

FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Peripheral and Central Nervous System Drugs
Advisory Committee Meeting

Fingolimod (NDA 22-527) Background Package

June 10, 2010

Table of Contents

1. Questions for the Advisory Committee
2. Deputy Division Director Memo
3. Clinical Safety Review
4. Clinical Efficacy Review
5. Statistics Review
6. Conditions for requirement of a Risk Evaluation and Mitigation Strategy (REMS) and types of REMS

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought this issue to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Peripheral and Central Nervous System Drugs Advisory Committee Meeting

QUESTIONS TO THE ADVISORY COMMITTEE

June 10, 2010

- 1) Has the sponsor demonstrated substantial evidence of effectiveness of fingolimod for the treatment of patients with relapsing remitting multiple sclerosis? **[Voting Question]**
- 2) If so, should the sponsor be required to evaluate the effects of doses lower than 0.5 mg QD? **[Voting Question]**
- 3) If so, should this be required prior to approval? **[Voting Question]**
- 4) If substantial evidence of effectiveness has been demonstrated, do you conclude that there are conditions under which fingolimod could be considered safe in use for this indication? **[Voting Question]**
- 5) First-dose effects of fingolimod include bradycardia and heart conduction abnormalities. Based on the data presented to you, should patients be required to receive the first dose in a monitored setting? **[Voting Question]**
- 6) If so, should that requirement apply to all patients, or to a specific subset?
- 7) Fingolimod causes macular edema, including at the dose proposed for marketing (0.5 mg). Is routine ophthalmic examination sufficient to monitor patients treated with fingolimod?
- 8) Fingolimod causes a gradual decline in pulmonary function, that appears partially reversible. Do you believe that routine pharmacovigilance will be sufficient to mitigate the risks associated with the pulmonary toxicity of fingolimod?
- 9) If not, what additional monitoring or study do you recommend?
- 10) The sponsor has proposed to conduct a 5-year post-marketing safety study in 5000 patients to further explore the safety of fingolimod 0.5 mg under routine clinical care. Do you believe that such a study would be sufficient to address safety issues observed in this database, or do you believe that other safety studies should be required to assess specific safety concerns? If so, please identify these concerns.
- 11) Considering the risks and benefits, do you believe that fingolimod should be generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate MS therapy? **[Voting Question]**

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration

Date: May 18, 2010
From: Eric Bastings, MD. Deputy Director, Division of Neurology Products
Through: Russell Katz, MD. Director, Division of Neurology Products
To: Members of the Peripheral and Central Nervous System Drugs Advisory Committee
Subject: NDA 22,527 for fingolimod

As you know, the Peripheral and Central Nervous System Drugs Advisory Committee will meet on June 10, 2010 to discuss New Drug Application (NDA) 22,527 for fingolimod. In preparation for that meeting, the division is providing the following reviews for your consideration:

- Clinical safety, by Dr. Lourdes Villalba
- Clinical efficacy, by Dr. Heather Fitter
- Statistics, by Dr. Sharon Yan.

Please note that fingolimod may also be identified as FTY, FTY720 or Gilenia (proposed tradename) in the review documents. Also, NDA 22,527 is a priority review, with a six-month clock. The advisory meeting briefing package is being prepared at a time when the review team is still assessing data and analyses from the 4-month safety update, and from various FDA requests to the sponsor. The division will update the members of the Peripheral and Central Nervous System Drugs Advisory Committee about any relevant new finding from the ongoing NDA review.

1. Introduction

Novartis submitted a new drug application (NDA) to support the marketing of fingolimod (Gilenia), the first oral drug to be indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.

Fingolimod is a new molecular entity, and a first in class sphingosine 1 phosphate (S1P) receptor modulator. Fingolimod acts as a functional antagonist of the S1P1 receptor on lymphocytes, inducing its uncoupling/internalization. Under normal circumstances, T-cells selectively require S1P1 activation for emigration from the thymus, and both T- and B-cells require this receptor to egress from peripheral lymphoid organs. The internalization 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. This effect results in a dose-dependent reduction of the peripheral lymphocyte count.

The proposed mechanism of action in MS is that fingolimod induces a reversible retention of CD4 and CD8 T-cells and B-cells into lymph nodes and Peyer's patches

which in turn reduces the number of these cells that may have access to sites of MS related inflammation in the brain.

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

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

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

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

2. CMC

No major CMC issue has been identified.

3. Clinical Pharmacology/Biopharmaceutics (OCPB)

The absorption of fingolimod is slow (T_{max} 12-16 hours) but nearly complete. Fingolimod is phosphorylated to its active moiety, S-enantiomer fingolimod-P which in turn is dephosphorylated back to the inactive form fingolimod. At steady state, fingolimod and fingolimod-P are in dynamic equilibrium. Fingolimod is extensively distributed to body tissues, and is believed to be metabolized mainly via the cytochrome P450 4F2 isoenzyme. The average apparent terminal half-life for both fingolimod and fingolimod-P is 6-9 days. Steady-state exposure is reached after 1 to 2 months.

4. Clinical/Statistical- Efficacy

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

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

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

In Study 2301, testing was made in the following order:

1. 24-month relapse rate of fingolimod 1.25mg vs. placebo
2. 24-month relapse rate of fingolimod 0.5mg vs. placebo
3. Time to 3-month confirmed disability progression of fingolimod 1.25mg vs. placebo
4. Time to 3-month confirmed disability progression of fingolimod 0.5mg vs. placebo

In Study 2302, testing was made in the following order:

1. 12-month relapse rate of fingolimod 1.25mg vs. Avonex
2. 12-month relapse rate of fingolimod 0.5mg vs. Avonex
3. New and newly enlarged T2 lesions of fingolimod 1.25mg vs. Avonex at 12 months
4. New and newly enlarged T2 lesions of fingolimod 0.5mg vs. Avonex at 12 months
5. Time to 3-month confirmed disability progression of fingolimod 1.25mg vs. Avonex
6. Time to 3-month confirmed disability progression of fingolimod 0.5mg vs. Avonex

Fingolimod effect on relapse rate

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

Study 2301

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

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

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

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

Study 2302

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

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

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

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

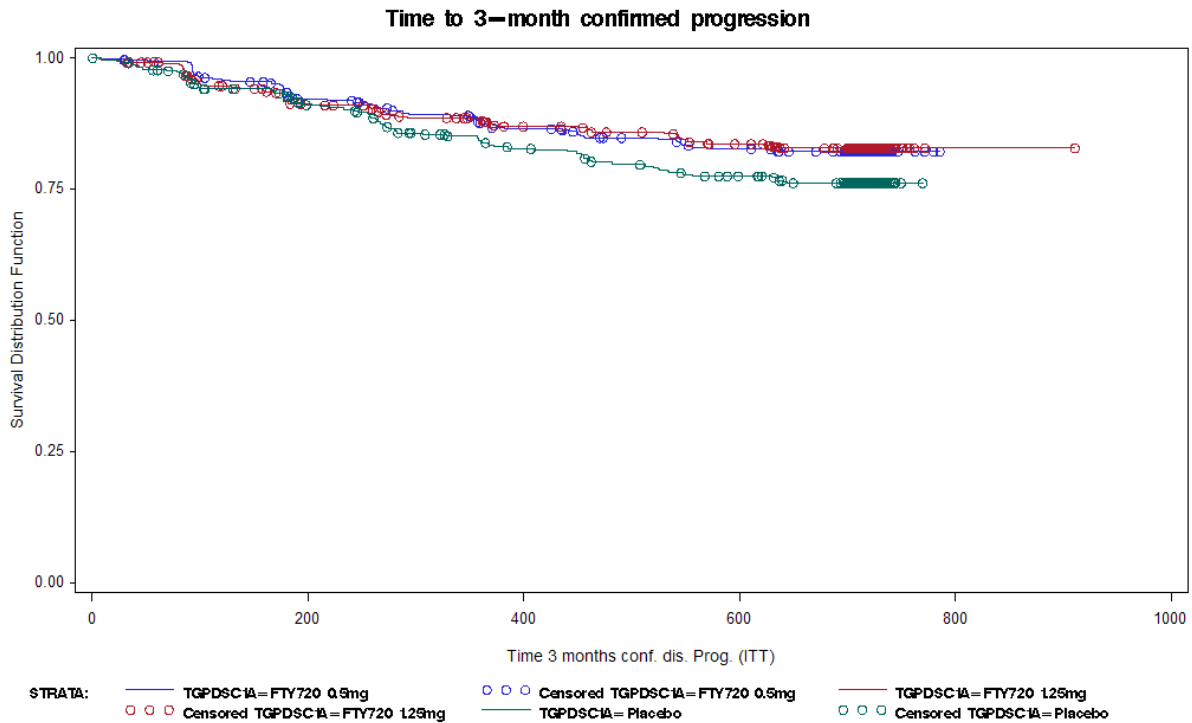
Fingolimod effect on disability progression

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

Study 2301

Fingolimod 1.25mg and 0.5mg significantly delayed the time to 3-month confirmed disability progression compared to placebo ($p=0.012$ and $p=0.026$, respectively) (Figure 1). 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.

Figure 1: Cumulative plot of time to 3-month confirmed disability progression in Study 2301 (copied from Figure 2 of Dr. Yan's review)



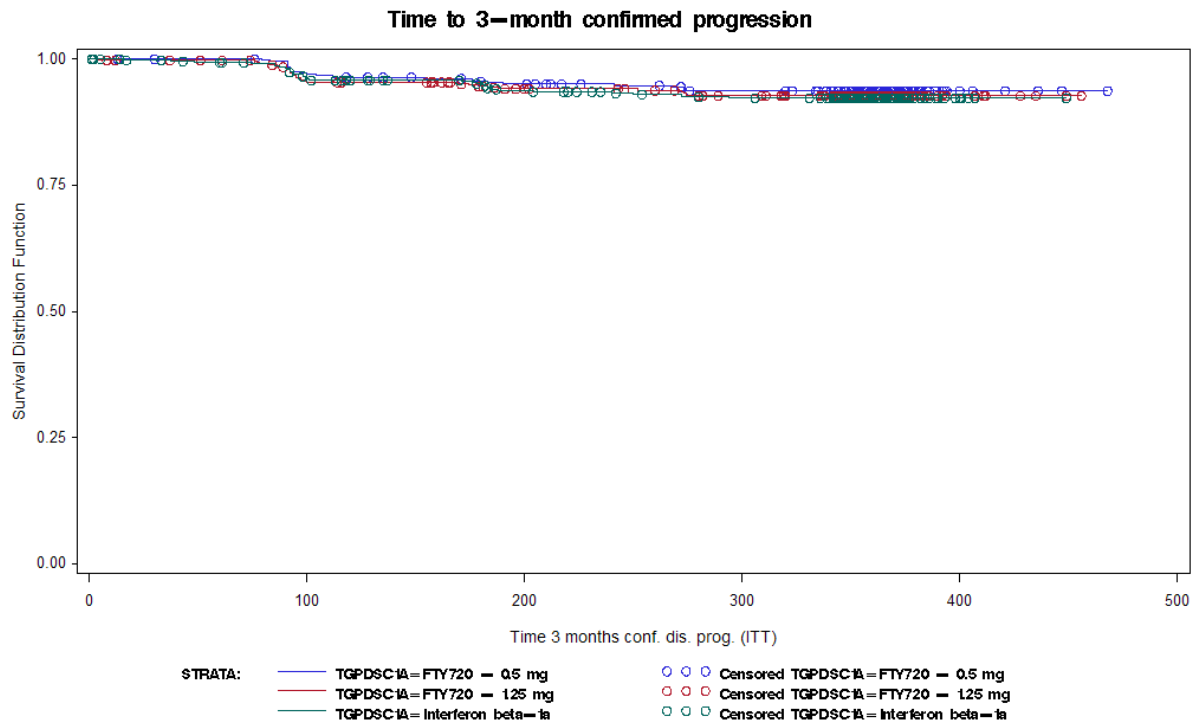
Study 2302

The significant delay in confirmed disability progression seen for both doses for fingolimod in Study 2301 was not independently substantiated in Study 2302, as there was no difference between either of the two fingolimod treatment groups and the Avonex 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 Avonex).

Two important factors may account for the lack of demonstrated effect on disability progression in Study 2302: the relatively short duration of the study, and the active comparator. It is important to remember that the lack of significant difference between fingolimod and Avonex should not be inferred to mean that they are “similar” on that

endpoint, as the study was not designed to test for non-inferiority of fingolimod to Avonex.

Figure 2: Cumulative plot of time to 3-month confirmed disability progression in Study 2302 (copied from Figure 4 of Dr. Yan’s review)



Fingolimod effect on the number of T2 lesions

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

Study 2301

In Study 2301, the nominal p value¹ (without multiplicity adjustment) for the contrast between either dose of fingolimod and placebo for the number of new or newly enlarged T2 lesions was under 0.001, with also a rather large effect size (see Table 3).

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

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

	FTY720 1.25 mg N** = 337	FTY720 0.5 mg N** = 370	Placebo N** = 339
Number of lesions¹			
Median (mean)	0.0 (2.5)	0.0 (2.5)	5.0 (9.8)
p-value vs. placebo (negative binomial regression with covariates)	< 0.001*	< 0.001*	
Proportion (%) of patients free of lesions	51.9	50.5	21.2
p-value vs. placebo	< 0.001*	< 0.001*	

¹ Number of lesions at Month 24 were obtained by adding the Month 0 - 12 results to the Month 12 - 24.
p-value for number of lesions is calculated using a negative binomial model adjusted for treatment and country. p values for proportion of patients free of lesions was calculated using the logistic regression model adjusting for treatment and country

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

** Results are presented for ITT patients who had a T2-weighted scan at both baseline and Month 24.

Study 2302

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

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

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

n=the number of patients with evaluable MRI at baseline and Month 12

P-value is calculated using a negative binomial model adjusting for treatment, country, baseline number of relapses in the previous 2 years, and baseline EDSS.

As discussed by Dr. Fitter, Novartis proposed a revised (post-hoc) analysis for the number of “new and newly enlarged T2 lesions²” in Study 2302, that uses a different method for counting the lesions, and also excludes 18 patients that prematurely discontinued from the study. In that revised analysis, the contrast between fingolimod 0.5 mg and placebo for the number of new and newly enlarged T2 lesions becomes statistically significant (p=0.004). At the time of redaction of this document, the proposed change is under review.

Dose response

In terms of efficacy, the dose-response between 0.5 mg and 1.25 mg is essentially flat. No statistically significant difference was seen in either pivotal study between fingolimod

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

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 2301, while the reverse was true in Study 2302. The effect of fingolimod 1.25 mg and 0.5 mg on the number of new or newly enlarging T2 MRI lesions was also very similar. These findings suggest that the fingolimod development program may not have identified the lowest effective dose.

In addition, the FDA pharmacometrics team performed modeling analyses that suggest a 0.25mg/day fingolimod dose may provide effectiveness comparable to 0.5mg/day. The issue of identifying the lowest effective dose is particularly important for drugs associated with dose-dependent potentially irreversible toxicities.

5. Safety

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

5.1 Deaths

Dr. Villalba notes that out of 14 deaths reported in the fingolimod MS development program, nine occurred during or after exposure to fingolimod (plus one still blinded at the time of her review). Dr. Villalba's assessment of causality is shown in Table 5.

Table 5: Summary of deaths in the fingolimod MS program (adapted from Table 8 of Dr. Villalba's review)

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

5.2 Serious adverse events (SAEs)

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

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

Table 6: SAEs with incidence $\geq 3/1000$, and with incidence higher with fingolimod 1.25mg/day or 0.5mg/day than with placebo (adapted from Table 10, Table 13, and Table 17 of Dr. Villalba's review)

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

[^] Based on FDA analysis

^{*}Pooling of grand mal convulsion, epilepsy, status epilepticus, partial onset seizure

⁺ Based on FDA analysis; includes one death due to disseminated zoster infection and one death due to herpes simplex encephalitis infection that was coded as Viral infection NEC.

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

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

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

5.3 AEs leading to study discontinuation

Dr. Villalba notes that overall, the risk of AEs leading to study drug discontinuation (“adverse dropouts”) was higher for fingolimod 1.25mg/day (12%) than for fingolimod 0.5mg/day (7%), placebo (7%) or Avonex (3%). Dr. Villalba notes that the difference was driven by dose-related adverse reactions in three system organ classes: Investigations (mostly liver-related), Cardiac, and Eye disorders. Table 7 shows adverse events leading to drug discontinuation that were more common on fingolimod than on placebo in controlled trials.

Table 7: Most frequent ($\geq 2/1000$ and more frequent with fingolimod than with placebo) discontinuations due to adverse events in controlled MS clinical studies (adapted from Table 33 and 35 of Dr. Villalba's review)

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

	Fingolimod 1.25mg/day (N=943) %	Fingolimod 0.5 mg/day (N=854) %	Placebo (N=511) %	Interferon (N=431) %
Thrombocytopenia	0	0.2	0	0
Metabolism and nutrition	0.2	0	0	0

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

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

5.4 Common adverse events

Table 8 shows common adverse events in fingolimod controlled trials. The events with the greater difference in risk between fingolimod and placebo were ALT increased, GGT increase, bronchitis, melanocytic nevus, leukopenia (expected based on fingolimod mechanism of action) and influenza like illness (which was also much more frequent with Avonex).

Table 8: Percentage of patients with common AEs in MS controlled trials(>5% in a fingolimod treatment group and ≥1 % higher with fingolimod 1.25mg/day or 0.5mg/day than with placebo; adapted from table 52 of Dr. Villalba’s review)*

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

Chest pain	1	1	1	1
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*AEs are listed according to decreasing frequency on fingolimod 0.5mg/day; bolded AEs are those at least twice as frequent with fingolimod 1.25mg/day than with placebo

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

5.4 Laboratory data

Hematology

Fingolimod causes lymphopenia. Lymphocyte counts dropped to a mean of about $0.5 \times 10^9/L$ for fingolimod 0.5mg/day (28% of baseline), and $0.4 \times 10^9/L$ for fingolimod 1.25mg/day (23% of baseline). The decrease in lymphocyte count was observed after 1-2 weeks and was maintained on treatment. After drug discontinuation, lymphocyte counts recovered to a mean of 5% below baseline within 3 months. There were slight decreases in mean neutrophil and platelet counts, of no apparent clinical significance. Analysis of outliers for hematologic parameters did not identify any safety signal, other than the known effect on lymphocyte counts. About 20% of patients who received fingolimod 0.5mg/day reached nadir of lymphocytes counts under $0.2 \times 10^9/L$.

Electrolytes

As discussed by Dr. Villalba, electrolytes (sodium, potassium, bicarbonate, calcium, magnesium) were not collected in phase 2 and phase 3 MS studies. This is of concern to Dr. Villalba, particularly for patients who developed adverse events that could be associated with electrolyte disturbances (e.g. bradycardia, extrasystoles). Dr Villalba requested additional electrolytes analyses from a 28-day clinical pharmacology study, which are pending at the time of redaction of this document.

Liver enzymes

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

5.4 Vital signs

Acute effects

There was an acute hypotensive effect, mostly seen with the 1.25mg/day dose (Table 9).

Table 9: Notable blood pressure abnormalities upon first dose administration (adapted from Table 68 of Dr. Villalba's review)

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

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

Table 10: Notable pulse rate abnormalities upon first dose administration (adapted from Table 68 of Dr. Villalba's review)

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

Chronic effects

Chronic use of fingolimod causes a dose-response increases in systolic and diastolic blood pressure (after a transient decrease after the first dose). That effect was present at the month 1 evaluation, reached a plateau after 6 months and was maintained throughout the study (Table 11).

Table 11: Changes from baseline (mmHg) in systolic and diastolic blood pressure (BP) in fingolimod controlled studies (adapted from table 65 of Dr. Villalba's review)

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

*Study 2201, 2301 and 2302

^Study 2301 only

Outlier analyses of vital signs with chronic use are consistent with the analyses of mean changes and show that more patients fulfilled "notable criteria" for high blood pressure in the fingolimod groups, particularly at 1.25mg/day and 5 mg/day (Table 12 and Table 13). The difference between fingolimod 0.5mg/day and placebo was minimal.

Table 12: Notable increases in blood pressure (Increase in systolic BP from baseline ≥20mmHg or increase in diastolic BP from baseline ≥15 mmHg)

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

	≥20mmHg increase in systolic BP	≥15 mmHg increase in diastolic BP
Placebo	20%	20%
Avonex	15%	17%

Table 13: Notable increases in blood pressure (systolic ≥160mmHg or diastolic ≥100mmHg)

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

5.5 Safety issues of possible concern with fingolimod

A. Infections

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

Infection-related deaths and SAEs

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

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

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

Additionally, six SAE of herpetic infection (one on fingolimod 5-1.25mg/day, four on fingolimod 1.25mg/day and one on fingolimod 0.5mg/day) occurred in long-term extension studies, and one patient developed atypical MS and was treated with acyclovir 2 months after last dose of fingolimod 1.25mg.

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

Infections-related adverse events leading to discontinuation

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

Infections-related common adverse events

Bronchitis was the only common (incidence $\geq 5\%$) adverse event reported more frequently higher with fingolimod 1.25mg/day (7%) and fingolimod 0.5mg/day (6%) than with placebo (3%) or Avonex (3%).

Division of Special Pathogens consult

The division consulted Dr. Marc Cavaille Coll, from the Division of Special Pathogens (DSPTP), regarding the risk for opportunistic infections with fingolimod. Dr. Cavaille Coll notes that fingolimod causes a redistribution (rather than a depletion) of lymphocytes, and that lymphocyte count therefore should not be interpreted as reflective of the net state of immunosuppression in patients on fingolimod. Dr. Cavaille Coll does not believe that there is a compelling signal for a significantly increased risk for opportunistic infections at the proposed fingolimod daily dose of 0.5mg/day.

Dr Cavaille Coll also notes that exploratory analyses of the relationship between infection and lymphocyte counts were not conclusive. Dr. Cavaille Coll recommends consideration of vaccination, in particular for varicella zoster virus (VZV), prior to initiation of long-term immunosuppressant therapy. Dr. Cavaille Coll notes that vaccination may be less effective during treatment with immunosuppressants, and that live vaccines should be avoided in that situation³. He recommends consideration of post exposure prophylaxis in patients seronegative for VZV at risk of developing varicella after primary exposure.

B. Pulmonary toxicity

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

³ Live vaccines may include, but are not limited to measles, mumps, rubella, oral polio, BCG, yellow fever, and Ty21a typhoid³.

Chest HRCTs

In Study 2301, 360 patients (one third of those randomized) 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). However, there was no particular pattern of toxicity and no evidence of pulmonary fibrosis.

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

Preliminary chest HRCT data from Study 2309 show no significant difference between fingolimod 0.5mg/day and placebo, but final data from that study are pending.

PFTs

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

Figure 3: FEV1 change from baseline (pooled data from Study 2301 and 2302; copied from Figure 4 of Dr. Villalba's review)

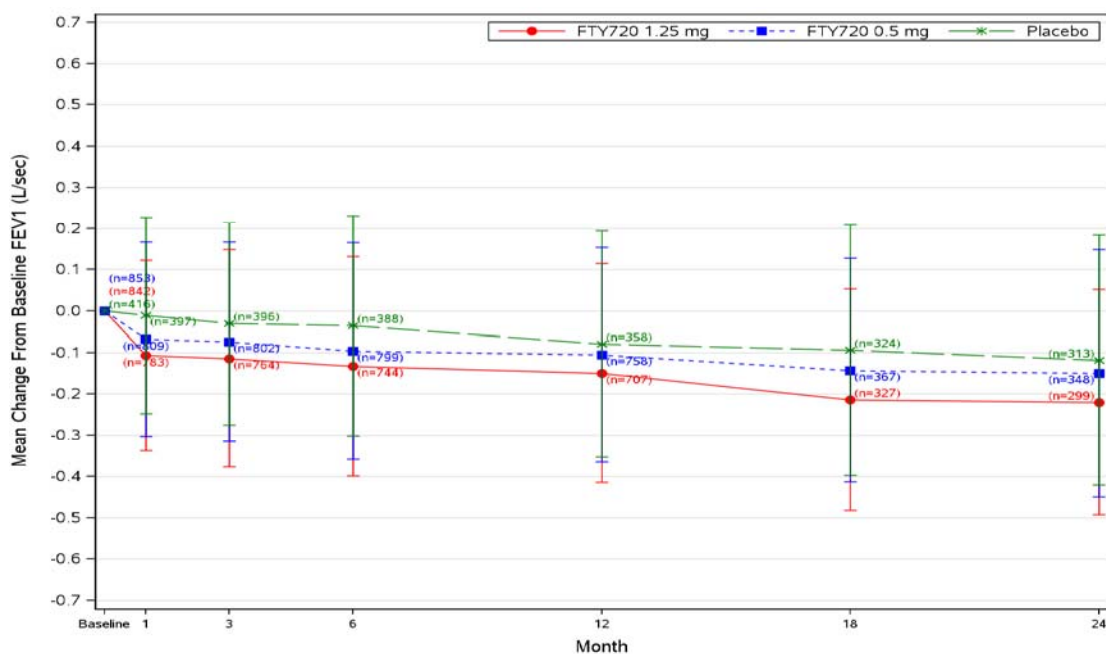


Figure 4: FEV1 change from baseline (Study 2309; copied from Figure 7 of Dr. Villalba's review)

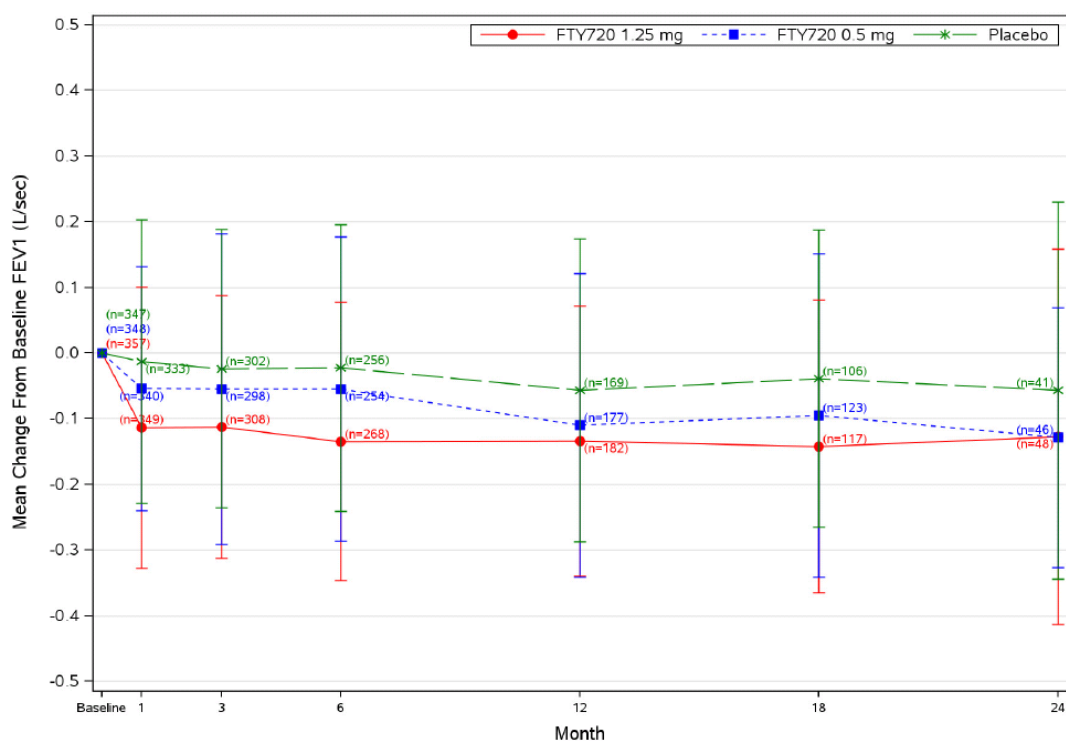


Figure 5: DLCO changes from baseline (pooled data from Study 2301 and 2302; copied from Figure 6 of Dr. Villalba's review)

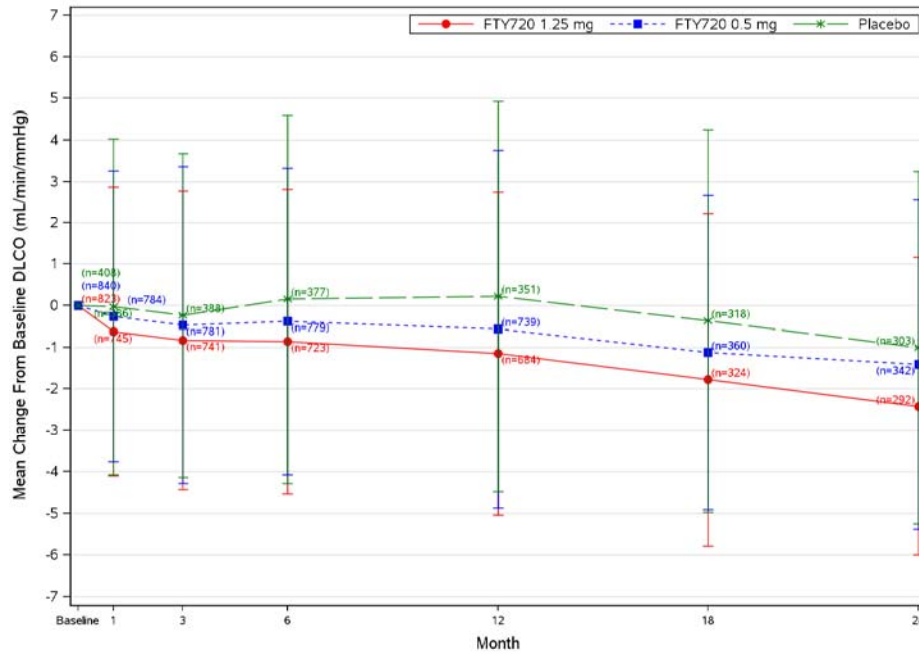
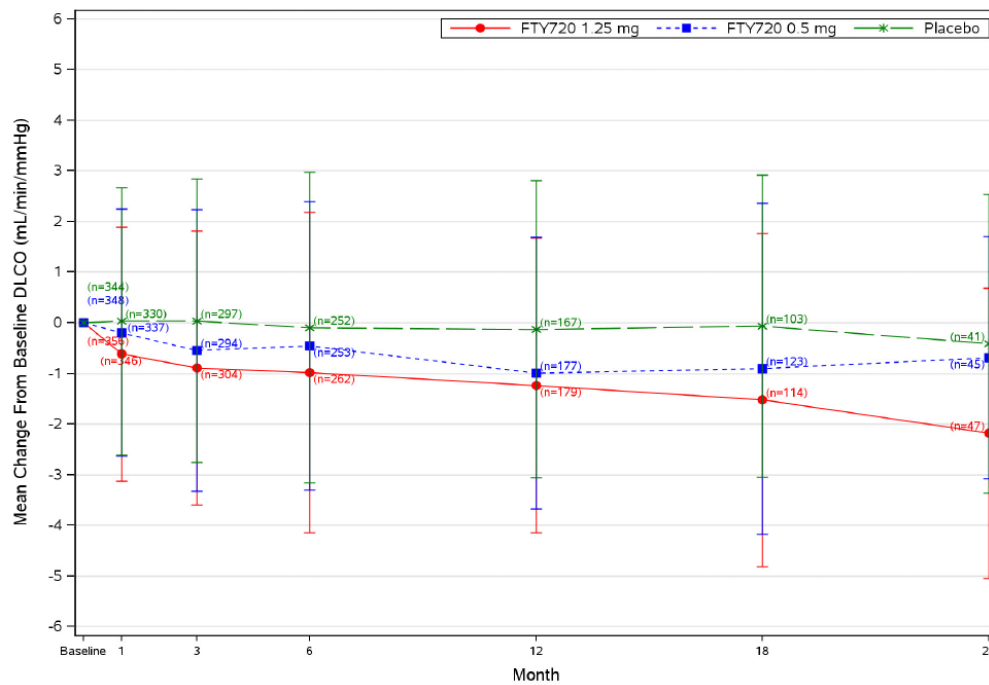


Figure 6: DLCO change from baseline (Study 2309; copied from Figure 8 of Dr. Villalba's review)



On treatment, there was also a dose-response for the proportion of patients with a PFT parameter <80% of baseline (Table 14 and Table 15).

Table 14: PFT outliers (pooled data from Study 2301 or 2302; copied from table 81 of Dr. Villalba's review)

	FTY720 1.25 mg (N=849)		FTY720 0.5 mg (N=854)		Placebo (N=418)		Interferon (N=431)	
	n	(%)	n	(%)	n	(%)	n	(%)
<80% of baseline PFT absolute values at any post-baseline visit								
FEV1	64	(7.5%)	39	(4.6%)	24	(5.7%)	15	(3.5%)
FVC	36	(4.2%)	23	(2.7%)	17	(4.1%)	11	(2.6%)
DLCO	157	(18.5%)	133	(15.6%)	50	(12.0%)	62	(14.4%)

Table 15: PFT outliers (Study 2309; copied from table 84 of Dr. Villalba's review)

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

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

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

Asthma

Subjects with asthma were allowed in fingolimod studies if they did not require active treatment. No adverse event related to asthma occurred at the 0.5mg/day dose proposed for marketing in fingolimod clinical studies.

Division of Pulmonary, Allergy and Rheumatology Products (DPARP) consult

The division consulted Dr. Brian Porter (DPARP) regarding the pulmonary toxicity of fingolimod. Dr. Porter believes the data do not support requesting routine PFT monitoring or routine HRCT screening of patients treated with fingolimod. However, Dr. Porter recommends a description of the pulmonary findings in labeling and in communications part of a Risk Evaluation and Mitigation Strategy (REMS) for

fingolimod. Dr. Porter also recommends further study of the stability and reversibility of pulmonary function deficits with long-term use of fingolimod.

C. Cardiac toxicity

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

Bradycardia- and atrioventricular block-related SAEs

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

Cardiac disorders-related adverse events leading to discontinuation

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

Heart conduction and bradycardia

Patients in Study 2301 and 2302 (as well as in long-term extension studies) were monitored in the clinic (heart rate and blood pressure) for at least 6 hours after taking the first dose of study drug. After 6 hours of observation, patients could be discharged if the maximal lowering effect on heart rate had already been observed (i.e. after observing a decrease, heart rate should already have been increasing at the time of discharge), the patient was asymptomatic, and the 6-hour ECG did not show any new relevant abnormality. Patients not meeting these criteria had to be observed longer (until criteria were met). In addition, patients showing a strong sensitivity to the drug (defined as a heart rate decrease of more than 30% or the presence of symptomatic bradycardia) had to return to the clinic for the same 6-hour monitoring for the second dose of study drug. Compared to placebo, more patients who received fingolimod 1.25 mg and 0.5 mg required extended monitoring and hospitalization. The rate of discontinuation was however no higher after the first dose of fingolimod 0.5 mg dose than after the first dose of placebo (Table 16).

Table 16: First dose administration monitoring experience

	FTY720 1.25 mg (N=849) n (%)	FTY720 0.5 mg (N=854) n (%)	Placebo (N=418) n (%)	Interferon (N=431) n (%)
Discharged at 6 hours	645 (76.0)	700 (82.0)	356 (85.2)	422 (97.9)
Required extended monitoring after 6 hours	153 (18.0)	105 (12.3)	14 (3.3)	6 (1.4)
Hospitalized	23 (2.7)	15 (1.8)	0	2 (0.5)
Required Day 2 monitoring	62 (7.3)	19 (2.2)	3 (0.7)	4 (0.9)
Study drug permanently discontinued	12 (1.4)	2 (0.2)	1 (0.2)	0

Source: ISS

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

Table 17: ECG abnormalities 6 hours after the first fingolimod dose (adapted from Table 70 of Dr. Villalba's review)

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

A 24-hour holter monitoring substudy in 129 patients showed that the decline in heart rate was observed as early as 1 hour post-dose, reaching a maximum decrease at 5 hours post-dose in the fingolimod 1.25mg group (mean drop of approximately 28 bpm) and at 6 hours post-dose in the fingolimod 0.5mg group (mean drop of approximately 22 bpm). The largest holter database comes from Study 2309 (366 patients on fingolimod 1.25mg/day, 356 patients on fingolimod 0.5mg/day, and 353 patients on placebo). In Study 2309, second degree AV blocks (Mobitz 1 or 2:1 blocks) were observed in 6.6% of patients on fingolimod 1.25mg/day, 3.4% of patients on fingolimod 0.5mg/day and 2% of patients on placebo. Bradycardia⁴ was observed after the first dose in 1.4% of patients on fingolimod 1.25mg/day, 0.3% of patients on fingolimod 0.5mg/day and none on placebo. SAEs related to AV block or bradycardia within 6 hours of the first dose were reported in 3 patients on fingolimod 1.25mg/day who were symptomatic and hospitalized for observation. They fully recovered by Day 2 and discontinued study drug.

Novartis proposes monitoring for six hours after the first fingolimod dose only in patients on beta blockers and low baseline heart rate. Dr. Villalba notes that labeling is imprecise as to the location for first dose monitoring. Dr. Villalba believes that all patients should be monitored for the first dose in a medical unit capable of immediate treatment for

⁴ defined as average heart rate of 40 bpm for anyone hour during 24-hour Holter monitoring

severe cases of bradycardia and heart block. In addition, Dr. Villalba notes that the fingolimod studies excluded patients with pre-existent diseases such as diabetes mellitus, heart conduction disorders, taking antiarrhythmics medications or having pulmonary disease. Dr. Villalba believes that patients with any of these disorders might not tolerate bradycardia or AV block as well as the patients who participated to fingolimod clinical studies. Dr. Villalba also recommends a study in that more vulnerable population.

Left ventricular function and ischemic heart disease

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

A total of 183 patients were included in the echocardiography substudy (64 patients on fingolimod 1.25mg/day, 60 patients on fingolimod 0.5mg/day, 48 patients on placebo and 11 patients on Avonex). Unfortunately, available echocardiographic evaluations are limited and incomplete, as at the time of the original submission, only 17 patients had paired echocardiograms for up to 2 years⁵. Some of the analyses of echocardiographic data were still ongoing at the time of redaction of this document, but preliminary data did not show evidence for a fingolimod effect on left ventricular function. Of note, there was no excess of congestive heart failure or ischemic heart disease with fingolimod in controlled MS studies.

Division of Cardio-Renal Products (DCRDP) consult

The division consulted Dr. Shari Targum (DCRDP) regarding the echocardiographic data. Dr. Targum believes that available echocardiographic evaluations are limited and incomplete, but did not reveal a large safety signal. Dr. Targum observes that depressed left ventricular systolic function was not observed. As actual echocardiograms were not submitted, Dr. Targum was unable to comment on the quality of images, or where or how the measurements were taken. Dr Targum notes that no Doppler results or any evaluations of valve morphology were submitted. Dr. Targum emphasizes that if one were concerned about papillary muscle fibrosis, one would have evaluated the mitral and tricuspid valves, including an assessment of regurgitation, but those examinations were not part of this application.

Nevertheless, Dr. Targum believes that if there were a large signal, for example, an imbalance in severe chronic mitral regurgitation in the fingolimod group, one would expect consequences of chronic volume overload such as left ventricular and left atrial dilatation, in addition to a holosystolic murmur heard best at the apex. Dr. Targum therefore finds somewhat reassuring that the 12 month left atrial volume, end-diastolic and end-systolic dimensions were not increased from baseline. However, Dr. Targum cannot exclude a smaller signal, or a signal that would appear over a longer time period. Finally, since the study population excluded diabetics and subjects with significant heart

⁵ only data on 30 patients exposed for 2 years are expected during the NDA review cycle .

disease, Dr. Targum cannot exclude safety signals that might surface in a more vulnerable population.

D. Ocular toxicity

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

Eye disorders-related SAEs

In controlled MS studies, there was a dose-related increase in the incidence of macular edema reported as a SAE: 4 cases were reported on fingolimod 1.25mg/day (0.4%), and one case was reported on fingolimod 0.5mg/day (0.1%), with no case for placebo or Avonex. When the entire (controlled and uncontrolled) MS database is considered, the same dose-response relationship is seen, with a 0.8% incidence of macular edema reported as an SAE for fingolimod 1.25mg/day, versus 0.2% for fingolimod 0.5 mg/day. Four additional cases of macular edema-related SAE were reported in ongoing Study 2309 (two on fingolimod 1.25mg/day, one on fingolimod 0.5mg/day and one on placebo). Macular edema in the patient on fingolimod 0.5mg/day was serious enough to warrant ocular surgery to repair a macular hole, with a reasonably good outcome, as six months after surgery, visual acuity was 20/40 in the affected eye.

Dr. Villalba notes that some patients had symptoms at the time of diagnosis (decreased vision, blurred vision, feeling of pressure in one eye or visual acuity testing decreased), but most were asymptomatic. Most cases were diagnosed by dilated ophthalmologic evaluation or Optical Coherence Tomography⁶ (OCT) at protocol scheduled timepoints. In some cases, fluorescein angiography was used to confirm macular edema suspected with OCT. Some cases were bilateral but most cases involved only one eye.

Onset of macular edema was reported as early as 11 days and as late as 932 days into study treatment, however the two cases with the longer time to onset were not confirmed by OCT. Most cases occurred earlier than 3-4 months into treatment (mean 207 days; median 99 days).

All cases of serious macular edema led to study drug discontinuation (one was diagnosed after drug discontinuation). Some patients received additional treatment (NSAIDs, topical steroids). Dr. Villalba notes that most patients recovered completely within a few weeks or months after drug discontinuation.

Eye disorders adverse events leading to discontinuation

Dr. Villalba notes that 20 patients had adverse events that led to drug discontinuation in the Eye disorders system organ class in fingolimod controlled studies. Some of them

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

were coded as serious (4 cases of macular edema on fingolimod 1.25mg/day and one on fingolimod 0.5mg/day described above), but some events of interest were coded as non serious. These include eight cases of macular edema in the fingolimod 1.25mg/day group, one in the fingolimod 0.5mg/day group and one in a subject receiving Avonex (not confirmed by DSMB ophthalmologist). Dr. Villalba also describes a few non-serious cases of retinal hemorrhage and retinal aneurysms, all in the fingolimod treatment groups. There were 4 additional cases in Study 2309 that led to discontinuation of fingolimod 0.5mg/day because of macular edema.

Optical coherence tomography monitoring

In controlled studies other than Study 2309, Dr. Chambers notes a higher proportion of patients with a central foveal thickness of >200 but ≤250 microns in the fingolimod treatment groups than in the placebo group (12.5% with fingolimod 1.25mg/day, 13% with fingolimod 0.5mg/day group, and 9.3% with placebo). Dr. Chambers found no difference between the groups with regard to the percentage of patients with a central foveal thickness of >250 to ≤300 microns, and no patients in the fingolimod 0.5mg/day group with a central foveal thickness of greater than 300 microns at either Month 24 or the last visit on study drug, compared with 3 patients in the fingolimod 1.25mg/day group and 1 patient in the placebo group (Table 18).

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

	Fingolimod 1.25 mg	Fingolimod 0.5mg	Placebo
Number of Patients	429	425	418
Number of Eyes	520	581	511
Change from baseline			
<-40	15 (3%)	20 (3%)	23 (5%)
≥-40 and ≤-21	40 (8%)	38 (7%)	33 (6%)
>-21 and ≤20	375 (72%)	417 (72%)	376 (74%)
>20 and ≤40	45 (9%)	69 (12%)	54 (11%)
>40	45 (9%)	37 (6%)	25 (5%)

In Study 2309, Dr. Chambers also observed small, dose-dependent effects of fingolimod on central foveal thickness (difference from placebo in mean/median change from baseline was 5 microns/4 microns for fingolimod 1.25mg/day, and 4 microns/3 microns for fingolimod 0.5mg/day). These effects were observed at Month 1 and did not increase over time. Central foveal thickness >300 microns was observed in 3 patients on fingolimod 1.25mg/day, 3 patients on fingolimod 0.5mg/day, and 1 patient on placebo at Month 1. At Month 3, the number of patients with central foveal thickness >300 microns was 3, 1, and 1 for fingolimod 1.25mg/day, fingolimod 0.5mg/day, and placebo, respectively.

Dr. Chambers notes that a diagnosis of macular edema was made by the local ophthalmologist for 7 (2.0%) patients on fingolimod 1.25mg/day, 5 (1.4%) patients on fingolimod 0.5mg/day, and 2 (0.6%) patients on placebo. The retinal expert on the Data and Safety Monitoring Board (DSMB) confirmed the macular edema diagnosis in only 3 (0.8%) patients on fingolimod 1.25mg/day, 3 (0.9%) patients on fingolimod 0.5mg/day,

and 1 (0.3%) patient on placebo, with one case (on fingolimod 1.25 mg/day) listed as pending. Of the 7 cases confirmed as macular edema by the DMSB ophthalmologist, 5 had central foveal thickness >300 microns. For the 6 cases not considered as macular edema by the DMSB ophthalmologist, the maximal central foveal thickness was 262 microns; central foveal thickness in the 5 other non-confirmed cases was <210 microns. Central foveal thickness in the case pending DSMB confirmation was >300 microns.

Dr. Chambers observes that at the dose currently proposed for the treatment of multiple sclerosis (0.5 mg) there have been a limited number of cases of macular edema. Dr. Chambers notes that patients with multiple sclerosis are often recommended to be followed with a full ophthalmic examination including dilated funduscopy (and ocular coherence tomography as needed) every six months. Dr. Chambers believes that ocular findings in the fingolimod NDA do not suggest that ophthalmologic follow up needs to be more frequent than routine ophthalmic monitoring for multiple sclerosis unless an ocular adverse event is identified by history or routine monitoring.

E. Hepatotoxicity

Fingolimod causes frequent liver enzymes elevations, and a potential for serious liver toxicity is currently under review.

Hepatobiliary-related SAEs (including liver enzyme abnormalities)

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

Late in the review cycle (4/29/2010), a report of a patient who developed ALT 20 times the upper limit of normal (ULN) and jaundice while receiving fingolimod was submitted to the FDA. The implications of that case for the fingolimod NDA are under review. In response to this case, Novartis submitted revised proposed labeling, to describe the following: *Liver injury, including the rare occurrence of clinically significant injury associated with jaundice, has occurred. In clinical trials, liver transaminase elevations of 3-fold or greater occurred in 8% of patients on 0.5 mg. Assess liver enzymes if symptoms suggestive of hepatic injury develop. Gilenia should be discontinued if significant liver injury is confirmed. Use with caution in patients with a history of significant liver disease.*

Hepatobiliary-related adverse events leading to discontinuation

The majority of hepatobiliary adverse events leading to discontinuation were non serious (i.e. 74/85 cases). Dr. Villalba notes most of the non-serious events were associated with increases in ALT or GGT elevation 3 to 5x ULN, without associated increase in bilirubin or alkaline phosphatase, and resolved two weeks to several months after drug discontinuation. However, some cases were associated with markedly abnormal ALT elevation ($>5x$ ULN) and some cases had not fully resolved at the time of last testing after drug discontinuation. Dr. Villalba reports cases with positive de-challenge, and several cases of positive re-challenge.

Liver enzymes elevations

Fingolimod is associated with a lasting increase (15-20 IU/L) in mean blood levels of transaminases, mostly ALT and GGT (but not total or direct bilirubin). There was also an excess of patients with liver enzymes abnormalities in fingolimod-treated patients (Table 19). ALT $\geq 3x$ the upper limit of normal (ULN) was seen respectively in 9, 10 and 12% of patients in the fingolimod 0.5mg/day, 1.25mg/day and 5mg/day group, as compared to only 2% in the placebo or Avonex group. The proportion of patients with ALT $\geq 5x$ ULN was also slightly higher in the fingolimod treated groups. Dr. Villalba notes that the great majority of these cases had normal bilirubin and alkaline phosphatase. At the time of her initial review, there were five cases in the fingolimod safety database with increase in transaminases $\geq 3x$ ULN and increase in bilirubin $\geq 2x$ ULN. One of them was the case of hepatic necrosis in a patient who died of disseminated herpes zoster; one was a patient who received intravenous acetaminophen for hip pain; 2 cases occurred in subjects suspected of having Gilbert's disease, and one occurred on placebo. However, as noted above, a report of a patient who developed ALT 20xULN and jaundice while receiving fingolimod was submitted to the FDA late in the review cycle, and is under review.

