	369	325
Mean (SD)	0.38 (2.126)	0.32 (2.070)	0.66 (3.334)
P-value for treatment comparison of FTY720 vs. placebo	0.062	0.005 *	
MSFC subscale: 9-hole peg test (seconds)			
n	337	365	328
Mean (SD)	-0.31 (3.366)	0.36 (9.097)	0.61 (7.440)
P-value for treatment comparison of FTY720 vs. placebo	<0.001*	<0.001*	
MSFC subscale: PASAT-3 (number of correct answers)			
n	337	366	326
Mean (SD)	2.4 (7.74)	2.3 (7.71)	1.5 (6.81)
P-value for treatment comparison of FTY720 vs. placebo	0.085	0.252	

n = the number of patients who had MSFC values at both baseline and Month 24.
P-value is calculated using rank ANCOVA with covariates of treatment, country, the corresponding baseline value, and age.
* Indicates two-sided statistical significance at 0.05 level

Subgroup analyses

ARR (aggregate and patient-level)

Aggregate ARRs based on confirmed relapses for subgroups defined by sex, age, prior MS disease-modifying treatment, EDSS at baseline and the number of Gd-enhancing T1 lesions at baseline are shown in Table 36. Lower aggregate ARRs were observed across all subgroups in both FTY720 treatment groups compared to the placebo group, and are consistent with results observed in the overall population. Post-hoc analyses showed statistically significant lower ARRs for both FTY720 treatment groups compared to placebo, for all of these subgroups ($p<0.05$, all comparisons). The data suggest that patients who have been previously treated for MS, have a higher EDSS score at baseline and have Gd-enhancing lesions at baseline, have higher on-study ARR but still demonstrate comparable treatment effects while on FTY720 compared to the complementary subgroup.

Table 36: Study FTY720D2301 - Aggregate annualised relapse rate (ARR) up to Month 24 (confirmed relapses) by subgroup (ITT population)

	FTY720 1.25mg N=429	FTY720 0.5mg N=425	Placebo N=418
Overall population			
n	429	425	418
ARR (unadjusted)	0.188	0.212	0.468
Sex			
Male, n	134	129	120
ARR	0.206	0.181	0.536
Female, n	295	296	298
ARR	0.180	0.225	0.442
Age			
≤ 37.0 years, n	204	237	215
ARR	0.189	0.198	0.535
> 37.0 years, n	225	188	203
ARR	0.187	0.231	0.400
Prior MS disease-modifying treatment			
Treatment-naïve, n	259	244	249
ARR	0.170	0.165	0.448
Previously treated, n	170	181	169
ARR	0.214	0.278	0.501
EDSS at baseline			
EDSS < 3, n	274	281	255
ARR	0.146	0.169	0.427
EDSS ≥ 3.0, n	155	144	163
ARR	0.261	0.300	0.537
Number of Gd-enhancing T1 lesions at baseline			
0, n	257	263	262
ARR	0.154	0.174	0.357
1-2, n	97	93	89
ARR	0.230	0.242	0.516
≥3, n	70	68	65
ARR	0.265	0.320	0.896

n = number of patients in the given category.
Treatment-naïve patients are defined as those not having received any of the 5 MS disease-modifying drugs or any other MS medications.

Time to 3-month disability progression

The time to confirmed 3-month disability progression was delayed in both FTY720 treatment groups compared to placebo across all subgroups with the exception of the subgroup of patients with a baseline EDSS < 3.0 by baseline EDSS).

Other efficacy topics

EQ-5D

Changes from baseline in EQ-5D utility scores at Month 24 were not statistically significantly different among the three treatment groups. Mean changes from baseline in EQ-5D Visual Analog Scale score at Month 24 were 1.05, -0.23, and -1.04 for the FTY720 1.25 mg, 0.5 mg and placebo treatment groups, respectively. Similar results were seen at Month 12.

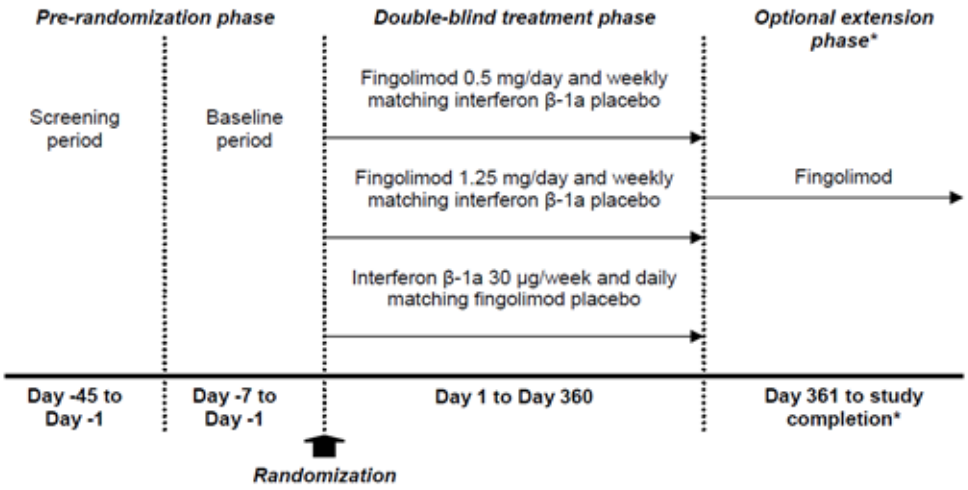
Study FTY720D2302

Study design

This was a 12-month, randomised, multicentre, double-blind, double-dummy active-controlled, parallel-group study that was planned to be conducted in approximately 130 centres and 1275 patients with RRMS. Patients were randomised to receive a fixed dose of FTY720 0.5 mg/day orally, FTY720 1.25 mg/day orally, or interferon β -1a 30 µg/week intramuscularly (IM) (hereafter referred to as interferon β -1a IM) in a double dummy design. The study consisted of three phases: a

pre-randomisation phase (lasting for up to 45 days), a double-blind treatment phase (lasting for up to 12 months), and an optional extension phase (see Figure 19).

Figure 19: Study FTY720D2302



*The optional extension phase was expected to last until FTY720 was commercially available or development was stopped.

The core phase of the study was considered completed for an individual patient when he/she completed the double-blind treatment phase. The core phase of the study as a whole was considered completed when all randomised patients remaining in the core phase had completed the double-blind treatment phase.

Patients who completed the 12-month double-blind treatment phase while taking study drug had the option to enter the extension phase, which is expected to last until FTY720 is commercially available or development is stopped. The current submission presented the efficacy and safety results from the core phase of the study only. No formal interim efficacy analyses were planned for this study. There were interim analyses for the DSMB to monitor drug safety, all of which resulted in the DSMB recommending continuation of the study.

Study objectives

Primary objective

The primary objective was to compare two doses of FTY720 (1.25 mg and 0.5 mg) with interferon β -1a IM to demonstrate that at least 1.25 mg FTY720 is superior to interferon β -1a IM in terms of ARR in patients with RRMS treated for up to 12 months.

Secondary objectives

Key secondary objectives:

To demonstrate superiority of FTY720 1.25 mg and 0.5 mg over interferon β -1a IM in patients with RRMS treated for up to 12 months with respect to:

1. The effect on inflammatory disease activity as measured by the number new/ newly enlarged T2 lesions after up to 12 months of treatment.

2. The effect on disability progression as measured by the time to 3-month confirmed disability progression as measured by EDSS.

Other secondary objectives:

3. To evaluate the safety and tolerability of FTY720 1.25 mg and 0.5 mg compared to interferon β-1a IM in patients with RRMS treated for up to 12 months.

4. To evaluate the effects of FTY720 1.25 mg and 0.5 mg over interferon β -1a IM in patients with RRMS treated for up to 12 months with respect to relapse related parameters:

- Time to first relapse
- Proportion of relapse-free patients

5. To evaluate the effects of FTY720 1.25 mg and 0.5 mg over interferon β -1a IM in patients with RRMS treated for up to 12 months with respect to MRI parameters of inflammatory disease activity, burden of disease and axonal tissue damage.

6. To evaluate the PK/PD relationship of FTY720 1.25 mg and 0.5 mg for main efficacy and safety outcomes in patients with RRMS.

Additional objectives

7. To evaluate the effects of FTY720 1.25 mg and 0.5 mg compared to interferon β -1a IM on the following patient reported outcomes:

- health-related quality of life (QoL) as measured by the Patient Reported Indices in Multiple Sclerosis (PRIMUS-QoL) and the Patient Utility Index derived from the EuroQoL (EQ-5D) questionnaire,
- performance of daily activities as measured by the Patient Reported Indices in Multiple Sclerosis (PRIMUS-Activities) instrument; and
- fatigue as measured by the Modified Fatigue Impact Scale (mFIS).

8. To assess brain atrophy in patients treated for up to 12 months.

9. To conduct pharmacogenetic studies to identify inherited genetic factors that may (1) be related to MS, (2) predict response to treatment with FTY720, (3) predict relative susceptibility to drug-drug interactions, or (4) predict genetic predisposition to side effects.

10. To conduct proteomic/metabolomic studies in plasma and cerebral spinal fluid (CSF) (in selected centres) to monitor the products of gene expression at pre-treatment and post-treatment with FTY720 as well as to identify proteins, and metabolites in plasma that are associated with the treatment response to FTY720.

Study participants

The study population consisted of a representative group of patients with RRMS. Treatment naïve patients and patients previously treated with MS drugs were allowed to participate in this study. It was planned to randomise approximately 1275 patients.

Inclusion criteria

For Study D2302 inclusion and exclusion criteria were the same as for Study D2301 except that patients could be randomised without a wash-out period (they could be switched from IFNβ-1a or glatiramer to study treatment).

Treatments

Investigational drug

- FTY720 1.25 mg capsules for oral administration once daily
- FTY720 0.5 mg capsules for oral administration once daily

Control therapy

- Interferon β -1a 30 μg in pre-filled syringes for IM injection once weekly

Reference therapy

- Matching FTY720 placebo in capsules for oral administration once daily

- Matching interferon β -1a placebo in pre-filled syringes for IM injection once weekly FTY720 capsules and their matching placebo were identical in appearance and were packed in identical bottles. Interferon β -1a IM and its matching placebo were packed and supplied in pre-filled syringes.

Randomised patients were assigned in a ratio of 1:1:1 in a double-dummy design to receive:

1. FTY720 0.5 mg orally once daily plus once-weekly IM interferon β -1a matching placebo

2. FTY720 1.25 mg orally once daily plus once-weekly IM interferon β -1a matching placebo

3. Interferon β -1a 30 μg IM once weekly plus once-daily oral FTY720 matching placebo

FTY720 study drug and matching FTY720 placebo were to be taken preferably at the same time every day, with or without food. Interferon β -1a (INFβ-1a) study drug and matching interferon β -1a placebo were to be injected IM once a week. Site personnel trained patients and caregivers on the correct procedure for administration of IM injections.

Study medications (FTY720, FTY720 matching placebo, interferon β -1a IM, and interferon β -1a IM matching placebo) were dispensed at the randomisation visit (Visit 3). The first dose of study drug (capsules and syringe injection) administered at Visit 3 were taken in the clinic before 12:00 PM (noon). After the first dose intake, the patient was monitored in the clinic for at least 6 hr or longer if discharge criteria were not met. Subsequent doses were taken at home.

Outcomes/endpoints

Definitions for MS relapses were the same as those in Study FTY720D2301.

Primary variable

The primary endpoint was the ARR, which is defined as the number of relapses in a year. Only confirmed relapses were considered for the primary analyses. This endpoint was chosen as primary endpoint because it measures MS disease activity over the duration of a year on treatment.

Key secondary variables

Two key secondary variables were tested:

- MRI key secondary efficacy endpoint: This endpoint determined the effect on inflammatory disease activity as measured by the number of new/newly enlarged T2 lesions at 12 months. This endpoint was chosen as a key secondary endpoint because it measured any new inflammatory activities detectable by MRI over the duration of a year on treatment.

- Disease progression key secondary efficacy endpoint: This endpoint determined the time to 3-month confirmed disability progression as measured by EDSS during 12 months. The effect on disability progression as measured by the time to 3-month confirmed disability progression as measured by EDSS was chosen as a key secondary endpoint because this measure indicates a sustained effect on disease progression.

Other efficacy variables

Other efficacy variables were defined as the following.

- All relapses (confirmed and unconfirmed)

- Proportion of relapse-free patients
- Proportion of patients with 3-month confirmed disability progression
- Time to confirmed disability progression sustained until last observation
- Time to severe disability (EDSS score ≥6.0)
- EDSS score
- MSFC z-score
- MSFC subscales
- Proportion of patients free of Gd-enhanced T1 lesions
- Proportion of patients free of new or newly enlarged T2 lesions at Month 12
- Number of Gd-enhanced T1 lesions
- Volume of Gd-enhanced T1 lesions
- Change and % change from baseline in volume of T2 lesions at 12 months
- Change and % change from baseline in volume of T1 hypointense lesions at 12 months
- Normalised brain volume at baseline and percent brain volume change from baseline at 12 months as measured using the structural image evaluation using normalization of atrophy (SIENA) method.

Determination of sample size

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

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

A simulation study confirmed that the sample size of 425 per group would provide an adequate power for the primary efficacy analysis using the negative binomial regression model and demonstrate robustness for the specified dropout rate.

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

1) Treatment comparison for FTY720 1.25 mg versus interferon β -1a IM on the number of new or newly enlarged T2 lesions at Month 12.

Based on historical data, it is reasonable to assume that the mean (SD) for the number of new or newly enlarged T2 lesions at Month 12 for the interferon β -1a IM group is 2.4 (4.1) (Rudick *et al* 2006). It was assumed that the FTY720 1.25 mg group would have an effect size of 25% on the number of new or newly enlarged T2 lesions at 12 Month versus interferon β -1a IM (the mean is

1.375 or 25% of 2.4). With the sample size of 368 patients completing the 12-month study, the power to detect a treatment difference for the FTY720 1.25 mg group versus the interferon β -1a IM group was 90% using a conservative Wilcoxon rank-sum test at a two-sided 0.05 significance level.

2) Treatment comparison for FTY720 1.25 mg versus interferon β -1a IM on the time to 3- month confirmed disability progression based on EDSS.

Based on historical data for interferon β -1a IM, it is reasonable to assume that 15% of patients in the interferon β -1a IM group would have 3-month confirmed disability progression. With 425 randomised patients and 57 dropout patients in each group (exponentially distributed), assuming the 12-month progression rate for the FTY720 group was 12% (a relative reduction of 20% from interferon β -1a IM), the power for detecting a treatment difference was 22% using a log-rank test at a two-sided 0.05 significance level. The above calculation was done using the commercial software nQuery version 5.0.

Blinding

Study medication assignments were blinded for the entire double-blind treatment phase and remained blinded until the data base lock and data analysis for the double-blind treatment phase had been completed. In order to maintain the blind, patients were instructed to cover injection sites (with a plaster or appropriate clothing to completely cover the injection sites) before all scheduled visits and relapse-related neurologic examinations and not to discuss AEs (for example, injection site reactions or flu-like symptoms) with the independent evaluating physician.

Patients, investigators, site personnel, independent evaluating physician, first dose administrator, and all Novartis personnel involved in the FTY720D2302 study, with the exception of Novartis DSM, Novartis independent statistician, and an independent programmer for the DSMB, remained blinded to the identity of the treatment from the time of randomisation of the first patient until data base lock. During this time period, treatment codes were accessible only to authorised personnel (DSM, DSMB members). Un-blinding only occurred in the case of patient emergencies and at the conclusion of the double-blind phase.

Statistical and analytical plans

The populations used for the analyses were similar to those defined for Study FTY720D2301.

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

FTY720 1.25 mg, ARR

FTY720 0.5 mg, ARR

FTY720 1.25 mg, the number of new and newly enlarged T2 lesions at 12 months

FTY720 0.5 mg, the number of new and newly enlarged T2 lesions at 12 months

FTY720 1.25 mg, disability progression

FTY720 0.5 mg, disability progression.

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

Primary efficacy variable

The primary variable was the ARR, which is defined as the number of relapses in a year. The ARR of the treatment group was calculated by taking the total number of confirmed relapses for all the patients in the treatment group divided by the total number of days on study for all patients in the

group and multiplied by 365.25 to obtain the annual rate. Only confirmed relapses were considered for the primary analyses.

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

Secondary efficacy variables

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

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

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

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

Cox proportional hazard model was used for the time to 3-month confirmed disability progression adjusting for treatment, country, and baseline EDSS and age. Hazard ratios and p-values for the Cox proportional hazard model were provided.

There were two treatment comparisons for the time to 3-month confirmed disability progression: 1.25 mg FTY720 versus IFNβ-1a IM and 0.5 mg FTY720 against IFNβ-1a IM. If disability progression did not occur by the 9 month visit, patients were censored for this endpoint since confirmation could not be obtained 3 months later within the planned 12 month study duration.

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

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

Participant flow

A total of 1573 patients were screened for participation in this study; of those, 1292 (82.1%) were randomised and the remaining 281 (17.9%) patients were screening failures. Patient disposition for the randomised population is presented in Table 37.

Of the 1292 patients who were randomised, 1153 (89.2%) completed the study (86.6% in the FTY720 1.25 mg group, 92.3% in the FTY720 0.5 mg group, and 88.7% in the interferon β-1a IM group). A total of 1123 (86.9%) completed the study on study drug (84.0% in the FTY720 1.25 mg group, 89.3% in the FTY720 0.5 mg group, and 87.4% in the interferon β-1a IM group). The most common reason for discontinuation of study drug overall was AEs (4.6% of all patients, 7.5% for FTY720 1.25 mg, 3.7% for FTY720 0.5 mg, and 2.8% for interferon β-1a IM), followed by withdrawal of consent (2.7% of all patients; 2.3% for FTY720 1.25 mg, 2.1% for FTY720 0.5 mg, and 3.7% for interferon β-1a IM). Of 157 patients who discontinued study drug, 30 patients

remained in the study and completed the abbreviated schedule of assessments through the Month 12 visit.

Table 34: Study FTY720D2302 - Patient disposition (Study phase completion) (Randomised population)

	FTY720 1.25mg N=426 n (%)	FTY720 0.5mg N=431 n (%)	Interferon beta-1a i.m. N=435 n (%)	Total N=1292 n (%)
Completed study	369 (86.6)	398 (92.3)	386 (88.7)	1153 (89.2)
On study drug*	358 (84.0)	385 (89.3)	380 (87.4)	1123 (86.9)
Off study drug**	11 (2.6)	13 (3.0)	6 (1.4)	30 (2.3)
Discontinued from the study	57 (13.4)	33 (7.7)	49 (11.3)	139 (10.8)
Adverse event(s)	26 (6.1)	9 (2.1)	9 (2.1)	44 (3.4)
Subject withdrew consent	11 (2.6)	9 (2.1)	16 (3.7)	36 (2.8)
Administrative problems	6 (1.4)	2 (0.5)	7 (1.6)	15 (1.2)
Unsatisfactory therapeutic effect	3 (0.7)	3 (0.7)	7 (1.6)	13 (1.0)
Abnormal laboratory value(s)	4 (0.9)	6 (1.4)	1 (0.2)	11 (0.9)
Abnormal test procedure result(s)	4 (0.9)	3 (0.7)	3 (0.7)	10 (0.8)
Lost to follow-up	1 (0.2)	1 (0.2)	4 (0.9)	6 (0.5)
Death	2 (0.5)	0	0	2 (0.2)
Protocol violation	0	0	2 (0.5)	2 (0.2)
Discontinued study drug	62 (14.6)	44 (10.2)	51 (11.7)	157 (12.2)
Adverse event(s)	32 (7.5)	16 (3.7)	12 (2.8)	60 (4.6)
Subject withdrew consent	10 (2.3)	9 (2.1)	16 (3.7)	35 (2.7)
Abnormal laboratory value(s)	8 (1.9)	7 (1.6)	3 (0.7)	18 (1.4)
Unsatisfactory therapeutic effect	5 (1.2)	5 (1.2)	7 (1.6)	17 (1.3)
Abnormal test procedure result(s)	3 (0.7)	4 (0.9)	4 (0.9)	11 (0.9)
Administrative problems	1 (0.2)	2 (0.5)	3 (0.7)	6 (0.5)
Lost to follow-up	1 (0.2)	0	4 (0.9)	5 (0.4)
Protocol violation	0	1 (0.2)	2 (0.5)	3 (0.2)
Death	1 (0.2)	0	0	1 (0.1)
Subject's condition no longer requires study drug	1 (0.2)	0	0	1 (0.1)

* 'On study drug': Patients who took study drug until the study completion.
** 'Off study drug': Patients who completed the study but discontinued study drug.
Note: The total number of patients who discontinued the study includes 12 patients who were randomized in error and never received study drug.
Note: This table displays the number of patients with the primary reason for discontinuation recorded as "adverse event;" tables in Section 12 display patients with AEs with outcome of "discontinuation of study drug" and therefore numbers can be expected to differ.
Note: 2 additional patients in the FTY720 1.25 mg treatment group died after data base lock: patients PID 254/00011 and PID 331/00011, further discussed in Section 12.3. The events occurred 3 and 6 months after data base lock, respectively, and therefore do not appear in the tables and listings but do appear in the patient narratives.

Recruitment

The study was conducted in 172 centres in 18 countries. The first patient was enrolled on 30 May 2006 and the last patient completed the study on 11 November 2008.

Conduct

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

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

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

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

In the data submitted for evaluation the sponsor sent an addendum to the clinical study report to correct (after data lock) the statistical analysis for key secondary endpoints and other related efficacy endpoints. The addendum was dated 22 November 2009. This addendum was sent in response to the identification by the sponsor that the variable new and newly enlarged T2 lesions was not counted and analysed according to the methods described in protocol.

The purpose of this addendum was to provide the analysis of the key secondary endpoint as described in the protocol-defined study objectives. The first key secondary objective of this study was to demonstrate superiority of FTY720 1.25 mg and 0.5 mg over interferon β -1a IM in patients with RRMS with respect to the effect on inflammatory disease activity as measured by the number of new or newly enlarged T2 lesions at Month 12 of treatment. This endpoint was chosen as a key secondary endpoint because T2 lesions reflect the result of new inflammatory activity as detected by MRI over a time interval, in this case the duration of one year on treatment.

After finalisation of the FTY720D2302 clinical study report (CSR), the Novartis Clinical Team became aware of two issues that affected the analysis of MRI data for the number of new or newly enlarged T2 lesions. The sponsor stated the issues as follows:

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

Issue 2: The definition of the number of new or newly enlarged T2 lesions at 12 months as intended by the FTY720D2302 protocol includes all new or newly enlarged T2 lesions as counted on the Month 12 MRI, irrespective of whether such lesions were also Gd-enhancing on T1 sequences. The presence of a corresponding Gd-enhanced T1 lesion at Month 12 does not alter the classification of a T2 lesion as new or newly enlarged. However, the evaluation of new or newly enlarged T2 lesions by the central MRI reader followed the “combined unique active lesion” approach. By using this analysis approach, new or newly enlarged T2 lesions observed at the Month 12 MRI were counted as “new or newly enlarged T2 lesions” if they were not associated with Gd-enhancement or as “Gd-enhanced T1 lesions” if there was evidence of any Gd-enhancement for the lesion. This approach underestimates the number of new or newly enlarged T2 lesions.

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

Therefore, to obtain the total number of new or newly enlarged T2 lesions at Month 12 as intended by the FTY720D2302 protocol, reflecting any new inflammatory activity detectable over the duration of a year of treatment, the result called “new or newly enlarged T2 lesions” currently in the database will be added to the result called “Gd-enhanced T1 lesions” currently in the database to

obtain the protocol intended “number of new or newly enlarged T2 lesions at Month 12”. The data to be used is the same raw data as previously included in the locked database. No changes have been made to the database since the original database lock.

The sponsor contended that the addendum to the FTY720D2302 CSR presents the analysis of the effect of FTY720 1.25 mg and 0.5 mg compared to interferon β -1a IM on the number of new or newly enlarged T2 lesions after up to 12 months based on the measurement of any new inflammatory activity detectable by MRI over the duration of a year of treatment as originally intended in the study protocol.

The sponsor stated that the following changes to the analyses were made after database lock:

a) Data from patients with follow-up Visits 501 or 603 were excluded from the analysis of the number of new or newly enlarged T2 lesions at Month 12.

b) The variable, the number of new or newly enlarged T2 lesions at Month 12, as intended by the FTY720D2302 protocol, is derived by adding the result called “new or newly enlarged T2 lesions” currently in the database to the result called “Gd-enhanced T1 lesions” currently in the database.

Evaluator’s comment: *The methods used in the addendum to assess this key secondary endpoint are questionable. The sponsor has not included the MRI data from 18 patients that prematurely discontinued (Issue 1). In relation to Issue 2, all new or newly enlarged T2 lesions were counted only if there was not Gd enhancement on T1 by the central MRI reader for the original analysis, but the lesions should have been counted as T2 lesions whether or not there was Gd enhancement. The sponsor proposed adding the T2 lesion variable with the Gd-enhanced variable to yield the new “T2 lesion variable”. They have directly added variables rather than reviewing the MRI scans or data collection sheets again and assigning lesions appropriately.*

The sponsor should go back to the MRIs or the data collection sheets and recount the lesions directly rather than adding the variables. In addition, it is suggested that data from the 18 patients without the 12 months MRI scans be included by using data from the last MRI scan obtained using the last observation carried forward method. It should be requested that this re-analysed data be submitted to the TGA when available. More accurate interpretation of this endpoint will be possible after the new analysis is submitted.

Data sets analysed

A summary of the study populations for analysis is presented by treatment group in Table 38.

Table 35: Study FTY720D2302 - Analysis populations by treatment group - n (%) of patients

Population	FTY720 1.25mg n (%)	FTY720 0.5mg n (%)	Interferon beta-1a i.m. n (%)	Total n (%)
Randomized population	426 (100.0)	431 (100.0)	435 (100.0)	1292 (100.0)
Intent-to-treat (ITT) population	420 (98.6)	429 (99.5)	431 (99.1)	1280 (99.1)
Per-protocol (PP) population	406 (95.3)	418 (97.0)	422 (97.0)	1246 (96.4)
Safety population	420 (98.6)	429 (99.5)	431 (99.1)	1280 (99.1)
Follow-up population	91 (21.4)	74 (17.2)	89 (20.5)	254 (19.7)

Baseline data

The demographic and background characteristics of patients are summarised by treatment in Table 39.

Table 39: Study FTY720D2302 - Demographic summary by treatment group (Randomised population)

		FTY720 1.25mg (N=426)	FTY720 0.5mg (N=431)	Interferon beta-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
Age group	<18	0	0	0	0
(years) n (%)	18-30	125 (29.3)	117 (27.1)	113 (26.0)	355 (27.5)
	31-40	160 (37.6)	150 (34.8)	185 (42.5)	495 (38.3)
	41-55	141 (33.1)	164 (38.1)	137 (31.5)	442 (34.2)
	>55	0	0	0	0
Sex n (%)	Male	133 (31.2)	149 (34.6)	140 (32.2)	422 (32.7)
	Female	293 (68.8)	282 (65.4)	295 (67.8)	870 (67.3)
Race n (%)	Caucasian	404 (94.8)	404 (93.7)	408 (93.8)	1216 (94.1)
	Black	6 (1.4)	4 (0.9)	6 (1.4)	16 (1.2)
	Asian	7 (1.6)	7 (1.6)	4 (0.9)	18 (1.4)
	Native American	1 (0.2)	1 (0.2)	1 (0.2)	3 (0.2)
	Other	8 (1.9)	15 (3.5)	16 (3.7)	39 (3.0)
Weight (kg)	Mean (SD)	71.17 (16.783)	71.50 (16.145)	71.46 (17.323)	71.38 (16.746)
	Median	69.00	69.00	69.00	69.00
	Range	42.0-130.0	37.0-126.5	43.0-139.7	37.0-139.7
Height (cm)	Mean (SD)	168.7 (9.11)	169.1 (9.95)	168.3 (9.00)	168.7 (9.36)
	Median	168.0	168.0	167.0	168.0
	Range	147 - 194	145 - 206	147 - 196	145 - 206
BMI (kg/m^2)	Mean (SD)	24.96 (5.105)	24.95 (4.702)	25.15 (5.392)	25.02 (5.072)
	Median	24.10	24.20	24.00	24.10
	Range	16.4- 52.1	16.4- 43.8	16.5- 51.9	16.4- 52.1

The groups were balanced for age, sex, and race. As expected in a population of RRMS patients, approximately two-thirds of patients were female (67.3% female versus 32.7% male) and the majority (94.1%) of patients in all groups were Caucasian. The median age was 36 years. Treatment groups were also balanced for demographic characteristics in the subsets of patients who underwent Holter monitoring, chest HRCT, or had patient reported outcomes measured with PRIMUS or mFIS.

The MS disease characteristics of patients at baseline are summarised by treatment group in Table 40.

Table 40: Study720D2302 - Clinical MS baseline characteristics by treatment group (Randomised population)

	FTY720 1.25mg N=426	FTY720 0.5mg N=431	Interferon beta-1a i.m. N=435	Total N=1292
Duration of MS since first symptom (years)				
n	420	429	431	1280
Mean (SD)	7.3 (5.96)	7.5 (6.20)	7.4 (6.33)	7.4 (6.16)
Median	6.0	5.8	5.8	5.9
Range	0 - 33	0 - 34	0 – 40*	0 - 40*
Number of relapses in the last year				
n	425	431	435	1291
Mean (SD)	1.5 (0.87)	1.5 (1.19)	1.5 (0.79)	1.5 (0.97)
Median	1.0	1.0	1.0	1.0
Range	0 - 7	0 - 20*	0 - 6	0 – 20*
Number of relapses in the last 2 years				
n	425	431	434	1290
Mean (SD)	2.2 (1.19)	2.3 (2.20)	2.3 (1.22)	2.2 (1.61)
Median	2.0	2.0	2.0	2.0
Range	1 - 8	1 – 40*	1 - 12	1 - 40
EDSS				
n	420	429	431	1280
Mean (SD)	2.21 (1.311)	2.24 (1.326)	2.19 (1.261)	2.21 (1.299)
Median	2.00	2.00	2.00	2.00
Range	0.0 - 5.5	0.0 - 5.5	0.0 - 5.5	0.0 - 5.5
MSFC z-score				
n	416	424	423	1263
Mean (SD)	-0.006 (0.7272)	0.007 (0.6327)	0.005 (0.6159)	0.002 (0.6595)
Median	0.106	0.159	0.128	0.124
Range	-5.35 – 2.04	-5.23 – 1.19	-2.81 – 2.51	-5.35 – 2.51
MSFC subscale: 25-foot timed walking test (seconds)				
n	420	427	428	1275
Mean (SD)	7.20 (10.690)	6.71 (7.499)	6.47 (5.736)	6.79 (8.216)
Median	5.00	5.15	5.00	5.05
Range	2.9 - 126.0	2.3 - 121.0	2.7 - 55.0	2.3 - 126.0
MSFC subscale: 9-hole peg test (seconds)				
n	420	426	428	1274
Mean (SD)	22.58 (14.344)	22.34 (10.091)	21.98 (7.992)	22.30 (11.100)
Median	20.10	20.03	20.00	20.04
Range	8.8 - 196.8	11.0 - 120.5	4.8 - 101.0	4.8 - 196.8
MSFC subscale: PASAT-3 (number of correct answers)				
n	416	424	424	1264
Mean (SD)	47.9 (11.15)	48.3 (11.09)	47.7 (11.94)	48.0 (11.39)
Median	51.0	51.0	52.0	52.0
Range	2 - 60	0 - 60	0 - 60	0 - 60

* The investigator confirmed that patient PID 447/00003 in the FTY720 0.5 mg group reported 20 relapses in the past year and 40 relapses in the past 2 years.

Across all treatment groups the mean (SD) duration of MS since first symptoms was 7.4 (6.16) years (median 5.9 years) with an average of 2.2 relapses in the previous 2 years, 1.5 relapses in the previous year, and a mean baseline EDSS score of 2.21. Overall, the groups were balanced for all MS disease baseline characteristics. However, the proportion of patients with EDSS 5.5 at baseline was highest in the FTY720 1.25 mg group (14/420, 3.33%) compared to 11/429 (2.56%) for the FTY720 0.5 mg group and 6/431 (1.39%) for the interferon β-1a IM group.

MRI characteristics for patients at baseline are summarised by treatment group in Table 41. The mean number of Gd-enhanced T1-weighted lesions at baseline was slightly higher in the FTY720

1.25 mg group (1.49) than in the FTY720 0.5 mg group (0.98) and the interferon β -1a IM group (1.06), but the difference (versus the INF beta-1a IM group) was not statistically significant (p=0.068). The total volume of T2 lesions, as well as all other baseline MRI characteristics, was comparable among treatment groups.

Table 41: Study FTY720D2302 - MRI baseline characteristics by treatment group (Randomised population)

	FTY720 1.25mg N=426	FTY720 0.5mg N=431	Interferon beta-1a i.m. N=435	Total N=1292
Proportion of patients free of Gd-enhanced T1 lesions n (%)				
n	412	427	425	1264
	270 (65.5)	288 (67.4)	268 (63.1)	826 (65.3)
Number of Gd-enhanced T1 lesions				
n	412	427	425	1264
Mean (SD)	1.5 (4.77)	1.0 (2.81)	1.1 (2.80)	1.2 (3.57)
Median	0.00	0.00	0.00	0.00
Range	0.0 - 66	0.0 - 29	0.0 - 36	0.0 - 66
Volume of Gd-enhanced T1 lesions (mm^3)				
n	412	427	425	1264
Mean (SD)	147.5 (667.21)	93.9 (288.05)	100.7 (263.55)	113.7 (443.54)
Median	0.0	0.0	0.0	0.0
Range	0 - 11507	0 - 3250	0 - 2609	0 - 11507
Total volume of T2 lesions (mm^3)				
n	413	428	425	1266
Mean (SD)	5085.4 (5962.05)	5169.6 (6641.97)	4923.6 (5710.90)	5059.5 (6116.41)
Median	3095.9	2381.8	2901.1	2786.6
Range	0 - 38870	0 - 46280	0 - 38712	0 - 46280
Total volume of T1 hypointense lesions (mm^3)				
n	413	428	425	1266
Mean (SD)	1386.7 (2298.52)	1620.4 (3107.07)	1404.2 (2357.82)	1471.6 (2618.03)
Median	454.9	444.9	420.6	439.2
Range	0 - 20399	0 - 30610	0 - 19561	0 - 30610
Normalized brain volume (cc)				
n	409	421	420	1250
Mean (SD)	1526.2 (76.37)	1524.1 (83.88)	1526.7 (77.93)	1525.7 (79.43)
Median	1527.8	1526.2	1533.3	1529.5
Range	1300 - 1794	1185 - 1862	1231 - 1762	1185 - 1862

n=number of patients with an evaluable MRI scan at baseline

A summary of MS medications used at any time prior to the start of study drug treatment is presented by treatment group in Table 42.

Table 42: Study FTYD2302 - MS medication history of approved disease-modifying drugs (Randomised population)

	FTY720 1.25mg (N=426) n (%)	FTY720 0.5mg (N=431) n (%)	Interferon beta-1a i.m. (N=435) n (%)	Total (N=1292) n (%)
Treatment-naïve patients*	177 (41.5)	193 (44.8)	190 (43.7)	560 (43.3)
Previously treated patients	249 (58.5)	238 (55.2)	245 (56.3)	732 (56.7)
Any interferon beta	209 (49.1)	219 (50.8)	207 (47.6)	635 (49.1)
Interferon beta 1a i.m.	118 (27.7)	119 (27.6)	118 (27.1)	355 (27.5)
Interferon beta 1a s.c.	79 (18.5)	89 (20.6)	72 (16.6)	240 (18.6)
Interferon beta 1b s.c.	57 (13.4)	59 (13.7)	69 (15.9)	185 (14.3)
Glatiramer acetate	67 (15.7)	57 (13.2)	67 (15.4)	191 (14.8)
Natalizumab	3 (0.7)	4 (0.9)	1 (0.2)	8 (0.6)

* Treatment-naïve patients are defined as those not receiving any of the approved 5 MS disease-modifying drugs listed above (Section 9.7.1.1.3).

About 40-45% of the patients were treatment-naïve. There was a slightly higher proportion of previously-treated patients in the FTY720 1.25 mg group than in the other two treatment groups. Approximately one third of these patients had received treatment with 2 or more MS disease-modifying drugs.

Patients who were receiving MS medications prior to the start of study drug treatment were allowed to enter the study without a washout period. A summary of the time since last dose of interferon-β and glatiramer acetate is presented by treatment group in Table 43.

Table 43: Study FTY720D2302 - Time since last dose of first-line approved MS disease-modifying drug (Randomised population)

	FTY720 1.25mg (N=426) n (%)	FTY720 0.5mg (N=431) n (%)	Interferon beta-1a i.m. (N=435) n (%)	Total (N=1292) n (%)
Interferon beta 1a i.m., n	118	119	118	355
≤3 months, n (%)	88 (74.6)	88 (74.0)	77 (65.2)	253 (71.3)
>3 months, n (%)	28 (23.7)	31 (26.0)	39 (33.0)	98 (27.6)
Missing, n (%)	2 (1.7)	0	1 (0.8)	3 (0.8)
Interferon beta 1a s.c., n	79	89	72	240
≤3 months, n (%)	40 (50.6)	55 (61.8)	34 (47.2)	129 (53.7)
>3 months, n (%)	37 (46.8)	34 (38.2)	37 (51.4)	108 (45.0)
Missing, n (%)	2 (2.5)	0	1 (1.4)	3 (1.3)
Interferon beta 1b s.c., n	57	59	69	185
≤3 months, n (%)	26 (45.6)	28 (47.5)	32 (46.4)	86 (46.5)
>3 months, n (%)	31 (54.4)	30 (50.8)	37 (53.6)	98 (53.0)
Missing, n (%)	0	1 (1.7)	0	1 (0.5)
Glatiramer acetate, n	67	57	67	191
≤3 months, n (%)	26 (38.8)	20 (35.1)	38 (56.7)	84 (44.0)
>3 months, n (%)	41 (61.2)	36 (63.2)	28 (41.8)	105 (55.0)
Missing, n (%)	0	1 (1.8)	1 (1.5)	2 (1.0)

Percentages in the table are calculated by using the total number of patients who used that medication as the denominator.

Of the 732 patients who were previously treated with at least one MS disease-modifying drug, 552 patients were still receiving an MS disease-modifying drug within the 3 months prior to the start of study drug treatment. Approximately one third of the patients randomised to receive INF beta-1a IM were already been receiving a form of interferon β within the 3 months prior to the start of study drug treatment.

The most commonly reported medical history and continuing medical conditions at baseline were nervous system disorders (57.5% of all patients), followed by psychiatric disorders (24.4% of all patients), with depression (13.8% of all patients) as the most common condition within this category, and infections and infestations (23.5% of all patients). Medical history did not show clinically relevant differences between treatment groups.

At screening, MS symptoms prior to randomisation were listed by the investigator. The most commonly reported MS symptoms present prior to randomisation in all patients were sensory symptoms (50.1%), followed by "other" (41.6%, most commonly fatigue), motor (39.8%), brainstem (30.0%), and coordination symptoms (25.6%). The most frequently reported individual symptoms (≥30% of all patients) were fatigue (38.9%), numbness (31.1%), lower limb weakness (30.3%) and paresthaesias (30.0%).

Symptoms were predominantly mild or moderate in severity and occurred in comparable proportions of patients across treatment. The most frequently reported severe symptoms in ≥2.0% of all patients were fatigue (2.9%), blurred vision (2.1%) and heat intolerance (2.0%).

There were no relevant differences in eye history among treatment groups. History of optic neuritis was most commonly reported, affecting 40.1% of all patients. A history of uveitis was reported in 1.2% of patients. Among the 1573 patients screened, 9 were found to have macular oedema at screening; these patients were excluded from the study, with the exception of one patient (who was diagnosed with bilateral macular oedema during the screening, randomised to FTY720 0.5 mg, and then requested to discontinue study drug after 11 days). Although macular oedema can appear as complication of MS-related uveitis (Towler & Lightman 2000), and therefore cases of macular oedema are not unexpected in the MS population, no patients reported as having a history of macular oedema were included in the study.

There were no relevant differences between treatment groups for pulmonary history. Overall, 27.6% of all patients were active smokers, 3.0% reported a history of asthma, 0.5% reported a history of chronic obstructive pulmonary disease (COPD), and 2.2% reported history of other respiratory disorders.

Outcomes

Primary efficacy results

The primary efficacy objective was to compare FTY720 1.25 mg and FTY720 0.5 mg with interferon β -1a IM and to evaluate if at least FTY720 1.25 mg was superior to interferon β -1a IM in terms of ARR for patients with RRMS treated for up to 12 months. The results for the primary efficacy analysis (aggregate ARR analysed using negative binomial regression) are shown in Table 44.

Table 44: Study FTY720D2302 - Aggregate annualised relapse rate (ARR) up to Month 12 (confirmed relapses) (ITT population)

	FTY720 1.25mg N=420	FTY720 0.5mg N=429	Interferon beta-1a i.m. N=431
Number of relapses	105	89	179
Time on study (days)	147663	155100	151844
Aggregate ARR	0.26	0.21	0.43
ARR estimate	0.203	0.161	0.331
(95% CI)	(0.157,0.264)	(0.122,0.212)	(0.262,0.417)
ARR ratio for treatment comparison of FTY720 vs. Interferon beta-1a i.m.	0.617	0.484	–
P-value for treatment comparison of FTY720 vs. interferon beta-1a i.m.	<0.001*	<0.001*	–

ARR estimate (95% CI), ARR ratio, p-value are calculated using negative binomial regression adjusted by treatment, country, number of relapses in the previous 2 years, and baseline EDSS.
Log(time of study) is the offset variable.
* Indicates two-sided statistical significance at 0.05 level.

Treatment with both FTY720 1.25 mg and FTY720 0.5 mg resulted in a significantly lower ARR compared to treatment with IFNβ-1a IM, with ARR estimates of 0.20 and 0.16 versus 0.33, respectively. This corresponded to reductions of 38% and 52% in ARR estimates, respectively, which were highly statistically significant ($p<0.001$ for both comparisons).

Results for the two types of supportive analyses performed for the primary endpoint in the comparison of FTY720 1.25 mg versus interferon β -1a IM and FTY720 0.5 mg versus Interferon β -1a IM were as follows:

1. The ARRs based on confirmed relapses for the PP population were consistent with the results observed for the ITT population. Both the FTY720 1.25 mg and FTY720 0.5 mg treatment groups experienced a significantly lower ARR compared to interferon β -1a IM with ARR estimates of 0.21, 0.17 and 0.35, respectively, with $p<0.001$ for both comparisons. This corresponded to a 40% and 53% reduction for FTY720 1.25 mg and FTY720 0.5 mg compared to interferon β -1a IM, respectively.

2. The patient-level ARRs (confirmed relapses with imputation) for the ITT population were consistent with the results observed for the aggregate ARR estimates in both the ITT and PP populations. Both the FTY720 1.25 mg and FTY720 0.5 mg treatment groups experienced a significantly lower patient-level ARR compared to IFNβ-1a IM: 0.26 for FTY720 1.25 mg, 0.21 for FTY720 0.5 mg, and 0.43 for IFNβ-1a IM, with $p\leq0.001$ (Rank ANCOVA) for both comparisons to interferon β -1a IM

Evaluator's comments: *The primary analyses for the study support a treatment effect of FTY720 over control on the ARR in RRMS. These results are consistent with results observed in Study FTY720D2301. In both studies the relapse rates recorded for both FTY720 treatment groups are lower than what has been documented with other approved therapies for RRMS.*

Key secondary efficacy endpoints

Key secondary efficacy endpoints were:

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

2. New or newly enlarged T2 lesions up to Month 12

The number of new or newly enlarged T2 lesions at Month 12 was compared between the treatment groups using a negative binomial regression model adjusting for the same covariates used in the

primary efficacy analysis (treatment, country, baseline number of relapses in the previous 2 years and baseline EDSS), and the results are shown in Table 45.

Table 45: Study FTY720D2302 - Number of new or newly enlarged T2 lesions at Month 12 (ITT population)

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

n=the number of patients with evaluable MRI at baseline and Month 12
P-value is calculated using a negative binomial model adjusting for treatment, country, baseline number of relapses in the previous 2 years, and baseline EDSS.
* Indicates two-sided statistical significance at 0.05 level.
** Eighteen patients were excluded from analysis because the Month 12 T2 MRI was not compared to the Screening MRI.
# Calculated by adding the number of new or newly enlarged T2 lesions and the number of Gd-enhanced T1 lesions (both as recorded in the database) observed on the Month 12 MRI.

For the ITT population both the FTY720 1.25 mg and FTY720 0.5 mg treatment groups had a lower mean number of new or newly enlarged T2 lesions at Month 12 compared to the interferon β -1a IM group, which reached statistical significance for both the FTY720 1.25 mg group (p<0.001) and the FTY720 0.5 mg group (p=0.004). Statistical significance was also observed for the FTY720 1.25 mg group (p=0.017) and the FTY720 0.5 mg group (p=0.041) compared to the interferon β -1a IM group when using the same analysis approach as described in the CSR with the exclusion of data from the 18 patients with invalid values for new or newly enlarged T2 lesions.

For the PP population, both the FTY720 1.25 mg and FTY720 0.5 mg treatment groups had a lower mean number of new or newly enlarged T2 lesions at Month 12 compared to the interferon β -1a IM group, which reached statistical significance for both the FTY720 1.25 mg group (p=0.004) and the FTY720 0.5 mg group (p=0.005). Similar findings were observed but did not reach statistical significance when using the same analysis approach as described in the CSR with the exclusion of data from the 18 patients with invalid values for new or newly enlarged T2 lesions.

Other secondary efficacy endpoints

Comparisons between FTY720 1.25 mg and FTY720 0.5 mg treatment group

There was no statistically significant difference in the mean number of new or newly enlarged T2 lesions between the FTY720 1.25 mg and the FTY720 0.5 mg treatment groups (p=0.619 p=0.662) for the ITT population. Results for the PP population were similar.

Other MRI endpoints

Inflammatory disease activity as measured by MRI

Inflammatory activity based on MRI at Month 12 is summarised in Table 46.

Table 46: Study FTY720D2302 - Inflammatory activity on MRI at Month 12 (ITT population)

	FTY720 1.25mg N=420	FTY720 0.5mg N=429	Interferon beta-1a i.m. N=431
...			
As Intended per Protocol			
Patients with evaluable T2-weighted MRI at baseline and Month 12**	350	372	361
Number (%) of patients free of new/newly enlarged T2 lesions#	168 (48.0)	204 (54.8)	165 (45.7)
P-value for treatment comparison of FTY720 vs. interferon beta-1a i.m.	0.372	0.010	–
As analyzed by MRI Central reader			
Patients with evaluable T2-weighted MRI at baseline and Month 12**	350	372	361
Number (%) of patients free of new/newly enlarged T2 lesions	172 (49.1)	209 (56.2)	177 (49.0)
P-value for treatment comparison of FTY720 vs. interferon beta-1a i.m.	0.776	0.032	–

* Any Gd-enhanced T1 data obtained less than 30 days after the steroid used to treat MS relapses were excluded from the analysis.

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

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

The proportion of patients free of new or newly enlarged T2 lesions at Month 12 was higher in the FTY720 0.5 mg group (54.8%) compared to the FTY720 1.25 mg (48.0%) and interferon β -1a IM treatment groups (45.7%), and was statistically significant for the FTY720 0.5 mg group versus the interferon β -1a IM group (p=0.010). Statistical significance was also observed for the FTY720 0.5 mg group (p=0.032) compared to the interferon β -1a IM group when using the same analysis approach as described in the CSR with the exclusion of data from the 18 patients with invalid values for new or newly enlarged T2 lesions.

Time to 3-month confirmed disability progression at Month 12

The proportion of patients free of 3-month confirmed disability progression at Month 12 is shown in Table 47. There was no difference between the two FTY720 treatment groups and the interferon β -1a IM group in the time to 3-month confirmed disability progression as based on Kaplan-Meier estimates for the ITT population. Results for the PP population were similar.

Evaluator's comment: *In contrast to results from Study FTY720D2301, this second pivotal efficacy trial did not provide substantiation of a delay in time to 3- month confirmed disability progression on FTY720* versus *control as was seen in trial D2301.*

Table 47: Study FTY720D2302 - Proportion of patients free of disability progression at Month 12 (ITT population)

	FTY720 1.25mg N=420	FTY720 0.5mg N=429	Interferon beta-1a i.m. N=431
Kaplan–Meier estimate (SE) of % free of disability progression at Month 12 (360 days)	93.3 (1.24)	94.1 (1.15)	92.1 (1.33)
95% CI	(90.92, 95.77)	(91.82, 96.33)	(89.45, 94.66)
Treatment comparison of FTY720 vs. interferon beta-1a i.m.			
Difference of Kaplan–Meier estimates (95% CI)	1.30 (-2.26,4.86)	2.03 (-1.42,5.47)	–
P-value (Log-rank test)	0.498	0.247	–

SE=standard error
P-value from Log-rank test is used to compare the survival distributions between treatment groups.
* Indicates two-sided statistical significance at 0.05 level.

Annualised relapse rates by subgroups

For all subgroups except EDSS ≥5.5 at baseline, lower aggregate ARRs were observed for the FTY720 treatment groups compared to the interferon β -1a IM group. The subgroup of patients with EDSS ≥5.5 at baseline was small (31 patients), and imbalances across treatment groups were noted at baseline.

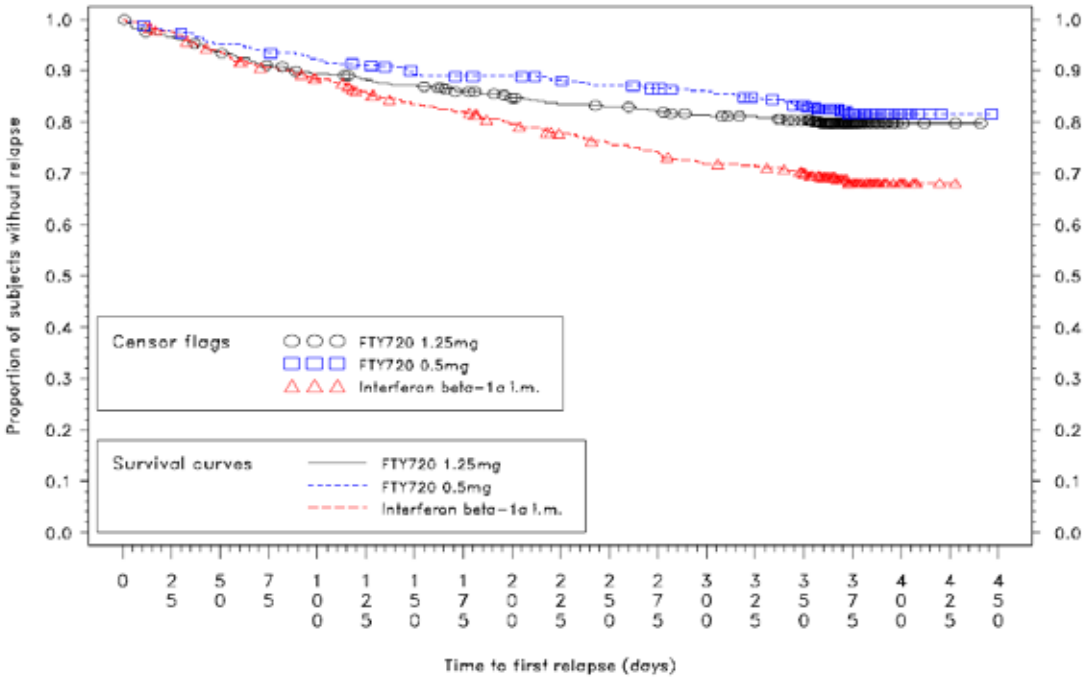
In the two FTY720 treatment groups, the ARRs were similar for men and women and for younger (≤37 years) and older (>37 years) patients, whereas for the interferon β -1a IM treatment group, women and younger patients had higher ARRs than males and older patients in the same treatment group. In all groups, previously treated patients showed higher ARRs than treatment-naïve patients; and patients with higher inflammatory activity at baseline (by MRI or number of relapses in the last two years) or higher EDSS at baseline tended to show higher ARRs during the study.

Time to first confirmed relapse

Time to first confirmed relapse is presented in Figure 20 below. The proportion of patients who were relapse-free at Month 12 was higher in the FTY720 treatment groups (79.8% for FTY720 1.25 mg and 82.6% for FTY720 0.5 mg treatment groups) compared to the interferon β -1a IM group (69.3%) (Log-rank test p<0.001 for both FTY720 treatment groups). There was no statistically significant difference between the FTY720 treatment groups (Log-rank test p=0.322).

The time to second confirmed relapse was also prolonged in both FTY720 treatment groups compared to the interferon β -1a IM group. Based on the Kaplan-Meier estimate for time to second confirmed relapse, the proportion of patients without a second relapse at Month 12 was 94.8% in the FTY720 1.25 mg group, 97.1% in the FTY720 0.5 mg group and 90.8% in the interferon β -1a IM group. Comparisons to the interferon β -1a IM group reached statistical significance for both FTY720 treatment groups (Log-rank test, p=0.022 for FTY720 1.25 mg and p<0.001 for FTY720 0.5 mg). There was no statistically significant difference between the FTY720 1.25 mg and FTY720 0.5 mg treatment groups (p=0.082).

Figure 20: Study FTY720D2302 - Kaplan-Meier plot for time to first confirmed relapse (ITT population)



Characteristics of MS relapses

The majority of all relapses were characterised as mild or moderate. Consistent with the results of ARR, fewer relapses were observed for the two FTY720 treatment groups than in the interferon β -1a IM group. The reduction effect on relapses seen for both FTY720 groups versus the interferon β -1a IM group was independent of the severity of the relapses, as the same amount of reduction was observed for mild, moderate and severe relapses. The absolute number of severe relapses in the FTY720 treatment groups was approximately half the number observed for the interferon β -1a IM group.

Based on all confirmed relapses, the proportion of relapses classified as severe based on EDSS was lower in the FTY720 0.5 mg group (11.2%) compared to the FTY720 1.25 mg (16.2%) and interferon β -1a IM (16.8%) treatment groups. There was a higher proportion of confirmed relapses classified as mild in both FTY720 treatment groups compared to the interferon β -1a IM group. There was no statistical significant difference in the distribution of the severity of confirmed relapses among treatment groups.

Disability-related parameters

There was no statistically significant difference in the proportion of patients with 3-month confirmed disability progression as measured by EDSS among the three treatment groups for the ITT population.

Based on the Kaplan-Meier estimate, the proportion of patients meeting this endpoint was comparable across the treatment groups: 4.8% for the FTY720 1.25 mg group, 5.4% for the FTY720 0.5 mg group and 5.8% for the interferon β -1a IM group. There was no statistically significant difference in the time to 3-month confirmed disability progression sustained until last observation as measured by EDSS among the three treatment groups for the ITT population.

Based on the Kaplan-Meier estimates of time to severe disability, the proportion of patients with severe disability was 3.8% (16/420) in the FTY720 1.25 mg group, 2.6% (11/429) in the FTY720 0.5 mg group and 1.6% (7/431) in the interferon β -1a IM treatment group. Treatment comparisons indicated that the proportion of patients with severe disability was significantly higher in the

FTY720 1.25 mg group than in the interferon β -1a IM group (p=0.048), but that the difference between the FTY720 0.5 mg group and the interferon β -1a IM treatment group was not significant.

EDSS score

Change from baseline in EDSS score at Month 12 is presented in Table 48.

Table 48: Study FTY720D2302 - Change from baseline in EDSS at Month 12 (ITT population)

	FTY720 1.25mg N=420	FTY720 0.5mg N=429	Interferon beta-1a i.m. N=431
n	369	394	377
Mean (SD)	-0.11 (0.897)	-0.08 (0.794)	0.01 (0.783)
Median	0.00	0.00	0.00
Range	-3.0 - 5.0	-3.0 - 2.5	-2.0 - 3.0
P-value for treatment comparison of FTY720 vs. interferon beta-1a i.m.	0.016*	0.059	–

n = the number of patients who had EDSS values at both baseline and Month 12.
P-value is calculated using Wilcoxon rank sum test.
* Indicates two-sided statistical significance at 0.05 level.

There was a statistically significant difference in the mean change in the EDSS score at Month 12 compared to baseline for the FTY720 1.25 mg group versus the interferon β -1a IM group (p=0.016) with a mean improvement of 0.11 points in the FTY720 1.25 mg group. A similar trend was observed in the FTY720 0.5 mg group compared to the interferon β -1a IM group, which did not reach statistical significance (p=0.059). The improvement in EDSS score for both FTY720 treatment groups was apparent from Month 3 onwards and consistently observed at the Month 3, 6, 9 and 12 visits.

Evaluator's comment*: Data from this study showed that there was a nominally significant change from baseline in the EDSS score at Month 12 for the FTY 1.25 mg treatment group, however not for the FTY 0.5 mg treatment group* versus *active control. This is in contrast to the results from the other pivotal study (FTY720D2301).*

MSFC z-score and subscales

The change from baseline at Month 12 in the MSFC z-score and subscale scores are summarised in Table 49 below.

Table 49: Study FTY720D2302- Change from baseline in MSFC at Month 12 (ITT population)

	FTY720 1.25mg N=420	FTY720 0.5mg N=429	Interferon beta-1a i.m. N=431
MSFC z-score			
n	359	383	366
Mean (SD)	0.08 (0.463)	0.04 (0.418)	-0.03 (0.478)
P-value for treatment comparison of FTY720 vs. interferon beta-1a i.m.	<0.001*	0.024*	–
MSFC subscale: 25-foot timed walking test (seconds)			
n	363	389	371
Mean (SD)	-0.71 (7.611)	-0.08 (7.259)	-0.05 (6.252)
P-value for treatment comparison of FTY720 vs. interferon beta-1a i.m.	0.243	0.898	–
MSFC subscale: 9-hole peg test (seconds)			
n	366	389	371
Mean (SD)	-1.53 (13.530)	-0.79 (7.846)	0.17 (3.813)
P-value for treatment comparison of FTY720 vs. interferon beta-1a i.m.	0.053	0.302	–
MSFC subscale: PASAT-3 (number of correct answers)			
n	362	385	370
Mean (SD)	1.56 (6.548)	1.51 (6.386)	0.47 (7.161)
P-value for treatment comparison of FTY720 vs. interferon beta-1a i.m.	0.012*	0.025*	–

n = the number of patients who had MSFC values at both baseline and Month 12.
P-value is calculated using Wilcoxon rank sum test.
* Indicates two-sided statistical significance at 0.05 level

There was a statistically significant difference in the mean change from baseline in the MSFC z-score at Month 12 with improvement for both FTY720 treatment groups compared to the interferon β -1a IM group: p<0.001 for the FTY720 1.25 mg group and p=0.024 for the FTY720 0.5 mg treatment group. The improvement in MSFC z-score for both FTY720 treatment groups was apparent from Month 6 onwards and consistently observed at the Month 6 and 12 visits. There was a trend for improvement in the FTY720 1.25 mg group compared to interferon β -1a IM for the mean change in seconds from baseline at Month 12 in the 9-hole peg test (p=0.053). The improvement for the FTY720 1.25 mg treatment group was apparent from Month 6 onwards and consistently observed at the Month 6 and 12 visits. There was a statistically significant difference in the mean change from baseline in the number of correct answers on the PASAT- 3 at Month 12 with a greater improvement in scores for both FTY720 groups compared to interferon β -1a IM (p=0.012 for the FTY720 1.25 mg group and p=0.025 for the FTY720 0.5 mg treatment group). No statistically significant differences were observed among the treatment groups for the 25-foot timed walking test.

Other MRI endpoints

Inflammatory disease activity as measured by MRI

Inflammatory activity based on MRI at Month 12 is summarised in Table 50.

Table 50: Study FTY720D2302 - Inflammatory activity on MRI at Month 12 (ITT population)

	FTY720 1.25mg N=420	FTY720 0.5mg N=429	Interferon beta-1a i.m. N=431
Patients with evaluable Gd-enhanced T1-weighted MRI at Month 12	352	374	354
Number (%) of patients free of Gd-enhanced T1 lesions*	321 (91.2)	337 (90.1)	286 (80.8)
P-value for treatment comparison of FTY720 vs. interferon beta-1a i.m.	<0.001	<0.001	–
Number of Gd-enhanced T1 lesions*			
Mean (SD)	0.14 (0.575)	0.23 (0.970)	0.51 (1.856)
Median	0.00	0.00	0.00
Range	0.0 - 6.0	0.0 - 11.0	0.0 - 24.0
P-value for treatment comparison of FTY720 vs. interferon beta-1a i.m.	<0.001	<0.001	–
Total volume of Gd-enhanced T1 lesions (mm^3)*			
Mean (SD)	19.54 (109.095)	22.61 (111.591)	50.68 (198.158)
Median	0.00	0.00	0.00
Range	0.0 - 1442.3	0.0 - 1359.0	0.0 - 2237.5
P-value for treatment comparison of FTY720 vs. interferon beta-1a i.m.	<0.001	<0.001	–
Patients with evaluable T2-weighted MRI at baseline and Month 12	356	380	365
Number (%) of patients free of new/newly enlarged T2 lesions	177 (49.7)	211 (55.5)	180 (49.3)
P-value for treatment comparison of FTY720 vs. interferon beta-1a i.m.	0.729	0.058	–
Patients with evaluable Gd-enhanced T1-weighted* at Month 12 and T2-weighted MRI at baseline and Month 12	352	374	354
Number (%) of patients free of new MRI activity (Gd+ lesions and new/newly enlarged T2 lesions)	169 (48.0)	202 (54.0)	163 (46.0)
P-value for treatment comparison of FTY720 vs. interferon beta-1a i.m.	0.361	0.018	–

* Any Gd-enhanced T1 data obtained less than 30 days after the steroid used to treat MS relapses were excluded from the analysis.

A statistically significantly greater proportion of patients in both FTY720 treatment groups was free of Gd-enhanced T1 lesions at Month 12 compared to the interferon β-1a IM group (91.2% for FTY720 1.25 mg, 90.1% for FTY720 0.5 mg, and 80.8% for interferon β-1a IM treatment groups) with p-values <0.001 for both FTY720 groups compared to interferon β-1a IM The mean number and mean volume of Gd-enhanced T1 lesions at Month 12 were also statistically significantly lower in the FTY720 treatment groups compared to the interferon β-1a IM group (p<0.001).

The proportion of patients free of new or newly enlarged T2 lesions at Month 12 was higher in the FTY720 0.5 mg group (55.5%) compared to the FTY720 1.25 mg (49.7%) and interferon β-1a IM treatment groups (49.3%), but statistical significance was not reached for the FTY720 0.5 mg group versus the interferon β-1a IM group (p=0.058).

The proportion of patients free of new MRI activity at Month 12 was higher in the FTY720 treatment groups (48% for the FTY720 1.25 mg and 54% for the FTY720 0.5 mg treatment groups) compared to the interferon β-1a IM group (46%), which reached statistical significance for the FTY720 0.5 mg group versus the interferon β -1a IM group (p=0.018).

Brain volume change

Brain volume change as measured by the SIENA method is summarised by treatment in Table 51.

Table 51: Study FTY720D2302 - Percent brain volume change from Month 0 to Month 12 (ITT population)

	FTY720 1.25mg N=420	FTY720 0.5mg N=429	Interferon beta-1a i.m. N=431
n	345	368	359
Mean (SD)	-0.297 (0.6494)	-0.307 (0.6450)	-0.453 (0.7272)
Median	-0.200	-0.200	-0.400
Range	-2.90 - 2.20	-3.70 - 2.00	-3.40 - 2.60
P-value for treatment comparison of FTY720 vs. interferon beta-1a i.m.	<0.001*	<0.001*	–

n = the number of patients who had evaluable SIENA assessments at both baseline and Month 12.
P-value is calculated using Wilcoxon rank sum test.
* Indicates two-sided statistical significance at 0.05 level.

There was statistically significantly lower reduction in the brain volume in the FTY720 treatment groups versus the interferon β-1a IM group at Month 12 compared to baseline, with p<0.001 (Wilcoxon rank-sum test) for both FTY720 treatment groups.

Other efficacy topics: patient reported outcome assessments

Mean changes from baseline in PRIMUS-QoL scores were not statistically significantly different among the three treatment groups at Month 12.

Mean change from baseline in EQ-5D utility scores were not statistically significantly different among the three treatment groups at Month 12. For all three treatment groups, changes from baseline in EQ-5D Visual Analog Scale score at Month 12 were small (0.6 to 1.9) and not statistically significantly different among the three treatment groups.

Clinical studies in special populations

Not applicable.

Analysis performed across trials (pooled analyses and meta-analysis)

Data from studies D2301 and D2302 were pooled for analyses of the primary efficacy endpoint, the ARR, specifically for subgroups. Otherwise no pooling of data across studies was performed.

The pooled analysis showed a statistically significant reduction in aggregate ARR for both FTY720 doses compared to placebo in all subgroups of patients by age or gender (pooled ITT population). In line with previously published data, younger MS patients tend to have higher ARR than older patients. Treatment with both doses of FTY720 results in similar ARRs observed in younger versus older patients as well as in females versus males.

Both doses of FTY720 showed a statistically significant reduction in aggregate ARR compared to placebo or IFN β-1a IM in both treatment-naïve and previously treated patients.

Supportive studies

Supportive efficacy data were provided from Studies FTY720D2201 and FTY720D2201E1.

Study FTY720D2201

The Phase II placebo-controlled (Study FTY720D2201) was a 6-month, double-blind, randomised, placebo-controlled, parallel-group, multi-centre study evaluating safety, tolerability and effect on MRI lesion parameters of FTY720 versus placebo in patients with relapsing MS. The study was conducted at 32 centres in 11 countries.

The primary objective of the study was to evaluate the effect of two doses of

FTY720 (5 mg and 1.25 mg) on the total number of Gd-enhancing lesions seen on monthly post baseline MRI scans during 6 months of treatment. Secondary objectives included effect on other MRI endpoints and exploration of the effect on clinical relapses.

The study randomised 281 patients. The ITT population (randomised, treated and with at least one valid post-baseline MRI scan) included 277 patients, 246 patients with RRMS and 31 patients with SPMS, aged 18 to 60 years, with evidence of clinical or MRI disease activity prior to study entry with an EDSS score of 0 to 6.0. Key exclusion criteria were the same as in study D2301 except that treatment with cyclophosphamide was allowed after a wash-out period of 12 months and mitoxantrone or cladribine after a wash-out period of 24 months.

Efficacy assessments included monthly MRI scans, assessment of MS relapses, EDSS determination quarterly and during MS relapses, and MSFC quarterly. EDSS was performed by a second physician blinded to all other information related to the patient. MRIs were evaluated by blinded raters at the MS MRI Evaluation Center, University Hospital, Basel, Switzerland.

MRI related analyses used the evaluable population (all randomised patients with no major protocol violation, no premature study drug discontinuation, had baseline MRI scan and at least three valid post-baseline scans) and were repeated on the ITT population as a sensitivity analysis. Analysis of clinical endpoints (relapses, EDSS, MSFC) was conducted on the ITT population.

The primary endpoint was analysed using the non-parametric Wilcoxon rank sum test in the evaluable population. Secondary MRI efficacy variables were assessed using analyses similar to those used for the primary efficacy variable. The proportions of relapse-free patients at month 6 were compared using z-test. Kaplan-Meier estimates of survival curves were constructed for the probability of experiencing the first confirmed relapse over time. A comparison of the survival curves among treatment groups was made with the log-rank tests. Relapse rates were compared using a Poisson regression model.

Treatment groups for the ITT (n=277) and evaluable (n=241) populations were well balanced for baseline demographic characteristics, MS history and MRI characteristics. In the ITT population, the overall mean duration of disease ranged 8.4 to 9.5 years with a mean of 1.9 relapses in the previous 2 years and mean EDSS of 2.6.

In total, 255 (92.1%) patients of the 277 ITT patients completed the study: 81 (88.0%) patients in the FTY720 5.0 mg, 88 (94.6%) patients in the FTY720 1.25 mg and 86 (93.5%) patients in the placebo group.

Efficacy results

Treatment with FTY720 5.0 mg and FTY720 1.25 mg significantly reduced the total number of monthly MRI Gd-enhancing lesions compared to placebo. Consistent results were observed on the cumulative volume of Gd-enhancing lesions and cumulative number of new T2 lesions. The onset of effect of both doses of FTY720 on reducing MRI lesion activity was seen by 2 months of treatment. While no change was observed in total volume of T2 lesions on placebo, a slight decrease was observed on both FTY720 treatment group, more marked in the FTY720 5.0mg group where the difference versus placebo was statistically significant. This was the only MRI efficacy parameter where the difference between the FTY720 5.0 mg and FTY720 1.25 mg dose groups was statistically significant (p=0.011). The mean brain volume loss did not differ between treatment groups.

The aggregate annualised relapse rate was 0.35 and 0.36 in the 1.25 mg and 5.0 mg groups respectively compared to 0.77 in the placebo group ($p = 0.009$ and $p = 0.014$, respectively). This result was supported by a significant delay in the time to first relapse and higher proportion of patients free of relapses on both FTY720 groups at 6 months compared to placebo. No statistically significant difference was observed on parameters of clinical efficacy between the two FTY720 doses tested, 5.0 mg and 1.25 mg.

Regarding the small population of SPMS patients (n = 31), treatment with FTY720 5.0 mg and FTY720 1.25 mg reduced new MRI activity compared to placebo as observed in the number of Gd-

enhancing lesions and the number of new T2 lesions over 6 months. The reductions were of similar magnitude as observed in the full population. The change in total volume of T2 lesions was also in line with the results observed in the full population. The aggregate ARR was reduced in both FTY720 dose groups, being 0.21 and 0.54 in the 1.25 mg and 5.0 mg groups respectively, compared to 1.25 in the placebo group. This result was supported by a higher proportion of SPMS patients without relapses in both FTY720 groups compared to placebo. The low number of SPMS patients resulted in wide 95% confidence intervals for the results, thus overlapping with those of the placebo group.

Long-term efficacy data: 5 years data (including 6-month core) from Phase II extension study D2201E1

Study FTY720D2201E1 was an extension to the 6-month, multicentre, multinational, randomised, double-blind, parallel-group, placebo-controlled, Phase II study of FTY720 in patients with relapsing MS (Study FTY720D2201). All patients who completed the 6-month core period on study treatment could continue in the extension phase. Patients who were randomised to FTY720 1.25 mg or 5.0 mg in the core study continued on the same dose of study medication in the extension and patients randomised to placebo in the core study were re-randomised in a 1:1 ratio to either FTY720 1.25 mg or 5.0 mg in the extension. Upon review of the results of the core study and the first 6 months of this extension study, it was decided to switch all patients on the 5.0 mg dose to receive 1.25 mg once daily, as both doses tested demonstrated similar efficacy but the 1.25 mg dose showed a more favourable safety profile. At that time patients were between Month 15 and 24 visits (9 to 12 months in the extension). Consequently, all patients have received FTY720 1.25 mg in the open-label treatment phase from Month 24 onwards.

The objective of this extension study was to provide long-term data on MS clinical parameters, MRI parameters and safety data from patients treated with FTY720. While these measures provided important longer-term safety and efficacy assessments, the lack of a control group, and knowledge that all patients were on active drug means that caution should be exercised in interpreting the results.

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

There was no primary efficacy endpoint for this open-label extension so only descriptive statistics are provided. Month 60 analyses were conducted using all available data in the core ITT population, defined as any patient who was randomised in the core study and received study medication.

Of the 255 patients who completed the core study, 250 entered the extension. A total of 140 patients from the originally 281 patients randomised in the core study (49.8%) completed the Month 60 visit. The most common reasons for premature discontinuation were AEs (19.9%) and withdrawal of consent (14.6%). Unsatisfactory therapeutic effect was reported as reason for discontinuation in 16 patients (5.7%) over 5 years.

Results from the Month 60 interim analysis showed that, after the initial reduction in MRI and clinical disease inflammatory activity observed during the first 6 months of treatment, disease inflammatory activity remained low throughout the extension study. MRI results showed that at each yearly scan more than 70% of patients were free from inflammatory activity on MRI (no new T2-weighted compared to the previous yearly scan and no Gd-enhanced T1-weighted lesions at that scan). For the patients who completed 5 years, a median decrease of 6% in the total volume of T2 lesions since baseline, and a 2.32% mean loss of brain volume since baseline were observed.

Clinical results showed that between 61% and 68% of patients were still free of relapses after 5 years of treatment with FTY720, a higher proportion than what has been observed on placebo

patients after 2 years in recent clinical trials (approximately 40%, Polman *et al* 2006). The annualised relapse rate over 5 years of treatment was low at 0.20 for the overall group. At Year 5, 60 to 71% of the patients were free of 6 month confirmed disability progression.

Analysis of Clinical Information Relevant to Dosing Recommendations

FTY720 was first tested at doses of 0.125-5.0 mg. Efficacy appeared to be dose dependent over this range, and the lowest incidence of rejection was seen with FTY720 in combination with conventional doses of cyclosporin at 2.5 mg and with 5.0 mg when combined with reduced doses of cyclosporin. In patients with MS a dose range of 0.5-5.0 mg FTY720 was studied.

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

Modelling of the exposure-response relationship in patients from the Phase III Studies D2301 and D2302 showed that lymphocyte counts decrease with increasing FTY720-P concentration with an estimated maximum reduction of 85% in female and 80% in male patients. The 0.5 mg dose is on the shoulder of the response curve while the 1.25 mg dose is on the plateau (see Figure 21 below).

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

Further modelling was performed by the sponsor to predict potency of FTY720 in relation to reduction of new T2 lesions counts and annualised relapse rate and in both cases the 0.5 mg dose was at the shoulder of the curve with a steep exposure response predicted for lower FTY720 concentrations (see Figures 22 and 23).

Figure 21: Predicted potency of FTY720-P to reduce the lymphocyte counts at steady state

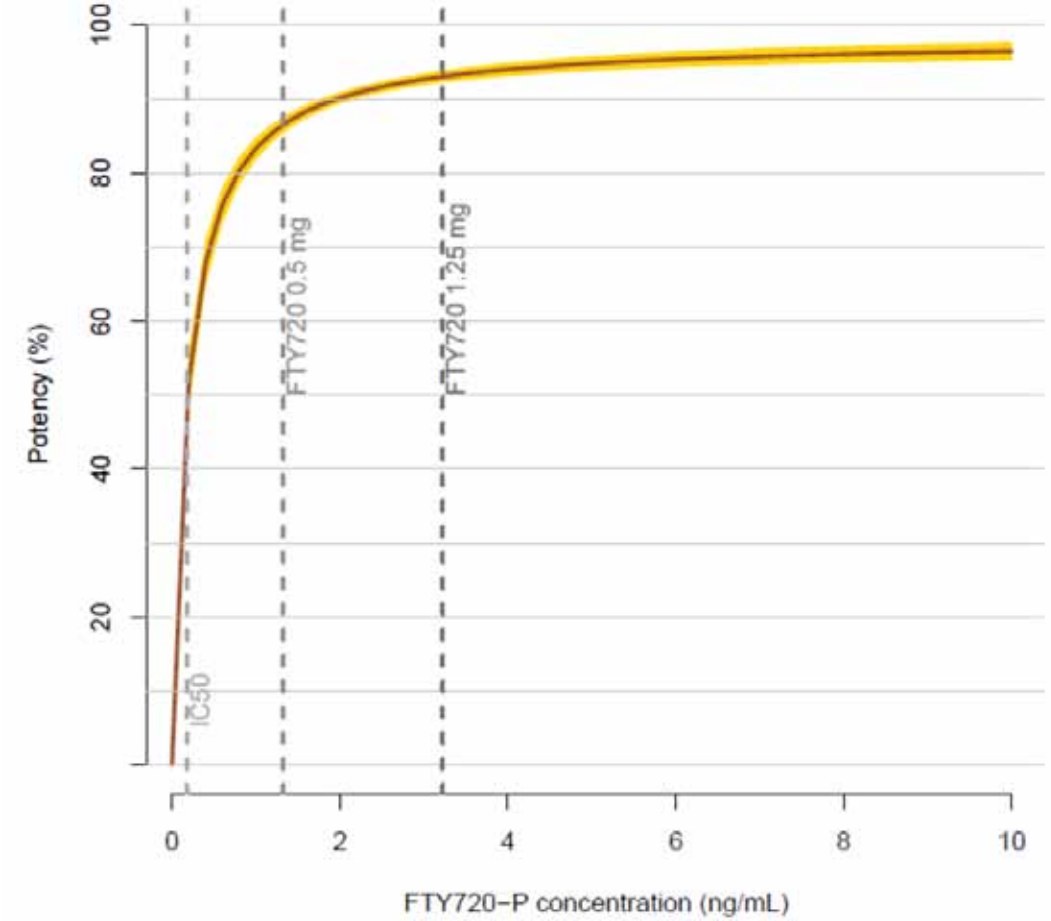


Figure 22: Predicted potency of FTY720-P to reduce the number of new T2 lesions at Month 12

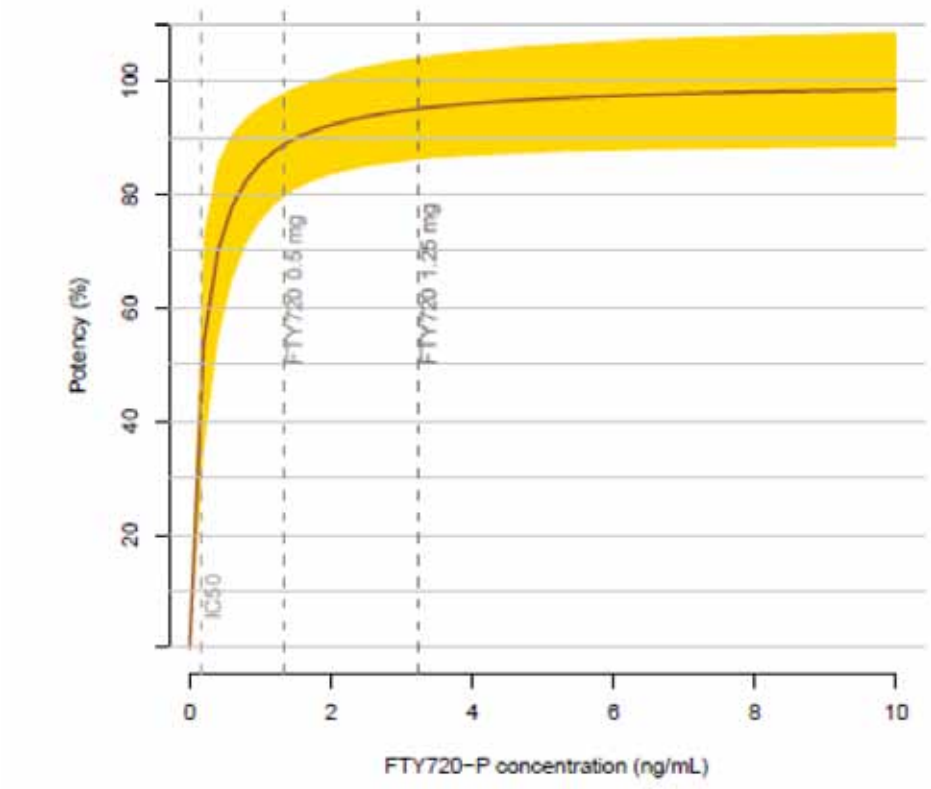
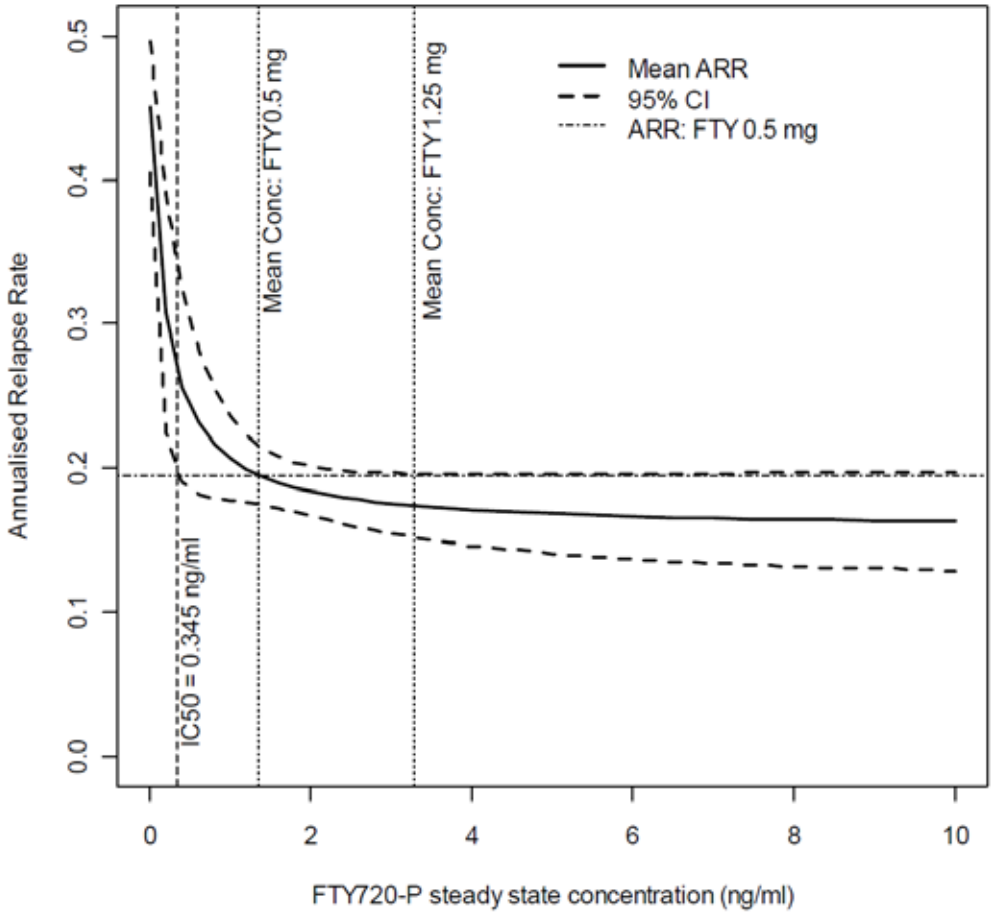


Figure 23: ARR versus predicted FTY720-P steady state concentration model with no covariates and approximate 95% confidence band



In Study FTY720D2201, FTY720 1.25 mg and 0.5 mg reduced the number of circulating lymphocytes by 75% and 78% from baseline respectively. Phase I/II data from the studies, showed that 0.5 mg FTY720 reduced circulating lymphocytes approximately 70% relative to baseline. After completion of both pivotal efficacy trials the DSMB made a formal suggestion to the sponsor to discontinue the 1.25 mg dose in their MS development program due to an increased incidence of vascular events.

Evaluator's comment*: The Phase II Study FTY720 D2201, did not adequately assess a dose response for FTY720 on inflammatory MRI activity as the study did not examine doses below 1.25 mg daily. A lower dose, 0.5 mg was explored in the Phase III studies. Although modelling can be helpful in predicting drug effects, information from modelling alone cannot definitively predict clinical response. Given the data submitted the true clinical effect of a lower dose than 0.5 mg has not been determined.*

Product information (PI) with respect to efficacy

Information in relation to Studies FTY720D2301 and FTY720D2302 is consistent with the current data submitted for evaluation. PI data in relation to FTY720D2302 should be reviewed after the sponsor has submitted revised analyses of new and/ or newly enlarging T2 lesions.

Evaluator's overall conclusions on clinical efficacy

Studies FTY720D2301 and FTY720D2302 were appropriately designed and conducted to assess the efficacy of fingolimod in treatment of patients with RRMS, and data from these studies can be considered pivotal in terms of efficacy analysis.

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

In FTY720D2301 treatment with fingolimod 1.25mg and 0.5mg resulted in significantly lower annualised relapse rate compared to placebo. The difference between the two fingolimod doses was not statistically significant.

For study FTY72D2302, treatment with both fingolimod doses resulted in a significantly lower annualised relapse rates compared to IFN β-1a. It is of some note that in this study, fingolimod 0.5mg was numerically (but not statistically) better than fingolimod 1.25 mg for the annualised relapse rate.

Time to 3-month confirmed disability progression (measured by the EDSS scale) was the only key secondary endpoint in Study 2301, and a second key secondary endpoint in Study 2302 (T2 MRI lesions was the first secondary endpoint in Study 2302). Both doses of fingolimod delayed the time to 3month confirmed disability progression compared to placebo in study 2301; however no significant difference between either dose of fingolimod and IFN β-1a was found in Study 2302.

In Study FTY720D2301, fingolimod 1.25mg and 0.5mg significantly delayed the time to 3-month confirmed disability progression compared to placebo (p=0.012 and p=0.026, respectively). The two fingolimod dose groups were not significantly different (p=0.7427). In a sensitivity analysis of the time to 6-month confirmed disability, results were very similar (nominal p-values of 0.0044 and 0.0112 for fingolimod 1.25mg and 0.5mg versus placebo). The percentage of patients without 3-month confirmed disability progression at Month 24 was higher in both fingolimod treatment groups (85% and 83% for 1.25 mg and 0.5 mg) compared with placebo (78%). The pairwise comparisons yielded nominal p-values of 0.008 and 0.043 for fingolimod 1.25 mg and 0.5 mg versus placebo, respectively.

Results from Study FTY720D2302 were in contrast to results from study FTY720D2301; a significant delay in confirmed disability progression was not substantiated in Study 2302. There was no difference between either of the two fingolimod treatment groups and the IFN β-1a group in the time to 3-month confirmed disability progression based on log-rank test (p values 0.4979 and .2475 for fingolimod 1.25mg and 0.5mg versus IFN β-1a).

Two important factors may have contributed to this lack of demonstrated effect on disability progression in Study 2302: the relatively short duration of the study, and the active comparator. The lack of significant difference between fingolimod and IGN β-1a does not mean they are "similar" for this endpoint as the study was not designed to test for non-inferiority of fingolimod to IGN β-1a.

The number of new or newly enlarged T2 lesions was not identified as a key secondary endpoint in Study FTY720D2301, and results for this endpoint should therefore be interpreted with caution.

For this endpoint, in the original analysis of Study FTY720D2302 only the 1.25 mg fingolimod dose reached statistical significance for the number of new or newly enlarged T2 lesions, compared to IFN â-1a. The sponsor submitted a revised (post-hoc) analysis (presented in the CSR addendum) for the number of "new and newly enlarged T2 lesions" that used a different method for counting the lesions, and also excluded 18 patients that prematurely discontinued from the study. In that revised analysis, the results between fingolimod 0.5 mg and IGN â-1a for the number of new and newly enlarged T2 lesions becomes statistically significant (p=0.004).

As has been discussed earlier in this report the methods used in the addendum to assess this key secondary endpoint are questionable. Variables have been added directly rather than reviewing the MRI scans or data collection sheets again and assigning lesions appropriately. It should be requested that the results of any re-analyses of these data be presented to the TGA as soon as they are available.

In terms of dose-response, efficacy results indicate that the dose-response between 0.5 mg and 1.25 mg is essentially flat. No statistically significant difference was seen in either of the pivotal studies between fingolimod 1.25mg and 0.5mg for both relapse rate and time to disability progression. For both of these endpoints, fingolimod 1.25mg was numerically better than fingolimod 0.5mg in study FTY720D2301. In Study FTY720D2302 the reverse was observed. The effect of fingolimod 1.25 mg and 0.5 mg on the number of new or newly enlarging T2 MRI lesions was similar.

Overall however, the clinical evaluator believed that the efficacy data submitted for evaluation are adequate to support that fingolimod is effective in treatment of patients with relapsing MS. The data support the indication as proposed by the sponsor.

Safety

Introduction

The sponsor provided safety data from all the studies submitted in the dossier. In the Summary of Clinical Safety (SCS) safety data were provided from Studies D2302, D2302 and D2201.

Interim data from two ongoing extension studies were included in the safety summary: study D2302E1 (interim data available up to cut-off 01 June 2009 or Month 24 (12 months core D2302 plus 12 months extension), whichever came first; and study D2201E1 (interim data up to Month 60 (6 months core 2201 study plus 54 months extension).

Study D2302E1 is the extension to the 12-month Study D2302. This extension is ongoing and only interim safety data have been pooled for analyses in the SCS. At the completion of the core phase of Study D2302, patients could continue into the optional extension phase in which all patients received oral FTY720. Patients treated with FTY720 during the core phase remained on the same dose of FTY720 (0.5 mg/day or 1.25 mg/day) in the extension phase. Patients who received interferon β -1a IM were re-randomised in a 1:1 ratio to receive either FTY720 1.25 mg/day or 0.5 mg/day. The original treatment assignment in the core study and dose of study drug administered to all patients in the extension remained blinded to the investigators. The objectives are to obtain long-term safety and efficacy data in patients treated with FTY720 and to examine the safety and efficacy of converting patients from interferon β -1a treatment to FTY720 treatment. Safety data up to June 1 2009 or Month 24, whichever came first, have been integrated into the pooled analyses.

A narrative description of the ongoing D2201E1 extension study was provided in *Efficacy* section of this evaluation report.

Ongoing clinical studies in MS

A number of additional clinical studies in MS patients are ongoing (see Table 52). These are three double-blind, placebo-controlled studies (D2309; D1201; D2306), plus the long-term extensions to two of these (D2309E1; D1201E1), and three ongoing long-term extensions of studies for which the core studies are complete (D2301E1; D2302E1; D2201E1). Note that the ongoing extension studies D2302E1 and D2201E1 are also listed here.

The ongoing Phase III study D2309 includes special safety assessments (24-hour Holter ECG, echocardiography, frequent OCT, chest HRCT) to further characterise the safety profile of FTY720 in areas of special interest. Interim safety data from these assessments (cut-off 01 June 2009) were included in this submission. In order to preserve the blinding of this study, these data were not integrated into the SCS but were reported separately.

Reports of deaths and SAEs from the ongoing studies which were submitted to the Novartis Drug Safety and Epidemiology Department by 30 September 2009 were also summarised.