Table 19: Distribution of patients with liver enzyme abnormalities in fingolimod controlled studies (copied from table 62 of Dr. Villalba's review)

Parameter	Criterion	FTY720 5 mg (N=94)	FTY720 1.25 mg (N=943)	FTY720 0.5 mg (N=854)	Placebo (N=511)	Interferon (N=431)
		n (%)	n (%)	n (%)	n (%)	n (%)
ALT	Total	93	934	851	506	429
	No abnormalities	40 (43.0)	505 (54.1)	461 (54.2)	388 (76.7)	322 (75.1)
	> 1 x ULN	53 (57.0)	429 (45.9)	390 (45.8)	118 (23.3)	107 (24.9)
	≥ 2 x ULN	20 (21.5)	173 (18.5)	148 (17.4)	29 (5.7)	26 (6.1)
	≥ 3 x ULN	11 (11.8)	91 (9.7)	72 (8.5)	8 (1.6)	10 (2.3)
	≥ 5 x ULN	1 (1.1)	21 (2.2)	14 (1.6)	4 (0.8)	6 (1.4)
	≥ 10 x ULN	0	0	1 (0.1)	0	2 (0.5)
	≥ 20 x ULN	0	0	0	0	1 (0.2)
AST	Total	93	934	851	506	429
	No abnormalities	69 (74.2)	673 (72.1)	636 (74.7)	455 (89.9)	370 (86.2)
	> 1 x ULN	24 (25.8)	261 (27.9)	215 (25.3)	51 (10.1)	59 (13.8)
	≥ 2 x ULN	6 (6.5)	50 (5.4)	36 (4.2)	8 (1.6)	13 (3.0)
	≥ 3 x ULN	1 (1.1)	14 (1.5)	17 (2.0)	5 (1.0)	8 (1.9)
	≥ 5 x ULN	0	2 (0.2)	2 (0.2)	1 (0.2)	3 (0.7)
	≥ 10 x ULN	0	0	0	0	2 (0.5)
	≥ 20 x ULN	0	0	0	0	1 (0.2)
GGT	Total		840	851	414	429
	No abnormalities		537 (63.9)	580 (68.2)	378 (91.3)	383 (89.3)
	> 1 x ULN		303 (36.1)	271 (31.8)	36 (8.7)	46 (10.7)
	≥ 2 x ULN		144 (17.1)	119 (14.0)	10 (2.4)	16 (3.7)
	≥ 3 x ULN		72 (8.6)	56 (6.6)	3 (0.7)	6 (1.4)
	≥ 5 x ULN		23 (2.7)	15 (1.8)	0	2 (0.5)
	≥ 10 x ULN		0	1 (0.1)	0	1 (0.2)
	≥ 20 x ULN		0	1 (0.1)	0	0
Total Bilirubin	Total	93	934	851	506	429
	No abnormalities	90 (96.8)	854 (91.4)	763 (89.7)	463 (91.5)	398 (92.8)
	> 1 x ULN	3 (3.2)	80 (8.6)	88 (10.3)	43 (8.5)	31 (7.2)
	≥ 2 x ULN	0	7 (0.7)	8 (0.9)	3 (0.6)	2 (0.5)

F. Blood and Lymphatic system disorders

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

G. Neoplasia

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

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

H. Seizures

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

5.6 Sponsor proposed Risk Evaluation and Mitigation Strategy (REMS)

Novartis proposes to address bradycardia/bradyarrhythmia, infections, macular edema and teratogenicity in a REMS, that would include a medication guide and a communication plan consisting on a Dear HCP letter and a product Brochure. Novartis is not proposing elements to assure safe use. Novartis does not plan to address the potential for lung disease toxicity or liver toxicity in the REMS.

6. Questions to the Peripheral and Central Nervous System Drugs Advisory Committee

We are asking the Committee's help in addressing whether the benefit to be obtained with fingolimod is justified by the risks to be expected in a population of MS patients who would be expected to receive the treatment if the application is approved. In this regard, we would like the Committee to consider the following questions:

- 1) Has the sponsor demonstrated substantial evidence of effectiveness of fingolimod for the treatment of patients with relapsing remitting multiple sclerosis?
- 2) If so, should the sponsor be required to evaluate the effects of doses lower than 0.5 mg QD?
- 3) If so, should this be required prior to approval?
- 4) If substantial evidence of effectiveness has been demonstrated, do you conclude that there are conditions under which fingolimod could be considered safe in use for this indication?
- 5) First-dose effects of fingolimod include bradycardia and heart conduction abnormalities. Based on the data presented to you, should patients be required to receive the first dose in a monitored setting?
- 6) If so, should that requirement apply to all patients, or to a specific subset?
- 7) Fingolimod causes macular edema, including at the dose proposed for marketing (0.5 mg). Is routine ophthalmic examination sufficient to monitor patients treated with fingolimod?
- 8) Fingolimod causes a gradual decline in pulmonary function, that appears partially reversible. Do you believe that routine pharmacovigilance will be sufficient to mitigate the risks associated with the pulmonary toxicity of fingolimod?
- 9) If not, what additional monitoring or study do you recommend?

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

11) Considering the risks and benefits, do you believe that fingolimod should be generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate MS therapy?

A potential signal for a risk of serious hepatotoxicity of fingolimod has been identified late in the review cycle, and is being assessed by the Agency. Once we complete our review, we may have additional questions to the committee regarding that risk.

We look forward to seeing you in June, and thank you for the work you have done in preparation for the meeting, and for your efforts at the meeting itself.

CLINICAL REVIEW - SAFETY

Application Type	NDA
Submission Number(s)	22-527
Priority or Standard	P

Submit Date	December 18, 2009
Received Date	December 21, 2009
PDUFA Goal Date	June 21, 2010

Reviewer Name(s)	Lourdes Villalba, M.D.
Team Leader	Sally Yasuda, Pharm D.
Interim Review	
Completion Date	May 12, 2010

Established Name	Fingolimod
(Proposed) Trade Name	Gilenia™
Therapeutic Class	Sphingosine-1 Phosphate modulator
Applicant	Novartis

Formulation	Oral capsules
Dosing Regimen	0.5 mg daily
Indication(s)	Treatment of patients with relapsing MS to reduce the frequency of relapses and to delay the progression of disability (Applicant's proposed indications).
Intended Population(s)	Adults

TABLE OF CONTENTS

1 RECOMMENDATIONS/RISK BENEFIT ANALYSIS	8
2 INTRODUCTION AND REGULATORY BACKGROUND	8
2.1 Product Information	8
2.2 Available Treatments for Proposed Indications	8
2.3 Availability of Proposed Active Ingredient in the United States	8
2.4 Important Safety Issues With Consideration to Related Drugs	9
2.5 Summary of Presubmission Regulatory Activity Related to Submission	9
2.6 Other Relevant Background Information	10
3 ETHICS AND GOOD CLINICAL PRACTICES	10
4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	10
4.3 Preclinical Pharmacology/Toxicology	10
4.4 Clinical Pharmacology	12
5 SOURCES OF CLINICAL DATA	15
5.1 Tables of Clinical Studies	15
5.2 Review Strategy	18
5.3 Discussion of Individual Studies	18
6 REVIEW OF EFFICACY	18
7 REVIEW OF SAFETY	18
Safety Summary as of May 12, 2010	18
7.1 Methods	22
7.1.1 Clinical Studies Used to Evaluate Safety	22
7.1.2 Categorization of Adverse Events	22
7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence	22
7.2 Adequacy of Safety Assessments	24
7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations	24
7.2.2 Explorations for Dose Response	31
7.2.3 Special Animal and/or In Vitro Testing	32
7.2.4 Routine Clinical Testing	32
7.2.5 Metabolic, Clearance, and Interaction Workup	35
7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class	35
7.3 Major Safety Results and Discussion	35
7.3.1 Deaths	35
7.3.2 Nonfatal Serious Adverse Events (SAE)	40
7.3.3 Adverse Events leading to study drug discontinuation	86
7.3.4 Significant Adverse Events	109
7.3.5 Submission Specific Primary Safety Concerns	117
7.4 Supportive Safety Results and Discussion	127
7.4.1 Common Adverse Events	127
7.4.2 Laboratory Findings	129
7.4.3 Vital Signs	139
7.4.4 Electrocardiograms (ECGs)	142
7.4.5 Special Safety Studies	153
7.4.6 Immunogenicity	177
7.5 Other Safety Explorations	178
7.5.1 Dose Dependency for Adverse Events	178
7.5.2 Time Dependency for Adverse Events	178
7.5.3 Drug-Demographic Interactions	178
7.5.4 Drug-Disease Interactions	178
7.5.5 Drug-Drug Interactions	179

Interim review, 5 12 10.
 Lourdes Villalba, M.D
 NDA 22-527. Fingolimod

7.6 Additional Safety Evaluations	179
7.6.1 Human Carcinogenicity	179
7.6.2 Human Reproduction and Pregnancy Data	179
7.6.3 Pediatrics and Assessment of Effects on Growth.....	179
7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound	179
7.7 Additional Submissions	180
8 POSTMARKETING EXPERIENCE	180
9 APPENDICES.....	180
9.1 Narratives.....	180
9.2 Labeling Recommendations.....	219
9.3 Advisory Committee Meeting.....	219
9.4 Information from the transplant population	219

Table of Tables

Table 1. Fingolimod in multiple sclerosis. Studies included in the ISS.....	16
Table 2. Ongoing clinical studies of Fingolimod in MS ¹	17
Table 3. Table of Safety Analysis Pools in MS ISS	23
Table 4. Duration of exposure to study drug after randomization in Group E (all FTY-treated patients, safety population)	25
Table 5. Exposure in study 2309.....	26
Table 6. Number of patients undergoing special safety evaluations in study 2309.....	27
Table 7. Assessments in study 2302	34
Table 8. Summary of deaths in the fingolimod MS program*	36
Table 9. Brief narratives of deaths during Fingolimod MS studies	37
Table 10. Patients with SAE in at least 2 patients in any treatment group or fatal up to 90 days after last dose, safety pool D.....	40
Table 11. Serious AE, Cardiac SOC, pool D	42
Table 12. Patients with SAEs, Cardiac disorder SOC, Pool E	43
Table 13. Patients who developed SAE of bradycardia or AV Block, safety pool D	45
Table 14. SAES in Nervous system disorders SOC, safety pool D.	55
Table 15. Serious AE, Infections and Infestations SOC, safety pool D	61
Table 16. SAES in Infections and Infestations SOC, Safety Pool E	62
Table 17. SAE in Infections and infestations SOC, by HLT, safety pool D.	64
Table 18. SAE in the Neoplasm disorders SOC, Pool D	67
Table 19. SAE in the Neoplasm disorders SOC, Pool E	68
Table 20. Incidence rate of serious neoplasms (events/100 PYRs), safety pools D and E.....	69
Table 21. Serious AE, Eye Disorders SOC, safety pool D	70
Table 22. SAE in the Eye Disorders SOC, Safety pool E (updated)	71
Table 23. Serious AE, Respiratory, thoracic & mediastinal disorders SOC, safety pool D. 74	
Table 24. Serious AE, Respiratory, thoracic & mediastinal disorders SOC, safety pool E.	74
Table 25. Serious AE, Vascular disorders SOC, safety pool D	75
Table 26. SAES in Vascular disorders SOC, Pool E	75
Table 27. Serious AE, General disorders and administration site conditions, safety pool D	80
Table 28. Serious AE, Hepatobiliary disorders SOC, safety pool D.	81
Table 29. Serious AE, Hepatobiliary disorders SOC, safety pool E.....	81
Table 30. Patients with SAE in Hepatobiliary and Investigations (liver-related) SOC, safety pool D.....	82
Table 31. Serious AE, Blood and Lymphatic system disorders SOC, safety pool D	84
Table 32. Serious AEs, Blood and Lymphatic disorders SOC, safety pool E	85
Table 33. Patients with AE leading to drug discontinuation in fingolimod MS studies, safety pool D*	86
Table 34. Patients with AE leading to study drug discontinuation in fingolimod by SOC, safety pool E*	88
Table 35. Patients who discontinued due to hepatobiliary SOC and liver related investigations in fingolimod controlled studies	89
Table 36. Patients with liver-related investigations AE leading to drug discontinuation in pool E (SUR)	93
Table 37. AE leading to drug discontinuation, Eye disorders SOC, safety pool D	93

Table 38. AE leading to drug discontinuation, Cardiac SOC, pool D	97
Table 39. AE leading to drug discontinuation in the Infections and Infestation SOC, safety pool D, by high level group term (HLGT).....	100
Table 40. AE leading to drug discontinuation, Nervous system disorders SOC, safety pool D.	102
Table 41. AE leading to drug discontinuation, General disorders SOC, safety pool D.....	102
Table 42. AE leading to drug discontinuation in the Respiratory SOC and respiratory related Investigations SOC, safety pool D.....	104
Table 43. AE that led to study drug discontinuation in Vascular SOC, pool D	106
Table 44. Selected serious and non-serious AE in the Eye disorders SOC, pool D	110
Table 45. Serious and non-serious ischemic heart disease in safety pool D.....	110
Table 46. Serious and non-serious AE consistent with ischemic heart disease in people below 40 years of age, safety pool D.....	111
Table 47. Serious and non-serious hypertension- related events in pool D.....	111
Table 48. Serious and non-serious AE, Respiratory thoracic and mediastinal disorders, pool D (selected AEs)	112
Table 49. Seizure related events in Safety pool D	115
Table 50. Selected serious and non-serious events in the Neoplasms SOC, safety pool D	116
Table 51. Liver-related analyses in pool D.....	125
Table 52. Number of patients with AE in $\geq 5\%$ of patients, safety pool D.....	127
Table 53. Change in selected hematologic parameters over time in Safety pool A in Fingolimod studies.	129
Table 54. Percentage Change in absolute lymphocyte count in study 2301	131
Table 55. Change in absolute basophil count in study 2301.....	132
Table 56. Change in lymphocyte % in E follow up cohort.....	132
Table 57. Outlier analysis of hematologic abnormalities in Safety Pool D.....	134
Table 59. Change from baseline in ALT at time of last available measurement, pool D	135
Table 60. Mean changes from baseline in BR at last available measurement, safety pool D ...	135
Table 61. Mean changes from baseline in serum Alkaline phosphatase at last available measurement, safety pool D.....	136
Table 62. Distribution of patients with liver enzyme abnormalities, pool D.....	136
Table 63. Outlier analysis of metabolic parameters, safety pool D	137
Table 64. Percentage of patients with protein in urine in Safety pool D	138
Table 65. Changes from baseline in Systolic and diastolic blood pressure in Safety pool D....	139
Table 66. Outlier analyses of VS	140
Table 67. Notable abnormalities in VS in Safety Pool D	141
Table 68. Notable abnormalities upon first dose administration, safety pool A.....	141
Table 69. First dose administration experience in safety pool A.....	145
Table 70. ECG abnormalities upon first dose fingolimod in safety pool A	145
Table 71. Changes from baseline in ECG parameters after first dose, safety pool A	148
Table 72. Number of patients with abnormal ECG parameters in safety pool D by visit	149
Table 73. Changes from baseline in ECG parameters by visit for safety pool D.....	151
Table 74. Outlier analysis of QT changes in safety pool D	152
Table 75. Mean hourly rate (bpm) for 24 hour Holter in study 2201	156
Table 76. Summary of notable Holter findings, study 2201	157
Table 77. Change from baseline for estimated pulmonary artery pressure (mm(Hg), pooled echo analysis set.	160

Table 78. Percentage change of predicted FEV1 in studies 2301 and 2302 core studies.....	163
Table 79. Percentage of predicted FVC in 2301 and 2302 core studies.....	164
Table 80. Percentage of predicted DLCO in studies 2301 and 2302 core studies.....	165
Table 81. PFT outlier analysis in studies 2301 and 2302 core studies	165
Table 82. Percentage of PFT changes from baseline, safety pool E (SUR)	166
Table 83. Outlier analysis, PFTs in safety pool E (SUR)	166
Table 84. Outlier analysis of PFTs in study 2309, PFT analysis set.	168
Table 85. Percentage of predicted FEV1 in E follow up population (SUR).....	169
Table 86. Percentage of predicted DLCO corrected for Hg in E follow up population (SUR)..	169
Table 87. HRCT abnormalities in 2301 by visit (does not include unscheduled tests).....	170
Table 88. Table Chest HRCT in 2302 by visit.....	171
Table 89. Chest high resolution CT in 2309 (original application)	173
Table 90. Mean changes from baseline in CFT in Study 2301	174
Table 91. Distribution for change from baseline in central foveal thickness, study 2301.....	174
Table 92. Change from baseline in central foveal thickness (microns), Ophtalmology analysis set, study 2309	175
Table 93. Distribution of change from baseline in central foveal thickness, study 2309	176
Table 94. SAE in clinical pharmacology studies	177
Table 95. Phase 2 & 3 studies of fingolimod in the transplant population	220
Table 96. Key safety population (controlled data). Cumulative duration of exposure.....	222
Table 97. Deaths in the renal transplant Key safety population	224
Table 98. SAE in the Renal transplant Key Safety population by SOC	226

Table of Figures

Figure 1. Effects of fingolimod on percentage absolute lymphocyte counts in Study FTY720AB102 (renal transplant population).....	13
Figure 2. Line plot of change from screening to Day 1 in Holter hourly mean heart rate, study 2302.....	154
Figure 3. 24 hour Holter in study 2309.....	158
Figure 4. Changes from baseline in FEV1 in pooled studies 2301 and 2302 core studies.....	162
Figure 5. Changes from baseline in FVC in pooled studies 2301 and 2302 core studies.....	163
Figure 6. Changes from baseline in DLCO in pooled studies 2301 and 2302 core studies.....	164
Figure 7. Mean change from baseline in FEV1 in study 2309.	167
Figure 8. Mean change from baseline in absolute value DLCO in study 2309.	168

1 Recommendations/Risk Benefit Analysis

This is the preliminary review of the safety of fingolimod as of May 12, 2010. The efficacy of fingolimod in MS is being reviewed by Dr. Fitter. Final recommendations will be provided following discussions at the Advisory Committee Meeting scheduled for June 10, 2010.

2 Introduction and Regulatory Background

2.1 Product Information

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

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

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

2.2 Available Treatments for Proposed Indications

For available therapies the reader is referred to Dr. Fitter’s review.

2.3 Availability of Proposed Active Ingredient in the United States

None.

2.4 Important Safety Issues With Consideration to Related Drugs

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

2.5 Summary of Presubmission Regulatory Activity Related to Submission

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

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

The FDA recommended that the phase 3 study should include special follow up for potential lung toxicity (High Resolution Computerized Tomography [HRCT] every 6 months in at least a subgroup of subjects; real time Pulmonary Function Tests [PFT]); cardiac toxicity (keeping patients in-house for 24 hours post dose with Holter or telemetry for bradycardia in at least 600 patients; cardiac echo every 6 months in at least a subgroup of patients; conduction of a QTc study; a Data Safety Monitoring Board [DSMB] should monitor CV adverse events and decide if longer follow up was needed), and eye toxicity (optical coherence tomography [OCT] monitoring at baseline, close follow up for up to 3 months and then periodically thereafter in the first 300 patients enrolled in the study).

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

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

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

2.6 Other Relevant Background Information

- The IND was granted fast track designation in June 7, 2007.
- The NDA application was submitted as a rolling NDA, with the first piece submitted on June 5, 2009. The clinical piece for MS was submitted on December 18, 2009.
- The application was granted priority review on February 18, 2010.
- The PDUFA goal date for the review of this application is June 21, 2010.
- A FDA Advisory Committee meeting is scheduled for June 10, 2010.
- This interim review of the safety of fingolimod was completed on May 12, 2010.

3 Ethics and Good Clinical Practices

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

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.3 Preclinical Pharmacology/Toxicology

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

Fingolimod is phosphorylated *in vivo* by sphingosine kinase to form the active metabolite fingolimod phosphate (fingolimod-P). Fingolimod-P binds four of the five G protein-coupled sphingosine 1-phosphate (S1P) receptors (S1P₁, S1P₃, S1P₄ and S1P₅) and induces receptor internalization. With initial dosing of fingolimod, there is agonism of S1P receptors and transient signaling. However, with continued fingolimod dosing, functional antagonism occurs with internalization of S1P receptors.

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

Reviewer's comment: An increasing body of literature indicates that S1P has a role in the regulation of endothelial permeability and vascular tone.^{2,3} The FDA requested an updated literature search in this area.

² L.Want & S Dudek. Regulation of vascular permeability by Sphingosine 1-Phosphate. Microvascular Research, 2009, January; 77 (1) 39-45.

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

- Lymphoid-related effects

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

- Non-lymphoid toxicities

- In a 26-week oral toxicity in Wistar rats, reversible increases in lung weight were seen for males at 1.5 or 7.5 mg/kg/day and all treated female groups. Isolated incidences of foamy bronchial outflow or reddish foci in the lungs of treated animals were observed at necropsy on completion of the treatment or recovery periods. Smooth muscle cell hypertrophy in the alveolar ducts was observed microscopically in all treated groups and was still present after recovery but showed a tendency to be reversible. Additionally, there was increased serum urea and creatinine concentrations in all treatment groups, some of which presented basophilic hyaline casts. Systemic vascular lesions were observed in multiple organs. These changes were reversible.
- In 4-week oral toxicity studies in dogs, macroscopic examination showed enlarged and dark red lungs and intratracheal foamy contents at ≥ 0.1 mg/kg/day. At the end of the recovery period, pleural adhesions and white areas on the lungs were observed in both males at 10 mg/kg/day and in one female at 30 mg/kg/day. Vascular wall thickening and perivascular and focal perimysial fibrosis of the left ventricular papilla in the heart at ≥ 3 mg/kg/day were observed. Microscopic examination showed pulmonary alveolar infiltrates and pneumonia at ≥ 0.1 mg/kg/day. In addition, at 30 mg/kg/day, there was perivascular mononuclear cell infiltration in the gray matter of the brain and peripheral nerve degeneration in the heart. At the end of the recovery period, subpleural fibrosis and focal bronchiolar alterations of the lung were found in females at 0.01 mg/kg/day. Similar findings in the lung, heart and brain were observed at doses of 1 to 10 mg/kg/day, in a 26-week oral toxicity study in the dog.
- In a 13-week oral toxicity study in monkey, there was smooth muscle hypertrophy of the lung and increased pulmonary weight was observed with doses ≥ 1 mg/kg/day.
- In a 39-week oral toxicity study in monkey at doses of 0.5 and 3 mg/kg/day, a trend towards increased mean lung weights in females (high dose) and males (low and high dose) was noted, which was partially reversible following a 13 and 26-week recovery period and correlated with microscopic compound-related lung changes. Gross changes consisted of decreased pulmonary collapse, which correlated, in most animals with hypertrophy of pulmonary smooth muscle fibers

³ J. Igarashi and T. Michel. Sphingosine-1-phosphate and modulation of vascular tone. Cardiovascular Research 2009, 82 (2): 212-220

and/or increased collagen. The principal test article-related findings consisted of pulmonary smooth muscle hypertrophy and/or increased collagen occasionally accompanied by distended alveoli. Smooth muscular hypertrophy and/or increased collagen, was most commonly seen in walls of alveolar ducts and respiratory bronchioles. The lung alterations aforementioned were occasionally observed in control animals; however, the incidence and/or severity of these lesions increased in compound-treated groups.

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

In summary, in several non-clinical studies (rat, dog, monkey) of different doses and durations, there was evidence of pulmonary congestion, smooth muscular hypertrophy and increased collagen in walls of alveolar ducts and respiratory bronchioles, and subpleural fibrosis at doses as low as 0.01 mg/kg/day in the dog. There was also evidence of vascular wall thickening and perivascular and focal perimysial fibrosis of the left ventricular papilla in the heart in the dog at doses \geq 1 mg/kg/day.⁴ All these areas will be extensively evaluated in this clinical review.

4.4 Clinical Pharmacology

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

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

- Decreased lymphocyte count

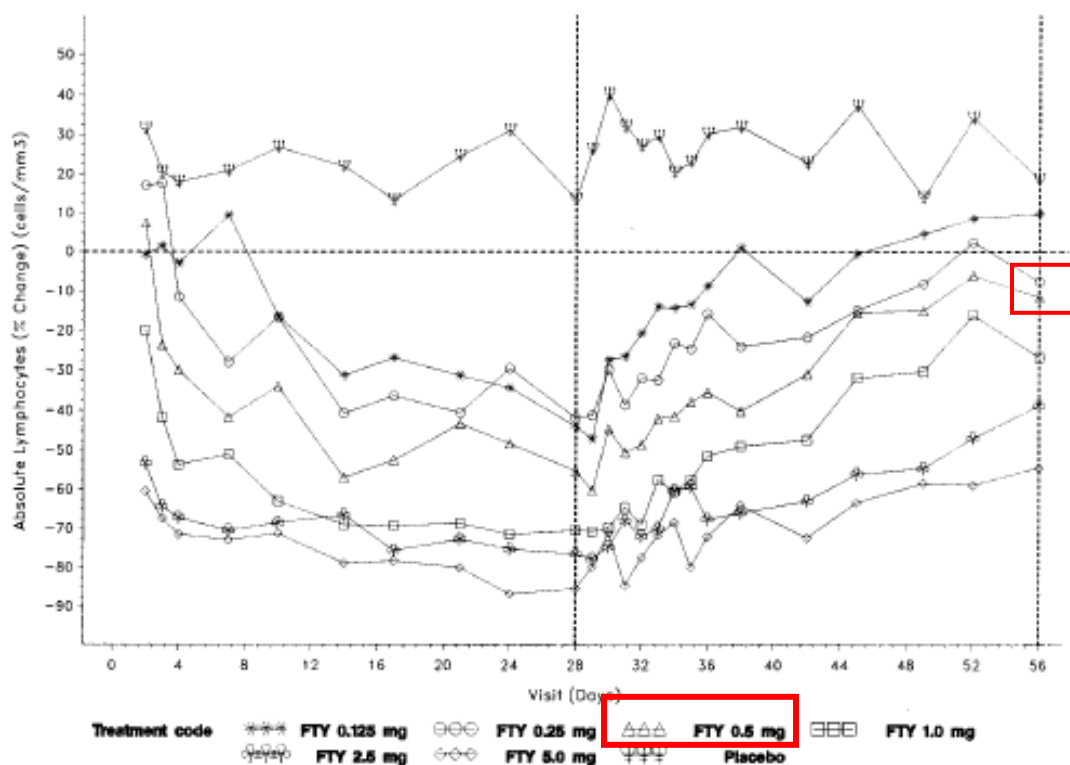
Single doses of fingolimod from 0.5 to 5.0 mg result in a dose dependent decrease in lymphocyte count (all, B and T [helper, suppressor, memory and naïve T]). This decrease occurs rapidly, within 3-4 hours of the first oral dose. With single doses from 5 to 40 mg, there is minimal additional effect on the lymphocyte count. With multiple dosing of fingolimod from 0.125 mg to

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

5 mg there is a dose-dependent decrease in lymphocyte count, resulting in counts from 60% of baseline count to as low as 10- 15% of baseline count, respectively. In a multiple dose study (FTY720AB102) in renal transplant patients all lymphocyte subsets (CD20 [B cell], CD3 [T cell], CD4 [T helper], CD8 [T suppressor], CD16 [Natural killer], CD45RO [T memory], CD45RA [T naïve] were found to decrease in a dose dependent manner in the setting of multiple doses of fingolimod. The monocyte count was not affected by multiple dose fingolimod treatment. The figure below shows changes in absolute lymphocyte count in study FTY720AB102.

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

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



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

Three-month follow-up data on lymphocyte recovery are available from the renal transplant study B201 which evaluated the safety, tolerability and efficacy of four doses of FTY720 (0.25, 0.5, 1.0 and 2.5 mg/day) given for 12 weeks in combination with a full dose of Neoral and

Interim review, 5 12 10.

Lourdes Villalba, M.D

NDA 22-527. Fingolimod

corticosteroids. In all four FTY720 dose groups, absolute lymphocyte counts returned to baseline values within 3 months after the discontinuation of study medication [FTY720 B201CSR].

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

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

- Evaluation of cerebrovascular flow

Study FTY270D2113 was an exploratory, randomized, blinded, placebo-controlled, parallel group, multiple-dose study to assess the effect of FTY720 0.5 and 1.25 mg on mean flow velocity in cerebral vessels, platelet function, and macular thickness following once daily dosing for 4 weeks in 88 healthy subjects 18 to 50 years of age. This study was conducted because of the potential signal for increased ischemic/thrombotic cerebrovascular events observed in the phase 2-3 studies. Pharmacodynamic endpoints included:

Primary

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

Secondary

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

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

Comment: this negative study does not rule out an effect on these parameters with longer term exposure or in subjects with underlying cardiovascular or metabolic diseases such as hypertension or diabetes. The study did not find an increase in foveal thickness, while several subjects developed macular edema with the 1.25 and 0.5 mg doses in the phase 2 and 3 studies. The study did not evaluate all factors that may be involved in hypercoagulability. These are evaluations that need to be considered for pre-or post-marketing studies.

5 Sources of Clinical Data

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

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

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

Five additional clinical studies in MS patients were ongoing at the time of the original NDA submission. Safety from these studies was not pooled for analysis into the ISS. For these studies (see Table 4) blinded narratives of deaths and selected SAE and blinded listings of serious AEs were provided. Additionally, special safety evaluations from Study 2309 were not part of the integrated analysis but were reported separately in a Special Safety Interim report (SN 004).

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

The 4-month Safety Update Report (SUR) was submitted on April 21, 2010 and contained safety data through January 29, 2010. It includes updated analyses of safety pool E; serious AEs in ongoing studies; an updated Special safety Interim Report (SSIR) from 2309; two clinical study reports (Study FTY720D2109 (antibody response study) and Study FTY720D2302E1-24 month report); updated analyses of ECG data for all populations and a revised package insert. During the review cycle, the applicant responded diligently to multiple FDA informational requests. The applicant's responses up to April 30, 2010 have been reviewed. Review of the SUR and SSIR update has not been completed at the time of this review.

There is no available postmarketing data for this NME.

5.1 Tables of Clinical Studies

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

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

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

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

In addition to the extension studies 23021E1 and 2201E1 which were included in the ISS, five clinical studies in MS patients are ongoing (Table 2) and were not pooled into the ISS.

Table 2. Ongoing clinical studies of Fingolimod in MS¹

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

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

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

The clinical pharmacology studies included a total of 1079 unique subjects, including 843 exposed to FTY at doses of 0.125 to 40 mg/day, 611 to placebo of 174 to non-FTY treatments (some subjects received more than one treatment in crossover studies). These were 60% male/40% female; mean age was 35 years (range 18-70, including 7 subjects <18 years). For listing of studies, see Clinical Pharmacology review.

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

5.2 Review Strategy

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

5.3 Discussion of Individual Studies

Characteristics of the studies have been described in Table 2 of this review.

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

6 Review of Efficacy

Please refer to Dr. Heather Fitter's review.

7 Review of Safety

Safety Summary as of May 12, 2010

As of the cut-off date of September 30, 2009, a total of 2315 subjects had been exposed to fingolimod (FTY) (any dose or duration) in phase 2 and 3 MS studies and 843 subjects had been exposed to fingolimod in phase 1 clinical pharmacology studies (any dose or duration). Additional data were available from renal transplant patients who received doses of FTY 2.5 mg and FTY 5 mg a day. The 4-month Safety Update Report (SUR) contains additional information up to January 10, 2010, with a total of 2615 patients in the ISS, including 567 patients at the dose of 0.5 mg/day (the dose proposed for marketing in MS) for 2 years. Additional studies are being conducted with fingolimod that are still blinded and partial information is available from those studies. Review of the SUR, submitted on April 21, 2010, is ongoing.

Two deaths occurred during the controlled period of the studies (one disseminated varicella zoster infection and one herpes simplex encephalitis) in young subjects taking FTY 1.25 mg (<0.1% of all FTY patients included in the ISS). No infection-related deaths occurred in the FTY 0.5 mg, placebo or interferon groups. As of April 30, 2010, a total of 14 deaths occurred in the fingolimod MS program, including 10 during or after FTY treatment. No particular pattern was observed among these deaths. Of note, in the renal transplant key safety population 8 patients (1.7%) died of cardiac causes in the FTY 5mg group, as compared with no patients in the FTY 2.5mg and active comparator groups. No cardiovascular deaths were reported in the MS trials.

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

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

Evaluation of vital signs shows a clear dose-related increase in systolic and diastolic blood pressure. The mean change from baseline to the last non missing value on treatment in the

controlled studies for the FTY 0.5 mg group was 2 mmHg increase in SBP and 1 mmHg increase in DBP. The clinical significance of this change is unclear.

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

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

Special safety evaluations were incorporated into the MS trials submitted in the original application and in the ongoing study 2309. Review of the Safety update report (SUR) and updated Special safety interim report (SSIR) submitted 4/21/10 is ongoing. Preliminary findings are as follows:

- 24 hour Holter evaluations showed a decrease in HR of approximately 28 bpm for FTY 1.25 and 22 bpm for FTY 0.5 mg, at around 6 hours post first FTY dose. This was not observed at the 3 month Holter evaluation.
- PFT evaluation found a decrease in PFTs, particularly FEV1 and DLCO for FTY 1.25 mg, and to a lesser extent for FTY 0.5 mg. These changes are observed at the one month and 3 month visit and appear to improve overtime, in the subset of patients who remained in the studies and have at least one post-baseline measurement. The observed change in FEV1 of >100 mL for FTY 0.5 mg appears to be clinically meaningful, as it exceeds the changes observed with patients with COPD and MS in general. Evaluation of PFTs in a

subset of patients who were followed after drug discontinuation (safety pool E follow up) suggests that the changes in FEV1 were reversible, but the changes in DLCO were not reversible within the 3 month evaluation period.

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

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

The risk of macular edema has been fully characterized. However, the long-term effects of fingolimod on immunosurveillance (risk of infections and malignancy), lung, liver and vascular toxicity are not fully characterized. It is also unclear whether fingolimod may be associated with increased risk of seizures.

There are several ongoing studies from which the FDA has received only selected information. Information submitted with the SUR is being reviewed. Several requests for clarification are pending. Whether this drug will be approved at this time or not, depends on its risk/benefit profile and the need for additional assessments, some of which could be made postmarketing. If approved, fingolimod will need a Risk Evaluation and Mitigation Strategy (REMS) and postmarketing safety studies.

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

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

7.1.2 Categorization of Adverse Events

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

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

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

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

Table 3. Table of Safety Analysis Pools in MS ISS

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

Source: Table 1-5 Integrated Summary of Safety; Tables 2-5, 2-8, 2-12, 2-17. Cut-off date: June 1, 2009.

Note: FTY 0.5 mg–1.25 mg indicates the treatment regimen of FTY720 5 mg switched to FTY 1.25 mg during D2201E1. Interferon–FTY indicates the interferon treatment group switched after completing core D2302 to either FTY 0.5 mg or 1.25 mg in D2302E1. Likewise, Placebo–FTY indicates the placebo treatment group switched to FTY 1.25 mg or 5 mg in D2201E1; the Placebo–FTY 5 mg–1.25 mg indicates the treatment regimen of placebo in D2201 initially switched to FTY 5 mg in D2201E1 and then switched to FTY 1.25 mg during D2201E1.

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

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

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

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

7.2 Adequacy of Safety Assessments

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

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

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

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

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

Interim review, 5 12 10.

Lourdes Villalba, M.D

NDA 22-527. Fingolimod

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

Table 4. Duration of exposure to study drug after randomization in Group E (all FTY-treated patients, safety population)

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

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

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

NOTE: This interim review includes most responses to FDA requests for clarification submitted up to May 11, 2010, however, review of the SUR and SSIR is ongoing. All tables and comments that refer to safety pool E (controlled and open label studies) and the Special safety interim report from study 2309 apply to the information submitted with the original application, unless noted otherwise.

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

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

Interim review, 5 12 10.

Lourdes Villalba, M.D

NDA 22-527. Fingolimod

data became available from the core studies. Standard ECG data has also been updated for the other pools due to an incorrect exclusion of some ECG abnormal findings at baseline (this review does not include the updated ECG tables).

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

- Exposure in study 2309 (ONGOING and BLINDED), original application.

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

Table 5. Exposure in study 2309

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

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

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

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

The number of patients who underwent special safety evaluations in study D2309 at the time of the original application is summarized in the following table. Of note, some echocardiograms done in study 2302 were pooled with some of those done in 2309 into a “pooled echo analysis set”.

Table 6. Number of patients undergoing special safety evaluations in study 2309

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

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

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

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

There are several ongoing studies from which we only have “selected” information. Therefore, the fingolimod program exceeds minimum ICH guidance recommendations and includes special safety evaluations to address specific safety concerns; however, the data made available to FDA may still be insufficient to fully address the long term safety of fingolimod. Review of the SUR is ongoing.

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

- Baseline characteristics of the population in MS studies

The demographics and disease characteristics of the MS population in the ISS are consistent with those in other applications for MS. Demographic characteristics of the different safety pools were similar. Differences between treatment groups were not clinically meaningful.

Approximately 70% of patients were female, with a mean age of 37 years; 95% were Caucasian, and the mean weight was approximately 70 kg. Of note, study 2201 and 2301 were conducted entirely outside the US. The only completed study that has participating sites in the US was 2302, with a total of 144 patients including 16 African American.

The applicant states that MS is not a disease that has known geographical differences in terms of clinical phenotype or severity and that the demographics and disease

characteristics of patients from the US who enrolled into 2302 are similar to the overall study population. US patients tend to be slightly older and to have a higher BMI, but as per PK data, adjustment is not needed based on body weight. Moreover, the applicant states that MS practice patterns are homogeneous around the world.

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

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

- Prior and concomitant diseases and medications at baseline

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

Exclusion criteria:

Patients who meet any of the following exclusion criteria during the Pre-Randomization Phase will not be eligible for enrollment in the study:

1. A manifestation of MS other than RRMS
2. A history of chronic disease of the immune system other than MS or a known immunodeficiency syndrome
3. A history of epileptic seizures within 3 months of randomization
4. A history or presence of malignancy (except for successfully treated basal or squamous cell carcinoma of skin)
5. A known or 'new' diagnosis of diabetes mellitus (if screening blood glucose is suspicious for diabetes ≥ 126 mg/dL or ≥ 7 mmol/L if fasting; ≥ 200 mg/dL or 11.1 mmol/L if random testing] a patient should be further evaluated for diabetes mellitus)
6. A diagnosis of macular edema during Pre-randomization Phase
7. Active systemic bacterial, viral or fungal infections, or diagnosis of AIDS
8. Have received total lymphoid irradiation or bone marrow transplantation
9. Have been treated with:
 - corticosteroids or adrenocorticotrophic hormones (ACTH) within 1 month prior to randomization
 - immunosuppressive medications such as azathioprine or methotrexate within 6 months prior to randomization
 - immunoglobulins and/or monoclonal antibodies (including natalizumab) within 6 months prior to randomization
 - cladribine, cyclophosphamide or mitoxantrone at any time

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

11. Any of the following cardiovascular conditions:

- myocardial infarction within the past 6 months prior to enrollment or current unstable ischemic heart disease
- history of angina pectoris due to coronary spasm or history of Raynaud's phenomenon
- cardiac failure at time of Screening (Class III, according to NYHA Classification; or any severe cardiac disease as determined by the investigator
- history of cardiac arrest
- history of symptomatic bradycardia
- resting pulse rate <55 bpm prior to randomization
- history of sick sinus syndrome or sino-atrial heart block
- History or presence of a second degree AV block or a third degree AV block or an increased QTc interval >440 ms on Screening ECG
- arrhythmia requiring current treatment with Class III antiarrhythmic drugs (e.g., amiodarone, bretylium, sotalol, ibutilide, azimilide, dofetilide)
- history of a positive tilt test from workup for vasovagal syncope
- hypertension, uncontrolled by medication

12. Any of the following pulmonary conditions:

- severe respiratory disease or pulmonary fibrosis
- tuberculosis, except for history of successfully treated tuberculosis or history of prophylactic treatment after positive PPD skin reaction
- abnormal chest High Resolution Computer Tomography (HRCT) [or chest x-ray in case HRCT is not permitted by local regulations] suggestive of active pulmonary disease
- abnormal Pulmonary Function Tests: FEV1, FVC values lower than 70% of predicted value, DLCO values lower than 60% of predicted value
- patients receiving daily therapies for asthma

13. Any of the following hepatic conditions:

- known history of alcohol abuse, chronic liver or biliary disease, with the exception of Gilbert's syndrome
- total or conjugated bilirubin greater than the upper limit of the normal range
- alkaline phosphatase (AP) greater than 1.5 times the upper limit of the normal range
- AST (SGOT), ALT (SGPT) greater than 2 times the upper limit of the normal range
- gamma-glutamyl-transferase (GGT) greater than 3 times the upper limit of the normal range

14. Any of the following abnormal laboratory values:

- serum creatinine greater than 1.7 mg/dL (150 µmol/L)
- white blood cell (WBC) count <3,500/mm³ (<3.5 X 10⁹ / L)
- lymphocyte count <800/mm³ (<0.8 X 10⁹ / L)

15. Any of the following neurologic/psychiatric disorders:

- severe depression within three months of randomization
- relevant history of suicide attempt or who are at risk of suicide attempt
- history of substance abuse (drug or alcohol) or any other factor that may interfere with the subject's ability to cooperate and comply with the study procedures;
- progressive neurological disorder, other than MS, which may affect participation in the study or require the use of medications not allowed by the protocol.

16. unable to undergo MRI scans
17. history of hypersensitivity to natural or recombinant interferon beta, human albumin, or any other component of the formulation
18. participation in any clinical research study evaluating another investigational drug or therapy within 6 months prior to randomization, or history of fingolimod therapy.

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

- Medical history at baseline

As per Post table 3.7-1 of the ISS (Relevant medical history and continuing medical condition in the randomized population, pool D – all controlled studies-) 90 % of patients in this group had at least one past or ongoing continuing medical condition, the most common being nervous system disorders (55% overall). Some events of interest are discussed as follows for pool D (percentages for the FTY 5 mg group are not included because they were usually different from the other groups).

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

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

Of note, patients with diabetes were excluded per protocol. However, as per Post table 3.7-1 of the ISS, a few patients reported a history of diabetes mellitus. Two patients reported diabetes mellitus, two reported Type 2 diabetes mellitus and one reported Type 1 diabetes mellitus in the FTY 1.25 mg dose. Glucose tolerance impaired was reported in 1 patient in the FTY 1.25 and 1 in the FTY 0.5 mg dose. Hyperglycemia was reported in 1 patient in the FTY 0.5 mg dose. It is unclear if some of these numbers refer to the same patient. In any case, this is less than 10

Interim review, 5 12 10.

Lourdes Villalba, M.D

NDA 22-527. Fingolimod

subjects with diabetes in the entire application. The lack of data on the use of fingolimod in patients with diabetes is of concern, because diabetes is a prevalent disease.

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

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

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

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

- Prior and concomitant medications at baseline

The most common medications at baseline were Progesterone and estrogens fixed combinations, which were taken by 15.5%, 16.7%, 18.2% and 11.8% of subjects in the FTY 1.25, FTY 0.5, IFN and placebo groups, respectively, followed by selective serotonin reuptake inhibitors (mean 9% in each treatment group) and benzodiazepine derivatives (mean 7.5% in each treatment group). The most common drug used at baseline was paracetamol (used by approximately 7% of patients).

7.2.2 Explorations for Dose Response

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

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

7.2.3 Special Animal and/or In Vitro Testing

Please refer to the pharmacology toxicology review.

7.2.4 Routine Clinical Testing

- Routine clinical and laboratory evaluations in MS studies

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

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

Comment: It is unusual that routine testing such as sodium, potassium and bicarbonate were not analyzed in the phase 2 and 3 studies of a new molecular entity. I find this troublesome. The fact that data on electrolytes at the time of ECG changes during first dose monitoring are not available is disturbing.

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

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

“Patients who were varicella-zoster virus IgG negative were informed of their status and of the increased risk for serious and potentially fatal primary infection, should the patient be exposed to varicella zoster virus in a setting of potential immunosuppression related to study drug and/or the use of corticosteroids. These patients were instructed that they must promptly report any possible exposure to a person with chicken-pox or shingles to the investigator. In the event of such exposure, the investigator was to promptly initiate the appropriate antiviral therapy and passive immunization with varicella-zoster immunoglobulin in consultation with a local infectious diseases expert. Varicella-zoster IgG negative patients in the study were allowed to continue on study drug provided the above risk and actions needed to mitigate risk were clearly explained and accepted by the patient.

Patients who were negative for HSV-1 IgG, HSV-2 IgG or rubeola IgG antibodies were informed of their status and were instructed to promptly report any exposure to these viruses, e.g. to a person with cold sores, herpes genitalis, or measles, respectively. In case of exposure, early treatment with appropriate antiviral drugs and/or immunoglobulin was considered in consultation with a local infectious disease expert.

Patients with prior infection may be at risk of viral reactivation (e.g. cold sores, genital ulcers or shingles) and should be instructed to inform the investigator of any signs or symptoms suggestive of these conditions, so that prompt treatment may be initiated.”

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

- Vital signs

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

- ECG

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

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

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

- Special safety assessments

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

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

Interim review, 5 12 10.

Lourdes Villalba, M.D

NDA 22-527. Fingolimod

Table 7. Assessments in study 2302

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

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

Comment: Comprehensive special safety evaluations in the MS program to address safety concerns of first dose conduction disorders, macular edema, potential cardiac and lung

Interim review, 5 12 10.
Lourdes Villalba, M.D
NDA 22-527. Fingolimod

toxicity, and assessment of skin malignancies were implemented as part of protocol 2302 (completed) and study 2309 (ongoing), after extensive discussions with the FDA. Study 2301 also included some of the special assessments (it did not include echocardiogram and 24 hour Holter). Routine monitoring in the MS program is notable for the lack of evaluation of electrolytes and coagulation parameters in the phase 2 and 3 studies.

7.2.5 Metabolic, Clearance, and Interaction Workup

Please see clinical pharmacology review by Clinical pharmacology team.

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

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

7.3 Major Safety Results and Discussion

7.3.1 Deaths

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

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

Deaths in the Fingolimod MS program with this reviewer's interpretation of the relationship to study drug, are summarized in the following table (as of 4/26/10).

Table 8. Summary of deaths in the fingolimod MS program*

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

*As of 4/26/10. Attribution of relationship to study drug as per FDA reviewer. Additionally, two deaths occurred during the screening period, before randomization (1 suicide and one sudden death). Brief narratives of the deaths that occurred in the fingolimod MS program are summarized in the following table.

Narratives for these cases are summarized in the following table.