Table 52: Ongoing clinical studies

Study design and purpose	Planned /actual number of patients	Treatment duration	Treatment/dose	Type of control/blinding
FTY720D2309 Efficacy and safety of FTY720 in patients with relapsing-remitting MS	1080 planned 1089 actual	24 months	FTY720 0.5 mg/day FTY720 1.25 mg/day Placebo orally	Placebo-controlled; double-blind
FTY720D2301E1 Long-term efficacy and safety of FTY720 in patients with relapsing-remitting MS	Not specified*	Open-ended	FTY720 0.5 mg/day FTY720 1.25 mg/day orally	Dose-blinded (FTY720 patients continued on their original dose; placebo patients re-randomized to FTY720 either 0.5 mg or 1.25 mg)
FTY720D2302E1 Long-term efficacy and safety of FTY720 in patients with relapsing-remitting MS	Not specified* 1030 actual	Open-ended	FTY720 0.5 mg/day FTY720 1.25 mg/day orally	Dose-blinded (FTY720 patients continued on their original dose; interferon patients re-randomized to FTY720 either 0.5 mg or 1.25 mg)
FTY720D2309E1 Long-term efficacy and safety of FTY720 in patients with relapsing-remitting MS	Not specified*	Open-ended	FTY720 0.5 mg/day FTY720 1.25 mg/day orally	Dose-blinded (FTY720 patients continued on their original dose; placebo patients re-randomized to FTY720 either 0.5 mg or 1.25 mg)
FTY720D2201E1 Long-term safety and effect on efficacy parameters of FTY720 in patients with relapsing MS	Not specified* 250 actual	Open-ended	FTY720 1.25 mg/day orally. Initially included the FTY720 5.0 mg dose.	Open-label. Initially dose-blinded (FTY720 patients continued on their original dose; placebo patients were re-randomized to FTY720 1.25 mg or 5.0 mg). When patients were 15-24 months in study (9-18 months in extension), the FTY720 5.0 mg dose was discontinued and patients switched to 1.25 mg
FTY720D1201 Efficacy and safety of FTY720 in patients with relapsing MS in Japan	165 planned	6 months	FTY720 0.5 mg/day FTY720 1.25 mg/day Placebo orally	Placebo-controlled; double-blind
FTY720D1201E1 Long-term efficacy and safety of FTY720 in patients with relapsing MS in Japan	Not specified*	At least 12 months	FTY720 0.5 mg/day FTY7201.25 mg/day orally	Dose-blinded (FTY720 patients continue on their original dose; placebo patients re-randomized to FTY720 either 0.5 mg or 1.25 mg)
FTY720D2306 Efficacy and safety of FTY720 in patients with primary progressive MS	650 planned	Up to 4-5 years**	FTY720 1.25 mg/day Placebo orally	Placebo-controlled; double-blind

*There was no specific sample size for the extension studies. Generally, patients could enter the extensions if they completed the respective core study.
**The double-blind phase continues until the last randomized patient completes 36 months (unless discontinued earlier)
All E1 extensions will continue until drug is available on the market.

Population groupings for safety assessment in the MS studies

The safety population in the MS studies comprised all patients who received at least one dose of study drug. Safety data while patients were on drug and up to 45 days after study drug discontinuation have been included. All SAEs for which the information has been received have been included regardless of the 45 day cut-off.

The data from three completed, double-blind, controlled MS studies and interim data from two long term extension studies in MS patients were pooled into 5 datasets using appropriate cut-offs to accommodate differences between studies in duration of treatment, doses, and comparators:

• Group A, all patients in double-blind, randomised, and placebo or active-controlled studies.,12 months treatment data (Studies D2301 and D2302 cut-off at the Month 12 visit). Because of the extent of exposure (in terms of patient years) and the comparable duration of double-blind treatment in the two pooled studies, Group A is the most appropriate dataset to characterise the safety profile of FTY720 versus interferon and provides the most rigorous comparison between FTY720 and placebo and between the two FTY doses for 12-month treatment.

• Group B, all patients in double-blind, randomised and placebo-controlled studies ,24- months treatment data (Study D2301 with a cut-off at the Month 24 visit). This dataset enables the most rigorous characterisation of the safety profile of FTY720 versus that of placebo, and of the 0.5 mg and 1.25 mg doses of FTY720.

• Group C , all patients in the double-blind, randomised and placebo or active-controlled studies,6 months treatment data (Studies D2301, D2302 and D2201 cut-off at the Month 6 visit). Group C allows evaluation of dose dependency of FTY720-related events over the entire dose range (0.5 mg to 5.0 mg) and the most rigorous comparisons between FTY720, placebo and interferon for 6-month treatment.

• Group D, all patients in double-blind, controlled studies (D2301 cut-off at the Month 24 visit, study D2302 cut-off at the Month 12 visit, Study D2201 cut-off at the Month 6 visit). This group contains all data from the randomised, double-blind and controlled studies regardless of differences in treatment duration or comparators.

• Group E ,all FTY720-treated patients, including studies D2301, D2302, and D2201, extension studies D2302E1 with cut-off 01-Jun-2009 or visit Month 24 (12 month extension), whichever came first, and D2201E1 with cut-off at the Month 60 visit. Group E includes all safety data which were collected on FTY720 treatment and up to 45 days after the discontinuation of FTY720 treatment. It provides supplementary information on the long-term safety of the FTY720 1.25 mg and 0.5 mg doses.

• Group E follow-up population , all FTY720-treated patients from Studies D2301 and D2302 who received a cumulative dose of at least 3 months (90 days) of study drug and had any follow-up data beyond 14 days after study drug discontinuation, and all patients who entered Study D2201E1 and received a cumulative dose of at least 3 months (90 days) of FTY720 and had any follow-up data beyond 14 days after study drug discontinuation. This group was primarily defined to monitor the reversibility of treatment-emergent safety events of interest.

Table 53 provides a summary of the pooled treatment groups. For all in-text tables and supporting statistical tables on pooled datasets, the pooled treatment groups are displayed as indicated in this table, except for the majority of the tables for Group B which come from the D2301 study report.

Table 53: Summary of pooled treatment groups

Analysis datasets, number of patients	Studies (cut-off)	Treatment regimens	Pooled treatment groups
Group A (12-month treatment) N = 2552	D2301 (up to Month 12 visit)	FTY720 1.25 mg FTY720 0.5 mg Placebo	FTY720 1.25 mg FTY720 0.5 mg Placebo Interferon beta-1a i.m.
	D2302	FTY720 1.25 mg FTY720 0.5 mg Interferon beta-1a i.m.	
Group B (24-month treatment) N = 1272	D2301	FTY720 1.25 mg FTY720 0.5 mg Placebo	FTY720 1.25 mg FTY720 0.5 mg Placebo
Group C (6-month treatment) N = 2833	D2301 (up to Month 6 visit)	FTY720 1.25 mg FTY720 0.5 mg Placebo	FTY720 5 mg FTY720 1.25 mg FTY720 0.5 mg Placebo Interferon beta-1a i.m.
	D2302 (up to Month 6 visit)	FTY720 1.25 mg FTY720 0.5 mg Interferon beta-1a i.m.	
	D2201	FTY720 5 mg FTY720 1.25 mg Placebo	
Group D (all patients from randomized, double-blind, controlled studies regardless of differences in treatment duration or comparators) N = 2833	D2301	FTY720 1.25 mg FTY720 0.5 mg Placebo	FTY720 5 mg FTY720 1.25 mg FTY720 0.5 mg Placebo Interferon beta-1a i.m.
	D2302	FTY720 1.25 mg FTY720 0.5 mg Interferon beta-1a i.m.	
	D2201	FTY720 5 mg FTY720 1.25 mg Placebo	
Group E (all FTY720-treated population) N = 2315	D2301	FTY720 1.25 mg FTY720 0.5 mg Placebo	FTY720 5 mg–1.25 mg* FTY720 1.25 mg FTY720 0.5 mg
	D2302, D2302E1 (up to 01-Jun-2009 or Month 24, whichever came first)	FTY720 1.25 mg FTY720 0.5 mg Interferon–FTY720 0.5 mg Interferon–FTY720 1.25 mg	
	D2201, D2201E1 (up to the Month 60 visit)	FTY720 5 mg–1.25 mg* FTY720 1.25 mg Placebo–FTY720 1.25 mg Placebo–FTY720 5 mg–1.25 mg	
Group E follow-up population N = 538	D2301	FTY720 1.25 mg FTY720 0.5 mg Placebo	FTY720 5 mg–1.25 mg* FTY720 1.25 mg FTY720 0.5 mg
	D2302	FTY720 1.25 mg FTY720 0.5 mg Interferon–FTY720 0.5 mg Interferon–FTY720 1.25 mg	
	D2201E1 (up to the Month 60 visit)	FTY720 5 mg–1.25 mg* FTY720 1.25 mg Placebo–FTY720 1.25 mg Placebo–FTY720 5 mg–1.25 mg	

Note: FTY720 5 mg–1.25 mg indicates the treatment regimen of FTY720 5 mg switched to FTY720 1.25 mg during D2201E1. Interferon–FTY720 1.25 mg and 0,5 mg Interferon–FTY720 0.5 mg indicate the treatment regimen of interferon during D2302 core study switched to FTY720 1.25 mg or 0.5 mg, respectively, in D2302E1. Likewise, Placebo–FTY720 1.25 mg indicates the treatment regimen of placebo during D2201 switched to FTY720 1.25 mg in D2201E1. Placebo–FTY720 5 mg–1.25 mg indicates the treatment regimen of placebo in D2201 initially switched to FTY720 5 mg in D2201E1 and then switched to FTY720 1.25 mg during D2201E1.
*The Group E FTY720 5 mg–1.25 mg pooled treatment group includes all patients who took either FTY720 5 mg only or FTY720 5 mg and were switched to FTY720 1.25 mg.

In addition to the data outlined above, the sponsor provided a Special Safety Interim Report including: 24-hour Holter monitoring, chest high resolution computed tomography and optical coherence tomography data from ongoing Study D2309 up to a cut-off date of 01 June 2009, and pooled echocardiography data from Study D2309 and completed Study D2302 in patients with relapsing-remitting multiple sclerosis. This report was released on 12 November 2009.

Based upon discussions with the FDA, additional specialised safety data collection and assessments were included in study D2309 to further characterise the effects of FTY720 on the heart, lung and eye. These assessments included:

- 24 hour Holter monitoring: at screening, Day 1 and Month 3 to evaluate the incidence of any new onset threatening bradyarrhythmias, third degree AV blocks, prolonged sinus pauses during FTY720 treatment.

- Echocardiography: at screening, month 12 and 24 in a subset of patients was implemented (based on an increased number of cases of pulmonary oedema reported in FTY720 treated transplant patients; primarily in the first month post transplant) to evaluate effects, if any, on left ventricular function. Other two dimensional echocardiography and Doppler assessments of other parameters were also performed.

- Chest high resolution computed tomography (HRCT): at screening (all patients) and at Month 24 in a subset of patients, to better characterize the risk, if any, of pulmonary toxicity including pulmonary fibrosis.

- Frequent optical coherence tomography (OCT) assessments: at screening, Months 1, 3, 6, 12, 18, and 24 to evaluate the potential effects of FTY720 on foveal thickness to evaluate subtle longitudinal changes, if any.

These specialised safety assessments were also performed in a subset of patients in completed Study D2302. The results were provided in the full clinical study report of Study D2302 and were also described in the Multiple Sclerosis Integrated Summary of Safety (ISS) and the Summary of Clinical Safety (SCS).

Since the number of patients with echocardiography assessments in Study D2309 is smaller than originally planned, for echocardiography, the interim data from Study D2309 was pooled with the echocardiography data from completed Study D2302, to provide an integrated analysis in a larger population and increase the power available to discern effects on left ventricular function, if any.

In the D2309 safety evaluations presented:

- The safety population included 1083 patients with relapsing remitting MS in ongoing Study D2309 up to the interim cut-off date of 01 June 2009. At this time, 728 adults aged ≥18 years, had received FTY720 1.25 or 0.5 mg/day treatment corresponding to 747 patient years of exposure.

- Results of 24-hour Holter ECG evaluations are available for a total of 1075 patients: 366 on FTY720 1.25 mg, 356 on FTY720 0.5 mg and 353 on placebo from Study D2309.

Patient exposure

Exposure in Group A (double-blind, randomised, active and placebo-controlled studies, 12-month treatment)

A summary of the overall number of patients exposed and the duration of exposure for Group A is presented in Table 54. Mean and median duration of exposure were similar in all treatment groups. Note that the lower proportion of patients observed at a duration of ≥ 360 days is due to visit schedule issues, not to a high proportion of late withdrawals.

Table 54: Duration of exposure to study drug after randomization in Group A -12 months treatment (Safety population)

	FTY720 1.25 mg (N=849)	FTY720 0.5 mg (N=854)	Placebo (N=418)	Interferon (N=431)	Total (N=2552)
By exposure intervals (days) - n (%):					
≥ 1	849 (100.0)	854 (100.0)	418 (100.0)	431 (100.0)	2552 (100.0)
≥ 7	838 (98.7)	852 (99.8)	416 (99.5)	430 (99.8)	2536 (99.4)
≥ 14	834 (98.2)	848 (99.3)	414 (99.0)	429 (99.5)	2525 (98.9)
≥ 30	818 (96.3)	844 (98.8)	410 (98.1)	425 (98.6)	2497 (97.8)
≥ 60	798 (94.0)	835 (97.8)	405 (96.9)	417 (96.8)	2455 (96.2)
≥ 90	783 (92.2)	827 (96.8)	399 (95.5)	413 (95.8)	2422 (94.9)
≥ 180	745 (87.8)	803 (94.0)	384 (91.9)	399 (92.6)	2331 (91.3)
≥ 270	720 (84.8)	779 (91.2)	369 (88.3)	386 (89.6)	2254 (88.3)
≥ 330	684 (80.6)	732 (85.7)	351 (84.0)	379 (87.9)	2146 (84.1)
≥ 360	449 (52.9)	444 (52.0)	144 (34.4)	300 (69.6)	1337 (52.4)
Duration of exposure (days):					
n	849	854	418	431	2552
Mean	321.3	339.2	329.2	340.6	331.8
SD	99.06	71.98	80.38	81.84	85.14
Median	361.0	361.0	357.0	365.0	361.0
Minimum	1	2	1	6	1
Maximum	428	429	406	446	446
Patient-years	746.8	793.2	376.7	401.9	2318.5

The duration of exposure is the total actual days patients took the study medication.
Patients are cumulatively counted by each level of the duration of exposure intervals.
Patient-years are defined as the sum of the number of days on study drug for all patients in each treatment group divided by 365.25.

Mean exposure to FTY720 1.25 mg and 0.5 mg was slightly higher in females than males (FTY720 1.25 mg: males 305.6 days versus females 328.4 days. FTY720 0.5 mg: males 322.8 days versus females 347.1 days) whereas in the placebo and interferon groups mean exposure was comparable between males and females.

Mean exposure was similar for the three age groups in all treatment groups except placebo. Mean exposure in placebo patients was slightly higher in the ≥41 years age group (341.9 days) compared with the ≤30 years (327.2 years) and 31 to 40 years (318.2 years) age groups.

Mean exposure was similar for patients previously treated with disease-modifying drugs and treatment-naïve patients.

Exposure in Group B (double-blind, randomised, controlled study, 24-month treatment)

A summary of the overall number of patients exposed and the duration of exposure for Group B is presented in Table 55.

Table 55: Duration of exposure to study drug after randomisation in Group B -24 month treatment (Safety population)

	FTY720 1.25 mg (N=429)	FTY720 0.5 mg (N=425)	Placebo (N=418)	Total (N=1272)
By exposure intervals (days) - n (%):				
≥ 1	429 (100.0)	425 (100.0)	418 (100.0)	1272 (100.0)
≥ 7	423 (98.6)	424 (99.8)	416 (99.5)	1263 (99.3)
≥ 14	420 (97.9)	421 (99.1)	414 (99.0)	1255 (98.7)
≥ 30	407 (94.9)	419 (98.6)	410 (98.1)	1236 (97.2)
≥ 60	394 (91.8)	415 (97.6)	405 (96.9)	1214 (95.4)
≥ 90	385 (89.7)	412 (96.9)	399 (95.5)	1196 (94.0)
≥ 180	370 (86.2)	400 (94.1)	384 (91.9)	1154 (90.7)
≥ 270	358 (83.4)	393 (92.5)	372 (89.0)	1123 (88.3)
≥ 300	355 (82.8)	390 (91.8)	370 (88.5)	1115 (87.7)
≥ 330	352 (82.1)	384 (90.4)	361 (86.4)	1097 (86.2)
≥ 360	349 (81.4)	378 (88.9)	356 (85.2)	1083 (85.1)
≥ 390	343 (80.0)	375 (88.2)	343 (82.1)	1061 (83.4)
≥ 420	337 (78.6)	375 (88.2)	342 (81.8)	1054 (82.9)
≥ 480	327 (76.2)	368 (86.6)	333 (79.7)	1028 (80.8)
≥ 540	316 (73.7)	363 (85.4)	324 (77.5)	1003 (78.9)
≥ 600	306 (71.3)	352 (82.8)	319 (76.3)	977 (76.8)
≥ 660	291 (67.8)	335 (78.8)	306 (73.2)	932 (73.3)
≥ 720	183 (42.7)	196 (46.1)	199 (47.6)	578 (45.4)
≥ 750	17 (4.0)	16 (3.8)	15 (3.6)	48 (3.8)
Duration of exposure (days):				
n	429	425	418	1272
Mean	581.3	644.8	614.5	613.4
SD	242.70	179.98	207.43	213.1
Median	715.0	717.0	718.5	717.0
Minimum	1	2	1	1
Maximum	836	865	825	865
Patient-years	682.8	750.2	703.2	2136.2

The duration of exposure is the total actual days patients took the study medication.
Patients are cumulatively counted by each level of the duration of exposure intervals.
Patient-years are defined as the sum of the number of days on study drug for all patients in each treatment group divided by 365.25.

Mean exposure was lower in males compared with females for FTY720 1.25 mg (males 534.3 days versus females 602.7 days) and FTY720 0.5 mg (males 604.5 days versus females 662.3 days). Exposure was comparable between males and females in the placebo group. Mean exposure was comparable between the age groups for the FTY720 1.25 mg and 0.5 mg groups, but mean exposure to placebo was slightly higher in the ≥41 years age group (639.1 days) compared with the ≤30 and 31-40 years age groups (604.9 and 596.8 days, respectively). Mean exposure to FTY720 1.25 mg and 0.5 mg was comparable between patients previously treated with disease-modifying drugs and treatment-naïve patients. In the placebo group, mean exposure in previously treated patients (590.0 days) was lower than in treatment-naïve patients (631.1 days).

Exposure in Group C

For this group mean and median duration of exposure were similar for all treatment groups. Results from this group will not be presented in detail in this report.

Exposure in Group D

Exposure in Group D is summarised in Table 56.

Table 56: Duration of exposure to study drug after randomisation - Safety population

(All double-blind, randomised and controlled studies)

Duration of Exposure (days)	FTY720 5 mg (N=96)	FTY720 1.25 mg (N=943)	FTY720 0.5 mg (N=854)	Placebo (N=511)	Interferon (N=431)	Total (N=2833)
>= 1	96 (100%)	943 (100%)	854 (100%)	511 (100%)	431 (100%)	2833 (100%)
>= 7	92 (97.9%)	932 (98.8%)	852 (99.8%)	508 (99.4%)	430 (99.8%)	2814 (99.3%)
>= 14	92 (97.5%)	926 (98.2%)	848 (99.3%)	506 (99.0%)	429 (99.5%)	2801 (98.9%)
>= 30	90 (95.7%)	910 (96.5%)	844 (98.8%)	502 (98.2%)	426 (98.8%)	2771 (97.8%)
>= 60	88 (93.6%)	889 (94.3%)	835 (97.8%)	493 (96.5%)	417 (96.8%)	2722 (96.1%)
>= 90	86 (91.5%)	874 (92.7%)	827 (96.8%)	487 (95.3%)	413 (95.8%)	2687 (94.8%)
>= 180	52 (55.3%)	800 (84.8%)	803 (94.0%)	433 (84.7%)	399 (92.6%)	2487 (87.8%)
>= 270	0 (0.0%)	726 (77.0%)	784 (91.8%)	372 (72.8%)	386 (89.6%)	2268 (80.1%)
>= 360	0 (0.0%)	623 (66.1%)	671 (78.6%)	356 (69.7%)	300 (69.6%)	1950 (68.8%)
>= 450	0 (0.0%)	332 (35.2%)	371 (43.4%)	339 (66.3%)	0 (0.0%)	1042 (36.8%)
>= 540	0 (0.0%)	316 (33.5%)	363 (42.5%)	324 (63.4%)	0 (0.0%)	1003 (35.4%)
>= 630	0 (0.0%)	300 (31.8%)	346 (40.5%)	314 (61.4%)	0 (0.0%)	960 (33.9%)
>= 690	0 (0.0%)	272 (29.0%)	317 (37.1%)	295 (57.7%)	0 (0.0%)	885 (31.2%)
>= 720	0 (0.0%)	183 (19.4%)	196 (23.0%)	195 (38.9%)	0 (0.0%)	575 (20.4%)
n	96	943	854	511	431	2833
Mean	167.7	430.4	493.2	533.9	340.6	445.6
SD	45.84	226.83	203.93	254.38	81.84	220.88
Median	181.5	371.0	378.0	708.0	365.0	371.0
Minimum	1	1	2	1	6	1
Maximum	232	836	865	835	446	865
Patient years	43.2	1111.2	1153.2	746.9	401.9	3456.3

- The duration of exposure is the total actual days patients took the study medication.
- Patients will be cumulatively counted by each level of the duration of exposure.
- Patient years is defined as the sum of the number of days on study drug for all patients in each treatment group divided by 365.25.

Exposure in Group E (all FTY720-treated safety population)

A summary of the overall number of patients exposed and the duration of exposure for Group E is presented in Table 57. The duration of exposure for the dose groups in Group E is driven by the 5 studies included and the FTY720 doses evaluated (D2201: 6 months 1.25 mg and 5.0 mg; D2302: 12 months 0.5 mg and 1.25 mg; D2301: 24 months 0.5 mg and 1.25 mg; D2302 E1: 24 months 0.5 mg and 1.25 mg; D2201 E1: 60 months 1.25 mg and 5 mg). Note that the lower proportion of patients at ≥ 630 and beyond is not due to a high proportion of late withdrawals but rather to visit schedule issues.

Table 57: Duration of exposure to study drug after randomisation in Group E (all FTY720-treated patients Safety population)

	FTY720 5 mg–1.25 mg (N=137)	FTY720 1.25 mg (N=1157)	FTY720 0.5 mg (N=1021)	Total (N=2315)
By exposure intervals - n (%):				
≥ 1	137 (100.0)	1157 (100.0)	1021 (100.0)	2315 (100.0)
≥ 7	135 (98.5)	1140 (98.5)	1019 (99.8)	2294 (99.1)
≥ 14	134 (97.8)	1134 (98.0)	1015 (99.4)	2283 (98.6)
≥ 30	131 (95.6)	1118 (96.6)	1011 (99.0)	2260 (97.6)
≥ 60	128 (93.4)	1092 (94.4)	997 (97.6)	2217 (95.8)
≥ 90	126 (92.0)	1074 (92.8)	986 (96.6)	2186 (94.4)
≥ 180	118 (86.1)	1027 (88.8)	958 (93.8)	2103 (90.8)
≥ 270	111 (81.0)	969 (83.8)	907 (88.8)	1987 (85.8)
≥ 360	108 (78.8)	831 (71.8)	781 (76.5)	1720 (74.3)
≥ 450	104 (75.9)	755 (65.3)	715 (70.0)	1574 (68.0)
≥ 540	101 (73.7)	715 (61.8)	691 (67.7)	1507 (65.1)
≥ 630	98 (71.5)	653 (56.4)	630 (61.7)	1381 (59.7)
≥ 720	96 (70.1)	354 (30.6)	289 (28.3)	739 (31.9)
≥ 810	94 (68.6)	94 (8.1)	2 (0.2)	190 (8.2)
≥ 900	91 (66.4)	87 (7.5)	0 (0.0)	178 (7.7)
≥ 990	89 (65.0)	85 (7.3)	0 (0.0)	174 (7.5)
≥ 1080	85 (62.0)	85 (7.3)	0 (0.0)	170 (7.3)
≥ 1170	83 (60.6)	82 (7.1)	0 (0.0)	165 (7.1)
≥ 1260	77 (56.2)	79 (6.8)	0 (0.0)	156 (6.7)
≥ 1350	74 (54.0)	79 (6.8)	0 (0.0)	153 (6.6)
≥ 1440	70 (51.1)	79 (6.8)	0 (0.0)	149 (6.4)
≥ 1530	69 (50.4)	77 (6.7)	0 (0.0)	146 (6.3)
≥ 1620	58 (42.3)	70 (6.1)	0 (0.0)	128 (5.5)
≥ 1710	42 (30.7)	48 (4.1)	0 (0.0)	90 (3.9)
≥ 1800	33 (24.1)	36 (3.1)	0 (0.0)	69 (3.0)
Duration of exposure (days):				
n	137	1157	1021	2315
Mean	1171.6	606.1	566.4	622.1
SD	667.16	386.18	208.39	373.07
Median	1534.0	663.0	680.0	679.0
Minimum	1	1	2	1
Maximum	1891	1891	865	1891
Patient-years	439.5	1919.9	1583.3	3942.7

The FTY720 5 mg–1.25 mg group includes patients who received either FTY720 5 mg alone or FTY720 5 mg switched to 1.25 mg.
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 are defined as the sum of the number of days on study drug for all patients in each treatment group divided by 365.25.

The cumulative duration of exposure to study drug for the safety population in study D2309 is summarised by treatment group in Table 58.

Table 58: Duration of exposure – Study D2309

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

Adverse events

The proportion of patients with AEs occurring in at least 5% of patients in any of the four treatment groups in Group A is summarised by preferred term in Table 59. As expected for interferon, the most common AE was influenza-like illness, which occurred at more than 10-fold higher incidence in the interferon group than in the other three treatment groups. Other AEs characteristics of the AE profile for interferon (pyrexia and myalgia) were also observed with much lower incidence in the other three treatment groups.

AEs which occurred at a higher incidence in both FTY720 groups compared with placebo or interferon included headache, diarrhoea, back pain, cough, dizziness, and elevations in liver enzymes (ALT increased and GGT increased), bronchitis, and hypertension. Of these AEs, increased GGT, bronchitis, and hypertension showed a trend for higher incidence in patients in the FTY720 1.25 mg group than in the FTY720 0.5 mg group.

Table 59: Number (%) of patients with AEs by preferred term (>=5% patients in any treatment group) in Group A (12-month treatment)

Preferred term	FTY720 1.25 mg N=849 n (%)	FTY720 0.5 mg N=854 n (%)	Placebo N=418 n (%)	Interferon N=431 n (%)
Any preferred term	**769 (90.6)**	**752 (88.1)**	**369 (88.3)**	**396 (91.9)**
Headache	196 (23.1)	195 (22.8)	79 (18.9)	88 (20.4)
Nasopharyngitis	175 (20.6)	166 (19.4)	81 (19.4)	88 (20.4)
Fatigue	97 (11.4)	86 (10.1)	36 (8.6)	45 (10.4)
Upper respiratory tract infection	86 (10.1)	86 (10.1)	58 (13.9)	27 (6.3)
Alanine aminotransferase increased	66 (7.8)	61 (7.1)	11 (2.6)	8 (1.9)
Diarrhoea	66 (7.8)	67 (7.8)	26 (6.2)	21 (4.9)
Back pain	61 (7.2)	62 (7.3)	24 (5.7)	23 (5.3)
Nausea	61 (7.2)	75 (8.8)	30 (7.2)	29 (6.7)
Cough	55 (6.5)	53 (6.2)	23 (5.5)	16 (3.7)
Dizziness	52 (6.1)	49 (5.7)	19 (4.5)	21 (4.9)
Influenza	52 (6.1)	64 (7.5)	30 (7.2)	32 (7.4)
Melanocytic naevus	50 (5.9)	40 (4.7)	11 (2.6)	26 (6.0)
Bronchitis	46 (5.4)	39 (4.6)	11 (2.6)	11 (2.6)
Gamma-glutamyltransferase increased	46 (5.4)	28 (3.3)	3 (0.7)	1 (0.2)
Hypertension	43 (5.1)	36 (4.2)	11 (2.6)	9 (2.1)
Arthralgia	40 (4.7)	37 (4.3)	25 (6.0)	24 (5.6)
Dyspnoea	39 (4.6)	36 (4.2)	17 (4.1)	7 (1.6)
Pharyngitis	37 (4.4)	31 (3.6)	16 (3.8)	13 (3.0)
Urinary tract infection	37 (4.4)	48 (5.6)	36 (8.6)	22 (5.1)
Depression	36 (4.2)	47 (5.5)	17 (4.1)	33 (7.7)
Pain in extremity	36 (4.2)	41 (4.8)	18 (4.3)	28 (6.5)
Oropharyngeal pain	34 (4.0)	39 (4.6)	22 (5.3)	15 (3.5)
Pyrexia	26 (3.1)	24 (2.8)	7 (1.7)	77 (17.9)
Myalgia	20 (2.4)	22 (2.6)	9 (2.2)	44 (10.2)
Influenza like illness	17 (2.0)	21 (2.5)	2 (0.5)	159 (36.9)

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.

The proportion of patients with AEs occurring in at least 5% of patients in any of the three treatment groups in Group B is summarised by preferred term in Table 60. For the three most common AEs (headache, nasopharyngitis, and upper respiratory tract infection) there were no noteworthy differences among the dose groups.

Table 60: Number (%) of patients with AEs by preferred term (>=5% patients in any treatment group) in Group B (24-month treatment)

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.
This table contains AEs whose missing start dates were imputed as part of the analyses performed for the D2301 CSR, contrary to the convention used for the other pooled analyses in this submission (see Table 2-1).

The proportion of patients with AEs occurring in at least 5% of patients in any of the five treatment groups in Group C is summarised by preferred term in Table 61. Preferred terms that were noted in the D2201 CSR as having a higher proportion of patients in the FTY720 treatment groups than for the placebo group were nasopharyngitis (in particular for the FTY720 5 mg group), diarrhoea, nausea, abdominal pain upper, headache, somnolence, dyspnoea and wheezing (only for the FTY720 5.0 mg group), leucopaenia, ALT increased and hypertension.

In the context of Group C, the preferred terms that were reported in a clinically relevantly higher proportion of patients in all FTY720 treatment groups than for the placebo and interferon groups (among those that occurred in at least 5% of patients in any treatment group) were nasopharyngitis, nausea, ALT increased, diarrhoea, hypertension and leucopaenia.

Preferred terms that were reported with higher frequency mainly in the FTY720 5 mg group were dyspnoea, dizziness, abdominal pain upper, rash, gastroenteritis, constipation, somnolence and chest pain.

Consistent with the findings for Group A, influenza-like illness, the most common AE for the interferon group, occurred at more than 15-fold higher incidence in the interferon group than all

other treatment group, and pyrexia, also characteristic of the profile interferon, was also observed with much lower incidence across the other treatment groups.

Table 58: Number (%) of patients with AEs by preferred term (>=5% patients in any treatment group) in Group C (6-month treatment)

Preferred term	FTY720 5 mg N=94 n (%)	FTY720 1.25 mg N=943 n (%)	FTY720 0.5 mg N=854 n (%)	Placebo N=511 n (%)	Interferon N=431 n (%)
Any preferred term	**90 (95.7)**	**790 (83.8)**	**691 (80.9)**	**419 (82.0)**	**374 (86.8)**
Headache	18 (19.1)	188 (19.9)	160 (18.7)	81 (15.9)	83 (19.3)
Nasopharyngitis	26 (27.7)	142 (15.1)	119 (13.9)	61 (11.9)	61 (14.2)
Fatigue	8 (8.5)	92 (9.8)	75 (8.8)	35 (6.8)	40 (9.3)
Upper respiratory tract infection	2 (2.1)	70 (7.4)	59 (6.9)	50 (9.8)	16 (3.7)
Nausea	10 (10.6)	63 (6.7)	69 (8.1)	29 (5.7)	27 (6.3)
Alanine aminotransferase increased	7 (7.4)	61 (6.5)	43 (5.0)	8 (1.6)	6 (1.4)
Diarrhoea	12 (12.8)	61 (6.5)	55 (6.4)	22 (4.3)	18 (4.2)
Dizziness	7 (7.4)	48 (5.1)	46 (5.4)	24 (4.7)	17 (3.9)
Back pain	8 (8.5)	43 (4.6)	42 (4.9)	21 (4.1)	14 (3.2)
Cough	5 (5.3)	42 (4.5)	36 (4.2)	25 (4.9)	13 (3.0)
Dyspnoea	12 (12.8)	36 (3.8)	31 (3.6)	17 (3.3)	7 (1.6)
Hypertension	6 (6.4)	33 (3.5)	29 (3.4)	10 (2.0)	6 (1.4)
Influenza	7 (7.4)	31 (3.3)	36 (4.2)	21 (4.1)	25 (5.8)
Pain in extremity	5 (5.3)	31 (3.3)	27 (3.2)	16 (3.1)	20 (4.6)
Abdominal pain upper	5 (5.3)	26 (2.8)	18 (2.1)	9 (1.8)	10 (2.3)
Pyrexia	7 (7.4)	23 (2.4)	19 (2.2)	4 (0.8)	72 (16.7)
Urinary tract infection	3 (3.2)	21 (2.2)	32 (3.7)	26 (5.1)	11 (2.6)
Rash	5 (5.3)	18 (1.9)	14 (1.6)	14 (2.7)	6 (1.4)
Gastroenteritis	5 (5.3)	16 (1.7)	10 (1.2)	9 (1.8)	10 (2.3)
Leukopenia	5 (5.3)	15 (1.6)	10 (1.2)	0	0
Influenza like illness	1 (1.1)	13 (1.4)	19 (2.2)	3 (0.6)	154 (35.7)
Constipation	6 (6.4)	12 (1.3)	18 (2.1)	11 (2.2)	5 (1.2)
Somnolence	6 (6.4)	11 (1.2)	9 (1.1)	10 (2.0)	4 (0.9)
Chest pain	5 (5.3)	7 (0.7)	5 (0.6)	6 (1.2)	1 (0.2)

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

Events suspected to be drug-related in Group B (double-blind, randomised, controlled study, 24 month treatment)

Drug-related AEs occurring in at least 2% of patients in any of the three treatment groups in Group B are summarised by SOC and preferred term in Table 62. The overall proportion of patients with drug related AEs was higher in the FTY720 treatment groups compared to the placebo group. This was mainly due to the events of liver enzyme elevation (including ALT, GGT and AST), leucopaenia, and hypertension. Headache, the second most common drug-related AE, was reported by a similar proportion of patients in all treatment groups. Most of the trends noted for the profile of common AEs for Group B were also evident for drug-related AEs, that is, the proportion of patients with AEs in investigations and blood and lymphatic system disorders was higher for the FTY720 1.25 mg and 0.5 mg groups compared to placebo.

Of the preferred terms describing elevations in liver enzymes, the proportions of patients with drug-related GGT increased and AST increased demonstrated dose dependence. No dose -dependence was evident for the drug related AEs of diarrhoea, bronchitis and hypertension. No new preferred terms were identified as occurring with greater frequency as drug-related AEs that had not already been identified in the common AE profile.

As an additional method of investigating drug-related differences among the treatment groups, adverse drug reactions (ADR) were identified. An ADR is an undesirable event that can be reasonably associated with the use of a drug. ADRs were identified primarily on the basis of the safety experience in the 2-year, placebo-controlled Study D2301 (Group B) and were defined as those AEs that occurred at a ≥1% higher rate in the FTY720 0.5 mg dose group than in the placebo group. In addition, based on experience in other FTY720 clinical trials, events were included as ADRs which did not otherwise meet these criteria in Group B, but where an imbalance in incidence has been observed in other studies and there is evidence of a dose-response relationship (macular oedema, pneumonia). Both preferred terms (individual or grouped for similar types of events) and high-level terms were used in this analysis to ensure that the emerging signals of events with reasonable association to fingolimod treatment were captured.

For Group B, AEs identified as ADRs are provided in Table 63. Preferred terms occurring more frequently for FTY720 groups compared to placebo that were not identified in the profile for common or drug-related AEs include macular oedema (in the FTY720 1.25 mg group only; no cases in the FTY720 0.5 mg and placebo groups), liver disorder, blood ALP increased and abnormal liver function test.

The resulting list of ADRs in Group B is representative of the safety profile of FTY720 across the MS program. Group B was chosen as the basis for the ADR table as it included a large placebo-controlled study where patients were observed over a long and uniform time period (2 years). Furthermore, the placebo control in Group B is the most appropriate control with which to contrast the intrinsic safety profile of FTY720.

Table 62: Number (%) of patients with drug-related AEs by preferred term (>=2% patients in any treatment group) in Group B (24-month treatment)

Primary system organ class Preferred term	FTY720 1.25mg N=429 n (%)	FTY720 0.5mg N=425 n (%)	Placebo N=418 n (%)
Any drug-related AE	**295 (68.8)**	**263 (61.9)**	**222 (53.1)**
Blood and lymphatic disorders	27 (6.3)	26 (6.1)	7 (1.7)
Leukopenia	15 (3.5)	9 (2.1)	1 (0.2)
Lymphopenia	13 (3.0)	12 (2.8)	2 (0.5)
Ear and labyrinth disorders	11 (2.6)	6 (1.4)	8 (1.9)
Vertigo	9 (2.1)	5 (1.2)	8 (1.9)
Gastrointestinal disorders	69 (16.1)	55 (12.9)	41 (9.8)
Nausea	22 (5.1)	17 (4.0)	19 (4.5)
Diarrhoea	14 (3.3)	16 (3.8)	7 (1.7)
General and administration site disorders	44 (10.3)	39 (9.2)	29 (6.9)
Fatigue	14 (3.3)	16 (3.8)	7 (1.7)
Infections and infestations	109 (25.4)	110 (25.9)	107 (25.6)
Upper respiratory tract infection	26 (6.1)	29 (6.8)	27 (6.5)
Nasopharyngitis	24 (5.6)	31 (7.3)	32 (7.7)
Pharyngitis	16 (3.7)	10 (2.4)	9 (2.2)
Bronchitis	12 (2.8)	15 (3.5)	4 (1.0)
Urinary tract infection	5 (1.2)	6 (1.4)	9 (2.2)
Influenza	3 (0.7)	13 (3.1)	12 (2.9)
Investigations	116 (27.0)	98 (23.1)	52 (12.4)
Alanine aminotransferase increased	46 (10.7)	39 (9.2)	14 (3.3)
Gamma-glutamyltransferase increased	29 (6.8)	21 (4.9)	3 (0.7)
Hepatic enzyme increased	18 (4.2)	14 (3.3)	1 (0.2)
Aspartate aminotransferase increased	15 (3.5)	6 (1.4)	5 (1.2)
White blood cell count decreased	14 (3.3)	3 (0.7)	0
Carbon monoxide diffusing capacity decreased	13 (3.0)	8 (1.9)	10 (2.4)
Lymphocyte count decreased	9 (2.1)	3 (0.7)	0
Metabolism and nutritional disorders	19 (4.4)	17 (4.0)	17 (4.1)
Hypercholesterolaemia	15 (3.5)	11 (2.6)	11 (2.6)
Nervous system disorders	67 (15.6)	59 (13.9)	59 (14.1)
Headache	33 (7.7)	28 (6.6)	30 (7.2)
Dizziness	22 (5.1)	12 (2.8)	14 (3.3)
Respiratory, thoracic and mediastinal disorders	48 (11.2)	49 (11.5)	40 (9.6)
Dyspnoea	15 (3.5)	20 (4.7)	14 (3.3)
Cough	10 (2.3)	10 (2.4)	14 (3.3)
Oropharyngeal pain	4 (0.9)	10 (2.4)	8 (1.9)
Vascular disorders	16 (3.7)	17 (4.0)	15 (3.6)
Hypertension	12 (2.8)	13 (3.1)	3 (0.7)

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.
System organ classes with no preferred terms that occurred in ≥2% patients in any treatment group not shown.

Table 63: Adverse drug reactions in the FTY720 0.5 mg group (Group B)

Primary system organ class	Preferred Term	FTY720 1.25mg † N=429 n (%)	FTY720 0.5mg N=425 n (%)	Placebo N=418 n (%)
Infections*	Influenza viral infections	40 (9.3)	55 (12.9)	41 (9.8)
	Bronchitis	39 (9.1)	34 (8.0)	15 (3.6)
	Sinusitis	27 (6.3)	28 (6.6)	19 (4.5)
	Gastroenteritis	18 (4.2)	19 (4.5)	13 (3.1)
	Pneumonia	7 (1.6)	2 (0.5)	1 (0.2)
	Herpes viral infections	25 (5.8)	37 (8.7)	33 (7.9)
	Tinea infections	6 (1.4)	16 (3.8)	6 (1.4)
Cardiac Disorders	Bradycardia**	10 (2.3)	15 (3.5)	4 (1.0)
Nervous system disorders	Headache	114 (26.6)	107 (25.2)	96 (23.0)
	Dizziness	30 (7.0)	31 (7.3)	23 (5.5)
	Paresthesia	17 (4.0)	23 (5.4)	18 (4.3)
	Migraine	15 (3.5)	20 (4.7)	6 (1.4)
Gastrointestinal disorders	Diarrhea	40 (9.3)	50 (11.8)	31 (7.4)
Gen disorders and admin. site conditions	Asthenia	9 (2.1)	11 (2.6)	5 (1.2)
Musculoskeletal and connective tissue disorders	Back pain	45 (10.5)	50 (11.8)	29 (6.9)
Skin and subcutaneous tissue disorders	Eczema	15 (3.5)	14 (3.3)	8 (1.9)
	Alopecia	9 (2.1)	15 (3.5)	10 (2.4)
	Pruritus	4 (0.9)	11 (2.6)	5 (1.2)
Investigations	ALT increased	50 (11.7)	43 (10.1)	16 (3.8)
	GGT increased	32 (7.5)	22 (5.2)	4 (1.0)
	Hepatic enzyme increased	22 (5.1)	14 (3.3)	1 (0.2)
	Weight decreased	15 (3.5)	20 (4.7)	14 (3.3)
	Blood triglycerides increased	8 (1.9)	11 (2.6)	5 (1.2)
	Liver function test abnormal	7 (1.6)	6 (1.4)	1 (0.2)
Resp., thoracic and mediastinal disorders	Cough	37 (8.6)	43 (10.1)	34 (8.1)
	Dyspnea***	28 (6.5)	34 (8.0)	19 (4.5)
Psychiatric disorders	Depression	26 (6.1)	33 (7.8)	28 (6.7)
Eye disorders	Eye pain	8 (1.9)	11 (2.6)	6 (1.4)
	Vision blurred	8 (1.9)	15 (3.5)	6 (1.4)
	Macular edema	7 (1.6)	0 (0.0)	0 (0.0)
Vascular disorders	Hypertension****	28 (6.5)	27 (6.4)	16 (3.8)
Blood and lymphatic system disorders	Leukopenia[v]	27 (6.3)	12 (2.8)	1 (0.2)
	Lymphopenia[vi]	23 (5.4)	15 (3.5)	2 (0.5)

* Includes Microorganism-related high-level terms; ** Includes events coded as "Heart rate decreased", "Sinus bradycardia" and "Bradyarrhythmia"; *** Includes events coded as "Dyspnea exertional" and "Orthopnea"; ****Includes events coded as "Labile hypertension" and "Diastolic hypertension"; [v] Includes events coded as "White blood cell count decreased"; [vi] Includes events coded as "Lymphocyte count decreased"
† 1.25 mg dose group is presented in this table for comparison and completeness

Severity of AEs in Group B (double-blind, randomised, controlled study, 24-month treatment)

The overall proportion of patients with mild, moderate, and severe AEs for Group B is presented in Table 64. The patterns of distribution of mild, moderate and severe AEs were similar in Group A. Most AEs were categorised as mild or moderate. Overall, severe AEs were reported for a similar proportion of patients in the FTY720 1.25 mg and placebo groups and for a lower proportion of patients in the FTY720 0.5 mg.

Table 64: Number (%) of patients with AEs by maximum severity in Group B (24-month treatment)

Maximum severity	FTY720 1.25mg N=429 n (%)	FTY720 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)

Note one additional patient in the FTY720 0.5 mg group had an AE graded as "asymptomatic" for its maximum severity.

A higher proportion of patients with severe AEs were seen for the investigations SOC in the FTY720 1.25 mg group and the FTY720 0.5 mg group compared to the placebo group. This difference was primarily attributable to the higher incidence of elevated liver enzymes. The proportion of patients with severe AEs occurring in at least two patients in any of the three treatment groups in Group B is summarised in Table 65.

Table 65: Number (%) of patients with severe AEs by SOC and preferred term (at least 2 patients in any treatment group) in Group B (12 month Safety population)

System organ class Preferred term	FTY720 1.25 mg (N=429) n (%)	FTY720 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)
Hepatobiliary disorders	3 (0.7)	2 (0.5)	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)
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
Metabolism and nutritional disorders	1 (0.2)	0	2 (0.5)
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
Pregnancy, puerperium and perinatal conditions	0	0	2 (0.5)
Abortion	0	0	2 (0.5)
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)
Renal and urinary disorders	0	1 (0.2)	2 (0.5)
Respiratory, thoracic and mediastinal disorders	3 (0.7)	1 (0.2)	4 (1.0)
Skin and subcutaneous tissue disorders	0	0	2 (0.5)
Rash pruritic	0	0	2 (0.5)

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.

Severity of AEs in Group C (double-blind, randomised, controlled studies, 6-month treatment)

The proportion of patients with mild, moderate and severe AEs is presented for Group C in Table 66.