Table 9. Brief narratives of deaths during Fingolimod MS studies

SubjID	Age Sex	Treat. group (mg/day)	AE Rel day	AE term	Comment
Original submission (12 18 09, cut-off September 30 2009)					
Study 2301 (2-year study)					
708-00011	53 M	FTY 1.25	359	Suicide	Approximately 6 months prior to his death, the patient had experienced depression for which he was hospitalized and received treatment. The patient was reported to have recovered from depression within 3 months. Unlikely to be drug related.
304-00045	52 M	Placebo	657	Pulm. Embolism	Patient presented with acute periodontitis with pyrexia and died approximately 1 week later due to pulmonary embolism 6 days after last dose of placebo. Not drug related.
702-00005	37 F	Placebo	365	Road traffic accident	Patient was hit by a car while walking, receiving multiple injuries 58 days after last dose of placebo. Not drug related.
Study 2302 (1-year study)					
0212-00021	29 F	FTY 1.25	320	Hepatic failure. Herpes zoster disseminated.	MS symptoms for 3 years. Prior history of treatment with IFNβ1a. EDSS=1. Patient had started high dose steroid therapy for an MS relapse approximately 8 days prior to the onset of the event. She continued to work in a child care/nursery center where recent cases of chickenpox had been reported. She was varicella-zoster virus IgG negative at study entry. She died approx. 11 months into fingolimod treatment. Autopsy showed hepatic necrosis and multiorgan failure. For details, see Appendix 9.1.1.
0821-00007	23 M	FTY 1.25	407	Herpes simplex encephalitis HSV 1	MS symptoms for 2 ½ months. Prior history of treatment with IFNβ1b. EDSS=3. He developed fever and headache approx. 11 months into fingolimod treatment, followed by intermittent high fever and seizures despite antiepileptic therapy. He was treated with high dose steroid therapy for suspected MS relapse. Seven days later, he was diagnosed with viral encephalitis and treated with acyclovir. His brain function did not improve and he died 67 days after last fingolimod dose. For details, see Appendix 9.1.1.
0254-00011	42 M	FTY 1.25	187 days after last	Acute disseminated Encephalomyelitis-like symptoms, aspiration pneumonia	MS diagnosed 2 ½ years prior to entry. Prior history of treatment with IFNβ1a. Baseline EDSS of 5. He developed fever, cough and mild hemoptysis approx. 11 months into fingolimod treatment. Study drug was discontinued. Three days later he developed generalized seizures and confusion. An MRI showed a new T2 lesion that did not explain the extent of neurologic changes. JC virus testing done at a laboratory in Europe was negative (no samples remain for additional testing.). A diagnosis of acute disseminated encephalomyelitis (ADEM) was made. The

					patient's neurological condition continued to decline and he died of aspiration pneumonia approx. 6 months after drug discontinuation. He did not have an autopsy. This case was evaluated by Dr. Heather Fitter, DNP neurologist, who offered the following differential diagnoses: MS relapse in the setting of multiple infections, seizures and steroid induced encephalopathy, and PML. For details, see Appendix 9.1.1.
331-00011	53 F	FTY 1.25	-	Breast cancer metastatic	Patient was diagnosed with invasive breast cancer approximately 11 months after commencing FTY720 1.25 mg. She died due to metastatic breast cancer 305 days after last fingolimod dose. Unlikely to be drug related but the role of fingolimod can not be ruled out.
Study 2306 (ongoing study)					
362-00005	46 M	FTY 1.25	103	Rapidly deteriorating MS Severe respiratory infection	2 and ½ years history of MS. No prior immunomodulators for MS. EDSS at entry =6. Nine days into fingolimod treatment developed muscle spasm and deterioration of neurologic status that was thought to be related to a urinary infection. Two months into fingolimod treatment he died of a severe respiratory infection. There was no autopsy, no following MRI, no information on level of immuno suppression, no adequate work up to rule out opportunistic infections. For details, se Appendix 9.1.1.
2201E1 (OL extension, ongoing)					
029-00007*	55 F	FTY 5	-	Ovarian adenocarcinoma	Cancer diagnosed 5 months after stopping drug. Died 3 years after stopping drug. Unlikely to be drug related but the role of fingolimod can not be ruled out.
003-00016	35 F	FTY 1.25	E638	Road traffic accident	Not drug related.
Deaths reported after original submission.					
1201E-0005-00001	42 M	FTY 0.5	Died 1 year after last dose but brain mass dx during therapy	Multiple tumors Possible Malignant lymphoma	MS diagnosed 4 ½ years prior to entry. He received fingolimod 0.5 mg/day for 7 ½ months. At the 6-month core study evaluation he was found to have new brain lesions consistent with MS relapse. He was treated with pulse steroids without improvement. He discontinued drug 1 ½ months into the study extension and received a total of 7 IV steroid pulses over 2 ½ months followed by oral steroids. He was admitted to the hospital with aspiration pneumonia. CT scans showed multiple lung and kidney tumors along with enlarged lymph nodes and hepatosplenomegaly. Brain MRI showed multiple ring enhancing lesions, consistent with metastatic disease of unknown primary or a malignant lymphoma. A kidney biopsy was consistent with renal cell cancer or EBV-related lymphoproliferative disease. The biopsy of a skin rash showed T cell lymphoma. He died approximately one year after study drug discontinuation. For details, see

					Appendix 9.1.1.
2309 0507 00028	55 F	blinded	2 months after drug dc	Dissecting aortic aneurism	As per IND safety report, 7 months into study treatment, a routine mammogram showed 10 nodules in her left breast. A sonogram showed they were benign. No surgery was done. She stopped blinded treatment. Two months after drug dc she went to the ER after using methamphetamines and having a seizure. She had back and abdominal pain and hypotension. A CT scan showed thoracic and abdominal dissecting aneurysm. She was DNR Concomitant conditions included hyperlipide mia, HTN, LVH, mitral, aortic and tricuspid valve incompetence (recorded as ongoing and trivial), tobacco and drug abuse. Treatment is blinded.

Source: Narratives and CRFs. Additionally, two deaths occurred during the screening period before receiving study drug (sudden death [ID# 1201 106 00005], and suicide [2306 461-00006]). EDSS= Expanded Disability Status Scale. For details about these cases see Appendix 9.1.1.

Reviewer's comment:

Given fingolimod's pharmacologic effects (decrease circulation of peripheral lymphocytes), some degree of immunosuppression is not unexpected. However, the fact that two patients died due to herpes infections in this database is of concern (subject 2302-0212-00021, disseminated varicella zoster infection and subject 2302-0821-00007, herpes simplex encephalitis). Both patients were young (23 and 29 years), were taking fingolimod 1.25 mg/day and had received a short course of high dose iv steroids for empiric treatment of MS relapses before they developed these fatal herpes infections. Lymphocyte levels are not available at the time of the fatal infection. Subsequently to these cases, the applicant appropriately modified the protocols to include IgG antibody testing for several viral infections and included specific guidance to investigators regarding procedures in case of a viral infection. Physicians and patients need to be aware of the risk of serious viral infections associated with fingolimod use. The applicant has proposed to address this issue with a Risk Evaluation and Mitigation Strategy (REMS).

Differential diagnoses for the cases of ADEM (2302-0254-00011) and rapidly deteriorating MS (2306-362-00005) include CNS opportunistic infections. In one case, extensive work up was done and an infection was not identified (however, PML is not completely ruled out). In the second case, there was worsening of the neurologic condition without any assessments to rule out causes other than MS progression. Both cases were complicated by fatal respiratory infections. No data on lymphocyte counts are available at the time of the deaths.

In my opinion, patient 1201E-0005-00001's clinical picture could be explained by a single disseminated tumor (lymphoma) of brain, lung, kidneys, skin, rather than different tumors in the same patient. It is unclear if at that time of identification of the initial brain lesion a complete work up to identify lymphoma (or other malignancy) in other parts of the body was conducted. It is possible that the brain tumor was detected first because the patient was getting regular MRIs as part of the MS study, but other areas may have been involved at the time. Or the brain lesion may have been an infectious process or a non-lymphoma tumor. The kidney biopsy was read as possible renal cell carcinoma or EBV lymphoproliferative disease. In any case, the skin biopsy was definitive of a T cell lymphoma. This case was reviewed by Dr. Gwynn Ison, FDA oncologist, who concluded the following:

“Although lymphoma is a possibility, as speculated in the history, there is no definitive biopsy-proven evidence to support this suspicion. The reported skin biopsy was read as “suspicious”, but it is impossible to make a determination without an official pathology report, including special immunostains for B and T lymphocyte markers in the specimen. It is equally possible that this patient had an infectious process, as suggested by the fevers and lung infiltrates. A lymph node biopsy would likely have been the most helpful diagnostic aid in determining a diagnosis in this case, but an infection should have been ruled out, as well. Also, it would be worthwhile to suggest that the Sponsor obtain tissue biopsies and immunostaining, as mentioned, for all future cases that are similar in nature.”

7.3.2 Nonfatal Serious Adverse Events (SAE)

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

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

Table 10. Patients with SAE in at least 2 patients in any treatment group or fatal up to 90 days after last dose, safety pool D.

	FTY 1.25 (N=943)	FTY 0.5 (N=854)	Placebo (N=511)	INF (N=431)
Primary system organ class Preferred term	n (%)	n (%)	n (%)	n (%)
Any primary system organ class	100 (10.6)	73 (8.5)	61 (11.9)	25 (5.8)
Cardiac disorders	23 (2.4)	10 (1.2)	4 (0.8)	1 (0.2)
Bradycardia	11 (1.2)	5 (0.6)	1 (0.2)	0
Atrioventricular block first degree	4 (0.4)	1 (0.1)	0	0
Atrioventricular block second degree	4 (0.4)	1 (0.1)	1 (0.2)	0
Sinus bradycardia	2 (0.2)	1 (0.1)	0	0
Supraventricular extrasystoles	2 (0.2)	1 (0.1)	0	0
Nervous system disorders	18 (1.9)	12 (1.4)	5 (1.0)	3 (0.7)

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

	FTY 1.25 (N=943)	FTY 0.5 (N=854)	Placebo (N=511)	INF (N=431)
Primary system organ class Preferred term	n (%)	n (%)	n (%)	n (%)
Traffic accident*	0	0	1 (0.2)	0

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

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

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

The following tables present patients with SAE in safety pools D and E for selected MedDRA System Organ Classes (SOCs) (those in which the rate of SAE was higher in any fingolimod group than placebo, or for events of special interest, e.g. malignancies). In these tables, a patient with multiple occurrences of the same AE under one treatment is counted only once in the AE preferred term for that treatment. A patient with different adverse events within a primary system organ class is counted only once in the total row. For some events (e.g. infections & malignancies), the rate of events (n events/patient years) are also presented.

- Cardiac related SAEs

The most common SAEs in the Cardiac disorders SOC were bradycardia and AV block. There was evidence of a dose response for the three fingolimod doses and higher risk of bradycardia and AV block on fingolimod as compared to placebo and IFN.

Table 11. Serious AE, Cardiac SOC, pool D

	FTY720 5 mg (N=94)	FTY720 1.25 mg (N=943)	FTY720 0.5 mg (N=854)	Placebo (N=511)	Interferon (N=431)
Primary system organ class Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)
Cardiac disorders					
-Total	3 (3.2)	23 (2.4)	10 (1.2)	4 (0.8)	1 (0.2)
Bradycardia	3 (3.2)	11 (1.2)	5 (0.6)	1 (0.2)	0 (0.0)
Atrioventricular block first degree	0 (0.0)	4 (0.4)	1 (0.1)	0 (0.0)	0 (0.0)
Atrioventricular block second degree	0 (0.0)	4 (0.4)	1 (0.1)	1 (0.2)	0 (0.0)
Sinus bradycardia	0 (0.0)	2 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)

Supraventricular extrasystoles	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Angina pectoris	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)
Arrhythmia	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Palpitations	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)
Pericarditis	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Sinus tachycardia	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Ventricular extrasystoles	1 (1.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Angina unstable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Extrasystoles	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Left ventricular dysfunction	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Tachycardia paroxysmal	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Ventricular tachycardia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

Source: Post Table 4.4-9, ISS. All three placebo controlled studies. N= randomized. n= patients with events. A patient with multiple occurrences of the same AE under one treatment is counted only once in the AE preferred term for that treatment. A patient with different adverse events within a primary system organ class is counted only once in the total row.

The most common SAE in the Cardiac SOC was bradycardia and atrioventricular block.

Table 12. Patients with SAEs, Cardiac disorder SOC, Pool E

Primary system organ class Preferred term	FTY720 5 mg - 1.25 mg (N=137) n (%)	FTY720 1.25 mg (N=1157) n (%)	FTY720 0.5 mg (N=1021) n (%)
Cardiac disorders			
-Total	4 (2.9)	29 (2.5)	11 (1.1)
Bradycardia	3 (2.2)	15 (1.3)	6 (0.6)
Atrioventricular block second degree	0 (0.0)	6 (0.5)	1 (0.1)
Atrioventricular block first degree	0 (0.0)	4 (0.3)	1 (0.1)
Palpitations	1 (0.7)	2 (0.2)	0 (0.0)
Sinus bradycardia	0 (0.0)	2 (0.2)	1 (0.1)
Supraventricular extrasystoles	0 (0.0)	2 (0.2)	0 (0.0)
Angina pectoris	0 (0.0)	1 (0.1)	1 (0.1)
Arrhythmia	0 (0.0)	1 (0.1)	0 (0.0)
Atrioventricular block complete	0 (0.0)	1 (0.1)	0 (0.0)
Extrasystoles	1 (0.7)	1 (0.1)	0 (0.0)
Hypertensive heart disease	0 (0.0)	1 (0.1)	0 (0.0)
Pericarditis	0 (0.0)	1 (0.1)	0 (0.0)
Sinus tachycardia	0 (0.0)	1 (0.1)	0 (0.0)
Ventricular extrasystoles	1 (0.7)	1 (0.1)	0 (0.0)

Source: Post Table 4.5-12 original ISS. Controlled and open label studies. N= randomized. n=patients with event. A patient with multiple occurrences of the same AE under one treatment is counted only once in the AE preferred term for that treatment. A patient with different adverse events within a primary system organ class is counted only once in the total row.

Interim review, 5 12 10.
Lourdes Villalba, M.D
NDA 22-527. Fingolimod

Of note, pool E includes subjects who received FTY in pool D plus those who received FTY during extensions, after receiving placebo or IFN during the core studies. Several subjects developed bradycardia and AVB upon first fingolimod dose in the extension studies.

- SAE of Bradycardia and Atrio-ventricular block (AV B) events

A summary table of the risk of bradycardia and AV block in safety pool D is presented in the following table:

Table 13. Patients who developed SAE of bradycardia or AV Block, safety pool D

	FTY 5 mg N=94 n (%)	FTY 1.25 mg N=943 n (%)	FTY 0.5 mg N=854 n (%)	IFN N=431 n (%)	Placebo ¹ N= 511 n (%)
Any event	3 (3.0)	22 (2.3)	7 (0.8)	0	2 (0.4)
Led to drug dc	2 (2.0) ²	9 (1.0) ³	1 (0.1) ⁴		1 (0.2)
Bradycardia	3 (3.0)	15 (1.6)	6 (0.7)	-	1 (0.2)
dc	2	5	-		1
AV B 1st degree	-	4 (0.4)	1 (0.1)	-	-
dc		2	-		
AV B 2 nd degree	-	4 (0.4)	1 (0.1)	-	1 (0.2)
dc		3	1		-

Source: FDA analysis of AE datasets and narratives. dc= led to study drug discontinuation. ¹ Events on placebo were not upon first dose; bradycardia occurred on Day 121; AV B occurred on Day 684 (patient had prior episodes of first and second AVB and had sick sinus syndrome). All cases of AV Block in FTY occurred upon first dose.

²One with bigiminism; one with chest pain. ³One recurrent brady+ dyspnea on re-dosing; 3 associated with chest pain/pressure/discomfort. ⁴Recurrent event upon re-dosing 70 days after the first dose; not listed as leading to drug discontinuation, but patient withdrew consent after second event. For details see Appendix 9.1.2.

Brief narratives of patients with SAEs in the Cardiac disorders SOC, related to rhythm and conduction disorders in the original ISS for FTY 0.5 mg are summarized as follows.

Brief narratives of SAE in Cardiac SOC, rhythm and conduction disorders, for FTY 0.5 mg group.

Controlled studies					
Patient ID	Age /sex	Preferred term	Rel Study day		Comment
2302 0207_00001	49 F	Sinus bradycardia AVB 1 st degree AVB 2 nd degree AVB 2 nd degree	1 1 1 (re dosing)	- - dc	No CV history. Smoker. PR at screening was 209 msec. Sitting pulse 76 bpm. On Day 1, monitor showed sinus bradycardia 3 hours post dose. Lowest HR= 46 bpm. She was hospitalized. ECG showed sinus bradycardia and 2 nd degree AVB (Mobitz 1) and 1 st degree AVB with occasional supraventricular premature complexes. PR ranged from 188 to 237 msec. She was treated with isoproterenol. Study drug was temporarily interrupted The AE resolved on Day 2 (lasted 21 hours). A Holter ECG on Day 11 showed increased PR interval, supraventricular arrhythmias and 2 nd degree AVB. When restarted on Day 71, HR 4 hrs post dose was 36 bpm and 6 hrs post dose was 52. The patient was monitored again on Day 73 and also showed drop in pulse as low as 38 bpm 4 hrs post dose. The patient withdrew her informed consent on Day 76. <i>(As per patient profile re-dosing was on day 70, pre dose she had first degree AVB [PR 230 msec]. After the second re-dose, ECG 6 hours post dose showed 2nd degree AVB (Mobitz I)</i>
2302 0252_00009	28 F	AVB first degree	1	-	No CV history. Non smoker. On day 1, pt experienced dizziness, nausea and palpitations 6 hrs after first dosing. ECG showed 1 st degree AVB. HR was 42 bpm and BP was 130/90. She was hospitalized but no treatment was given. Maximum PR interval measured was approx. 260 msec. Event resolved the following day. No action taken with study drug.
2301 0109_00002	41 F	Bradycardia	1	-	No CV history or risk factors, but active smoker 1pack/day x 27 years. On day 1, HR noted to be below 80% of baseline. The lowest HR was 66 bpm 6 hours after the first dose. Asymptomatic. ECG showed no other changes.
2301 0404_00004	20 F	Bradycardia	1	-	No CV MHx. On day one: 3 hrs & 5 hrs after first dose HR 60 pm. Asymptomatic. ECG no other changes. No further events with second dose. No action taken with drug.
2301 0707_00001	52 F	Tachycardia paroxysmal	1	-	No significant medical history other than MS. On Day 1 ECG post dose showed changes in V2 (intraventricular conduction disturbances). She was hospitalized. Echocardiography was normal. At 6 hours, ECG showed a “different” QRS morphology in V2. She was asymptomatic. The following day, morphology was normal. She was discharged and continued in the trial.
2301 0707_00002	40 M	Bradycardia	1	-	No history of heart disease. Non-smoker. Baseline HR= 76 bpm; 5 hours after first dose HR= 56-60 bpm. Lowest HR =55 bpm. Asymptomatic. At 10pm HR= 80 bpm.

Interim review, 5 12 10.
 Lourdes Villalba, M.D
 NDA 22-527. Fingolimod

					Event resolved without intervention.
2301 0903_00005	45 M	Bradycardia	1	-	No history of heart disease. Non-smoker. Baseline HR= 57 bpm. Six hours after first dose HR= 43 bpm, associated with non-specific chest pain. ECG HR 45 bpm, no other changes; chest xray and cardiac enzymes normal. BP= 132/77. He recovered without specific treatment the following day.
2302 0904_00006	52 M	Bradycardia	1	-	No CV history. On Day 1, 4 hrs after first dose, developed severe bradycardia and was hospitalized. No action taken with study drug. No other meds were given. Pt recovered completely the same day. Drug not discontinued.
Extension studies					
2302E_ 0252_00002	42 F	Bradycardia		dc	Received IFN during core. HR down to 36 bpm 4 hours after 1 st dose. Received atropine. Discharged the following day. Discontinued from study on Day 118 due to lack of efficacy.

Source: original AE datasets submitted 12/18/09. Narratives (12/18/09) & patient profiles (2/16/10). Rel study day: relative day of study at onset of study day. Rel day FTY: relative day on fingolimod treatment during extension study. DC: drug discontinuation Y= yes; N= no.

Narratives of SAE related to rhythm and conduction disorders for placebo (1 bradycardia, one 2nd degree AV block) and FTY 1.25 (15 bradycardia, four 1st degree and four 2nd degree AV block) are presented in Appendix 9.1.2.

Five additional cases of¹ bradycardia and/or atrioventricular block (AVB) upon first fingolimod dosing were reported in the extension studies in the original ISS with FTY 1.25, including a case of 3rd degree AVB.

The case of 3rd degree AV block upon first FTY 1.25 dose in the extension studies is as follows

- 2302E 0141_00004.** 39 F. AVB 3rd degree with loss of consciousness on Day 1 of FTY 1.25 therapy. She received IFN during core study. No cardiovascular history. Non smoker. Concomitant meds included oral contraceptive, magnesium-vitamin B. On Day 372, extension day 1, 2 hrs after first dose the patient had no complaints but her pulse went from 74 at baseline to 50 bpm, irregular. An ECG showed 1st degree AVB, 59 bpm. One minute later, an ECG showed 2nd degree AVB type I (Wenckebach) with a heart rate of 55 bpm. No meds were given. Approx. 3 hours after the first dose the patient complained that she was not feeling well and reported having strange dreams. She lost consciousness. A heart monitor showed 3rd degree AVB which lasted 30 seconds, followed by an escape rhythm for 19 seconds. She recovered spontaneously and heart rate returned to the 40's. Heart monitoring showed irregular rhythm with 2nd degree AV B type II. BP was low. Atropine 0.125 mg was given because of low heart rate. She was transferred to ICU. 11 hours post dose, monitor showed 2nd degree AVB type I. Few minutes later she was in sinus rhythm. Drug was discontinued. An echo showed mild mitral valve insufficiency that was not considered to be significant. The drug was discontinued (she only received one dose). The patient recovered completely and was discharged home one day after the event.

Review of the available narratives of bradycardia and AVB during core and extension studies indicates that all adverse events of bradycardia or AV block in the fingolimod groups had an onset within the first 6 hours after first dosing and resolved within 24 hours. Most cases were not medically severe and required overnight hospitalization by protocol. However, not all events were benign.

- In the controlled studies, almost half of patients with bradycardia or AV B discontinued after the event in the FTY 1.25 mg dose group. No patient discontinued upon first dose from the FTY 0.5 mg group.
- Several patients had recurrent bradycardia/AV B upon first re-dosing, leading to study drug discontinuation. One patient had recurrent bradycardia and dyspnea upon first re-dosing on Day 11 (2301_0176_00001; another patient developed bradycardia upon first dose, and recurrent bradycardia with chest pain and pressure on Day 4 (2201_0025_00016). One event led to study drug discontinuation from the FTY 0.5 mg dose group (patient 2302 0207_00001 withdraw her consent when the event recurred upon first re-dosing).
- One subject developed AVB upon first dose, and chest pain/pressure on Day 16, apparently without having stopped medication after the first event (2301 0651 00016 on FTY 1.25). This second event led to drug discontinuation.
- Some events required specific treatment (at least four patients received atropine (3 on FTY 1.25 mg, one on FTY0.5) and one received isoproterenol (2301 0101 00003 on FTY 0.5mg).
- One subject on FTY 5 mg (a dose 10-fold the proposed dose for marketing) (2201 0066 00006) woke up with chest pain/pressure 10 hours after first FTY dose. 4 hours post dose she had a pulse of 54 bpm with no change in BP. She went home after 6 hour observation, with a Holter monitor. The Holter recording showed a HR of 34 bpm, right before the episode of chest pain. Some subjects on FTY 1.25 who were hospitalized for observation, presented the lowest heart rate 10 hours after the first dose (2301 0612_00002, 2302 0361_00013) and 13 hours after the first dose (2301 0101_00003).
- One case of 3rd degree AV B occurred in a 39 year old female receiving FTY 1.25 mg during the extension period (she received IFN in the core study [2302 0141_00004]) and one case of AVB 2nd degree with competing junctional rhythm (which technically could not be interpreted as 3rd degree AV B) occurred in a 26 year old female upon first FTY 1.5 mg in the extension (she had received placebo during core study [2301E 0707 00055]).

The applicant proposes some labeling to address the risk of bradycardia and proposes 6 hours observation for those on beta blockers and low baseline HR. It is unclear who should “observe” the patient and which kind of setting would be required. I would think one would want all patients to receive the first dose under

medical/nurse supervision in a medical setting that allows use of atropine and isoproterenol.

Of note, these events were pretty well tolerated but the population in this NDA is very selected and excluded patients with diabetes and prior history of arrhythmias. Very few patients in the NDA were taking beta blockers. No patient was taking calcium channel blockers or other antiarrhythmics. Very few had a history of CHF or coronary artery disease. Some had underlying first degree AV block (by ECG) at screening, but no patient had second degree AV block or higher. Subjects with pre-existing cardiovascular disease will not tolerate bradycardia and AV block as well as these patients with healthy hearts.

- SAE of Ischemic heart disease in controlled studies

Five serious events of ischemic heart disease (2 MI on placebo, 1 angina unstable on IFN, 1 angina pectoris on FTY 1.25, and one on FTY 0.5mg) were identified in the controlled population during treatment and up to 90 days after study drug dc. Of note, all cases in FTY were female, while the cases on placebo and IFN were male.

One additional non serious AE of myocardial ischemia occurred in the FTY 0.5 mg dose 15 days after discontinuation of FTY 1.25 mg due to “lung disorder” and two subjects receiving FTY had angina pectoris that was not coded as serious but nonetheless led to drug discontinuation in the controlled studies (described under AE leading to drug discontinuation). Additionally, several subjects presented events of angina pectoris that were not considered serious (from the regulatory point of view) and did not lead to study discontinuation. These cases are discussed under “Other significant AEs”

Brief narratives of SAE of ischemic heart disease in controlled studies are summarized in Appendix 9.1.3.

The applicant proposes to explore the potential for increased risk of myocardial infarction (among other safety issues) in a post-authorization safety study (PASS) in patients with MS under conditions of routine clinical care.

In addition to these cases, there was a serious AE of unexplained lung edema in which the possibility of myocardial ischemia was considered, but the case was confounded by exposure to alternative medicine (snake venom) and to varnish prior to the event. The narrative of the case of lung edema is as follows:

- **2301 0408_00009** – Left ventricular dysfunction and pulmonary edema, myocardial ischemia?

This 21 year old female with MS was randomized to fingolimod 0.5 mg/day. She had no history of CV disease and did not smoke. She was taking oral contraceptive. Two days prior to hospital admission she had received an intramuscular injection of an alternative medicine therapy (Horvi-Crotalus-Reintoxin forte –containing snake venom) for MS. On **Day 8** of study she felt unwell. She had dyspnea and abundant secretions of upper respiratory tract. Oxygen saturation was 88%. Initial suspicion was pulmonary edema or pneumonia. Admitted to hospital: HR 100 bpm, BP 85/45, O2

saturation 74%. Chest X-ray: bilateral infiltrates compatible with pulmonary edema. Empirical treatment with ceftriaxone and erythromycin for possible pneumonia. Labs showed CK-MB elevation (17 U/L, normal 0-6 U/L). troponin positive. WBC: 22,000 per mm³. ECG: ST elevation in anterior leads. Echocardiography in ICU: akinesia in septum and apical areas. Initial diagnosis anterior MI and pulmonary edema. Patient intubated and received IV dobutamine. Coronary angiography showed normal coronary arteries. LVEF 48%. Unclear abnormalities of the LV wall movement. Pressure values:

Pulmonary artery: Systolic=40/Diastolic=14/median=29 (after contrast media)

Aortic arch: Systolic=118/Diastolic=73/median=91(after contrast media)

LV: Systolic=131/End diastolic=37 (at rest)

LV: Systolic=132/End diastolic=35 (after contrast media)

Repeat ECG showed no abnormalities.

Day 9: febrile, stable vital signs on dobutamine and mechanical ventilation. WBC 16,800 mm³, lymphocytes 200 mm³. CK 1819/ MB 20 UI/L. Imipenem added. Study drug discontinued. On Day 10 patient was extubated and hemodynamically stable. Chest x-ray showed bilateral consolidation and possible pleural effusion. Culture of bronchial secretions obtained by bronchoscopy showed β -hemolytic Streptococcus type C with evidence of inflammatory cells. Cultures from the patient's mouth, central catheter and vaginal smear revealed a yeast-like fungi. On Day 16 she was improved and ambulatory, and was transferred to the Dept. of Neurology at the investigator's site. On Day 19 chest and abdominal CT were normal. Echocardiogram was normal. Physical exam was normal. MRI of brain showed new T2 enhancing lesion in the brainstem. The patient completely recovered for pulmonary edema, temporary ventricular dysfunction on Day 21. The etiology of the pulmonary edema remains unclear. Further diagnostic work-up, including evaluation by a pulmonologist and a cardiologist at the investigational site were done. Investigator suspected relationship with study drug.

In response to an FDA request for clarification, the sponsor submitted the following follow up information on 3/4/10:

The consultant cardiologist reviewed the original angiography and confirmed that the patient had had temporarily reduced left ventricular function but "could not find any evidence for Takotsubo cardiomyopathy." Myocardial infarction was also excluded. He reported that although left ventricular function was reduced, that reduction did not appear enough to have induced the pulmonary edema. In his opinion, the pulmonary edema may possibly have been stress induced temporary myocardial ischemia. The final etiology of the pulmonary edema was considered to be either toxic due to exposure to varnish (the day before the event the patient had been varnishing the whole day with a product containing 2-Butanonxin, a toxin known to have the potential to initiate pulmonary edema) or neurogenic due to a new brain stem lesion seen on the brain MRI. Follow up information received confirmed that the patient had completely recovered from the events.

This patient presented a complex picture of pulmonary edema and pneumonia 8 days into treatment, with LV dysfunction and elevated CK MB and troponin suggestive of myocardial ischemia. She was lymphopenic (200 mm³) but had total WBC of 16,800. She required intravenous antibiotics and antifungals, vasopressors and mechanical ventilation. She improved after 2 weeks. A following CT scan and echocardiogram were normal. The patient may have been septic. Relationship to study drug is possible but given the long half life of fingolimod such a rapid recovery would be somewhat unexpected. The case is confounded by the use of alternative medicine (snake venom injected during the study 2 days prior to hospitalization) and exposure to varnish.

- Serious cardiac-related SAE in the Investigations SOC in controlled studies

Cardiac related serious AE in the Investigations SOC in the controlled studies included 4 cases of ECG change on Day 1 (one case on FTY 1.25 mg (PR prolongation) and 3 on FTY 0.5 mg (including one ECG change (unspecified); one QT prolongation; and one ECG ST segment elevation). None of the cases led to study drug discontinuation. The case of ST segment elevation is as follows.

- **2302_0535_00002.** 39 M – ECG ST segment elevation Day 1. As per pt profile, the patient had hypertension but no other cardiac history. ST elevation was noted 6 hours post FTY 0.5 mg dose and lasted 3 days. Pre-dose pulse 90 bpm. Post dose there was bradycardia with mild dizziness. 24 hour Holter showed bradycardia with lowest HR 43 bpm 19 hours post dose. No cardiac enzymes provided. Drug interrupted. Patient started on low dose aspirin (for MI prophylaxis) and lisinopril (for hypertension). Drug re-started 13 days later. No report of AE with second dose. Subject discontinued study due to administrative problems on Day 191 (patient moved out of state). *This appears to be an episode of ischemia upon first dose fingolimod, although no further symptoms were reported.*

- SAE of Chest pain in controlled studies

In addition to the cases coded as angina or ischemic heart disease in the Cardiac disorders SOC, several events of “chest pain” and “non-cardiac chest pain” are described under the General disorders and administration site conditions SOC. Some of these cases appear to have had insufficient work-up to rule out a cardiac cause.

- Additional SAEs of interest in the Cardiac disorders SOC

The following case occurred in the controlled studies:

- **2301 0601_00012.** Pericarditis, pleuritis, pneumonitis and liver enzyme elevation

24 year old female with MS randomized to FTY 1.25 mg in study 2301. No CV history. OCD treated with paroxetine. Non-smoker. On Day 65: chest pain, dyspnea, nausea/vomiting. Echocardiogram showed pericarditis. CT scan showed pleuritis and mild pneumonic infiltration. Drug was stopped on Day 69.

On Day 71, WBC was 2.8 (nl 3.5 – 10.9 E9/L), absolute lymphocyte count was 0.28 (nl 0.8 to 2.8 E9/L); neutrophil count was 2.1 (nl 2.1 – 7.8 E9/L); ALT= 122 U/L (nl up to 40), Alk Phosphatase 446 U/L (nl up to 125), BR was 24 umol/L (nl 2-21). She was treated with clindamycin and improved. AutoAB panel was negative; Viral panel negative except for EBV-VCA IgG and Parvovirus IgG. This was considered by the investigator to be a likely a viral infection but the agent could not be identified. A per the patient profile, viral titers done 1 ½ years after the event, showed high IGG for HSV, Arbovirus and VZV, which indicate past infection. Relationship to study drug was suspected. By Day 77, liver enzymes had decreased and were close to normal. First available normal lymphocyte count was on Day 150, approximately 80 days after drug discontinuation. Liver enzymes were normal. There were no major changes on Hgb, hematocrit, platelet counts, neutrophil and monocyte counts. Two follow up HRCTs (Date not provided) showed mild-moderate pericardial fluid and left posterobasal pleural thickening

respectively. There were no changes in PFT's. A subsequent HRCT, done approximately 1 month later, was normal.

This is a case of pericarditis, pleuritis and possible pneumonic infiltrate on Day 65 of FTY 1.25 treatment, associated with transient increase in liver enzymes. Hepatitis serology was negative. Potential viral agent causing the event was not identified. I agree that this was likely a viral infection.

- The following SAE occurred in extension studies:

- **2201E1_0049_00001** Hypertensive heart disease

44 F. No CV history. Received 1.25 mg during core. She developed epigastric pain and worsening anemia on Day 182. Developed leg swelling on Day 1329 (1508 of FTY treatment); HTN diagnosed on Day 1471. Drug discontinued because of HTN heart disease.

- The following occurred in the ongoing blinded studies not included in the ISS.

- **1201-0019-00005** - Transient inverted T wave and LV dysfunction ("Suspicious Takotsubo [stress] cardiomyopathy)

51 year old, Japanese female, receiving blinded treatment in study 1201. Event suspected to be related to study drug and led to study discontinuation. She was diagnosed with MS approximately 1 year prior to study entry, and received INF treatment up to 5 months before entering this study. Medical history included anxiety. The patient was receiving concomitant medications for constipation and allergic rhinitis.

Three months into the study she was hospitalized with eye pain and double vision, and was diagnosed with MS relapse. At that time an ECG showed negative T-waves in all precordial leads. Echocardiography revealed apex hypomotility from the papillary muscle level to apex area. The patient had no associated clinical symptoms. Creatine phosphokinase (CPK) and creatine kinase myocardial band (CPK-MB) was normal. Takotsubo cardiomyopathy, ischemic heart disease, myocarditis and drug-induced myocardial disorder were suspected, the study medication was permanently discontinued. The patient was transferred to another hospital to receive a detailed check-up by a cardiovascular specialist.

Four days later, the cardiologist did not detect any abnormality on ECG and did not find significant constriction on cardiac catheter test. The cardiologist suspected that there had been Tako-tsubo cardiomyopathy, although he did not diagnose the cardiomyopathy definitely. The patient completely recovered. The investigator did not exclude the possibility of a causal relationship between this event and this investigational drug, since ECG before starting the study medication was normal.

51 yo woman with no cardiovascular history, admitted for MS relapse, incidentally found to have inverted T waves in all ECG leads, associated with apex hypomotility on echocardiogram. The patient was asymptomatic. Drug was discontinued. Four days later, repeated tests were normal. The cause of the transient LV dysfunction remains unclear.

- **2309-0585-00008** – Papillary muscle disorder

A 53 year old, male (0585/00008) diagnosed with MS 8 years prior to entry. The patient's medical history included bladder spasm hypercholesterolaemia, and he was an active smoker for 27 years. Concomitant medication taken prior to randomization included modafinil sildenafil, and pregabalin. The patient had no cardiac co-morbidities or history, and was not receiving any cardiovascular comedications.

On Day 113 of blinded treatment an abnormal Holter revealed non-sustained ventricular tachycardia (3-10 beats, 1 episode) which was a change from the baseline Holter. An echocardiogram was abnormal and the conclusion was: lesion in left ventricle hyperechoic and close to septum (can't rule out possible left ventricular lymphoma, possible prominent papillary muscle). The investigator described this event as 'tumor on heart'. The investigator assessed this event as life threatening and medically significant, and the study medication was temporarily interrupted pending outcome of the event.

On Day 122, the patient underwent a non-scheduled Transoesophageal echocardiogram (TEE) which revealed a prominent papillary muscle in the left ventricle, mild mitral valve prolapse with mild mitral regurgitation and mild aortic atherosclerosis. The patient was subsequently 'cleared to resume study drug' and an unscheduled visit was to be arranged with the patient to resume study drug.

The investigator confirmed that there was no tumor but a prominent papillary muscle in the left ventricle and this was considered a 'variant of normal'. LV myxoma was ruled out. The investigator considered that non-sustained ventricular tachycardia, mixomatous mitral valve prolapse (mild) with mild regurgitation, and mild aortic atherosclerosis were all non-serious events. The study medication was re-started Day 141. The patient did not receive any treatment for this event and was reported to have completely recovered on Day 122.

According to the investigator, the event (papillary muscle disorder) was considered medically significant, and life-threatening. However, the investigator indicated that this event was due to progression of underlying illness and did not suspect a relationship between the event and the study medication. The patient completed the study in January 2010. He discontinued study drug in April 2009 following a diagnosis of asthma and remained in treatment-free follow-up. The patient has not had any signs or symptoms of cardiac disease. No cardiac examinations (echocardiograms, Holter ECG, etc.) were performed outside the study protocol. The site has re-assessed this event as not serious. The final diagnosis was a prominent papillary muscle in the left ventricle."

It would be interesting to know what the bases for the diagnosis of asthma were, and whether the echocardiogram continued to show prominent papillary muscle.

In summary, evaluations of SAE in the cardiac SOC in the controlled studies showed a clear dose response in terms of rhythm and conduction disorders (bradycardia and AVB) in the fingolimod treatment group.

In the controlled studies, the risk of developing SAE of first or second AVB upon first dose with FTY 1.25 was 0.4% and 0.4%, respectively; the risk for FTY 0.5 mg was 0.1% and 0.1%, respectively.

Approximately half of the patients with these events discontinued from the FTY 1.25 mg group, and one discontinued due to 2nd degree AVB from the FTY 0.5 mg group.

There was one case of Complete AVB upon first dose of FTY 1.25 mg in this database (in the extension studies).

There was no imbalance in the number of cases of serious MI or angina in the controlled studies but the numbers are small. Additionally, several cases of angina were coded as non-serious, and it is unclear how the diagnosis of angina was made. Most of these events occurred in young people without prior cardiovascular risks.

Three cases of SAE of LV hypokinesia were reported in this application. Two were thought to be related to transient myocardial ischemia (one during the controlled studies on FTY 0.5 mg, and one in the ongoing blinded studies); and one was confounded by the use of alternative medicine and varnish previous to the event.

One case of pericarditis and pleuritis (probably viral) occurred in the FTY 0.5 mg group in the controlled studies. Additionally a SAE of prominent papillary muscle occurred in the ongoing study 2309 (he eventually discontinued because of asthma).

- SAEs in the Nervous system disorders SOC

SAES in the Nervous system disorders SOC in Safety pool D are summarized in the following table.

Table 14. SAES in Nervous system disorders SOC, safety pool D.

Primary system organ class Preferred term	FTY/20 5 mg (N=94)	FTY/20 1.25 mg (N=943)	FTY/20 0.5 mg (N=854)	Placebo (N=511)	Interferon (N=431)
	n (%)	n (%)	n (%)	n (%)	n (%)
Nervous system disorders					
-Total	1 (1.1)	18 (1.9)	12 (1.4)	5 (1.0)	3 (0.7)
Multiple sclerosis relapse	0 (0.0)	3 (0.3)	3 (0.4)	2 (0.4)	1 (0.2)
Epilepsy	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Grand mal convulsion	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Central nervous system lesion	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Cerebrovascular accident	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Cervicobrachial syndrome	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Coma	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Dural fistula	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Ischaemic stroke	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Monoparesis	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Neuropathy peripheral	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Paraparesis	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Presyncope	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)
Radicular syndrome	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Spinal cord ischaemia	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Status epilepticus	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Syncope	0 (0.0)	1 (0.1)	1 (0.1)	1 (0.2)	0 (0.0)
Amnesia	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Migraine with aura	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Monoplegia	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Multiple sclerosis	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)
Nerve root lesion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Optic neuritis	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Partial seizures with secondary generalisation	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Reversible posterior leukoencephalopathy syndrome	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sciatica	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)
Somnolence	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

Source: Post Table 4.4-9, ISS. All three placebo controlled studies. A patient with multiple occurrences of the same AE under one treatment is counted only once in the AE preferred term for that treatment. A patient with different adverse events within a primary system organ class is counted only once in the total row.

The most common SAES in this SOC were MS relapse and seizure-related events, followed by terms consistent with MS manifestations. The SAE profile in safety pool E was similar to that in the controlled population (data not shown). Review of the SUR is ongoing.

-Seizures

Five subjects presented seizure-related SAE (grand mal convulsion, epilepsy, status epilepticus, partial onset seizure) in the controlled studies (4 on FTY 1.25mg and 1 on FTY 0.5 mg). No SAE of seizures occurred on IFN or placebo. Additional cases of non-serious seizures occurred in the fingolimod program. Seizures are discussed in section 7.3.4 of this review (Other significant AEs).

-MS relapse

The primary outcome measure in this application was the annualized rate of relapse. MS relapse was defined in Phase III studies as the appearance of a new neurological abnormality or worsening of previously stable or improving pre-existing neurological abnormality, separated by at least 30 days from onset of a preceding clinical demyelinating event (McDonald et al, 2001). The abnormality must have been present for at least 24 hours and occurred in the absence of fever ($< 37.5^{\circ}\text{C}$) or known infection. If relapse was suspected, a neurological examination was performed by a blinded EDSS rater. Some of these neurological abnormalities were reported as an adverse event of relapse, at the investigator's discretion.

In the original ISS, 16 SAE of MS/MS relapse were reported in 15 subjects. Of those, 9 occurred during the controlled phase, 2 during the extension and 4 after study drug discontinuation. The listing of patients with serious AEs of MS and MS relapse is presented in Appendix 9.1.4.

Notwithstanding the limitations of subjective reporting of MS relapse as an adverse event, the reported risk of serious AE of MS relapse was low and similar in all treatment groups in the controlled studies (0.2% on FTY 1.25, 0.5% on FTY 0.5 mg, 04% on placebo and 0.2 % on IFN). Narratives of selected cases of AE of MS relapse and other neurologic diagnoses of interest in the MS program are summarized as follows.

Brief narratives of patients with unusual MS relapse or uncommon neurologic diagnosis in the fingolimod program

CONTROLLED STUDIES
FTY 5 mg
<p>2201-0004-00014 – Posterior Reversible Encephalopathy Syndrome (PRES) – FTY 5mg. 52 F, Day 73 MS dx 8 yrs prior. EDSS= 2.5. She had 2 relapses in the 2 years prior to randomization, 2 relapses in the year prior to randomization and her most recent relapse was 9 months prior to randomization. Active smoker. She was taking conjugated estrogens and medroxyprogesterone. <u>On Day 73</u> she was hospitalized with vomiting, rapid onset of blindness and slurred speech. Study drug was discontinued. Four days later, the patient's condition improved. She had left hemianopsia, left hyperreflexia and bilateral Babinski. An MRI done 10 days later showed improvement of previously noted T2 and Flair hyperintensity in all areas but the left occipital lobe, which had changes that could be pre-ischemic in nature. There was progressive improvement, although there were residual symptoms of R homonymous hemianopsia, mild paraparesis, mild ataxia and mild bilateral dysmetria. A diagnosis of PRES (Posterior reversible encephalopathy syndrome) was made. The investigator suspected a relationship to study medication. <i>This case was reviewed by Dr. Heather Fitter, DNP neurologist, who suggested an alternative diagnosis of embolic stroke. Of note, a case of PRES was diagnosed in the renal transplant population.</i></p>
FTY 1.25 mg
<p>2301_0409_00008 - Unusual MS relapse. 6 months into study 27 F. MS dx 2 years prior. EDSS at baseline= 0. No prior immunosuppressants. One relapse in the 2 years prior to random. 2 relapse in the year prior to randomiz, last relapse 3 months prior to random. MS had manifested by optic neuritis with multiple subcortical T2 hyperintense MRI lesions & CSF oligoclonal bands. Most recent relapse prior to entry: gait ataxia, fatigue and numbness of both hands which improved after steroid Rx. The patient's medical history included headache and optic neuritis. Approximately 6 months into FTY 1.25 treatment she presented to the ER with headache and vomiting, without fever. CSF showed 88 WBCs, mostly activated lymphocytes and no granulocytes, with normal protein. An MRI showed a new left parieto-occipital mass (2x3 cm). CSF cultures; PCR for JC virus, herpes and TB and autoantibodies were negative. She developed neurologic symptoms, partial complex and generalized seizures and cognitive impairment. The investigator provided a differential diagnosis of autoimmune encephalitic disease (ADEM) versus opportunistic infection versus hematologic malignancy. At some point the possibility of sinus vein thrombosis was considered, but later thought to be unlikely. She was treated with IV acyclovir, antibiotics and antifungals, as well as with heparin. The patient recovered from the event (MS relapse) with sequelae on an unspecified date. The investigator did suspect a relationship between the events 'overall weak', brain mass, new MS lesions and the complex partial seizures and the study medication. The final diagnosis was unusual MS relapse. Differential diagnoses discussed by the investigator included CNS infection, ADEM and malignancy. See text for more details. At the FDA request, on 2/12/10 the sponsor provided additional follow up on this patient as follows: "Follow-up: Patient has intermittent symptoms of vertigo and tingling which are discussed as minor seizures. She is now on lamotrigine (125mg) for seizures. Her neurological condition is otherwise stable under Copaxone. MRI in April-09 showed residual lesion but no new disease activity. There have been no relapses." <i>Comment: Patient is stable on current treatment. Although final diagnosis was MS relapse, she was treated as if she had a viral infection and also treated with heparin, therefore, the role of fingolimod in this event can not be ruled out. It is somewhat surprising that she did not have a biopsy for the "brain mass", which is still present.</i></p>
<p>2302 0254-00011. Acute Disseminated Encephalomyelitis (ADEM) 11 months into treatment presented with fever, cough and seizures (described under Deaths).</p>

<p>FTY 0.5 mg</p> <p>2301-0453-00003 – MS relapse, subarachnoid hemorrhage, seizure 19 M. MS dx 4 ½ years prior. EDSS= 1.5. Had 1 relapse in 2 yrs prior and one relapse in the year prior to study entry. Most recent relapse was 6 mo. prior to randomization. Treated with IFN and glatiramer up to 6 mo. prior to entry. Hx of optic neuritis. Smoker. On Day 308 of FTY 0.5 mg he had partial seizure with secondary generalization. CT scan showed subarachnoidal bleeding thought to be due to head trauma during seizure. He recovered from the event. On Day 365 MRI showed an active MS lesion very close to the cortex. It was suggested that this lesion could be the cause of the seizure. This was considered an MS relapse and was treated with methylprednisolone. The event did not lead to drug dc. The clinical course was favorable with no new neurological symptoms. <i>Comment: New onset seizure in a patient with 4 ½year history of MS but MRI suggested active MS lesion that could explain the seizure.</i></p>
<p>2302-0822-00003 – Atypical MS. Sjögren’s syndrome. 46 Asian male. MS dx 2 ½ yrs prior. Prior hx of optic neuritis 5 years earlier. He had 4 relapses in the 2 yrs prior to randomization and 1 relapse in the year prior to randomiz. Most recent relapse was 3 months prior to first dose (optic neuritis treated with iv MP). On Day 16 of FTY treatment, he experienced impaired memory, dysarthria, emotional lability, generalized weakness, abnormal behavior, abulia, left hemiparesis with increased deep tendon reflexes on the left side and generalized paresthesia. Study medication was permanently discontinued on Day 18. Differential diagnoses included MS relapse, strategic infarct and drug-related side effect. MRI showed increased lesion extent of high signal intensity. The subcortical white matter was involved extensively in both frontal lobes, both thalami and in both parieto-occipital regions. The diffusion-weighted image showed a pattern consistent with vasogenic and cytotoxic edema. Salivary gland and lower lip biopsies revealed lymphocytic adenitis consistent with Sjögren’s syndrome. Laboratory data included a positive anti-RoAb test and a positive Schirmer test. CSF and frozen serum were sent to NIH for JC virus testing and the Mayo Laboratories for NMO IgG testing. PCR assay for JCV DNA indicated that the virus was undetectable in CSF but detectable in serum (which does not mean an infection since 3% of the population is viremic). On 1-Nov-2007, the investigator concluded that the laboratory results were consistent with Sjögren’s syndrome. The investigator did suspect a relationship between this event and the study drug. <i>Comment: Neurologic manifestations of Sjogren’s syndrome include MS-like symptoms. Still, Sjogren’s syndrome is characterized by lymphocytic infiltration. The role of fingolimod in this event can not be ruled out.</i></p>
<p>EXTENSION STUDIES – FTY 0.5 mg</p> <p>2302_0202_00010 Unusually Severe MS relapse. 33 F, MS dx 5 yrs prior. EDSS=3.5. Five relapses in the 2 yrs prior to randomization; 2 relapses in the year prior to randomization. Most recent relapse was 5 months prior to randomization. She had received azathioprine in the past, and glatiramer acetate for 4 years, until one month prior to starting FTY. Medical history included optic neuritis, hypothyroidism, urinary urgency and fatigue. On Day 590 of FTY 0.5 mg treatment she presented hyposthenia of R leg and pain on legs. An MRI showed increased lesion load and active lesions. She discontinued drug due to the event on Day 616. There is no description of the symptoms associated with this “unusually severe relapse.” After 3 months she started treatment with natalizumab and she is neurologically stable.</p>
<p>ONGOING STUDIES</p> <p>1201E1-0112-00004 (Blinded Japanese study) – Multifocal diffuse leukoencephalopathy. 48 F, MS dx 2 ½ yrs prior. EDSS=2.5. She had 2 relapses in the 2 years prior to randomization, 1 relapse in the year prior to randomization and her last relapse prior to randomization was 3 months prior, treated with steroids. MS manifested as difficulty moving R hand, decreased sensation and dyslalia. She had received with IFN and immunoabsorption in the past. History of venous thrombosis and hypothyroidism. <i>There is limited information from this case to draw definitive conclusions.</i></p>

1201E1-0005-00001. 42 M. Possible T cell lymphoma, initially presented with brain lesion consistent with MS or lymphoma. Described under Deaths.
2306 0406 00007. 43 M with PPMS. Blinded (IND report PHHO2010ES02722). During treatment an MRI done by protocol showed new atypical left frontal hyperintense T2 lesion. Differential dx were PML, brain lymphoma, posterior reversible leukoencephalopathy and diffuse inflammatory demyelinating lesion but the subject had no new symptoms. CSF PCR for JCV was negative at NIH, although JCV was present in urine. Biopsy of the brain lesion did not indicate evidence of viral infection (he had been treated with mefloquine). Histology was normal with minimal infiltration of lymphocytes. There were no genetic markers for lymphoma. The local pathologist was not sure about the diagnosis but thought it could have an inflammatory lesion.
CASES AFTER FINGOLIMOD DISCONTINUATION
2301_0407_00021 – 34 M. Unusually severe MS relapse. Received FTY 1.25 during controlled study. Discontinued on Day 141 of core study because of lack of efficacy. Treated with Rebif for 5 months. After Rebif presented severe relapse with tetraparesis, ataxia, required PEG and tracheostomy. Treated with plasmapheresis, now on natalizumab. Tracheostomy closed. Pt improved but remains bedridden.
2301E1_0412_00004 – Impairment of MS symptoms. Received placebo during core and FTY 1.25 in Extension. On day 1638 (1449 of FTY treatment) the patient withdrew consent and discontinued from the study for unclear reason. 57 days after the last dose of the study drug, she had vertigo and tiredness, progressive hemiparesis and decline in cognition. Hospitalized. An MRI showed large demyelinating lesions, and new enlarging lesions with edema. She was treated with solumedrol & antibiotics. LP: JCV negative. EEG: intermittent slow waves discharges with epileptiform features. Possibility of viral encephalitis was considered. Treated with acyclovir infusions and MP infusions. Patient improved. She recovered with sequelae.

Therefore, there are some unusual cases of severe MS relapse and uncommon neurological diagnoses in this database in the fingolimod treatment groups, but the numbers are too small to draw definitive conclusions.

- Serious vascular events within the Nervous system disorders SOC

Three cases of cerebral ischemia/stroke were reported with FTY 1.25 mg in the fingolimod original ISS (one during the controlled studies and two during the extensions). One additional stroke was reported in a patient receiving FTY 1.25 in study 2309. An additional case in 2309 was initially reported as stroke was later changed to a transient ischemic attack. This patient was on placebo. Brief narratives of serious vascular events in the nervous system disorders SOC are as follows. More details are presented in Appendix 9.1.5. The following case occurred in patients receiving FTY 1.25 mg.

- **2301 0108 00010** was a 40 year old that collapsed and was found to have a large Middle Cerebral artery stroke. She had mildly elevated homocysteine. Based on the CT angiography there was a suspicion that she may have had arteriopathy, consistent with a possible vasculitic process.
- **2302E1 0142 00005** was a 25 year old with left sided headache and photophobia and tingling and heaviness on the right. Stroke work up was negative, and it was suspected that she had a complicated migraine. Although this could have been a TIA, it doesn't sound consistent with that due to the photophobia that was present on presentation.
- **2302E1 0365 00002** was a 40 yo smoker and had herpes zoster ophthalmicus, then developed left cerebral ischemia due to an arterial occlusion. This patient had several risk factors that may have been in play (he was a smoker which can contribute to a hypercoagulable state and then had herpes zoster which may have contributed to the development of vasculitis).
- **2309 0567 00008** was a 41 yo with a hemorrhagic stroke of the occipital lobe. No source of an embolis was found, and a hypercoagulable risk factor work up was negative. Embolic stroke was suspected.

No thrombus or a source of emboli was found in the fingolimod cases. No coagulation abnormalities were found, however, the workup was not complete in all cases.

Although these are few cases, they raise concern about the possibility of increased risk of ischemic/thrombotic cerebrovascular events with FTY 1.25.

The applicant conducted a 28-day clinical pharmacology study evaluating cerebrovascular flow and platelet function in normal volunteers. The study did not show abnormalities at the doses of 1.25 and 0.5 mg a day for 28 days, but it does not rule out an effect with longer duration of treatment.

The applicant proposes to address the possibility of an increased risk for ischemic/thrombotic cerebrovascular events in the PASS registry, a 5000-patient, 5-year postmarketing registry in patients receiving FTY 0.5mg under routine clinical care.

Interim review, 5 12 10.
 Lourdes Villalba, M.D
 NDA 22-527. Fingolimod
 - Syncope

3 subjects presented SAE of syncope in the controlled studies. One occurred on placebo, on Day 163; one on FTY 1.25 on Day 724 and one on FTY 0.5, on Day 203.

- SAE in the Infections and Infestations SOC

SAE in the Infections and Infestations SOC in Safety Pool D is presented in the following table.

Table 15. Serious AE, Infections and Infestations SOC, safety pool D

Primary system organ class Preferred term	FTY720 5 mg (N=94)		FTY720 1.25 mg (N=943)		FTY720 0.5 mg (N=854)		Placebo (N=511)		Interferon (N=431)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
-Total	0	(0.0)	18	(1.9)	8	(0.9)	8	(1.6)	6	(1.4)
Appendicitis	0	(0.0)	2	(0.2)	0	(0.0)	1	(0.2)	2	(0.5)
Abscess	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Abscess jaw	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Acute sinusitis	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Anal abscess	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Dermo-hypodermatitis	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Encephalitis herpes	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Encephalitis viral	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Genital herpes	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Helicobacter gastritis	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Herpes zoster	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Herpes zoster disseminated	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Lower respiratory tract infection	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Mastoiditis	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Otitis media acute	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumonia	0	(0.0)	1	(0.1)	1	(0.1)	0	(0.0)	0	(0.0)
Pyelonephritis acute	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Pyelonephritis chronic	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Respiratory tract infection	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Streptococcal abscess	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Tonsillitis	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Tooth abscess	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Urosepsis	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Administration site infection	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)
Bartholin's abscess	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)
Clostridial infection	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Cystitis	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
Gastroenteritis	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.2)	0	(0.0)
Herpes virus infection	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.2)
Herpes zoster ophthalmic	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
Incision site abscess	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)
Peritoneal abscess	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Peritonsillitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Pharyngitis	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.2)	0	(0.0)
Pharyngotonsillitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Pyelonephritis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Sinusitis	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
Upper respiratory tract infection	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Urinary tract infection	0	(0.0)	0	(0.0)	2	(0.2)	0	(0.0)	1	(0.2)

Source: Post Table 4.4-9, ISS. All three placebo controlled studies. N= patients randomized. n= patients with events. A patient with multiple occurrences of the same AE under one treatment is counted only once in the AE preferred term for that treatment. A patient with different adverse events within a primary system organ class is counted only once in the total row.

Evaluation of overall serious infections and infestations does not indicate a major difference in the risk of these events between fingolimod groups and placebo or interferon in the controlled studies. The percentage of SAEs in this SOC suggests a dose response between fingolimod doses in safety pool E. The analysis of event rates (events per 100 PYRs) in safety pool E also suggests a higher rate in fingolimod 5 and 1.25 as compared to 0.5, but the numbers are small.

Patients with serious events in the Infections and Infestations SOC in safety Pool E are presented as follows:

Table 16. SAES in Infections and Infestations SOC, Safety Pool E

Primary system organ class Preferred term	FTY720 5 mg - 1.25 mg (N=137)		FTY720 1.25 mg (N=1157)		FTY720 0.5 mg (N=1021)	
	n	(%)	n	(%)	n	(%)
-Total	5	(3.6)	30	(2.6)	13	(1.3)
Appendicitis	1	(0.7)	3	(0.3)	0	(0.0)
Herpes zoster	1	(0.7)	3	(0.3)	0	(0.0)
Herpes zoster ophthalmic	0	(0.0)	2	(0.2)	1	(0.1)
Pneumonia	0	(0.0)	2	(0.2)	1	(0.1)
Abscess	0	(0.0)	1	(0.1)	0	(0.0)
Abscess jaw	0	(0.0)	1	(0.1)	0	(0.0)
Acute sinusitis	0	(0.0)	1	(0.1)	0	(0.0)
Anal abscess	0	(0.0)	1	(0.1)	1	(0.1)
Cholecystitis infective	0	(0.0)	1	(0.1)	0	(0.0)
Dengue fever	0	(0.0)	1	(0.1)	0	(0.0)
Dermo-hypodermatitis	0	(0.0)	1	(0.1)	0	(0.0)
Encephalitis herpes	0	(0.0)	1	(0.1)	0	(0.0)
Encephalitis viral	0	(0.0)	1	(0.1)	0	(0.0)
Gastroenteritis	0	(0.0)	1	(0.1)	1	(0.1)
Genital herpes	0	(0.0)	1	(0.1)	0	(0.0)
Helicobacter gastritis	0	(0.0)	1	(0.1)	0	(0.0)
Herpes zoster disseminated	0	(0.0)	1	(0.1)	1	(0.1)
Lower respiratory tract infection	0	(0.0)	1	(0.1)	0	(0.0)
Mastoiditis	0	(0.0)	1	(0.1)	0	(0.0)
Otitis media acute	0	(0.0)	1	(0.1)	0	(0.0)
Papilloma viral infection	0	(0.0)	1	(0.1)	0	(0.0)
Pyelonephritis	0	(0.0)	1	(0.1)	0	(0.0)
Pyelonephritis acute	1	(0.7)	1	(0.1)	0	(0.0)
Pyelonephritis chronic	0	(0.0)	1	(0.1)	0	(0.0)
Respiratory tract infection	0	(0.0)	1	(0.1)	0	(0.0)
Streptococcal abscess	0	(0.0)	1	(0.1)	0	(0.0)

Primary system organ class Preferred term	FTY720 5 mg - 1.25 mg (N=137)		FTY720 1.25 mg (N=1157)		FTY720 0.5 mg (N=1021)	
	n	(%)	n	(%)	n	(%)
Tonsillitis	0	(0.0)	1	(0.1)	0	(0.0)
Tooth abscess	0	(0.0)	1	(0.1)	0	(0.0)
Urinary tract infection	1	(0.7)	1	(0.1)	2	(0.2)
Urosepsis	0	(0.0)	1	(0.1)	0	(0.0)
Bartholin's abscess	0	(0.0)	0	(0.0)	1	(0.1)
Cystitis	0	(0.0)	0	(0.0)	1	(0.1)
Herpes virus infection	0	(0.0)	0	(0.0)	1	(0.1)
Infection	0	(0.0)	0	(0.0)	1	(0.1)
Otitis externa	1	(0.7)	0	(0.0)	0	(0.0)
Pharyngitis	0	(0.0)	0	(0.0)	1	(0.1)
Salpingitis	1	(0.7)	0	(0.0)	0	(0.0)
Sinusitis	0	(0.0)	0	(0.0)	1	(0.1)
Viral infection	0	(0.0)	0	(0.0)	1	(0.1)

Source: Post table 4.5-12. ISS

Rate of serious Infections and infestations (in PYRs of exposure), safety Pool E

Primary system organ class Preferred term	FTY720 5 mg - 1.25 mg (Ny=439.5)		FTY720 1.25 mg (Ny=1919.9)		FTY720 0.5 mg (Ny=1583.3)	
	n	(PR)	n	(PR)	n	(PR)
Infections and infestations -Total	6	(1.4)	35	(1.8)	15	(0.9)

Source: Table 4.2-5a. Response to request for information submitted 2/24/10, refers to original ISS.

In the renal transplant population, the overall risk of infections was similar or lower than with MMF (average 35% of patients had serious infections with FTY as compared to 42% with MMF in the primary population). Of note, there were two cases of aspergillosis, one cryptococcal meningitis, and one pneumocystis jaroveci pneumonia among fingolimod treated patients in the renal transplant population. However, these patients were taking concomitant Cyclosporin A and corticosteroids. No opportunistic infections have been identified in the MS population.

Evaluation of serious infections and infestations over time did not suggest an increased risk of infections with longer exposure (data not shown).

- Analyses of serious Infections and infestations by High level term group

As per the AE datasets, there were 46 serious AES in 37 subjects in the Infections and Infestations SOC, in all controlled studies (pool D). Analysis of serious infections and infestations by High level term (HLT) group in the controlled database is shown as follows:

Table 17. SAE in Infections and infestations SOC, by HLT, safety pool D.

HLT	FTY 1.25 N= 943	FTY 0.5 N= 854	Placebo N= 511	IFN N= 431
	n (%)	n (%)	n (%)	n %
Total	18 (1.9)	8(0.9)	8 (1.6)	6 (1.4)
Herpes viral infections	4(0.4) ¹	2 (0.2)	-	1 (0.2)
Urinary tract infections	2 (0.2)	3 (0.3)	1 (0.2)	1 (0.2)
Lower respiratory tract and lung infections	2 (0.2)	2 (0.2)	-	-
Upper respiratory tract infections	2 (0.2)	2 (0.1)	4 (0.9)	-
Abdominal and gastrointestinal infections	2 (0.2)	-	3 (0.7)	2 (0.4)
Ear infections	2 (0.2)	-	-	-
Infections NEC	2 (0.2)	-	-	2 (0.4)
Bone and joint infections	1 (0.1)	-	-	-
Dental and oral soft tissue infections	1 (0.1)	-	-	-
Helicobacter infections	1 (0.1)	-	-	-
Skin structures and soft tissue infections	1 (0.1)	-	-	-
Streptococcal infections	1 (0.1)	-	-	-
Clostridia infections	-	-	1 (0.2)	-
Female reproductive tract infections	-	-	-	1 (0.2)

Source: FDA MO analysis of AE datasets 12/18/09. One patient may have had events in more than one HLT.

¹Includes one death due to disseminated zoster infection and one death due to herpes simplex encephalitis infection that was coded as Viral infection NEC.

- SAE of herpetic infections

In the controlled studies, serious herpes viral infections requiring hospitalization occurred only in the active treatment groups. In the FTY 1.25 mg group there were 2 fatal cases (disseminated varicella zoster and herpes simplex encephalitis), one polysegmental herpes zoster and one herpes zoster genitalis that required intravenous acyclovir. In the FTY 0.5 mg group there were one herpes zoster ophthalmic and one herpes simplex associated with pneumococcal pneumonia.

It is unclear why the case of serious herpes infection in the IFN group was coded as serious, since the patient told the investigator about the AE several months later, at the 12-month visit and there is no mention of hospitalization or iv treatment in the narrative.

Six SAE of herpes infections were reported in the extension studies in the original ISS (one on FTY 5-1.25 mg; four on FTY 1.25 mg –including 2 herpes zoster ophthalmic and one varicella zoster with lung involvement thought to be viral reactivation- and one on FTY 0.5 mg). Two cases were treated with intravenous acyclovir (one on FTY 1.25 and one on FTY 0.5 mg). Brief narratives for serious herpes viral infections in the original submission are presented in Appendix 9.1.6.

In addition to these cases, two subjects presented with atypical MS relapses (with decreased cognitive function and seizure activity) and their treatment included intravenous acyclovir because of the possibility of viral encephalitis (2301_0409_0008, who also had a differential diagnosis of brain tumor and 2301_0412_00004). These cases were described in the Nervous system disorders section.

- SAE of lower respiratory infections

In the controlled studies, SAE of lower respiratory tract infections were reported only in the FTY 1.25 and 0.5 mg treatment groups (2 in each). Brief narratives of these cases are presented below, however, there is very limited information in these cases.

Brief narratives of serious lower respiratory tract infections in the fingolimod trials.

CONTROLLED STUDIES
FTY 1.25 mg
<ul style="list-style-type: none"> 2302_0254_00011. - Lower respiratory tract infection 42 M. This patient developed ADEM complicated with lower respiratory tract infection. He died approximately 6 months after last dose of FTY. No information about possible agent or treatment. Narrative of ADEM is under Deaths. 2301_0601_00012 - Pneumonic infiltrate, pleurisy 24 F. This patient developed pneumonic infiltration, atelectasies, pleurisy, pericarditis and elevated liver enzymes on Day 65. The case was described under serious cardiac disorders (pericarditis). It was thought to be viral.
FTY 0.5 mg
<ul style="list-style-type: none"> 2301_0652_00013 – Pneumonia Pneumococcal sepsis 49 F. Diagnosed with MS 5 years prior. She received corticosteroids for MS relapses until 2 months prior to randomization. Prior history of cystitis and pyelonephritis. Non smoker. On Day 566 she had fever and dyspnea, Xray showed basal infiltrate, WBC was 14.500. She was treated with amoxicillin for pneumonia and discharged without sequelae. On Day 622 she again developed dyspnea and fever, with sores on the lip and nose. She was hospitalized with pneumococcal sepsis and herpes simplex virus type 1. Blood culture showed pneumococcus. She was treated with penicillin and acyclovir. She recovered.
EXTENSION studies
FTY 1.25 mg
<ul style="list-style-type: none"> 2302E1_0445_00006. 43 M. Pneumonia. The patient presented several episodes of nasopharyngitis during core. On Day 517 again mild upper respiratory tract infection. On Day 533 he had MS relapse and band like tightness, treated with steroids. On Day 551 he had persistent relapse and was to the ER. Work up showed in infection with increased LFTs and decreased sodium. A chest x-ray showed pneumonia. He underwent bronchoscopy. He was treated with ceftriaxone, azithromycin and acyclovir and discharged on Day 570. Drug was interrupted but re-started. Last lab evaluation prior to infection showed absolute lymphocyte count of 190.

As per the original AE database, only four patients developed serious lower respiratory tract infections in the fingolimod MS studies, while receiving fingolimod treatment. However, some events coded under other MedDRA SOC from the extension studies, could potentially be infectious-related:

- ID # 2201E1-0004-00004** was reported to have a “benign solid mass lesion of the left lower lung lobe” (Neoplasms SOC).
 52 y.o female, randomized to FTY 5 mg during the core study and switched to FTY 1.25 mg during the extension study. No history of asthma. Three years into FTY treatment she presented “asthma exacerbation”. On Day 1347 a CT scan showed a mass/tumor (3.25cm x 4.64 cm) located in the lower left lung (tumor or infection). Study medication was discontinued. On Day 1399 the patient underwent lung lobectomy. Biopsy showed necrotizing granulomatous pneumonitis with no evidence

of malignancy, metastases or lymph node reactive changes, and mid centrilobular emphysema. Cultures were negative. Although no organisms were identified the possibility of tuberculosis was considered. Laboratory results 82 days after study drug discontinuation showed absolute lymphocyte counts of $0.1 \times 10^9/L$ and $0.3 \times 10^9/L$. The patient discontinued from the study on Day 1454. No further laboratory results are available.

- **2302E1-0124-00001** Lung disorder, Benign mediastinal neoplasm. (Respiratory SOC and Neoplasm SOCs)

43 year old female. On Day 205 of FTY 1.25 mg treatment had acute chest pain, dyspnea and hypoxia. Hospitalized. CT scan showed pneumopathy with basal infiltrates in inferior lobe, a benign mediastinal lesion/mass, parenchymatous opacities left side and mild pleural disorder. A BAL showed "hypercellularity" and discrete eosinophilia (4%). Treatment included paracetamol and dextropropoxyphene (no mention of antibiotics). The events of chest pain and dyspnea resolved the same day. The patient was discharged from the hospital 5 days after the last dose of the study medication. A follow-up CT scan performed 8 days after the last dose of the study medication showed complete recovery from parenchymatous and pleural lesions. The CT scan also showed a "supracentrimetric nodule" located in the left cardiophrenic angle. The functional respiratory tests were normal on the same day. The event of mediastinal mass is said to have resolved 89 days after the last dose of study drug.

This event appears to be an infection, perhaps viral, that resolved within a few days without antibiotic treatment.

- **Patient D2302E1-0525-00002**, Pneumothorax (acinetobacter pneumonia) (Respiratory SOC)

At the one-year visit after treatment with FTY 1.25 mg he was found to have "scattered benign pulm nodules" and bronchiectasis. The baseline HRCT showed interlobular septal thickening, ground glass opacities and traction bronchiectasis. A month after the one-year visit, while in the extension study, the subject had a bronchoscopy with biopsy. The procedure was complicated by pneumothorax. Cultures taken at the time of the bronchoscopy grew acinetobacter and he was diagnosed with acinetobacter pneumonia. Drug was discontinued. He was reported to improve with intravenous antibiotic treatment (tobramycin and pepercillin).

Acinetobacter infection is usually seen after prolonged hospitalization and is most associated with ventilated patients or those with repeated procedures (such as bronchoscopies). This patient apparently had no previous procedures.

The FDA requested the applicant to provide WBC, neutrophil and lymphocyte counts for patient who had serious infections, at the time of the infection. This information was not available for most patients. A table providing the last available value prior to the SAE of infection showed that, as expected, that lymphocyte counts were lower than baseline in FTY-treated subjects, as compared to INF and placebo-treated subjects (data not shown). Only 2 subjects had a lymphocyte count <200 (at the time of last measurement before the infection) in the controlled studies (a subject with helicobacter pylori infection and a subject with non-fatal disseminated herpes zoster infection) both with FTY 1.25 mg. Three additional subjects had a lymphocyte count <200 in the extension studies (one subject with pneumonia, one with gastroenteritis and one with respiratory tract infection).

In summary, a review of serious infections in the MS program suggests an increased risk of serious viral herpetic infections. There does not appear to be an increased risk of bacterial, mycobacterial, opportunistic or fungal infections. No leukocyte counts, lymphocyte counts or immunoglobulin levels were available at the time of the serious infections. An analysis of the most recent laboratory evaluations before the diagnosis of the serious infection showed that five subjects had lymphocyte counts <200 in the FTY 1.25 mg treatment group in the ISS database. No patient was neutropenic at that time.

- SAEs in Neoplasms benign, malignant and unspecified (including cyst and polyps) SOC

There did not seem to be an increased risk of serious neoplasms in the analysis of Safety Pool D or E. In safety pool D, the overall risk of neoplasms was lower in the fingolimod treatment groups. In Safety Pool E, there was no dose response between fingolimod doses. The most common SAE in the Neoplasms SOC was basal cell carcinoma. There seems to be a suggestion of a greater risk/rate of basal cell carcinoma in the FTY 0.5 mg and placebo, but the numbers are small.

Table 18. SAE in the Neoplasm disorders SOC, Pool D

Primary system organ class Preferred term	FTY720 5 mg (N=94) n (%)	FTY720 1.25 mg (N=943) n (%)	FTY720 0.5 mg (N=854) n (%)	Placebo (N=511) n (%)	Interferon (N=431) n (%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
-Total	1 (1.1)	9 (1.0)	14 (1.6)	12 (2.3)	2 (0.5)
Basal cell carcinoma	0 (0.0)	3 (0.3)	6 (0.7)	2 (0.4)	0 (0.0)
Breast cancer	0 (0.0)	3 (0.3)	1 (0.1)	3 (0.6)	0 (0.0)
Bowen's disease	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Brain neoplasm benign	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Malignant melanoma	0 (0.0)	1 (0.1)	2 (0.2)	1 (0.2)	0 (0.0)
Benign breast neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Benign ovarian tumour	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Breast cancer in situ	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Cervix carcinoma stage 0	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Endometrial cancer	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Malignant melanoma in situ	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Ovarian adenoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Ovarian neoplasm	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Prostate cancer	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Squamous cell carcinoma	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Uterine leiomyoma	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	1 (0.2)

Source: Post Table 4.4-9, ISS. All three placebo controlled studies. A patient with multiple occurrences of the same AE under one treatment is counted only once in the AE preferred term for that treatment. A patient with different adverse events within a primary system organ class is counted only once in the total row.

The most common SAE in this SOC was basal cell carcinoma. The percentage of patients with basal cell carcinoma was similar for FTY 1.25 and placebo (0.3 - 0.4%) and slightly higher for FTY 0.5 mg (0.7%). The difference is small and the diagnosis whether the skin lesion was there before treatment could not always be made because some subjects underwent their first dermatologic examination several months into treatment. However, one

case of basal cell carcinoma on FTY 0.5 is notable for presenting at multiple sites. This case is as follows.

- **2301_0412_00004.** 45 F. On day 104 of FTY 0.5 mg she presented a “macular rash.” She noted red macular lesions on her skin in three different locations, two on the back and one in the R arm, of about 0.5 cm. The lesions were not present at the time of screening. Biopsies showed basal cell carcinoma at all 3 sites. Subsequently she was also found to have a new dysplastic nevus on the thigh. Drug was discontinued. The lesions were thought to be related to study drug.

Table 19. SAE in the Neoplasm disorders SOC, Pool E

Primary system organ class Preferred term	FTY720 5 mg - 1.25 mg (N=137) n (%)	FTY720 1.25 mg (N=1157) n (%)	FTY720 0.5 mg (N=1021) n (%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
-Total	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 (0.0)	3 (0.3)	2 (0.2)
Benign mediastinal neoplasm	0 (0.0)	1 (0.1)	0 (0.0)
Bowen's disease	1 (0.7)	1 (0.1)	0 (0.0)
Brain neoplasm benign	0 (0.0)	1 (0.1)	0 (0.0)
Squamous cell carcinoma of skin	0 (0.0)	1 (0.1)	1 (0.1)
Benign lung neoplasm	1 (0.7)	0 (0.0)	0 (0.0)
Benign uterine neoplasm	0 (0.0)	0 (0.0)	1 (0.1)
Breast cancer in situ	0 (0.0)	0 (0.0)	1 (0.1)
Malignant melanoma in situ	0 (0.0)	0 (0.0)	1 (0.1)
Ovarian cancer metastatic	1 (0.7)	0 (0.0)	0 (0.0)
Ovarian neoplasm	0 (0.0)	0 (0.0)	1 (0.1)
Squamous cell carcinoma	1 (0.7)	0 (0.0)	0 (0.0)
Thyroid cancer	1 (0.7)	0 (0.0)	0 (0.0)
Uterine leiomyoma	0 (0.0)	0 (0.0)	4 (0.4)

Source: Post text Table 4.6-12 original ISS

The analyses of rates (n/PYRS of exposure) were consistent with the analysis of risk (n/pts randomized) (see table below).

Table 20. Incidence rate of serious neoplasms (events/100 PYRs), safety pools D and E.

	FTY 5	FTY 1.25	FTY 0.5	Placebo	IFN
All controlled studies (Pool D)	43.2 PYRs	1111.2 PYRs	1153.2 PYRs	746.9 PYRs	401.9 PYRs
All neoplasm	1 (2.3)	15 (1.3)	14 (1.2)	12 (1.6)	2 (0.5)
Basal cell carcinoma	0	3 (0.3)	6 (0.7)	2 (0.4)	0
Controlled and extensions (Pool E)	FTY 5 to 1.25 439.6 PYRs	FTY 1.25 1919.9 PYRs	FTY 0.5 1583.3 PYRs	-	-
All neoplasms	6(1.4)	19 (1.0)	20 (1.3)	-	-
Basal cell carcinoma	1 (0.2)	3 (0.2)	7(0.4)	-	-

Source: Tables 4.2-4b and 4.2-5a. Response to FDA request for information submitted 2/22/10. Patient year defined as sum of no. days on study drug for all patients in each treatment group divided by 365.25. - n = Number of adverse events that occurred to a patient. PR = 100 Patient year rate calculated as $n/Ny \times 100$. - If a patient had multiple AEs (or different occurrences of AEs) with different preferred terms on the same date then the AEs will be counted differently. - If a patient had multiple AEs (or different occurrences of AEs) on the same date and with the same preferred term but different levels of severity, then the AE will be counted only once using the maximum severity.

Non-clinical carcinogenicity studies showed an increase incidence of lymphoma. For details the reader is referred to the Pharm tox review by Dr. Siarey.

In the renal transplant population, the risk of neoplasms (all) seemed to be higher with FTY 5 mg as compared to FTY 2.5 and MMF (5.3%, 3.4% and 2.8%, respectively. The tumors that seem to be contributing to the difference in overall risk were squamos cell carcinoma (0.6% and 0.4% in FTY 5 and 2.5, respectively, as compared to 0.2% on MMF) and Kaposi sarcoma (also 0.6% and 0.4% in FTY 5 and 2.5, respectively, as compared to 0.2% on MMF). Of note, there were two T-cell lymphoma (one in each FTY group), one lymphoproliferative, one disorder and one B-cell lymphoma and one myelodysplastic syndrome in the FTY 2.5 mg group, and one brain lymphoma in the MMF group.

In the MS population, there were no reported lymphoproliferative disorders or lymphoma. However, subject 1201E1-0005-00001 presented a brain mass that was thought to be MS relapse and later developed tumors in the kidney, liver, lungs and lymph nodes, and a rash consistent with T cell lymphoma. In my opinion, this case is a case of disseminated malignant lymphoma, however, a definitive diagnosis can not be made. The full narrative of this subject has been presented in the Deaths section of this review.

In summary, the analysis of serious neoplasms in the MS database does not suggest an increase risk of serious neoplasms or malignancies in the fingolimod treatment group in the present database. In particular, there is no increase of lymphoproliferative disorders, although one possible case of lymphoma was diagnosed after 9 months of fingolimod discontinuation. There is a suggestion of increased risk of basal cell carcinoma for FTY 0.5 mg, but not for FTY 1.25 mg as compared to placebo. The long term exposure in this database is limited, and data are uncontrolled. Given the known effect of fingolimod on circulating lymphocytes and the potential effect on immunosurveillance, an increased risk

of malignancy with longer exposure can not be ruled out. This issue should be addressed with longer term data.

- SAES in Investigations SOC

Individual AE in the Investigation disorders SOC have been incorporated into the respective SOC (e.g ECG under Cardiac SOC, etc.).

- SAEs in the Eye disorders SOC

Analyses of SAE in the Eye disorders SOC in Safety pool D is presented in the following table.

Table 21. Serious AE, Eye Disorders SOC, safety pool D

Primary system organ class Preferred term	FTY720 5 mg (N=94)		FTY720 1.25 mg (N=943)		FTY720 0.5 mg (N=854)		Placebo (N=511)		Interferon (N=431)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Eye disorders										
-Total	0	(0.0)	7	(0.7)	2	(0.2)	1	(0.2)	0	(0.0)
Macular oedema	0	(0.0)	4	(0.4)	1	(0.1)	0	(0.0)	0	(0.0)
Eye pain	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Papilloedema	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Photopsia	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Retinal disorder	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Retinitis	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Iridocyclitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Keratitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Retinal detachment	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)

Source: Post Table 4.4-9, ISS. All three placebo controlled studies. A patient with multiple occurrences of the same AE under one treatment is counted only once in the AE preferred term for that treatment. A patient with different adverse events within a primary system organ class is counted only once in the total row.

Eye disorders are common in patients with MS, and it is sometimes difficult to distinguish if the reported AEs are truly AEs or part of the disease. Reports of SAE in this SOC were higher in the FTY 1.25, as compared to FTY 0.5, placebo or IFN.

There were four cases of serious ME in the FTY 1.25 mg group, and 1 in the FTY 0.5 mg group. There were no cases on INF or placebo. Four of the subjects had no prior history of MS ocular symptoms, one subject had a history of optic neuritis. Diagnoses of ME were made 1 to 4 months into treatment. Three subjects had decreased or loss of vision in one eye at the time of the event. The other two were asymptomatic and diagnosed by dilated ophthalmoscopy/OCT during protocol scheduled ophthalmic evaluations. In all cases macular edema resolved 2 to 4 ½ months after drug discontinuation. However, 3 out of 4 cases on FTY 1.25 and 1/1 on FTY 0.5 recovered from the ME with decreased vision at the time of the last available evaluation. In addition to these cases, there were cases of macular edema coded as non-serious that led to study drug discontinuation (8 in the FTY 1.25 mg group and 1 in the FTY 0.5 mg group). They are described in the Discontinuation section of this review.

As seen in the following table, in Safety pool E there was evidence of a dose response between the 1.25 and 0.5 mg doses for macular edema.

Table 22. SAE in the Eye Disorders SOC, Safety pool E (updated)

Primary system organ class Preferred term	FTY720 5 mg - 1.25 mg (N=137) n (%)	FTY720 1.25 mg (N=1302) n (%)	FTY720 0.5 mg (N=1176) n (%)
Eye disorders			
-Total	1 (0.7)	12 (0.9)	3 (0.3)
Macular oedema	1 (0.7)	9 (0.7)	2 (0.2)
Eye pain	0 (0.0)	1 (0.1)	0 (0.0)
Papilloedema	0 (0.0)	1 (0.1)	0 (0.0)
Photopsia	0 (0.0)	1 (0.1)	0 (0.0)
Retinal disorder	0 (0.0)	1 (0.1)	0 (0.0)
Retinitis	0 (0.0)	1 (0.1)	0 (0.0)
Retinal detachment	0 (0.0)	0 (0.0)	1 (0.1)

Source: SUR. Post text table 4.5-12.

Seven SAE of macular edema (ME) were reported in the extension studies original ISS (1 on FTY 5 mg, 5 on FTY 1.25 and 1 on FTY 0.5). No additional case was reported from the extension studies at the time of the SUR.

Brief narratives of SAE of macular edema in the Eye disorders SOC with FTY 0.5 mg are described as follows. Cases for other doses are presented in Appendix 9.1.7.

- **2302_0424_00010 (controlled study).** 41 M, randomized to FTY 0.5 mg. MS diagnosed 2 ½ years earlier. Had received IFN in the past. History of epilepsy. No prior history of eye problems. Non smoker but started to smoke during first month of study. Concomitant meds at entry: carbamazepine. Screening visual acuity: 20/20. OCT CFT: 169/170 L/R. On 1-month visit: dilated ophthalmoscopy showed unspecific maculopathy bilaterally. On Day 94, there was a suspicion of classical macular edema in the left eye (severe intensity) which was confirmed by FA. The patient denied any visual symptoms. Drug was discontinued on Day 95. (Patient profile states that on Day 94 there was a macular hole on L eye) OCT FT at 4 ½ months: 250/171 L/R. He was treated with ketorolac eye drops. 61 days after receiving the last dose of the study medication, an ophthalmoscopy with three mirrored lens revealed fovea brightness loss in the right eye with no other changes. In the left eye, there was fovea brightness loss with macular pigment epithelium recovery without edema. The patient's visual acuity was 20/25 in the right eye and 20/50 in left eye.
 - **2302E1_0211_00008 (extension study).** 36 M. Randomized to IFN in core study. Received FTY 0.5 mg during the extension. Diagnosed with MS 2 years prior to randomization. EDSS score at entry= 1. Prior history of IFN treatment. No history of optic neuritis or eye symptoms. On Day 189 of FTY 0.5 mg during regular ophthalmic assessment, OCT revealed thickening of the macula in the left eye (CFT= 203 microns compared to 152 at the end of the core study). He was asymptomatic. Visual acuity was 20/20. FA was not done. No treatment was given. Drug was discontinued. The event of macular edema was resolved 18 days after drug dc. At this time a repeat OCT showed CFT= 164 microns and FA showed no macular edema.
- Serious AE of macular edema in study 2309

At the time of the original application, one SAE of ME was reported from study 2306, and 4 from study 2309 (all blinded). At the time of the Special safety interim report update, the SAE of ME from study 2309 were unblinded (2 on FTY 1.25, 1 on FTY 0.5 and one on placebo). The case on FTY 0.5mg is described below. It required surgery for repair of a macular hole.

- **2309-0547-00007. 37 F. Macular edema on Day 114, requiring surgery (FTY 0.5)**

20 year history of MS. Hx optic neuritis of L eye 4 years prior to entry and depression. No evidence of retinopathy at study entry. Concomitant meds bupropion, lorazepam, floxetine, levothyroxine. Screening VA 20/30+1 R, 20/25-2 L. CFT 186 microns in L and 220 in R. She complained of blurred vision in L eye. On day 36 she complained of stabbing pain in R eye. Fundoscopic exam showed epiretinal membrane (ERM) in R eye. OCT showed CFT 209 in L and 253 in R. Foveal contour was irregular in R eye but the overall assessment was negative for ME. **On Day 114** she c/o 1 week hx of decreased vision in R eye. VA was 20/30-2 in L and 20/50+ in R. Cystoid macular edema was dx in R eye. CFT was 198 in L and 471 microns in R eye. Drug was dc. For the ensuing 3 months she reported having a line across her field of vision but did not see an ophthalmologist. 3 months after drug dc VA was 20/200 at R and unchanged at L. Fundus exam showed a stage 4 macular hole in R eye. CFT was 504 microns in R eye and 208 in L eye. One image showed full thickness macular hole. She underwent ocular surgery to repair macular hole in R and ERM in L. Six months after surgery VA was 20/30 in L and 20/40 in R.

- Summary of review of cases of SAE of macular edema in fingolimod MS studies

Five patients presented serious macular edema with FTY in the controlled studies in the ISS (four in the FTY 1.25 group (0.4%) and one in the FTY 0.5 mg group (0.1%)). There were no such cases in the placebo and IFN treatment groups. Seven SAE of macular edema were reported from extension studies included in the ISS (1 on FTY 5mg, 5 on FTY 1.25mg and 1 on FTY 0.5 mg). Four SAE of macular edema were reported in study 2309 (2 on FTY 1.25, 1 on FTY 0.5 and 1 on placebo).

Of the 12 patients who developed SAE of macular edema in the ISS, 4 had a past history of optic neuritis or uveitis before entering the study. None of the patients was diabetic. Except for one subject who retrospectively may have had active uveitis at the time of randomization, no patients had active uveitis or macular edema at screening (because that would be an exclusion criterion).

Few patients had symptoms at the time of the diagnosis of macular edema (decreased vision, blurred vision, feeling of pressure in one eye or visual acuity testing decreased) but most were asymptomatic. Most cases were diagnosed by dilated ophthalmologic evaluation or OCT at protocol scheduled timepoints. In some cases CFT measured by OCT was obviously increased; in others it was mildly increased, but fluorescein angiography (FA) confirmed capillary leaking consistent with macular edema. Some cases were bilateral but most cases involved only one eye.

Onset of SAE of macular edema in the ISS was reported as early as 11 days and as late as 932 days into study treatment, however the two cases with the longer time to onset were actually not confirmed by OCT. Most cases occurred earlier than 3-4 months into treatment (mean= 207 days; median 99 days).

SAEs of ME led to drug discontinuation. Few patients received additional treatment (NSAIDs, topical steroids). Most patients recovered completely within a few weeks or months after drug discontinuation, with or without additional treatment but some recovered with sequelae of decreased vision.

It appears clear that fingolimod causes macular edema, including at the dose recommended for marketing (0.5 mg/day).

- SAE in the Eye disorders SOC, other than macular edema

There were three SAE of note other than macular edema, in the controlled studies. Two were in the FTY 1.25 mg group (one papilledema and one retinal micro-thrombosis), and one in the FTY 0.5 mg group (retinal detachment).

SAE in the Eye disorders SOC other than macular edema with FTY 1.25 in Pool D are as follows:

- **2301_0701_00036.** 18 F. Papilloedema on Day 11. Drug dc.
Optic neuritis and blurred vision 15 months prior to study entry. OCT CFT at screening; 186/175 L/R. On Day 7, pain of L side of head without visual symptoms. On Day 11, left papilloedema. Day 40, OCT CFT: 192/183 L/R. Drug discontinued. Later treated with IFN on Day 116. FU on Day 100, OCT CFT: 194/199; FU Day 198, OCT CFT: 192/195. Ophthalmologic evaluation 30 days after drug dc still showed papilledema. Pt withdrew consent. On a f/u visit, 188 days after drug discontinued, an ophthalmologist said that papilloedema was still present but improved from prior visit. *The DSMB ophthalmologist thought it was most likely related to papillophlebitis due to oral contraceptive use and not related to drug.*
- **2301_0458_00002.** 30 M. Retinal disorder (retinal micro-thrombosis) on Day 29.
No history of eye problems. On Day 29 presented retinal microthrombosis (MTHFR mutation +hyperhomocysteinemia). Drug permanently discontinued. Relationship to study drug was suspected. Treated with folic acid. CFT at screening: 150/153 L/R; CFT at End of study (D29) 165/156 L/R.

The narrative of the case on FTY 0.5 mg is as follows

- **2301_0851_00019.** 51 M. Retinal detachment on days 136, 189 and 261. MS diagnosed 4 years prior. No history of eye problems. Concomitant meds: oxcarbazepine. On Day 136 he suffered a loss of vision in one eye. He was diagnosed with retinal detachment. Treated with surgery x 3 (because of recurrent detachment). Investigator thought it was not related to drug.

In addition to the serious AE in the Eye disorders SOC there were some cases that led to drug discontinuation were coded as non-serious, including one case of “bilateral retinal ischemia/retinal occlusive disease/vasculitis”, in the fingolimod 1.25 mg treatment group. These cases are described among cases leading to discontinuation in the Eye disorders SOC.

- SAE in the Respiratory, Thoracic and mediastinal disorders SOC and Investigations (respiratory related) SOC.

The number of patients with SAE in the Respiratory SOC in safety pool D and E are presented in the following tables.

Table 23. Serious AE, Respiratory, thoracic & mediastinal disorders SOC, safety pool D.

Primary system organ class Preferred term	FTY720 5 mg (N=94)	FTY720 1.25 mg (N=943)	FTY720 0.5 mg (N=854)	Placebo (N=511)	Interferon (N=431)
	n (%)	n (%)	n (%)	n (%)	n (%)
Respiratory, thoracic and mediastinal disorders					
-Total	1 (1.1)	6 (0.6)	3 (0.4)	3 (0.6)	1 (0.2)
Dyspnoea	1 (1.1)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Pleurisy	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperventilation	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia aspiration	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Productive cough	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Asthma	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Chronic obstructive pulmonary disease	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Dyspnoea exertional	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Pneumothorax	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)
Pulmonary embolism	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Pulmonary oedema	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)

Source: Post Table 4.4-9, ISS. All three placebo controlled studies. A patient with multiple occurrences of the same AE under one treatment is counted only once in the AE preferred term for that treatment. A patient with different adverse events within a primary system organ class is counted only once in the total row.

Most episodes of dyspnea in the controlled studies appear to be cardiac-related, but the work-up was incomplete to adequately characterize them. Of note, one subject on placebo developed worsening asthma. There were no reports of asthma/worsening asthma/bronchoconstriction in the fingolimod treatment groups. Brief narratives of SAE in this SOC in the controlled studies are presented in Appendix 9.1.8.a.

Table 24. Serious AE, Respiratory, thoracic & mediastinal disorders SOC, safety pool E.

Primary system organ class Preferred term	FTY720 5 mg - 1.25 mg (N=137)	FTY720 1.25 mg (N=1157)	FTY720 0.5 mg (N=1021)
	n (%)	n (%)	n (%)
-Total	5 (3.6)	9 (0.8)	4 (0.4)
Dyspnoea	2 (1.5)	5 (0.4)	3 (0.3)
Lung disorder	0 (0.0)	1 (0.1)	0 (0.0)
Obstructive airways disorder	1 (0.7)	1 (0.1)	0 (0.0)
Pleurisy	0 (0.0)	1 (0.1)	0 (0.0)
Pneumothorax	0 (0.0)	1 (0.1)	0 (0.0)
Asthma	1 (0.7)	0 (0.0)	0 (0.0)
Bronchospasm	1 (0.7)	0 (0.0)	0 (0.0)
Pulmonary oedema	0 (0.0)	0 (0.0)	1 (0.1)

Source Table 4.5-13 ISS.

In the original ISS, there were 9 SAE in the Respiratory, thoracic and mediastinal disorders in the fingolimod extension studies. These included 3 cases of asthma/bronchospasm in the FTY 5 – 1.25 mg group; one of exacerbation of asthma, one lung disorder and one pneumothorax/ acinetobacter pneumonia in the FTY 1.25 mg group (this one was described under SAE of Infections); and one pulmonary embolism in the FTY 0.5 mg group. Brief narratives of these cases are presented in Appendix 9.1.8.b

Four subjects presented asthma/bronchospasm during the extension studies: three in the 5 to 1.25 mg/day treatment group (two of them were new onset and one was exacerbation in subject with a history of asthma) and one in the FTY 1.25 mg group (in a subject with a prior history of mild asthma). Although they occurred in the uncontrolled portion of the studies, the finding is consistent with known effects of SP1 (increasing bronchoconstriction). No episodes of asthma occurred in the 0.5 mg group.

- SAES in Vascular disorders SOC

Two serious AE of peripheral artery disease occurred in the FTY 1.25 mg group in the controlled studies. SAE in the vascular disorders SOC are presented in the following tables, for safety pools D and E.

Table 25. Serious AE, Vascular disorders SOC, safety pool D

Primary system organ class Preferred term	FTY720 5 mg (N=94)	FTY720 1.25 mg (N=943)	FTY720 0.5 mg (N=854)	Placebo (N=511)	Interferon (N=431)
	n (%)	n (%)	n (%)	n (%)	n (%)
Vascular disorders					
-Total	1 (1.1)	3 (0.3)	1 (0.1)	2 (0.4)	0 (0.0)
Arterial occlusive disease	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Hypertensive crisis	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Peripheral arterial occlusive disease	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Circulatory collapse	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Hypertension	1 (1.1)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Varicose vein	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)

Source: Post Table 4.4-9, ISS. All three placebo controlled studies. A patient with multiple occurrences of the same AE under one treatment is counted only once in the AE preferred term for that treatment. A patient with different adverse events within a primary system organ class is counted only once in the total row.

Table 26. SAES in Vascular disorders SOC, Pool E

Primary system organ class Preferred term	FTY720 5 mg - 1.25 mg (N=137)	FTY720 1.25 mg (N=1157)	FTY720 0.5 mg (N=1021)
	n (%)	n (%)	n (%)

Vascular disorders			
-Total	3 (2.2)	5 (0.4)	1 (0.1)
Arterial occlusive disease	0 (0.0)	1 (0.1)	0 (0.0)
Deep vein thrombosis	0 (0.0)	1 (0.1)	0 (0.0)
Flushing	0 (0.0)	1 (0.1)	0 (0.0)
Hypertensive crisis	0 (0.0)	1 (0.1)	0 (0.0)
Peripheral arterial occlusive disease	0 (0.0)	1 (0.1)	0 (0.0)
Hypertension	1 (0.7)	0 (0.0)	0 (0.0)
Varicose ulceration	1 (0.7)	0 (0.0)	0 (0.0)
Varicose vein	1 (0.7)	0 (0.0)	1 (0.1)

Table 4.5-12 original ISS.

As seen in these tables, the number of vascular disorders was small and there did not seem to be a difference in risk among groups in the controlled studies. Overall, there seemed to be a dose response in terms of vascular events among fingolimod 1.25 and 0.5 mg in safety Pool E.

The two cases of peripheral arterial occlusion are described in detail below.

- **2302_0330_00005 - Peripheral arterial occlusive disease**

41 y.o. female. MS diagnosed 24 years prior to study entry. No treatment with other immuno suppressors prior to entry. Concomitant meds included carbamazepine (started 38 days prior to entry for brainstem paroxysms). She was not taking other concomitant medications. On **Day 7** of FTY 1.25 mg she had pain in the left hand. Fingertips were blue but not cold. The following morning there were splinter hemorrhages in all fingernails of L hand. This resolved within 2 days and patient remained asymptomatic. She was treated with ibuprofen for Raynaud's phenomenon. On Day 13 she awoke with a similar episode. On physical exam she had normal appearing left hand with symmetrical radial pulse and splinter hemorrhages. Drug was discontinued on Day 14. Laboratory findings on Day 15 showed no evidence of vasculitis, thrombosis or Thrombotic Thrombocytopenic Purpura (D dimer, fibrinogen, platelet count, ANA, ANCA, cardiolipin IgG, cardiolipin IgM, rheumatoid factor, C3c-complement, C4- complement, cryoglobulins, immunofixation and C reactive protein normal). The consulting rheumatologist suggested the diagnosis of a "non-specific collagenosis." Blood pressure was normal. No values for CBC including lymphocyte and platelet count were provided in the narrative or in the patient profile.

Two days after the last dose of the study medication, duplex ultrasound of the arteries of the left arm was normal. There was increased blood pressure to 165/85 mmHg (HR 80 bpm) for 30-60 minutes in relationship to emotional stress. Complete normalization was seen within 1 hour.

Eleven days after study drug discontinuation, the patient experienced worsening of the symptoms (increase in left hand pain and fingers getting blue and cold) and tramadol was added as treatment.

Two days later (13 days after drug dc) she presented to the emergency room with increasing pain. She had a livid and cold left hand and fingers with a decreased left radial pulse. An emergency Doppler-duplex scan showed evidence of left hand hypoperfusion clearly asymmetric compared with the right hand. Additionally, an emergency angiography (performed via the femoral artery) revealed the absence of distal perfusion of all lower arm and hand arteries in the left upper extremity. Ulnar and radial arteries were visible but with somewhat delayed outflow. There was no Doppler signal in the arterial arch of left hand. Arteries in the R hand appeared normal. The right radial pulse was detectable. The patient was hospitalized in the intensive care unit. An intra-arterial angiography catheter was placed and left in the brachial artery for monitoring and treatment. She was given

fibrinolytic therapy (intraarterial urokinase) and infusions of alprostadil (PG E1) and heparin. The following morning (14 days after drug dc), the distal pulse in her left upper extremity was absent and further empirical therapy was administered. The patient had an elevated blood pressure to a maximum of 190/115 mmHg between [REDACTED] (b) (6) measurement in femoral artery and right arm).

Fifteen days after drug dc, angiography showed a thrombus in the radial artery which was treated with intra-arterial fibrinolysis (rtPA bolus). Concomitant medication was given. Between [REDACTED] (b) (6) [REDACTED] (b) (6) progressive clinical improvement was seen. The patient's left hand was warm but with livid and blue fingertips (especially 2nd finger) and blisters on her fingertips. Her radial pulse was absent.