Table 66: Number (%) of patients with AEs by maximum severity in Group C (6-month treatment)

Maximum severity	FTY720 5 mg N=94 n (%)	FTY720 1.25 mg N=943 n (%)	FTY720 0.5 mg N=854 n (%)	Placebo N=511 n (%)	Interferon N=431 n (%)
Any AE	**90 (95.7)**	**790 (83.8)**	**691 (80.9)**	**419 (82.0)**	**374 (86.8)**
Mild	39 (41.5)	339 (35.9)	307 (35.9)	211 (41.3)	182 (42.2)
Moderate	42 (44.7)	369 (39.1)	329 (38.5)	176 (34.4)	162 (37.6)
Severe	9 (9.6)	80 (8.5)	55 (6.4)	30 (5.9)	30 (7.0)

One patient in the FTY720 1.25 mg group had an AE with maximum severity not stated. One additional patient in the FTY720 0.5 mg group and two in the placebo group had an AE graded as "asymptomatic" for its maximum severity.

Most AEs were categorised as mild or moderate. Overall, severe AEs were reported for a similar proportion of patients across all treatment groups. In the D2201 CSR, no noteworthy differences were observed among the FTY720 5 mg, 1.25 mg, and placebo groups.

Table 67 shows the proportion of patients with severe AEs (occurring in at least 2 patients in any of the five treatment groups) in Group C. Other than the higher frequency of severe elevated liver enzymes, no particular type of AE was more severe for the FTY720 treatment groups compared to the interferon or placebo groups.

Table 67: Number (%) of patients with severe AEs by system organ class and preferred term (at least 2 patients in any treatment group) in Group C (6-month treatment)

System organ class Preferred term	FTY720 5 mg N=94 n (%)	FTY720 1.25 mg N=943 n (%)	FTY720 0.5 mg N=854 n (%)	Placebo N=511 n (%)	Interferon N=431 n (%)
Any severe AE	**9 (9.6)**	**80 (8.5)**	**55 (6.4)**	**30 (5.9)**	**30 (7.0)**
Blood and lymphatic system disorders	2 (2.1)	2 (0.2)	2 (0.2)	0	0
Leukopenia	2 (2.1)	1 (0.1)	1 (0.1)	0	0
Cardiac disorders	0	9 (1.0)	4 (0.5)	0	0
Atrioventricular block second degree	0	3 (0.3)	0	0	0
Bradycardia	0	3 (0.3)	3 (0.4)	0	0
Eye disorders	0	4 (0.4)	1 (0.1)	0	0
Macular oedema	0	3 (0.3)	1 (0.1)	0	0
Gastrointestinal disorders	1 (1.1)	11 (1.2)	7 (0.8)	0	3 (0.7)
Nausea	0	3 (0.3)	0	0	2 (0.5)
Toothache	0	2 (0.2)	0	0	0
Vomiting	0	2 (0.2)	0	0	1 (0.2)
Diarrhoea	1 (1.1)	1 (0.1)	2 (0.2)	0	0
General disorders and administration site conditions	1 (1.1)	6 (0.6)	2 (0.2)	3 (0.6)	14 (3.2)
Fatigue	1 (1.1)	6 (0.6)	1 (0.1)	1 (0.2)	5 (1.2)
Influenza like illness	0	0	0	0	6 (1.4)
Pain	0	0	0	0	2 (0.5)
Pyrexia	0	0	0	0	2 (0.5)
Hepatobiliary disorders	0	4 (0.4)	3 (0.4)	0	0
Cholelithiasis	0	1 (0.1)	2 (0.2)	0	0
Infections and infestations	0	11 (1.2)	7 (0.8)	6 (1.2)	2 (0.5)
Influenza	0	0	2 (0.2)	1 (0.2)	0
Injury, poisoning and procedural complications	1 (1.1)	0	2 (0.2)	4 (0.8)	1 (0.2)
Investigations	0	14 (1.5)	9 (1.1)	0	3 (0.7)
Alanine aminotransferase increased	0	4 (0.4)	3 (0.4)	0	1 (0.2)
Hepatic enzyme increased	0	3 (0.3)	2 (0.2)	0	0
Liver function test abnormal	0	3 (0.3)	1 (0.1)	0	1 (0.2)
Transaminases increased	0	3 (0.3)	1 (0.1)	0	0
Musculoskeletal and connective tissue disorders	0	8 (0.8)	8 (0.9)	2 (0.4)	5 (1.2)
Myalgia	0	1 (0.1)	2 (0.2)	0	1 (0.2)
Arthralgia	0	0	2 (0.2)	0	1 (0.2)
Neck pain	0	0	3 (0.4)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.1)	4 (0.5)	1 (0.2)	0
Nervous system disorders	1 (1.1)	20 (2.1)	10 (1.2)	8 (1.6)	10 (2.3)
Headache	0	8 (0.8)	3 (0.4)	2 (0.4)	6 (1.4)
Migraine	0	6 (0.6)	1 (0.1)	0	1 (0.2)
Multiple sclerosis relapse	0	1 (0.1)	0	2 (0.4)	0
Trigeminal neuralgia	0	0	0	2 (0.4)	0
Psychiatric disorders	0	5 (0.5)	2 (0.2)	1 (0.2)	3 (0.7)
Anxiety	0	2 (0.2)	0	0	0
Respiratory, thoracic and mediastinal disorders	1 (1.1)	3 (0.3)	3 (0.4)	2 (0.4)	1 (0.2)
Pleurisy	0	2 (0.2)	0	0	0
Skin and subcutaneous tissue disorders	0	0	1 (0.1)	2 (0.4)	2 (0.5)
Rash pruritic	0	0	0	2 (0.4)	0
Vascular disorders	1 (1.1)	3 (0.3)	0	1 (0.2)	0

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency for the FTY720 1.25 mg group.
A patient with multiple AEs 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.

Serious adverse events and deaths

Serious adverse events (SAEs)

The numbers of patients experiencing SAEs in the development programs are as follows:

Number of patients with SAEs in the clinical pharmacology studies (all completed):

12 patients

Number of patients with SAEs in the MS studies (including ongoing studies up to a cut-off date of 30 September 2009):

615 patients of whom 190 remain blinded

Number of patients with SAEs in other studies (all completed):

1335 patients

Number of patients with SAEs in all development programs, including ongoing studies up to a cut-off date of 30 September 2009: 1962 patients of whom 190 remain blinded.

Serious adverse events in Group A (double-blind, randomised, active and placebo-controlled studies, 12 month treatment)

The proportion of patients with SAEs by primary SOC and preferred terms that occurred in at least 2 patients in any treatment group are presented for Group A in Table 68. The overall proportion of patients with SAEs was higher in the FTY720 1.25 mg group, although overall differences between groups were small. In the FTY720 0.5 mg group, the overall proportion of patients with SAEs was slightly lower than that of the placebo group.

In the FTY720 1.25 mg group, the most frequently reported SAEs were cardiac disorders, particularly bradycardia and AV block. The majority of cardiac-related SAEs were asymptomatic bradycardia events on the first day of treatment leading to overnight hospitalisation for monitoring as required per protocol.

The incidence of infection and infestation SAEs was similar in the FTY720 1.25 mg group compared to the interferon group and was lowest in the FTY720 0.5 mg group.

SAEs consistent with the mechanism of action or known safety profile of FTY720 (for example, bradycardia, macular oedema, and liver function abnormalities) were infrequent in the FTY720 0.5 mg group. Apart from the AEs of bradycardia and low grade AV block, the profile of SAEs for the FTY720 0.5 mg group was similar to that of the placebo and interferon groups.

Table 68: Number (%) of patients with SAEs (at least 2 patients in any treatment group) by primary SOC and preferred term in Group A (12 month treatment)

Primary system organ class Preferred term	FTY720 1.25 mg (N=849) n (%)	FTY720 0.5 mg (N=854) n (%)	Placebo (N=418) n (%)	Interfero (N=431) n (%)
Any primary system organ class	**79 (9.3)**	**55 (6.4)**	**36 (8.6)**	**25 (5.8)**
Blood and lymphatic system disorders	2 (0.2)	1 (0.1)	0	0
Lymphopenia	2 (0.2)	0	0	0
Cardiac disorders	22 (2.6)	9 (1.1)	2 (0.5)	1 (0.2)
Bradycardia	11 (1.3)	5 (0.6)	1 (0.2)	0
Atrioventricular block second degree	4 (0.5)	1 (0.1)	0	0
Atrioventricular block first degree	3 (0.4)	1 (0.1)	0	0
Sinus bradycardia	2 (0.2)	1 (0.1)	0	0
Supraventricular extrasystoles	2 (0.2)	0	0	0
Eye disorders	7 (0.8)	2 (0.2)	1 (0.2)	0
Macular oedema	4 (0.5)	1 (0.1)	0	0
Gastrointestinal disorders	7 (0.8)	3 (0.4)	3 (0.7)	3 (0.7)
Constipation	2 (0.2)	0	1 (0.2)	0
General disorders and administration site conditions	2 (0.2)	1 (0.1)	1 (0.2)	2 (0.5)
Hepatobiliary disorders	1 (0.1)	4 (0.5)	1 (0.2)	1 (0.2)
Infections and infestations	15 (1.8)	3 (0.4)	4 (1.0)	6 (1.4)
Appendicitis	2 (0.2)	0	0	2 (0.5)
Injury, poisoning and procedural complications	1 (0.1)	5 (0.6)	5 (1.2)	5 (1.2)
Investigations	6 (0.7)	6 (0.7)	0	1 (0.2)
Liver function test abnormal	2 (0.2)	0	0	0
Musculoskeletal and connective tissue disorders	4 (0.5)	2 (0.2)	3 (0.7)	1 (0.2)
Intervertebral disc protrusion	0	0	2 (0.5)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6 (0.7)	11 (1.3)	8 (1.9)	2 (0.5)
Basal cell carcinoma	2 (0.2)	4 (0.5)	1 (0.2)	0
Breast cancer	2 (0.2)	1 (0.1)	2 (0.5)	0
Malignant melanoma	1 (0.1)	2 (0.2)	0	0
Nervous system disorders	12 (1.4)	11 (1.3)	3 (0.7)	3 (0.7)
Multiple sclerosis relapse	2 (0.2)	3 (0.4)	1 (0.2)	1 (0.2)
Multiple sclerosis	0	2 (0.2)	0	0
Pregnancy, puerperium and perinatal conditions	0	0	3 (0.7)	1 (0.2)
Abortion	0	0	2 (0.5)	1 (0.2)
Renal and urinary disorders	0	2 (0.2)	0	1 (0.2)
Nephrolithiasis	0	2 (0.2)	0	1 (0.2)
Respiratory, thoracic and mediastinal disorders	5 (0.6)	2 (0.2)	1 (0.2)	1 (0.2)
Dyspnoea	2 (0.2)	0	0	0
Pleurisy	2 (0.2)	0	0	0
Vascular disorders	3 (0.4)	1 (0.1)	1 (0.2)	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 one treatment group is counted only once in the AE preferred term for that treatment group.

Serious adverse events in Group B (double-blind, randomised, controlled study, 24 month treatment)

SAEs occurring in at least two patients in any treatment group in Group B are presented by primary SOC, preferred term, and treatment group in Table 69.

Table 69: Number (%) of patients with SAEs (at least 2 patients in any treatment group) by primary SOC and preferred term in Group B (24 month treatment)

Primary system organ class Preferred term	FTY720 1.25 mg N=429 n (%)	FTY720 0.5 mg N=425 n (%)	Placebo N=418 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 oedema	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
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)
Reproductive system and breast disorders	2 (0.5)	1 (0.2)	2 (0.5)
Hepatobiliary disorders	1 (0.2)	2 (0.5)	1 (0.2)
Injury, poisoning and procedural complications	1 (0.2)	3 (0.7)	6 (1.4)
Renal and urinary disorders	1 (0.2)	1 (0.2)	1 (0.2)
Pregnancy, puerperium and perinatal conditions	0	0	4 (1.0)
Abortion	0	0	3 (0.7)
Vascular disorders	0	1 (0.2)	2 (0.5)

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

The overall proportion of patients with SAEs was highest in the placebo group, without evidence of substantial differences between groups. Infection and infestation SAEs were reported more commonly in the FTY720 1.25 mg group compared to FTY720 0.5 mg and placebo. The only infection and infestations SAE term reported by >1 patient in any treatment group was urinary tract infection (2 patients in the FTY720 0.5 mg group). SAEs consistent with the mechanism of action or known safety profile of FTY720 (bradycardia, macular oedema and liver function abnormalities) were reported more commonly in the FTY720 treatment groups (mainly in the FTY720 1.25 mg group) compared to placebo.

Other SAEs of interest that occurred in only one patient per treatment group (and thus are not shown in Table 69) included: pneumonia (one patient each for FTY720 1.25 and 0.5 mg treatment groups); herpes virus infection (one1 patient in the FTY720 0.5 mg group); malignant melanoma (one patient each for the FTY720 1.25 mg and placebo groups); asthma (one patient in the placebo group); ischaemic stroke (one patient in the FTY720 1.25 mg group); first degree AV block (one patient in the FTY720 1.25 mg group); and second degree AV block (one patient each for the FTY720 1.25 mg and placebo groups).

Serious adverse events in Group E (all FTY720-treated safety population)

The proportion of patients with SAEs by primary SOC and preferred term in at least 2 patients in any treatment group is presented for Group E in Table 70. Note that the FTY720 5 mg- 1.25 mg group is presented here in order to provide a complete summary of SAEs in Group E. The overall proportion of patients with SAEs was higher in the FTY720 5 mg-1.25 mg group and 1.25 mg group compared to the 0.5 mg group.

The profile of SAEs observed for Group E is consistent with the findings from Groups A and B. One patient in the FTY720 1.25 mg group experienced an SAE of goitre that started prior to the first dose of study drug in the D2302E1 extension. This SAE is counted in Groups A, C, D, and E but not Group B.

Table 70: Number (%) of patients with SAEs (at least 2 patients in any treatment group) by primary SOC and preferred term in Group E (all FTY720- treated Safety population)

System organ class Preferred term	FTY720 5 mg - 1.25 mg N=137 n (%)	FTY720 1.25 mg N=1157 n (%)	FTY720 0.5 mg N=1021 n (%)
Any system organ class	**36 (26.3)**	**146 (12.6)**	**99 (9.7)**
Blood and lymphatic system disorders	1 (0.7)	5 (0.4)	3 (0.3)
Lymphopenia	0	4 (0.3)	0
Cardiac disorders	4 (2.9)	29 (2.5)	11 (1.1)
Bradycardia	3 (2.2)	15 (1.3)	6 (0.6)
Atrioventricular block second degree	0	6 (0.5)	1 (0.1)
Atrioventricular block first degree	0	4 (0.3)	1 (0.1)
Palpitations	1 (0.7)	2 (0.2)	0
Sinus bradycardia	0	2 (0.2)	1 (0.1)
Supraventricular extrasystoles	0	2 (0.2)	0
Ear and labyrinth disorders	0	3 (0.3)	1 (0.1)
Vertigo	0	3 (0.3)	0
Eye disorders	1 (0.7)	12 (1.0)	3 (0.3)
Macular oedema	1 (0.7)	9 (0.8)	2 (0.2)
Gastrointestinal disorders	3 (2.2)	12 (1.0)	5 (0.5)
Constipation	0	2 (0.2)	0
General disorders and administration site conditions	2 (1.5)	7 (0.6)	6 (0.6)
Chest pain	2 (1.5)	1 (0.1)	2 (0.2)
Non-cardiac chest pain	0	1 (0.1)	2 (0.2)
Hepatobiliary disorders	0	5 (0.4)	5 (0.5)
Biliary colic	0	2 (0.2)	2 (0.2)
Cholelithiasis	0	2 (0.2)	2 (0.2)
Infections and infestations	5 (3.6)	30 (2.6)	13 (1.3)
Appendicitis	1 (0.7)	3 (0.3)	0
Herpes zoster	1 (0.7)	3 (0.3)	0
Herpes zoster ophthalmic	0	2 (0.2)	1 (0.1)
Pneumonia	0	2 (0.2)	1 (0.1)
Urinary tract infection	1 (0.7)	1 (0.1)	2 (0.2)
Injury, poisoning and procedural complications	6 (4.4)	3 (0.3)	9 (0.9)
Investigations	0	10 (0.9)	6 (0.6)
Alanine aminotransferase increased	0	2 (0.2)	1 (0.1)
Hepatic enzyme increased	0	2 (0.2)	1 (0.1)
Liver function test abnormal	0	2 (0.2)	0
Musculoskeletal and connective tissue disorders	0	7 (0.6)	7 (0.7)
Back pain	0	1 (0.1)	2 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (5.1)	13 (1.1)	20 (2.0)
Basal cell carcinoma	1 (0.7)	3 (0.3)	7 (0.7)
Breast cancer	1 (0.7)	3 (0.3)	2 (0.2)
Malignant melanoma	0	3 (0.3)	2 (0.2)
Uterine leiomyoma	0	0	4 (0.4)

Table 70(cont.): Number (%) of patients with SAEs (at least 2 patients in any treatment group) by primary SOC and preferred term in Group E (all FTY720 treated Safety population)

System organ class Preferred term	FTY720 5 mg - 1.25 mg N=137 n (%)	FTY720 1.25 mg N=1157 n (%)	FTY720 0.5 mg N=1021 n (%)
Nervous system disorders	6 (4.4)	24 (2.1)	13 (1.3)
Multiple sclerosis relapse	2 (1.5)	4 (0.3)	4 (0.4)
Cerebral ischaemia	0	2 (0.2)	0
Epilepsy	1 (0.7)	2 (0.2)	0
Grand mal convulsion	0	2 (0.2)	0
Headache	0	2 (0.2)	0
Paraparesis	0	2 (0.2)	0
Multiple sclerosis	1 (0.7)	0	2 (0.2)
Psychiatric disorders	1 (0.7)	6 (0.5)	1 (0.1)
Anxiety	0	2 (0.2)	1 (0.1)
Depression	0	2 (0.2)	0
Renal and urinary disorders	0	2 (0.2)	2 (0.2)
Nephrolithiasis	0	1 (0.1)	2 (0.2)
Renal and urinary disorders	0	2 (0.2)	2 (0.2)
Nephrolithiasis	0	1 (0.1)	2 (0.2)
Reproductive system and breast disorders	1 (0.7)	3 (0.3)	3 (0.3)
Cervical dysplasia	0	2 (0.2)	0
Respiratory, thoracic and mediastinal disorders	4 (2.9)	9 (0.8)	4 (0.4)
Dyspnoea	1 (0.7)	3 (0.3)	0
Pleurisy	0	2 (0.2)	0
Asthma	2 (1.5)	1 (0.1)	0
Skin and subcutaneous tissue disorders	1 (0.7)	2 (0.2)	1 (0.1)
Vascular disorders	3 (2.2)	5 (0.4)	1 (0.1)

The FTY720 5 mg–1.25 mg group includes patients who received either FTY720 5 mg alone or FTY720 5 mg switched to 1.25 mg.
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 one treatment group is counted only once in the AE preferred term for that treatment group.

Deaths

The total numbers of deaths in the development programs were as follows:

MS studies (completed and ongoing up to a cut-off date of 30 September 2009): 12 patients

Transplantation studies (all completed): 72 patients

Total (MS plus transplantation studies, completed and ongoing, up to a cut off date of 30 September 2009): 84 patients

Deaths in the MS studies

As of 30 September 2009, 12 deaths occurred in the MS program. These deaths are summarised in Table 71.

Two of these deaths occurred in placebo patients and two prior to randomisation, leaving eight deaths in patients exposed to FTY720 – seven in patients who had been randomised to FTY720 1.25mg and one on FTY720 5 mg. No deaths have been reported in patients receiving the FTY720 0.5 mg dose. Three of the deaths occurred while the patients were on therapy or had recently discontinued (depression/suicide, herpes zoster disseminated, and herpes simplex encephalitis).

The small number of deaths, and the heterogeneity of events leading to death, mean that no assessment can be made regarding any difference between treatment groups in incidence rate, relation to duration of therapy, demographic factors or use of concomitant medication.

Table 71: Deaths in all MS studies, completed and ongoing as of 30 September 2009

Age (y)	Gender	Treatment group	Timing relative to last dose	Cause Preferred term (completed studies) or investigator term (ongoing studies)
55	F	FTY720 5 mg	Died 3 years after last dose Cancer diagnosed 5 months after stopping study drug.	Ovarian adenocarcinoma
53	M	FTY720 1.25 mg	Died Day 539 of the study (last dose on Day 539)	Depression, suicide
29	F	FTY720 1.25 mg	Died Day 320 of study (last dose on Day 317)	Herpes zoster disseminated
23	M	FTY720 1.25 mg	Died Day 407 of study (last dose on Day 339)	Herpes simplex encephalitis
42	M	FTY720 1.25 mg	Died 187 days after last dose	Aspiration pneumonia, acute disseminated encephalomyelitis, lower respiratory tract infection
53	F	FTY720 1.25 mg	Died 305 days after last dose	Breast cancer metastatic
35	F	FTY720 1.25 mg	Died on extension Day 638	Road traffic accident
52	M	Placebo	Died on Day 657 of the study (6 days after last dose)	Pulmonary embolism
37	F	Placebo	Died on Day 365 of the study (58 days after last dose)	Road traffic accident
46	M	FTY720 1.25 mg	Died 103 days after commencing study medication	Rapidly deteriorating MS
35	F	–	Died in the screening period, (prior to receiving any study drug)	Sudden death at home
54	M	–	Died in the screening period, (prior to receiving any study drug)	Suicide

Deaths in ongoing MS studies

There were five deaths in ongoing studies reported to Novartis up to 30 September 2009: one patient in the FTY720 5 mg group, two patients in the FTY720 1.25 mg group, and two patients who died prior to receiving the first dose of study medication. The three patients from the FTY720 treatment groups died of ovarian cancer (FTY720 5 mg group), rapidly deteriorating primary progressive MS (FTY720 1.25 mg group) and road traffic accident (FTY720 1.25 mg group). The two patients who had not received study medication died of suicide and sudden unexplained death at home.

Laboratory findings

Data analysis in the MS studies

Assessment of clinical laboratory parameters in Studies D2301 and D2302 took place at screening, baseline, 2 weeks and Months 2, 3, 6, 9, and 12 post-baseline. Study D2301 continued assessments at Months 15, 18, 21, and 24 post baseline. The extension D2302E1 continued assessments at Month 12.5, Months 13, 14, 15, and then at 3-month intervals up to either Month 24 or the cut-off date of 1 June 2009.

Laboratory assessments in Study D2201 took place at screening, baseline, after 1 week and Months 1, 3, and 6 post baseline; the extension D2201E1 continued the assessments at Months 7, 9, and then at 3 month intervals up to Month 60. The database included data on drug and up to 45 days after study drug discontinuation.

Haematology

Haematology changes from baseline in Group A (double-blind, randomised, active and placebo-controlled studies, 12 month treatment)

The principal pharmacodynamic effect of FTY720 is to retain lymphocytes in secondary lymphoid organs and thus substantial reductions in circulating white blood cell (WBC) are an expected finding in patients receiving FTY720. Change from baseline is shown at Month 1, 6 and 12 for WBC, absolute lymphocytes, absolute neutrophils and platelet count for Group A in Table 72. At 2 weeks post-baseline, the mean lymphocyte count in the FTY720 1.25 mg group was reduced by approximately 75% which can be compared to a 70% reduction in the FTY720 0.5 mg group. Lymphocyte counts then remained stable throughout the 12 month treatment period. At Month 12, mean lymphocyte counts were reduced by approximately 77% in the FTY720 1.25 mg group and 73% in the FTY720 0.5 mg group. In the placebo and interferon groups, no relevant changes in mean lymphocyte counts were seen.

Mean neutrophil counts were reduced from baseline by approximately 20% in the FTY720 1.25 mg group and by approximately 13% in the FTY720 0.5 mg group at 2 weeks. At subsequent visits mean neutrophil counts remained relatively stable and at Month 12 were reduced by approximately 25% in the FTY720 1.25 mg group and by 18% in the FTY720 0.5 mg group. There were no noteworthy reductions in mean neutrophil counts in the placebo and interferon groups over the 12 month treatment period.

Mean total WBC counts were reduced from baseline by approximately 35% in the FTY720 1.25 mg group and by approximately 29% in the FTY720 0.5 mg group at 2 weeks. During the treatment period, total WBC count remained relatively stable in the FTY720 groups. At Month 12, mean total WBC counts were reduced from baseline by approximately 40% in the FTY720 1.25 mg group and 34% in the FTY720 0.5 mg group. There were no noteworthy differences in mean total WBC counts in the placebo and interferon groups.

Mean platelet counts were slightly reduced relative to baseline in the FTY720 groups at 2 weeks post-baseline (approximately 5% in the FTY720 1.25 mg group and approximately 2% in the FTY720 0.5 mg group). Mean platelet counts recovered after Month 2 in the FTY720 groups and at Month 12 were reduced by approximately 2.5% in the FTY720 1.25 mg group and 1.3% in the FTY720 0.5 mg group. No noteworthy changes in mean platelet counts were seen in the placebo and interferon groups.

Table 72: Mean change from baseline in WBC, absolute lymphocytes, absolute neutrophils and platelet count, by visit and treatment for Group A (Safety population)

	Statistics	FTY720 1.25 mg N=849	FTY720 0.5 mg N=854	Placebo N=418	Interferon N=431
WBC (total) (10^9/L)					
	n	793	801	401	402
Baseline	Mean (SD)	6.57 (1.93)	6.46 (1.81)	6.69 (1.90)	6.47 (1.76)
Month 1	Mean (SD)	4.33 (1.73)	4.43 (1.50)	6.54 (1.82)	6.19 (1.78)
Change from baseline to Month 1	Mean (SD)	-2.24 (1.77)	-2.03 (1.48)	-0.15 (1.70)	-0.28 (1.58)
	n	733	784	384	382
Baseline	Mean (SD)	6.56 (1.91)	6.46 (1.80)	6.70 (1.86)	6.49 (1.79)
Month 6	Mean (SD)	3.98 (1.50)	4.30 (1.47)	6.54 (2.03)	6.33 (1.89)
Change from baseline to Month 6	Mean (SD)	-2.59 (1.69)	-2.16 (1.54)	-0.16 (1.74)	-0.16 (1.84)
	n	696	748	354	365
Baseline	Mean (SD)	6.60 (1.93)	6.46 (1.80)	6.68 (1.86)	6.44 (1.76)
Month 12	Mean (SD)	3.99 (1.53)	4.26 (1.65)	6.44 (1.77)	6.30 (1.99)
Change from baseline to Month 12	Mean (SD)	-2.61 (1.75)	-2.20 (1.71)	-0.24 (1.47)	-0.14 (1.83)
Absolute lymphocytes (10^9/L)					
	n	780	785	399	398
Baseline	Mean (SD)	1.81 (0.54)	1.82 (0.59)	1.82 (0.57)	1.77 (0.54)
Month 1	Mean (SD)	0.42 (0.24)	0.49 (0.24)	1.76 (0.52)	1.69 (0.56)
Change from baseline to Month 1	Mean (SD)	-1.39 (0.52)	-1.33 (0.56)	-0.06 (0.41)	-0.07 (0.50)
	n	714	772	378	380
Baseline	Mean (SD)	1.81 (0.54)	1.81 (0.58)	1.83 (0.58)	1.77 (0.53)
Month 6	Mean (SD)	0.39 (0.23)	0.49 (0.29)	1.77 (0.59)	1.71 (0.57)
Change from baseline to Month 6	Mean (SD)	-1.41 (0.53)	-1.33 (0.56)	-0.06 (0.47)	-0.06 (0.53)
	n	685	736	353	359
Baseline	Mean (SD)	1.81 (0.54)	1.82 (0.58)	1.82 (0.59)	1.74 (0.52)
Month 12	Mean (SD)	0.41 (0.26)	0.49 (0.32)	1.76 (0.57)	1.69 (0.57)
Change from baseline to Month 12	Mean (SD)	-1.40 (0.53)	-1.33 (0.55)	-0.06 (0.44)	-0.05 (0.49)
Absolute neutrophils (10^9/L)					
	n	780	786	399	400
Baseline	Mean (SD)	4.09 (1.57)	4.00 (1.45)	4.21 (1.57)	4.04 (1.45)
Month 1	Mean (SD)	3.36 (1.60)	3.39 (1.36)	4.13 (1.51)	3.84 (1.50)
Change from baseline to Month 1	Mean (SD)	-0.73 (1.57)	-0.61 (1.30)	-0.09 (1.55)	-0.20 (1.40)
	n	715	775	380	381
Baseline	Mean (SD)	4.08 (1.54)	4.00 (1.44)	4.21 (1.54)	4.04 (1.47)
Month 6	Mean (SD)	3.07 (1.37)	3.28 (1.30)	4.15 (1.65)	3.96 (1.65)
Change from baseline to Month 6	Mean (SD)	-1.01 (1.47)	-0.71 (1.27)	-0.06 (1.58)	-0.08 (1.71)
	n	686	739	353	360
Baseline	Mean (SD)	4.12 (1.54)	3.99 (1.44)	4.20 (1.53)	4.02 (1.45)
Month 12	Mean (SD)	3.07 (1.36)	3.26 (1.45)	4.06 (1.46)	3.96 (1.69)
Change from baseline to Month 12	Mean (SD)	-1.05 (1.50)	-0.73 (1.49)	-0.14 (1.34)	-0.05 (1.67)

Table 72(cont.): Mean change from baseline in WBC, absolute lymphocytes, absolute neutrophils and platelet count, by visit and treatment for Group A (Safety population)

	Statistics	FTY720 1.25 mg N=849	FTY720 0.5 mg N=854	Placebo N=418	Interferon N=431
Platelet count (10^9/L)					
	n	792	799	401	403
Baseline	Mean (SD)	269.97 (65.56)	268.68 (64.76)	270.16 (63.16)	268.48 (61.78)
Month 1	Mean (SD)	256.72 (62.00)	259.95 (57.36)	268.08 (59.94)	267.55 (65.56)
Change from baseline to Month 1	Mean (SD)	-13.26 (38.89)	-8.73 (37.18)	-2.08 (38.26)	-0.93 (47.38)
	n	733	783	384	383
Baseline	Mean (SD)	270.06 (65.13)	269.14 (65.11)	269.58 (62.98)	268.16 (60.88)
Month 6	Mean (SD)	265.37 (65.39)	268.05 (64.26)	274.55 (65.45)	276.29 (62.48)
Change from baseline to Month 6	Mean (SD)	-4.70 (44.20)	-1.09 (44.33)	4.98 (45.25)	8.13 (45.92)
	n	694	746	354	364
Baseline	Mean (SD)	270.58 (66.03)	269.91 (65.11)	269.26 (63.74)	267.28 (61.06)
Month 12	Mean (SD)	263.86 (65.11)	266.35 (64.07)	269.97 (65.08)	268.89 (66.54)
Change from baseline to Month 12	Mean (SD)	-6.71 (42.70)	-3.56 (44.10)	0.71 (45.69)	1.61 (46.81)

Haematology changes from baseline in Group B (double-blind, randomised, controlled study, 24-month treatment)

Change from baseline is shown at Month 1, 6, 12, 18 and 24 for WBC, absolute lymphocytes, absolute neutrophils and platelet count for Group B in Table 73. Mean changes from baseline in haematology parameters for FTY720 1.25 mg and 0.5 mg in Group B were consistent with those seen for Group A.

Table 73: Mean change from baseline in WBC, absolute lymphocytes, absolute neutrophils and platelet count, by visit and treatment for Group B (Safety population)

	Statistics	FTY720 1.25 mg N=429	FTY720 0.5 mg N=425	Placebo N=418
WBC (total) (10^9/L)				
	n	402	399	401
Baseline	Mean (SD)	6.74 (2.00)	6.58 (1.90)	6.69 (1.90)
Month 1	Mean (SD)	4.45 (1.85)	4.42 (1.55)	6.5378 (1.82)
Change from baseline to Month 1	Mean (SD)	-2.29 (2.02)	-2.16 (1.62)	-0.1480 (1.70)
	n	372	402	384
Baseline	Mean (SD)	6.75 (1.97)	6.52 (1.84)	6.70 (1.86)
Month 6	Mean (SD)	4.01 (1.54)	4.1991 (1.44)	6.54 (2.03)
Change from baseline to Month 6	Mean (SD)	-2.74 (1.74)	-2.3165 (1.49)	-0.16 (1.74)
	n	352	385	357
Baseline	Mean (SD)	6.78 (1.98)	6.55 (1.86)	6.67 (1.87)
Month 12	Mean (SD)	3.94 (1.58)	4.18 (1.57)	6.46 (1.81)
Change from baseline to Month 12	Mean (SD)	-2.84 (1.88)	-2.38 (1.72)	-0.21 (1.55)
	n	316	361	325
Baseline	Mean (SD)	6.83 (1.98)	6.52 (1.79)	6.66 (1.89)
Month 18	Mean (SD)	4.17 (1.53)	4.26 (1.52)	6.64 (2.08)
Change from baseline to Month 18	Mean (SD)	-2.65 (1.82)	-2.26 (1.62)	-0.02 (1.90)
	n	298	348	308
Baseline	Mean (SD)	6.81 (2.01)	6.50 (1.81)	6.64 (1.88)
Month 24	Mean (SD)	4.03 (1.44)	4.24 (1.61)	6.47 (1.93)
Change from baseline to Month 24	Mean (SD)	-2.78 (1.67)	-2.26 (1.69)	-0.16 (1.70)
Absolute lymphocytes (10^9/L)				
	n	394	392	399
Baseline	Mean (SD)	1.84 (0.55)	1.87 (0.63)	1.82 (0.57)
Month 1	Mean (SD)	0.45 (0.26)	0.51 (0.27)	1.76 (0.52)
Change from baseline to Month 1	Mean (SD)	-1.39 (0.53)	-1.36 (0.61)	-0.06 (0.41)
	n	364	396	378
Baseline	Mean (SD)	1.84 (0.55)	1.84 (0.62)	1.83 (0.58)
Month 6	Mean (SD)	0.42 (0.26)	0.48 (0.28)	1.77 (0.59)
Change from baseline to Month 6	Mean (SD)	-1.42 (0.55)	-1.36 (0.60)	-0.06 (0.47)
	n	348	380	356
Baseline	Mean (SD)	1.84 (0.54)	1.85 (0.62)	1.82 (0.58)
Month 12	Mean (SD)	0.42 (0.26)	0.50 (0.33)	1.76 (0.56)
Change from baseline to Month 12	Mean (SD)	-1.41 (0.53)	-1.35 (0.58)	-0.06 (0.44)
	n	313	357	323
Baseline	Mean (SD)	1.84 (0.53)	1.84 (0.62)	1.81 (0.56)
Month 18	Mean (SD)	0.46 (0.33)	0.50 (0.33)	1.77 (0.56)
Change from baseline to Month 18	Mean (SD)	-1.39 (0.54)	-1.34 (0.59)	-0.05 (0.49)
	n	292	339	304
Baseline	Mean (SD)	1.85 (0.54)	1.84 (0.62)	1.82 (0.56)
Month 24	Mean (SD)	0.42 (0.26)	0.49 (0.34)	1.76 (0.57)
Change from baseline to Month 24	Mean (SD)	-1.43 (0.52)	-1.36 (0.59)	-0.06 (0.47)

Table 73(cont.): Mean change from baseline in WBC, absolute lymphocytes, absolute neutrophils and platelet count, by visit and treatment for Group B (Safety population)

	Statistics	FTY720 1.25 mg N=429	FTY720 0.5 mg N=425	Placebo N=418
Absolute neutrophils (10^9/L)				
	n	394	392	399
Baseline	Mean (SD)	4.22 (1.63)	4.08 (1.53)	4.21 (1.57)
Month 1	Mean (SD)	3.46 (1.73)	3.35 (1.42)	4.13 (1.51)
Change from baseline to Month 1	Mean (SD)	-0.77 (1.79)	-0.73 (1.46)	-0.09 (1.55)
	n	365	398	380
Baseline	Mean (SD)	4.23 (1.62)	4.03 (1.49)	4.21 (1.54)
Month 6	Mean (SD)	3.05 (1.37)	3.18 (1.28)	4.15 (1.65)
Change from baseline to Month 6	Mean (SD)	-1.18 (1.54)	-0.85 (1.22)	-0.06 (1.58)
	n	348	382	356
Baseline	Mean (SD)	4.26 (1.62)	4.06 (1.50)	4.19 (1.54)
Month 12	Mean (SD)	3.00 (1.38)	3.17 (1.38)	4.05 (1.46)
Change from baseline to Month 12	Mean (SD)	-1.26 (1.62)	-0.89 (1.51)	-0.15 (1.34)
	n	313	358	323
Baseline	Mean (SD)	4.30 (1.61)	4.04 (1.43)	4.19 (1.58)
Month 18	Mean (SD)	3.23 (1.34)	3.23 (1.31)	4.24 (1.80)
Change from baseline to Month 18	Mean (SD)	-1.12 (1.53)	-0.80 (1.36)	0.04 (1.74)
	n	295	342	307
Baseline	Mean (SD)	4.28 (1.64)	4.02 (1.45)	4.16 (1.54)
Month 24	Mean (SD)	3.06 (1.28)	3.22 (1.42)	4.07 (1.57)
Change from baseline to Month 24	Mean (SD)	-1.23 (1.44)	-0.79 (1.47)	-0.10 (1.58)
Platelet count (10^9/L)				
	n	401	398	401
Baseline	Mean (SD)	269.56 (65.15)	270.06 (63.40)	270.16 (63.16)
Month 1	Mean (SD)	254.64 (59.28)	259.08 (57.75)	268.08 (59.94)
Change from baseline to Month 1	Mean (SD)	-14.92 (36.99)	-10.98 (35.42)	-2.08 (38.26)
	n	370	402	384
Baseline	Mean (SD)	270.61 (66.07)	268.79 (61.62)	269.58 (62.98)
Month 6	Mean (SD)	260.62 (65.05)	264.06 (62.48)	274.55 (65.45)
Change from baseline to Month 6	Mean (SD)	-9.99 (41.80)	-4.72 (40.24)	4.98 (45.25)
	n	350	384	356
Baseline	Mean (SD)	270.86 (66.64)	269.60 (62.30)	269.20 (63.57)
Month 12	Mean (SD)	263.45 (64.88)	266.28 (62.72)	270.48 (64.80)
Change from baseline to Month 12	Mean (SD)	-7.41 (41.06)	-3.32 (42.84)	1.28 (45.97)
	n	319	362	326
Baseline	Mean (SD)	271.52 (66.48)	268.81 (62.18)	270.22 (63.45)
Month 18	Mean (SD)	263.87 (66.85)	265.72 (63.18)	275.13 (67.33)
Change from baseline to Month 18	Mean (SD)	-7.65 (45.83)	-3.09 (45.00)	4.91 (46.85)
	n	297	346	308
Baseline	Mean (SD)	270.27 (64.51)	269.06 (61.15)	271.34 (65.09)
Month 24	Mean (SD)	261.75 (67.21)	264.75 (64.91)	270.05 (65.02)
Change from baseline to Month 24	Mean (SD)	-8.52 (40.43)	-4.31 (47.10)	-1.28 (45.67)

Haematology changes from baseline in Group E (all FTY720-treated safety population)

Group E provides the longest exposure period and the greatest numbers of patients receiving FTY720 1.25 mg and 0.5 mg. Change from baseline for FTY720 1.25 mg and FTY720 0.5 mg groups is shown at Month 1, 6, 12, 18, 24 and 60 for WBC, absolute lymphocytes, absolute neutrophils and platelet count in Table 74.

Table 74: Mean change from baseline in WBC, absolute lymphocytes, absolute neutrophils and platelet count, by visit and treatment for Group E (Safety population)

	Statistics	FTY720 1.25 mg N=1157	FTY720 0.5 mg N=1021
WBC (total) (10^9/L)			
	N	1041	955
Baseline	Mean (SD)	6.54 (1.95)	6.44 (1.81)
Month 1	Mean (SD)	4.31 (1.65)	4.45 (1.49)
Change from baseline to Month 1	Mean (SD)	-2.24 (1.79)	-1.99 (1.52)
	N	1005	938
Baseline	Mean (SD)	6.56 (1.94)	6.43 (1.81)
Month 6	Mean (SD)	4.02 (1.46)	4.31 (1.47)
Change from baseline to Month 6	Mean (SD)	-2.54 (1.72)	-2.11 (1.57)
	N	866	809
Baseline	Mean (SD)	6.61 (1.96)	6.44 (1.81)
Month 12	Mean (SD)	4.05 (1.45)	4.29 (1.51)
Change from baseline to Month 12	Mean (SD)	-2.56 (1.72)	-2.15 (1.64)
	N	701	678
Baseline	Mean (SD)	6.64 (1.88)	6.43 (1.74)
Month 18	Mean (SD)	4.18 (1.45)	4.38 (1.52)
Change from baseline to Month 18	Mean (SD)	-2.46 (1.70)	-2.05 (1.63)
	N	501	462
Baseline	Mean (SD)	6.76 (1.90)	6.47 (1.80)
Month 24	Mean (SD)	4.20 (1.60)	4.22 (1.55)
Change from baseline to Month 24	Mean (SD)	-2.57 (1.78)	-2.25 (1.67)
	N	48	
Baseline	Mean (SD)	6.99 (2.00)	
Month 60	Mean (SD)	4.43 (1.20)	
Change from baseline to Month 60	Mean (SD)	-2.56 (1.73)	
Absolute lymphocytes (10^9/L)			
	N	1027	939
Baseline	Mean (SD)	1.80 (0.56)	1.80 (0.59)
Month 1	Mean (SD)	0.43 (0.25)	0.49 (0.27)
Change from baseline to Month 1	Mean (SD)	-1.38 (0.55)	-1.31 (0.57)
	N	986	925
Baseline	Mean (SD)	1.81 (0.55)	1.79 (0.58)
Month 6	Mean (SD)	0.41 (0.25)	0.49 (0.30)
Change from baseline to Month 6	Mean (SD)	-1.39 (0.55)	-1.31 (0.58)
	N	855	798
Baseline	Mean (SD)	1.81 (0.55)	1.81 (0.58)
Month 12	Mean (SD)	0.43 (0.26)	0.49 (0.30)
Change from baseline to Month 12	Mean (SD)	-1.38 (0.53)	-1.31 (0.55)
	N	695	670
Baseline	Mean (SD)	1.83 (0.53)	1.80 (0.58)
Month 18	Mean (SD)	0.46 (0.29)	0.49 (0.29)
Change from baseline to Month 18	Mean (SD)	-1.37 (0.53)	-1.31 (0.55)

Table 74(cont.): Mean change from baseline in WBC, absolute lymphocytes, absolute neutrophils and platelet count, by visit and treatment for Group E (Safety population)

	Statistics	FTY720 1.25 mg N=1157	FTY720 0.5 mg N=1021
	N	495	451
Baseline	Mean (SD)	1.86 (0.55)	1.83 (0.60)
Month 24	Mean (SD)	0.44 (0.28)	0.47 (0.31)
Change from baseline to Month 24	Mean (SD)	-1.42 (0.54)	-1.36 (0.57)
	N	47	
Baseline	Mean (SD)	1.96 (0.69)	
Month 60	Mean (SD)	0.46 (0.21)	
Change from baseline to Month 60	Mean (SD)	-1.50 (0.61)	
Absolute neutrophils (10^9/L)			
	N	1027	940
Baseline	Mean (SD)	4.08 (1.60)	4.00 (1.45)
Month 1	Mean (SD)	3.33 (1.52)	3.40 (1.33)
Change from baseline to Month 1	Mean (SD)	-0.75 (1.60)	-0.59 (1.31)
	N	987	928
Baseline	Mean (SD)	4.09 (1.59)	3.99 (1.44)
Month 6	Mean (SD)	3.09 (1.32)	3.29 (1.29)
Change from baseline to Month 6	Mean (SD)	-1.00 (1.49)	-0.70 (1.29)
	N	856	801
Baseline	Mean (SD)	4.13 (1.61)	3.98 (1.44)
Month 12	Mean (SD)	3.10 (1.26)	3.28 (1.32)
Change from baseline to Month 12	Mean (SD)	-1.03 (1.47)	-0.70 (1.40)
	N	695	672
Baseline	Mean (SD)	4.14 (1.53)	3.97 (1.38)
Month 18	Mean (SD)	3.19 (1.27)	3.34 (1.34)
Change from baseline to Month 18	Mean (SD)	-0.95 (1.42)	-0.63 (1.37)
	N	498	454
Baseline	Mean (SD)	4.24 (1.54)	4.00 (1.42)
Month 24	Mean (SD)	3.20 (1.43)	3.23 (1.36)
Change from baseline to Month 24	Mean (SD)	-1.05 (1.55)	-0.77 (1.42)
	N	47	
Baseline	Mean (SD)	4.46 (1.63)	
Month 60	Mean (SD)	3.46 (1.06)	
Change from baseline to Month 60	Mean (SD)	-1.00 (1.52)	
Platelet count (10^9/L)			
	N	1039	951
Baseline	Mean (SD)	268.82 (64.35)	269.34 (65.77)
Month 1	Mean (SD)	255.32 (60.69)	260.74 (57.81)
Change from baseline to Month 1	Mean (SD)	-13.50 (38.35)	-8.61 (38.26)
	N	1006	936
Baseline	Mean (SD)	268.55 (63.74)	269.29 (66.29)
Month 6	Mean (SD)	263.96 (64.08)	267.34 (63.84)
Change from baseline to Month 6	Mean (SD)	-4.59 (44.01)	-1.94 (44.90)
	N	864	808
Baseline	Mean (SD)	269.87 (64.20)	270.43 (65.47)
Month 12	Mean (SD)	261.88 (62.05)	264.11 (62.02)

Table 74(cont.): Mean change from baseline in WBC, absolute lymphocytes, absolute neutrophils and platelet count, by visit and treatment for Group E (Safety population)

	Statistics	FTY720 1.25 mg N=1157	FTY720 0.5 mg N=1021
Change from baseline to Month 12	Mean (SD)	-7.99 (40.81)	-6.32 (43.226)
	N	703	678
Baseline	Mean (SD)	269.34 (63.02)	268.96 (63.84)
Month 18	Mean (SD)	267.94 (64.70)	270.35 (66.29)
Change from baseline to Month 18	Mean (SD)	-1.40 (45.30)	1.39 (47.07)
	N	500	460
Baseline	Mean (SD)	267.93 (61.57)	270.33 (62.33)
Month 24	Mean (SD)	263.73 (65.92)	265.71 (65.39)
Change from baseline to Month 24	Mean (SD)	-4.21 (44.01)	-4.62 (46.07)
	N	48	
Baseline	Mean (SD)	273.44 (58.46)	
Month 60	Mean (SD)	274.06 (63.96)	
Change from baseline to Month 60	Mean (SD)	0.62 (46.14)	

At 2 weeks post-baseline (Week 1 in D2201, Week 2 in D2301, D2302), the mean lymphocyte count in the FTY720 1.25 mg group was reduced by approximately 75% (which can be compared to a 70% reduction in the FTY720 0.5 mg group). As with Group B, lymphocyte counts then remained relatively stable during the 24 month treatment period. Lymphocyte count for the 1.25 mg dose also remained stable up to Month 60. At each visit up to Month 24, reductions from baseline were slightly greater for the 1.25 mg dose than the 0.5 mg dose.