A follow up angiography showed the absence of representation of radial and ulnar artery with distal perfusion of the hand via the interosseus artery. The patient was discharged from the intensive care unit to the vascular surgery department.

24 days after drug dc, due to persistent pain and in order to improve distal perfusion, it was decided to implant a catheter for continuous anesthetic treatment in the left brachial plexus. Symptoms of MS relapse were reported to be resolved. 28 days after drug dc her hand appeared warm, with good color in most fingers but evidence of necrosis in 2nd and 5th left fingertips. The radial and ulnar pulses were absent.

The patient was discharged home with continuous analgesic and anesthetic therapy via catheter in the region of the left brachial plexus. Surgical sympathetic block of the left brachial plexus planned for beginning of May as analgesic therapy and in order to permanently improve distal perfusion in left upper extremity.

Two months after drug dc the patient experienced an MS relapse that improved after steroid treatment. Finger necrosis was reported to have decreased and the functionality of her hand had improved. The sympathetic blockade that was planned initially was not carried out.

Hypercoagulability workup showed mild hyperhomocysteinemia: 14.8 $\mu\text{mol/l}$ (nl <12) but otherwise was unremarkable. She had heterozygote polymorphism of the MTHFR 677T gene. Serum testing for antibody to β -2-glycoprotein 1 was negative. Specific platelet function/activation tests were not performed. Transesophageal echocardiography revealed no evidence for a cardiac embolism source. There was moderate reduced systolic function of the left ventricle and the cardiologist believed this to be of no clinical relevance and not related to the left forearm event.

She recovered with sequelae (left hand still felt cooler than right). No further occurrences of hypoperfusion or Raynaud symptoms have been observed since the SAE. After changing the therapy to interferon-beta, no further clinical relapses of MS were reported. The patient discontinued from the core phase of the study.

- **2302_0306_00011 - Peripheral artery disease**

MS diagnosed 17 years prior. History of optic neuritis, sinus tachycardia, migraines. Smoker until 1 year prior. Family history of cardiac disorders. She had no other vascular risk factors such as HTN or diabetes and was not taking hormones. Received IFN in the past. Concomitant meds: bisoprolol for sinus tachycardia for several years. On Day 130 she had nonserious migraine-like headache and was treated with naratriptan. On Day 140, she presented with peripheral arterial occlusion in both feet, with "necrosis and hemorrhages" under the nails in digit 3 and 4 of R foot and digit 5 of L foot. She had coldness of the skin and discoloration of toes. On Day 144 the 5 toe of L foot had a dark red

discoloration. Study drug was discontinued due to arterial occlusive disease on Day 145. Lesions looked like those seen with skin embolism.

A color coded Doppler sonography of the arteries of the right distal lower leg was performed and revealed a patent but narrow pedal dorsal artery with a spastic flow profile, a patent posterior tibial artery that could be traced down to the tarsal bones and a fibular artery that faded away on the distal lower leg. The popliteal artery was noted to be of normal caliber with a pronounced collateral in the first posterior branch (P1), the cause of which was not apparent. The patient was started on acetylsalicylic acid and clopidogrel.

Nine days after the discontinuation of the study medication, the blood flow disorders in the forefoot had markedly regressed and the investigator was able to palpate the dorsal pedal artery well on both sides again. The feet were less cold and the livid alterations and bleeding in the toes were noted to be regressing. There was no hypercoagulable state. The patient's condition was further improved at this visit, but was not completely resolved. The patient still had livid coloring (though better than the previous week) on digit I and V of the right foot and digit V on the left foot. The patient had no motor impairment and the arteries were palpable.

On (b) (6) a magnetic resonance angiography (MRA) of the arteries of both legs was performed and revealed no pathological findings. The event (arterial occlusive disease) resolved on (b) (6), 37 days after the last dose of the study medication.

In addition to these cases, a patient in study 2309 (2309 510-6) developed right leg vasospasm. The case is blinded.

Because of these events of arterial occlusive disease, the applicant was asked to submit brief narratives of cases suggestive of arterial ischemia/thrombosis in the renal transplant population. Review of these cases identified two cases of finger or toe necrosis, one in a patient receiving FTY 2.5 mg and one in a patient receiving MMF. Both were diabetic. The first patient had inadequate glycemic control during the study. On Day 197 post transplant/FTY treatment she presented necrosis of the right big toe requiring amputation. The second patient approximately 2 months into MMF treatment, developed ulceration and necrosis of the fingertips of both hands. Review of these cases did not provide any clue as to the potential mechanism of toe/finger ischemia in the MS population.

An increasing body of literature indicates that SIP has a role in the regulation of vascular tone and vascular permeability, raising the possibility that SIP receptor modulation by fingolimod might have some effects (favorable or deleterious) in the CV system. The number of serious ischemic/thrombotic events is too small to draw definitive conclusions. However, it suggests an increased risk of ischemic/thrombotic events with FTY 1.25 mg. This concern should be explored further, in pre- or postmarketing studies. The applicant proposes to explore the possibility of increased risk of cerebrovascular disease in a post-marketing registry (PASS). The potential increase of peripheral vascular disease could also be explored in such a study.

- SAES in the General disorders and administration site conditions

Interim review, 5 12 10.

Lourdes Villalba, M.D

NDA 22-527. Fingolimod

SAES in the General disorders and administration site conditions SOC are presented in the following table for Safety Pool D.

Table 27. Serious AE, General disorders and administration site conditions, safety pool D

Primary system organ class Preferred term	FTY720 5 mg (N=94) n (%)	FTY720 1.25 mg (N=943) n (%)	FTY720 0.5 mg (N=854) n (%)	Placebo (N=511) n (%)	Interferon (N=431) n (%)
General disorders and administration site conditions					
-Total	2 (2.1)	5 (0.5)	5 (0.6)	2 (0.4)	2 (0.5)
Chest pain	2 (2.1)	1 (0.1)	2 (0.2)	0 (0.0)	0 (0.0)
Fatigue	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Haemorrhagic cyst	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Multi-organ failure	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Pyrexia	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.2)
Inflammation	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Influenza like illness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Non-cardiac chest pain	0 (0.0)	0 (0.0)	2 (0.2)	2 (0.4)	0 (0.0)

Source: ISS Table 4.4-9. A patient with multiple occurrences of the same AE under one treatment is counted only once in the AE preferred term for that treatment. - A patient with different adverse events within a primary system organ class is counted only once in the total row.

Within the General disorders and administration site conditions, the only events that occurred in more than one patient were chest pain and non-cardiac chest pain.

There was no imbalance in the distribution of these cases and all were thought to be non-cardiac, and only one required drug discontinuation. However, some appear to have had incomplete work up to determine the etiology of the chest pain. Three cases occurred within the first few days of FTY treatment, in association with bradycardia, dizziness or increased blood pressure. Narratives of the cases in safety pool D are presented in Appendix 9.1.10.

Other events occurred in one patient only and were similarly distributed among groups. Of note, the patient listed as having multi-organ failure was the patient who died of disseminated herpes infection.

The analysis in Pool E was consistent with the analysis in pool D(data not shown).

- SAEs reported in the Hepatobiliary disorders SOC

SAES in the Hepatobiliary disorders SOC are shown in the following tables for Safety Pool D and E.

Table 28. Serious AE, Hepatobiliary disorders SOC, safety pool D.

Primary system organ class Preferred term	FTY720 5 mg (N=94) n (%)	FTY720 1.25 mg (N=943) n (%)	FTY720 0.5 mg (N=854) n (%)	Placebo (N=511) n (%)	Interferon (N=431) n (%)
Hepatobiliary disorders					
-Total	0 (0.0)	2 (0.2)	4 (0.5)	1 (0.2)	1 (0.2)
Biliary colic	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)
Cholelithiasis	0 (0.0)	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.2)
Jaundice	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Cholecystitis acute	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Cytolytic hepatitis	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Hepatic steatosis	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Hepatomegaly	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)

Source: Post Table 4.4-9, ISS. All three placebo controlled studies. A patient with multiple occurrences of the same AE under one treatment is counted only once in the AE preferred term for that treatment. A patient with different adverse events within a primary system organ class is counted only once in the total row.

Table 29. Serious AE, Hepatobiliary disorders SOC, safety pool E.

Primary system organ class Preferred term	FTY720 5 mg - 1.25 mg (N=137) n (%)	FTY720 1.25 mg (N=1157) n (%)	FTY720 0.5 mg (N=1021) n (%)
Hepatobiliary disorders			
-Total	0 (0.0)	5 (0.4)	5 (0.5)
Biliary colic	0 (0.0)	2 (0.2)	2 (0.2)
Cholelithiasis	0 (0.0)	2 (0.2)	2 (0.2)
Hepatitis	0 (0.0)	1 (0.1)	0 (0.0)
Jaundice	0 (0.0)	1 (0.1)	0 (0.0)
Cholecystitis acute	0 (0.0)	0 (0.0)	1 (0.1)
Cytolytic hepatitis	0 (0.0)	0 (0.0)	1 (0.1)
Hepatic steatosis	0 (0.0)	0 (0.0)	1 (0.1)
Hepatomegaly	0 (0.0)	0 (0.0)	1 (0.1)

Source Table 4.5-12 original ISS.

The most common serious events in this SOC were cholelithiasis and biliary colic in the FTY treatment groups. One episode of cholelithiasis was accompanied by jaundice (2201_0023_00003, 52 year old male). None of the cases led to drug discontinuation. Review of these cases does not suggest that the events are drug related. Other than cholelithiasis and biliary colic, there was one case of cytolytic hepatitis/esteatosis/ hepatosplenomegaly (ID# 2301.0109-00002) and one “hepatitis toxic” (2201 0002_0001) in subjects receiving fingolimod in the controlled studies, and one case coded as “hepatitis” in the extension studies (E12201_0061_00011).

Additionally, 8 subjects presented liver-related SAEs in the Investigations SOC (5 on FTY 1.25, 2 on FTY 0.5 and one on placebo). Most SAE of liver-related investigations led to study drug discontinuation. On the other hand, there were many liver-related events that led to study

discontinuation but were not coded as serious (these are discussed in the Discontinuation due to AE section).

The number of patients with SAE in the Hepatobiliary disorders SOC and Investigations SOC in the controlled studies is presented as follows.

Table 30. Patients with SAE in Hepatobiliary and Investigations (liver-related) SOCs, safety pool D

MedDRA SOC	FTY 5 mg N=94	FTY 1.25 N= 943	FTY 0.5 N= 854	Placebo N= 511	IFN N= 431
	n (%)	n (%)	n (%)	n (%)	n (%)
Total	0	7 (0.7)	5 (0.5)	1 (0.2)	1 (0.2)
Hepatobiliary	-	2	4	-	1
Investigations ¹	-	5	2	1	-

Source: AE datasets. ¹Investigations include: liver function test abnormal, ALT increased, GGT increased, AST increased and hepatic enzyme increased.

This analysis suggests a increased risk of liver-related SAES in the FTY treatment groups as compared to placebo, but the numbers are small.

Review of the available narratives indicated that except for 1 case, bilirubin (BR) and alkaline phosphatase (ALK P) were within normal values. This case is presented as follows. Additional narratives are presented in Appendix 9.1.10.

- 2301_0109_00002. 41 F.** Cytolytic hepatitis on Day 301. Led to dc. On FTY 0.5 mg. Concomitant use of iv paracetamol.
 Medical hx of depression, elevated GGT for one year, taking multiple concomitant meds. On Day 203 of FTY 0.5 mg she was admitted to hospital for a few days with vomiting, syncope and elevated liver enzymes (GGT was 4x ULN and AST 2x ULN). She was diagnosed with anorexia, depression, exacerbation of consumption of alcoholic drinks and stable MS. On Day 298 of FTY 0.5 mg treatment, she was hospitalized with MS relapse and pain on L hip. On admission AST was 121 U/L (nl <37), and ALT was 101 U/L (nl <40). BR was 0.57 mg/dl (nl 0.2-1.0). Patient was treated with IV paracetamol for 3 days. On Day 301 the patient had an abrupt elevation in liver enzymes with AST was 9580 U/L ALT was 4332 U/L, GGT was 160 U/L (reference range: 5 – 36), and AP (alkaline phosphatase) 123 U/L (reference range: 5 – 36). Total bilirubin was not reported. Study medication was permanently discontinued on Day 304 due to the event. Hepatitis serology was negative. Negative HSV and EVB IgM serology. An abdominal US on Day 304 showed moderate hepatomegaly and steatosis. Discharge diagnosis was hepatomegaly and steatosis and episode of “acute hepatic cytolysis of undetermined origin”. This patient had pre-existent elevated liver enzymes (AST>ALT), and suspected alcohol abuse. She received intravenous and oral paracetamol (up to 4 g i.v. on the second day of admission). These two factors (alcohol abuse and paracetamol use) may explain the dramatic increase in liver enzymes and hepatic steatosis, although the role of FTY in the underlying liver enzyme elevation can not be ruled out.

In the extension studies in the original ISS, one case of hepatitis, one biliary cholic and two cases of cholelithiasis were reported as SAEs in the Hepatobiliary system disorders SOC. Only one subject reported a serious liver-related event in the Investigations SOC in the extension studies in the original ISS (hepatic enzyme increased, that did not lead to drug dc). The case of hepatitis is as follows.

- **2201E_0061_00011.** 23 F. Hepatitis on Day 179.

Concomitant medication taken prior to randomization included alprazolam, gabapentin and omeprazole for 2 months prior to study entry. On Day 153 started oxybutinin for urinary incontinence. On Day 179 of FTY treatment (day 1 of extension study) she had elevated transaminases with normal BR and ALK Phos (ALT 250 U/L, AST 147 U/L, bilirubin 3.4 µmol/L (normal up to 20.5) and Alkaline Phosphatase 41 U/L. She was subsequently diagnosed with hepatitis. Oxybutinin was stopped on Day 189. No treatment was reported to be given for this event. On Day 207, there was further increase of liver enzymes with ALT of 644 U/L, AST 288 U/L, bilirubin 5.1 µmol/L and alkaline phosphatase 45 U/L. The study medication was permanently discontinued due to the event (hepatitis) and the patient received the last dose of the study medication on Day 213, extension Day 35. The last available laboratory showed ALT 45 and AST 35 U/L, respectively.

Review of liver related SAE indicates a relationship between the use of fingolimod and liver enzyme elevation, mostly transaminase and GGT elevation, with normal BR and alkaline phosphatase. Patients were asymptomatic and the diagnosis was made during protocol scheduled laboratory examinations, as early as 2-3 weeks into the study (mean 162 days, range 19 to 301 days in the FTY group; the case on placebo was diagnosed on day 540). Several cases were confounded by the use of concomitant medications that may have caused hepatotoxicity, such as paracetamol or other analgesics. However, all cases improved and most fully resolved after fingolimod discontinuation (10 days to 3 months after dc). One patient who was on FTY received intravenous paracetamol and developed ALT > 4000. There was at least one clean case with FTY 0.5 mg where there was no use of concomitant medications (2302_0330_00004).

On 4/29/10, an IND report of a patient who developed ALT >20x ULN and jaundice while receiving fingolimod was submitted to the FDA. The case is under review.

- SAE in Blood and lymphatic system disorders SOC in Safety pools D and E

There were few serious events in the Blood and lymphatic system disorders SOC. The most common event was lymphopenia, although there were two serious cases of thrombocytopenia with fingolimod (one thrombocytopenia at the 0.5 mg dose during the controlled studies and one autoimmune thrombocytopenia at the 1.25 mg dose during the extension studies). SAES in this SOC are shown in the following tables.

Table 31. Serious AE, Blood and Lymphatic system disorders SOC, safety pool D

Primary system organ class Preferred term	FTY720 5 mg (N=94)	FTY720 1.25 mg (N=943)	FTY720 0.5 mg (N=854)	Placebo (N=511)	Interferon (N=431)
	n (%)	n (%)	n (%)	n (%)	n (%)
Blood and lymphatic system disorders					
-Total	0 (0.0)	3 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)
Lymphopenia	0 (0.0)	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Leukopenia	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Thrombocytopenia	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)

Source: Post Table 4.4-9, ISS. All three placebo controlled studies. A patient with multiple occurrences of the same AE under one treatment is counted only once in the AE preferred term for that treatment. A patient with different adverse events within a primary system organ class is counted only once in the total row.

Three cases of Lymphopenia on FTY 1.25 and one thrombocytopenia on FTY 0.5 were reported in the controlled studies. The narrative of the case of thrombocytopenia is as follows. Listing of the cases of lymphopenia are in Appendix 9.1.11.

- 2301_0501_00005.** 45 M. Thrombocytopenia on Day 122. Led to dc. (On FTY 0.5 mg in pool D)
 On Day 97 of FTY 0.5 mg, laboratory showed platelet count = 85,000/ul. He was receiving gabapentin and pregabalin for neuropathic pain. Patient advised to discontinue these antiepileptic drugs and retest in 3 weeks. Repeat testing on Day 122 confirmed platelet count= 64,000/ ul. Pt hospitalized. Bone marrow biopsy on Day 122 showed slight reduction of cellularity and normal levels of megakaryocytes with hypolobulated nuclei. Antiplatelet antibodies were negative. Serum protein electrophoresis was within normal. US of spleen was normal. Fingolimod was discontinued on Day 122 due to this event. Repeat test 18 days after the last dose, platelet = 56,000/ul, without evidence of bleeding. He was treated with i.v. immunoglobulin therapy x 5 days. Platelet count was follow regularly at the local lab, the lowest count was 53,000 (48 days after drug discontinuation). The latest platelet count was 160,000 2 months after drug discontinuation. Follow up 9 ½ months after drug discont: platelet count remained 88-105,000, without bleeding. The patient continues to get iv immunoglobulin. Bone marrow biopsy showed “bone marrow with a low degree of cellularity reduction” with “megakaryocytes at the upper limit of normal” Spleen was normal. No autoantibodies detected.

This AE was temporarily related to initiation of FTY therapy but the patient did not fully recovered 9 months after drug discontinuation. The role of FTY in development of thrombocytopenia is unlikely but can not be ruled out. Gabapentin and pregabalin may have also played some role in this case.

Table 32. Serious AEs, Blood and Lymphatic disorders SOC, safety pool E

Primary system organ class Preferred term	FTY720 5 mg - 1.25 mg (N=137) n (%)	FTY720 1.25 mg (N=1157) n (%)	FTY720 0.5 mg (N=1021) n (%)
-Any primary system organ class			
-Total	36 (26.3)	146 (12.6)	99 (9.7)
Blood and lymphatic system disorders			
-Total	1 (0.7)	5 (0.4)	3 (0.3)
Lymphopenia	0 (0.0)	4 (0.3)	0 (0.0)
Autoimmune thrombocytopenia	0 (0.0)	1 (0.1)	0 (0.0)
Leukopenia	0 (0.0)	1 (0.1)	1 (0.1)
Lymphadenopathy	0 (0.0)	0 (0.0)	1 (0.1)
Neutropenia	1 (0.7)	0 (0.0)	0 (0.0)
Thrombocytopenia	0 (0.0)	0 (0.0)	1 (0.1)

Source Table 4.5-12 original ISS.

The case of SAE of autoimmune thrombocytopenic purpura in the extension studies is as follows.

- **2302E1-0316-00010.** FTY 1.25 mg . 44 F Idiopathic thrombocytopenic purpura on Day 181 of FTY treatment. Received IFN during core study. MS dx 10 years prior to randomization. Hx of hyperthyroidism and menopause, taking levothyroxine and estrogens. Druing screening platelet count was $236 \times 10^9/L$. On day 487 it was $209 \times 10^9/L$. On day 181 of FTY treatment platelet count was $4 \times 10^9/L$. An hematologist diagnosed ITP. Drug was discontinued and patient was treated with steroids. At the time of last reporting, 5 months after drug dc the patient was considered completely recovered from ITP.

Listings of other SAE in the Blood and lymphatic system disorders SOC are in Appendix 9.1.11.

Of note, in the renal transplant database, there were two events of autoimmune hemolytic anemia, seven of hemolytic uremic syndrome and 3 of thrombotic microangiopathy in the FTY treatment group, with no such cases in the MMF treated group. Findings in the renal program can not be extrapolated to the MS program, but raise concerns about additional hematologic fingolimod effects other than “redistribution of lymphocytes.” No hematologic concerning events such as those observed in the renal transplant program were observed in the MS program. However, two SAE of thrombocytopenia were reported with FTY (one in the controlled period with FTY 0.5 and one in the extension studies with FTY 1.25).

7.3.3 Adverse Events leading to study drug discontinuation

235 subjects discontinued drug because of AEs in safety pool D (10.6% of subjects on FTY 5; 11.9% of FTY 1.25; 7% of FTY 0.5; 7% of placebo and 2.9% of IFN treated subjects). Overall, the risk of AE leading to study drug discontinuation was higher in the FTY 1.25 group as compared to placebo, FTY 0.5 and interferon. The difference was driven by AE in the Investigations (mostly liver-related investigations), Cardiac, and Eye disorders SOC, which were the most common events leading to drug discontinuation. There was a dose response between FTY 1.25 and FTY 0.5 in these three SOC.

The number of patients with adverse events that led to study drug discontinuation in pool D are presented in the following table, by SOC, for those events that occurred in at least 2 patients in at least one treatment group.

Table 33. Patients with AE leading to drug discontinuation in fingolimod MS studies, safety pool D*

System organ class Preferred term	FTY 1.25 (N=943) n (%)	FTY 0.5 (N=854) n (%)	Placebo (N=511) n (%)	Interferon (N=431) n (%)
Any AE leading to study drug discontinuation	112 (11.9)	60 (7.0)	36 (7.0)	17 (3.9)
Investigations	47 (5.0)	30 (3.5)	7 (1.4)	9 (2.1)
ALT increased	21 (2.2)	16 (1.9)	3 (0.6)	3 (0.7)
Hepatic enzyme increased	8 (0.8)	7 (0.8)	0 (0.0)	2 (0.5)
AST increased	5 (0.5)	6 (0.7)	1 (0.2)	1 (0.2)
GGT increased	5 (0.5)	9 (1.1)	1 (0.2)	0 (0.0)
Transaminases increased	5 (0.5)	1 (0.1)	0 (0.0)	0 (0.0)
DLCO decreased	4 (0.4)	0 (0.0)	2 (0.4)	2 (0.5)
Liver function test abnormal	4 (0.4)	0 (0.0)	0 (0.0)	2 (0.5)
Blood ALK P increased	1 (0.1)	2 (0.2)	0 (0.0)	0 (0.0)
Eye Disorders	15 (1.6)	2 (0.2)	2 (0.4)	1 (0.2)
Macular edema	10 (1.1)	1 (0.1)	0 (0.0)	1 (0.2)
Cardiac disorders	12 (1.3)	1 (0.1)	2 (0.4)	1 (0.2)
Bradycardia	5 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
AV block 2nd degree	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
AV 1 st degree	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9 (1.0)	8 (0.9)	9 (1.8)	1 (0.2)
Basal cell carcinoma	3 (0.3)	3 (0.4)	2 (0.4)	0 (0.0)
Breast cancer	3 (0.3)	1 (0.1)	3 (0.6)	0 (0.0)
Malignant melanoma	1 (0.1)	2 (0.2)	1 (0.2)	0 (0.0)
Infections and infestations	7 (0.7)	2 (0.2)	2 (0.4)	1 (0.2)
General disorders and administration site conditions	6 (0.6)	1 (0.1)	5 (1.0)	0 (0.0)

System organ class Preferred term	FTY 1.25 (N=943) n (%)	FTY 0.5 (N=854) n (%)	Placebo (N=511) n (%)	Interferon (N=431) n (%)
Fatigue	2 (0.2)	0 (0.0)	2 (0.4)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	5 (0.5)	2 (0.2)	2 (0.4)	0 (0.0)
Dyspnea	3 (0.3)	1 (0.1)	2 (0.4)	0 (0.0)
Nervous system disorders	4 (0.4)	3 (0.4)	6 (1.2)	1 (0.2)
Dizziness	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Multiple sclerosis relapse	0 (0.0)	1 (0.1)	2 (0.4)	0 (0.0)
Psychiatric disorders	3 (0.3)	1 (0.1)	2 (0.4)	2 (0.5)
Depression	2 (0.2)	1 (0.1)	0 (0.0)	1 (0.2)
Vascular disorders	3 (0.3)	1 (0.1)	1 (0.2)	0 (0.0)
Gastrointestinal disorders	3 (0.3)	3 (0.4)	3 (0.6)	0 (0.0)
Dyspepsia	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	1 (0.1)	1 (0.1)	2 (0.4)	0 (0.0)
Skin and subcutaneous tissue disorders	2 (0.2)	3 (0.4)	1 (0.2)	0 (0.0)
Dermatitis allergic	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	2 (0.2)	3 (0.4)	0 (0.0)	1 (0.2)
Myalgia	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)
Blood and lymphatic system disorders	2 (0.2)	3 (0.4)	0 (0.0)	0 (0.0)
Thrombocytopenia	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)
Metabolism and nutrition	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

Source: ISS Post table 4.4-10 (*only those in two or more subjects in any group) -Primary SOC's are sorted descending frequency for the FTY720 1.25 mg group. A patient with multiple AEs within a primary SOC may be counted under more than one preferred term but is counted only once in the Total row. A patient with multiple occurrences of an AE under one treatment group is counted only once in the AE preferred term for that treatment group.

The safety profile of fingolimod in safety pool E (which included the double blind and open label extensions, which included some exposure up to 5 ½ years in study 2201E1 and up to 4 years in study 2302E1) was consistent with that of the core studies. There was a mild increase in the overall risk of discontinuations with longer exposure.

Patients with AE leading to discontinuation in safety pool E (original ISS) are presented as follows, for those events that occurred in at least 2 patients in at least one treatment group in descending order of frequency.

Table 34. Patients with AE leading to study drug discontinuation in fingolimod by SOC, safety pool E*

System organ class Preferred term	FTY 1.25 N=1157 n(%)	FTY 0.5 N=1021 n (%)
Any AE leading to drug discontinuation	169 (14.6)	84 (8.2)
Investigations	61 (5.3)	42 (4.1)
Eye disorders	21 (1.8)	3 (0.3)
Cardiac disorders	19 (1.6)	1 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	12 (1.0)	10 (1.0)
Infections and infestations	11 (1.0)	4 (0.4)
Nervous system disorders	7 (0.6)	4 (0.4)
Gastrointestinal disorders	5 (0.4)	4 (0.4)
Hepatobiliary disorders	5 (0.4)	2 (0.2)
Metabolism and nutrition disorders	4 (0.3)	0
Vascular disorders	4 (0.3)	2 (0.2)
Psychiatric disorders	3 (0.3)	1 (0.1)
Skin and subcutaneous tissue disorders	3 (0.3)	3 (0.3)
Musculoskeletal and connective tissue disorders	2 (0.2)	3 (0.3)

Source: Post text Table 4.5-13, original ISS. * At least 2 patients in any treatment group). Primary SOC's are sorted descending frequency for the FTY720 1.25 mg group. A patient with multiple AEs within a primary SOC is counted only once in the total row. A patient with multiple occurrences of an AE under one treatment group is counted only once in the AE preferred term for that treatment group.

Analyses patients with AE events leading to drug discontinuation for selected SOC's are discussed as follows, in descending order of frequency in the controlled population.

- AE leading to drug discontinuation in the Investigations SOC

The SOC that led to most study drug discontinuations was the Investigations SOC (5.0% of subjects receiving FTY 1.25 mg group, 3.5% of those receiving FTY 0.5 mg, 1.4% of those on placebo and 2.1% of those on IFN). Discontinuations in this SOC were mostly due to liver related tests, lymphopenia, respiratory-related investigations and cardiac related investigations. These events will be discussed under their organ-related SOC.

- AE leading to drug dc in the Hepatobiliary system disorders SOC and Investigations (liver related terms)

Eighty five subjects discontinued drug treatment because of either hepatobiliary disorders (n= 7) or liver related Investigations (n=78). Altogether, 43 pts in FTY 1.25; 31 in FTY 0.5; 4 on placebo; 7 on IFN discontinue drug because of hepatobiliary or liver related investigations AEs. This analysis is shown in the following table:

Table 35. Patients who discontinued due to hepatobiliary SOC and liver related investigations in fingolimod controlled studies

	FTY 1.25 N= 943	FTY 0.5 N=854	Placebo N=511	IFN N=431
	n (%)	n (%)	n (%)	n (%)
Total number of patients	43 (4.6%)	31 (3.6)	4 (0.8)	7 (1.6)
Hepatobiliary disorders SOC	4 (0.4)	2 (0.2)	1 (0.2)	0
Liver-related investigations ¹	39 (4.1)	29 (3.4)	3 (0.6)	7 (1.6)

Source: AE datasets submitted 12 18 09. n= patients with events. ¹ Liver-related investigations include the following preferred terms (PT): ALT increased, AST increased, GGT increased, transaminases increased, blood Alkaline phosphatase increased, blood bilirubin increased, hepatic enzymes increased, hepatic enzyme abnormal.

There is a clear signal for liver toxicity, with a dose response between FTY 1.25 and FTY 0.5 mg.

Liver related AEs that were serious and led to drug discontinuation were described earlier in this review. Seventy four subjects had liver-related AE leading to drug dc that were coded as non serious in the controlled database. In addition to these subjects, some subjects who presented liver enzyme elevation at the end of the core study evaluation, did not appear in the dataset as leading to drug discontinuation, however, they did not enter the extension studies.

I reviewed the narratives of all events that led to study discontinuation in the controlled studies. Overall, most of these non-serious events were associated with increases in ALT or GGT elevation 3 to 5x ULN, without associated increase in BR or alkaline phosphatase and resolved two weeks to several months after drug discontinuation, however, some cases were associated with markedly abnormal ALT elevation (>5x ULN) and some cases had not fully resolved at the time of last testing after drug dc.

Many events were confounded by concomitant use of other medications that are known to induce liver toxicity such as paracetamol or other analgesics, or had a baseline ALT or GGT that was already above normal. However, even in those cases, there was improvement in transaminase values after fingolimod discontinuation (positive de-challenge). In several cases liver enzyme elevation led to drug interruption but recurred when the drug was re-started (positive re-challenge).

Selected cases of non-serious AE of elevated liver enzymes leading to drug dc are summarized as follows:

Interim review, 5 12 10.
 Lourdes Villalba, M.D
 NDA 22-527. Fingolimod

Brief narratives of selected non-serious AE leading to drug discontinuations in the Hepatobiliary SOC and Investigations SOC (hepatobiliary HLGT), in the controlled studies (Pool D).

FTY 1.25 mg
2301_0606_00014. 53 F. ALT increased on Day 83. History of hyperlipidemia and anemia, treated with rosuvastatin and pyridoxine. ALT up to 248 U/L (nl up to 45 U/L), AST 227 (nl up to 41 U/L) and GGT 164 (nl up to 66 U/L), with normal BR and ALK Phosphatase. Resolved 50 days after drug dc.
2301_0657_00012. 39 M. GGT increased on Day 13. During study received paracetamol for headaches. On Day 13 GGT was 75 U/L; on Day 27 ALT was 103 U/L (nl up to 45) and GGT was 160 (nl up to 66). Drug was discontinued. Seven days after drug DC ALT was 100; ALT 43; GGT was 298 U/L (almost 5xULN) and BR was 42 µmol/L (nl up to 21), with normal ALK P. Liver enzymes and BR were still elevated 35 days after drug dc. Liver enzymes resolved on Day 118, although GGT persisted elevated <2xULN.
2301_0701_00007. 27 M. ALT increased on Day 81. On day 15, mild increase in GGT. Progressive increase in liver enzymes up to Day 278, when ALT was 230 U/L (>5xULN), AST 90 U/L and GGT 208 U/L (nl up to 65). He received amoxicillin during the study. Liver enzymes decreased 6 days after study drug dc. At last evaluation still mild ALT elevation (61 U/L). BR and ALK phosphatase remained normal.
2301_0752_00001. 31 M. ALT increased day 29. He had mild ALT elevation at screening (ALT=61, nl up to 45 U/L); On day 29 ALT was 434 (9xULN); AST 192 (nl up to 41 U/L). BR and ALK phosp were normal. Liver enzyme elevation resolved 60 days after drug dc.
2301_0758_00001. 40 M. Transaminase increased on day 24: ALT 222 U/L (>5xULN) with AST 2x ULN and GGT 3x ULN. Enzymes continued to increase up to ALT 293; AST 121 & GGT 296 on day 26, with normal BR and ALK P. Resolved 3 months after drug dc.
2302_0215_00001. 35 M. Transaminase increased on day 15. Normal liver enzymes at screening. On Day 15 ALT 251 U/L, AST 96 U/L GGT 178 U/L. BR and ALK normal. Drug discontinued. At last follow up 10 days after last dose, ALT was still 158 U/L and GGT was 193 U/L.
2302_0426_00005. 40 M. Transaminases and BR increased on Day 74. Medical hx of Gilbert's syndrome, optic neuritis, abnormal CT scan. During study he received paracetamol for myalgia and back pain. Screening ALT was normal, but there was mild increase in GGT (76 U/L), and BR was 36 µmol/L (nl 2-21). On Day 17 ALT was 96 U/L, GGT was 356 U/L (>5xULN) and BR was 45. Drug dc on Day 131. BR and ALK P were normal. ALT normalized while GGT was still mildly elevated 46 days after last dose of study drug.
FTY 0.5 mg
2302_0322_00006. 28 F. Isolated Hyper BR on Day 92. History of tension headache treated with paracetamol. At screening total BR was 17 (nl up to 21 µmol/L). On Day 92 total BR was 33. ALT, AST and ALK P were normal. Drug was discontinued. Last dose of study drug was Day 111. Five days later, BR was 21. She discontinued from the study.
2301_0701_00031. 18 M. Hyper BR on day 458. History of acne treated with nicotinamide, clindamycin and isotretinoin. ALT a screening was 68 U/L (nl up to 41), but at month 2 it was 28 U/L. Other medications prior to randomization included "phospholipids and protective diet for prophylaxis of liver parameters dysfunction." During the study he also received amoxicillin clavulanate for eczema. On Day 458 he had hyperbilirubinemia (BR 35 U/L). On the same day ALT was 67 U/L. Drug was discontinued due to the event (last dose Day 461). On day 472, BR had decreased to 21 and the event was considered resolved.
2301_0701_00039. 39 F. ALT increased 11x ULN on Day 360 Concomitant meds prior to randomization included betahistine, pentoxifylline and oral contraceptive. During the study she also received acetylcysteine, amoxicillin for bronchitis, paracetamol for pain. Patient reported arthralgia on Day 354. On day 360 she was noted to have increased ALT (11x ULN and AST >5x ULN (<i>before paracetamol</i>). She received paracetamol (1x 0.5g) on Day 361. Drug was discontinued because of

Interim review, 5 12 10.
 Lourdes Villalba, M.D
 NDA 22-527. Fingolimod

elevated liver enzymes on Day 362. Eleven days after drug discontinuation liver enzymes were down to normal. BR was normal at all times. See labs below.

Selected Laboratory Values (Blood Chemistry)

Visit, Visit Date (Days since first dose)	ALT (NR 0-45 U/L)	AST (NR 0-41 U/L)	GGT (NR 2-65 U/L)	Total Bilirubin (NR 2-21 µmol/L)	Alkaline Phos (NR 30-125 U/L)	Creatinine (NR 44-80 µmol/L)
Screening						
(b) (6)	18	20	10	8	48	76
Month 12						
(b) (6)	522	225	87	12	128	74
Day (360)						

Selected Laboratory Values (Blood Chemistry) after the study drug discontinuation

(b) (6)						
(2 days since study drug discontinuation)	249	85	86	7	119	75
Follow-up						
(b) (6)						
(97 days since study drug discontinuation)	19	23	10	11	47	85

Apparently only one dose of paracetamol 500mg was given, and the increased ALT preceded the single dose of paracetamol.

2301 0702 000011. 35 F. ALT increased on Day 541. During the study she received ranitidine and omeprazole, thiamine, cyanocobalamin, magnesium aspartic acid, and betahistidine, asparigines, hydroxyzine, zolpidem . On Day 541 she was noted to have increased ALT $\geq 7 \times \text{ULN}$. The study medication was discontinued due to this event. Last dose was on Day 543. On follow up 88 days after drug discontinuation ALT was almost normal. ALT normalized 181 days after last dose. BR remained normal throughout the study.

Selected Laboratory Values (Blood Chemistry)

Visit, Visit Date (Days since first dose)	ALT (NR 0-45 U/L)	AST (NR 0-41 U/L)	GGT (NR 2-65 U/L)	Total Bilirubin (NR 2-21 µmol/L)	Alkaline Phos (NR 30-125 U/L)	Creatinine (NR 44-80 µmol/L)
Screening						
(b) (6)	17	19	14	11	48	54
(b) (6)	81	35	29	9	35	56
(Day 450)						
Month 18	326	174	27	12	32	55

Selected Laboratory Values (Blood Chemistry) after the study drug discontinuation

Unscheduled						
(b) (6)						
(5 days since study drug discontinuation)	282	94	27	12	37	49
(b) (6)						
(97 days since study drug discontinuation)	26	21	20	11	38	55

2301-0852 00007. 40 M. Hepatic enzymes increased on Day 261.

History of headache and insomnia. Concomitant meds included codeine phosphate guaifenesin. During the study, the patient received carnitine,

Interim review, 5 12 10.
 Lourdes Villalba, M.D
 NDA 22-527. Fingolimod

<p>magnesium, vitamins and mineral supplement for nutrition supplement, levocarnitine and magnesium for diet supplement, ciclopirox for sealing redness of face and scalp and acetanilide-ascorbic acid-pheniramine maleate-phenylephrine hydrochloride (Neocitran) and paracetamol for common cold. On Day 261 was noted to have increased hepatic enzyme with ALT >6x ULN, AST >2 ULN. Drug was discontinued on Day 264 due to this event. Liver enzymes were back to normal 36 days after drug dc. BR and Alk phosp remained normal.</p>
<p>2302_0202_00006. 37 F. ALT, AST and GGT elevation on Day 195 Medical hx of headaches, urinary tract infections, esophagitis, insomnia. Smoker. During the study she received lorazepam, zolpidem and amitriptylin and nimesulide. On Day 93 ALT was 63 U/L. On Day 195 ALT was 382 (>8xULN) AST was 178 (>4xULN) and GGT was >4 ULN. BR was 7 µmol/L and ALK P was <2xULN. Drug was dc. Liver enzymes were normal 64 days after drug dc.</p>
<p>2302_0308_00003, 21 M. Hepatic enzyme increase days 14 and 72 No significant hx. Normal enzymes at entry. On Day 14, ALT was 88 U/L, AST was 54 U/L. On Day 71 ALT was 269 U/L (>5xULN) and AST was 161 U/L, GGT was 5xULN. Drug was dc. The event resolved 127 days after drug dc. Total BR remained below 10 during the study.</p>
<p>2302_0327_00001. 34M. Hepatic enzymes increased on Day 36 Liver enzymes at baseline were normal. On Day 36 ALT was 65 U/L (nl up to 45). On Day 84 ALT was 172 U/L, GGT was 164 (nl up to 65). BR remained <8µmol/L. Drug was discontinued. ALT and GGT normalized 59 days after drug dc.</p>

- Discontinuations due to hepatobiliary disorders and Investigations (liver-related) SOC in the extension studies

The number of patients with AE leading to study drug discontinuation in safety pool E (UPDATED) is presented as follows.

Table 36. Patients with liver-related investigations AE leading to drug discontinuation in pool E (SUR)

	FTY 1.25	FTY 0.5
	N= 1302 n%	N= 1176 n%
Total unique patients	54 (4.2)	40 (3.4)
ALT increased	25 (1.9)	20 (1.7)
Hepatic enzyme increased	15 (1.2)	13 (1.1)
AST increased	6 (0.5)	6 (0.5)
GGT increased	7 (0.5)	10 (0.9)
Transaminases increased	7 (0.5)	2 (0.2)
Liver function test abnormal	4 (0.3)	0 (0.0)
Blood alkaline phosphatase increased	1 (0.1)	2 (0.2)
Blood bilirubin increased	0 (0.0)	2 (0.2)

n= number of patients with event. Source: n for individual preferred terms is from SUR Table 4.5-13. Total number of unique patients is from the SUR AE dataset. Include events in the Investigations SOC, Hepatobiliary investigations HLGT.

Narratives for all cases that led to study discontinuation for a liver-related event in the extension studies were not submitted in the initial application. They were submitted on 4 2 10 at the FDA request. Review is still ongoing but cases are consistent with pattern observed in controlled studies, with increases in ALT and GGT, without increases in BR and ALK phosphatase and reversible within weeks to several months after drug dc. One additional case of ALT elevation and jaundice leading to study drug discontinuation has been recently submitted.

- AE leading to drug dc in the Eye disorders SOC

A total of 20 subjects had AE that led to drug dc in the Eye disorders SOC in the fingolimod controlled studies. Some of them were coded as serious and already described in the SAE section of this review, but some events of interest such as a case of bilateral retinal ischemia/vasculitis were coded as non serious.

Table 37. AE leading to drug discontinuation, Eye disorders SOC, safety pool D

PT	FTY 1.25 N= 943	FTY 0.5 N=854	Placebo N=511	IFN N=431
	n (%)	n (%)	n (%)	n (%)
Total	15 (1.6)	2 (0.2)	2 (0.4)	1 (0.2)
Ischemic retinopathy	1	-	-	-
Macular edema	10	1	0	1
Retinitis	1	-	-	-
Detachment of retinal pigment	-	1	-	-
Papilledema	1	-	-	-
Retinal disorder	1	-	-	-
Eyelide edema	1	-	-	-
Iridocyclitis	-	-	1	-

Keratitis	-	-	1	-
Conjunctivitis	-	-	1	-

Source: Post text Table 4.4-10. ISS.. n= number of patients with events

Non-serious cases leading to discontinuation in this SOC in the controlled studies included eight cases of macular edema in the FTY 1.25 mg group, one in the FTY 0.5 mg group and one in a subject receiving IFN therapy.

The subject with non-serious macular edema in the IFN group was a 22 year old female diagnosed by dilated ophthalmoscopy on day 37 of study treatment. The case was not confirmed by OCT and by the DSMB ophthalmologist.

The case of non-serious macular edema in the FTY 0.5 mg treatment group in the controlled studies is as follows.

- **2302 0408 00005**, 53 F, Macular edema. Day 367. Did not recover. *(in dataset coded as non-serious, not leading to discontinuation, as per narrative, led to drug dc)*
 No history of eye problems. MS diagnosed 5 yrs prior. 2 relapse during previous 2 years. Previous treatment: glatiramer, IFN beta 1b and beta 1a. History of HTN. On Day 367 of FTY 0.5 mg, OTC showed macular edema. She did not have any symptoms but on examination had mild visual acuity loss in the right eye. The ophthalmologist reported bleeding surrounding the upper temporal vein and venous thrombosis of upper temp. vein in R eye, with macular edema. On Day 374, FA showed moderated macular edema in R eye. The patient discontinued drug due to macular edema on Day 375. Three months after drug dc digital angiography showed that macular edema was still present. Eight months after drug dc angiography still showed mild macular edema. Nine months after drug dc macular edema was still present although it was improving. As per the DSMB ophthalmologist, pt had a superotemporal retinal branch vein occlusion in the R eye, most likely secondary to HTN.

This patient had no prior history of uveitis or ME. The ME was diagnosed at the 1-year visit. ME improved after drug discontinuation but was still present 9 months after drug dc.

In the FTY 1.25 mg group in the controlled studies eight patients had non-serious ME leading to drug discontinuation. Four of the 8 cases had not fully recovered from ME at the time of the last available evaluation in the original ISS. These cases are listed in Appendix 9.1.12.a.

- Macular edema leading to drug discontinuation in extension studies

Nine cases of ME led to drug discontinuation in the extension studies (one from the FTY 5-1.25 mg group, 6 from the FTY 1.25 mg group and two from the FTY 0.5 mg group). SAE were described in the SAE section. The case of non-serious ME with FTY 0.5 mg leading to drug discontinuation in the extension studies is as follows:

- **2301E1 0657 00005**. 50 F. FTY 0.5 mg. Hx of HTN, amblyopia, migraine, palpitations, insomnia, prior treatment for suspected Lyme disease. No diabetes or CV disease. During the core phase while on placebo she developed non-serious eye hemorrhage. On **Day 106** of FTY 0.5 mg she was noted with moderate macular edema confirmed by OCT (CFT of 339 microns L, and 283 microns R) and FA (retinal capillary leakage both eyes). Visual acuity was not done, as patient refused. Drug was discontinued. Two months after drug dc a follow OCT and FA showed persistent cystoid macular

edema L>R. As per the DSMB ophthalmologist the case could represent persistent Cystoid ME due to study drug despite discontinuation of therapy or a case of MS associated uveitis, or other cause of uveitis (such as Lyme disease, for which the patient had been treated previously).

One non-serious ME led to study drug discontinuation in the FTY 1.25 mg group in the extension studies (Appendix 9.1.12.b).

- Macular edema leading to study drug discontinuation in study 2309

At the time of the Special safety interim report update submitted 4/21/10, 14 cases of macular edema were reported and unblinded from study 2309. Of the 14 cases, five (1.4%), five (1.4%) and one (0.3%) led to study drug discontinuation in the FTY 1.25, FTY 0.5 and placebo groups, respectively. A summary of AE of ME in the FTY 0.5 mg dose group in study 2309 is as follows.

Macular edema leading to drug discontinuation, FTY 0.5, study 2309.

Patient ID	Age/ sex/ race †	History of ME, uveitis	Treat- ment	Baseline CFT µm OS, OD	Post-baseline CFT, study day & OS, OD values		ME SAE/AE start day (date) (action taken)	ME confirme by DSMB	Comment
0524-00004	51/F/ Ca	none	FTY720 0.5 mg	OS 189 OD 180	day 99	OS 196 OD 191	AE: ME OD Day 99 (b) (6) (discont.)	No	1
					day 135#	OS 186 OD 236			
0547-00007	37/F/ Ca	none	FTY720 0.5 mg	OS 186 OD 220	day 114	OS 198 OD 471	SAE: ME OD day 114 (b) (6) (discont.)	Yes	2
0548-00003	49/F/ Ca	none	FTY720 0.5 mg	OS 164 OD 166 (OCT2)	day 98	OS 164 OD 151	AE: ME OS day 98 (b) (6) (discont. on day (b))	No	3
					day 196	OS 154 OD 147			
0601-00009	49/F/ Ca	none	FTY720 0.5 mg	OS 263 OD 199	day 52	OS 425 OD 195	AE: ME OS day (b) (6) (discont.)	Yes	4
					day 87#	OS 268 OD 290			
					day 101#	OS 251 OD 236			
0616-00002	41/F/ Ca	ME, uveitis	FTY720 0.5 mg	OS 180 OD 205	day 34	OS 327 OD 462	AE: ME OD day (b) (6) (discont.)	Yes	5
					day 93#	OS 185 OD 198			

Source: Table 5-4 Special safety interim report update (4/21/10). OS = left eye, OD = right eye, BL = baseline, discont. = discontinued study drug, # Off-study drug. Comments:

- 0524-00004. Hx of HTN, mitral valve incompetence. Unclear how the diagnosis of ME was made, as visual acuity and dilated ophthalmoscopy were normal. Drug was dc and event resolved 6 months later. DSMB ophthalmologist did not find evidence of ME, although FA showed evidence of mild bilateral papillitis and vasculitis in the temporal parafoveal region of R eye.
- 0547 00007. Described in SAE section.
- 0548 00003. Unclear how diagnosis was made. Event resolved DSMB ophthalmologist stated OCT and FA did not confirm diagnosis. Medication was re-started.
- 0601 00009. Hx of HTN, prior optic neuritis, hypothyroidism and osteoarthritis. Diagnosis confirmed by OCT and FA. VA was normal; 2 weeks after drug dc VA decreased to 0.4 on L and was normal on R; 35 days after drug dc VA was 0.5 on L and 0.7 on R. 5 weeks after drug dc VA was normal.
- 0616 00002. Hx of uveitis and macular edema 1 year prior to randomization (no data on which eye). Dx by ophthalmic exam and OCT. Day 34 VA decreased to 0.5 on R; bilateral ME by ophthalmoscopy. VA

restored within 2 months of study discontinuation. 5 months after drug dc, ophthalmoscopy showed ME on R eye. One year after drug dc, VA R eye decreased to 0.3125.

Of the 5 cases of ME on FTY 0.5 in study 2309 reported so far, three were confirmed and 2 were not. One case was serious and has been described under SAEs (this case required surgery and recovered with loss of some visual acuity). One case resolved and recurred with decreased vision one year after drug dc. This patient had a history of uveitis and ME prior to study entry. The episode of ME one year after drug dc is probably related to the underlying MS and unlikely related to FTY; however, the role of FTY in the episode of ME that occurred while she was on FTY treatment can not be ruled out. One of the not confirmed cases showed papillitis and vasculitis of R eye.