Mean neutrophil counts were reduced from baseline by approximately 20% in the FTY720 1.25 mg group and by approximately 13% in the FTY720 0.5 mg group at 2 weeks. At subsequent visits the neutrophil counts remained relatively stable in both FTY720 treatment groups, up to Month 24 for FTY720 0.5 mg and up to Month 60 for FTY720 1.25 mg. At each visit up to Month 24, reductions from baseline were greater for the 1.25 mg dose compared with the 0.5 mg dose.

Mean total WBC counts were reduced from baseline by approximately 34% in the FTY720 1.25 mg group and by approximately 28% in the FTY720 0.5 mg group at 2 weeks. Thereafter WBC levels remained largely stable for both groups. Reductions from baseline in total WBC were consistently greater for the FTY720 1.25 mg compared to the FTY720 0.5 mg group up to Month 24.

Mean platelet counts were slightly reduced relative to baseline in the FTY720 groups at 2 weeks post-baseline; approximately 5% for the FTY720 1.25 mg group and approximately 2% for the FTY720 0.5 mg group. Levels returned towards baseline values at Month 3.

No noteworthy changes from baseline in mean values were seen for any of the other haematology parameters.

Haematology changes from baseline in Group E by subgroup

There was a trend towards slightly greater mean reductions from baseline in lymphocyte counts for females compared to males in both FTY720 1.25 mg and 0.5 mg groups. At Month 24, mean lymphocyte count in females was reduced by approximately 78% (versus 71% in males) for FTY720 1.25 mg and by approximately 75% (versus 72% in males) for FTY720 0.5 mg. There were no noteworthy gender differences in the other haematology parameters. No clinically relevant differences were seen between age groups.

Summary of haematology abnormalities across populations

In the MS studies, treatment-emergent clinically notably low WBC and lymphocyte counts occurred at higher frequencies on FTY720 treatment than in the control groups across Groups A, B, and C. Also the proportion of patients with clinically notably low neutrophil counts tended to be higher on

FTY720 treatment, in particular the 1.25 mg and 5.0 mg doses. Other haematology parameters did not show clinically relevant differences between FTY720 and the control groups.

The incidence of clinically notably low values for WBC, lymphocytes, and neutrophils was higher on FTY720 1.25 mg than on 0.5 mg across Groups A, B, C, D, and E. As expected, the majority of shifts were from normal to low for lymphocytes, neutrophils and WBC. The most noticeable shifts were for lymphocytes counts. Shifts to low for WBC and neutrophil counts were more frequent in the 1.25 mg group than the 0.5 mg group.

Clinical chemistry

Clinical chemistry changes from baseline in Group B (double-blind, randomised, controlled study, 24-month treatment)

Mean changes from baseline at Month 1, 6, 12, 18 and 24 for ALT, AST, alkaline phosphatase, bilirubin, cholesterol and creatinine are summarised in Table 75. Mean ALT values for the FTY720 1.25 mg and 0.5 mg groups were increased from Week 2 and tended to increase further until Month 9. Subsequently values decreased slightly up to Month 24 when mean increases from baseline in ALT values were 13.30 U/L and 13.52 U/L in the FTY720 1.25 mg and 0.5 mg groups, respectively. There were no meaningful changes in mean ALT values over the treatment period for placebo.

Mean AST values in the FTY720 groups increased from Week 2 and tended to stabilize at subsequent visits from Month 1. At Month 24, mean ALT had increased from baseline by 4.77 U/L and 5.34 U/L in the FTY720 1.25 mg and 0.5 mg groups, respectively. There were no meaningful changes in mean AST values over the treatment period for placebo.

Mean GGT values increased in both FTY720 treatment groups tending to stabilise from Month 9. At Month 24, mean GGT increases from baseline were 36.12 U/L and 31.80 U/L for FTY720 1.25 mg and 0.5 mg, respectively. No clinically relevant changes in the placebo group were observed.

Table 75: Mean change from baseline in ALT, AST, alkaline phosphatase, bilirubin, cholesterol and creatinine, by visit and treatment for Group B (Safety population)

	Statistics	FTY720 1.25 mg N=429	FTY720 0.5 mg N=425	Placebo N=418
ALT (U/L)				
	n	403	403	400
Baseline	Mean (SD)	20.42 (12.03)	20.21 (12.35)	20.69 (12.79)
Month 1	Mean (SD)	34.20 (39.61)	27.48 (20.28)	20.40 (12.55)
Change from baseline to Month 1	Mean (SD)	13.78 (31.86)	7.27 (14.22)	-0.29 (11.42)
	n	375	402	388
Baseline	Mean (SD)	19.58 (10.64)	20.50 (12.80)	20.73 (12.94)
Month 6	Mean (SD)	34.53 (27.67)	35.18 (26.84)	21.29 (14.55)
Change from baseline to Month 6	Mean (SD)	14.95 (23.97)	14.68 (23.72)	0.56 (16.05)
	n	354	386	359
Baseline	Mean (SD)	19.21 (10.53)	20.22 (12.34)	20.96 (13.23)
Month 12	Mean (SD)	34.32 (25.03)	35.18 (30.27)	21.54 (19.14)
Change from baseline to Month 12	Mean (SD)	15.11 (21.68)	14.96 (28.47)	0.58 (19.33)
	n	324	366	327
Baseline	Mean (SD)	18.89 (10.40)	19.93 (11.81)	20.90 (13.15)
Month 18	Mean (SD)	33.57 (24.31)	34.17 (25.80)	20.81 (11.79)
Change from baseline to Month 18	Mean (SD)	14.68 (21.82)	14.24 (24.12)	-0.09 (13.98)
	n	306	347	311
Baseline	Mean (SD)	18.85 (10.40)	19.81 (11.46)	20.60 (13.30)
Month 24	Mean (SD)	32.15 (21.24)	33.33 (23.13)	21.19 (13.98)
Change from baseline to Month 24	Mean (SD)	13.30 (18.93)	13.52 (19.67)	0.59 (15.79)
AST (U/L)				
	n	403	403	400
Baseline	Mean (SD)	19.81 (6.10)	19.35 (6.09)	20.08 (7.56)
Month 1	Mean (SD)	25.19 (16.69)	22.10 (8.22)	19.70 (6.99)
Change from baseline to Month 1	Mean (SD)	5.38 (13.77)	2.76 (7.03)	-0.38 (7.15)
	n	375	402	388
Baseline	Mean (SD)	19.48 (5.82)	19.54 (6.56)	20.19 (7.80)
Month 6	Mean (SD)	25.14 (11.40)	25.39 (10.68)	20.15 (7.05)
Change from baseline to Month 6	Mean (SD)	5.66 (9.75)	5.85 (10.66)	-0.05 (8.44)
	n	354	386	359
Baseline	Mean (SD)	19.42 (5.87)	19.33 (5.82)	20.36 (7.98)
Month 12	Mean (SD)	24.85 (10.19)	25.45 (12.21)	20.87 (9.87)
Change from baseline to Month 12	Mean (SD)	5.43 (9.41)	6.12 (11.78)	0.51 (10.62)
	n	324	366	327
Baseline	Mean (SD)	19.34 (5.86)	19.25 (5.79)	20.39 (7.97)
Month 18	Mean (SD)	24.97 (10.40)	24.77 (10.16)	20.73 (7.87)
Change from baseline to Month 18	Mean (SD)	5.63 (9.53)	5.53 (10.15)	0.33 (8.65)
	n	306	347	311
Baseline	Mean (SD)	19.38 (5.97)	19.21 (5.63)	20.25 (8.07)
Month 24	Mean (SD)	24.15 (9.82)	24.55 (10.20)	20.25 (7.04)
Change from baseline to Month 24	Mean (SD)	4.77 (8.54)	5.34 (9.51)	0.00 (8.76)

Table 75(cont.): Mean change from baseline in ALT, AST, alkaline phosphatase, bilirubin, cholesterol and creatinine, by visit and treatment for Group B (Safety population)

	Statistics	FTY720 1.25 mg N=429	FTY720 0.5 mg N=425	Placebo N=418
Alkaline phosphatase (U/L)				
	n	404	404	402
Baseline	Mean (SD)	63.92 (18.23)	63.12 (18.08)	64.55 (19.93)
Month 1	Mean (SD)	66.20 (23.87)	64.47 (19.64)	64.67 (20.41)
Change from baseline to Month 1	Mean (SD)	2.28 (13.20)	1.36 (9.46)	0.12 (8.79)
	n	378	403	388
Baseline	Mean (SD)	63.32 (17.95)	63.53 (18.79)	64.78 (20.05)
Month 6	Mean (SD)	66.79 (31.47)	65.30 (22.71)	65.27 (20.16)
Change from baseline to Month 6	Mean (SD)	3.47 (25.03)	1.77 (14.83)	0.49 (12.01)
	n	354	387	360
Baseline	Mean (SD)	63.23 (18.11)	63.50 (19.01)	64.44 (19.83)
Month 12	Mean (SD)	66.15 (26.23)	65.46 (22.43)	64.68 (19.95)
Change from baseline to Month 12	Mean (SD)	2.92 (19.09)	1.96 (16.03)	0.24 (11.70)
	n	324	267	327
Baseline	Mean (SD)	63.23 (18.17)	63.15 (19.04)	64.40 (19.96)
Month 18	Mean (SD)	66.14 (23.90)	65.43 (22.11)	63.85 (19.45)
Change from baseline to Month 18	Mean (SD)	2.91 (17.19)	2.28 (15.34)	-0.56 (12.00)
	n	307	348	313
Baseline	Mean (SD)	63.40 (18.23)	63.20 (18.91)	64.33 (20.10)
Month 24	Mean (SD)	67.81 (26.26)	65.84 (21.44)	63.48 (19.08)
Change from baseline to Month 24	Mean (SD)	4.41 (17.83)	2.65 (16.32)	-0.85 (11.81)
Bilirubin (µmol/L)				
	n	404	404	402
Baseline	Mean (SD)	9.09 (4.91)	9.21 (4.32)	9.13 (4.72)
Month 1	Mean (SD)	9.99 (5.84)	10.20 (5.25)	9.34 (5.09)
Change from baseline to Month 1	Mean (SD)	0.89 (4.28)	0.99 (3.71)	0.21 (3.80)
	n	378	403	388
Baseline	Mean (SD)	9.13 (4.96)	9.26 (4.33)	9.10 (4.72)
Month 6	Mean (SD)	9.76 (4.93)	9.93 (4.54)	9.43 (5.39)
Change from baseline to Month 6	Mean (SD)	0.62 (3.97)	0.67 (3.74)	0.32 (3.75)
	n	354	388	360
Baseline	Mean (SD)	9.08 (4.75)	9.23 (4.32)	9.25 (4.87)
Month 12	Mean (SD)	9.70 (4.97)	10.07 (5.12)	9.63 (5.85)
Change from baseline to Month 12	Mean (SD)	0.62 (3.62)	0.84 (3.85)	0.38 (4.02)
	n	324	367	327
Baseline	Mean (SD)	9.08 (4.81)	9.25 (4.30)	9.39 (5.05)
Month 18	Mean (SD)	9.72 (5.01)	10.09 (5.10)	9.66 (5.74)
Change from baseline to Month 18	Mean (SD)	0.65 (3.72)	0.84 (3.74)	0.27 (4.15)
	n	307	349	313
Baseline	Mean (SD)	9.16 (4.86)	9.36 (4.38)	9.29 (4.93)
Month 24	Mean (SD)	8.82 (4.38)	9.29 (4.74)	8.95 (6.17)
Change from baseline to Month 24	Mean (SD)	-0.35 (4.36)	-0.07 (3.95)	-0.34 (4.05)

Table 75(cont.): Mean change from baseline in ALT, AST, alkaline phosphatase, bilirubin, cholesterol and creatinine, by visit and treatment for Group B (Safety population)

	Statistics	FTY720 1.25 mg N=429	FTY720 0.5 mg N=425	Placebo N=418
Cholesterol (mmol/L)				
	n	279	380	382
Baseline	Mean (SD)	5.09 (1.00)	5.11 (1.05)	5.04 (0.96)
Month 1	Mean (SD)	5.14 (1.01)	5.19 (1.07)	5.02 (0.98)
Change from baseline to Month 1	Mean (SD)	0.05 (0.64)	0.07 (0.63)	-0.02 (0.58)
	n	352	379	371
Baseline	Mean (SD)	5.06 (1.00)	5.090 (1.04)	5.04 (0.96)
Month 6	Mean (SD)	5.30 (1.04)	5.32 (1.12)	5.13 (0.96)
Change from baseline to Month 6	Mean (SD)	0.24 (0.69)	0.23 (0.72)	0.10 (0.60)
	n	329	364	346
Baseline	Mean (SD)	5.05 (1.01)	5.08 (1.03)	5.04 (0.96)
Month 12	Mean (SD)	5.42 (1.07)	5.36 (1.06)	5.14 (1.01)
Change from baseline to Month 12	Mean (SD)	0.36 (0.77)	0.28 (0.75)	0.10 (0.67)
	n	304	344	315
Baseline	Mean (SD)	5.05 (1.0)	5.08 (1.05)	5.04 (0.94)
Month 18	Mean (SD)	5.36 (0.95)	5.35 (1.03)	5.11 (0.99)
Change from baseline to Month 18	Mean (SD)	0.31 (0.78)	0.27 (0.81)	0.07 (0.72)
	n	287	326	302
Baseline	Mean (SD)	5.02 (1.00)	5.08 (1.04)	5.02 (0.94)
Month 24	Mean (SD)	5.43 (1.05)	5.43 (1.09)	5.11 (0.93)
Change from baseline to Month 24	Mean (SD)	0.41 (0.75)	0.36 (0.82)	0.09 (0.70)
Creatinine				
	n	404	404	402
Baseline	Mean (SD)	68.62 (11.85)	69.12 (12.27)	68.79 (11.92)
Month 1	Mean (SD)	67.10 (11.46)	68.67 (11.22)	68.82 (12.35)
Change from baseline to Month 1	Mean (SD)	-1.52 (6.14)	-0.45 (6.94)	0.03 (6.26)
	n	378	403	388
Baseline	Mean (SD)	68.37 (11.67)	68.84 (11.72)	68.91 (11.97)
Month 6	Mean (SD)	67.80 (11.83)	69.04 (13.7)	69.55 (11.8)
Change from baseline to Month 6	Mean (SD)	-0.57 (7.47)	0.20 (10.47)	0.64 (7.33)
	n	354	388	360
Baseline	Mean (SD)	68.29 (11.64)	68.71 (11.40)	69.17 (12.01)
Month 12	Mean (SD)	68.19 (11.13)	69.55 (11.40)	69.48 (11.26)
Change from baseline to Month 12	Mean (SD)	-0.11 (7.58)	0.84 (6.98)	0.31 (7.09)
	n	324	367	327
Baseline	Mean (SD)	68.15 (11.54)	68.53 (11.39)	68.87 (11.81)
Month 18	Mean (SD)	68.24 (11.20)	69.23 (12.08)	69.61 (11.48)
Change from baseline to Month 18	Mean (SD)	0.10 (7.53)	0.69 (7.62)	0.74 (6.92)
	n	307	349	313
Baseline	Mean (SD)	68.30 (11.63)	68.63 (11.39)	68.93 (11.97)
Month 24	Mean (SD)	68.78 (11.11)	69.34 (11.06)	69.74 (11.34)
Change from baseline to Month 24	Mean (SD)	0.49 (7.66)	0.71 (7.17)	0.81 (7.81)

Clinical chemistry in changes from baseline in Group E (all FTY720 treated Safety population)

Mean changes from baseline at Month 1, 6, 12, 18, 24 and 60 for ALT, AST, alkaline phosphatase, bilirubin, cholesterol and creatinine are summarised in Table 76. ALT values in the two FTY720 groups tended to increase from Week 2 until Month 6 when they stabilised. At Month 24 mean increases from baseline were 14.14 U/L and 13.18 U/L for the FTY720 1.25 mg and 0.5 mg groups. ALT values remained relatively stable in the FTY720 1.25 mg group until Month 60. Increases from baseline for ALT tended to be greater in the FTY720 1.25 mg dose group than in the 0.5 mg dose group.

Mean AST values in the FTY720 groups increased from Week 2 and tended to stabilise from Month 1 for the FTY720 1.25 mg group and from Month 6 in the FTY720 0.5 mg group. At Month 24, mean AST had increased from baseline by 4.67 U/L and 5.02 U/L in the FTY720 1.25 mg and 0.5 mg groups, respectively. There was no evidence of dose dependency for AST change from baseline values.

Mean GGT values increased in both FTY720 treatment groups at Week 2 tending to stabilise from Month 12 to Month 18. At Month 24, GGT values had increased from baseline by 36.04 U/L and 30.83 U/L in the FTY720 1.25 mg and 0.5 mg groups, respectively. Increases from baseline for GGT tended to be greater in the FTY720 1.25 mg group compared with the FTY720 0.5 mg group.

Table 76: Mean change from baseline in ALT, AST, alkaline phosphatase, bilirubin, cholesterol and creatinine, by visit and treatment for Group E (Safety population)

	Statistics	FTY720 1.25 mg N=1157	FTY720 0.5 mg N=1021
ALT (U/L)			
	n	1057	976
Baseline	Mean (SD)	21.06 (12.36)	21.17 (12.43)
Month 1	Mean (SD)	33.44 (41.79)	29.43 (29.25)
Change from baseline to Month 1	Mean (SD)	12.38 (36.89)	8.26 (25.02)
	n	1036	962
Baseline	Mean (SD)	20.62 (11.78)	21.26 (12.62)
Month 6	Mean (SD)	35.19 (29.20)	35.00 (27.45)
Change from baseline to Month 6	Mean (SD)	14.57 (26.82)	13.74 (24.80)
	n	874	821
Baseline	Mean (SD)	19.98 (11.07)	20.84 (12.16)
Month 12	Mean (SD)	34.60 (26.38)	34.84 (27.63)
Change from baseline to Month 12	Mean (SD)	14.62 (24.18)	14.00 (25.78)
	n	722	694
Baseline	Mean (SD)	19.54 (10.70)	20.33 (11.72)
Month 18	Mean (SD)	34.06 (23.75)	34.08 (24.56)
Change from baseline to Month 18	Mean (SD)	14.51 (21.95)	13.75 (23.03)
	n	510	461
Baseline	Mean (SD)	19.31 (10.86)	19.99 (11.23)
Month 24	Mean (SD)	33.45 (22.63)	33.17 (22.21)
Change from baseline to Month 24	Mean (SD)	14.14 (20.49)	13.18 (18.77)
	n	48	
Baseline	Mean (SD)	20.10 (9.47)	
Month 60	Mean (SD)	35.43 (22.89)	
Change from baseline to Month 60	Mean (SD)	15.32 (20.13)	
AST (U/L)			
	n	1057	976
Baseline	Mean (SD)	19.81 (6.11)	19.66 (6.60)
Month 1	Mean (SD)	24.80 (22.03)	22.64 (11.93)
Change from baseline to Month 1	Mean (SD)	5.00 (20.82)	2.98 (10.64)
	n	1036	962
Baseline	Mean (SD)	19.58 (5.89)	19.74 (6.76)
Month 6	Mean (SD)	24.91 (12.04)	24.94 (11.02)
Change from baseline to Month 6	Mean (SD)	5.33 (11.37)	5.20 (10.70)
	n	874	821
Baseline	Mean (SD)	19.48 (5.93)	19.48 (6.08)
Month 12	Mean (SD)	24.51 (10.02)	25.05 (11.85)
Change from baseline to Month 12	Mean (SD)	5.03 (9.77)	5.56 (11.31)
	n	722	694
Baseline	Mean (SD)	19.34 (5.92)	19.31 (6.02)
Month 18	Mean (SD)	24.88 (11.87)	24.45 (9.55)
Change from baseline to Month 18	Mean (SD)	5.54 (11.23)	5.14 (9.62)

Table 76(cont.): Mean change from baseline in ALT, AST, alkaline phosphatase, bilirubin, cholesterol and creatinine, by visit and treatment for Group E (Safety population)

	Statistics	FTY720 1.25 mg N=1157	FTY720 0.5 mg N=1021
	n	510	461
Baseline	Mean (SD)	19.44 (6.09)	19.31 (5.66)
Month 24	Mean (SD)	24.11 (9.62)	24.33 (9.56)
Change from baseline to Month 24	Mean (SD)	4.67 (8.87)	5.02 (8.83)
	n	48	
Baseline	Mean (SD)	19.83 (5.77)	
Month 60	Mean (SD)	24.24 (10.21)	
Change from baseline to Month 60	Mean (SD)	4.41 (9.05)	
Alkaline phosphatase (U/L)			
	n	1058	978
Baseline	Mean (SD)	63.03 (19.23)	62.76 (17.75)
Month 1	Mean (SD)	65.00 (23.17)	64.27 (20.96)
Change from baseline to Month 1	Mean (SD)	1.97 (13.17)	1.52 (11.67)
	n	1040	963
Baseline	Mean (SD)	62.40 (18.80)	62.83 (17.96)
Month 6	Mean (SD)	65.09 (26.32)	65.37 (24.38)
Change from baseline to Month 6	Mean (SD)	2.69 (19.63)	2.54 (17.54)
	n	874	823
Baseline	Mean (SD)	62.68 (19.02)	63.00 (18.26)
Month 12	Mean (SD)	65.27 (24.48)	64.98 (22.76)
Change from baseline to Month 12	Mean (SD)	2.58 (17.74)	1.98 (16.26)
	n	722	696
Baseline	Mean (SD)	62.68 (19.10)	62.83 (17.79)
Month 18	Mean (SD)	66.37 (24.03)	65.58 (22.13)
Change from baseline to Month 18	Mean (SD)	3.70 (17.32)	2.75 (15.42)
	n	513	462
Baseline	Mean (SD)	62.54 (18.26)	63.01 (17.83)
Month 24	Mean (SD)	67.35 (25.03)	65.38 (20.43)
Change from baseline to Month 24	Mean (SD)	4.81 (18.03)	2.37 (15.24)
	n	48	
Baseline	Mean (SD)	64.00 (17.85)	
Month 60	Mean (SD)	72.85 (27.05)	
Change from baseline to Month 60	Mean (SD)	8.85 (20.18)	
Bilirubin (µmol/L)			
	n	1058	978
Baseline	Mean (SD)	8.80 (4.97)	9.13 (4.46)
Month 1	Mean (SD)	9.56 (5.59)	9.99 (5.48)
Change from baseline to Month 1	Mean (SD)	0.78 (3.80)	0.86 (3.95)
	n	1041	964
Baseline	Mean (SD)	8.86 (5.13)	9.17 (4.49)
Month 6	Mean (SD)	9.39 (5.45)	9.83 (5.03)
Change from baseline to Month 6	Mean (SD)	0.53 (4.11)	0.66 (3.87)
	n	874	824
Baseline	Mean (SD)	8.82 (4.90)	9.20 (4.41)
Month 12	Mean (SD)	9.66 (5.21)	10.10 (5.36)

Table 76(cont.): Mean change from baseline in ALT, AST, alkaline phosphatase, bilirubin, cholesterol and creatinine, by visit and treatment for Group E (Safety population)

	Statistics	FTY720 1.25 mg N=1157	FTY720 0.5 mg N=1021
Change from baseline to Month 12	Mean (SD)	0.84 (3.77)	0.91 (3.83)
	n	722	696
Baseline	Mean (SD)	8.82 (4.92)	9.23 (4.48)
Month 18	Mean (SD)	9.45 (5.37)	9.94 (5.54)
Change from baseline to Month 18	Mean (SD)	0.63 (4.18)	0.71 (4.04)
	n	513	463
Baseline	Mean (SD)	8.93 (4.96)	9.33 (4.54)
Month 24	Mean (SD)	9.27 (5.67)	9.33 (5.10)
Change from baseline to Month 24	Mean (SD)	0.34 (4.80)	0.00 (4.13)
	n	48	
Baseline	Mean (SD)	8.36 (5.35)	
Month 60	Mean (SD)	9.27 (7.11)	
Change from baseline to Month 60	Mean (SD)	0.91 (4.13)	
Cholesterol (mmol/L)			
	n	1033	954
Baseline	Mean (SD)	4.99 (0.94)	5.02 (0.98)
Month 1	Mean (SD)	5.12 (1.00)	5.12 (1.00)
Change from baseline to Month 1	Mean (SD)	0.13 (0.60)	0.10 (0.64)
	n	1014	939
Baseline	Mean (SD)	5.00 (0.98)	5.00 (0.96)
Month 6	Mean (SD)	5.28 (1.03)	5.27 (1.06)
Change from baseline to Month 6	Mean (SD)	0.27 (0.72)	0.27 (0.72)
	n	849	800
Baseline	Mean (SD)	5.00 (0.96)	5.00 (0.97)
Month 12	Mean (SD)	5.32 (1.00)	5.28 (1.01)
Change from baseline to Month 12	Mean (SD)	0.31 (0.75)	0.28 (0.71)
	n	702	673
Baseline	Mean (SD)	5.02 (0.98)	5.04 (0.97)
Month 18	Mean (SD)	5.30 (0.98)	5.31 (0.99)
Change from baseline to Month 18	Mean (SD)	0.28 (0.76)	0.28 (0.79)
	n	493	440
Baseline	Mean (SD)	5.05 (1.00)	5.05 (0.99)
Month 24	Mean (SD)	5.40 (1.05)	5.43 (1.04)
Change from baseline to Month 24	Mean (SD)	0.35 (0.79)	0.38 (0.79)
	n	48	
Baseline	Mean (SD)	5.14 (0.94)	
Month 60	Mean (SD)	5.63 (1.06)	
Change from baseline to Month 60	Mean (SD)	0.50 (0.97)	
Creatinine (µmol/L)			
	n	1058	978
Baseline	Mean (SD)	67.74 (12.48)	68.77 (13.69)
Month 1	Mean (SD)	67.37 (12.42)	68.42 (11.88)
Change from baseline to Month 1	Mean (SD)	-0.37 (6.96)	-0.34 (9.37)

Table 76(cont.): Mean change from baseline in ALT, AST, alkaline phosphatase, bilirubin, cholesterol and creatinine, by visit and treatment for Group E (Safety population)

	Statistics	FTY720 1.25 mg N=1157	FTY720 0.5 mg N=1021
	n	1040	963
Baseline	Mean (SD)	67.48 (12.31)	68.56 (13.43)
Month 6	Mean (SD)	67.86 (12.05)	69.10 (12.73)
Change from baseline to Month 6	Mean (SD)	0.39 (7.36)	0.53 (11.16)
	n	874	824
Baseline	Mean (SD)	67.46 (12.27)	68.68 (13.54)
Month 12	Mean (SD)	68.57 (11.57)	69.86 (11.59)
Change from baseline to Month 12	Mean (SD)	1.11 (7.43)	1.18 (10.16)
	n	722	696
Baseline	Mean (SD)	67.57 (12.15)	68.64 (13.71)
Month 18	Mean (SD)	68.51 (11.74)	69.30 (12.21)
Change from baseline to Month 18	Mean (SD)	0.95 (7.71)	0.67 (11.06)
	n	513	463
Baseline	Mean (SD)	67.59 (11.88)	68.19 (11.18)
Month 24	Mean (SD)	69.01 (11.73)	69.15 (10.86)
Change from baseline to Month 24	Mean (SD)	1.43 (7.96)	0.96 (7.08)
	n	48	
Baseline	Mean (SD)	66.24 (12.19)	
Month 60	Mean (SD)	68.45 (10.84)	
Change from baseline to Month 60	Mean (SD)	2.21 (7.43)	

Summary of clinical chemistry changes from baseline across populations

In the MS studies, change from baseline in clinical chemistry parameters showed a consistent pattern across Groups A, B, C, D and E. Elevated mean levels of ALT, AST and GGT were seen post-baseline in the FTY720 treatment groups, while other biochemistry parameters did not show clinically relevant differences between the treatment groups. Following study drug discontinuation, liver enzyme levels (AST, GGT, and ALT) that were seen to increase in the FTY720 groups tended to return to near baseline values within 6 months post-discontinuation of study drug.

Clinical chemistry abnormalities

Clinical chemistry abnormalities in Group A (double-blind, randomised, active and placebo-controlled studies, 12 month treatment)

For ALT and GGT, a higher proportion of patients in the FTY720 groups had abnormally high levels compared with placebo and interferon. The frequency distribution for abnormal liver function tests relative to normal ranges at any post-baseline visit are presented for Group A in Table 77.

ALT levels >1 x ULN occurred at approximately a 2-3 fold higher frequency for the FTY720 treatment groups compared with placebo, and at approximately a 1.5 fold higher frequency compared with interferon. Results were comparable between the two FTY720 doses at each abnormality level.

For AST, the frequency of abnormal levels > 1 x ULN were approximately 3-4 fold higher in the FTY720 groups compared with the placebo group and 2-fold higher compared with the interferon group.

GGT levels ≥1 x ULN were approximately 4-5 fold more frequent in the FTY720 groups compared with placebo and approximately 3-fold more frequent compared with the interferon group. Results were generally comparable between the two FTY720 doses at each abnormality level.

ALT levels ≥ 3 x ULN were reported at an approximately 4-fold higher frequency for males than for females in both FTY720 treatment groups. In contrast, there were no noteworthy gender differences in the placebo and interferon groups. ALT levels ≥ 5 x ULN were also (3-4 fold) more frequent in FTY720-treated men than in FTY720-treated women. For ALT levels ≥ 5 x ULN, a higher frequency on FTY720 treatment compared with the two control groups was seen only in men but not in women. GGT levels ≥ 3 x ULN were reported at an approximately 2-3-fold higher frequency for males than for females in both FTY720 treatment groups. In contrast, there were no noteworthy gender differences in the placebo and interferon groups.

Table 77: Frequency (%) distribution of liver function tests for Group A (12- month treatment)

Parameters	Criterion	FTY720 1.25 mg (N=849) n (%)	FTY720 0.5 mg (N=854) n (%)	Placebo (N=418) n (%)	Interferon (N=431) n (%)
ALT	n	840	851	414	429
	No abnormalities	482 (57.4)	487 (57.2)	337 (81.4)	322 (75.1)
	> 1 × ULN	358 (42.6)	364 (42.8)	77 (18.6)	107 (24.9)
	≥ 2 × ULN	143 (17.0)	137 (16.1)	15 (3.6)	26 (6.1)
	≥ 3 × ULN	70 (8.3)	65 (7.6)	4 (1.0)	10 (2.3)
	≥ 5 × ULN	15 (1.8)	11 (1.3)	3 (0.7)	6 (1.4)
	≥ 10 × ULN	0	1 (0.1)	0	2 (0.5)
	≥ 20 × ULN	0	0	0	1 (0.2)
AST	n	840	851	414	429
	No abnormalities	620 (73.8)	661 (77.7)	385 (93.0)	370 (86.2)
	> 1 × ULN	220 (26.2)	190 (22.3)	29 (7.0)	59 (13.8)
	≥ 2 × ULN	38 (4.5)	32 (3.8)	5 (1.2)	13 (3.0)
	≥ 3 × ULN	10 (1.2)	14 (1.6)	3 (0.7)	8 (1.9)
	≥ 5 × ULN	1 (0.1)	2 (0.2)	0	3 (0.7)
	≥ 10 × ULN	0	0	0	2 (0.5)
	≥ 20 × ULN	0	0	0	1 (0.2)
GGT	n	840	851	414	429
	No abnormalities	562 (66.9)	604 (71.0)	386 (93.2)	383 (89.3)
	> 1 × ULN	278 (33.1)	247 (29.0)	28 (6.8)	46 (10.7)
	≥ 2 × ULN	133 (15.8)	97 (11.4)	9 (2.2)	16 (3.7)
	≥ 3 × ULN	63 (7.5)	51 (6.0)	3 (0.7)	6 (1.4)
	≥ 5 × ULN	21 (2.5)	14 (1.6)	0	2 (0.5)
	≥ 10 × ULN	0	1 (0.1)	0	1 (0.2)
	≥ 20 × ULN	0	1 (0.1)	0	0
Total bilirubin	n	840	851	414	429
	No abnormalities	773 (92.0)	769 (90.4)	380 (91.8)	398 (92.8)
	> 1 × ULN	67 (8.0)	82 (9.6)	34 (8.2)	31 (7.2)
	≥ 2 × ULN	7 (0.8)	8 (0.9)	2 (0.5)	2 (0.5)

The highest ratio of actual lab value/upper limit value was used. If the value is ≥ 20 × ULN, it is also included in the >= 10 × ULN category and all the above categories.
n = Number of patients with the given criterion.
Total = total number of patients with the parameter value at the respective time point.

Clinical chemistry abnormalities in Group E (all FTY720 treated safety population)

The frequency distribution for abnormal liver function tests relative to normal ranges at any post-baseline visit is presented for Group E for the FTY720 1.25 mg and FTY720 0.5 mg groups in Table 78.

ALT levels >1 × ULN were comparable between FTY720 1.25 mg and 0.5 mg. ALT level ≥2 x ULN were slightly more frequent in the FTY720 1.25 mg group than the 0.5 mg group. ALT levels ≥3 x ULN and upwards were seen with similar frequency in the FTY720 1.25 mg and 0.5 mg groups. For AST, the frequency of abnormal levels > 1 x ULN was higher in the FTY720 1.25 mg group compared with the 0.5 mg group. AST level ≥2 x ULN and upwards were seen at a similar frequency between the two FTY720 dose groups. GGT levels > 1 x ULN and upwards to ≥5 x ULN were slightly higher in the FTY720 1.25 mg group compared with the FTY720 0.5 mg group.

Summary of clinical chemistry abnormalities across populations

Clinical chemistry abnormalities showed a generally consistent pattern across the datasets for the MS studies. A higher proportion of patients in the FTY720 groups had treatment emergent abnormally high levels of ALT and GGT compared with the controls across Groups A, B, C, and D. The incidence of these abnormalities was similar on 1.25 mg and 0.5 mg. In Group C, the 5 mg dose appeared to further increase the incidence of abnormally high ALT and AST values. FTY720 treatment had no clinically relevant effect on clinical chemistry parameters other than ALT, AST and GGT. The incidence of abnormally high ALT, AST and GGT levels on FTY720 treatment was greater in males than in females.

Table 78: Frequency (%) distribution of liver function tests for Group E (all FTY720-treated safety population)

Parameters	Criterion	FTY720 1.25 mg (N=1157) n (%)	FTY720 0.5 mg (N=1021) n (%)
ALT	N	1143	1017
	No abnormalities	559 (48.9)	524 (51.5)
	> 1 × ULN	584 (51.1)	493 (48.5)
	≥ 2 × ULN	257 (22.5)	190 (18.7)
	≥ 3 × ULN	134 (11.7)	87 (8.6)
	≥ 5 × ULN	32 (2.8)	17 (1.7)
	≥ 10 × ULN	4 (0.3)	2 (0.2)
	≥ 20 × ULN	1 (<0.1)	0 (0.0)
AST	N	1143	1017
	No abnormalities	773 (67.6)	746 (73.4)
	> 1 × ULN	370 (32.4)	271 (26.6)
	≥ 2 × ULN	74 (6.5)	52 (5.1)
	≥ 3 × ULN	20 (1.7)	25 (2.5)
	≥ 5 × ULN	6 (0.5)	6 (0.6)
	≥ 10 × ULN	2 (0.2)	0 (0.0)
	≥ 20 × ULN	0 (0.0)	0 (0.0)
GGT	N	1010	1017
	No abnormalities	622 (61.6)	663 (65.2)
	> 1 × ULN	388 (38.4)	354 (34.8)
	≥ 2 × ULN	189 (18.7)	153 (15.0)
	≥ 3 × ULN	99 (9.8)	68 (6.7)
	≥ 5 × ULN	32 (3.2)	17 (1.7)
	≥ 10 × ULN	1 (<0.1)	2 (0.2)
	≥ 20 × ULN	0 (0.0)	1 (<0.1)
Total bilirubin	N	1143	1017
	No abnormalities	1027 (89.9)	910 (89.5)
	> 1 × ULN	116 (10.1)	107 (10.5)
	≥ 2 × ULN	12 (1.0)	10 (1.0)

n = number of patients with the notable abnormality criterion
Total = Total number of patients with the parameter value

Vital signs

Vital signs in Group B (double-blind, randomised, controlled study, 24 month treatment)

Clinically notable abnormalities for vital signs are presented for Group B in Table 79.

Table 79: Number (%) of patients with clinically notable abnormalities in vital signs for Group B (24-month treatment)

Vital Signs (units)	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: ≥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: ≥100	29 (6.8)	31 (7.3)	17 (4.1)
	≥15 increase from baseline	113 (26.3)	93 (21.9)	84 (20.1)
Sitting pulse (bpm)	Low: <50	6 (1.4)	5 (1.2)	6 (1.4)
	≥15 decrease from baseline	60 (14.0)	85 (20.0)	94 (22.5)
	High: >120	0	0	0
	≥15 increase from baseline	126 (29.4)	105 (24.7)	139 (33.3)

The highest (lowest) value is the maximum (minimum) of all post-baseline values excluding hourly dose monitoring values. The highest (lowest) change from baseline value is the maximum (minimum) of all change from baseline to post-baseline values excluding hourly dose monitoring values.
A patient can be counted in every category.

A higher percentage of patients in both FTY720 groups reported at least one notably high or notable increase in systolic or diastolic blood pressure (BP) compared to the placebo group. In contrast, there were higher percentages of patients with notably low measurements or notable decreases from baseline in the placebo group compared to the FTY720 groups. The incidence of hypertension AEs was also higher in both FTY720 groups compared to placebo for Group B.

Vital signs in Group E (all FTY720-treated safety population)

Consistent with Group B, increases in systolic, diastolic and arterial BP up to Month 24 were more pronounced in the FTY720 1.25 mg group compared to the FTY720 0.5 mg group. The proportion of patients with notably high or notable increases from baseline in systolic or diastolic BP was higher in the FTY720 1.25 mg group compared to the FTY720 0.5 mg group. The proportion of patients in Group E who experienced hypertension AEs appeared to be dose dependent. The incidence of hypertension reported as an AE was 7.3% and 5.7% in the FTY720 1.25 mg and 0.5 mg groups, respectively.

The dose-dependent increases in systolic, diastolic and mean arterial BP were seen in both genders. There were no clinically-relevant gender-related differences in the pulse measured when sitting. Dose-dependent changes in systolic, diastolic and mean arterial BP were observed in all age groups.

Adverse events of special interest

Subsets of AEs (SOCs and/or preferred terms) were defined based on emerging clinical experience to evaluate the incidence of certain events that are of value in understanding the safety profile of FTY720.

Subsets of particular interest include:

• Infections and infestations

• Pulmonary disorders

• Cardiac disorders

• Eye disorders

• Neoplasias

• Nervous system disorders

Infections and infestations

Adverse events in infections and infestations in Group A (double-blind, randomised, active and placebo-controlled studies, 12 month treatment)

The organ-related high-level terms are shown in Table 80. Of the organ-related terms, upper respiratory tract infections were the most frequently reported (more than 30% in each group) and occurred most frequently in the placebo group. Lower respiratory tract and lung infections were reported in a slightly higher proportion of patients in the two FTY720 groups compared to the placebo and interferon groups. Urinary tract infections were reported in a lower proportion of patients in the FTY720 1.25 mg group compared to the other three groups.

Of the microorganism-related terms, herpes viral infections were reported in a higher proportion of patients in the FTY720 1.25 mg group compared to the FTY720 0.5 mg, placebo, and interferon groups. There were two patients in the FTY720 1.25 mg group in Group A who had fatal infections (disseminated primary herpes zoster infection and herpes simplex encephalitis).

Table 80: Number (%) of patients with infections and infestations AEs by organ-related high-level term and preferred term in Group A (12-month treatment)

Organ-related high-level term	FTY720 1.25 mg (N=849) n (%)	FTY720 0.5 mg (N=854) n (%)	Placebo (N=418) n (%)	Interferon (N=431) n (%)
Any high level term	**468 (55.1)**	**467 (54.7)**	**245 (58.6)**	**220 (51.0)**
Upper respiratory tract infections	313 (36.9)	300 (35.1)	168 (40.2)	133 (30.9)
Lower respiratory tract and lung infections	58 (6.8)	49 (5.7)	19 (4.5)	15 (3.5)
Influenza viral infections	52 (6.1)	64 (7.5)	30 (7.2)	32 (7.4)
Urinary tract infections	49 (5.8)	68 (8.0)	50 (12.0)	30 (7.0)
Abdominal and gastrointestinal infections	33 (3.9)	29 (3.4)	14 (3.3)	16 (3.7)
Infections NEC	24 (2.8)	26 (3.0)	12 (2.9)	12 (2.8)
Dental and oral soft tissue infections	19 (2.2)	12 (1.4)	6 (1.4)	9 (2.1)
Ear infections	18 (2.1)	11 (1.3)	1 (0.2)	6 (1.4)
Female reproductive tract infections	11 (1.3)	7 (0.8)	6 (1.4)	6 (1.4)
Skin structures and soft tissue infections	8 (0.9)	11 (1.3)	5 (1.2)	0
Eye and eyelid infections	2 (0.2)	4 (0.5)	3 (0.7)	1 (0.2)
Bone and joint infections	1 (0.1)	0	1 (0.2)	0
Breast infections	0	0	2 (0.5)	0
Male reproductive tract infections	0	1 (0.1)	0	0
Muscle and soft tissue infections	0	1 (0.1)	0	0

High level terms are sorted in descending frequency for the FTY720 1.25 mg group.
A patient with multiple AEs within a High level term is counted only once in the total row.

The sponsor analysed the total number of infections (irrespective of type) by the lowest lymphocyte count measured during the 3 months prior to the onset of infection. The results are summarised by treatment group in Table 81.

Table 81: Infections and infestations AEs by nadir lymphocyte count in the 3 months before infection onset in Group A (12-month treatment)

	FTY720 1.25 mg (N=849)	FTY720 0.5 mg (N=854)	Placebo (N=418)	Interferon (N=431)
Total number of infections in the SOC infections and infestations (all infections i.e. all events, not by patient)	963	941	503	421
Total number of infections with a lymphocyte count available within 3 months before infection start date	846	832	440	364
Number of infections by lowest lymphocyte count before infection				
<200 cells/mm^3, n (%)	135 (16.0)	37 (4.4)	0	0
200-400 cells/mm^3, n (%)	476 (56.3)	421 (50.6)	1 (0.2)	0
>400 cells/ mm^3, n (%)	235 (27.8)	374 (45.0)	439 (99.8)	364 (100.0)

Percentages are calculated using the total number of infections with a lymphocyte count available 3 months before start date as denominator.
When determining available lymphocyte counts within 3 months of start date, only those on treatment were considered.

The total number of infections with a lymphocyte count available in the 3 months before infection start date was not higher in the FTY720 groups than on placebo (when corrected for the number of patients) although it tended to be higher than on interferon treatment. In the two FTY720 treatment groups, there was no clear relationship between lymphocyte count and the occurrence of infections.

Adverse events in infections and infestations in Group B (double-blind, randomised, controlled study, 24 month treatment)

Upper respiratory tract infections were the most frequently reported with no noteworthy differences among the treatment groups (about 50% in each treatment group). There were a dose dependent higher proportion of patients with lower respiratory tract and lung infections in both FTY720 treatment groups compared to the placebo group. Ear infections were also slightly higher in both FTY720 treatment groups. Urinary tract infections were reported for a greater proportion of placebo patients than the FTY720 patients.

The microorganism related high level terms are shown in Table 82. The most common high level microorganism terms were influenza viral infections and herpes viral infections, which occurred in a higher proportion of patients in the FTY720 0.5 mg group. The sponsor added the comment that both infection terms were reported less frequently in the FTY720 1.25 mg group than in the placebo group.

Table 82: Number (%) of patients with infections and infestations AEs by microorganism related high level term in Group B (24-month treatment)

Microorganism-related high-level term	FTY720 1.25 mg (N=429) n (%)	FTY720 0.5 mg (N=425) n (%)	Placebo (N=418) n (%)
Any high level term	**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)
Infections NEC	19 (4.4)	20 (4.7)	18 (4.3)
Fungal infections NEC	17 (4.0)	17 (4.0)	19 (4.5)
Bacterial infections NEC	11 (2.6)	3 (0.7)	9 (2.2)
Tinea infections	6 (1.4)	16 (3.8)	6 (1.4)
Candida infections	5 (1.2)	2 (0.5)	1 (0.2)
Papilloma viral infections	5 (1.2)	2 (0.5)	2 (0.5)
Borrelial infections	2 (0.5)	0	3 (0.7)
Sepsis, bacteraemia, viraemia and fungaemia NEC	2 (0.5)	0	1 (0.2)
Molluscum contagiosum viral infections	2 (0.5)	0	0
Bordetella infections	1 (0.2)	0	1 (0.2)
Campylobacter infections	1 (0.2)	0	0
Coxsackie viral infections	1 (0.2)	0	0
Enteroviral infections	1 (0.2)	0	0
Flaviviral infections	1 (0.2)	0	0
Streptococcal infections	1 (0.2)	1 (0.2)	1 (0.2)
Adenoviral infrections	0	0	1 (0.2)
Clostridia infections	0	0	1 (0.2)
Ectoparasitic infestations	0	1 (0.2)	1 (0.2)
Helminthic infections NEC	0	0	1 (0.2)
Mycoplasma infections	0	1 (0.2)	0
Nematode infections	0	0	1 (0.2)
Staphylococcal infections	0	1 (0.2)	0
Trichomonas infections	0	0	1 (0.2)

High level terms are sorted in descending frequency for the FTY720 1.25 mg group.
A patient with multiple AEs within a High level term is counted only once in the total row.

The rate of infections overall was not increased in patients treated with fingolimod 1.25 mg or 0.5 mg for up to 12 months in Group A compared to the control groups. The relative risk of infection compared to placebo of 0.94 (0.85, 1.04 95%CI) for fingolimod 1.25 mg and 0.93 (0.84, 1.03, 95% CI) for fingolimod 0.5 mg. Up to 24 months in Group B, a dose-dependent increased risk of lower respiratory tract infections (mainly bronchitis, few cases of pneumonia) was noted with fingolimod (6.8%, 5.7% and 4.5% in Group A and 11.4%, 9.6% and 6.0% in Group B for fingolimod 1.25 mg, 0.5 mg and placebo respectively) compared to placebo.

There were 3 cases of disseminated herpes infection reported in patients treated with fingolimod. Two fatal cases were 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; fulminant primary varicella infection with hepatitis in a sero-negative patient receiving concomitant high dose steroid therapy for a MS relapse. The third case 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 (for example systemic fungal or protozoal infections) were not reported.

Analyses of the relationship of nadir blood lymphocyte counts and occurrence of infections in Group A (Table 81) did not demonstrated a clearly increased risk of infection with reduced lymphocyte count. It is of interest that the lowest rates of infection (45.0%) occurred in the fingolimod group with blood lymphocyte counts above 0.4×10^9/L. Using data from Group A, the sponsor conducted modelling analyses to explore whether a relationship exists between lymphocyte count and infection. Results of this analysis did not find such a relationship. Low lymphocyte

counts were not predictive of infection, including serious infection, nor were higher counts protective.

Pulmonary disorders

In studies D2301, D2302, and D2201, pulmonary function tests (PFTs) evaluating FEV1, FVC, and carbon monoxide diffusing capacity (DLCO) were performed at the following time points:

• Study D2301: screening, Month 1, Month 3, Month 6, Month 12, Month 18 and Month 24

• Study D2302: screening, Month 1, Month 3, Month 6 and Month 12

• Study D2201: screening and Month 6

PFTs Group A (double-blind, randomised, active and placebo-controlled studies, 12 month treatment)

There was a small decrease in FEV_1 in both FTY720 groups starting at Month 1 and remaining stable thereafter. At Month 12, decreases in percent of predicted FEV1 were observed in both FTY720 groups and the placebo group but not in the interferon group; this corresponded to changes in absolute FEV_1 values of -0.15 L/s, -0.10 L/s, -0.08 L/s, and -0.02 L/s in the FTY720 1.25 mg, FTY720 0.5 mg, placebo and interferon groups, respectively. A different pattern was observed for changes from baseline in FVC: the FTY720 1.25 mg group had minor decreases over 12 months, whereas the FTY720 0.5 mg group had similar changes as the placebo and interferon groups. Mean percent of predicted FEV_1 values remained within the normal range across the treatment groups.

Frequency distribution of decreased FEV_1, FVC, and DLCO to less than 60% or 80% of baseline at a single visit or confirmed at 2 consecutive visits for Group A is shown in Table 83. A small number of patients experienced decreases in PFTs, mainly DLCO values, to less than 60% of baseline. There were no clinically meaningful differences between FTY720 dose groups in the frequency of changes in PFTs.

Table 83: Frequency distribution of decreased pulmonary function tests for Group A (12-month treatment)

	FTY720 1.25 mg (N=849) n (%)	FTY720 0.5 mg (N=854) n (%)	Placebo (N=418) n (%)	Interferon (N=431) n (%)
<80% of baseline PFT absolute values at any post-baseline visit				
FEV_1	45 (5.3)	34 (4.0)	14 (3.3)	15 (3.5)
FVC	24 (2.8)	17 (2.0)	8 (1.9)	11 (2.6)
D_LCO	121 (14.3)	104 (12.2)	29 (6.9)	62 (14.4)
<80% of baseline PFT absolute values at 2 consecutive post-baseline visits				
FEV_1	5 (0.6)	6 (0.7)	0	1 (0.2)
FVC	4 (0.5)	1 (0.1)	0	1 (0.2)
D_LCO	36 (4.2)	36 (4.2)	12 (2.9)	24 (5.6)
<60% of baseline PFT absolute values any post-baseline visit				
FEV_1	3 (0.4)	1 (0.1)	0	0
FVC	1 (0.1)	1 (0.1)	0	0
D_LCO	12 (1.4)	9 (1.1)	3 (0.7)	7 (1.6)
<60% of baseline PFT absolute values at 2 consecutive post-baseline visits				
FEV_1	0	0	0	0
FVC	0	0	0	0
D_LCO	5 (0.6)	3 (0.4)	2 (0.5)	3 (0.7)

Study 2201 (or 2201E1) data are not included in this summary as the data were not collected.

Few patients with a history of asthma experienced changes in PFTs to <80% of baseline values at a single visit or on two consecutive visits. There were no reports of PFT values decreasing to below 60% of baseline. Overall, patients with a history of asthma do not appear to be at increased risk of pulmonary function changes.

Chest high resolution computer tomography

Chest HRCT was performed for selected sites 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 specific PFT decreases (unscheduled HRCTs). Pooled analyses were not performed.

In Study D2301, 360 patients had chest HRCT scans at screening. Of these, 259 patients had the assessment at Month 24, and another 34 patients had an end-of-study scan performed outside of the 24-month visit window. At Month 24, the percentage of patients with chest HRCTs showing new or worsened abnormalities was higher in the fingolimod groups than in the placebo group (14.1% with fingolimod 1.25mg/day, 14.4% with fingolimod 0.5mg/day and 9.5% with placebo). No particular pattern of toxicity was noted and there was and no evidence of pulmonary fibrosis.

In Study D2302, chest HRCTs were performed in 478 patients at screening and 421 patients at Month 12. The proportion of patients with chest HRCTs showing new or worsening abnormalities compared to baseline was similar across groups (fingolimod 1.25mg/day, 0.5mg/day and placebo).

In Study D2309 preliminary data submitted for evaluation show no significant difference between fingolimod 0.5mg/day and placebo; however it should be requested that the sponsor submit further data when they become available.

Cardiac disorders

A transient decrease in heart rate and slowing of atrioventricular (AV) conduction upon treatment initiation are known pharmacodynamic effects of fingolimod. 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 hr 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 predefined discharge criteria (patients could only be discharged if maximal lowering effect on heart rate had already been observed in the first 6 hr, the heart rate was at least 51 bpm, the patient was asymptomatic, and the 6-hour ECG did not show any new relevant abnormality).

In the pooled Group A dataset the majority of patients in all treatment groups were discharged after 6 hr observation. Extended monitoring after 6 hr was more frequently required in patients receiving fingolimod 1.25 mg (18%) than in patients receiving fingolimod 0.5 mg (12%), placebo (3%) or IFN β-1a (1.4%). The number of patients required to return for Day 2 second-dose monitoring was higher for fingolimod groups than for placebo, with evidence of a dose effect. Symptomatic events on Day 2 occurred in 3 patients on fingolimod 1.25 mg and no patient on fingolimod 0.5 mg. Study drug was permanently discontinued after the first dose for 12 (1.4%) patients receiving fingolimod 1.25 mg compared to 2 (0.2%) patients receiving 0.5 mg and one (0.2%) patient receiving placebo.

Initiation of fingolimod treatment was associated with dose-dependent reductions in sitting pulse, starting as early as 1 hour after dosing. The decreases in sitting pulse on Day 1 peaked at 4-5 hr 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.

Adverse events in cardiac disorders in Group A (double-blind, randomised, active and placebo-controlled studies, 12 month treatment)

The proportion of patients with AEs in the SOC cardiac disorders is presented by preferred term for Group A in Table 83. The proportion of patients with cardiac disorder AEs was higher in the

FTY720 1.25 mg group compared to the FTY720 0.5 mg, placebo, and interferon groups, mainly due to the higher incidence of bradycardia, as well as first and second degree AV blocks.

The majority of bradycardia events occurred on Day 1. The proportion of patients (0.7%; six cases) with bradycardia occurring after Day 1 in the FTY720 1.25 mg group (five cases) and FTY720 0.5 mg group (one case) was similar to that in the placebo and interferon treatment groups. These events resolved without treatment and did not lead to discontinuation.

The overall incidence of second degree AV block was low, but was reported for a higher proportion of patients in the FTY720 1.25 mg group compared to the other treatment groups. For one patient in the FTY720 1.25 mg group second degree AV block was reported as an SAE and occurred in the first hr after treatment initiation.

Table 84: Number (%) of patients with cardiac disorders AEs by preferred term for Group A (12-month treatment)

Preferred term	FTY720 1.25 mg (N=849) n (%)	FTY720 0.5 mg (N=854) n (%)	Placebo (N=418) n (%)	Interferon (N=431) n (%)
Any preferred term	**63 (7.4)**	**39 (4.6)**	**19 (4.5)**	**23 (5.3)**
Bradycardia	20 (2.4)	10 (1.2)	2 (0.5)	2 (0.5)
Palpitations	13 (1.5)	9 (1.1)	7 (1.7)	6 (1.4)
Atrioventricular block first degree	7 (0.8)	3 (0.4)	2 (0.5)	3 (0.7)
Atrioventricular block second degree	5 (0.6)	1 (0.1)	0	0
Tachycardia	5 (0.6)	3 (0.4)	4 (1.0)	5 (1.2)
Angina pectoris	4 (0.5)	3 (0.4)	2 (0.5)	1 (0.2)
Arrhythmia	4 (0.5)	0	0	0
Ventricular extrasystoles	3 (0.4)	1 (0.1)	0	1 (0.2)
Sinus bradycardia	2 (0.2)	3 (0.4)	0	1 (0.2)
Supraventricular extrasystoles	2 (0.2)	1 (0.1)	0	0
Bradyarrhythmia	1 (0.1)	0	0	0
Bundle branch block left	1 (0.1)	1 (0.1)	0	0
Bundle branch block right	1 (0.1)	1 (0.1)	1 (0.2)	0
Extrasystoles	1 (0.1)	0	0	0
Mitral valve incompetence	1 (0.1)	0	0	0
Myocardial ischaemia	1 (0.1)	0	0	0
Pericarditis	1 (0.1)	0	0	0
Sinus tachycardia	1 (0.1)	0	0	0
Tricuspid valve incompetence	1 (0.1)	0	0	0
Acute myocardial infarction	0	0	0	1 (0.2)
Angina unstable	0	0	0	1 (0.2)
Cardiovascular disorder	0	1 (0.1)	1 (0.2)	0
Conduction disorder	0	0	0	1 (0.2)
Coronary artery disease	0	0	1 (0.2)	0
Heart valve incompetence	0	0	0	1 (0.2)
Left ventricular dysfunction	0	1 (0.1)	0	0
Mitral valve disease	0	2 (0.2)	0	0
Mitral valve prolapse	0	0	0	1 (0.2)
Myocardial infarction	0	0	1 (0.2)	0
Pulmonary valve disease	0	1 (0.1)	0	0
Tachycardia paroxysmal	0	1 (0.1)	0	0
Tricuspid valve disease	0	2 (0.2)	0	0
Ventricular tachycardia	0	1 (0.1)	0	0
Wolff-Parkinson-White syndrome	0	1 (0.1)	0	0

Preferred terms are sorted in descending frequency for the FTY720 1.25 mg group.
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.

ECG data analysis

In the MS studies, ECGs were performed at the following time points:

Study D2301: screening, on the day of first dose administration (prior to dosing and 6 hr post-dose), Month 1, Month 6, every subsequent 6 months up to Month 24, and as needed if study drug was interrupted.

Study D2302: screening, on the day of first dose administration (prior to dosing and 6 hr post-dose), Month 1, Month 6 and Month 12, and as needed if study drug was interrupted.

For the extension Study D2302E1, first dose assessments were repeated and assessments continued every subsequent 6 months, and as needed if study drug was interrupted.

Study D2201: screening, on the day of first dose administration (prior to dosing and 4 hr post-dose), Week 1, Month 1, Month 3, Month 6. For the extension D2201E1, first dose assessments were repeated and performed at Month 12 and as needed if study drug was interrupted.

ECG findings: A clear dose-dependent increase in the proportion of patients with first-degree AV block on the Day 1 ECG performed at 6 hr post-dose was seen. In the fingolimod 1.25 mg and 0.5 mg groups this was seen in 9.8% and 4.7% of the patients, respectively, compared to 1.5% for placebo and 2.8% for IFN β-1a (see Table 85). Second-degree Mobitz I AV block was seen in 0.7% and 0.2% of patients in the fingolimod 1.25 mg and 0.5 mg groups, respectively In addition, 0.2% of the fingolimod 1.25 mg group had 2:1 AV block, whereas no patients in the fingolimod 0.5 mg, placebo or IFN β-1a groups reported 2:1 AV block.

Table 85: Table 4-36 Incidence of abnormal ECGs by type of abnormality at 6 hr after the first dose administration for Group A (12-month treatment)

Timepoint Abnormality type	Finding	FTY720 1.25 mg (N=849) n (%)	FTY720 0.5 mg (N=854) n (%)	Placebo (N=418) n (%)	Interferon (N=431) n (%)
Day 1 post-dose (6 hours)					
No. of patients with ECG		840	837	413	422
Any abnormality		134 (16.0)	80 (9.6)	26 (6.3)	38 (9.0)
Conduction	Total	108 (12.9)	59 (7.0)	17 (4.1)	19 (4.5)
	First degree AV block	82 (9.8)	39 (4.7)	6 (1.5)	12 (2.8)
	LAH	15 (1.8)	16 (1.9)	9 (2.2)	5 (1.2)
	AV Mobitz I	6 (0.7)	2 (0.2)	0	0
	IVCD	3 (0.4)	2 (0.2)	1 (0.2)	0
	2:1 AV block	2 (0.2)	0	0	0
	IRBBB	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.2)
	RBBB	1 (0.1)	3 (0.4)	0	2 (0.5)
Ectopy	Total	4 (0.5)	2 (0.2)	1 (0.2)	0
	APC	3 (0.4)	0	0	0
	VPC	1 (0.1)	2 (0.2)	1 (0.2)	0
Myocardial infarction	Total	2 (0.2)	1 (0.1)	0	0
	Antero septal MI V1-V4	1 (0.1)	0	0	0
	Septal MI V1, V2, (V3)	1 (0.1)	1 (0.1)	0	0
Rhythm	Total	25 (3.0)	7 (0.8)	3 (0.7)	7 (1.7)
	Sinus bradycardia	19 (2.3)	5 (0.6)	2 (0.5)	0
	Other Rhythm	3 (0.4)	1 (0.1)	0	0
	Ectopic Supraventricular Rhythm	2 (0.2)	0	1 (0.2)	1 (0.2)
	Junctional rhythm	1 (0.1)	0	0	0
	Junctional Tachycardia	0	1 (0.1)	0	0

Table 85(cont.): Incidence of abnormal ECGs by types of abnormality at 6 hr after the first dose administration for Group A (12-month treatment)

Day 1 post-dose (6 hours)					
	Sinus tachycardia	0	0	0	6 (1.4)
ST segment	Total	4 (0.5)	2 (0.2)	1 (0.2)	5 (1.2)
	Depressed ST segment	4 (0.5)	2 (0.2)	1 (0.2)	5 (1.2)
T waves	Total	10 (1.2)	17 (2.0)	9 (2.2)	11 (2.6)
	Flat T waves	6 (0.7)	11 (1.3)	3 (0.7)	6 (1.4)
	Inverted T waves	4 (0.5)	4 (0.5)	5 (1.2)	4 (0.9)
	Biphasic T waves	0	2 (0.2)	1 (0.2)	1 (0.2)
U waves	Total	3 (0.4)	0	0	0
	Abnormal	3 (0.4)	0	0	0
Day 1 post-dose (>6 hours)					
No. patients with ECG		61	47	10	14
Any abnormality		18 (29.5)	8 (17.0)	0	1 (7.1)
Conduction	Total	17 (27.9)	7 (14.9)	0	1 (7.1)
	First degree AV block	12 (19.7)	4 (8.5)	0	1 (7.1)
	AV Mobitz I	4 (6.6)	1 (2.1)	0	0
	LAH	2 (3.3)	0	0	0
	IVCD	0	1 (2.1)	0	0
	Prolonged QTc	0	1 (2.1)	0	0
Ectopy	Total	1 (1.6)	1 (2.1)	0	0
	APC	1 (1.6)	0	0	0
	VPC	0	1 (2.1)	0	0
Rhythm	Total	2 (3.3)	0	0	0
	Sinus bradycardia	2 (3.3)	0	0	0
T waves	Total	2 (3.3)	1 (2.1)	0	0
	Flat T waves	2 (3.3)	0	0	0
	Biphasic T waves	0	1 (2.1)	0	0

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

The ECG findings on Day 1 were further supported by Day 1 24-hour Holter monitoring data which were collected in 1290 patients which included a subset of patients in Studies D2302 and D2201 and all patients in study D2309 (the latter representing 83% of the data). Second-degree Mobitz I AV block (Wenckebach) was detected in 17.9% (5/28) of fingolimod 5.0 mg patients, 7.1% (31/435) of 1.25 mg patients, 3.0% (12/398) in 0.5 mg patients, 1.8% (7/384) of placebo patients but not in any IFN β-1a patients (0/45). In addition, 2:1 AV block was reported in 3.4% (12/435) of patients on fingolimod 1.25 mg and 1.5% (6/398) of those on fingolimod 0.5 mg with no cases reported in the placebo or IFN β-1a groups. Of the three patients with second degree AV block on Holter monitoring, all were receiving 1.25 mg.

Holter ECG in study D2309

Results of 24-hour Holter ECG evaluations are available for a total of 1075 patients (366 on FTY720 1.25 mg, 356 on FTY720 0.5 mg and 353 on placebo) from Study D2309. Upon treatment initiation, second degree AV blocks (Mobitz I or 2:1 blocks) were observed in all three treatment groups but most frequently with the FTY720 1.25 mg dose (6.6% versus 3.4% on 0.5 mg and 2.0% on placebo). For the majority of patients on FTY720, the second degree AV blocks were first seen within 6 hr post-first dose, whereas for the placebo-treated patients, these events first occurred >12 hr post-dose during the night.

Bradycardia, defined as average heart rate of ≤40 BPM for any one hour during 24-hour Holter monitoring, was observed in 1.4% of patients on FTY720 1.25 mg compared with 0.3% of patients on FTY720 0.5 mg after the first dose only.

Mobitz I, 2:1 AV block and bradycardia within 6 hr of the first dose of FTY720 1.25 mg were reported as SAEs for three patients who were symptomatic and hospitalised for observation. These three patients had fully recovered by Day 2 and had discontinued the study drug.

One patient on FTY720 0.5 mg had ventricular tachycardia during Holter monitoring on Day 1 (scheduled) and Day 44 (unscheduled) which was reported as an SAE. The patient was asymptomatic but the study drug was discontinued on Day 65 due to this event.

Echocardiography

To investigate the effect of FTY720 on cardiac structure and valve function, 2-D Doppler echocardiography was performed at selected sites in Studies D2302 and in ongoing study D2309.

There were no relevant changes in left ventricular ejection fraction noted in patients treated with FTY720 1.25 mg or 0.5 mg up to 12 months. There were no relevant changes in any other parameter of left ventricular function such as cardiac output, cardiac index, stroke volume, left ventricular fractional shortening, left ventricular internal dimension in diastole, left ventricular internal dimension in systole, left atrial volume, left ventricular end-diastolic volume, or left ventricular end-systolic volume at Month 3 or Month 12. There were no relevant changes in pulmonary or systemic vascular resistance as measured by estimated pulmonary artery pressure or systemic vascular resistance. There were no changes suggestive of left ventricular hypertrophy as seen in the interventricular septum thickness, left ventricular posterior ventricular wall thickness, left ventricular mass, or left ventricular mass index.

Evaluator's comment*: The echocardiography data are relatively limited at this point. The data cannot exclude that safety changes would not appear over a longer time period of observation. In addition, because the study population excluded subjects with significant heart disease, one cannot exclude that safety signals may emerge with longer observation in a broader patient population*.

Eye disorders

Visual acuity in Group A (double-blind, randomised, active and placebo-controlled studies, 12 month treatment)

Visual acuity was comparable across all 4 treatment groups and remained stable (all mean changes were less than ± 0.2 points in decimal score) at all time points during 12 months of treatment. At baseline, mean visual acuity was 0.967, 0.973, 0.964 and 0.969 for the FTY720 1.25 mg, FTY720 0.5 mg, placebo and interferon groups, respectively. At Month 12, mean visual acuity was 0.989, 0.990, 0.982 and 0.974, respectively.

Visual acuity in Group B (double-blind, randomised, controlled study, 24 month treatment)

Visual acuity was collected in all patients at Screening (baseline), Month 1, Month 3, Month 6, Month 12, Month 18 and Month 24. Visual acuity was comparable across all three treatment groups at all time points and stable throughout the study.

Frequent optical coherence tomography (OCT) in a subset of patients in study D2302

In Study D2302 for a subset of patients at selected US sites, central foveal thickness was also evaluated at Months 1, 3 and 6. Mean central foveal thickness remained stable at Month 12. There was no evidence of an increase in central foveal thickness observed at regular OCT assessments in the patients treated with FTY720 compared to interferon during the study.

Ocular findings in Study D2309

Frequent, serial OCT measurements of central foveal thickness were done in a total of 1053 patients from Study D2309 (357 on FTY720 1.25 mg and 348 on FTY720 0.5 mg, 348 on placebo). OCTs were performed at screening, Month 1, Month 3, Month 6, Month 12, Month 18 and Month 24.

There were small, dose-dependent effects of FTY720 on central foveal thickness (difference from placebo in mean/median change from baseline was 5 microns/4 microns for FTY720 1.25 mg, and 4 microns/3 microns for FTY720 0.5 mg). These effects were observed at Month 1 and did not increase over time.

Central foveal thickness >300 microns was observed in three patients on FTY720 1.25 mg, three patients on FTY720 0.5 mg, and one patient on placebo at Month 1. At Month 3, the number of patients with central foveal thickness >300 microns was three, one and one for FTY720 1.25 mg, FTY720 0.5 mg, and placebo respectively. A diagnosis of macular oedema was made by the local ophthalmologist for 7 (2.0%) patients on FTY720 1.25 mg, 5 (1.4%) patients on FTY720 0.5 mg, and 2 (0.6%) patients on placebo. The retinal expert on the Data and Safety Monitoring Board (DSMB) confirmed the macular oedema diagnosis in only 3 (0.8%) patients on FTY720 1.25 mg, 3 (0.9%) patients on FTY720 0.5 mg, and 1 (0.3%) patient on placebo, with one case (on FTY720 1.25 mg) listed as pending. Of the 7 cases confirmed as macular oedema by the DMSB ophthalmologist, 5 had central foveal thickness >300 microns.

In summary, there was a small increase in mean central foveal thickness for both FTY720 1.25 mg and 0.5 mg relative to placebo. This increase was detected from Month 1 onward, remained stable thereafter, and appeared to resolve after treatment discontinuation.

Macular oedema

The incidence of macular oedema assessed by the local ophthalmologist for Group B is shown in Table 86. Macular oedema was diagnosed by the local ophthalmologist in patients only from the FTY720 1.25 mg group (7 patients, 1.7%).

Table 86: Incidence of macular oedema assessed by the local ophthalmologist, for Group B (24-month treatment)

Assessment of macular edema by the local ophthalmologist	FTY720 1.25 mg (N=429) n (%)	FTY720 0.5 mg (N=425) n (%)	Placebo (N=418) n (%)
Eyes assessed	840	846	826
Eyes with macular edema*	12 (1.4)	0	0
Associated with visual impairment*	7 (0.8)	0	0
Patients assessed	420	423	413
Patients with macular edema**	7 (1.7)	0	0
Treated for macular edema**	5 (1.2)	0	0

* Number of eyes assessed is denominator.
** Number of patients assessed is denominator.

Macular* oedema in Group E (all FTY720 treated safety population*)

The incidence of macular oedema assessed by the local ophthalmologist for Group E is shown in Table 87. The incidence of macular oedema as assessed by the local ophthalmologist was low in the FTY720 0.5 mg but notably higher in the FTY720 1.25 mg group, confirming the dose-dependent results observed for Groups A and B.

Table 87: Incidence rate of macular oedema assessed by the local ophthalmologist for Group E (all FTY720-treated safety population)

Assessment of macular edema by the local ophthalmologist	FTY720 5 mg - 1.25 mg (N=137) n (%)	FTY720 1.25 mg (N=1157) n (%)	FTY720 0.5 mg (N=1021) n (%)
Eyes assessed	212	2226	2022
Eyes with macular edema*	1 (0.5)	24 (1.1)	2 (0.1)
Associated with visual impairment*	0	13 (0.6)	2 (0.1)
Patients assessed	106	1113	1011
Patients with macular edema**	1 (0.9)	16 (1.4)	2 (0.2)
Treated for macular edema**	0	6 (0.5)	1 (0.1)

* Number of eyes assessed is denominator.
** Number of patients assessed is denominator.
This table does not include a patient in the FTY720 1.25 mg group (PID D2301/0708/00020) with macular edema diagnosed at an unscheduled baseline visit.

Three additional cases of macular oedema were reported as AEs, which are not included in Table 87. Two of these cases were in Study D2302E1. One case in a patient on FTY720 0.5 mg was not confirmed by the DSMB retinal specialist and the second case in a patient on FTY720 1.25 mg was confirmed. A third case of macular oedema in the left eye was reported in a patient from Study D2301 on FTY720 1.25 mg, which was confirmed by the DSMB retinal specialist. This case is not included in the Group E table due to differences in programming rules for Study D2301.

In total, 14 of the 19 cases of macular oedema diagnosed by the local ophthalmologist in Group E were confirmed by the DSMB retinal specialist.

Macular oedema (ophthalmic population)

The ophthalmic screening for macular oedema was implemented cross-sectionally around the end of the conduct of the transplant program. A total of 1375 patients (62-75% of all randomised transplant patients) underwent ophthalmic evaluations. Approximately 55% were on study drug and 45% were off study drug.

An approximately two-fold increased incidence of macular oedema was observed in FTY720-treated patients compared to MMF. The occurrence of macular oedema was particularly pronounced in patients with diabetes mellitus. In non-diabetics, macular oedema was diagnosed in approximately 4% of patients in treatment groups containing FTY720 versus 2% in the MMF group. In diabetics, the incidence of macular oedema was 28-29% with FTY720 versus 15% with MMF.

Follow-up data of more than 90% of all patients with diagnosis of macular oedema were available from the Novartis ARGUS safety data base. Overall, 56 % reported either complete recovery (38.5%), a recovery with sequelae (1.0%) or improving conditions (16.5%). One third was diagnosed with stable conditions at the time of the follow-up assessment. In one diabetic patient the evaluation revealed deterioration.

Evaluator's comment: *In all MS datasets, the incidence of macular oedema was higher in the FTY720 groups compared to the placebo and interferon groups and showed dose dependence (lowest incidence in the FTY720 0.5 mg group). The incidence of macular oedema in the MS studies was much lower than the incidence in other patient populations.*

Neoplasias

Adverse events in neoplasms benign, malignant and unspecified (including cysts and polyps) in Group E (all FTY720 treated safety population)

Melanocytic naevus, the most common AE in the FTY720 groups for neoplasms benign, malignant and unspecified (including cysts and polyps), showed no evident dose dependence between the FTY720 1.25 mg and 0.5 mg groups in Group E.

Malignant neoplasms are summarised in Table 88. All other neoplasms were of benign nature. Across all FTY720 treatment groups there were 32 cases of malignancy. Of these, skin malignancy occurred in 23/2315 (1.0%) patients. Of these 23 skin malignancies, fourteen were basal cell carcinoma, six were malignant melanoma and three were squamous cell carcinoma. Across all FTY720 treatment groups the total proportion of patients diagnosed with breast cancer was 7/2315 (0.3%).

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

Evaluator's comment*: Despite the results outlined above it should be acknowledged that long term experience with fingolimod is limited. Given the known effect of fingolimod on circulating lymphocytes it is possible that an increased risk of malignancy with longer exposure may emerge. The sponsor should be required to collect longer term data, perhaps with a patient registry or longer term clinical studies.*

Table 88: Number (%) of patients with malignant neoplasms in Group E (all FTY720-treated safety population)

Preferred term	FTY720 5 mg - 1.25 mg N=137 n (%)	FTY720 1.25 mg N=1157 n (%)	FTY720 0.5 mg N=1021 n (%)	Total N=2315 n (%)
Basal cell carcinoma	3 (2.2)	3 (0.3)	8 (0.8)	14 (0.6)
Breast cancer	1 (0.7)	3 (0.3)	2 (0.2)	6 (0.3)
Malignant melanoma	0	3 (0.3)	2 (0.2)	5 (0.2)
Squamous cell carcinoma of skin	0	1 (0.1)	1 (0.1)	2 (0.1)
Breast cancer in situ	0	0	1 (0.1)	1 (0.0)
Malignant melanoma in situ	0	0	1 (0.1)	1 (0.0)
Ovarian cancer metastatic	1 (0.7)	0	0	1 (0.0)
Squamous cell carcinoma	1 (0.7)	0	0	1 (0.0)
Thyroid cancer	1 (0.7)	0	0	1 (0.0)

The FTY720 5 mg–1.25 mg group includes patients who received either FTY720 5 mg alone or FTY720 5 mg initially and were later switched to 1.25 mg.

Nervous system disorders

In Group A headache occurred at a slightly higher incidence in the fingolimod treatment groups (23%) than in either control group (19-20%). A similar pattern, but at a much lower frequency, was found for migraine headaches (2.6-2.8% for fingolimod compared to 0.7-1.6% for control). There was no clear difference across the groups in any other individual nervous system preferred term. A similar picture was seen in Group B patients (treated for up to 24 months).

A higher percentage of 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. In the MS studies, epilepsy (various preferred terms) occurred in 5 patients in Group A and 6 patients in Group B. For Group E, seizures were reported in 13 patients (0.6%) in total, of whom 4 (2.9%) were in the fingolimod 5.0 – 1.25 mg group, 7 (0.6%) on 1.25 mg fingolimod and 2 (0.2%) on 0.5 mg fingolimod. Several of these events had reasons other than

fingolimod as plausible explanations, included other medical illnesses and MS relapses associated with seizures. Additionally, seizures have been reported to occur in about 2–3% of all patients with MS (Koch *et al* 2008, Kelley and Rodriguez 2009). The rate of convulsions observed in the fingolimod MS clinical studies is therefore believed to be in line with the epidemiological experience. However, the lack of cases in the control groups suggests that additional data will be needed to better evaluate the risk of seizures with fingolimod.

Safety in special population

No trials have been conducted in any special MS populations.

Safety related to drug-drug interactions and other interactions

Relevant drug-drug interactions have been discussed in the Clinical Pharmacology section of this evaluation report.

Discontinuation due to adverse events

In Group B, 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%) compared to the fingolimod 0.5 mg (7.5%) and the placebo (7.7%) groups. The most common reason for stopping drug was in SOC terms 'investigations' (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 ≥ 5×ULN increase in ALT or AST, 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 Group E, where differences in discontinuation rate may become most apparent between fingolimod doses over time, the proportions with AE discontinuations were 14.6% for fingolimod 1.25 mg and 8.2% for 0.5 mg. As in Groups A and B, patients in the fingolimod 1.25 mg group experienced bradycardia and AV block more frequently leading to study drug discontinuation. Comparable numbers from both fingolimod dose groups stopped the study drug due to elevations in liver enzymes.

Post marketing experience

No data were submitted for evaluation.

The clinical evaluator concluded that the pharmacokinetic data submitted suggest that the pharmacokinetics of fingolimod is substantially different in patients with severe renal impairment or severe hepatic impairment and that coadministration of fingolimod with ketoconazole is not recommended. This information should be included in the PI. The clinical evaluator also believed that it should be recommended that baseline and periodic on-therapy ECGs are collected for safety assessments when fingolimod is used in clinical practice.

Evaluator's overall conclusions on clinical safety

The safety profile of fingolimod has been assessed in over 2300 MS patients treated with fingolimod in the clinical programme, comprising almost 4,000 patient-years of exposure. The sponsor proposes that fingolimod be used at a dose of 0.5 mg daily.

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)

• Bradycardia – transient, on treatment initiation (Day 1)

• Macular oedema

• Hypertension

• Dyspnoea

• Bronchitis

• Diarrhoea

The AEs most prominently associated with fingolimod treatment, e.g. liver enzyme elevations, bradycardia, and macular oedema appeared to show a dose response. Recommendations for monitoring are stated in the PI (bradycardia, p11; ophthalmic, p10). In general, the AE profile of fingolimod in MS patients did not depend on gender, age, or previous treatment with disease-modifying drugs. The only exception was liver enzyme elevations which were more frequent in male patients than in female patients treated with fingolimod.

The overall incidence of infections, including serious infections, was similar in the fingolimod 0.5 mg treatment groups and the comparator arms (interferon or placebo) in both completed Phase III studies. 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. There was no clear relationship between lymphocyte count and the incidence of infections on fingolimod treatment. The data available to date from the MS program do not show an association of fingolimod therapy with the development of malignancies, including skin cancer.

List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a “list of questions” to the sponsor is generated.

Pharmacokinetics/ Pharmacodynamics

There are no questions for the sponsor.

Efficacy

1) The Phase II Study FTY720 D2201 did not adequately assess a dose response for FTY720 on inflammatory MRI activity as the study did not examine doses below 1.25 mg daily. A lower dose, 0.5 mg was explored in the Phase III studies. Although PK modelling data were submitted, information from modelling alone cannot definitively predict clinical response. Given the data submitted, the true clinical effect of a lower dose than 0.5 mg has not been determined. The sponsor should be asked to comment on whether any further studies are ongoing or proposed to characterise the optimal therapeutic dose for MS patients.

Safety

It should be requested that the sponsor submit the final CSR from Study D2309 as soon as the data become available.

The sponsor responded to all the questions raised in the Clinical Evaluation Report.

Clinical Summary and Conclusions

Clinical aspects

The pivotal studies (FTY720D2301 and FTY720D2302) were appropriately designed and conducted to assess the efficacy of fingolimod in treatment of patients with RRMS. The studies provide substantial evidence for an effect of a 0.5mg dose of fingolimod on relapse rate in MS patients, as the contrasts between fingolimod and placebo for the primary endpoints and for various sensitivity analyses of the relapse rate showed robust clinical and statistical significance.

In Study FTY720D2301 treatment with fingolimod 1.25mg and 0.5mg resulted in significantly lower annualised relapse rate compared to placebo. The difference between the two fingolimod doses was not statistically significant.

For Study FTY72D2302, treatment with both fingolimod doses resulted in a significantly lower annualised relapse rates compared to IFN β-1a. It is notable that in this study, fingolimod 0.5mg was numerically (but not statistically) better than fingolimod 1.25 mg for the annualised relapse rate.

Time to 3-month confirmed disability progression (measured by the EDSS scale) was the only key secondary endpoint in Study D2301, and a second key secondary endpoint in Study D2302 (T2 MRI lesions was the first secondary endpoint in Study 2302). Both doses of fingolimod delayed the time to 3-month confirmed disability progression compared to placebo in Study D2301; however no significant difference between either dose of fingolimod and IFN β-1a was found in Study D2302.

In Study FTY720D2301, fingolimod 1.25mg and 0.5mg significantly delayed the time to 3-month confirmed disability progression compared to placebo (p=0.012 and p=0.026, respectively). The two fingolimod dose groups were not significantly different (p=0.7427). In a sensitivity analysis of the time to 6-month confirmed disability, results were very similar (nominal p-values of 0.0044 and 0.0112 for fingolimod 1.25mg and 0.5mg versus placebo). The percentage of patients without 3-month confirmed disability progression at Month 24 was higher in both fingolimod treatment groups (85% and 83% for 1.25 mg and 0.5 mg) compared with placebo (78%). The pairwise comparisons yielded nominal p-values of 0.008 and 0.043 for fingolimod 1.25 mg and 0.5 mg versus placebo, respectively.

Results from Study FTY720D2302 were in contrast to results from Study FTY720D2301; a significant delay in confirmed disability progression was not substantiated in Study 2302. There was no difference between either of the two fingolimod treatment groups and the IFN β-1a group in the time to 3-month confirmed disability progression based on log-rank test (p values 0.4979 and 0.2475 for fingolimod 1.25mg and 0.5mg versus IFN β-1a). Two important factors may have contributed to this lack of demonstrated effect on disability progression in Study 2302: the relatively short duration of the study and the active comparator.

The number of new or newly enlarged T2 lesions was not identified as a key secondary endpoint in study FTY720D2301, and results for this endpoint should therefore be interpreted with caution.

For this endpoint, in the original analysis of Study FTY720D2302 only the 1.25 mg fingolimod dose reached statistical significance for the contrast for the number of new or newly enlarged T2 lesions, compared to IFN β-1a. The sponsor submitted a revised (post-hoc) analysis for the number of “new and newly enlarged T2 lesions2” that used a different method for counting the lesions, and also excluded 18 patients that prematurely discontinued from the study. In that revised analysis, the results between fingolimod 0.5 mg and IGN β-1a for the number of new and newly enlarged T2 lesions become statistically significant (p=0.004).

As has been discussed earlier in this report the methods used in the addendum to assess this key secondary endpoint were not ideal.

In terms of dose-response, efficacy results indicate that the dose-response between 0.5 mg and 1.25 mg is essentially flat. In both pivotal studies no statistically significant difference was seen between fingolimod 1.25mg and 0.5mg for both relapse rate and time to disability progression. For both of these endpoints, fingolimod 1.25mg was numerically superior to fingolimod 0.5mg in study FTY720D2301. In Study FTY720D2302 the reverse was observed. The effect of fingolimod 1.25 mg and 0.5 mg on the number of new or newly enlarging T2 MRI lesions was similar.

Overall however, the clinical evaluator believed that the efficacy data submitted for evaluation are adequate to support that fingolimod 0.5mg once daily is effective in treatment of patients with relapsing MS. The data support the indication as proposed by the sponsor.

The safety profile of fingolimod has been assessed in over 2300 MS patients treated with fingolimod in the clinical program, comprising almost 4,000 patient-years of exposure.

Specific AEs that were reported more commonly in MS patients treated with fingolimod than in placebo-treated patients and other safety concerns were summarised under Evaluator's overall conclusions on clinical safety above.

Benefit risk assessment

Benefits

The fingolimod clinical development programme in MS has demonstrated consistent and robust efficacy over placebo, and over a current first-line MS therapy (IFN β-1a) in patients with RRMS. As a once-daily oral therapy, fingolimod treatment addresses an unmet medical need for oral disease-modifying treatment for MS patients that is more effective and convenient than the current first-line therapies, with an acceptable safety profile.

Fingolimod at the proposed 0.5 mg dose demonstrated efficacy across all clinical and other measures of disease activity compared to placebo in a 2-year study pivotal efficacy study (D2301) and to an active comparator, IFN β-1a in a 1-year study (D2302).

Fingolimod reduced the frequency of relapses by 54% versus placebo and by 52% versus IFN beta-1a. The ARR estimate over 2 years was 0.18 for fingolimod 0.5 mg versus 0.40 for placebo ($p<0.001$) and 0.16 for fingolimod 0.5 mg versus 0.33 for IFN β-1a over 1 year ($p<0.001$). Fingolimod reduced the risk of relapse by 52% versus placebo ($p<0.001$) and 48% versus IFN β-1a ($p<0.001$).

Fingolimod reduced the risk for 3-month confirmed disability progression by 30% versus placebo over 2 years (HR: 0.70, $p=0.024$) and the risk of 6-month confirmed progression by 37% (HR: 0.63, $p=0.012$). It also reduced MRI inflammatory activity (new or newly-enlarged T2 lesions, Gd-enhancing lesions) by 74-82% compared to placebo over 2 years.

Fingolimod reduced brain volume loss (atrophy) by over 30% versus placebo over 2 years ($p<0.001$) and versus IFN β-1a over 1 year ($p<0.001$).

In terms of other benefits not directly related to the disease, fingolimod confers a benefit associated with oral dosing compared to injection therapies. The convenient oral administration avoids the need for frequent injections and associated issues resulting in non-compliance, or avoidance of therapy entirely, due to needle fear or injection site reactions/soreness or issues with IV infusions.

Risks

There are several adverse events associated with the biologic effects of fingolimod involving cardiac, ocular, infectious, hepatic and pulmonary systems that bring attendant risks. Adverse event related drug discontinuations for the 0.5 mg patients in Group B were comparable to those of the placebo group and approximately half that of the 1.25 mg group. This indicated 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.

Cardiac toxicity

Initiation of fingolimod treatment is associated with a reduction in heart rate in most patients, due to the known stimulation of S1P1 receptors on myocytes. In patients who have interrupted dosing for 2 weeks or more, first-dose cardiac effects may recur upon re-initiation of fingolimod therapy. 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. 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 is not required, except in those at potentially higher risk (use of beta blockers, resting bradycardia, high grade atrioventricular blocks or sick sinus syndrome). In these patients, clinical observation for 6 hr following first-dose administration is recommended.

Fingolimod should not be co-administered with Class Ia and III anti-arrhythmics due to the potential risk for Torsades de Pointes. The slight increase in blood pressure (~1mmHg 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.

Ocular toxicity

Macular oedema has been associated with fingolimod therapy. It occurs less frequently with the 0.5 mg dose (<0.5%), and usually occurs within 3-4 months of treatment initiation and is usually symptomatic leading to clinical evaluation. Asymptomatic macular oedema can also be detected on ophthalmologic evaluation. Ophthalmologic assessment is recommended in all patients at 3-4 months after treatment initiation.

Patients with a history of uveitis or diabetes mellitus appear to have an increased risk of macular oedema 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.

It is not clear whether it is safe to continue dosing with fingolimod during macular oedema and the effect of a rechallenge after macular oedema has resolved is unknown.

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 and the incidence of serious or severe infections was relatively low. Apart from an increase in lower respiratory tract infections and two fatal herpes infections, no other infectious signal was seen.

No clear relationship between lymphocyte count and the occurrence of infections has been shown such that low cell counts do not reliably predict an increased risk of infection, nor do higher counts guarantee protection. Vigilance on the part of physicians and patients for signs and symptoms of infections is important while on therapy and for up to 2 months after cessation of treatment.

Concomitant use of anti-neoplastic, immunosuppressive or immune-modulating therapies should be undertaken with caution due to the risk of additive immune system effects.

No data are currently available regarding immunisations in MS patients. 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.

Hepatic

Generally asymptomatic elevations of liver transaminases occurred predominantly within the first 3-4 months of therapy. Enzyme elevation improved once therapy was discontinued and no patient developed liver failure. There are only limited data on continued dosing despite elevated enzymes. The mechanism by which fingolimod may cause liver enzyme elevation is unknown. Patients with signs or symptoms of liver disturbance should be evaluated for liver abnormalities. Suspending, discontinuing or re-initiating therapy should be based on severity of findings and overall assessment of benefit versus risk.

Pulmonary

Fingolimod induces a mild, dose-dependent increase in airway resistance upon treatment initiation with no evidence of further progression with continuous therapy. In the MS Phase III program, no clinically relevant changes in pulmonary function were observed in any treatment group, although reports of dyspnoea were more frequent in the fingolimod treatment groups compared to controls. The reduced findings related to pulmonary function in the MS Phase III program may reflect the use of lower doses compared to earlier clinical studies. Patients with asthma treated with fingolimod were not at an increased risk of experiencing respiratory symptoms compared to the comparator groups.