The findings in 2309 are consistent with those in the ISS. FTY is associated with dose-related macular edema, including the 0.5 mg dose. The question is whether FTY it is associated with other eye toxicities and what kind of monitoring would be recommended.

A case of bilateral ischemic retinopathy/vasculitis with FTY 1.25 is described as follows

- **2301 0456_0008** bilateral ischemic retinopathy, intravitreal hemorrhage, vasculitis
32 yo F, no history of eye problems. History of migraines. Approximately one year into treatment, she complained of phosphenes. On day 358 (12 mo visit) she was noted to have severe ischemic retinopathy. Fundoscopic exam showed vaso-occlusive retinopathy with very thin, thread-like vessels and adjacent retinal ischemia with multiple retinal hemorrhages in the peripheral area, R>L eye. There was no evidence of ME. Visual acuity remained unchanged. FA showed very thin arteries with evidence of ischemic retinopathy in both eyes. Drug was discontinued on Day 395. She was treated with trimetazidine and laser photocoagulation x 3 within the ensuing 3 months. 3 months after drug dc, there were no changes. Visual acuity 10/10 for both eyes. Eye fundus: both eyes, multiple peripheral zones with vascular microinvasion. FA: no new ischemic zone but vascular rearrangement increased. Ophthalmologist indicated that there was a vascular progression nearby the ischemic zones despite the lasers. 8 months after drug dc, OCT showed normal CFT at L; dense macula, retinal detachment associated to vitreoretinal tension syndrome at R. 320 days since study medication discontinuation, an increase in central foveal thickness of 15 and 73 microns was observed for the left and right eye, respectively, compared to screening values. Visual acuity assessments were normal in both eyes. Fluorescein angiography showed retinal capillary leakage in both eyes that was not consistent with macular edema; “ischemic retinopathy” was observed in the right eye. One year after drug dc ischemic retinopathy was present and the patient still required laser treatments. 383 days since study medication discontinuation retinopathy was ongoing. The investigator did suspect a relationship between the event (retinopathy) and the study medication. Approximately 15 months after discontinuing study medication, the patient experienced an intravitreal hemorrhage. The DSMB ophthalmologist stated that the fluorescein angiogram showed definite evidence of peripheral vasculitis. There was mild peripheral intraretinal hemorrhage and a suggestion of peripheral capillary dropout on the fluorescein angiogram. There was no evidence of retinal neovascularization but the patient should be followed in this respect. “In addition to the possibility that study medication is the cause of the peripheral retinal vascular changes, other possible causes should be considered and ruled out including: blood dyscrasia (CBC, serum viscosity, hemoglobin electrophoresis (e.g., thalassemia, sickle cell disease)), aortic arch syndrome (e.g., Takayasu disease; Doppler imaging), multiple emboli (e.g., intravenous drug abuse, atrial myxoma; transesophageal echocardiography); idiopathic uveitis (e.g., Eale’s disease; audiology, chest x-ray, PPD); drug use (e.g., birth control pills), and metabolic abnormalities (e.g., diabetes mellitus).”

This is a single case of bilateral retinal ischemia/vasculitis and one can not draw conclusions from one case. However, there was also one case of retinal artery microthrombosis (described in the SAE section of this review), and few non-serious retinal hemorrhage and retinal aneurysms (that did not lead to drug discontinuation) in this database, all in the FTY treatment groups (discussed in the Other Significant AEs section), suggesting that there could be some deleterious vascular effect in the retina besides macular edema.

- AE leading to discontinuation in Cardiac disorders SOC and Investigations (cardiac related) SOC.

Patients with events leading to drug discontinuation in the Cardiac SOC for safety pool D are presented in the following table:

Table 38. AE leading to drug discontinuation, Cardiac SOC, pool D

	FTY720 5 mg	FTY720 1.25 mg	FTY720 0.5 mg	Placebo	Interferon
	(N=94)	(N=943)	(N=854) n	(N=511)	(N=431) n
Preferred term	n (%)	n (%)	(%)	n (%)	(%)
-Total	2 (2.1)	12 (1.3)	1 (0.1)	2 (0.4)	1 (0.2)
Bradycardia	2 (2.1)	5 (0.5)	-	1 (0.2)	-
AVB block 2 nd degree	-	3 (0.3)	-	-	-
AVB block 1 st degree	-	2 (0.2)	-	-	-
Angina pectoris	-	1 (0.1)	-	-	1 (0.2)
Arrhythmia	-	1 (0.1)	-	-	-
Pericarditis	-	1 (0.1)	-	-	-
Tachycardia	-	1 (0.1)	-	-	-
Ventricular extrasystoles	1 (1.1)	1 (0.1)	-	-	-
Diastolic dysfunction	-	-	-	1 (0.2)	-
Extrasystoles	1 (1.1)	-	-	-	-
LV dysfunction	-	-	1 (0.1)	-	-
Palpitations	-	-	-	1 (0.2)	-

Source: Post text Table 4.4-10, original ISS.

There was a dose response in the number of patients who discontinued drug due to events in the Cardiac events SOC (1.3% in FTY 1.25 as compared to FTY 0.5 mg). The most common cause of discontinuation was bradycardia, followed by second and first degree AV Block.

Most cases of discontinuations in the Cardiac SOC were serious and were described earlier in this review. The following cases were not coded as serious but led to study drug discontinuation in the controlled studies.

Subjects who discontinued due to non-serious AE in the Cardiac SOC, safety pool D

Placebo	2301_0610_00003	49 F	Diastolic dysfunction on day 596. No date of recovery was provided.
Interferon	2302_0407_00003	48 M	Angina pectoris on day 383. Resolved after 5 days.
FTY720 1.25 mg	2301_0180_00007	53 M	Bradycardia on day 1. Resolved on the same day.

FTY720 1.25 mg	2301_0757_00011	52 F	Tachycardia on day 20. resolved after 10 days.
FTY720 1.25 mg	2301_0176_00001	45 F	Bradycardia on day 11, resolved in 2 days.
FTY720 1.25 mg	2301_0413_00003	41 F	Ventricular extrasystoles on day 1. Resolved on the same day.

The cases on placebo and IFN occurred late in the study (days 596 and 383, respectively), while the events on FTY 1.25 occurred within the first 3 weeks of study treatment, including two cases bradycardia upon the first dose, which is consistent with the analysis of SAEs.

The following case in the Investigations SOC led to study drug dc but was coded as non-serious in the controlled studies

- 2302_0216_00013: Electrocardiogram T wave inversion 30 M, Day 62 on 1.25. MS was diagnosed five years prior to study entry. He had been previously treated with IFN beta-1a, IFN beta 1-b in the past. MS relapses had been treated with corticosteroids. He had no history of diabetes and did not smoke. He was not taking concomitant medications. This subject had an AE of intermittent chest pain coded as “non-serious angina pectoris” on Day 56. On Day 62 an ECG showed inverted T waves. The event of chest pain resolved on Day 64. The inverted T wave resolved on Day 69. Drug was discontinued on Day 69. The investigator did not suspect a relationship to study drug. No further work up is available from this patient.

This young subject with no risk factors presented intermittent chest pain described as non-serious angina, associated with inverted T waves. The drug was discontinued and there is no further workup available.

- Case of discontinuation due to AE in the Cardiac SOC in ongoing study 2309

- **2309-0528-00003** – Pulmonary artery hypertension (on FTY 1.25 mg).

This narrative was submitted by the applicant in response to the FDA request of results of unscheduled echocardiograms in study 2309.

A 48 year old black female had MS for 11 years. Medical history included chest discomfort, dizziness and anxiety. No cardiovascular history.

On Day 253 of blinded study therapy, the patient was seen by a cardiologist and was diagnosed with labile hypertension. It is unclear for how long she had seen a cardiologist. Blood pressure measurements taken during the office visit ranged from 136-152 mmHg/80-88 mmHg. No anti-hypertensive medications were started. The patient was instructed to continue home blood pressure monitoring.

On Day 283, the patient was seen at an unscheduled study visit for complaints of shortness of breath when speaking for a long period time. The patient was evaluated by her pulmonologist on the same day and no new acute pulmonary pathology was detected. Follow-up pulmonary function tests were performed on Day 288, as shown below.

Rel Day	FEV1	Change from baseline	FVC	Change from baseline	DLCO	Change from baseline
288	2.77	4.53%	3.47	6.77%	20.8	6.67%

Study medication was temporarily interrupted for these symptoms from Day 284 to Day 289. On Day 349 the patient had her Month 12 visit and the regularly scheduled echocardiogram was performed. (The results of which became available at a later date.)

On Day 406, the patient had a routine follow-up visit with her cardiologist. At the time of the visit, the patient denied having any shortness of breath or any chest discomfort. The cardiologist noted a gradual increase in her pulmonary artery pressure estimate since her baseline visit. Her pulmonary artery pressure estimates were 32 mmHg at baseline, 37 mmHg at Month 3 and 49 mm Hg at Month 12, Day 349. The cardiologist also noted a worsening of her baseline tricuspid regurgitation. Her tricuspid regurgitation was mild to moderate at baseline and month 3 but worsened to moderate to severe at Month (Day 349) on the echocardiogram. In light of the increasing pulmonary artery pressure estimate and worsening tricuspid regurgitation, the investigator and cardiologist decided to permanently discontinue study medication on Day 407.

A follow up (unscheduled) echocardiogram was performed Day 475. According to the local echocardiogram report, pulmonary artery pressure estimate had improved to 35.2 mmHg and the tricuspid regurgitation improved to moderate in severity. The patient subsequently saw her cardiologist on Day 503. He reports that she remains clinically stable from a cardiac standpoint with no cardiac symptoms. All her other parameters, including pulmonary artery pressure, tricuspid regurgitation as well as blood pressure are improved. The case was reviewed by the DSMB cardiologist and he concurs with the interpretations of the Echocardiograms.

Date	Pulmonary artery pressure- local echocardiogram report (mmHg)	Pulmonary artery pressure estimate (RV-RA systolic gradient + 10 mmHg) – central reader	Tricuspid valve regurgitation – local echocardiogram report
Screening	32	27.2	Mild to moderate
3 months (scheduled)	37	34.3	Mild to moderate
12 months (scheduled)	49	47.3	Moderate to severe
Day 475 (unscheduled)	35.2	33.7	Moderate

According to the investigator this event (pulmonary arterial hypertension) was non-serious. The investigator did suspect a relationship between the event (pulmonary arterial hypertension) and the study medication.

Patient seems to have developed pulmonary hypertension during fingolimod treatment. She did not have a known history of pulmonary hypertension at entry. It is unclear why she saw a cardiologist on Day 253. Of note, a Holter monitoring done at month 3 as part of study 2309 scheduled assessments had shown intermittent ectopic atrial

rhythm. No AE were reported at that time. On Day 283 she developed increasing shortness of breath. Study drug was interrupted and then re-started after a few days with no apparent complaints. On Day 407 the cardiologist noted increased pulmonary artery pressure in an echocardiogram done as part of study 2309 scheduled 12-month assessments. I believe that this case could be related to study drug use because it improved after drug discontinuation.

- AE leading to drug dc in the Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC

A total of 27 subjects discontinued study drug because of an AE of neoplasm in the controlled database. The number, percentage and rate per 100 PYRs was similar among treatment groups (0.8%, 0.7%, 1.2% and 0.2% in the FTY 1.25 mg, 0.5 mg, placebo and IFN groups, respectively). Twenty six of the 27 were serious. The only non-serious case that led to discontinuation occurred in a 39 year old subject who was diagnosed with uterine leiomyoma Day 42 of FTY 1.25 mg treatment.

Additionally, nine subjects discontinued from the extension studies up to the cut-off date of the original submission. All of them were serious and described earlier in this review. Of note, one patient with a “benign lung neoplasm” showed to be a necrotizing granulomatous pneumonitis. This case was described in the Serious infections and infestations section of this review.

- AE leading to drug discontinuation in the Infectious & infestations disorders SOC

Fourteen subjects discontinued study drug because of events in the infections and infestations SOC in the controlled database: 2 on FTY5, 7 on FTY 1.25, 3 on FTY 0.5 and 2 placebo, 1 IFN.

Table 39. AE leading to drug discontinuation in the Infections and Infestation SOC, safety pool D, by high level group term (HLGT)

PT	FTY 5 mg N=94	FTY 1.25 N= 943	FTY 0.5 N=854	Placebo N=511	IFN N=431
	n (%)	n (%)	n (%)	n (%)	n (%)
Total	2 (2.1)	7 (0.7)	2 (0.1)	2 (0.4)	1 (0.2)
Bacterial infectious disorders					
Cellulitis	1	-	-	-	-
Staphylococcal infection	-	1	-	-	-
Infections- pathogen unspecified					
Appendicitis	-	-	-	-	1
Genital infection female	1	-	-	-	-
Pneumonia	-	1	1 ³	-	-
Lower resp. tract infection	-	1	-	-	-
Viral infectious disorders					
Oral herpes	-	-	-	1	-
Genital herpes	-	-	-	1	-
Anogenital warts	-	1	-	-	-
Herpes zoster disseminated ¹	-	1	-	-	-
Viral pharyngitis	-	1	-	-	-
Encephalitis viral ²	-	1	-	--	-
Bronchiolitis	-	-	1	-	-
Herpes virus infection	-	-	1	-	-

Interim review, 5 12 10.

Lourdes Villalba, M.D

NDA 22-527. Fingolimod

Source: AE datasets. ^{1,2} Fatal infections. ³ One subject had pneumonia and herpes virus infection.

The numbers are small but suggest an increased risk of discontinuation due to infections in the FTY 1.25 mg group (but not in the FTY 0.5 mg group) as compared to placebo and INF.

Serious and fatal infections have been described earlier in this review. Non-serious infections that led to study drug discontinuation in the controlled database are listed as follows:

Listing of non-serious infections leading to drug discontinuation in the controlled studies.

ID	Age sex	PT	Rel day	Duration (days)
Placebo				
2301_0609_00003	40 F	Oral herpes	539	18
2301_0703_00005	45 M	Genital herpes	59	139
FTY 5 mg				
2201_0005_00005	42 F	Cellulitis	116	11
2201_0052_00005	32 F	Genital infection female	143	46
FTY 1.25 mg				
2301_0153_00002	35 F	Anogenital warts	389	250
2302_0447_00004	33 M	Viral pharyngitis	10	110
2302_0505_00010	41 F	Staphylococcal infection	101	NA
FTY 0.5 mg				
2301_0601_00007	46 F	Bronchiolitis	338	125

Discontinuations in the extensions studies are under review.

- AE leading to drug dc in the Nervous system disorders SOC

Fifteen subjects discontinued study drug because of AE in this SOC. These events are summarized in the following table.

Table 40. AE leading to drug discontinuation, Nervous system disorders SOC, safety pool D

PT	FTY 5 mg N=94	FTY 1.25 N= 943	FTY 0.5 N=854	Placebo N=511	IFN N=431
	n (%)	n (%)	n (%)	n (%)	n (%)
Total	1 (1.0)	4 (0.4)	3 (0.4)	6 (1.2)	1 (0.2)
Cerebrovascular accident	-	1	-	-	-
Cognitive disorder	-	-	1	-	-
Grand mal seizure, coma	-	1	-	-	-
Dizziness	-	-	-	2	-
Epilepsy	-	1	-	-	-
Headache	-	1	1	1	-
Multiple sclerosis relapse	-	-	1	2	-
Nerve root lesion	-	-	-	-	1
Presyncope	-	-	-	1	-
Posterior Reversible Leukoencephalopathy (PRES)	1	-	-	-	-

Source: AE dataset. Original ISS. n= number of patients with event.

There is no increased risk of discontinuations due to nervous system disorders AEs in the controlled database. Serious events were described in the SAE section of this review. Non serious events that led to discontinuation included two episodes of dizziness (both on placebo), three of headache (one in on placebo, one on FTY 1.25 and one on FTY 0.5mg) one case of cognitive dysfunction in a patient taking FTY 0.5 mg/day. This last case was the subject who was eventually diagnosed with Sjogren's syndrome and his narrative is under the serious AE section.

- AE leading to drug dc in the General disorders and administration site conditions SOC

A total of 13 subjects discontinued because of AE in this SOC in the controlled database.

Table 41. AE leading to drug discontinuation, General disorders SOC, safety pool D.

PT	FTY 5 mg N=94	FTY 1.25 N= 943	FTY 0.5 N=854	Placebo N=511	IFN N=431
	n (%)	n (%)	n (%)	n (%)	n (%)
Total	1 (1.0)	6 (0.6)	1 (0.1)	5 (1.0)	0
Asthenia	-	1	-	1	-
Chest pain	1	-	1	1	-
Fatigue	-	2	-	2	-
Generalized edema	-	1	-	-	-
Malaise	-	1	-	-	-
Non-cardiac chest pain	-	-	-	1	-
Pyrexia	-	1	-	-	-

Source: ISS table.

Serious AEs leading to drug discontinuation were described in the SAE section of this review. Non-serious AEs that led to discontinuation in the controlled studies were two cases of chest pain (one on FTY 5, one on FTY 0.5 mg); two cases of fatigue, one asthenia, one malaise, one generalized edema and one pyrexia in the FTY 1.25 group and two cases of fatigue, of one asthenia and one of chest pain (on Day 12 of the study) in the placebo group. The case of generalized edema is described as follows.

- **2301_0102_00001.** Generalized edema, Day 3 (FTY 1.25 mg)

53 year old female. No significant history of cardiac, respiratory, liver disease, hypertension or diabetes. On Day 3 of FTY treatment she developed generalized edema and eyelid edema. On Day 15 she was found to have elevated ALT and GGT (2x ULN). The study drug was discontinued. The generalized edema was treated with indapamide for 2 days. According to the investigator, the generalized edema resolved 15 days after drug discontinuation while the eyelid edema and elevated liver enzymes resolved 133 days after drug discontinuation. The investigator suspected that these events were related to study medication. Additional information regarding the generalized edema was provided on 4/22/10 at the FDA request.

On Day 3 of study therapy the patient developed generalized edema with symptoms of feeling bad, dyspnea, orthopnea and increase in bilateral pitting edema (edema in the face, eyelids, hands and feet). By Day 15 of the study, the patient had gained 8 kg from baseline. Biochemistry results taken at that time were normal (including the albumin and creatinine), except for ALT and GGT (which were 2-3 x ULN). Urinalysis results were indicative of urinary tract infection. PFT results showed normal lung function. A chest X-ray showed no signs of structural abnormality. ECG and Echo were both normal. An evaluation by a cardiologist concluded that there was no sign of cardiac failure and the complaints of the patient were not of cardiac origin. The drug was discontinued on Day 15, she was treated with indapamide for two days and events resolved 8 days after drug discontinuation.

This is a case of generalized edema with 8 kg weight gain from baseline over a 2-week period. Apparently all laboratory evaluations on Day 15 were within normal, except modest liver enzyme elevation. No electrolytes were mentioned in the narrative. It is unclear if she had proteinuria. She responded to diuretic treatment. The events appear to be drug related, because it started 3 days into treatment and improved after drug discontinuation, however, the cause of the edema remains unknown. It is unclear when the chest X-ray, PFTs and echocardiogram were done.

A case of drug discontinuation due to fluid retention during the controlled studies on FTY 1.25 mg was coded under the Metabolic disorders SOC. The case is included here, as follows.

- **2301_0206_00017.** 53 F, Fluid retention on day 36 of FTY 1.25. Medical Hx of asthma, hypersensitivity, epilepsy, among others; no history of diabetes or hypertension. Concomitant meds included hydroxychloroquine, pregabalin, minocyclin and baclofen. On Day 10 she complained of fatigue. On Day 36 presented water retention in lower body and extremities and abdominal distension with weight gain. Drug was discontinued on Day 121. Treated with furosemide. Weight, electrolytes and urinalysis not available in narrative or patient profile. Additional information has been requested.

There is limited information about this case. The relationship to study drug can not be ruled out.

One additional subject discontinued due to edema during the extension study, upon the first dose of FTY 0.5 mg, as follows.

- **2302E1-0145-00001.** Edema. Day 1 of extension study (FTY 0.5 mg)

42 F, diagnosed with MS 10 years earlier. Medical history included syncope, optic neuritis, hypercholesterolemia, hypertension and hypothyroidism. No history of diabetes or cardiovascular disease. She received INF during the core study for 1 year. On extension Day 1, upon first FTY 0.5 mg dose, she developed mild diffuse edema that led to drug discontinuation on extension Day 78. She was treated with furosemide. The event of edema resolved completely one day after the last dose of study medication. The investigator suspected a relationship to study drug. *Additional information has been requested.*

Three cases of fluid retention/edema with onset on Day 1, 3 and 36 led to study drug discontinuation in the original ISS database. No conclusions can be drawn based on a few cases, particularly with very limited information.

- AE leading to drug dc in the Respiratory, thoracic and mediastinal disorders SOC and Investigation (respiratory related) SOC

Twenty one subjects discontinued because of AE in the Respiratory, thoracic and mediastinal disorders SOC and or the Investigation (respiratory related) SOC.

Table 42. AE leading to drug discontinuation in the Respiratory SOC and respiratory related Investigations SOC, safety pool D.

SOC / PT	FTY 5 mg N=94	FTY 1.25 N= 943	FTY 0.5 N=854	Placebo N=511	IFN N=431
	n (%)	n (%)	n (%)	n (%)	n (%)
total	2 (2.1)	9 (1.1)	3 (0.4)	5 (1.0)	2 (0.4)
Respiratory, thoracic and mediastinal disorders SOC	2	5	2	2	-
Dyspnea	2	3	1	2	-
Obstructive airway disorder	-	1	-	-	-
Pleurisy	-	1	-	-	-
Pulmonary edema	-	-	1	-	-
Investigations - Respiratory and pulmonary investigations (excl blood gases)	-	4	1	3	2
Spirometry	-	-	-	1	-
DLCO decreased	-	4	-	2	2
PFT abnormal	-	-	1	-	-

Source: AE datasets and narratives submitted with original application. Infection-related events in the respiratory system are not included in this table.

Some events in the Respiratory SOC were coded as serious and were described in the SAE section of this review. None of the events in the Investigation SOC were coded as serious.

Overall, there was no excess of subjects discontinuing from the studies because of respiratory-related AEs. However, review of the narratives suggests that many of these patients did not have a complete evaluation at the time of the event.

Selected narratives of non-serious events leading to drug discontinuation are presented as follows.

- **2302_0307_00007**, 38 F. Dyspnea on Day 20.; duration 86 days .FTY 1.25 mg.
Non smoker. Concomitant meds: oral contraceptive. On Day 20 experienced dyspnea of mod intensity. Drug was discontinued on Day 103. No treatment reported. The event of dyspnea resolved 2 days after receiving last dose of study drug. *Time course suggests a drug-related event. No data on PFT, chest Xray or HRCT are available for this patient.*
- **2301_0754_00004**, 35 M. DLCO decreased on day 195. FTY 1.25 mg.
MS was Dx 4 months prior to study entry, treated with CS. No concomitant meds. Non-smoker. Screening PFTs showed FEV1 3.87 L; FVC 5.02 L, DLCO 11.86 mmol/min/kPa. On Day 368 14 months into FTY 1.25 mg treatment he developed acute bronchitis with DLCO reduction (69% from baseline). A pulmonologist diagnosed acute bronchitis with hyperactivity and bronchial asthma onset. A HRCT done one month later showed “local pneumofibrosis S5 from the R side and CT signs of abnormalities in the distal parts of the broncus”, however, no PFTs were done at that time. Follow up PFT on Day 466 showed that FEV1, FVC and DLCO continued to decline (DLCO decline >20% from baseline). No HRCT was done at that time. Drug was discontinued on Day 468 because this AE. No further PFT or HRCT are available for this patient. *Patient is said to have developed asthma but also has restrictive disease with decreased DLCO>30% from baseline that had not recovered at the time of last available PFT. No further evaluations are available for this patient.*
- **2301_0758_00012**, 35 F. DLCO decreased on day 547; duration 264 days. FTY 1.25
Smoker (1 pack per day per 16 years). At screening DLCO was 8.15 mmol/min/Kpa; FEV1 3.22 L; FVC 3.61 L. On Day 547 he was noted to have decreased DLCO of severe intensity. DLCO was 4.31 mmol/min/KPa, FEV1 2.82 L and FVC 2.99 L. Study drug was discontinued. DLCO decreased further but showed some increase 43 days after drug discontinuation. The event resolved 250 days after drug dc. *No HRCT was done for this patient.*
- **2301_0601_00007**, 46 F. Dyspnea. On Day 293, duration 56 days. FTY 0.5 mg
MS diagnosed 10 years prior. No immunomodulators. EDSS=2. Medical history, depression. Active smoker 1 pack x 20 years. Concomitant meds: oxacarbazepine and escitalopram. Dyspnea started 10 months into study “even without making any effort”. On day 336, a pulmonologist found normal physical exam and PFT but X-rays showed interstitial nodular increased shadowing at several places of the R lung. HRCT on Day 338 showed diffuse parenchymal changes consistent with panbronchiolitis. Repeated PFTs remained normal. At screening visit the HRCT had showed multiple findings but none were considered clinically significant. Drug was dc on Day 343. Dyspnea resolved on Day 348, five days after last dose. A follow up CT 4 months later showed improvement of radiological findings. A HRCT scan 9 months later was normal. *The time course suggests a drug-related event, as dyspnea started 10 months into the study and resolved 5 days after drug discontinuation. Radiologic findings resolved several months after drug discontinuation.*
- **2302_0608_00007**, 49 M. Pulmonary function test abnormal on day 154; duration 2 days. FTY 0.5.
Dx of MS 2 years prior. Treated with IFN in the past. Hx of headache. Concomitant meds: mirtazapine. On Day 154 she had abnormal PFTs and drug was dc, but it is unclear what the PFT abnormality was. She recovered the following day.

Additional narratives of respiratory related events from controlled studies are presented in Appendix 9.1.13.a. and for the extension studies in Appendix 9.1.13.b.

Comment: Patient 2302_0307_00007 discontinued because of dyspnea. Patient 2301_0758_00012 discontinued because of abnormal PFTs. No data on chest X-ray or HRCT are available for these patients. Moreover, some cases had not resolved at the time of last follow up (2301_0754_00004, 2302_0220_00013, 2302_0333_00008). Additional information is needed pre-or postmarketing to further characterize the effect of FTY 0.5mg in the lungs.

The applicant proposes to conduct a postmarketing registry to explore potential safety issues with FTY. The evaluation of lung toxicity is currently not included, but could be included in such a study.

- AE leading to drug dc in the Vascular disorders SOC

Six subjects discontinued because of AE in the Vascular disorders SOC in the controlled database.

Table 43. AE that led to study drug discontinuation in Vascular SOC, pool D

PT	FTY 5 mg N=94	FTY 1.25 N= 943	FTY 0.5 N=854	Placebo N=511	IFN N=431
	n (%)	n (%)	n (%)	n (%)	n (%)
total	1 (1.0)	3 (0.3)	1 (0.1)	1 (0.2)	-
Hypotension	-	-	-	1	-
Hypertension	1	1	1	-	-
Arterial occlusive disease	-	2 ¹	-	-	-

¹ One event described as vasospastic occlusion and one as occlusion.

The serious cases have been described in the SAE section (the two arterial occlusions). The 3 cases of hypertension leading to discontinuation that were coded as non-serious events are summarized as follows (all new onset HTN).

- **2201_0025_00009**, 49 M. Hypertension on day 127 of FTY 5 mg treatment; duration of event 87 days. Patient had total cholesterol level of 5.96 mmol/L (upper normal value 5.69 mmol/L) and sitting blood pressure of 126/82 mmHg at baseline. No hx of HTN. On Day 95 total cholesterol was 6.76 mmol/L. Treatment with simvastatin was initiated on day 113. The investigator suspected a relationship with the study medication. On day 127 the patient presented with mild hypertension showing a sitting blood pressure of 140/100 mmHg. No treatment for hypertension was initiated. No relationship to the study medication was suspected. On day 154 mild hypercholesterolaemia still persisted. A relationship with the study medication was suspected. The patient discontinued study medication on day 164.
- **2301_0757_00011**, 52 F. No Hx of HTN or diabetes. Non smoker. Baseline BP 131/75 mmHg. She developed moderate tachycardia and arterial HTN on day 20 of FTY 1.25 mg treatment (exact value

not provided); drug was discontinued and patient was treated with metoprolol. The event resolved 7 days after drug dc.

- **2302_0316_00013**, 39 F. Hypertension on day 2 of FTY 0.5 mg treatment; No history of HTN, diabetes or smoking. Prior to randomization sitting BP was 136.6/ 93.3 mmHg. On Day 2 of treatment she was noted with high BP. On Day 30. BP was 157/98 mmHg. Drug was discontinued. She was treated with amlodipine for HTN. Event was present at the time of last available report.

One subject was reported to have an AE of high blood pressure leading to drug dc in the extension studies (2302E_0307_00002, a 42 F on FTY 0.5mg).

Although the number is small, all cases of HTN leading to drug dc occurred in FTY treated patients.

- AE leading to drug dc in the Psychiatric disorders SOC

Seven subjects discontinued because of AE in the Psychiatric disorders SOC: one acute psychosis on placebo, on day 240 (described under SAES); four cases of depression (one IFN, 2 on FTY 1.25 and 1 on FTY 0.5mg) and one suicide attempt in the FTY 1.25 mg group (described under SAES). Depression is not uncommon among subjects with MS, and there was no increased risk with fingolimod.

- AE leading to drug dc in the Skin and subcutaneous disorders SOC

Six subjects discontinued because of AE in this SOC: one pruritic rash (on placebo), and five rashes in fingolimod in the controlled database (Two on FTY 1.25 – one eczema, one erythema, and 3 on FTY 0.5). Two cases on FTY 0.5 mg are as follows.

- **2301_0205_00002**. 49 M. Dermatitis allergic on day 1. Patient developed blister-like rash approximately 7 hours past first dose. The study medication was dc due to the event (dermatitis allergic) on Day 2. On day 3 there was slight blistering on the skin located on the arms and less apparent on the chest and back. She was treated with Benadryl. Rash 26 days after study drug discontinuation. The patient was then lost to follow-up.
- **2301_0302_00007**. 35 F. Dermatitis allergic on day 29. She presented allergic skin rash (moderate intensity, located on extremities). Drug was dc on day 30. No details were given about treatment. Rash resolved 47 days after drug discontinuation.

The third case was coded as macular rash but was actually basal cell carcinoma at 3 sites (described under Neoplasms).

In the renal transplant population there were two anaphylactic reactions and one case of serum sickness. A signal for hypersensitivity reactions was not observed in the MS database. Review of the SUR is ongoing.

- AE leading to drug dc in the Musculoskeletal system disorders SOC

Six events in this SOC led to drug discontinuation: two back pain (one on IFN, one on FTY 1.25), one muscle spasm (on FTY 1.25) and two myalgia (one on FTY 1.25 and one on FTY 0.5). None of these events were serious.

- AE leading to drug dc in the Metabolic disorders SOC

Three subjects discontinued due to AE in the metabolic disorders SOC in the controlled database: one case of abnormal loss of weight (on FTY 1.25), one case of hypercholesterolemia (on FTY 5 mg), one weight decreased (on FTY 1.25) and one fluid retention (also on FTY 1.25 mg). The case of fluid retention was described under AE leading to drug discontinuation in the General disorders section.

- AE leading to drug dc in the Blood and lymphatic SOC and blood-related Investigations SOC

Non-serious blood related AE that led to study drug discontinuation in the controlled studies were one case of platelet count decreased (Investigations SOC) on Day 90 of FTY 5 g, one case of lymphadenopathy on Day 101 with FTY 1.25 and one case of lymphopenia on Day 548 with FTY 0.5 mg. The case of platelet decreased is as follows.

- **2201_0031_00007**, on FTY 5 mg. 37 M. Platelet count decreased (investigations) on Day 90. Decreased platelet count of $28 \times 10^9/L$ on day 90. No known risk factors for the development of thrombocytopenia could be identified. The investigator suspected a relationship with the study medication. Treatment with study medication was discontinued on day 99. During a follow-up visit on day 120 a platelet count of $80 \times 10^9/L$ was measured. The patient discontinued the study on day 120 after withdrawal of consent.

Therefore, altogether, there were 3 cases of thrombocytopenia in the original ISS, two serious and one leading to discontinuation.

Additionally, 9 subjects discontinued from the extension studies due to non-serious AE of lymphopenia in the original ISS (2 from the FTY 5mg to 1.25 mg group, five from the FTY 1.25 mg group and two from the FTY 0.5 mg group).

In summary, AE leading to study drug discontinuation was higher in the FTY 1.25 group as compared to placebo, FTY 0.5 and interferon. The SOC with the highest incidence of AE leading to drug discontinuation were Investigations (mostly liver-related investigations), Cardiac, and Eye disorders SOC, There was a dose-response between FTY 1.25 and FTY 0.5 for these SOC.

In the controlled studies, hepatobiliary disorders and liver-related Investigations led to drug discontinuation in 4.6%, 3.6% and 0,8% of patient on FTY 1.25 mg, FTY 0.5 mg and placebo groups, respectively.

In the Eye disorders SOC, AE led to drug discontinuation in 1.6%, 0.2% and 0,4% of patients in the FTY 1.25 mg, FTY 0.5 mg and placebo groups, respectively, including 10 (1.1%), 1 (0.1%) and 1 (0.2%) cases of macular edema (ME) in the

FTY 1.25, FTY 0.5 and IFN groups, respectively. At the time of the SUR, 9 cases of ME had led to study drug discontinuation from the extension studies in the ISS, including 2 on FTY 0.5 mg. The special safety interim report update included 11 cases of ME that led to drug dc from study 2309, including 5 on FTY 1.25 (1.4%), 5 on FTY 0.5 (1.4%) and one on placebo (0.3%).

The risk of AE leading to drug discontinuation in the Cardiac SOC in the controlled studies was 1.3%, 0.1% and 0.4% for FTY 1.25 mg, FTY 0.5 mg and placebo, respectively. One patient discontinued drug because of pulmonary hypertension diagnosed during a scheduled echocardiogram in study 2309.

Several patients discontinued drug because of respiratory related events of dyspnea or abnormal PFTs in the controlled and extension studies. There was no excess of cases in the FTY treatment groups (1.1% and 0.4%) as compared to placebo (1.0%). However, most have a less than optimum work-up and discontinued without having PFT's, chest X-ray or HRCT. The cause of dyspnea/abnormal PFT remains unclear in these patients.

AEs leading to drug discontinuation in the Infections and infestations SOC in the controlled studies suggested an increased risk in the FTY 1.25 mg group (but not in the FTY 0.5 mg group) as compared to placebo (0.7%, 0.1% and 0.4%, respectively).

7.3.4 Significant Adverse Events

This section discusses AE that were non-serious or did not lead to discontinuation but are potentially relevant.

- AE in the Eye disorders SOC

There were four cases of retinal detachment coded as non-serious in the controlled database (3 on FTY 1.25 and 1 on FTY 0.5 mg). Except for one case that led to drug discontinuation (3 surgeries to repair detachment), no narratives are available for the other cases.

There were several non-serious AE related to the retinal artery: one bilateral ischemia/vasculitis, and 2 retinal microaneurysm in the FTY 1.25 group; one retinal vascular spasm and one splinter hemorrhage in the FTY 0.5 mg, and 6 retinal hemorrhages (3 in FTY 1.25 and 3 in the FTY 0.5 mg group). Cases that led to study drug discontinuation have been described. Narratives of those non-serious that did not lead to study discontinuation have been requested.

Selected serious and non-serious AE in the Eye disorders SOC in the controlled studies are presented as follows.

Table 44. Selected serious and non-serious AE in the Eye disorders SOC, pool D

	FTY 1.25 N= 943	FTY 0.5 N= 854	placebo N= 511	IFN N= 431
	n(%)	n(%)	n(%)	n(%)
Macular edema	12 (1.3)	2 (0.2)	0	1 (0.2)
Retinal detachment	3 (0.3)	1 (0.1)	0	0
Vascular				
Bilat ret ischem	1 (0.1)	-	-	-
Ret vasc. spasm	-	1 (0.1)	-	-
Splinter hemorr.	-	1 (0.1)	-	-
Ret microaneurysm	2 (0.2)	-	-	-
Retinal hemorr.	3 (0.3)	3 (0.3)	-	-

Source: AE dataset, ISS.

- Non serious events of ischemic heart disease

In addition to the cases of serious ischemic heart disease in the Cardiac SOC and the cases that led to study drug discontinuation in the Cardiac and Investigations (ECG SOC), some events of myocardial ischemia, myocardial infarction and angina pectoris were coded as non-serious.

Serious and non-serious AE reports with preferred terms consistent with coronary artery ischemia in the Cardiac SOC and Investigations SOC (ECG related) are summarized as follows.

Table 45. Serious and non-serious ischemic heart disease in safety pool D

FTY 5 mg N=94	FTY 1.25 N= 943	FTY 0.5 N= 854	Placebo N= 511	IFN N= 431
n (%)	n (%)	n (%)	n (%)	n (%)
-	5 (0.5)	7(0.7)	4 (0.8)	3 (0.6)

Source: AE datasets and narratives for Cardiac SOC and Investigations (ECG) SOC. Patients included in this analysis are presented in Appendix 9.1.14.

Review of serious and non-serious events consistent with ischemic disease does not show an imbalance of events in the controlled studies. However, most diagnoses were made based on limited or no additional cardiac work-up. Most patients continued in the trials without receiving specific treatment but without subsequent episodes.

An analysis of these events in people <40 years is as follows.

Table 46. Serious and non-serious AE consistent with ischemic heart disease in people below 40 years of age, safety pool D

FTY 5 mg N=94	FTY 1.25 N= 943	FTY 0.5 N= 854	Placebo N= 511	IFN N= 431
n (%)	n (%)	n (%)	n (%)	n (%)
-	5 (0.5)	4(0.4)	1 (0.1)	1 (0.1)

Source: AE datasets and narratives for Cardiac SOC and Investigations (ECG) SOC. Patients included in this analysis are presented in Appendix 9.1.14.

This analysis suggest an increased risk of ischemic heart disease for FTY 1.25 and FTY 0.5 mg as compared to placebo among people younger than 40 years, but the numbers are small.

Additionally, there were 4 cases of angina and one MI in the extension studies included in the original ISS, and two MI were recently reported from the ongoing studies as IND safety reports.

Of note, only “selected events of interest” were submitted to the NDA from the ongoing studies not included in the ISS pooled analysis. The FDA requested the listing of serious AE and AE leading to discontinuations from studies not included in the ISS - even if blinded-. Review is pending at the time of this review.

- Hypertension

There was only one serious AE of hypertension and three non-serious cases of HTN leading to drug discontinuation in the controlled population. However, there were several non-serious cases, as shown in the following table.

Table 47. Serious and non-serious hypertension- related events in pool D

	1.25 mg (N = 943) n (%)	0.5 mg (N = 854) n (%)	Placebo (N = 511) n (%)	Interferon (N = 431) n (%)
Total number of patients	56 (5.9)	43 (5.0)	17 (3.3)	9 (2.1)
Hypertension	55 (5.8)	42 (4.9)	17 (3.3)	9 (2.1)
Hypertensive crisis	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Secondary hypertension	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Systolic hypertension	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Diastolic hypertension	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)

Source: AE dataset. n= number of patients with events.

This finding is consistent with the analyses of vital sign evaluations have shown a dose-related increase in systolic and diastolic BP over time for FTY treatment groups.

Evaluation of medications after start of study drug suggests greater use of anti hypertensive medications in FTY groups (data not shown).

- Respiratory-related disorders, including serious and non-serious events

Overall, the risk of developing AEs in this SOC was similar among treatment groups. The AE with higher incidence for both FTY 1.25 and FTY 0.5 mg as compared to placebo and at least >1% difference was dyspnea. Dyspnea exertional was observed only in the active treatment groups. Other events that presented in the FTY groups but not on placebo were productive cough, respiratory disorder and wheezing. Of note, the number of patients with asthma, restrictive respiratory disease and obstructive pulmonary disease were no higher than placebo.

Table 48. Serious and non-serious AE, Respiratory thoracic and mediastinal disorders, pool D (selected AEs)

	5 mg	1.25 mg	0.5 mg	Placebo	Interferon
	(N = 94)	(N = 943)	(N = 854)	(N = 511)	(N = 431)
	n (%)	n (%)	n (%)	n (%)	n (%)
Any preferred term	31 (33.0)	198 (21.0)	168 (19.7)	109 (21.3)	63 (14.6)
Dyspnoea	12 (12.8)	50 (5.3)	38 (4.4)	20 (3.9)	7 (1.6)
Dyspnoea exertional	3 (3.2)	7 (0.7)	8 (0.9)	0 (0.0)	1 (0.2)
Productive cough	1 (1.1)	6 (0.6)	3 (0.4)	0 (0.0)	0 (0.0)
Respiratory disorder	0 (0.0)	1 (0.1)	2 (0.2)	0 (0.0)	1 (0.2)
Wheezing	3 (3.2)	1 (0.1)	3 (0.4)	0 (0.0)	0 (0.0)
Asthma	0 (0.0)	5 (0.5)	3 (0.4)	4 (0.8)	4 (0.9)
Lung disorder	0 (0.0)	4 (0.4)	1 (0.1)	1 (0.2)	1 (0.2)
Obstructive airways disorder	0 (0.0)	4 (0.4)	3 (0.4)	2 (0.4)	0 (0.0)
Bronchitis chronic	0 (0.0)	1 (0.1)	2 (0.2)	0 (0.0)	0 (0.0)
Emphysema	0 (0.0)	1 (0.1)	1 (0.1)	2 (0.4)	1 (0.2)
Increased upper airway secretion	0 (0.0)	1 (0.1)	0 (0.0)	3 (0.6)	0 (0.0)
Chronic obstructive pulm disease	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)

Source: ISS Post text table 4.41

- Lung neoplasm and benign lung neoplasm in the fingolimod database

Eight subjects were reported to have a lung neoplasm or a benign lung neoplasm in the controlled studies. Additionally 3 subjects were reported to have a benign lung neoplasm in the extension studies in the original application. Only one case was serious and led to study drug discontinuation (necrotizing granulomatous pneumonitis in a transbronchoscopic biopsy). The other diagnoses were based on imaging, not on tissue pathology. The listing of cases is below:

Listing of subjects with lung neoplasm

CONTROLLED		PT	Verbatim	Rel day
Placebo				
2301 0206 00025	46 M	Benign lung neoplasm.	Subpleura / left nodules along oblique tissues, lung	709
Interferon				
2302 0601 00015	35 M	Benign lung neoplasm	Nodule on left lower lung non malignant	184

FTY720 1.25 mg				
2301_0206_00028	46 F	Benign lung neoplasm	Lt posterior apical ground glass nodule - lung, benign	711
2302_0525_00002	41 F	Lung neoplasm	Scattered pulmonary nodules right middle lobe non specific benign	360
FTY720 0.5 mg				
2301_0211_00002	27 F	Benign lung neoplasm	Pulmonary node (benign)	370
2302_0141_00001	43 M	Lung neoplasm	Several nodular pulmonaire with nature unknown	359
2302_0535_00005	45 F	Lung neoplasm	Small nodule in lingual	351
EXTENSION				
2201_0004_00004 (FTY720 5 - 1.25)	52 F	Benign lung neoplasm	Benign solid mass lesion left lower lung lobe (Biopsy showed necrotizing granulomatous pneumonitis)	1356
2301_0109_00002 (FTY720 0.5 mg)	41 F	Benign lung neoplasm	Micro nodules bilateral sub-pleural (benign) (still observed but not treated)	367
2301_0703_00007 (FTY720 0.5 mg)	25 M	Benign lung neoplasm	Benign lung nodule (still observed but not treated in extension)	329

The percentage of these “lung neoplasms” appear to be similarly distributed among groups in the controlled studies.

- Pulmonary fibrosis

The FDA requested the sponsor to submit cases coded as pulmonary fibrosis. One of the cases was discussed under AE leading to discontinuation in the respiratory disorders SOC. The other case was coded as non-serious and did not lead to drug discontinuation, is as follows:

- **Patient 2301-0703-00016.** Coded as having “pulmonary fibrosis”.

44 F enrolled in 2301, received first dose in core phase on (b) (6) (FTY 1.25). Previously participated on monoclonal ab study (CNTO 1275) anti IL12 and IL23 from (b) (6) EDSS score: 3. Non smoker, no asthma or respiratory disorders.

End of study, (b) (6) (DAY 711) patient had a chest HRCT scan per protocol. HCRT reported abnormal findings of “fibrosis lingual of the left lung after inflammatory”. AE reported as fibrosis of the left lung inflammatory and left lung after inflammatory, which were coded as “Pulmonary fibrosis” and “pneumonia”.

During the study, the patient’s pulmonary function test DLCO had been 76% of baseline on visit 1 (Day 35) and 3 months (Day 117). An unscheduled PFT and HRCT were done on (b) (6) (day 167), which were normal. The patient continued treatment.

On Day 711, she had the abnormal HRCT finding at the end of study visit. Further details on the HRCT report was provided by the investigator as the following; “No focal lesions in the lungs, except for minor post-inflammatory fibrosis in the medial segment of the lingula of the left lung. No signs of diffuse fibrosis. Reduced lung aeration in the expiratory phase, proportional”. The finding was considered by the local radiologist to be abnormal compared to baseline but not of clinical significance. Patient was examined by the pulmonologist on (b) (6) (Month 24, EOS visit). The

Interim review, 5 12 10.
 Lourdes Villalba, M.D
 NDA 22-527. Fingolimod

patient's pulmonary function test was normal, no findings were reported, and the examination results were normal.

PFT evaluations in this patient are as follows.

Visit, Visit Date (Days since first dose)	FEV1 (L)	FVC (L)	Diffusion capacity for carbon monoxide (mmol/min/K Pa)	PI _{max} (cm H ₂ O)	PE _{max} (cm H ₂ O)	HRCT
(Screening)	2.88	3.82	6.93	103	125	Normal
(Day 35)	2.83	3.82	5.30	107	142	-
(Day 117)	2.78	3.7	5.31	130	133	-
(Unscheduled	2.63	4.11	7.56	105	84	Normal
(Day 188)	2.76	4.31	6.93	119	103	-
(Day 363)	2.65	4.62	7.72	127	109	-
(Day 549)	2.91	4.35	7.76	116	103	-
(Day 549)	2.91	4.35	7.76	116	103	-
(Day 711, EOS)	2.75	4.2	6.58	111	82	Fibrosis lingula of the left lung after inflammatory. Abnormal compared to baseline. Not clinically significant.
(Day 788, Ext Day 35)	2.7	3.87	7.36	121	101 -	-

Blank field = Not done

The patient completed the core phase of the study and entered the extension phase receiving the first dose of study medication (FTY720 1.25 mg) on (b) (6). The patient is still ongoing in the extension phase, and her last pulmonary function tests performed as per protocol on Month 1 of extension (Month 25 of study) were normal with no decrease in DLCO.

Comment: Asymptomatic, HRCT done per protocol. Normal PFTs. The clinical significance of the HCRT finding is unclear. Patient continued in study.

- Nervous system disorders SOC – Serious and non-serious events

- Seizures

A total of 14 patients had seizure-related events in the ISS database (epilepsy, convulsion, grand mal convulsion, partial seizures and petit mal) on FTY. Of those, 10 occurred during the controlled studies (9 on fingolimod and one on placebo). Although the numbers are small, the analysis suggests an increase risk of seizure related events in the fingolimod 5 and 1.25 mg groups as compared to placebo, which is consistent with the signal in the renal transplant database.

Table 49. Seizure related events in Safety pool D

	FTY720 5 mg N= 94 (Ny=43.2)	FTY720 1.25 mg N=943 (Ny=1111.2)	FTY720 0.5 mg N= 845 (Ny=1153.2)	Placebo N= 511 (Ny=746.9)	Interferon N= 431 (Ny=401.9)
Number of patients with event (%)	1 (1.1)	6 (0.6)	2 (0.2)	1 (0.2)	0
Number of events (rate per 100 PYRs)	1 (2.3)	13 (0.54)	4 (0.17)	1 (0.13)	0

Source: Response to request for information submitted 2/23/10.

Additionally, in the extension studies in the original ISS, six patients were reported to have seizures (4 in the FTY 5mg-1.25 mg, 4 in the FTY 1.25 mg group and 1 in the FTY 0.5 m group).

Brief narratives of the cases of seizure-related events in fingolimod controlled studies are included in Appendix 9.1.15. Of note, the narrative of the case of “convulsion” on placebo is as follows.

- **2201_0017_00004.** 45 F. No history of epilepsy. On Day 108 of placebo, the patient experienced “moderate convulsion which included dysesthesia in lower limbs and Lhermitte’s sign.”