Malignancy

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. 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 required while on therapy although physicians should remain alert to potential risks of immune modulating therapy and continue to report occurrences of malignancies with use of fingolimod therapy.

Other events of interest

An increase in the incidence of seizures/convulsions was reported in early clinical trials (using doses 2.5 mg and 5.0 mg of fingolimod in combination with immunosuppressive therapy). In the MS clinical studies, seizures/epilepsywere more common with fingolimod than placebo treatment, but in several instances, causes other than fingolimod were apparent. Overall, the incidence of seizures is not beyond expected rates for MS patients.

Dosing in specified subpopulations

Renal impairment: Severe renal impairment increases fingolimod C_{max} and AUC by 32% and 43%, respectively and fingolimod-P by 25% and 43%, respectively. The clinical evaluator recommended that fingolimod should not be used in patients with severe renal impairment.

Hepatic impairment: No fingolimod dose adjustments are needed in patients with mild or moderate hepatic impairment. In severe hepatic impairment, C_{max} and AUC were increased by 22% and 29%. The clinical evaluator recommended that fingolimod should not be used in patients with severe hepatic impairment (Child-Pugh class C).

Paediatric patients: Fingolimod has not been studied in MS patients below the age of 18. Fingolimod is not indicated for use in paediatric patients.

Elderly patients: There are limited data on the use of fingolimod in the elderly (age >65). In the MS program the median age was 37 years (range 17-59) and 46 years (range 18-70) in the other programs. A population pharmacokinetics evaluation, performed on the Phase II and III clinical studies and in transplant patients revealed that a patient aged 50% higher than that of a typical patient (44 years of age), would have a lower apparent clearance (by 10.7%) and apparent volume of distribution (by 8.5%) for both fingolimod and fingolimod-P compared to that of a typical patient. Based on these data, dose adjustment is not indicated in this age group. Nevertheless, fingolimod should be used with caution in patients age 65 years and over.

Diabetic patients: Fingolimod should be used with caution in patients with diabetes mellitus due to a potential increased risk of macular oedema.

Safety specification

The sponsor submitted a Safety Risk Management Plan. This summarised important identified risks and potential risks. Proposed action plans were detailed for each of the identified and potential risks. The Risk Management Plan is considered adequate.

Balance

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 (fewer relapses, fewer new brain lesions, a reduction in brain atrophy and ultimately a delay in disability progression) against short- and long-term safety risks.

Consistent and robust efficacy of fingolimod has been demonstrated in the clinical development programme, predominantly in patients with RRMS. Fingolimod has demonstrated an ability to reduce relapse rate by 54- 60% relative to placebo while also reducing the risk of disability progression by 30-32% relative to placebo over 2 years. In addition, fingolimod was superior to one of the currently approved first-line MS therapies (IFN β-1a; Avonex in reducing the frequency of relapses over 1 year. 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.

The key safety issues identified for fingolimod during clinical development include cardiac, ocular, infectious and hepatic effects. However, their overall importance needs to take into consideration both the severity of the events and any associated 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 low dose proposed, are usually asymptomatic without need for intervention. The blood pressure elevation is minor in population terms, and cases of hypertension that develop can be managed with anti-hypertensive medications. Macular oedema is infrequent at the target dose, can be readily detected and is generally reversible with discontinuation of therapy.

Hepatic dysfunction (seen with both first- and second-line currently approved MS therapies) can be reduced 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.

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.

At present, four classes of drugs are available as therapies for MS – interferon β (IFN β-1a and IFN β-1b – 2 products of each type of interferon are marketed), glatiramer acetate (GA), natalizumab and mitoxantrone. 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 interferon β -1a has shown 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 interferon, as are varying rates of neutralising antibody formation (2%-40%) that limits efficacy.

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 exceeds 1/1,000 for patients exposed for

more than 2 years to therapy. The drug is administered IV once monthly and has approximately 5% incidence of hypersensitivity reactions related to neutralising antibodies that also abrogate efficacy.

Usually therapy for MS patients starts with a first-line therapy that has modest relapse efficacy, potentially with no disability benefit and 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 fear injections sufficiently that they never begin therapy.

Fingolimod may provide a valuable addition to the therapeutic options for treatment of MS patients. The relapse benefit of fingolimod compares favourably against that of natalizumab and current first-line therapies. Additionally fingolimod has shown an effect on disability. Furthermore, in a direct comparative study, fingolimod 0.5 mg dose has demonstrated superiority to one of the first-line IFN products (Avonex, which has a disability indication) over 12 months on relapses and MRI measures.

Based on the efficacy and safety data submitted for evaluation the clinical evaluator believed that fingolimod should be considered as appropriate treatment for patients with RRMS.

Conclusions

Fingolimod has demonstrated efficacy both with respect to placebo and a current first-line therapy in patients with relapsing MS (IFN β-1a). 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. The clinical evaluator considered that fingolimod should be 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.

RECOMMENDED CONDITIONS FOR REGISTRATION

The clinical evaluator considered that the efficacy and safety data submitted for evaluation adequately support that fingolimod should be considered as appropriate treatment for patients with relapsing MS.

The indication proposed by the sponsor is acceptable, being as follows:

> "Gilenya 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."

V. Pharmacovigilance Findings

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Medicines Safety Monitoring (OMSM).

Risk Management Plan

Safety Specifications – Nonclinical

Toxicology

The Toxicology area of the Office of Scientific Evaluation (OSE) of the TGA has provided the following assessment of this aspect of the application:

> *Pulmonary changes, seen in all species, included increased alveolar macrophage levels, pneumonia, congestion and/or interstitial collagenisation. This chronic inflammation and collagenisation led to metaplastic ossification in the bronchi of rats and mice following long term treatment. Scarring was still evident after a 4 week treatment-free period in dogs and had only partially resolved after a 26 week treatment free period in monkeys. Given the nature of the effects, the low exposures (compared to clinical) and the poor reversibility of the effects, some concern with pulmonary function and pulmonary tissue damage exists with chronic*

administration of fingolimod, even if adequate monitoring were available. The current human safety database, limited by low patient numbers with >5 years exposure, may not be adequate to eliminate this as a clinical concern.

and

With the exception of potential pulmonary changes, the above toxicity concerns have been identified and adequately described in the Safety Specification in the Risk Management Plan (Module 1.13.1).

Consequently the evaluator has recommended that a paragraph describing the long term pulmonary effects of fingolimod in animals should be included in the PI. Thus:

Pulmonary effects

Persistent pulmonary inflammation and collagenisation with scarring and pulmonary remodelling were observed in association with fingolimod treatment in chronic animal studies (all tested species; mice, rats, dogs and monkeys). Bronchial metaplastic ossification was evident in mice and rats treated for 2 years, but not 6 months, at a dose of 0.25 mg/kg/day and 0.5 mg/kg/day, respectively. Exposure (AUC) at the no effect level was below the clinical exposure of a 0.5 mg dose in mice and 3 times the clinical exposure in rats. As these pulmonary changes occurred in multiple species, at low relative exposures and were poorly reversible, adequate pulmonary monitoring should be considered with long-term exposure.

OPR reviewer comment:

The nonclinical section of the RMP should be amended accordingly.

Safety Specifications – Clinical

Clinical safety

The Office of Medicines Authorisation (OMA) of the TGA has provided the following assessment of this aspect of the application:

The safety profile of fingolimod has been assessed in over 2,300 MS patients treated with fingolimod in the clinical programme, comprising almost 4,000 patient-years of exposure. The sponsor proposes that fingolimod be used at a dose of 0.5 mg daily.

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)*
- *Bradycardia – transient, on treatment initiation (Day 1)*
- *Macular oedema*
- *Hypertension*
- *Dyspnoea*
- *Bronchitis*
- *Diarrhoea*

The AEs most prominently associated with fingolimod treatment, liver enzyme elevations, bradycardia, and macular oedema appeared to show a dose response. In general, the AE profile of fingolimod in MS patients did not depend on gender, age, or previous treatment with disease-modifying drugs. The only exception was liver enzyme elevations which were more frequent in male patients than in female patients treated with fingolimod.

The overall incidence of infections, including serious infections, was similar in the fingolimod 0.5 mg treatment groups and the comparator arms (interferon or placebo) in both completed Phase III studies. 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. There was no clear relationship between lymphocyte count and the incidence of infections on fingolimod treatment.

The data available to date from the MS program do not show an association of fingolimod therapy with the development of malignancies, including skin cancer.

and

The sponsor submitted a Safety Risk Management Plan. This summarised important identified risks and potential risks. Proposed action plans were detailed for each of the identified and potential risks. The Risk Management Plan is considered adequate.

Summary – Ongoing Safety Concerns

Subject to the evaluation of the nonclinical aspects of the Safety Specification (SS) by the Toxicology area of the OSE and the clinical aspects of the SS by the OMA, the summary of the Ongoing Safety Concerns as specified by the sponsor is as follows (Table 89):

Table 89. Ongoing safety concerns

Status of risk	Type of risk
Important identified risks	Bradyarrhythmia (including conduction defects) occurring post-first dose Hypertension Liver transaminase elevation Macular edema Infections
Important potential risks	Reproductive toxicity Skin cancer Other malignant neoplasms Posterior Reversible Encephalopathy Syndrome (PRES) Thrombo-embolic events QT interval prolongation Bronchoconstriction
Other potential risks	Convulsions Pulmonary edema Decreased renal function
Important missing information	Elderly patients Pediatric patients Pregnant/nursing women Long-term risk of cardiovascular morbidity/mortality Long-term risk of malignant neoplasms

OPR reviewer comment:

Pursuant to the evaluation of the non-clinical and clinical aspects of the SS (see Sections 5.1 & 6.1), it is recommended that 'Pulmonary effects' be included as an important potential risk.

Pharmacovigilance Plan

Proposed pharmacovigilance activities

The sponsor states that routine pharmacovigilance practices, consistent with the activities outlined in *3.1.2 Routine pharmacovigilance practices, Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03)*[47], are proposed to monitor all of the specified ongoing safety concerns.

[47] http://www.tga.gov.au/docs/pdf/euguide/ich/571603en.pdf. Routine pharmacovigilance practices involve the following activities:

An additional pharmacovigilance activity proposed for the important identified risks: 'Hypertension', 'Liver transaminase elevation', Macular oedema' & 'Infections'; the important potential risks: 'Skin cancer', 'Other malignant neoplasms' & 'Thrombo-embolic events'; and the important missing information: 'Long-term risk of cardiovascular morbidity/mortality' & 'Long-term risk of malignant neoplasms' is a post-approval 5 year multi-national observational registry study to investigate the incidence of selected safety related outcomes, such as macular oedema, serious infections, liver injury, hypertension, symptomatic bradyarrhythmias, cardiovascular disease events (stroke, ischemic heart disease, myocardial infarction), and malignancies in patients with multiple sclerosis treated with fingolimod. The secondary objective is to further explore the overall safety of fingolimod.

This study will include patients with relapsing forms of multiple sclerosis who receive a prescription according to label from a prescribing physicians (those with experience in the treatment of the disease) in participating countries (potentially EU, USA, Canada, Australia and Switzerland). Depending on the countries and centres involved, the sponsor plans to include at least 5,000 patients. No internal comparator group will be included within this registry. However, incidence rates will be compared with background rates from other sources (data from unexposed MS cohorts or data from the general population).

With the proposed number of patients to be included and the duration of observation proposed, the sponsor expects to have a minimum of 17,000 person-years of exposure in the registry. This number of person-years of observation within the registry will enable the exclusion of a doubling of the incidence, on therapy, of events with a background incidence in the population as low as 47 per 100,000 person years (estimate based on a one-sided α of 0.05 and a β of 80%).

Follow-up assessment, according to recommendations and aligned with routine clinical care, Will involve an eye examination by an ophthalmologist is recommended at Month 3-4 after commencing fingolimod therapy and, also thereafter, if the patient develops visual symptoms or a decrease in visual acuity is noted on examination. Data on the selected safety related outcomes and on serious adverse events will be collected in the registry. In addition, results of eye examinations (fundoscopy, visual acuity), blood pressure, haematology, blood chemistry (in particular, liver), will be entered in the registry as recommended and available during routine clinical care.

An additional pharmacovigilance activity proposed for the important potential risks: 'Reproductive toxicity'; and the important missing information: 'Pregnant and lactating females' is a prospective multi-national observational registry in women with multiple sclerosis exposed to fingolimod during pregnancy. The purpose of this voluntary world-wide pregnancy registry is to provide an early signal of any major teratogenic effect during pregnancy in patients with MS exposed to fingolimod within clinical trials as well as in routine clinical practice. Data on the outcome of pregnancy will be collected, evaluated and compared with prevalence numbers of general surveillance systems. The reference data will come for general surveillance systems such as the Center for Disease Controls (CDC) surveillance system.

Baseline assessment will include maternal information (including last menstrual period, corrected estimated date of delivery, patient age, and race), results of prenatal tests, medical and family

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.
-

history, co-morbidities, medication and co-medications. Follow-up assessment will include active follow-up of the pregnancy outcome to be conducted from the registry via the provider of the initial baseline information by the time of the estimated delivery. The assessment will contain the following items:

- Maternal information (including whether mother is enrolled in a clinical study)
- Information about foetal outcome including birth defect noted, and outcome such as live infant, spontaneous abortion, induced abortion, stillbirth and respective date.
- Infants gender, length, gestational age, birth weight and head circumference
- Information whether defect was attributed to MS treatment
- Information whether other factors might have contributed to the outcome

An additional pharmacovigilance activity proposed for the important missing information: 'Paediatric patients' is a 24-month, open-label (but with blinded efficacy assessments), randomised, active-controlled, parallel-group, multi-centre study to evaluate the safety and efficacy of fingolimod on MRI measures of inflammation and clinical relapses compared to interferon β (Avonex) in children/adolescent patients (10-18 years old) with MS. Study D2311 is planned to be conducted at European and North American centres with expertise in paediatric MS. The sponsor states that a planned date for submission of interim data is yet to be determined, while the planned date for submission of final data is the end of 2015.

Other secondary objectives are

- To evaluate the efficacy of fingolimod compared to Avonex on relapse rate and other relapse-related parameters in children/adolescent MS patients treated for up to 24 months.
- Pharmacokinetics of fingolimod in children/adolescent patients with MS.
- To explore the pharmacokinetic/pharmacodynamic relationship for main safety and efficacy outcomes in children/adolescent patients with MS.

Eligible patients will be randomised in a 1:1 ratio to receive either fingolimod administered orally once daily (optimal dose to be determined), or Avonex administered once weekly by IM injection for up to 24 months.

The following key efficacy endpoints are proposed:

- proportion of patients free of new/newly enlarging T2 MRI lesions at 24 months (primary)
- annualised relapse rate over 24 months (key secondary)
- number of new/newly enlarging T2 MRI lesion at 12 and 24 months
- number of Gd-enhanced MRI lesions at 12 and 24 months
- proportion of patients free of new/newly enlarging T2 MRI lesions at 12 months
- proportion of patients free of new MRI activity (free of Gd-enhanced and free of new/newly enlarging T2 MRI lesions) at 12 and 24 months
- time to first relapse
- proportion of patients free of relapse up to 24 months

The assessment of safety will be based on the frequency of adverse events/serious adverse events, infections, incidence of notable laboratory abnormalities, as well as vital signs, ophthalmologic, dermatologic and ECG data. Other assessments and safety monitoring guidance will be defined and implemented as necessary based on adult Phase III outcome.

Based on adult historical data, the sponsor claims it is reasonable to assume that the Avonex group will have 30% of patients free of new or newly enlarging T2 lesions at Month 24. In the Phase II study extension (D2201E1), the proportion of patient free of new T2 lesions observed at Month 24 was 70%. Based on this it seems reasonable to assume that the fingolimod group will have 60% of patients free of new or newly enlarging T2 lesions at Month 24 (relative difference of 50% between fingolimod and Avonex). With these assumptions, a sample size of 49 patients per group is required to provide the study with 80% power to detect a treatment difference between fingolimod

and Avonex, using a continuity-corrected chi-squared test with a 0.05 two-sided significance level. To accommodate 20% drop-out rate, a total number of 118 patients is required. This sample size calculation was performed using nQuery Advisor 5.0.

The sponsor states that the following null hypothesis will be tested: there is no difference in the proportion of patients free of new or newly enlarging T2 lesions at Month 24 between patients treated with fingolimod and Avonex. The test of the hypothesis will be based on a logistic regression model. The logistic regression model will be adjusted for treatment, country, EDSS at baseline and the number of MS relapses in previous 2 years. The primary analysis will use ITT population.

OPR reviewer's summary in regard to the pharmacovigilance plan (PP) and appropriateness of milestones

In principle there is no objection to the sponsor implementing the proposed application of routine and additional pharmacovigilance activities for the ongoing safety concerns as detailed above.

However, only draft protocol synopses were provided for the proposed post-approval 5 year multi-national observational registry study and the world-wide pregnancy register. Final protocols for these additional pharmacovigilance activities should be provided to the TGA for review once they become available. In regard to the former it is also noted that the incidence of symptomatic bradyarrhythmias will be investigated, although it has not been formally listed as an additional pharmacovigilance activity for the important identified risk: 'Bradyarrhythmias (including conduction defects) occurring post-first dose'. The sponsor should comment on this apparent inconsistency and amend this part of the PP accordingly.

1. The draft protocol for Study D2311 appears to be reasonable. Nevertheless a final protocol for this study should be provided to the TGA for review once it becomes available. Updates on the progress/results/analysis of these additional pharmacovigilance activities will be expected in any future Periodic Safety Update Reports (PSURs).
In addition to the Ongoing Safety Concerns as specified by the sponsor it is recommended that 'Pulmonary effects' be included as an important potential risk and be monitored by routine pharmacovigilance activities.

Evaluation of the Need for Risk Minimisation Activities

Sponsor's conclusion in regard to the need for risk minimisation activities

The sponsor has proposed the application of routine risk minimisation activities for all of the important identified and potential risks, except for the important potential risk: 'Skin cancer' and the other potential risks: 'Convulsions', 'Pulmonary oedema' & 'Decreased renal function'. The sponsor justifies these exclusions due to the current lack of evidence for a significantly increased risk of these safety concerns with fingolimod therapy in MS patients at this time.

Additional risk minimisation activities have also been proposed for the important identified risks: 'Bradyarrhythmias (including conduction defects) occurring post-first dose', 'Macular oedema' & 'Infections'; and the important potential risk: 'Reproductive toxicity'.

OPR reviewer comment:

In the light of the evaluation of the non-clinical and clinical aspects of the SS, this would appear to be generally acceptable. However, the Toxicology evaluator has recommended that a paragraph describing the long term pulmonary effects of fingolimod in animals should be included in the PI.

In addition the sponsor has made no mention of the specified important missing information in the summary tables for the EU-RMP , detailing what will be put in the product information, labelling and packaging as routine risk minimisation activities to minimise these risks. When this detailed

information is provided an assessment of the proposed routine risk minimisation activities in relation to the specified important missing information can be conducted.

Potential for medication errors

The sponsor states that the therapeutic margin for fingolimod acute dosing is wide. Fingolimod was administered orally in two dose-escalation studies over a total single-dose range of 0.25 to 40 mg. Given that single doses of up to 40 mg of fingolimod were well tolerated, the risk of significant clinical AEs in case of medication error is judged to be low. No cases of significant medication errors, involving fingolimod, have been observed during clinical development. No special means are required to reduce or eliminate medications errors. The product must be stored out of the reach of children.

The potential for medication errors was considered taking into account the following common sources of errors:

Name confusion

Several trade names have been submitted to regulatory authorities for approval but as yet the final trade name has not been selected. As part of the authorisation procedure, the invented name or trade name has to be submitted for review to both the EMA and FDA. Both health authorities consider whether the proposed invented name of a medicinal product could create public health concerns and potential safety risks. The US submission contains a trade name safety evaluation report conducted by Medical Error Recognition and Revision Strategies, Inc. (Med-E.R.R.S.), and includes a survey of US healthcare practitioners to assess the potential for look-alike and sound-alike confusion. The EMA in conjunction with national EU health authorities, checks whether the invented name proposed for a medicinal product could create a public-health concern or potential safety risk. In particular, the invented name of a medicinal product should not be liable to cause confusion in print, handwriting or speech with the invented name of an existing medicinal product. It should not convey misleading therapeutic or pharmaceutical connotations, and should not be misleading with respect to the composition of the product.

Presentation

Fingolimod capsules have the strength (0.5 mg) clearly marked on them. This minimises the potential for medication errors. Patient-related reasons (visual impairment, cognitive dysfunction, clumsiness, and tremor) may predispose to medication errors. This risk has been addressed, when designing the fingolimod capsules, for example size, shape and colouring of the pharmaceutical form as well as primary and secondary packaging, in order to distinguish fingolimod from other concomitant drugs.

Instructions for use

There are no specific instructions for use in the CDS and derived labels, other than storage out of the reach and sight of children. Physician education material is designed to highlight identification of key clinical issues pertinent to specific patient populations.

OPR reviewer comment:

The sponsor's discussion of this matter is generally acceptable.

Risk Minimisation Plan

Planned actions

Routine risk minimisation activities will include warnings or notification of undesirable effects in the Australian PI for all the important identified and potential risks, except as specified (see above).

In regard to the proposed additional risk minimisation activities, the material is foreseen to be provided in both printed (as a product monograph) and multimedia formats (for example via a product-specific web portal). Local Marketing Authorisation Holders will distribute the printed material to those healthcare professionals involved in treatment with fingolimod.

For the important identified risk: 'Bradyarrhythmias (including conduction defects) occurring post-first dose', the educational material for physicians will describe this transient pharmacodynamic effect. It will highlight the patient groups, mentioned in the CDS, in which careful observation during initiation of therapy is recommended. It will also state that when fingolimod was administered in combination with the beta-blocker atenolol, a mild additive effect on heart rate decrease was observed. It will also be stated that, in patients restarting fingolimod after drug interruption of more than 14 days, bradycardia may occur. The sponsor states that the criteria to be used to verify the success of this additional risk minimisation activity will be the regular review of the number of clinically symptomatic episodes at the time of each PSUR, to determine if there is any significant increase in the incidence rate of such events over time.

For the important identified risk: 'Macular oedema', educational material for physicians includes a recommendation for ophthalmology assessment 3-4 months after commencing treatment with fingolimod. Thereafter, ophthalmology assessments are recommended if the patient complains of decreased vision or worsening of visual acuity while taking fingolimod. In addition, it is recommended that the prescribing physician assess the patient's visual function at routine clinic visits, as is usual for MS patients, and consider referral to an ophthalmologist in the event of newly detected abnormalities. Patients with a history of uveitis or diabetes mellitus should be managed in close consultation with an ophthalmologist who should determine the frequency of ophthalmologic examination required. Ophthalmology assessments are recommended at a minimum 3-4 months after commencing fingolimod therapy, or as needed based on patient symptoms. Thereafter, ophthalmology examinations are recommended at intervals determined by the ophthalmologist, or whenever the patient reports decreased vision or worsening of visual acuity. The sponsor states that the criteria to be used to verify the success of this additional risk minimisation activity will be the regular review of the number of macular oedema cases at the time of each PSUR, to determine if there is any significant increase in the reporting rate over time. In addition, due to under-reporting that occurs in the post-marketing setting, a better assessment of occurrence of macular oedema will be obtained from the planned 5,000 patient post-approval safety study.

For the important identified risk: 'Infections', the sponsor proposes to conduct education of physicians on:

- the need for vigilance for signs / symptoms of infection,
- need to institute appropriate anti-microbial therapy on suspicion of infection,
- the dose-dependent reduction of peripheral lymphocyte count to 20-30% baseline values with fingolimod treatment, and
- the risks of increased infection with fingolimod, especially when used concurrently with immunosuppressants.

Consideration will also be given in the educational material to symptoms and signs of herpes simplex or zoster reactivation (e.g. lancinating pain, skin lesions). It will be emphasised that appropriate antiviral therapy (e.g. acyclovir, valcyclovir) should be promptly initiated if such symptoms develop. The sponsor states that the criteria to be used to verify the success of this additional risk minimisation activity will be the regular review of the number, nature and severity of infections at the time of each PSUR, to determine if there is any significant increase in the incidence rate or severity of such events over time.

For the important potential risk: 'Reproductive toxicity', educational material for physicians will outline known teratogenic risks with fingolimod and explain the importance of avoiding pregnancy when undergoing treatment with fingolimod. Before starting treatment with fingolimod, patients

must be fully counselled on the potential for serious risk to a foetus and the need for effective contraception. If a woman becomes pregnant while taking fingolimod, the patient should be advised to consider treatment discontinuation and should be apprised of the potential hazard to the foetus and referred to an obstetrical care specialist. The sponsor states that the criteria to be used to verify the success of this additional risk minimisation activity will be the regular review of the number and outcome of pregnancies at the time of each PSUR, to determine if there is any significant increase in the incidence rate of congenital abnormalities in the children of females on fingolimod compared to reference data from general surveillance systems. In addition, data from the Registry on reasons for failure of the educational activities to prevent pregnancies, will be evaluated in order to identify required changes to the educational material.

Summary of Recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; and the submitted EU-RMP is applicable without modification in Australia unless so qualified:

- The nonclinical section of the SS of the RMP should be amended according to the assessment of the Toxicology area of the OSE of the TGA, as detailed in above.
- In principle there is no objection to the sponsor implementing the proposed application of routine and additional pharmacovigilance activities for the ongoing safety concerns as detailed above. However, only draft protocol synopses were provided for the proposed post-approval 5 year multi-national observational registry study and the world-wide pregnancy register. Final protocols for these additional pharmacovigilance activities should be provided to the TGA for review once they become available.
- In regard to the proposed post-approval 5 year multi-national observational registry study, it is also noted that the incidence of symptomatic bradyarrhythmias will be investigated, although it has not been formally listed as an additional pharmacovigilance activity for the important identified risk: 'Bradyarrhythmias (including conduction defects) occurring post-first dose'. The sponsor should comment on this apparent inconsistency and amend this part of the PP accordingly.
- The draft protocol for Study D2311 appears to be reasonable. Nevertheless a final protocol for this study should be provided to the TGA for review once it becomes available.
- Updates on the progress/results/analysis of these additional pharmacovigilance activities will be expected in any future PSURs.
- In addition to the Ongoing Safety Concerns as specified by the sponsor it is recommended that 'Pulmonary effects' be included as an important potential risk (see above) and be monitored by routine pharmacovigilance activities.
- The sponsor has proposed the application of routine risk minimisation activities for all of the specified ongoing safety concerns, except for the important potential risk: 'Skin cancer' and the other potential risks: 'Convulsions', 'Pulmonary oedema' & 'Decreased renal function'. The sponsor justifies these exclusions due to the current lack of evidence for a significantly increased risk of these safety concerns with fingolimod therapy in MS patients at this time. In the light of the evaluation of the nonclinical and clinical aspects of the SS, this would appear to be generally acceptable. However, the Toxicology evaluator has recommended that a paragraph describing the long term pulmonary effects of fingolimod in animals should be included in the PI (see above).
- In addition the sponsor has made no mention of the specified important missing information in the summary tables for the EU-RMP, detailing what will be put in the product information, labelling and packaging as routine risk minimisation activities to minimise these risks. When

this detailed information is provided an assessment of the proposed routine risk minimisation activities in relation to the specified important missing information can be conducted.

- Additional risk minimisation activities have also been proposed for the important identified risks: 'Bradyarrhythmias (including conduction defects) occurring post-first dose', 'Macular oedema' & 'Infections'; and the important potential risk: 'Reproductive toxicity' (see Section 10.1). The sponsor has acknowledged that under-reporting occurs in the post-marketing setting and a better assessment of occurrence of macular oedema will be obtained from the planned 5,000 patient post-approval safety study. However, the sponsor has not similarly made such an acknowledgement in relation to the important identified risks: 'Bradyarrhythmias (including conduction defects) occurring post-first dose' and 'Infections', despite stating that this study will investigate the incidence of selected safety related outcomes, such as serious infections and symptomatic bradyarrhythmias in patients with multiple sclerosis treated with fingolimod. The sponsor should comment on this apparent inconsistency and amend this part of the RMP accordingly.
- In regard to the proposed routine risk minimisation activities, the draft product information document is considered satisfactory. Nevertheless the Toxicology evaluator has recommended that a paragraph describing the long term pulmonary effects of fingolimod in animals should be included in the PI (see Section 5.1) and no assessment of the proposed routine risk minimisation activities in relation to the specified important missing information can be conducted at this time (see above).
- In regard to the proposed routine risk minimisation activities, the draft consumer medicine information document is considered satisfactory. Nevertheless it should adequately reflect any changes made to the Australian PI as a result of the Toxicology evaluator's recommendations and no assessment of the proposed routine risk minimisation activities in relation to the specified important missing information can be conducted at this time (see above).

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There were no pharmaceutical chemistry objections to registration. Fingolimod is a prodrug. It is reversibly phosphorylated by sphingosine kinase to the active form, (S)-fingolimod phosphate. Phosphorylation is stereospecific, producing only the (S)-enantiomer.

Fingolimod was discussed at the 134th PSC meeting in September 2010. The subcommittee supported registration but objected to the use of multiple tradenames for products containing the same drug substance. The PSC considered that the 34% decrease in C_{max} caused by a high fat meal is unlikely to be clinically relevant given the mechanism of action (related to exposure) and the very long half-life of fingolimod phosphate, the active metabolite.

Nonclinical

There were no nonclinical objections to registration. Toxicological issues identified include increased risk of: infection; lymphomas; sinus arrhythmias, bradycardia and dyspnoea at treatment initiation; pneumonia, congestion and bronchial collagenisation with long term scarring and subsequent deterioration of pulmonary function; and adverse fetal effects during pregnancy.

The nonclinical evaluator considered the identified risks, except the potential for pulmonary remodelling and deterioration of pulmonary function with long term exposure were adequately described in the sponsor's Risk Management Plan. An amendment to the Risk Management Plan to include this risk was recommended. Amendments were also recommended to the nonclinical sections of the Product Information. As fingolimod is a first-in-class immunosuppressant, there is inadequate long-term clinical experience with either fingolimod or other agents in the same class to

allay concerns regarding these animal findings. Until sufficient clinical information has been provided to eliminate the concerns of bronchial ossification associated with long-term fingolimod use, the nonclinical evaluator proposed a statement to this effect should be included in the PI.

Clinical

The key safety issues identified for fingolimod during clinical development include cardiac, ocular, infectious and hepatic effects. However, their overall importance needs to take into consideration both the severity of the events and any associated 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 low dose proposed, are usually asymptomatic without need for intervention. The blood pressure elevation is minor in population terms, and cases of hypertension that develop can be managed with anti-hypertensive medications. Macular oedema is infrequent at the target dose, can be readily detected and is generally reversible with discontinuation of therapy.

Hepatic dysfunction (seen with both first- and second-line currently approved MS therapies) can be reduced 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.

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.

Fingolimod may provide a valuable addition to the therapeutic options for treatment of MS patients. The relapse benefit of fingolimod compares favourably against that of natalizumab and current first-line therapies. Additionally fingolimod has shown an effect on disability. Furthermore, in a direct comparative study, fingolimod 0.5 mg dose has demonstrated superiority to one of the first-line IFN products (Avonex, which has a disability indication) over 12 months on relapses and MRI measures.

The clinical evaluator considered that the efficacy and safety data submitted for evaluation adequately support that fingolimod should be considered as appropriate treatment for patients with relapsing MS.

Risk Management Plan

The RMP reviewer has noted that in addition to routine pharmacovigilance, the sponsor proposes the following activities: an open study in children; a post-approval 5-year multi-national observational registry study to investigate the incidence of selected safety related outcomes; and a pregnancy registry.

The RMP reviewer had no in principle objection to the proposed pharmacovigilance activities but noted that only draft protocol synopses were provided for the proposed post-approval, 5-year multi-national observation study and the pregnancy register. Final protocols have been requested. The evaluator agreed with the nonclinical evaluator regarding the inclusion of a statement concerning pulmonary effects to be included in the PI.

Further negotiation of the RMP awaits submission of protocols for the above studies and identification of specified important missing information in summary tables for the EU-RMP Sections 3.1, 4 and 5 to the OPR.

Risk-Benefit Analysis

Delegate Considerations

Discussion

The effect on lymphocyte count at steady state was assessed primarily in combination with cyclosporine in the PD studies. Subjects in these studies had transplants and may not have had similar responses to the proposed patient group. However these studies and the pharmacology studies in healthy volunteers provided the basic pharmacology information about fingolimod. Physiological responses MS patients were not comprehensively examined.

Efficacy of fingolimod at the proposed dose in patients with RRMS has been well demonstrated to 2 years. Efficacy over 12 months in these patients was superior to a current treatment for RRMS. Longer term efficacy data is limited to that of a dose which is 125% higher than the proposed dose. Nevertheless continued efficacy was demonstrated. The proposed dose of 0.5 mg daily has similar efficacy to the 1.25 mg dose that was assessed in the same pivotal studies. This supports use of the lower dose but has not established a minimal effective dose or whether a lower dose would have similar efficacy to the 0.5 mg dose. It is also possible that longer term efficacy of the proposed dose is substantially different from that of the 1.25 mg dose that has been assessed longer term.

There was concern about the analysis of T2 lesions in study D2302. The Delegate did not consider that a sufficient reason to delay registration. The effect of fingolimod on disability progression and relapse rates is sufficient demonstration of efficacy.

The sponsor has proposed fingolimod be registered for all forms of RMS. The EU Guideline (referred to above) states that with respect to RMS, while the effect on relapse rate may be investigated in patients with any form of relapsing MS, it is advised to assess the effect on disability only in patients with relapsing remitting MS. The guideline accepts that the indication in RMS will mainly rely on the effects shown in patients with RRMS and that an effect on relapses in RRMS may be extrapolated to an effect on relapses in SPMS. No assessment of efficacy of fingolimod in patients with a single demyelinating clinical event who show lesion dissemination on subsequent MRI scans according to McDonald's criteria has been provided for fingolimod. These patients are also considered to have RMS. Given the lack of evidence of efficacy for this group it would be inappropriate to include all forms of RMS in the indications. Fingolimod should be restricted to patients with RRMS and SPMS. It is unnecessary to include the term *disease modifying therapy* in the indication because reduction in physical disability and reduction in frequency of relapse adequately describe the effect of fingolimod in patients with MS.

Conclusion and recommendation

The Delegate proposed to register fingolimod hydrochloride **(**Gilenya/Fynefta/Filosir) 0.5 mg hard capsules for *Treatment of Relapsing Remitting Multiple Sclerosis and Secondary Progressive Multiple Sclerosis with superimposed relapses to delay the progression of physical disability and reduce the frequency of relapse. The safety and efficacy of Gilenya/Fynefta/Filosir beyond 2 years are unknown.*

The Delegate requested the Advisory Committee on Prescription Medicines (ACPM's) advice particularly on the indication the Delegate proposed and whether the indication should include a maximum duration of treatment as has applied to cladribine (Movectro) or to include in the indications that safety and efficacy beyond 2 years are unknown as was applied to natalizumab (Tysabri).

Response from Sponsor

The sponsor argued that Gilenya showed robust efficacy against placebo at 2 years and against an active comparator (interferon beta-1a) at 12 months. Additional important information about the

persistence of the clinical benefits of the 0.5 mg dose beyond 2 years can be obtained from a longer term trial (over 5 years) conducted at higher doses. The fundamental differences between the off-set of effects of Gilenya and cladribine would make the restriction that was applied to cladribine inappropriate. In view of these points, the inclusion of a caution on the limitations of the data in the indication is more appropriate than imposing a restriction on the duration of use.

Advisory Committee Considerations

The ACPM (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

ACPM recommended approval of the submission from Novartis Pharmaceuticals Australia Pty Ltd to register the new chemical entity fingolimod hydrochloride (Gilenya/ Fynefta / Filosir) hard capsule, 0.5 mg for the indication:

> *Treatment of Relapsing Remitting Multiple Sclerosis and Secondary Progressive Multiple Sclerosis with superimposed relapses to delay the progression of physical disability and reduce the frequency of relapse. The safety and efficacy* of Gilenya/Fynefta/Filosir *beyond 2 years are unknown.*

In making this recommendation, the ACPM considered the overall risk benefit to be positive. In addition, the ACPM considered that safety issues had not been fully addressed in the PI and that there is a risk of patient confusion due to multiple trade names.

ACPM welcomed the sponsor's undertaking to establish a registry to monitor adverse events for 5 years in view of lack of safety and efficacy data beyond 2 years.

The specific conditions of registration should include:

Monitoring of the suicide rate in patients given fingolimod as part of the Risk Management Plan and the proposed registry.

Changes to the Product Information (PI) and Consumer Medicines Information (CMI) recommended prior to approval include:

Amendments to the Clinical Trials section to describe the patient groups not included in the evaluated supporting studies such as: depressed patients; patients infected with Hepatitis B or C; patients infected with tuberculosis; or patients infected with HIV.

Amendments to the Precautions section to include a statement on the need to monitor patients for signs and symptoms of macular oedema and lower respiratory tract infections.

Amendments to the Precautions section to include that prior to commencing fingolimod, patients are screened and receive preventative vaccination, if appropriate, for the following medical conditions that present safety risks: Tuberculosis; hepatitis B and C; Herpes; and heart rhythms (ECG).

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Gilenya fingolimod (as hydrochloride) 0.5mg hard capsule blister pack, Fynefta fingolimod (as hydrochloride) 0.5mg hard capsule blister pack and Filosir fingolimod (as hydrochloride) 0.5mg hard capsule blister pack for oral administration at0.5 mg/day, indicated for:

> *The treatment of Relapsing Remitting Multiple Sclerosis and Secondary Progressive Multiple Sclerosis with superimposed relapses to delay the progression of physical disability and reduce the frequency of relapse. Safety and efficacy of Gilenya/Fynefta/Filosir beyond 2 years are unknown.*

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

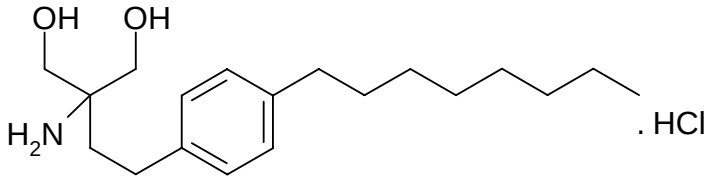
GILENYA®
fingolimod

NAME OF THE MEDICINE

The active ingredient of GILENYA is fingolimod.

Chemical name: 2-amino-2-(2-(4-octylphenyl)ethyl]propan-1,3-diol hydrochloride

Chemical structure:



Molecular formula: $C_{19}H_{33}NO_2 \cdot HCl$

CAS number: 162359-56-0

Molecular weight: 343.93

DESCRIPTION

Fingolimod hydrochloride is a white to almost white crystalline powder which is freely soluble in water. Fingolimod is a base with pKa of 7.82. Therefore, it has high solubility at low pH and very low solubility at high pH (e.g. < 0.01 mg/mL at pH 6.8). Relevant distribution coefficients are 22.3 in n-Octanol/water and 1290 in n-Octanol/hydrochloric acid 0.1N.

Each GILENYA capsule contains 0.56 mg fingolimod hydrochloride (equivalent to 0.5 mg fingolimod), mannitol, magnesium stearate, titanium dioxide and gelatin.

PHARMACOLOGY

Mechanism of action

Fingolimod is a sphingosine 1-phosphate receptor modulator. Fingolimod is metabolized by sphingosine kinase to the active metabolite fingolimod-phosphate. Fingolimod-phosphate, binds at low nanomolar concentrations to sphingosine 1-phosphate (S1P) receptors 1, 3, and 4 located on lymphocytes, and readily crosses the blood brain barrier to bind to S1P receptors 1, 3, and 5 located on neural cells in the central nervous system. By acting as a functional antagonist of S1P receptors on lymphocytes, fingolimod-phosphate blocks the capacity of lymphocytes to egress from lymph nodes, causing a redistribution, rather than depletion, of lymphocytes. This redistribution reduces the infiltration of pathogenic lymphocyte cells into

the central nervous system where they would be involved in nerve inflammation and nervous tissue damage. Animal studies and *in vitro* experiments indicate that fingolimod may also exert beneficial effects in multiple sclerosis via interaction with S1P receptors on neural cells.

Pharmacodynamics

Immune system

Effects on immune cell numbers in the blood

Within 4-6 hours after the first dose of fingolimod 0.5 mg, the lymphocyte count decreases to approximately 75% of baseline. With continued daily dosing, the lymphocyte count continues to decrease over a two week period, reaching a nadir count of approximately 500 cells/μL or approximately 30% of baseline. Eighteen percent of patients reached a nadir of < 200 cells/μL on at least one occasion. Low lymphocyte counts are maintained with chronic daily dosing. The majority of T and B lymphocytes regularly traffic through lymphoid organs and these are the cells mainly affected by fingolimod. Approximately 15-20% of T lymphocytes have an effector memory phenotype, cells that are important for peripheral immune surveillance. Since this lymphocyte subset typically does not traffic to lymphoid organs it is not affected by fingolimod. Peripheral lymphocyte count increases are evident within days of stopping fingolimod treatment and typically normal counts are reached within one to two months. Chronic fingolimod dosing leads to a mild decrease in the neutrophil count to approximately 80% of baseline. Monocytes are unaffected by fingolimod.

Heart rate and rhythm

Fingolimod causes a transient reduction in heart rate and atrio-ventricular conduction at treatment initiation (see **PRECAUTIONS; Bradyarrhythmia and ADVERSE EFFECTS**). The maximal decline of heart rate is seen in the first 4-5 hours post dose, with 70% of the negative chronotropic effect achieved on the first day. Heart rate progressively returns to baseline values within one month of chronic treatment.

Pooled analysis of studies with holter monitoring showed that fingolimod increased the rate of new onset first degree A-V heart block (PR > 200 ms) by 12% on Day 1 and that the incidence had reduced to < 1% after 1 week of treatment. Doses ≤ 1.25 mg were associated with a 7% incidence of heart block cf.3% in subjects given placebo. These blocks were usually asymptomatic and did not require treatment.

Autonomic responses of the heart, including diurnal variation of heart rate and response to exercise are not affected by fingolimod treatment.

With initiation of fingolimod treatment there is an increase in atrial premature contractions, but there is no increased rate of atrial fibrillation/flutter or ventricular arrhythmias or ectopy. Fingolimod treatment is not associated with a decrease in cardiac output.

The decrease in heart rate induced by fingolimod can be reversed by atropine, isoprenaline or salmeterol.

Potential to prolong the QT interval

In a thorough QT interval study of doses of 1.25 or 2.5 mg fingolimod at steady-state, when a negative chronotropic effect of fingolimod was still present, fingolimod treatment resulted in

a prolongation of QTcI, with the upper bound of the 90% CI ≤13.0 ms. There is no dose or exposure - response relationship of fingolimod and QTcI prolongation. There is no consistent signal of increased incidence of QTcI outliers, either absolute or change from baseline, associated with fingolimod treatment. In the multiple sclerosis studies, there was no clinically relevant prolongation of QT interval.

Pulmonary function

Persistent pulmonary inflammation and collagenisation with scarring and pulmonary remodelling were observed in association with fingolimod treatment in chronic animal studies (all tested species; mice, rats, dogs and monkeys). Focal pulmonary metaplastic ossification was evident in mice and rats treated for 2 years, but not 6 months, at a dose of 0.25 mg/kg/day and 0.5 mg/kg/day, respectively. Exposure (AUC) at the no effect level was below the clinical exposure in mice and 3 times the clinical exposure in rats. As these pulmonary changes occurred in multiple species, at low relative exposure and were incompletely reversible, adequate pulmonary monitoring should be considered with long-term treatment.

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 during expiration of 25 to 75% of the forced vital capacity (FEF_{25-75}). However, single fingolimod doses ≥5 mg (10-fold the recommended dose) are associated with a dose-dependent increase in airway resistance. 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.

Pharmacokinetics

Absorption:

Fingolimod absorption is slow (t_{max} of 12-16 hours) and extensive (≥85%, based on the amount of radioactivity excreted in urine and the amount of metabolites in faeces extrapolated to infinity). The apparent absolute oral bioavailability is high (93%).

Food intake does not alter C_{max} or exposure (AUC) of fingolimod or fingolimod-phosphate. Therefore GILENYA may be taken without regard to meals (see **DOSAGE AND ADMINISTRATION**).

Steady-state blood concentrations are reached within 1 to 2 months following once-daily administration and steady-state levels are approximately 10-fold greater than with the initial dose.

Distribution:

Fingolimod highly distributes in red blood cells, with the fraction in blood cells of 86%. Fingolimod-phosphate has a smaller uptake in blood cells of <17%. Fingolimod and fingolimod-phosphate are highly protein bound (>99.7%). Fingolimod and fingolimod-phosphate protein binding is not altered by renal or hepatic impairment.

Fingolimod is extensively distributed to body tissues with a volume of distribution of about 1200±260 L.

Metabolism:

The biotransformation of fingolimod in humans occurs by three main pathways; by reversible stereoselective phosphorylation to the pharmacologically active (*S*)-enantiomer of fingolimod-phosphate, by oxidative biotransformation mainly via the cytochrome P450 4F2 isoenzyme and subsequent fatty acid-like degradation to inactive metabolites, and by formation of pharmacologically inactive non-polar ceramide analogs of fingolimod.