Description in the narrative for the case on placebo does not suggest that it was a seizure. Therefore, all cases of seizures were on FTY treated patients. These included the case of fatal herpes simplex encephalitis, three cases in which seizures were thought to be due to MS relapse, and 3 cases in whom there was a previous history of seizures (2 on FTY720 1.25 mg and 1 on FTY720 0.5 mg). Of note, in the renal transplant population there was also a signal for increased risk of seizures in patients treated with FTY 2.5 and 5 mg as compared to MMF. The applicant proposes to address the potential risk of increased seizures in a postmarketing registry (PASS).

- Other events in the Nervous system disorders.

Other than seizure-related events, most AE in the Nervous system disorders SOC were actually slightly more common in the placebo arm than in the fingolimod groups, suggesting that they were related to MS. The only AE with a higher incidence in the fingolimod groups (both FTY 1.25 and FTY 0.5 mg) with >1% difference was migraine (3.2% on FTY 5mg, 3% on FTY 1.25, 3.4 on FTY 0.5%, 1.8% on placebo and 1.5% on IFN).

3 subjects presented SAE of syncope in the controlled studies. One occurred on placebo, on Day 163; one on FTY 1.25 on Day 724 and one on FTY 0.5, on Day 203. Evaluation of all cases (serious and non-serious) of syncope and loss of consciousness showed similar incidence in all treatment groups: 7 on FTY 1.25 (0.7%), 6 on FTY 0.5 (0.6%), 4 on placebo (0.8%) and 4 on

IFN (0.8%). Except for one case of syncope on Day 1 with IFN, events were spread throughout the whole duration of studies but they were most common within the first year.

- Metabolic disorders SOC

Non-serious abnormal weight gain were reported in two subjects in the controlled studies (one on FTY 0.5 mg [2302_0424_00004, a 36 yo M on day 199]; and one on IFN [2302_0543_00003, a 44 F on day 280]. Fluid retention was reported in two subjects on FTY 1.25 (one already described under discontinuations, a 53 F] and another one in a 42 F who developed fluid retention on day 356 [2302_0506_00006]). Additionally, one subject was reported to have overweight on Day 155 of FTY 1.25 mg treatment (2302_0101_00006). No narratives are available for these patients.

- Neoplasms benign, malignant and unspecified (including cysts and polyps) SOC

Given the potential long-term immunosuppressive effects of fingolimod, the possibility of an increased risk of neoplasms was evaluated in this database. The risk (n patients with event/N patients randomized) of any neoplasm (serious and non-serious) was similar among groups. However, the rate (number of patients with events/number of patient years of exposure) was higher in the FTY groups as compared to placebo, and similar to IFN.

Looking at the table of serious and non-serious cases in the controlled studies, there does not appear to be an increased risk of any particular neoplasm, except perhaps for melanocytic nevus, basal cell carcinoma and fibrous histiocytoma. These tumors have been reported to be associated with immunosuppression. However, 2201 did not have pre-specified dermatologic examinations and dermatologic examinations by a dermatologist were implemented in studies 2301 and 2302 when the studies were already ongoing. Most of the diagnoses of skin lesions were done at the first dermatologic examination, after the patients had been on treatment for several months, therefore there is a suggestion for an increase of skin tumors in FTY treated patients but prospective evaluation is needed. Study 2309 (the ongoing study) had dermatologic examinations from the start.

The risk of selected Neoplasms (serious and non-serious) in safety pool D is presented in the following table.

Table 50. Selected serious and non-serious events in the Neoplasms SOC, safety pool D

	FTY 1.25	FTY 0.5	Placebo	IFN
	N=943 n(%)	N=845 n(%)	N=511 n(%)	N=431 n(%)
All neoplasm	114 (12.1)	113 (13.2)	56 (11.0)	44 (10.2)
Melanocytic nevus	55 (5.8)	47 (5.5)	15 (2.9)	26 (6.0)
Fibrous histiocytoma	6 (0.6)	5 (0.6)	1 (0.2)	5 (1.2)
Basal cell carcinoma	3 (0.3)	7 (0.8)	3 (0.6)	1 (0.2)
Melanoma	1 (0.1)	3 (0.3)	1 (0.2)	0
Bening breast neoplasm	5 (0.5)	2 (0.2)	4 (0.8)	0
Breast cancer	3 (0.3)	1 (0.1)	3 (0.6)	0

	FTY 1.25 PYRs=1111.2	FTY 0.5 PYRs=1153.2	Placebo PYRs=746.9	IFN PYRs=401.9
All neoplasms Rate per 100 PYRS	10.3	9.8	4.9	10.9

Source: Original ISS tables.

Evaluation of cases in the controlled and OL database (safety group E) was consistent with findings in the controlled database (data not shown).

As discussed for SAE in this SOC, the lack of findings of increased malignancies in this database does not rule out an effect after long-term use. Additional information on long term effects of immunosuppression need to be collected with this drug. The applicant proposes to address this safety concern in a postmarketing registry (PASS).

7.3.5 Submission Specific Primary Safety Concerns

1. Increased risk of Infections

- Background
 - Anticipated possibility of an increased risk of infections because decreased peripheral lymphocytes.
- Findings in MS

There was no excess of overall infections, serious infections or opportunistic infections in the fingolimod groups. However, all serious herpetic infections occurred in fingolimod treated subjects, including two cases of fatal herpes virus infections (herpes encephalitis and disseminated zoster) in young people not taking concomitant MS immunomodulators but receiving IV methylprednisolone for empiric treatment of MS relapse and four other herpetic infections that required hospitalization and intravenous acyclovir.

Several but not all cases of AE of severe/atypical MS relapse in the fingolimod program underwent CSF PCR viral testing for JC virus, the agent associated with PML. All cases who underwent viral testing were negative. However, reliability of the results vary with the lab that conducts the analysis and the sequence that is used for the PCR, with sensitivity reportedly ranging from 60-80%.⁶ Dr. Major's lab at the NIH has been used for the evaluation of PML cases associated with natalizumab. Very few of the subjects with and AE of MS underwent PCR at the NIH. Of note, one patient with atypical MS who was eventually diagnosed with Sjogren's syndrome was found to have JC viral titers in serum, but not in the CSF (at NIH). The patient with a brain mass biopsy that showed lymphocytic infiltration had positive JV titers in urine, but not in the CSF (this patient had stopped drug treatment and had been treated with mefloquine for

⁶ Linda H, von Heijne A, Major E.O. et al. Progressive Multifocal Leukoencephalopathy after Natalizumab Monotherapy. New Engl J Med 2009; 361:1081-7.

some time before the biopsy). Presence of JC virus in serum or urine is not thought to mean infection.

Evaluation of SAE by HLGT suggests an increased risk of herpetic infections with FTY 1.25.

Evaluation of concomitant medications used after start of study drug in safety pool D (Post text Table 3.11-1 of ISS, data not shown) supports an increased risk of viral infections in the fingolimod treated groups as compared to placebo. The use of antiviral agents (systemic and topical) was 1.8%, 1.1%, 0.2% and 1.6%, for FTY 1.25mg, FTY 0.5 mg, placebo and IFN, respectively.

One question raised during this review is whether subjects should be immunized against varicella zoster before using fingolimod. Whether fingolimod affects naïve and acquired immunity to viral infections is unclear at this point.

It is also unclear how long the pharmacologic effect on lymphocytes lasts. The half life of fingolimod is 6 to 9 days. In clinical pharmacology study, most patients appeared to have recovered by day 56 after a 28-day course of fingolimod, although the FTY 0.5 mg dose still had a decrease of about 10%. Time to full recovery was not formally evaluated when fingolimod is given for one or two years.

The following are preliminary comments from Dr. Cavaille Coll, FDA immunologist consultant from the Division of Special Pathogens (DSPTP):

The risk of opportunistic infections in MS patients treated with fingolimod is not expected to be as great as that in solid organ transplantation patients or HIV-infected patients. Therefore, it is difficult to recommend that guidelines for monitoring, early treatment and prevention of opportunistic infections developed in solid organ transplant recipients or HIV-infected patients, should be systematically applied for MS patients treated with fingolimod. However, vaccination prior to initiation of long-term fingolimod therapy should be considered, as well as wording to the effect that immunosuppressants may affect vaccination, and therefore, vaccination may be less effective during treatment with fingolimod. (Note: this is class labeling for immunosuppressants in solid organ transplantation.)

Class labeling for immunosuppressants for the prevention of rejection in solid organ transplantation recommends that the use of live vaccines should be avoided; live vaccines may include, but are not limited to measles, mumps, rubella, oral polio, BCG, yellow fever, and TY 21a typhoid . A similar recommendation should be considered for fingolimod.

Peripheral blood lymphocyte counts and subsets cannot be used to reliably gauge the net state of immunosuppression in MS patients, treated with the proposed recommended dose of fingolimod, as these counts are used in HIV-infection. While peripheral blood lymphocyte counts may serve as a potential pharmacodynamic marker of fingolimod, to the extent that decreased lymphocyte counts may signify the presence of active drug on board, these counts appear to reflect redistribution and not lymphocyte depletion, and should not be interpreted as a reflection of infectious risk in the way they may be in HIV-infection.

Due to fingolimod's effect on lymphocyte circulation and distribution, fingolimod has the potential to modify the signs and symptoms of infection. Thus, one should maintain a higher

degree of suspicion for infection and atypical presentations in patients treated with fingolimod, as one would with other immunosuppressants or modulators of inflammation.

The question as whether to recommend cessation of fingolimod administration in the event of a new infection and for what type of infection, remains unresolved; however, the prolonged pharmacokinetic and pharmacodynamic half-life of fingolimod implies that the immunosuppressive effect may persist for several days after cessation of the drug.

Additional discussions regarding the role of lymphocyte monitoring and recommendations for vaccination prior to fingolimod use are expected at the June 10 2010 AAC.

2. Pulmonary toxicity

- Background
 - Non-clinical studies showed extensive lung toxicity
 - Increased bronchoconstriction in clinical pharmacology study at doses ≥ 5 mg day
 - In the renal transplant population, there was an excess of dyspnea and pulmonary edema in fingolimod treated subjects. It was unclear whether the cause was cardiac, pulmonary or infectious.
- Findings in MS population

Respiratory tract associated serious AE and discontinuations due to respiratory related AE (Respiratory, thoracic and mediastinal disorders SOC, and Investigations SOC –Pulmonary investigations HGLT) were not frequent, and there were no major differences between treatment groups in the controlled studies. However, evaluation in these subjects was not as complete as desirable. For instance, several subjects with dyspnea or chest pain were discontinued from the studies without having a chest XRay, HRCT, PFT, ECG or echocardiogram at the time of the event. Or if they did, it was several weeks or months after the event.

With regard to asthma, subjects with asthma were allowed in the study if they did not require active treatment for it. Only one patient had asthma exacerbation in the controlled database, and that occurred in a subject taking placebo. Three events of asthma (two exacerbation, one new onset) and one new onset broncho-constriction occurred in fingolimod treated patients during the extension studies (three in the FTY 5mg/1.25 mg; one on FTY 1.25 mg), suggesting that FTY may increase the risk of asthma exacerbation at least at the 5 and 1.25 doses. No events of asthma occurred at the 0.5 mg dose.

Across all trials, PFT measures (changes in percent predicted FEV1, FVC, and DLCO) consistently decreased from baseline to a greater degree in fingolimod-treated subjects versus placebo in a dose-dependent fashion. The changes in percent predicted PFT parameters correlated with changes in absolute values. The 0.5 mg dose group demonstrated declines in absolute FEV1 of ≥ 100 mL as early as 6 months after starting study drug, which is a greater annual decline in pulmonary function than is typically seen in healthy patients, patients with COPD, or MS patients in general. PFT decreases were not always associated with clinical symptoms, which may have been related to the high level of baseline pulmonary function in the

Phase III trial population, as FEV1 and FVC were consistently greater than 100% of predicted values. Evaluation of PFT outliers also suggested a dose response. This was observed in the controlled database (safety pool D) as well as in PFT analyses from study 2309 as discussed in section 7.4.5 (Special studies) below.

With regard to HRCT scan data, there appear to be more events of HRCT abnormal in the FTY treated groups but the incidence did not appear to be dose-dependent. The HRCT scans were read by local radiologists; no central adjudication of scans was performed in the phase 2 & 3 studies, which limits the interpretation of the results.

The following are the preliminary recommendations from Dr. Brian Porter, FDA pulmonologist consultant from the Division of Pulmonary, Allergy and Rheumatology Products (DPARP).

Based on these findings, DPARP recommends that DNP consider including information about the fingolimod-associated decline in pulmonary lung function and the higher incidence of new or worsened HRCT abnormalities in the fingolimod product label. At the current time, there are insufficient data to support a specific PFT monitoring schedule or to recommend routine HRCT screening of fingolimod recipients. However, providing information on the observed fingolimod-associated PFT and HRCT changes will facilitate the development of individualized monitoring plans by healthcare providers for MS patients on fingolimod. In turn, DPARP recommends that DNP consider inclusion of similar information about pulmonary toxicities in the REMS. Finally, DPARP recommends further study of pulmonary safety to determine the stability and reversibility of pulmonary function deficits with long-term use of fingolimod.

Additional discussions are expected at the June 10, 2010 AAC.

3. CV toxicity – Heart and rhythm disorders; LV function; ischemia/thrombosis

- Background
 - Known effect of S1P modulation on heart rate in vitro and in vivo
 - Renal patients had more cardiovascular deaths, MI and pulmonary edema at the 5 mg dose than the MMF group
 - Increased reports of S1P role in regulation of vascular permeability, vascular tone and angiogenesis
- Findings in MS

- Heart conduction disorders

There is a clear dose related effect in the heart conduction system upon first fingolimod treatment. 2.3% and 0.8 % of subjects in the FTY 1.25 mg and FTY 0.5 mg groups developed serious AE of bradycardia or 1st or 2nd degree AVB in the controlled studies. All had onset within 6 hours of first dose fingolimod treatment. One case of bradycardia and one of AVB occurred in

the placebo group, but the bradycardia was on day 121 and the AVB occurred on Day 684 (in a subject who had prior episodes of first and second AVB consistent with sick sinus syndrome).

Most cases of bradycardia/AVB recovered without intervention and continued treatment, however, one fifth of patients who developed bradycardia and half of the patients who developed AV block with FTY 1.25 mg discontinued the trial because of the AE. The cases that led to discontinuation were associated with chest pain/pressure/discomfort or dyspnea, and one was associated with bigeminism. Three subjects who interrupted treatment presented a similar episode of bradycardia or AVB when the drug was re-started. One subject who presented 2nd degree AVB on day one in the FTY 0.5 mg dose, presented chest pain/pressure leading to study discontinuation on Day 4.

Four subjects received atropine (3 on FTY 1.25 and 1 on FTY 0.5). One subject who developed 3rd degree AVB required isoproterenol, upon first dose of FTY 0.5 in the extension study.

The applicant proposes monitoring for six hours with the first fingolimod dose in subjects with sitting heart rate less than 55 bpm or receiving beta-blockers. However, patients who developed AE of bradycardia and AV block in fingolimod studies had normal HR and were not taking beta-blockers. Moreover, the studies included in the application excluded subjects with pre-existent diseases such as diabetes mellitus, heart conduction disorders taking antiarrhythmic medications or having pulmonary disease. It is anticipated that subjects with any of these disorders will not tolerate the events of bradycardia or AV block as well as these relatively healthy subjects. This population may need to be studied, at some point, before or after approval. Additionally, the labeling is imprecise as to where the monitoring needs to take place. That would likely be in a medical unit capable of immediate treatment for severe cases of bradycardia and heart block.

- LV function and ischemic heart disease

There was no excess of congestive heart failure or ischemic heart disease in the fingolimod treated groups in the controlled studies. However, not all patients who presented dyspnea, chest pain or angina underwent a complete cardiovascular evaluation and follow up (or if they were, they were not documented in the application).

There was only one event of serious pulmonary edema associated with transient LV dysfunction confounded by the use of alternative medicine and use of “varnish” preceding the event. There were no cases of congestive heart failure.

No evidence of effect on LV function was observed in the echocardiogram database but number of paired echoes is limited and long-term data are not available. Analysis of mean changes in LV function and wall thickness were unremarkable in the relatively small number of studies done in studies 2309/2302 (see review by Dr. Targum). A total of 183 subjects were included in the echocardiogram population. However, at the time of the original submission, only 17 pts had paired echocardiograms for up to 2 years.

One patient developed pulmonary hypertension during fingolimod treatment in study 2309. She was diagnosed during scheduled echocardiogram ongoing studies (the narrative is presented in

the AE leading to drug discontinuation section in the Cardiac SOC in study 2309). The possibility of fingolimod associated pulmonary hypertension needs further evaluation.

Additional echocardiographic evaluation of heart valves is pending from echocardiograms conducted in studies 2302 and 2309 is pending.

- Major ischemic/thrombotic events (CV death, non fatal MI and non fatal stroke)

There were no cardiovascular deaths in this application, and the number of myocardial infarction and stroke was small. Two MI were reported in the placebo group, one in the IFN group and none in the FTY groups in the controlled studies. There was one stroke at the 1.25 mg dose and no stroke in other treatment groups in the controlled studies.

Several cases of “angina pectoris” and “non-cardiac chest pain” were reported in this application, however, the reasons for the diagnosis and the work up done in these patients appears to be incomplete in most cases. These events have a similar distribution among treatment groups in the controlled studies.

Three additional strokes occurred in this application at the 1.25 mg dose (2 in the extension studies, one in study 2309). Additionally a TIA occurred on placebo in study 2309.

- Other vascular events

Two cases of peripheral vascular disease occurred in the controlled studies, both in the FTY 1.25 mg group, in association with nail splinter hemorrhages in both cases, and toe necrosis in one case.

There was one case of retinal artery microthrombosis, and one of bilateral retinal ischemia/vasculitis in the FTY 1.25 mg group in the controlled studies. Additionally, several non-serious vascular-related AE (retinal hemorrhage) occurred in the Eye disorders SOC.

One patient in study 2309 was diagnosed with pulmonary hypertension during fingolimod 1.25 mg treatment. Pulmonary artery pressure improved after drug discontinuation (the narrative is presented in the AE leading to drug discontinuation in the cardiac SOC, in ongoing studies). The possibility of fingolimod associated pulmonary hypertension needs further evaluation. Information on pulmonary artery pressure from the available echocardiograms from studies 2302 and 2309 is limited. Additional echocardiographic evaluation of heart valves from echocardiograms is pending.

The applicant proposes to explore the possibility of increased cardiovascular toxicity (MI, cerebrovascular events) in a post-marketing registry (PASS).

Additional discussions are expected at the June 10, 2010 AAC.

4. Eye toxicity

- Background
 - In the controlled renal transplant database, serious macular edema was reported in 4.1%, 3.9% and 1.5% of patients receiving FTY 5, FTY 2.5 mg and MMF, respectively.
- Findings in MS population

There was a clear dose response for serious and non-serious macular edema in the controlled studies (1.3% on FTY and 0.2% % on FTY 0.5). There was one case of ME in the IFN group (0.2%) and none in the placebo group. Serious and non-serious AE of macular edema were reported in twenty three subjects on FTY in the ISS database (13 in the controlled period, 9 during the extensions, including 4 cases on FTY 0.5 mg). As per the Special safety interim report update, 14 cases of ME were reported in study 2309, including 5 on FTY 0.5 mg (one was serious and all 5 led to study drug discontinuation).

The cases of ME on FTY 0.5 mg are summarized as follows (these are the same patients that were described in other sections of this review):

Controlled studies:

1. Patient # 2302_0424_00010. 41 M. No eye history. Visual acuity (VA) was 20/20 Bilaterally. OCT Central Foveal Thickness (CFT): 169 L & 170 R; At Month 1 dilated ophthalmoscopy (DO) showed unspecific maculopathy bilaterally. **On Day 94** DO was suspicious of classical macular edema (ME). Reported as SAE. Drug discontinued. CFT at 4/12 mo: 250 L, 171 R. treated with ketorolac eye drops. Treated with ketorolac eye drops, ME resolved 61 days after drug dc. At last assessment VA was 20/50 L, 20/25 R. CFT not available.
2. Patient # 2302 0408 00005.53 F. History of HTN. **On Day 367** dx with ME. At the time of dx of ME she had no eye symptoms but had mild decreased VA in R eye. DO showed bleeding surrounding upper temporal vein and venous thrombosis of upper temp vein in R eye, with macular edema. FA confirmed ME R eye. Reported as non-serious AE. Drug discontinued. Three months after drug discontinuation digital angiography showed that ME was still present but improving. Retinal branch vein occlusion was thought to be secondary to HTN.

Extension studies:

3. Patient # 2302E1 0211 00008. 36 M. No eye history. Screening VA 20/20. CFT on L eye at the end of core study was 152 microns. **On Day 189** of FTY treatment OCT showed CFT 203 microns. Reported as SAE. ME was not confirmed with FA. Pt was asymptomatic. Drug dc. No treatment. ME resolved 18 days after drug dc (VA 20/20; CFT 164 in L).

4. Patient # 2301E1 0657 00005. 50 F. Hx of HTN, amblyopia, prior treatment for suspected Lyme disease. Received placebo on core study. On **Day 106** CFT was 339 microns L, and 283 microns R; FA: retinal capillary leakage both eyes. VA not done. Reported as non serious AE. Drug was discontinued. Two months after drug dc a follow OCT and FA showed persistent cystoid macular edema L>R.

Study 2309:

5. Patient # 2309-0547-00007. 37 F. Hx of optic neuritis L eye since 4 years prior to entry. Screening VA 20/30+1 R, 20/25-2 L. CFC 186 microns in L and 220 in R. She complained of blurred vision in L eye. On day 36 she complained of stabbing pain in R eye. Fundoscopic exam showed epiretinal membrane (ERM) in R eye. OCT showed CFT 209 in L and 253 in R. Foveal contour was irregular in R eye but the overall assessment was negative for ME. **On Day 114** she c/o 1 week hx of decreased vision in R eye. VA was 20/30-2 in L and 20/50+ in R. Cystoid macular edema was dx in R eye. CFT was 198 in L and 471 microns in R eye. Reported as SAE. Led drug dc. For the ensuing 3 months she reported having a line across her field of vision but did not see an ophthalmologist. 3 months after drug dc VA was 20/200 at R and unchanged at L. Fundus exam showed a stage 4 macular hole in R eye. CFT was 504 microns in R eye and 208 in L eye. One image showed full thickness macular hole. She underwent ocular surgery to repair macular hole in R and ERM in L. Six months after surgery VA was 20/30 in L and 20/40 in R.

Four additional cases with FTY 0.5 mg (non-serious, leading to drug discontinuation) were submitted from study 2309 at the time of the safety update report (described in AE leading to drug discontinuation).

In addition to the cases of macular edema, there were 6 non-serious retinal hemorrhages in the controlled studies, all on FTY (3 on FTY 1.25 and 3 on FTY 0.5), and 4 cases of retinal detachment (3 on FTY 1.25 and 1 on FTY 0.5)(the one on FTY 0.5 led to drug discontinuation).

The ophthalmologic findings in FTY 0.5 deserve extensive discussion. FDA Ophthalmology consult is pending at the time of this review. Additional discussions are expected at the June 10 AAC.

5) Liver toxicity

- Background

The risk of ALT elevation >3xULN in the renal transplant population was around 20%, and slightly higher with FTY 5 and 2.5 mg as compared to MMF (19%, 20% and 15%, respectively).

- Finding sin MS

Review of liver-related adverse events and laboratory evaluations showed clear dose-related liver toxicity. The risk of ALT elevation ≥ 3 and ≥ 5 x ULN in the controlled studies and of drug discontinuation due to increase in liver-related enzymes in the controlled population are summarized in the following table.

Table 51. Liver-related analyses in pool D

	FTY 1.25 N= 943	FTY 0.5 N=854	Placebo N=511	IFN N=431
	n (%)	n (%)	n (%)	n (%)
ALT ≥ 3 x ULN	91 (9.7)	72 (8.5)	8 (1.6)	10 (2.3)
ALT ≥ 5 x ULN	21 (2.2)	14 (1.6)	4 (0.8)	2 (0.5)
Discontinuation due to Liver-related investigations ¹	39 (4.1)	29 (3.4)	3 (0.6)	7 (1.6)

¹ Hepatobiliary investigations HGLT

Review of SAE and discontinuations due to liver related events in the controlled and extension studies indicates that transaminase elevation occurred without increase in bilirubin and alkaline phosphatase in the great majority of cases. A total of 5 subjects presented ALT ≥ 3 x ULN and total BR ≥ 2 mg/dL in the original ISS. These cases are as follows

2301-0109-00002. Patient had been treated with FTY 0.5 mg for 10 months. She was hospitalized for pain on her hip and received IV paracetamol for 2 or 3 days. Before paracetamol ALT and AST were moderately elevated, but right after IV paracetamol, ALT was 4332 U/L and BR was 2.07 mg/dL. Liver enzymes started to decrease while the patient was still on FTY and resolved within 17 days after FTY discontinuation.

2301- 0307-00030 had liver transaminase elevations 5 days after dc placebo treatment.

2302E1-0724-00006 had history of Gilbert's disease. He had ALT < 3 x ULN and BR elevation up to > 2 x ULN intermittently during core study; during extension (FTY 0.5 mg) ALT > 3 xULN and BR > 2 x ULN on Day 14 and 66; drug was interrupted and restarted. ALT increased to 4x ULN leading to drug discontinuation on Day 214 of FTY treatment. Patient was asymptomatic. Liver enzyme elevation improved after drug discontinuation.

2201E1-0019-00004 also had a history of Gilbert's disease.

2302-0212-00021. 39 F. Herpes zoster disseminated, acute hepatic failure, multiorgan failure (narrative provided under Deaths.)

A case of ALT elevation and jaundice was reported as an IND safety report on 4/29/10. This case is under review.

On 5/11/10 the applicant submitted an amended REMS and amended labeling regarding liver toxicity.

5. Potential for Neurologic toxicity

- Background
 - Perivascular mononuclear infiltration was observed in the brain in 4-week and 26 week dog studies.
 - In the renal transplant population, the risk of seizures was slightly higher in the fingolimod 2.5 and 5 mg groups as compared to MMF.
- Findings in MS

5.1 Unusual relapse

Some uncommon neurologic conditions were diagnosed in subjects receiving FTY or after having received FTY (e.g ADEM). In addition to the cases in the ISS, one case of PRES and one case of diffuse multifocal leukoencephalopathy were diagnosed in blinded ongoing studies.

Three patients presented with a brain mass atypical for MS in this database. One in the controlled studies (subject #2301_0409_0008 with unusual MS relapse) and two in ongoing studies (subject #1201E_0005_00001 with tumors of the brain, liver, lung, etc, possible disseminated T cell lymphoma), and one in a study that is still blinded (submitted as IND safety report). This latter subject had a brain biopsy that did not show lymphoma but showed lymphocytic infiltration (he had been treated with mefloquine, for possible PML).

5.2 Seizures

Evaluation of tables of serious AE in the renal transplant population found 15 individual patients with seizure-related terms (e.g. epilepsy, convulsion, grand mal convulsion, partial seizures). The analysis of serious seizure related events suggested a higher risk of seizures with fingolimod 5 mg ($8/461 = 1.7\%$) and 2.5 mg ($6/456 = 1.3\%$) as compared to MMF ($1/461 = 0.2\%$) in the renal transplant population. These patients had renal failure, were taking concomitant Cyclosporin A and most had other acute problems at the time of the seizure.

A total of 14 patients had seizure-related events in the MS ISS database on FTY, one case of convulsion in the placebo group and no such cases in the INF group. Of those, 10 occurred during the controlled studies (9 on fingolimod and one on placebo). Three patients had a previous history of epilepsy and others presented in the setting of an unusual MS relapse. Although the numbers are small (0.5% with FTY 1.25, 0.2% with FTY 0.5 mg), the analysis suggests an increased risk with FTY 1.25 mg as compared to placebo (it is unclear if the case on placebo was a real seizure), which is consistent with the signal in the renal transplant database.

The applicant references a publication in which seizures have been reported to occur in about 2–3% of all patients with MS (Koch et al 2008, Kelley and Rodriguez 2009) suggesting that the rate of convulsions observed in the 0.5 mg FTY720 group in MS clinical studies would be within the epidemiological experience. A baseline history of epilepsy or seizures in the MS population was around 1%.

The applicant proposes to explore the possibility of a higher risk of seizures with a postmarketing registry (PASS).

7.4 Supportive Safety Results and Discussion

7.4.1 Common Adverse Events

A similar percentage of patients presented AE in the treatment groups in pool D (approximately 91%). The % in FTY 5 mg was slightly higher.

Number of patients with AE in $\geq 5\%$ of patients in pool D is presented in the following table

Table 52. Number of patients with AE in $\geq 5\%$ of patients, safety pool D

	FTY720 5 mg (N=94) n (%)	FTY720 1.25 mg (N=943) n (%)	FTY720 0.5 mg (N=854) n (%)	Placebo (N=511) n (%)	Interferon (N=431) n (%)
Any preferred term	90 (95.7)	864 (91.6)	771 (90.3)	464 (90.8)	396 (91.9)
Headache	18 (19.1)	233 (24.7)	207 (24.2)	109 (21.3)	88 (20.4)
Nasopharyngitis	26 (27.7)	221 (23.4)	203 (23.8)	128 (25.0)	88 (20.4)
Fatigue	8 (8.5)	114 (12.1)	92 (10.8)	54 (10.6)	45 (10.4)
Upper respiratory tract infection	2 (2.1)	102 (10.8)	104 (12.2)	76 (14.9)	27 (6.3)
Diarrhoea	12 (12.8)	84 (8.9)	82 (9.6)	33 (6.5)	21 (4.9)
Alanine aminotransferase increased	7 (7.4)	82 (8.7)	71 (8.3)	18 (3.5)	8 (1.9)
Back pain	8 (8.5)	76 (8.1)	76 (8.9)	32 (6.3)	23 (5.3)
Influenza	7 (7.4)	74 (7.8)	84 (9.8)	44 (8.6)	32 (7.4)
Nausea	10 (10.6)	74 (7.8)	78 (9.1)	38 (7.4)	29 (6.7)
Cough	5 (5.3)	69 (7.3)	63 (7.4)	37 (7.2)	16 (3.7)
Bronchitis	3 (3.2)	61 (6.5)	54 (6.3)	16 (3.1)	11 (2.6)

Interim review, 5 12 10.
 Lourdes Villalba, M.D
 NDA 22-527. Fingolimod

Dizziness	7 (7.4)	55 (5.8)	55 (6.4)	28 (5.5)	21 (4.9)
Hypertension	6 (6.4)	55 (5.8)	42 (4.9)	17 (3.3)	9 (2.1)
Melanocytic naevus	0 (0.0)	55 (5.8)	47 (5.5)	15 (2.9)	26 (6.0)
Gamma-glutamyltransferase increased	0 (0.0)	51 (5.4)	36 (4.2)	4 (0.8)	1 (0.2)
Pharyngitis	3 (3.2)	51 (5.4)	40 (4.7)	26 (5.1)	13 (3.0)
Dyspnoea	12 (12.8)	50 (5.3)	38 (4.4)	20 (3.9)	7 (1.6)
Sinusitis	2 (2.1)	49 (5.2)	38 (4.4)	21 (4.1)	11 (2.6)
Arthralgia	3 (3.2)	48 (5.1)	42 (4.9)	38 (7.4)	24 (5.6)
Pain in extremity	5 (5.3)	48 (5.1)	50 (5.9)	32 (6.3)	28 (6.5)
Urinary tract infection	3 (3.2)	48 (5.1)	60 (7.0)	50 (9.8)	22 (5.1)
Depression	4 (4.3)	47 (5.0)	54 (6.3)	34 (6.7)	33 (7.7)
Insomnia	2 (2.1)	42 (4.5)	39 (4.6)	28 (5.5)	13 (3.0)
Oropharyngeal pain	2 (2.1)	40 (4.2)	46 (5.4)	32 (6.3)	15 (3.5)
Abdominal pain upper	5 (5.3)	37 (3.9)	29 (3.4)	19 (3.7)	13 (3.0)
Hypercholesterolaemia	1 (1.1)	37 (3.9)	34 (4.0)	26 (5.1)	3 (0.7)
Pyrexia	7 (7.4)	35 (3.7)	26 (3.0)	9 (1.8)	77 (17.9)
Gastroenteritis	5 (5.3)	33 (3.5)	29 (3.4)	13 (2.5)	12 (2.8)
Rash	5 (5.3)	31 (3.3)	19 (2.2)	22 (4.3)	8 (1.9)
Rhinitis	2 (2.1)	30 (3.2)	38 (4.4)	27 (5.3)	11 (2.6)
Leukopenia	5 (5.3)	25 (2.7)	17 (2.0)	1 (0.2)	1 (0.2)
Myalgia	1 (1.1)	24 (2.5)	26 (3.0)	14 (2.7)	44 (10.2)
Constipation	6 (6.4)	22 (2.3)	28 (3.3)	23 (4.5)	10 (2.3)
Influenza like illness	1 (1.1)	19 (2.0)	24 (2.8)	6 (1.2)	159 (36.9)
Somnolence	6 (6.4)	11 (1.2)	9 (1.1)	11 (2.2)	4 (0.9)
Chest pain	5 (5.3)	9 (1.0)	7 (0.8)	7 (1.4)	2 (0.5)

Source: Table 4-2. ISS addendum, submitted in February 2010.

The following discussion will not involve FTY 5 because the number of patients is small and they were only exposed for ≤ 6 months. The most common events were headache, nasopharyngitis, fatigue and upper respiratory infection (with at $\geq 10\%$ of patients presenting the AE in any treatment group).

Events that occurred most frequently in the fingolimod treatment groups (FTY 1.25 and/or FTY 0.5 mg) with at least 1% higher risk as compared to placebo were: headache, fatigue, diarrhea, ALT increased, back pain, nausea, bronchitis, hypertension, melanocytic nevus, GGT increased, dyspnea, sinusitis, pyrexia, gastroenteritis, leukopenia and influenza like illness. Pyrexia and influenza like illness were much higher in the INF group (17.9% and 36.9%, respectively) as compared to fingolimod (2-4%) and placebo (1.8 for pyrexia, 1.2% for influenza-like illness).

The events with the greater difference in risk were ALT increased (at least twice as compared to placebo), GGT increase (at least 5 fold the risk on placebo), bronchitis (twice the risk as compared to placebo) and melanocytic nevus (almost twice as compared to placebo, but similar to IFN).

Evaluation of common AE is consistent with the analyses of serious AEs and discontinuations leading to AE, with a signal for increased liver enzymes. There is no signal for increased infections, except for bronchitis. It is unclear if the increased risk of melanocytic nevus is related to immunosuppression.

7.4.2 Laboratory Findings

Hematology mean changes from baseline in WBC, absolute lymphocyte, neutrophil and platelet counts at month 1 and month 12, by treatment in Pool A, are presented as follows:

Table 53. Change in selected hematologic parameters over time in Safety pool A in Fingolimod studies.

Parameter	FTY 1.25 N=849	FTY 0.5 N=854	Placebo N=418	Interferon N=431
WBC (total) ($10^9/L$)				
n	793	801	401	402
Baseline Mean (SD)	6.57 (1.93)	6.46 (1.81)	6.69 (1.90)	6.47 (1.76)
Month 1 Mean (SD)	4.33 (1.73)	4.43 (1.50)	6.54 (1.82)	6.19 (1.78)
Change from baseline Mean (SD)	-2.24 (1.77)	-2.03 (1.48)	-0.15 (1.70)	-0.28 (1.58)
n	733	784	384	382
Baseline Mean (SD)	6.56 (1.91)	6.46 (1.80)	6.70 (1.86)	6.49 (1.79)
Month 6 Mean (SD)	3.98 (1.50)	4.30 (1.47)	6.54 (2.03)	6.33 (1.89)
Change from baseline to Month 6 Mean (SD)	-2.59 (1.69)	-2.16 (1.54)	-0.16 (1.74)	-0.16 (1.84)
n	696	748	354	365
Baseline Mean (SD)	6.60 (1.93)	6.46 (1.80)	6.68 (1.86)	6.44 (1.76)
Month 12 Mean (SD)	3.99 (1.53)	4.26 (1.65)	6.44 (1.77)	6.30 (1.99)
Change from baseline to Month 12 Mean (SD)	-2.61 (1.75)	-2.20 (1.71)	-0.24 (1.47)	-0.14 (1.83)
Absolute lymphocytes ($10^9/L$)				
n	780	785	399	398
Baseline Mean (SD)	1.81 (0.54)	1.82 (0.59)	1.82 (0.57)	1.77 (0.54)
Month 1 Mean (SD)	0.42 (0.24)	0.49 (0.24)	1.76 (0.52)	1.69 (0.56)
Change from baseline to Month 1 Mean (SD)	-1.39 (0.52)	-1.33 (0.56)	-0.06 (0.41)	-0.07 (0.50)
n	714	772	378	380
Baseline Mean (SD)	1.81 (0.54)	1.81 (0.58)	1.83 (0.58)	1.77 (0.53)
Month 6 Mean (SD)	0.39 (0.23)	0.49 (0.29)	1.77 (0.59)	1.71 (0.57)
Change from baseline to Month 6 Mean (SD)	-1.41 (0.53)	-1.33 (0.56)	-0.06 (0.47)	-0.06 (0.53)
n	685	736	353	359
Baseline Mean (SD)	1.81 (0.54)	1.82 (0.58)	1.82 (0.59)	1.74 (0.52)
Month 12 Mean (SD)	0.41 (0.26)	0.49 (0.32)	1.76 (0.57)	1.69 (0.57)
Change from baseline to Month 12 Mean (SD)	-1.40 (0.53)	-1.33 (0.55)	-0.06 (0.44)	-0.05 (0.49)
Absolute neutrophils ($10^9/L$)				
n	780	786	399	400
Baseline Mean (SD)	4.09 (1.57)	4.00 (1.45)	4.21 (1.57)	4.04 (1.45)
Month 1 Mean (SD)	3.36 (1.60)	3.39 (1.36)	4.13 (1.51)	3.84 (1.50)
Change from baseline to Month 1 Mean (SD)	-0.73 (1.57)	-0.61 (1.30)	-0.09 (1.55)	-0.20 (1.40)
n	686	739	353	360
Baseline Mean (SD)	4.12 (1.54)	3.99 (1.44)	4.20 (1.53)	4.02 (1.45)
Month 12 Mean (SD)	3.07 (1.36)	3.26 (1.45)	4.06 (1.46)	3.96 (1.69)
Change from baseline to Month 12 Mean (SD)	-1.05 (1.50)	-0.73 (1.49)	-0.14 (1.34)	-0.05 (1.67)
Platelet count ($10^9/L$)				
n	792	799	401	400
Baseline Mean (SD)	269.97 (65.56)	268.68 (64.76)	270.16 (63.16)	268.48 (61.78)
Month 1 Mean (SD)	256.72 (62.00)	259.95 (57.36)	268.08 (59.94)	267.55 (65.56)
Change from baseline to Month 1 Mean (SD)	-13.26 (38.89)	-8.73 (37.18)	-2.08 (38.26)	-0.93 (47.38)
n	694	746	354	364
Baseline Mean (SD)	270.58 (66.03)	269.91 (65.11)	269.26 (63.74)	267.28 (61.06)
Month 12 Mean (SD)	263.86 (65.11)	266.35 (64.07)	269.97 (65.08)	268.89 (66.54)
Change from baseline to Month 12 Mean (SD)	-6.71 (42.70)	-3.56 (44.10)	0.71 (45.69)	1.61 (46.81)

Interim review, 5 12 10.

Lourdes Villalba, M.D

NDA 22-527. Fingolimod

Source: Modified from Post text Table 5.1-2, ISS.

As seen in this table, there was a clear decrease in mean absolute WBC and lymphocyte counts, but also a slight decrease in mean neutrophil and platelet counts from baseline in the fingolimod groups, as compared to placebo or interferon. The clinical significance of these small changes is unclear. Evaluation of median changes from baseline in hematologic parameters showed results similar to the evaluation of mean changes.

Percentage change in lymphocytes in Study 2301 (the 2 year study, also the only study in Safety pool B) presented in the following table:

Table 54. Percentage Change in absolute lymphocyte count in study 2301

Treatment	n	Baseline			Post-baseline			Percent of Baseline					
		Mean	SD	Med	Mean	SD	Med	Mean	SD	Min	Med	Max	
Week 2													
FTY720 1.25mg (N=429)	391	1.8225	0.54262	1.7500	0.4701	0.29886	0.4000	26.42	14.123	0.0	23.33	104.9	
FTY720 0.5mg (N=425)	403	1.8610	0.63279	1.7900	0.5492	0.23261	0.5200	30.86	12.401	10.1	28.57	92.6	
Placebo (N=418)	389	1.8170	0.57581	1.7600	1.7496	0.54376	1.6800	98.74	23.285	22.4	96.01	178.5	
Month 1													
FTY720 1.25mg (N=429)	394	1.8394	0.55265	1.7700	0.4452	0.26019	0.3900	25.15	14.351	4.2	21.65	106.8	
FTY720 0.5mg (N=425)	392	1.8702	0.63205	1.8000	0.5134	0.26984	0.4600	28.84	13.922	7.3	26.05	105.2	
Placebo (N=418)	399	1.8196	0.57269	1.7600	1.7631	0.52407	1.7000	99.38	22.067	31.4	98.34	202.4	
Month 2													
FTY720 1.25mg (N=429)	379	1.8473	0.55548	1.7700	0.4678	0.30584	0.3900	26.18	15.955	4.7	22.70	126.4	
FTY720 0.5mg (N=425)	391	1.8692	0.63338	1.7900	0.5014	0.26554	0.4300	28.21	14.151	6.5	25.19	96.2	
Placebo (N=418)	383	1.8270	0.58173	1.7800	1.7622	0.57525	1.6800	98.44	22.357	49.6	96.10	193.4	
Month 3													
FTY720 1.25mg (N=429)	383	1.8423	0.55144	1.7700	0.4537	0.32737	0.3700	25.33	16.484	5.1	21.05	181.5	
FTY720 0.5mg (N=425)	399	1.8690	0.63467	1.7900	0.4904	0.25452	0.4400	27.72	14.515	4.8	25.00	107.0	
Placebo (N=418)	390	1.8155	0.57550	1.7550	1.7422	0.51179	1.6800	98.77	22.247	21.5	96.16	181.9	
Month 6													
FTY720 1.25mg (N=429)	364	1.8433	0.55084	1.7700	0.4228	0.26132	0.3600	23.92	14.664	4.5	20.57	113.9	
FTY720 0.5mg (N=425)	396	1.8419	0.61568	1.7800	0.4830	0.27546	0.4200	27.54	15.063	5.1	24.09	93.8	
Placebo (N=418)	378	1.8288	0.58327	1.7650	1.7733	0.58608	1.7000	99.33	24.086	12.5	98.06	193.3	
Month 9													
FTY720 1.25mg (N=429)	356	1.8500	0.54847	1.7750	0.4343	0.26895	0.3600	24.11	13.356	4.2	20.40	75.5	
FTY720 0.5mg (N=425)	385	1.8456	0.61759	1.7900	0.4982	0.33823	0.4200	28.01	16.736	6.1	23.98	142.0	
Placebo (N=418)	368	1.8271	0.58341	1.7600	1.7682	0.58812	1.7300	99.51	26.755	19.8	96.64	221.2	
Month 12													
FTY720 1.25mg (N=429)	348	1.8370	0.54281	1.7650	0.4224	0.26068	0.3600	23.82	13.916	3.1	20.47	120.4	
FTY720 0.5mg (N=425)	380	1.8524	0.62069	1.7850	0.4985	0.33341	0.4100	27.72	15.687	5.0	23.72	107.7	
Placebo (N=418)	356	1.8228	0.58296	1.7550	1.7649	0.56413	1.7200	99.34	23.753	44.3	96.96	229.8	
Month 15													
FTY720 1.25mg (N=429)	335	1.8462	0.54429	1.7800	0.4385	0.26002	0.3700	24.79	14.343	5.1	21.05	122.8	
FTY720 0.5mg (N=425)	365	1.8340	0.61751	1.7700	0.5013	0.33380	0.4200	28.30	15.701	6.9	25.00	138.7	
Placebo (N=418)	343	1.8054	0.55237	1.7500	1.7699	0.59826	1.6700	100.43	29.263	36.9	96.75	411.9	
Month 18													
FTY720 1.25mg (N=429)	313	1.8441	0.52948	1.7900	0.4550	0.32688	0.3700	25.33	15.656	3.8	20.71	97.2	
FTY720 0.5mg (N=425)	357	1.8403	0.62244	1.7700	0.4970	0.32750	0.4200	27.91	15.156	5.5	24.55	126.0	
Placebo (N=418)	323	1.8147	0.55702	1.7600	1.7662	0.55842	1.7200	100.22	27.342	29.7	98.32	277.2	
Month 21													
FTY720 1.25mg (N=429)	304	1.8450	0.54365	1.7900	0.4495	0.31444	0.3700	25.34	16.795	4.9	21.05	117.3	
FTY720 0.5mg (N=425)	349	1.8296	0.61942	1.7600	0.5134	0.35579	0.4200	29.19	17.882	7.0	24.84	182.7	
Placebo (N=418)	319	1.8124	0.55609	1.7500	1.7532	0.56086	1.7000	99.53	26.007	18.7	98.08	205.7	
Month 24													
FTY720 1.25mg (N=429)	292	1.8487	0.54129	1.7850	0.4208	0.26175	0.3575	23.39	12.823	3.2	20.15	109.0	
FTY720 0.5mg (N=425)	339	1.8412	0.61544	1.7600	0.4855	0.34226	0.4100	27.23	15.549	6.4	23.53	135.4	
Placebo (N=418)	304	1.8154	0.56276	1.7500	1.7605	0.56800	1.6750	99.55	24.365	41.3	97.79	191.3	
Last assessment on study drug *													
FTY720 1.25mg (N=429)	415	1.8384	0.54581	1.7700	0.4324	0.28931	0.3600	24.47	15.680	3.2	20.67	110.1	
FTY720 0.5mg (N=425)	421	1.8559	0.62470	1.7900	0.4933	0.34283	0.4100	27.31	15.274	5.5	23.86	103.9	
Placebo (N=418)	413	1.8188	0.56878	1.7600	1.7846	0.62259	1.6900	100.53	26.083	18.7	98.55	210.4	

Source: Table 14.3-2.2d (pg 6) of CSR Lymphocyte % change over time in study 2301. - If a patient has more than one value in a visit window, the mean of the values is used. - n = patients with non-missing baseline and post-baseline values. - * The last laboratory value taken at or before last day of study drug is summarized in row 'Last assessment on study drug'.

As seen in these analyses, the absolute lymphocyte count went down by approximately 75%, and was as low as 23% and 28% of baseline at month 6, for fingolimod 1.25 and 0.5 mg, respectively. The decrease in lymphocyte count was observed at 2 weeks and was maintained

through the 2 year period among the patients who stayed in the study. There was some suggestion of a dose response, with slightly greater effect with fingolimod 1.25 mg.

There was no decrease in neutrophil, eosinophil, monocytes and RBC percentages over time, but there appear to be a tiny effect on platelet count (decrease by 3-5 % in mean counts, with wide standard deviation), that does not seem to be clinically relevant (data not shown) . There was also a decrease from baseline on basophil count as compared to placebo (approximately 80% for FTY and 35% for placebo, see table below). The clinical relevance of this change in basophil count is unclear.

Table 55. Change in absolute basophil count in study 2301

Treatment	n	Baseline			Post-baseline			Percent of Baseline				
		Mean	SD	Med	Mean	SD	Med	Mean	SD	Min	Med	Max
Month 6												
FTY720 1.25mg (N=429)	170	0.0994	0.01918	0.1000	0.0150	0.03503	0.0000	14.74	34.514	0.0	0.00	100.0
FTY720 0.5mg (N=425)	205	0.1005	0.01735	0.1000	0.0187	0.03914	0.0000	19.22	41.638	0.0	0.00	250.0
Placebo (N=418)	196	0.1011	0.02166	0.1000	0.0664	0.05469	0.1000	65.87	54.632	0.0	100.00	200.0

Source: Table 14.3-2.2d (pg 14) of ISS

A subset of patients in safety pool E was followed up after drug discontinuation (n=516 subjects). Analysis of % change from baseline in lymphocyte counts in this population is presented below.