Following single oral administration of [^{14}C] fingolimod, the major fingolimod-related components in blood, as judged from their contribution to the AUC up to 816 hours post dose of total radiolabeled components, are fingolimod itself (23.3%), fingolimod-phosphate (10.3%), and inactive metabolites (M3 carboxylic acid metabolite (8.3%), M29 ceramide metabolite (8.9%) and M30 ceramide metabolite (7.3%)).

Elimination:

Fingolimod blood clearance is 6.3±2.3 L/h, and the average apparent terminal half-life ($t_{1/2}$) is 6-9 days. Blood levels of fingolimod-phosphate 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-phosphate are not excreted intact in urine but are the major components in the faeces with amounts representing less than 2.5% of the dose each. After 34 days, the recovery of the administered dose is 89%.

Linearity

Fingolimod and fingolimod-phosphate concentrations increase in an apparent dose proportional manner after multiple once daily doses of fingolimod 0.5 mg or 1.25 mg.

<u>Pharmacokinetics in special patient groups</u>

Pharmacokinetics in children:

Safety and efficacy of GILENYA in paediatric patients below the age of 18 have not been studied. GILENYA is not indicated for use in paediatric patients.

Pharmacokinetics in the elderly:

The mechanism for elimination and results from population pharmacokinetics suggest that dose adjustment would not be necessary in elderly patients. However, clinical experience in patients aged above 65 years is limited.

Pharmacokinetics in patients with impaired renal or hepatic function:

Severe renal impairment increases fingolimod C_{max} and AUC by 32% and 43%, respectively, and fingolimod-phosphate C_{max} and AUC by 25% and 14%, respectively. The apparent elimination half-life is unchanged for both analytes. In severe renal impairment Cmax and AUC for M3, an inactive metabolite, were increased by 805% and 1356% respectively. No GILENYA dose adjustments are needed in patients with renal impairment.

The pharmacokinetics of single-dose fingolimod (1 or 5 mg), when assessed in subjects with mild, moderate and severe hepatic impairments, showed no change on fingolimod $C_{max,}$ but an increase in AUC by 12%, 44% and 103%, respectively. The apparent elimination half-life is unchanged in mild hepatic impairment but is prolonged by 49-50% in moderate and severe hepatic impairment. Fingolimod-phosphate was measured in severe hepatic impairment only, and $C_{max,}$ and AUC were decreased by 22% and 29%, respectively. Although hepatic impairment elicited changes in the disposition of fingolimod and fingolimod-phosphate, the magnitude of these changes suggests that the fingolimod dose does not need to be adjusted in mild or moderate hepatic impaired patients. Fingolimod should be used with caution in patients with severe hepatic impairment (Child-Pugh class C).

Ethnicity:

The effects of ethnic origin on fingolimod and fingolimod phosphate pharmacokinetics are not of clinical relevance.

Gender:

Gender has no influence on fingolimod and fingolimod-phosphate pharmacokinetics.

CLINICAL TRIALS

The efficacy of GILENYA has been demonstrated in two studies which evaluated once daily doses of GILENYA 0.5 mg and 1.25 mg in patients with relapsing remitting multiple sclerosis. Both studies included patients who had experienced at least 2 clinical relapses during the 2 years prior to randomization or at least 1 clinical relapse during the 1 year prior to randomization, and had an Expanded Disability Status Scale (EDSS) between 0 to 5.5.

Patients with the following conditions were excluded from these studies: other chronic disease of the immune system; known immune deficiency syndrome; history of malignancy other than cutaneous BCC or SCC of the skin; active systemic bacterial, viral or fungal infections; AIDS; HBsAg positive or hepatitis C antibody positive; serious psychiatric condition.

Study D2301 (FREEDOMS) was a 2-year randomized, double-blind, placebo-controlled Phase III study in patients with relapsing-remitting multiple sclerosis who had not received any interferon-beta or glatiramer acetate for at least the previous 3 months and had not received any natalizumab for at least the previous 6 months. Neurological evaluations were performed at Screening, every 3 months and at time of suspected relapse. MRI evaluations were performed at Screening, month 6, month 12 and month 24. The primary endpoint was the annualized relapse rate.

Median age was 37 years, median disease duration was 6.7 years and median EDSS score at baseline was 2.0. Patients were randomized to receive GILENYA 0.5 mg (n=425) or GILENYA 1.25 mg (n=429), or placebo (n=418) for up to 24 months. Median time on study drug was 717 days on 0.5 mg, 715 days on 1.25 mg and 718.5 days on placebo.

The annualized relapse rate was significantly lower in patients treated with GILENYA than in patients who received placebo. The key secondary endpoint was the time to 3-month confirmed disability progression as measured by at least a 1-point increase from baseline in EDSS (0.5 point increase for patients with baseline EDSS of 5.5) sustained for 3 months. Time to onset of 3-month confirmed disability progression was significantly delayed with

GILENYA treatment compared to placebo. There were no significant differences between the 0.5 mg and the 1.25 mg doses on either endpoint.

The results for this study are shown in Table 1 and Figure 1.

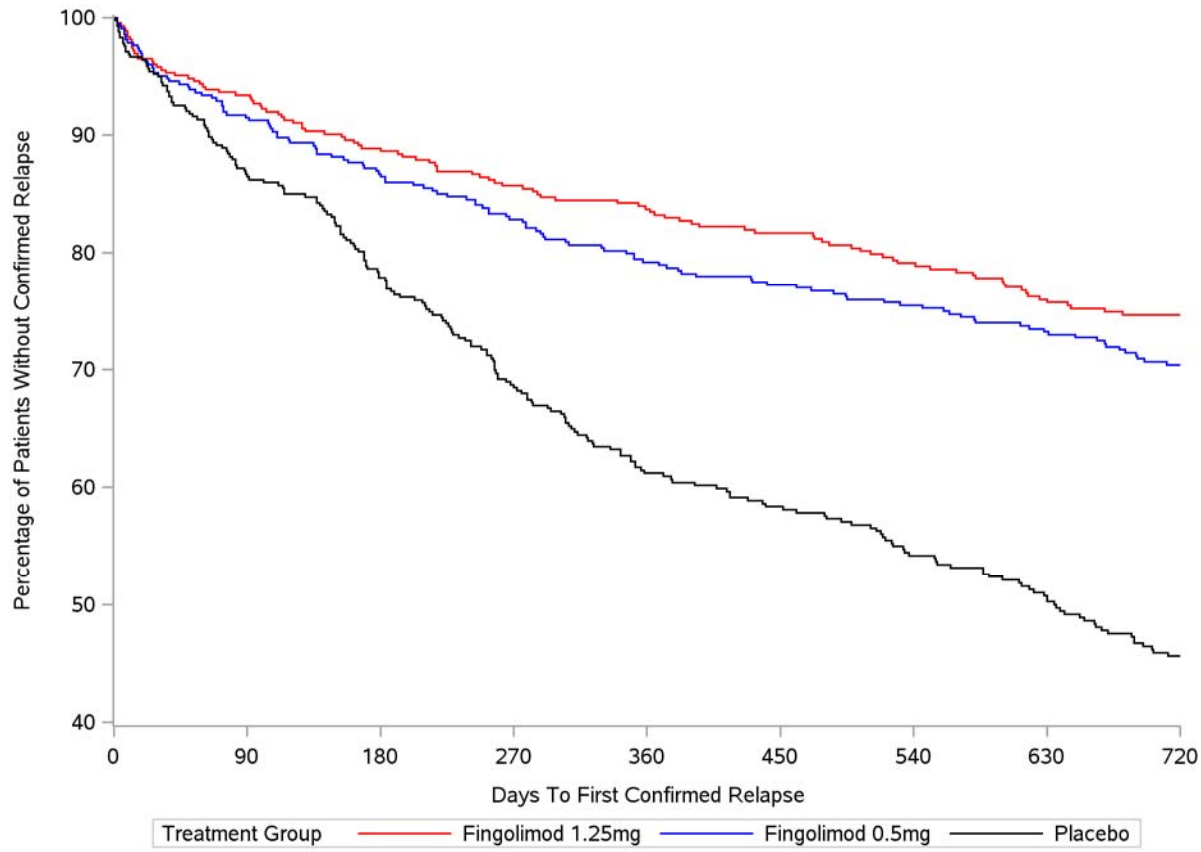
Table 1 Clinical and MRI results of Study D2301

	GILENYA 0.5 mg	GILENYA 1.25 mg	Placebo
Clinical Endpoints	**N=425**	**N=429**	**N=418**
Annualized relapse rate (primary endpoint)	**0.18 (p<0.001*)**	**0.16 (p<0.001*)**	**0.40**
Relative reduction (percentage)	**54**	**60**	
Percent of patients remaining relapse-free at 24 months	**70.4 (p<0.001*)**	**74.7 (p<0.001*)**	**45.6**
Risk of disability progression			
Hazard ratio (95% CI) (3-month confirmed)	**0.70 (0.52, 0.96) (p=0.024*)**	**0.68 (0.50, 0.93) (p=0.017*)**	
Hazard ratio (95% CI) (6-month confirmed)	**0.63 (0.44, 0.90) (p=0.012*)**	**0.60 (0.41, 0.86) (p=0.006*)**	
MRI Endpoints			
Number of new or newly enlarging T2 lesions	**n=370**	**n=337**	**n=339**
Median (mean) number over 24 months	**0.0 (2.5) (p<0.001*)**	**0.0 (2.5) (p<0.001*)**	**5.0 (9.8)**
Number of Gd-enhancing lesions	**n=369 (Month 24)**	**n=343 (Month 24)**	**n=332 (Month 24)**
Median (mean) number at			
Month 6	**0.0 (0.2)**	**0.0 (0.3)**	**0.0 (1.3)**
Month 12	**0.0 (0.2)**	**0.0 (0.3)**	**0.0 (1.1)**
Month 24	**0.0 (0.2) (p<0.001* at each timepoint)**	**0.0 (0.2) (p<0.001* at each timepoint)**	**0.0 (1.1)**
Percent change in T2 lesion total volume	**n=368**	**n= 343**	**n=339**
Median (mean) % change over 24 months	**-1.7 (10.6) (p<0.001*)**	**-3.1 (1.6) (p<0.001*)**	**8.6 (33.8)**
Change in T1 hypointense lesion volume	**n=346**	**n=317**	**n=305**
Median (mean) % change over 24 months	**0.0 (8.8) (p=0.012*)**	**-0.2 (12.2) (p=0.015*)**	**1.6 (50.7)**
Percent change in brain volume	**n=357**	**n=334**	**n=331**
Median (mean) % change over 24 months	**-0.7 (-0.8) (p<0.001*)**	**-0.7 (-0.9) (p<0.001*)**	**-1.0 (-1.3)**

All analyses of clinical endpoints were intent-to treat. MRI analyses used evaluable dataset.
*** Indicates statistical significance vs. placebo at two-sided 0.05 level.**

Determination of p-values: aggregate ARR by negative binomial regression adjusting for treatment, pooled country, number of relapses in previous 2 years and baseline EDSS; percent of patients maintaining relapse-free logistic regression adjusted for treatment, country, number of relapse in previous 2 years, and baseline EDSS; time to 3-month/6-month confirmed disability progression by Cox's proportional hazards model adjusted for treatment, pooled country, baseline EDSS, and age; new/newly enlarging T2 lesions by negative binomial regression adjusted for treatment and pooled country; Gd-enhancing lesions by rank ANCOVA adjusted for treatment, pooled country, and baseline number of Gd-enhancing lesions; and % change in lesion and brain volume by rank ANCOVA adjusted for treatment, pooled country, and corresponding baseline value.

Figure 1 **Kaplan-Meier plot for time to first confirmed relapse up to Month 24– Study D2301 (ITT population)**



Study D2302 (TRANSFORMS) was a 1-year randomized, double-blind, double-dummy, active (interferon beta-1a 30 micrograms, intramuscular, once weekly)-controlled Phase III study in patients with RRMS who had not received any natalizumab in the previous 6 months. Prior therapy with interferon-beta or glatiramer acetate up to the time of randomization was permitted.

Neurological evaluations were performed at Screening, every 3 months and at the time of suspected relapses. MRI evaluations were performed at Screening and at month 12. The primary endpoint was the annualized relapse rate.

Median age was 36 years, median disease duration was 5.9 years and median EDSS score at baseline was 2.0. Patients were randomized to receive GILENYA 0.5 mg (n=431) or 1.25 mg (n=426) or interferon beta-1a 30 micrograms via the intramuscular route once weekly (n=435) for up to 12 months. Median time on study drug was 365 days on 0.5 mg, 354 days on 1.25 mg and 361 days on interferon beta-1a IM.

The annualized relapse rate was significantly lower in patients treated with GILENYA than in patients who received interferon beta-1a IM. There was no significant difference between the GILENYA 0.5 mg and the 1.25 mg doses. The key secondary endpoints were number of new or newly enlarging T2 lesions and time to onset of 3-month confirmed disability progression as measured by at least a 1-point increase from baseline in EDSS (0.5 point increase for those with baseline EDSS of 5.5) sustained for 3 months. The number of new or newly enlarging T2 lesions was significantly lower in patients treated with GILENYA than in patients who received interferon beta-1a IM. There was no significant difference in the time

to 3-month confirmed disability progression between GILENYA and interferon beta-1a-treated patients at 1 year. There were no significant differences between the 0.5 mg and the 1.25 mg doses on either endpoint.

The results for this study are shown in Table 2 and Figure 2.

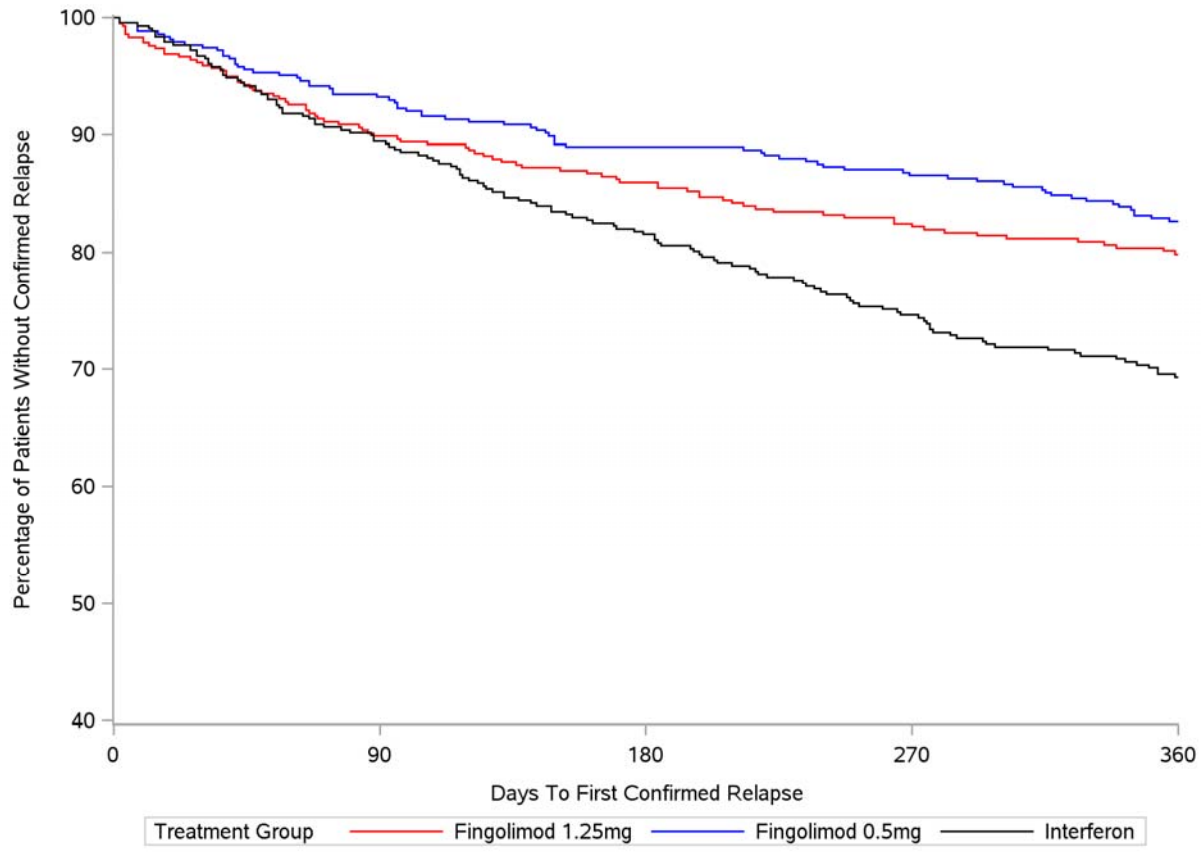
Table 2 Clinical and MRI results of Study D2302

	GILENYA 0.5 mg	GILENYA 1.25 mg	Interferon beta-1a IM, 30µg,
Clinical Endpoints	**N=429**	**N=420**	**N=431**
Annualized relapse rate (primary endpoint)	**0.16 (p<0.001*)**	**0.20 (p<0.001*)**	**0.33**
Relative reduction (percent)	**52**	**38**	
Percent of patients remaining relapse-free at 12 months	**82.5 (p<0.001*)**	**80.5 (p<0.001*)**	**70.1**
Risk of disability progression			
Hazard ratio (95% CI) (3-month confirmed)	**0.71 (0.42, 1.21) (p=0.209)**	**0.85 (0.51, 1.42) (p=0.543)**	
MRI Endpoints			
Number of new or newly enlarging T2 lesions	**n=380**	**n=356**	**n=365**
Median (mean) number over 12 months	**0.0 (1.7) (p=0.004*)**	**1.0 (1.5) (p<0.001*)**	**1.0 (2.6)**
Number of Gd-enhancing lesions	**n=374**	**n=352**	**n=354**
Median (mean) number at 12 months	**0.0 (0.2) (p<0.001*)**	**0.0 (0.1) (p<0.001*)**	**0.0 (0.5)**
Percent change in brain volume	**n=368**	**n=345**	**n=359**
Median (mean) % change over 12 months	**-0.2 (-0.3) (p<0.001*)**	**-0.2 (-0.3) (p<0.001*)**	**-0.4 (-0.5)**

All analyses of clinical endpoints were intent-to treat. MRI analyses used evaluable dataset.
*** Indicates statistical significance vs. Interferon beta-1a at two-sided 0.05 level.**

Determination of p-values: aggregate ARR by negative binomial regression adjusting for treatment, country, number of relapses in previous 2 years and baseline EDSS; percent of patients maintaining relapse-free logistic regression adjusted for treatment, country, number of relapse in previous 2 years, and baseline EDSS; risk of disability progression by Cox's proportional hazards model adjusted for treatment, country, baseline EDSS, and age; new/newly enlarging T2 lesions by negative binomial regression adjusted for treatment, country, number of relapses in previous 2 years and baseline EDSS; Gd-enhancing lesions by rank ANCOVA adjusted for treatment, country, and baseline number of Gd-enhancing lesions; and % change in brain volume by Wilcoxon rank sum test.

Figure 2 **Kaplan-Meier plot for time to first confirmed relapse up to Month 12 – Study D2302 (ITT population)**



Pooled results of studies D2301 and D2302 showed a consistent reduction of annualized relapse rate compared to comparator in subgroups defined by gender, age, prior multiple sclerosis therapy, disease activity or disability levels at baseline.

INDICATIONS

GILENYA is indicated for the treatment of Relapsing Remitting Multiple Sclerosis and Secondary Progressive Multiple Sclerosis with superimposed relapses to delay the progression of physical disability and reduce the frequency of relapse. Safety and efficacy of GILENYA beyond 2 years are unknown.

CONTRAINDICATIONS

GILENYA should not be administered to patients with known hypersensitivity to fingolimod or any of the excipients.

PRECAUTIONS

Infections

GILENYA causes a dose-dependent reduction in peripheral lymphocyte count to 20 - 30% of baseline values because of reversible sequestration of lymphocytes in lymphoid tissues (see **PHARMACOLOGY**). GILENYA may therefore increase the risk of infections, some

serious in nature. A recent complete blood count should be available before initiating treatment with GILENYA.

Because the elimination of fingolimod after discontinuation can take up to two months, continue monitoring for infections throughout this period. Instruct patients receiving GILENYA to report symptoms of infections to a physician. Patients with active acute or chronic infections should not start treatment until the infection(s) is resolved. In MS controlled studies, the overall rate of infections (72%) and serious infections (2%) with GILENYA 0.5 mg was similar to placebo. However, bronchitis and, to a lesser extent, pneumonia were more common in GILENYA-treated patients.

Vaccination

Vaccination may be less effective during and for up to two months after treatment with GILENYA (see **Stopping therapy**). The use of live attenuated vaccines should be avoided.

As could be considered for any immune modulating drug, before initiating GILENYA therapy, patients without a history of chickenpox or without vaccination against varicella zoster virus (VZV) should be tested for antibodies to VZV. VZV vaccination of antibody negative patients should be considered prior to commencing treatment with GILENYA, following which initiation of treatment with GILENYA should be postponed for 1 month to allow full effect of vaccination to occur.

Macular Oedema

Macular oedema can occur with or without visual symptoms. An ophthalmologic evaluation should be performed before starting GILENYA and at 3-4 months after treatment initiation. Monitor visual acuity at baseline and during routine evaluations of patients. Patients with diabetes mellitus or a history of uveitis are at increased risk and should have regular ophthalmologic evaluations.

If patients report visual disturbances at any time while on GILENYA therapy, evaluation of the fundus, including the macula, should be carried out.

Continuation of GILENYA in patients with macular oedema has not been evaluated. A decision on whether or not GILENYA therapy should be discontinued needs to take into account the potential benefits and risks for the individual patient.

Bradyarrhythmia

Initiation of GILENYA treatment results in a decrease in heart rate. To identify underlying risk factors for bradycardia and atrioventricular (AV) block, if a recent electrocardiogram (i.e. within 6 months) is not available, obtain one in patients using anti-arrhythmics including beta-blockers and calcium channel blockers, those with cardiac risk factors, as described below, and those who on examination have a slow or irregular heart beat prior to starting GILENYA. After the initial dose of GILENYA observe all patients for a period of 6 hours for signs and symptoms of bradycardia. Should post-dose bradyarrhythmia-related symptoms occur, initiate appropriate management and continue observation until the symptoms have resolved.

Initiation of GILENYA treatment has been associated with atrio-ventricular conduction delays, usually as first-degree atrio-ventricular blocks (prolonged PR interval on electrocardiogram). Second-degree atrio-ventricular blocks, usually Mobitz type I (Wenckebach) have been observed in less than 0.5% of patients receiving GILENYA 0.5 mg. The conduction abnormalities typically were transient, asymptomatic, usually did not require treatment and resolved within the first 24-hours on treatment (see **ADVERSE EFFECTS**).

GILENYA has not been studied in patients with sitting heart rate less than 55 bpm, in those receiving concurrent therapy with beta blockers or in those with a history of syncope. On initiation of GILENYA treatment in these patients, it is recommended that they be observed for a period of 6 hours after the first dose.

GILENYA has also not been studied in patients with 2nd-degree or higher AV blocks, sick-sinus-syndrome, ischemic cardiac disease, or congestive heart failure. Use of GILENYA in such patients should be based on overall benefit-risk assessment and careful observation during initiation of therapy is recommended due to potential for serious rhythm disturbances.

GILENYA has not been studied in patients with arrhythmias requiring treatment with Class Ia (e.g. quinidine, procainamide) or Class III anti-arrhythmic drugs (e.g., amiodarone, sotalol). Class Ia and Class III anti-arrhythmic drugs have been associated with cases of Torsades de Pointes in patients with bradycardia. Since initiation of GILENYA treatment results in decreased heart rate, GILENYA should not be co-administered with these drugs.

If GILENYA therapy is discontinued for more than 2 weeks the effects on heart rate and atrio-ventricular conduction may recur on reintroduction of GILENYA treatment and the same precautions as for initial dosing should apply.

Liver function

Patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained vomiting or jaundice, should have liver enzymes checked and GILENYA should be discontinued if significant liver injury is confirmed (see **ADVERSE EFFECTS**, **Liver Transaminase**).

Stopping therapy

If a decision is made to stop treatment with GILENYA, the physician needs to be aware that fingolimod remains in the blood and has pharmacodynamic effects, such as decreased lymphocyte counts, for up to two months following the last dose. Lymphocyte counts typically return to normal range within 1-2 months of stopping therapy (see **PHARMACOLOGY**). Starting other therapies during this interval will result in a concomitant exposure to fingolimod. Use of immunosuppressants soon after the discontinuation of GILENYA may lead to an additive effect on the immune system and therefore caution should be applied.

Effects on fertility

There are no human data on the effects of fingolimod on male or female fertility. Fingolimod had no effect on fertility in rats up to 10 mg/kg/day (estimated systemic exposure more than 100 times the anticipated clinical exposure) in a study in which both male and female animals were treated and mated. There was no apparent effect on sperm counts. Data from animals

does not suggest that fingolimod would be associated with an increased risk of reduced fertility.

Use in Pregnancy (Category D)

Fingolimod and/or its metabolites crossed the placental barrier in pregnant rats and rabbits. When administered during organogenesis, fingolimod was teratogenic in the rat at oral doses of 0.1 mg/kg/day or higher (similar to the clinical dose on a body surface area basis). The most common malformations were persistent truncus arteriosus and ventricular septal defect. At a lower dose (0.03 mg/kg/day), an increased incidence of left umbilical artery was the only finding. A pharmacological mechanism may be responsible as the sphingosine 1-phosphate receptor is involved in vascular formation during embryogenesis. Rabbits showed an increase in skeletal variations at exposures similar to clinical exposure. An increase in post-implantation loss and/or abortion was observed in rat (0.5 mg/kg/day or higher) and rabbit (5 mg/kg/day or higher) studies. Reduced perinatal survival was seen in offspring from rats treated orally from early gestation to weaning with 0.05 mg/kg/day or higher (similar to the clinical dose on a body surface area basis); a no effect dose was not established.

Before initiation of GILENYA treatment, women of childbearing potential should be counselled on the potential for serious risk to the foetus and the need for effective contraception during treatment with GILENYA and for at least 2 months following discontinuation of therapy, as it will take approximately 2 months to eliminate the compound from the body upon stopping treatment.

Lactation

Fingolimod and/or its metabolites was excreted in the milk of treated rats during lactation. There were no effects on bodv weight, development, behaviour, or fertility in rat pups from darns treated with oral fingolimod from early gestation to weaning. Reduced immunocompetence was evident in juvenile rats following oral administration. Because of the potential for serious adverse drug reactions from fingolimod in nursing infants, women receiving GILENYA should not breast feed.

Carcinogenicity

In a 2-year mouse study, an increased incidence of malignant lymphoma was seen at oral doses of 0.25 mg/kg/day and higher, with exposure (plasma AUC) 5-fold the human systemic exposure at a daily dose of 0.5 mg. Exposure at the NOEL was 0.6-fold human exposure. No evidence of carcinogenicity was observed in a 2-year bioassay in rats at oral doses of fingolimod up to 2.5 mg/kg/day, representing a 50-fold margin based on the human systemic exposure (AUC) at the 0.5 mg dose.

Genotoxicity

Fingolimod-induced numerical chromosomal aberrations (polyploidy) in Chinese hamster cells at concentrations more than three orders of magnitude greater than the clinical steady-state plasma levels, but not in human lymphocytes when tested at similar concentrations. Fingolimod was not clastogenic in the *in vivo* micronucleus tests in mice and rats at exposures at least 500 times that expected clinically.

Interactions with other medicines

Pharmacodynamic interactions

Anti-neoplastic, immunosuppressive or immune modulating therapies should be co-administered with caution due to the risk of additive immune system effects. Caution should also be applied when switching patients from long-acting therapies with immune effects such as natalizumab or mitoxantrone. In multiple sclerosis clinical trials the concomitant treatment of relapses with a short course of corticosteroids was not associated with an increased rate of infection.

Fingolimod treatment can be used in combination with heart rate lowering drugs such as atenolol and diltiazem. When fingolimod is used with atenolol, there is an additional 15% reduction of heart rate upon fingolimod initiation, an effect not seen with diltiazem. At treatment initiation in patients receiving beta blockers caution should be exercised because of the additive effects on heart rate.

During and for up to two months after treatment with GILENYA vaccination may be less effective. The use of live attenuated vaccines may carry the risk of infection and should therefore be avoided (see **ADVERSE EFFECTS**).

Pharmacokinetic interactions

Fingolimod is primarily metabolized *via* human CYP4F2 with some contribution also observed for CYP2D6*1, 2E1, 3A4, and 4F12. The potential of co-medications to inhibit the clearance of fingolimod seems low because very few medicinal products (e.g. ketoconazole) are known to inhibit CYP4F2.

Potential of fingolimod and fingolimod-phosphate to inhibit the metabolism of comedications:

In vitro inhibition studies in pooled human liver microsomes and specific metabolic probe substrates demonstrated that fingolimod and fingolimod-phosphate have little or no capacity to inhibit the activity of CYP450 enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, or CYP4A9/11. Therefore, fingolimod and fingolimod-phosphate are unlikely to reduce the clearance of drugs that are mainly cleared through metabolism by the major cytochrome P450 isoenzymes.

Potential of fingolimod and fingolimod-phosphate to induce its own and/or the metabolism of co-medications:

Fingolimod was examined for its potential to induce human CYP3A4, CYP1A2, CYP4F2, and MDR1 (P-glycoprotein) mRNA and CYP3A, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP4F2 activity in primary human hepatocytes. Fingolimod did not induce

mRNA or activity of the different CYP450 enzymes and MDR1 with respect to the vehicle control. Therefore no clinically relevant induction by fingolimod of the tested CYP450 enzymes or MDR1 are expected at therapeutic concentrations.

Transporters

Fingolimod as well as fingolimod-phosphate are not expected to inhibit the uptake of co-medications and/or biologics transported by OATP1B1, OATP1B3 or NTCP. Similarly, they are not expected to inhibit the efflux of co-medications and/or biologics transported by the breast cancer resistant protein (MXR), the bile salt export pump (BSEP), the multidrug resistance-associated protein 2 (MRP2) and MDR1-mediated transport at therapeutic concentrations.

Cyclosporine

The pharmacokinetics of single-dose fingolimod were not altered during co-administration with cyclosporine at steady-state, nor was cyclosporine steady-state pharmacokinetics altered by single-dose, or multi-dose (28 days) fingolimod administration. These data indicate that fingolimod is unlikely to reduce the clearance of drugs mainly cleared by CYP3A4 and show that the potent inhibition of transporters MDR1, MRP2 and OATP-C does not influence fingolimod disposition.

Ketoconazole

The co-administration of oral ketoconazole 200 mg twice daily at steady-state and a single dose of fingolimod 5 mg led to a modest increase in the AUC of fingolimod and fingolimod-phosphate (1.7-fold increase), indicating that potent inhibitors of CYP3A and CYP4F have a weak effect on fingolimod pharmacokinetics. Patients who use GILENYA and systemic ketoconazole concomitantly should be closely monitored, as the risk of adverse reactions is greater.

Isoproterenol, atropine, atenolol, and diltiazem

Single-dose fingolimod and fingolimod-phosphate exposure was not altered by co-administered isoproterenol or atropine. Likewise, the single-dose pharmacokinetics of fingolimod and fingolimod-phosphate and the steady-state pharmacokinetics of both atenolol and diltiazem were unchanged during the co-administration of the latter two drugs with fingolimod.

Population pharmacokinetics analysis of potential drug-drug interactions

A population pharmacokinetics evaluation, performed in multiple sclerosis patients, did not provide evidence for a significant effect of fluoxetine and paroxetine (strong CYP2D6 inhibitors) and carbamazepine (potent enzyme inducer) on fingolimod or fingolimod-phosphate concentrations. In addition, the following, commonly prescribed substances had no clinically relevant effect (≤20%) on fingolimod or fingolimod-phosphate concentrations: baclofen, gabapentin, oxybutynin, amantadine, modafinil, amitriptyline, pregabalin, corticosteriods and oral contraceptives.

Laboratory tests

Since fingolimod reduces blood lymphocyte counts via re-distribution in secondary lymphoid organs, peripheral blood lymphocyte counts cannot be utilized to evaluate the lymphocyte subset status of a patient treated with GILENYA.

Laboratory tests requiring the use of circulating mononuclear cells require larger blood volumes due to reduction in the number of circulating lymphocytes.

ADVERSE EFFECTS

A total of 1703 patients on GILENYA (0.5 or 1.25 mg dose) constituted the safety population in the two Phase III studies in patients with relapsing remitting multiple sclerosis (see section 12 Clinical studies). Study D2301 (FREEDOMS) was a 2-year placebo-controlled clinical study in 854 multiple sclerosis patients treated with fingolimod (placebo: 418). In this study the most serious adverse reactions (ADRs) for the 0.5 mg recommended therapeutic dose were infections, macular oedema and transient atrio-ventricular blocks on treatment initiation. The most frequent ADRs (incidence ≥10%) at the 0.5 mg dose were headache, influenza, diarrhoea, back pain, liver enzyme elevations and cough. The most frequent adverse event reported for GILENYA 0.5 mg at an incidence greater than 1% leading to treatment interruption included serum transaminase elevations (3.8%).

The ADRs in Study D2302 (TRANSFORMS), a 1-year controlled study using interferon beta-1a as comparator in 849 patients with multiple sclerosis treated with fingolimod, were generally similar to Study D2301, taking into account the differences in study duration.

ADRs are listed according to MedDRA system organ class. Frequencies were defined as follows: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Table 3 ADRs occurring in ≥1% of patients in Study D2301, and reported for GILENYA 0.5 mg at ≥1% higher rate than for placebo

Primary system organ class Preferred Term	Placebo N=418 %	Fingolimod 0.5mg N=425 %	Fingolimod 1.25mg N=429 %	Frequency range for the 0.5 mg dose
Infections				
Influenza viral infections	41 (9.8)	55 (12.9)	40 (9.3)	very common
Bronchitis	15 (3.6)	34 (8.0)	39 (9.1)	common
Sinusitis	19 (4.5)	28 (6.6)	27 (6.3)	common
Gastroenteritis	13 (3.1)	19 (4.5)	18 (4.2)	common
Pneumonia*	1 (0.2)	2 (0.5)	7 (1.6)	uncommon
Herpes viral infections*	33 (7.9)	37 (8.7)	25 (5.8)	common
Tinea infections	6 (1.4)	16 (3.8)	6 (1.4)	common
Cardiac Disorders				
Bradycardia	4 (1.0)	15 (3.5)	10 (2.3)	common

Primary system organ class Preferred Term	Placebo N=418 %	Fingolimod 0.5mg N=425 %	Fingolimod 1.25mg N=429 %	Frequency range for the 0.5 mg dose
Nervous system disorders				
Headache	**96 (23.0)**	**107 (25.2)**	**114 (26.6)**	**very common**
Dizziness	**23 (5.5)**	**31 (7.3)**	**30 (7.0)**	**common**
Paraesthesia	**18 (4.3)**	**23 (5.4)**	**17 (4.0)**	**common**
Migraine	**6 (1.4)**	**20 (4.7)**	**15 (3.5)**	**common**
Gastrointestinal disorders				
Diarrhoea	**31 (7.4)**	**50 (11.8)**	**40 (9.3)**	**very common**
General disorders and administration site conditions				
Asthenia	**5 (1.2)**	**11 (2.6)**	**9 (2.1)**	**common**
Musculoskeletal and connective tissue disorders				
Back pain	**29 (6.9)**	**50 (11.8)**	**45 (10.5)**	**very common**
Skin and subcutaneous tissue disorders				
Eczema	**8 (1.9)**	**14 (3.3)**	**15 (3.5)**	**common**
Alopecia	**10 (2.4)**	**15 (3.5)**	**9 (2.1)**	**common**
Pruritus	**5 (1.2)**	**11 (2.6)**	**4 (0.9)**	**common**
Investigations				
Alanine transaminase (ALT) increased	**16 (3.8)**	**43 (10.1)**	**50 (11.7)**	**very common**
Gamma-glutamyl transferase (GGT) increased	**4 (1.0)**	**22 (5.2)**	**32 (7.5)**	**common**
Hepatic enzyme increased	**1 (0.2)**	**14 (3.3)**	**22 (5.1)**	**common**
Weight decreased	**14 (3.3)**	**20 (4.7)**	**15 (3.5)**	**common**
Blood triglycerides increased	**5 (1.2)**	**11 (2.6)**	**8 (1.9)**	**common**
Liver function test abnormal	**1 (0.2)**	**6 (1.4)**	**7 (1.6)**	**common**
Respiratory, thoracic and mediastinal disorders				
Cough	**34 (8.1)**	**43 (10.1)**	**37 (8.6)**	**very common**
Dyspnoea	**19 (4.5)**	**34 (8.0)**	**28 (6.5)**	**common**
Psychiatric disorders				
Depression	**28 (6.7)**	**33 (7.8)**	**26 (6.1)**	**common**
Eye disorders				
Eye pain	**6 (1.4)**	**11 (2.6)**	**8 (1.9)**	**common**
Vision blurred	**6 (1.4)**	**15 (3.5)**	**8 (1.9)**	**common**
Macular oedema	**0 (0.0)**	**0 (0.0)**	**7 (1.6)**	**uncommon*†**
Vascular disorders				
Hypertension	**16 (3.8)**	**27 (6.4)**	**28 (6.5)**	**common**
Blood and lymphatic system disorders				
Leucopenia	**1 (0.2)**	**12 (2.8)**	**27 (6.3)**	**common**
Lymphopenia	**2 (0.5)**	**15 (3.5)**	**23 (5.4)**	**common**

*** Plausible relationship to study drug**

†Not reported in Study D2301 at the 0.5 mg dose; however cases were reported in other studies at that dose. Frequency category is based on the incidence at the 0.5 mg dose in Study D2302

Infections

In multiple sclerosis clinical trials, the overall rate of infections (72%) and serious infections (2%) at the 0.5 mg dose was similar to placebo. However, lower respiratory tract infections, bronchitis and pneumonia, were more common in GILENYA treated patients.

Two serious cases of disseminated herpes infection which were fatal have occurred on the 1.25 mg dose; a case of herpes encephalitis in a patient in whom initiation of acyclovir therapy was delayed by one week and a case of a primary disseminated varicella zoster infection in a patient not previously exposed to varicella receiving concomitant high-dose steroid therapy for a multiple sclerosis relapse.

Macular Oedema

In clinical trials, macular oedema occurred in 0.4% of patients treated with the recommended GILENYA dose of 0.5 mg and in 1.1% of patients treated with the higher 1.25 mg dose.

The majority of cases in multiple sclerosis clinical trials occurred within the first 3-4 months of therapy. Some patients presented with blurred vision or decreased visual acuity, but others were asymptomatic and diagnosed on routine ophthalmologic examination. The macular oedema generally improved or resolved spontaneously after drug discontinuation. The risk of recurrence after re-challenge has not been evaluated.

Macular oedema incidence is increased in multiple sclerosis patients with a history of uveitis (approximately 20% with a history of uveitis vs 0.6% without a history of uveitis).

GILENYA has not been tested in multiple sclerosis patients with diabetes mellitus. In renal transplant clinical studies where patients with diabetes mellitus were included, therapy with GILENYA 2.5 mg and 5 mg resulted in a 2-fold increase in the incidence of macular oedema. Multiple sclerosis patients with diabetes mellitus are therefore expected to be at a higher risk for macular oedema (see **PRECAUTIONS**).

Bradyarrhythmia

Initiation of GILENYA treatment results in a transient decrease in heart rate and may also be associated with atrio-ventricular conduction delays (see **PRECAUTIONS**).

In multiple sclerosis clinical trials the mean maximal decrease in heart rate after the first dose intake was seen 4 - 5 hours post-dose, with declines in mean heart rate of 8 beats per minute for GILENYA 0.5 mg. The second dose may result in a slight further decrease. Heart rates below 40 beats per minute were rarely observed in patients on GILENYA 0.5 mg. Heart rate returned to baseline within 1 month of chronic dosing.

In the multiple sclerosis clinical program first-degree atrio-ventricular block (prolonged PR interval on electrocardiogram) was detected following drug initiation in 4.7% of patients on GILENYA 0.5 mg, in 2.8% of patients on intramuscular interferon beta-1a and in 1.5% of patients on placebo. Second degree atrio-ventricular block were detected in less than 0.5 % patients on GILENYA 0.5 mg. The conduction abnormalities were typically transient, asymptomatic and resolved within 24 hours on treatment. Although most patients did not require medical intervention one patient on the 0.5 mg dose received isoprenaline for an asymptomatic second degree atrio-ventricular block.

One case of transient third-degree atrio-ventricular block occurred three hours after the first dose of GILENYA 1.25mg was administered and lasted for 30 seconds. The patient recovered spontaneously.

Blood pressure

In multiple sclerosis clinical trials GILENYA 0.5 mg was associated with a mild increase of approximately 1 mmHg on average in mean arterial pressure manifesting after approximately 2 months of treatment initiation. This increase persisted with continued treatment. Hypertension was reported in 6.1% of patients on GILENYA 0.5 mg and in 3.8 % of patients on placebo.

Liver transaminases

In multiple sclerosis clinical trials, 8.5% and 1.9% of patients treated with GILENYA 0.5mg experienced asymptomatic elevation in serum levels of hepatic transaminases ≥3x ULN and ≥5x ULN, respectively. The majority of elevations occurred within 3-4 months. Serum transaminase levels returned to normal after discontinuation of GILENYA within approximately 2 months. In a small number of patients, 10 patients on GILENYA 1.25 mg and 2 patients on GILENYA 0.5 mg, who experienced liver transaminase elevations ≥5x ULN and who continued on GILENYA therapy, the elevations returned to normal within approximately 5 months.

Respiratory system

Minor dose-dependent reductions in FEV_1 and diffusion capacity of the lung for carbon monoxide (DLCO) values were observed with fingolimod treatment starting at Month 1 and remaining stable thereafter. At Month 24, the reduction from baseline values in percent of predicted FEV_1 was 3.1% for fingolimod 0.5 mg and 2.0% for placebo. For DLCO the reductions at Month 24 were 3.8% for fingolimod 0.5 mg and 2.7% for placebo. The changes in FEV_1 were reversible following treatment discontinuation.

Vascular events

Rare cases of vascular events which occurred in patients treated with GILENYA at higher doses (1.25 or 5.0 mg) include ischemic and haemorrhagic strokes, peripheral arterial occlusive disease and posterior reversible encephalopathy syndrome.

Lymphomas

Cases of lymphoma (cutaneous T-cell lymphoproliferative disorders or diffuse B-cell lymphoma) were reported in premarketing clinical trials in MS patients receiving GILENYA at, or above, the recommended dose of 0.5 mg. Based on the small number of cases and short duration of exposure, the relationship to GILENYA remains uncertain.

DOSAGE AND ADMINISTRATION

The recommended dose of GILENYA is one 0.5 mg capsule taken orally once daily, which can be taken with or without food. If a dose is missed treatment should be continued with the next dose as planned.

Patients with high grade atrio-ventricular blocks or sick sinus syndrome should be observed for 6-hours after treatment initiation to confirm that GILENYA is well tolerated. Similar recommendations apply to patients with a low resting heart rate and patients receiving beta blockers (see **PRECAUTIONS, Bradyarrhythmia**).

Patients can switch directly from beta interferon or glatiramer acetate to GILENYA providing there are no signs of relevant treatment-related abnormalities e.g. neutropenia.

Children

GILENYA is not indicated for use in paediatric patients (See **PHARMACOLOGY**).

The Elderly (≥ 65 years)

GILENYA should be used with caution in patients aged 65 years and over (see **PHARMACOLOGY**).

Patients with Renal Impairment

No GILENYA dose adjustments are needed (see **PHARMACOLOGY**).

Patients with Hepatic Impairment

No GILENYA dose adjustments are needed in patients with mild or moderate hepatic impairment. GILENYA should be used with caution in patients with severe hepatic impairment (Child-Pugh class C) (see **PHARMACOLOGY**).

Ethnicity

No GILENYA dose adjustments based on ethnic origin are needed (see **PHARMACOLOGY**).

Gender

No GILENYA dose adjustments are needed based on gender (see **PHARMACOLOGY**).

Diabetic patients

GILENYA should be used with caution in patients with diabetes mellitus due to a potential increased risk of macular oedema (see **PRECAUTIONS**).

OVERDOSAGE

No cases of overdosage have been reported. However, single doses up to 80-fold the recommended dose (0.5mg) were well tolerated in healthy volunteers. At 40 mg, 5 of 6 subjects reported mild chest tightness or discomfort which was clinically consistent with small airway reactivity.

Neither dialysis nor plasma exchange would result in meaningful removal of fingolimod from the body.

Contact the Poisons Information Centre on 13 11 26 for advice on management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

GILENYA 0.5 mg : white to almost white powder in white opaque body and bright yellow opaque cap gelatin capsules, size 3, radial imprint with black ink "FTY 0.5 mg" on cap and two radial bands imprinted on body with yellow ink. Blister packs of 7, 28 and 84. Not all pack sizes marketed in Australia.

Storage: Store below 30 degrees Celsius. Protect from moisture.

NAME AND ADDRESS OF THE SPONSOR

Novartis Pharmaceuticals Australia Pty Limited
ABN 18 004 244 160
54 Waterloo Road
North Ryde NSW 2113

® = Registered Trademark

POISON SCHEDULE OF THE MEDICINE

Poison Schedule: S4

DATE OF APPROVAL

Approved by the Therapeutic Goods Administration: 19 January 2011

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