Table 56. Change in lymphocyte % in E follow up cohort

Visit	Treatment Group	n	Baseline			Endpoint		Post baseline			
			Mean	SD	Median	Mean	SD	Median	Change from Baseline	Mean	SD
TEP											
	FTY720 5 mg - 1.25 mg (N=47)	46	28.45	8.920	26.95	11.98	6.163	11.50	-16.47	10.162	-17.80
	FTY720 1.25 mg (N=297)	281	29.30	7.945	29.00	11.72	7.042	10.00	-17.57	8.239	-18.00
	FTY720 0.5 mg (N=194)	189	28.42	7.825	29.00	12.15	6.930	11.00	-16.27	7.889	-16.00
	Total (N=538)	516	28.90	7.988	28.45	11.90	6.917	11.00	-17.00	8.309	-17.00
Day 1-45 after drug discontinuation											
	FTY720 5 mg - 1.25 mg (N=47)	24	27.57	10.840	25.25	12.58	6.128	12.90	-15.00	10.121	-12.45
	FTY720 1.25 mg (N=297)	174	28.23	7.409	28.00	14.92	8.409	14.00	-13.31	10.737	-13.28
	FTY720 0.5 mg (N=194)	96	28.10	7.425	28.00	16.08	8.081	15.00	-12.03	8.143	-11.25
	Total (N=538)	294	28.14	7.716	28.00	15.11	8.169	14.00	-13.03	9.915	-13.00
Month 3 after drug discontinuation											
	FTY720 5 mg - 1.25 mg (N=47)	33	28.76	9.276	25.50	17.84	6.451	17.30	-10.92	9.521	-10.30
	FTY720 1.25 mg (N=297)	199	28.91	7.570	28.00	23.49	7.802	22.60	-5.42	8.161	-5.00
	FTY720 0.5 mg (N=194)	124	28.35	7.277	28.50	23.48	7.374	24.00	-4.87	7.280	-5.00
	Total (N=538)	356	28.70	7.625	28.00	22.96	7.696	22.00	-5.74	8.155	-5.00
Month 6 after drug discontinuation											
	FTY720 5 mg - 1.25 mg (N=47)	12	31.73	14.011	28.30	18.67	7.038	20.85	-13.07	11.663	-11.05

FTY720 1.25 mg (N=297)	72	28.22	7.977	27.00	24.94	8.710	24.50	-3.28	9.139	-3.00
FTY720 0.5 mg (N=194)	47	28.57	6.477	28.00	25.10	7.938	25.00	-3.48	7.160	-4.00
Total (N=538)	131	28.67	8.197	28.00	24.42	8.443	24.00	-4.25	9.120	-4.00
Month 9 after drug discontinuation										
FTY720 5 mg - 1.25 mg (N=47)	3	33.07	10.909	28.60	26.53	6.018	26.00	-6.53	12.007	-4.30
FTY720 1.25 mg (N=297)	43	28.38	7.455	28.00	25.91	8.706	24.00	-2.47	8.170	-3.00
FTY720 0.5 mg (N=194)	27	29.30	7.384	31.00	27.04	8.746	25.00	-2.26	8.036	-4.00
Total (N=538)	73	28.91	7.507	28.30	26.35	8.552	25.00	-2.56	8.183	-3.00
Month 12 after drug discontinuation										
FTY720 1.25 mg (N=297)	35	29.77	7.656	30.00	27.46	8.045	26.00	-2.32	7.523	-2.00
FTY720 0.5 mg (N=194)	20	27.35	7.132	26.00	26.85	9.708	29.00	-0.50	10.092	1.00
Total (N=538)	55	28.89	7.496	27.00	27.24	8.602	28.00	-1.66	8.500	-1.00
Month 15 after drug discontinuation										
FTY720 1.25 mg (N=297)	14	27.21	7.062	26.50	26.64	8.391	27.50	-0.57	7.439	0.50
FTY720 0.5 mg (N=194)	6	30.83	8.565	29.00	26.50	10.213	26.50	-4.33	10.152	-2.00
Total (N=538)	20	28.30	7.505	27.00	26.60	8.696	27.50	-1.70	8.253	-1.00
Month 18 after drug discontinuation										
FTY720 1.25 mg (N=297)	19	29.26	7.759	26.00	28.42	8.402	25.00	-0.84	7.625	-1.00
FTY720 0.5 mg (N=194)	10	27.60	6.150	26.00	25.00	9.580	27.00	-2.60	6.186	-1.50
Total (N=538)	29	28.69	7.177	26.00	27.24	8.810	26.00	-1.45	7.099	-1.00
Month 21 after drug discontinuation										
FTY720 1.25 mg (N=297)	7	26.57	6.161	25.00	29.21	8.999	28.50	2.64	9.059	0.00
FTY720 0.5 mg (N=194)	2	40.50	6.364	40.50	35.50	7.778	35.50	-5.00	1.414	-5.00
Total (N=538)	9	29.67	8.441	29.00	30.61	8.717	30.00	0.94	8.553	-2.00
Month 24 after drug discontinuation										
FTY720 1.25 mg (N=297)	9	31.00	8.201	27.00	30.22	6.741	31.00	-0.78	10.208	-2.00
FTY720 0.5 mg (N=194)	2	24.00	1.414	24.00	26.50	6.364	26.50	2.50	4.950	2.50
Total (N=538)	11	29.73	7.875	26.00	29.55	6.532	31.00	-0.18	9.358	-2.00

Source: Post Table 11.1-2 (pg 12 of 15), ISS. Change from baseline = endpoint - baseline. - For each laboratory test, only patients with a value at both baseline and post-baseline are included. - The last non-missing value on treatment is summarized in TEP (treatment end timepoint).

Analysis in this population shows that at the end of study evaluation in safety pool E, the lymphocyte count had decreased by 17 or 18%. By 3 months after drug discontinuation, the mean lymphocyte counts were still 5% (FTY 0.5 and FTY 1.25mg) or 10% (FTY 5-1.25 mg group) below baseline. A tiny effect in mean % lymphocyte count seems still present by 1 year and 18 months after drug discontinuation (<2% decrease from baseline). Such a small decrease in % of peripheral lymphocyte count as compared to baseline seems to be of no clinical relevance; however, it would suggest that the pharmacological effects of fingolimod might extend beyond the 45-day (5 half lives) period, at least in lymphoid tissues. Interpretation of these data are limited by the lack of a control arm.

- Analysis of outliers for hematologic abnormalities

Outlier analysis in Group D are presented in the following table.

Table 57. Outlier analysis of hematologic abnormalities in Safety Pool D

		FTY720 5 mg (N=94)	FTY720 1.25 mg (N=943)	FTY720 0.5 mg (N=854)	Placebo (N=511)	Interferon (N=431)
Parameter	Criterion	n (%)	n (%)	n (%)	n (%)	n (%)
WBC (total)	Total	93	934	851	506	429
	$\leq 2.0 \times 10^9/\text{L}$	8 (8.6)	100 (10.7)	64 (7.5)	0	0
	$\geq 15 \times 10^9/\text{L}$	0	6 (0.6)	3 (0.4)	12 (2.4)	7 (1.6)
Absolute Lymphocytes	Total	93	934	850	506	429
	$< 0.2 \times 10^9/\text{L}$	10 (10.8)	273 (29.2)	142 (16.7)	0	3 (0.7)
	$\geq 8 \times 10^9/\text{L}$	0	0	0	0	0
Absolute Neutrophils (Seg. + Bands)	Total	93	934	850	506	429
	$\leq 1 \times 10^9/\text{L}$	3 (3.2)	30 (3.2)	17 (2.0)	6 (1.2)	5 (1.2)
	$\geq 12 \times 10^9/\text{L}$	0	11 (1.2)	9 (1.1)	12 (2.4)	7 (1.6)
RBC	Total	0	840	851	414	429
	$< 3.3 \times 10^{12}/\text{L}$		2 (0.2)	0	1 (0.2)	0
	$> 6.8 \times 10^{12}/\text{L}$		0	0	0	1 (0.2)
Haemoglobin	Total	93	934	851	506	429
	$\leq 100 \text{ g/L}$	4 (4.3)	12 (1.3)	14 (1.6)	12 (2.4)	8 (1.9)
Platelet count (direct)	Total	93	934	850	506	429
	$\leq 100 \times 10^9/\text{L}$	2 (2.2)	2 (0.2)	5 (0.6)	5 (1.0)	1 (0.2)
	$\geq 600 \times 10^9/\text{L}$	1 (1.1)	2 (0.2)	1 (0.1)	3 (0.6)	1 (0.2)

Source: Post text Table 5.8-3, ISS. Submitted as Addendum ISS on February 2010. n = number of patients with the notable abnormality criterion. Total = Total number of patients with the parameter value Percentages are calculated as $n/\text{Total} \times 100$

Analysis of outliers for hematologic parameters did not suggest a safety signal, other than the known effect on lymphocyte counts.

Analysis of notable hematologic abnormalities in group E were consistent with those in the core studies.

- Shift analyses of hematologic values:

Shift analyses for hematologic values were unremarkable, other than the change from normal to below normal for WBC and lymphocyte count (data not shown).

- Chemistry evaluations

As discussed in section 7.2 Adequacy of routine testing, routine hematology, some chemistry (including cholesterol, triglycerides, albumin, creatinine and liver enzymes) and UA were conducted throughout the studies. However, electrolytes (sodium, potassium, bicarbonate, calcium, magnesium) were not collected in the phase 2 and 3 MS studies. The lack of electrolyte evaluations in this program is of concern, particularly the fact that electrolytes are missing from

the narratives and patient profiles of patients who developed adverse events that could be associated to electrolyte disturbances (e.g. bradycardia, extrasystoles, seizures).

An analysis of electrolytes was conducted in study 2113, a 28-day clinical pharmacology study. Standard analyses of mean changes from baseline, outlier analyses and shift analyses for sodium, potassium, magnesium, bicarbonate and calcium were unremarkable in this study. A retrospective analysis of electrolytes in a subset of blood samples from patients in study 2301 was submitted with the 120-day SUR. Review of that data are ongoing at the time of this review.

- Liver enzymes

Evaluation of liver enzymes indicated that fingolimod is associated with an increase in transaminases, mostly ALT and GGT. There was also a mild increase in mean alkaline phosphatase. There were no changes from baseline in mean total or direct BR.

Change from baseline in ALT are presented in the following table.

Table 58. Change form baseline in ALT at time of last available measurement, pool D

Table 58: Change from baseline in AET at time of last available measurement, pool D											
Visit	Treatment Group	n	Baseline			Endpoint			Post baseline		
			Mean	SD	Median	Mean	SD	Median	Change from Baseline	SD	Median
			Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
TEP											
	FTY720 5 mg (N=94)	92	20.03	9.622	17.50	35.42	23.954	27.50	15.39	20.842	9.00
	FTY720 1.25 mg (N=943)	925	20.58	12.005	17.00	40.05	41.436	27.00	19.48	37.160	9.00
	FTY720 0.5 mg (N=854)	848	20.89	12.207	17.00	38.32	40.030	26.00	17.44	38.281	8.00
	Placebo (N=511)	505	20.85	13.154	17.00	21.93	19.620	17.00	1.08	20.244	0.00
	Interferon (N=431)	428	24.78	62.003	18.00	30.90	77.196	19.00	6.11	97.535	1.00

Source: Post text Table 5 9-2 ISS

Source: Post text Table 5.9-2 ISS.

Table 59. Mean changes from baseline in BR at last available measurement, safety pool D

Table 39: Mean changes from baseline in DX at last available measurement, safety pool D											
Visit	Treatment Group	n	Baseline			Endpoint		Post baseline			
			Mean	SD	Median	Mean	SD	Median	Change from Baseline	SD	Median
TEP											
	FTY720 5 mg (N=94)	92	7.03	3.110	6.80	8.17	4.272	6.80	1.14	3.462	0.00
	FTY720 1.25 mg (N=943)	925	8.78	4.860	8.00	9.34	5.264	8.00	0.56	4.295	0.00
	FTY720 0.5 mg (N=854)	848	9.24	4.427	8.00	9.86	5.428	8.00	0.62	4.154	0.00
	Placebo (N=511)	505	8.87	4.619	8.00	8.86	5.632	7.00	-0.01	3.915	0.00
	Interferon (N=431)	428	9.09	5.642	8.00	8.69	5.024	8.00	-0.41	3.975	0.00
TEP											
	FTY720 1.25 mg (N=943)	823	2.37	1.299	2.00	2.43	1.326	2.00	0.06	1.181	0.00
	FTY720 0.5 mg (N=854)	842	2.43	1.228	2.00	2.53	1.354	2.00	0.10	1.159	0.00
	Placebo (N=511)	406	2.44	1.317	2.00	2.30	1.276	2.00	-0.15	1.161	0.00
	Interferon (N=431)	428	2.36	1.455	2.00	2.24	1.339	2.00	-0.12	1.212	0.00

Source: Post text Table 5.9-2 ISS.

Table 60. Mean changes from baseline in serum Alkaline phosphatase at last available measurement, safety pool D

Visit	Treatment Group	n	Baseline			Endpoint			Post baseline		
			Mean	SD	Median	Mean	SD	Median	Change from Baseline	SD	Median
TEP											
	FTY720 5 mg (N=94)	92	64.48	20.019	62.00	67.36	24.598	62.50	2.88	15.273	1.50
	FTY720 1.25 mg (N=943)	925	63.43	19.043	61.00	67.99	27.183	62.00	4.55	19.597	1.00
	FTY720 0.5 mg (N=854)	848	63.31	17.937	61.00	66.64	24.517	62.00	3.33	18.690	0.00
	Placebo (N=511)	505	63.59	19.500	61.00	63.16	18.787	60.00	-0.43	11.281	0.00
	Interferon (N=431)	428	63.86	20.548	61.00	62.32	24.704	58.00	-1.53	19.793	-2.00

Distribution of patients with liver enzyme abnormalities in fingolimod controlled studies is presented in the following table.

Table 61. Distribution of patients with liver enzyme abnormalities, pool D

		FTY720 5 mg (N=94)	FTY720 1.25 mg (N=943)	FTY720 0.5 mg (N=854)	Placebo (N=511)	Interferon (N=431)
Parameter	Criterion	n (%)	n (%)	n (%)	n (%)	n (%)
ALT	Total	93	934	851	506	429
	No abnormalities	40 (43.0)	505 (54.1)	461 (54.2)	388 (76.7)	322 (75.1)
	> 1 x ULN	53 (57.0)	429 (45.9)	390 (45.8)	118 (23.3)	107 (24.9)
	≥ 2 x ULN	20 (21.5)	173 (18.5)	148 (17.4)	29 (5.7)	26 (6.1)
	≥ 3 x ULN	11 (11.8)	91 (9.7)	72 (8.5)	8 (1.6)	10 (2.3)
	≥ 5 x ULN	1 (1.1)	21 (2.2)	14 (1.6)	4 (0.8)	6 (1.4)
	≥ 10 x ULN	0	0	1 (0.1)	0	2 (0.5)
	≥ 20 x ULN	0	0	0	0	1 (0.2)
AST	Total	93	934	851	506	429
	No abnormalities	69 (74.2)	673 (72.1)	636 (74.7)	455 (89.9)	370 (86.2)
	> 1 x ULN	24 (25.8)	261 (27.9)	215 (25.3)	51 (10.1)	59 (13.8)
	≥ 2 x ULN	6 (6.5)	50 (5.4)	36 (4.2)	8 (1.6)	13 (3.0)
	≥ 3 x ULN	1 (1.1)	14 (1.5)	17 (2.0)	5 (1.0)	8 (1.9)
	≥ 5 x ULN	0	2 (0.2)	2 (0.2)	1 (0.2)	3 (0.7)
	≥ 10 x ULN	0	0	0	0	2 (0.5)
	≥ 20 x ULN	0	0	0	0	1 (0.2)
GGT	Total		840	851	414	429
	No abnormalities		537 (63.9)	580 (68.2)	378 (91.3)	383 (89.3)
	> 1 x ULN		303 (36.1)	271 (31.8)	36 (8.7)	46 (10.7)
	≥ 2 x ULN		144 (17.1)	119 (14.0)	10 (2.4)	16 (3.7)
	≥ 3 x ULN		72 (8.6)	56 (6.6)	3 (0.7)	6 (1.4)
	≥ 5 x ULN		23 (2.7)	15 (1.8)	0	2 (0.5)
	≥ 10 x ULN		0	1 (0.1)	0	1 (0.2)
	≥ 20 x ULN		0	1 (0.1)	0	0
Total Bilirubin	Total	93	934	851	506	429
	No abnormalities	90 (96.8)	854 (91.4)	763 (89.7)	463 (91.5)	398 (92.8)
	> 1 x ULN	3 (3.2)	80 (8.6)	88 (10.3)	43 (8.5)	31 (7.2)
	≥ 2 x ULN	0	7 (0.7)	8 (0.9)	3 (0.6)	2 (0.5)

Source: ISS addendum, submitted February 2010.

ALT ≥3xULN was shown by 9.7% and 8.5% of subjects in the FTY 1.25 and 0.5 mg groups, respectively, as compared to 1.6% of those in the placebo group, in the controlled studies. The percentage of patients with ALT ≥5xULN was also higher in the FTY groups (2.2% and 1.6%)

as compared to placebo (0.8%). Therefore, there is a clear effect on increase in liver enzyme elevations. However, the great majority of these cases had normal BR and ALK Phosphatase.

There five cases in the entire ISS in which there was increase in transaminases $\geq 3 \times \text{ULN}$ and increase in BR $\geq 2 \times \text{ULN}$. One of them was the case of hepatic necrosis in a patient who died of disseminated herpes zoster; one was a patient who received intravenous paracetamol for hip pain; 2 cases occurred in subjects suspected of having Gilbert's disease, and one occurred on placebo.

- Analyses of metabolic parameters in pool D

There were no clinically relevant changes in total cholesterol, HDL, LDL or TG, creatinine, estimated creatinine clearance (Cockcroft-Gault), glucose or albumin in safety pool D (data not shown).

Outlier analyses of metabolic parameters in pool D are shown as follows:

Table 62. Outlier analysis of metabolic parameters, safety pool D

Parameter	Criterion	FTY720 5 mg (N=94)	FTY720 1.25 mg (N=943)	FTY720 0.5 mg (N=854)	Placebo (N=511)	Interferon (N=431)
		n (%)	n (%)	n (%)	n (%)	n (%)
Cholesterol (total)	Total	93	934	851	506	429
	$\geq 6.21 \text{ mmol/L}$	22 (23.7)	306 (32.8)	313 (36.8)	157 (31.0)	63 (14.7)
Triglycerides	Total	93	934	851	506	429
	$\geq 3.39 \text{ mmol/L}$	7 (7.5)	113 (12.1)	95 (11.2)	39 (7.7)	54 (12.6)
Glucose	Total	0	840	851	414	429
	$\geq 11.11 \text{ mmol/L}$		4 (0.5)	4 (0.5)	1 (0.2)	2 (0.5)
Amylase	Total	0	840	851	414	429
	$\geq 300 \text{ U/L}$		2 (0.2)	1 (0.1)	0	0
Creatinine	Total	93	934	851	506	429
	$\geq 176 \text{ umol/L}$	0	0	1 (0.1)	0	0

Source: ISS addendum 1 submitted February 2010.

The analysis of outliers suggests that a few more patients developed elevated glucose in the FTY groups as compared to placebo, but the numbers are small for definitive conclusions. This evaluation also suggests a greater number of subjects developed markedly elevated triglycerides (12.1% and 11.2% in the FTY group as compared to placebo (7.7%)), but the clinical significance of this difference is unclear. The analysis of cholesterol, amylase and creatinine outliers was unremarkable.

• Urinalysis

A categorical analysis of proteinuria was conducted in the clinical studies in the ISS. No other results were provided.

The frequency of patients with urine protein in Safety pool D is presented in the following table

Table 63. Percentage of patients with protein in urine in Safety pool D

Post-baseline extreme value	FTY720 5 mg (N=94)	FTY720 1.25 mg (N=943)	FTY720 0.5 mg (N=854)	Placebo (N=511)	Interferon (N=431)
	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with any urine protein value	93	869	820	489	404
-	89 (95.7)	775 (89.2)	745 (90.9)	445 (91.0)	385 (95.3)
+	4 (4.3)	76 (8.7)	57 (7.0)	38 (7.8)	17 (4.2)
++	0 (0.0)	12 (1.4)	14 (1.7)	5 (1.0)	2 (0.5)
+++	0 (0.0)	5 (0.6)	4 (0.5)	1 (0.2)	0 (0.0)
++++	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)

Source, ISS table.

In the controlled studies, there were more cases of 2+, 3+ and 4+ proteinuria in the FTY 1.25 and 0.5 mg groups as compared to placebo or IFN, but the numbers are small to draw definitive conclusions.

The applicant was asked to provide full urinalyses, chemistries and clinical correlation for cases of 3+ and 4+ proteinuria. Available electrolytes, creatinine and estimated creatinine clearance were normal in these patients, however it is unclear if they were taken on the same date as the event of 3+ or 4+ proteinuria. Overall, the data submitted did not help in the evaluation of proteinuria. None of the subjects had 24 hour protein collection.

Comment regarding potential kidney toxicity:

In renal transplant population, more patients with SAE of increased creatinine Investigations in patients treated with FTY as compared to MMF (of note, transplant rejection was higher in FTY as compared to MMF in this population).

No patient developed renal failure in the MS program. Analyses of creatinine changes from baseline and outliers as well as changes in estimated creatinine clearance did not show a signal for renal toxicity in the MS program. Analyses of electrolytes in studies 2113 (a 28-day clinical pharmacology study). However, standard data on electrolytes were not collected in phase 2&3 studies.

Three cases of unexplained edema (one of them with 8 kg weight gain) were observed in the fingolimod MS database shortly after initiation of treatment. These patients improved after diuretic treatment. Urinalyses (looking for protein) were not available from these patients.

An increasing body of literature indicates that SIP is involved in the regulation of vascular permeability and vascular tone. This might in part explain the finding of macular edema observed with FTY. Another target organ that could be affected by SIP modulation could be the glomerulus. 24 hour protein was not collected in the MS program. The risk for renal toxicity would be increased in patients with underlying

vascular problems, such as those with diabetes, but they were excluded from the phase 3 studies. The potential renal toxicity of fingolimod should be studied further. It could be done postmarketing.

- Coagulation parameters

PT and PTT were unremarkable in study 2113. PT and PTT were not collected in phase 2 & 3 studies.

7.4.3 Vital Signs

Evaluation of vital signs indicates that chronic use of fingolimod increases systolic and diastolic blood pressure in a dose-response manner. However, the immediate effect upon first dose is a decrease in BP. Evaluation of BP over time showed that the effect on BP was evident in the 1 month evaluation, reached plateau at 6 months and was maintained throughout the end of the evaluations. Changes in BP are presented in the following table. Of note, the 6 month evaluation includes all 3 studies; the 12 month evaluation includes only studies 2301 and 2302; the 24 month evaluation includes only study 2301.

Table 64. Changes from baseline in Systolic and diastolic blood pressure in Safety pool D

Visit		Post baseline									
		Baseline			Endpoint			Change from baseline			
		Mean	SD	Median	Mean	SD	Median	Mean	SD	Median	
Sitting Systolic BP											
Month 6											
	FTY720 5 mg (N=94)	84	116.07	15.336	115.50	123.33	15.821	120.00	7.26	12.402	6.58
	FTY720 1.25 mg (N=943)	856	117.78	13.311	117.33	121.06	14.352	120.00	3.28	12.649	3.33
	FTY720 0.5 mg (N=854)	808	118.14	12.648	117.67	119.88	13.373	120.00	1.74	11.522	1.67
	Placebo (N=511)	476	117.80	12.889	117.67	117.38	12.685	118.00	-0.42	11.799	0.00
	Interferon (N=431)	401	116.59	12.288	115.33	116.42	13.324	115.33	-0.17	12.642	0.00
Month 12											
	FTY720 1.25 mg (N=943)	716	117.53	13.042	117.50	120.48	13.203	120.00	2.95	12.204	3.00
	FTY720 0.5 mg (N=854)	773	118.03	12.609	117.33	119.72	12.490	120.00	1.69	11.789	1.33
	Placebo (N=511)	362	118.28	12.844	118.33	118.30	12.934	118.67	0.03	11.665	0.00
	Interferon (N=431)	383	116.43	12.285	115.00	115.65	12.897	115.00	-0.78	12.480	0.00
Month 24											
	FTY720 1.25 mg (N=943)	306	117.97	13.267	117.50	121.59	12.196	120.50	3.62	12.994	4.33
	FTY720 0.5 mg (N=854)	349	118.47	12.633	118.33	120.38	12.840	120.00	1.91	12.082	1.67
	Placebo (N=511)	313	117.88	12.793	118.00	117.47	12.571	118.33	-0.41	12.516	1.00

Sitting Diastolic BP											
Month 6											
	FTY720 5 mg (N=94)	84	73.94	10.477	75.00	79.16	10.601	79.00	5.22	8.842	3.75
	FTY720 1.25 mg (N=943)	856	75.48	10.048	75.33	77.54	9.964	78.00	2.07	9.563	1.67
	FTY720 0.5 mg (N=854)	808	75.90	9.421	76.50	77.24	9.630	77.33	1.35	8.902	0.67
	Placebo (N=511)	476	75.64	9.802	75.00	75.24	9.473	75.33	-0.40	9.229	0.00
	Interferon (N=431)	401	74.89	9.214	74.33	75.18	9.190	75.00	0.29	9.218	0.00
Month 12											
	FTY720 1.25 mg (N=943)	716	75.41	9.729	75.00	77.29	9.631	78.08	1.88	9.432	1.67
	FTY720 0.5 mg (N=854)	773	75.80	9.436	76.33	76.41	9.170	76.67	0.61	9.262	0.33
	Placebo (N=511)	362	76.19	9.473	76.33	75.27	8.797	75.00	-0.93	9.043	-0.33
	Interferon (N=431)	383	74.78	9.293	74.00	74.78	9.401	74.00	0.00	10.057	0.00

Month 24											
FTY720 1.25 mg (N=943)	306	75.49	9.784	74.67	77.61	8.188	78.33	2.12	8.972	2.67	
FTY720 0.5 mg (N=854)	349	76.03	9.367	76.67	76.77	9.532	76.67	0.74	8.850	0.00	
Placebo (N=511)	313	76.05	9.326	76.67	75.55	8.939	76.67	-0.50	9.673	0.00	

Sitting pulse (beats/min)	> 120 bpm or Increase of ≥ 15 bpm from baseline or < 50 bpm or Decrease of ≥ 15 bpm from baseline
Body weight (Kg)	$\pm 7\%$ from baseline weight

Table 66. Notable abnormalities in VS in Safety Pool D

Parameter Criterion	FTY720 5 mg N=94	FTY720 1.25 mg N=943	FTY720 0.5 mg N=854	Placebo N=511	Interferon N=431
Sitting systolic BP (mmHg) - n(%)					
Low: ≤ 90 or ≥ 20 decrease from baseline	16 (17.0%)	158 (16.8%)	158 (18.5%)	137 (26.8%)	88 (20.4%)
≤ 90	6 (6.4%)	46 (4.9%)	42 (4.9%)	45 (8.8%)	33 (7.7%)
≥ 20 decrease from baseline	11 (11.7%)	132 (14.0%)	130 (15.2%)	114 (22.3%)	68 (15.8%)
High: ≥ 160 or ≥ 20 increase from baseline	39 (41.5%)	264 (28.0%)	193 (22.6%)	101 (19.8%)	67 (15.5%)
≥ 160	6 (6.4%)	49 (5.2%)	22 (2.6%)	11 (2.2%)	7 (1.6%)
≥ 140	30 (31.9%)	225 (23.9%)	176 (20.6%)	94 (18.4%)	62 (14.4%)
≥ 20 increase from baseline	38 (40.4%)	256 (27.1%)	188 (22.0%)	101 (19.8%)	65 (15.1%)
Sitting diastolic BP (mmHg) - n(%)					
Low: ≤ 50 or ≥ 15 decrease from baseline	13 (13.8%)	156 (16.5%)	150 (17.6%)	128 (25.0%)	81 (18.8%)
≤ 50	5 (5.3%)	19 (2.0%)	9 (1.1%)	20 (3.9%)	3 (0.7%)
≥ 15 decrease from baseline	9 (9.6%)	146 (15.5%)	146 (17.1%)	118 (23.1%)	79 (18.3%)
High: ≥ 100 or ≥ 15 increase from baseline	39 (41.5%)	260 (27.6%)	213 (24.9%)	115 (22.5%)	80 (18.6%)
≥ 100	12 (12.8%)	78 (8.3%)	55 (6.4%)	24 (4.7%)	18 (4.2%)
≥ 90	29 (30.9%)	271 (28.7%)	257 (30.1%)	120 (23.5%)	92 (21.3%)
≥ 15 increase from baseline	34 (36.2%)	231 (24.5%)	187 (21.9%)	103 (20.2%)	71 (16.5%)

Source: Post text Table 6.3.3 ISS

- Notable abnormalities in vital signs upon first dose administration

Notable abnormalities in systolic and diastolic BP and pulse upon first dose in safety pool A are presented in the following table. (Since study 2201 did not have the same ECG monitoring as the phase 3 studies, only studies 2301 and 2302 presented, instead of pool D).

Table 67. Notable abnormalities upon first dose administration, safety pool A

Parameter Criterion	FTY720 1.25 mg N=849	FTY720 0.5 mg N=854	Placebo N=418	Interferon N=431
Sitting systolic BP (mmHg) - n(%)				
Low: <=90 or >=20 decrease from baseline	195 (23.0%)	158 (18.5%)	67 (16.0%)	55 (12.8%)
<=90	95 (11.2%)	65 (7.6%)	30 (7.2%)	21 (4.9%)
>=20 decrease from baseline	129 (15.2%)	114 (13.3%)	47 (11.2%)	38 (8.8%)
High: >=160 or >=20 increase from baseline	94 (11.1%)	96 (11.2%)	48 (11.5%)	73 (16.9%)
>=160	18 (2.1%)	21 (2.5%)	8 (1.9%)	11 (2.6%)
>=140	158 (18.6%)	142 (16.6%)	69 (16.5%)	75 (17.4%)
>=20 increase from baseline	86 (10.1%)	89 (10.4%)	46 (11.0%)	67 (15.5%)
Sitting diastolic BP (mmHg) - n(%)				
Low: <=50 or >=15 decrease from baseline	244 (28.7%)	195 (22.8%)	70 (16.7%)	60 (13.9%)
<=50	56 (6.6%)	36 (4.2%)	13 (3.1%)	13 (3.0%)
>=15 decrease from baseline	211 (24.9%)	180 (21.1%)	67 (16.0%)	52 (12.1%)
High: >=100 or >=15 increase from baseline	71 (8.4%)	85 (10.0%)	47 (11.2%)	54 (12.5%)
>=100	21 (2.5%)	28 (3.3%)	18 (4.3%)	15 (3.5%)
>=90	128 (15.1%)	181 (21.2%)	86 (20.6%)	82 (19.0%)
>=15 increase from baseline	55 (6.5%)	64 (7.5%)	35 (8.4%)	43 (10.0%)
Sitting pulse (bpm) - n(%)				
Low: <50 or >=15 decrease from baseline	404 (47.6%)	283 (33.1%)	54 (12.9%)	36 (8.4%)
<50	93 (11.0%)	52 (6.1%)	9 (2.2%)	2 (0.5%)
>=15 decrease from baseline	382 (45.0%)	258 (30.2%)	48 (11.5%)	36 (8.4%)
High: >120 or >=15 increase from baseline	19 (2.2%)	36 (4.2%)	54 (12.9%)	175 (40.6%)
>120	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
>=15 increase from baseline	19 (2.2%)	36 (4.2%)	54 (12.9%)	175 (40.6%)

Source: Post text Table 10.1-5b.

Of those subjects who presented marked VS abnormalities upon first dose, 10 to 25% presented VS abnormalities upon the second dose on Day 2.

Parameter Criterion	FTY720 1.25 mg N=59	FTY720 0.5 mg N=18	Placebo N=3	Interferon N=4
Sitting systolic BP (mmHg) - n(%)				
Low: <=90 or >=20 decrease from baseline	14 (23.7%)	2 (11.1%)	1 (33.3%)	0 (0.0%)
<=90	4 (6.8%)	1 (5.6%)	1 (33.3%)	0 (0.0%)
>=20 decrease from baseline	13 (22.0%)	2 (11.1%)	1 (33.3%)	0 (0.0%)
High: >=160 or >=20 increase from baseline	3 (5.1%)	2 (11.1%)	1 (33.3%)	0 (0.0%)
>=140	12 (20.3%)	3 (16.7%)	0 (0.0%)	0 (0.0%)
>=20 increase from baseline	3 (5.1%)	2 (11.1%)	1 (33.3%)	0 (0.0%)
Sitting diastolic BP (mmHg) - n(%)				
Low: <=50 or >=15 decrease from baseline	21 (35.6%)	3 (16.7%)	0 (0.0%)	1 (25.0%)
<=50	6 (10.2%)	1 (5.6%)	0 (0.0%)	0 (0.0%)
>=15 decrease from baseline	18 (30.5%)	2 (11.1%)	0 (0.0%)	1 (25.0%)
High: >=100 or >=15 increase from baseline	5 (8.5%)	4 (22.2%)	0 (0.0%)	0 (0.0%)
>=100	1 (1.7%)	1 (5.6%)	0 (0.0%)	0 (0.0%)
>=90	6 (10.2%)	4 (22.2%)	0 (0.0%)	0 (0.0%)
>=15 increase from baseline	5 (8.5%)	4 (22.2%)	0 (0.0%)	0 (0.0%)
Sitting pulse (bpm) - n(%)				
Low: <50 or >=15 decrease from baseline	46 (78.0%)	12 (66.7%)	0 (0.0%)	0 (0.0%)
<50	12 (20.3%)	2 (11.1%)	0 (0.0%)	0 (0.0%)
>=15 decrease from baseline	45 (76.3%)	11 (61.1%)	0 (0.0%)	0 (0.0%)
High: >120 or >=15 increase from baseline	0 (0.0%)	0 (0.0%)	1 (33.3%)	1 (25.0%)
>=15 increase from baseline	0 (0.0%)	0 (0.0%)	1 (33.3%)	1 (25.0%)

Source: ISS Post text Table 10.1-6a. N= number of subjects with 2nd day data.

7.4.4 Electrocardiograms (ECGs)

- **Study FTY720D 2101: Thorough QT study**

This was a randomized, parallel group, multiple-dose study to evaluate the effects of fingolimod on cardiac safety in healthy subjects vs. placebo, with positive Moxifloxacin control. Participating subjects were to be randomized to one of four treatment groups: moxifloxacin, placebo, FTY 1.25 mg, or FTY 2.5 mg group (21 to Moxifloxacin and 56 to each of the other groups). For the FTY treatment groups, a loading dose regimen was used over a 4 day period to achieve concentrations that would be expected at steady state before the 1.25 mg and 2.5 mg doses were administered from Day 5 to Day 7. For details about the study design the reader is referred to the Interdisciplinary Review Team (IRT) review dated October 10, 2008. The following are excerpts from the IRT Overall Summary of Findings):

“This study failed to exclude a 10 ms prolongation of the QT interval for both doses of FTY720 (1.25 and 2.5 mg). At 6 hours post-dosing on Day 7, the maximum mean $\Delta\Delta\text{QTcI}$ for both 1.25- and 2.5-mg doses was 10 ms with an upper one-sided 95% CI of ~14 ms (see Table 1).

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for FTY720 (1.25 mg and 2.5 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	$\Delta\Delta\text{QTcI}$ (ms)	90% CI (ms)
FTY720 1.25 mg	6	10.0	13.6
FTY720 2.50 mg	6	10.5	14.0
Moxifloxacin 400 mg*	6	10.5	5.7

* Multiple endpoint adjustment is not applied. The largest lower bound after Bonferroni adjustment for 3 timepoints is 4.3 ms. Note: The sponsor specified times 1.5, 3, and 6 as the times to be tested for Moxifloxacin. At 8 hours the estimated $\Delta\Delta\text{QTc}$ was 11.0 ms and the unadjusted lower bound of the 90% C.I. was 7.5 ms. Source: IRT review dated 10/20/08.

We do not have confidence in the accuracy of the estimated effect of administering FTY720 on the QTc interval for the following reasons:

1. The positive control, a single oral dose of 400 mg moxifloxacin, failed to have the expected effect on $\Delta\Delta\text{QTcI}$ (change from baseline and placebo corrected); the largest $\Delta\Delta\text{QTcI}$ for moxifloxacin was about 10.5 ms and occurred at 6 and 8 hours post-dose. This profile is not likely since the T_{max} of moxifloxacin observed in this study was 3 hours (see Figure 5). This is especially relevant, since the largest $\Delta\Delta\text{QTcI}$ for FTY720 was of the same magnitude and occurred at the same time points as that observed for moxifloxacin.
2. Despite a 2-fold increase in the exposure to FTY720 plasma concentrations, there was no dose-response relationship for QT prolongation. There was also not a concentration-QTc relationship for FTY720 and its metabolite FTY720-P. This does not, however, rule out the existence of a positive exposure-response relationship because of the small range of steady-state concentrations observed on Day 7.

We recommend baseline and periodic on-therapy ECGs are collected for safety assessments in clinical trials irrespective of the results of the TQT study because bradycardia and conduction defects have been noted in the clinical program (although there have been no cases of Mobitz II or 3rd degree blocks). According to the guidance to investigators in the current IB, vitals signs

(including BP, HR and ECG) are being monitored pre-dosing and following a 6-hour observation period after administration of FTY720.”

The ICH Guidance E14 states the following:

- If the “thorough QT/QTc study” is positive, analyses of the ECG and adverse event data from certain patient sub-groups are of particular interest, such as:

- Patients with electrolyte abnormalities (e.g., hypokalemia)
- Patients with congestive heart failure
- Patients with impaired drug metabolizing capacity or clearance (e.g., renal or hepatic impairment, drug interactions)
- Female patients
- Patients aged <16 and over 65 years

- Even if the “thorough QT/QTc study” is negative, if other evidence of an effect in a patient population from subsequent studies (e.g., marked QT/QTc interval prolongation, TdP) were to emerge, then additional investigation would be needed”

In the case of fingolimod, the TQT could not rule out a >10msec prolongation of the the QT interval at doses of 1.25 and 2.5 mg. Review of the available data (adverse events, ECG and Holter evaluations) from this clinical program does not suggest an increase risk of QT interval prolongation (see section below, Standard ECG data analysis). However, the population at risk for developing QT prolongation was not included in these trials, therefore, a significant effect on the QT interval can not be ruled out in these patients.

- **Standard ECG data analysis**

- ECG upon first dose administration

In study 2201, patients were monitored for 4 hours. Monitoring outcomes, symptomatic bradycardia AE and medications for bradycardia after the first dose were not captured as well or were captured differently than in the phase 3 studies.

Patients in studies D2301, and D2302 (as well as in extension studies D2201E1 and D2302E1) were monitored in the clinic for at least the first 6 hours after taking the first dose of study drug with hourly heart rate and BP. After 6 hours of observation, patients could be discharged if the maximal lowering effect on heart rate had already been observed (i.e. after observing a decrease, heart rate should already have been increasing at the time of discharge), the patient was asymptomatic, and the 6-hour ECG did not show any new relevant abnormality. Patients not meeting the per protocol predefined criteria had to be observed longer until criteria were met (even if it required overnight hospitalization).

In order to avoid unnecessary unblinding, monitoring after the first intake of the study drug was performed under the responsibility of an independent physician called the First Dose Administrator. This physician reviewed vital signs during 6-hour monitoring, post-dose ECG, assessed discharge criteria at 6 hours post-dose, and managed cardiac events when they occurred. The investigator/treating physician was informed of any SAEs that may have occurred, remaining otherwise blinded to the cardiac events happening on the first day.

In addition, patients showing a strong sensitivity to the drug, defined as a heart rate decrease of more than 30% or the presence of symptomatic bradycardia, had to return to the clinic for the same 6-hour monitoring for the second dose of study drug.

Data recorded as part of the first dose administration monitoring included hourly vital signs, ECG, and summaries of bradycardia events, symptoms, and medication. Bradycardia events were defined according to the investigator's clinical judgment and not pre-defined criteria. The following is an analysis of changes in ECG parameters upon first dose in safety pool A (both phase 3 studies).

Table 68. First dose administration experience in safety pool A

	FTY720 1.25 mg (N=849) n (%)	FTY720 0.5 mg (N=854) n (%)	Placebo (N=418) n (%)	Interferon (N=431) n (%)
Discharged at 6 hours	645 (76.0)	700 (82.0)	356 (85.2)	422 (97.9)
Required extended monitoring after 6 hours	153 (18.0)	105 (12.3)	14 (3.3)	6 (1.4)
Hospitalized	23 (2.7)	15 (1.8)	0	2 (0.5)
Required Day 2 monitoring	62 (7.3)	19 (2.2)	3 (0.7)	4 (0.9)
Study drug permanently discontinued	12 (1.4)	2 (0.2)	1 (0.2)	0

Source: ISS

More patients in FTY 1.25 and FTY 0.5 required extended monitoring and hospitalization, particularly the 1.25 mg dose. AE after first dose led to drug discontinuation in 1.4%, 0.2%, 0.2% and 0 subjects in the FTY 1.25, FTY 0.5, placebo and IFN groups.

Table 69. ECG abnormalities upon first dose fingolimod in safety pool A

Timepoint		FTY720 1.25 mg (N=849) n (%)	FTY720 0.5 mg (N=854) n (%)	Placebo (N=418) n (%)	Interferon (N=431) n (%)
Abnormality type	Finding				
Day 1 pre-dose					
No. of patients with ECG		848	852	418	431
Any abnormality		56 (6.6)	63 (7.4)	33 (7.9)	36 (8.4)
Conduction	Total	34 (4.0)	34 (4.0)	20 (4.8)	25 (5.8)
	LAH	13 (1.5)	15 (1.8)	12 (2.9)	6 (1.4)
	First degree AV block	12 (1.4)	17 (2.0)	6 (1.4)	15 (3.5)
	IVCD	6 (0.7)	2 (0.2)	1 (0.2)	1 (0.2)
	RBBB	3 (0.4)	4 (0.5)	0	2 (0.5)
	IRBBB	2 (0.2)	0	1 (0.2)	1 (0.2)
Ectopy	Total	4 (0.5)	2 (0.2)	0	0

Interim review, 5 12 10.
 Lourdes Villalba, M.D
 NDA 22-527. Fingolimod

Timepoint		FTY720 1.25 mg (N=849) n (%)	FTY720 0.5 mg (N=854) n (%)	Placebo (N=418) n (%)	Interferon (N=431) n (%)
Abnormality type	Finding				
Morphology	APC	2 (0.2)	0	0	0
	VPC	2 (0.2)	2 (0.2)	0	0
	Total	1 (0.1)	0	0	0
	LAA	1 (0.1)	0	0	0
	LVH	1 (0.1)	0	0	0
Myocardial infarction	Total	2 (0.2)	1 (0.1)	1 (0.2)	0
	Antero septal MI V1-V4	1 (0.1)	0	0	0
	Septal MI V1, V2, (V3)	1 (0.1)	1 (0.1)	1 (0.2)	0
Rhythm	Total	10 (1.2)	7 (0.8)	6 (1.4)	1 (0.2)
	Ectopic Supraventricular Rhythm	5 (0.6)	2 (0.2)	2 (0.5)	1 (0.2)
	Sinus tachycardia	2 (0.2)	3 (0.4)	4 (1.0)	0
	Junctional rhythm	1 (0.1)	0	0	0
	Other Rhythm	1 (0.1)	2 (0.2)	0	0
ST segment	Sinus bradycardia	1 (0.1)	0	1 (0.2)	0
	Total	3 (0.4)	5 (0.6)	6 (1.4)	0
	Depressed ST segment	3 (0.4)	5 (0.6)	5 (1.2)	0
	Elevated ST segment	0	0	1 (0.2)	0
T waves	Total	10 (1.2)	20 (2.3)	6 (1.4)	10 (2.3)
	Flat T waves	7 (0.8)	13 (1.5)	2 (0.5)	4 (0.9)
	Inverted T waves	3 (0.4)	3 (0.4)	3 (0.7)	5 (1.2)
	Biphasic T waves	0	4 (0.5)	1 (0.2)	1 (0.2)
U waves	Total	0	0	1 (0.2)	0
	Abnormal	0	0	1 (0.2)	0
Day 1 post-dose (6 hours)					
No. of patients with ECG		840	837	413	422
Any abnormality		134 (16.0)	80 (9.6)	26 (6.3)	38 (9.0)
Conduction	Total	108 (12.9)	59 (7.0)	17 (4.1)	19 (4.5)
	First degree AV block	82 (9.8)	39 (4.7)	6 (1.5)	12 (2.8)
	LAH	15 (1.8)	16 (1.9)	9 (2.2)	5 (1.2)
	AV Mobitz I	6 (0.7)	2 (0.2)	0	0
	IVCD	3 (0.4)	2 (0.2)	1 (0.2)	0
Ectopy	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)
	Total	4 (0.5)	2 (0.2)	1 (0.2)	0
	APC	3 (0.4)	0	0	0
Myocardial infarction	VPC	1 (0.1)	2 (0.2)	1 (0.2)	0
	Total	2 (0.2)	1 (0.1)	0	0
	Antero septal MI V1-V4	1 (0.1)	0	0	0
	Septal MI V1, V2, (V3)	1 (0.1)	1 (0.1)	0	0
Rhythm	Total	25 (3.0)	7 (0.8)	3 (0.7)	7 (1.7)
	Sinus bradycardia	19 (2.3)	5 (0.6)	2 (0.5)	0
	Other Rhythm	3 (0.4)	1 (0.1)	0	0
	Ectopic Supraventricular Rhythm	2 (0.2)	0	1 (0.2)	1 (0.2)

Timepoint		FTY720 1.25 mg (N=849) n (%)	FTY720 0.5 mg (N=854) n (%)	Placebo (N=418) n (%)	Interferon (N=431) n (%)
Abnormality type	Finding				
	Junctional rhythm	1 (0.1)	0	0	0
	Junctional Tachycardia	0	1 (0.1)	0	0
	Sinus tachycardia	0	0	0	6 (1.4)
ST segment	Total	4 (0.5)	2 (0.2)	1 (0.2)	5 (1.2)
	Depressed ST segment	4 (0.5)	2 (0.2)	1 (0.2)	5 (1.2)
T waves	Total	10 (1.2)	17 (2.0)	9 (2.2)	11 (2.6)
	Flat T waves	6 (0.7)	11 (1.3)	3 (0.7)	6 (1.4)
	Inverted T waves	4 (0.5)	4 (0.5)	5 (1.2)	4 (0.9)
	Biphasic T waves	0	2 (0.2)	1 (0.2)	1 (0.2)
U waves	Total	3 (0.4)	0	0	0
	Abnormal	3 (0.4)	0	0	0
Day 1 post-dose (>6 hours)					
	No. patients with ECG	61	47	10	14
	Any abnormality	18 (29.5)	8 (17.0)	0	1 (7.1)
Conduction	Total	17 (27.9)	7 (14.9)	0	1 (7.1)
	First degree AV block	12 (19.7)	4 (8.5)	0	1 (7.1)
	AV Mobitz I	4 (6.6)	1 (2.1)	0	0
	LAH	2 (3.3)	0	0	0
	IVCD	0	1 (2.1)	0	0
	Prolonged QTc	0	1 (2.1)	0	0
Ectopy	Total	1 (1.6)	1 (2.1)	0	0
	APC	1 (1.6)	0	0	0
	VPC	0	1 (2.1)	0	0
Rhythm	Total	2 (3.3)	0	0	0
	Sinus bradycardia	2 (3.3)	0	0	0
T waves	Total	2 (3.3)	1 (2.1)	0	0
	Flat T waves	2 (3.3)	0	0	0
	Biphasic T waves	0	1 (2.1)	0	0

Source: ISS table 4-51 and PT-Table 10.1-10. Abnormality types are presented alphabetically; findings are sorted within abnormality type by frequency from highest to lowest in the FTY 1.25 mg group. A patient with multiple occurrences of an abnormality is counted only once in the corresponding category. A patient with multiple findings within an abnormality type is counted only once in the total row of this abnormality type.

The incidence of ECG abnormalities at post-dose timepoints was higher than at pre-dose. The most frequently observed findings in the 6 hours post first dose ECG were related to conduction and rhythm disturbances (mostly AVB and sinus bradycardia) and were more frequently reported in the FTY 1.25 mg group compared to the FTY 0.5 mg, placebo and interferon groups. This finding is consistent with the review of SAEs in the Cardiac SOC). A few subjects had second degree AVB (Mobitz 1 and 2:1 AVB) in the 6-hour post dose ECG. Four subjects had second degree AVB among 61 who underwent >6hours post-dose ECG.

Changes from baseline in mean ECG parameters after first dose in safety pool A are presented in the following table.

Table 70. Changes from baseline in ECG parameters after first dose, safety pool A

Hour post-dose	FTY720 1.25mg N=849		FTY720 0.5mg N=854		Placebo N=418		Interferon N=431	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
QT interval (ms)								
6 hours	835	32.8 (21.02)	826	24.8 (20.46)	413	4.1 (18.25)	420	-19.1 (24.73)
> 6 hours	61	28.0 (30.42)	47	27.8 (26.13)	10	4.8 (23.19)	14	-17.0 (26.34)
QTc interval – Bazett (ms)								
6 hours	834	-3.6 (17.84)	826	-1.4 (17.93)	413	1.6 (17.28)	420	3.6 (17.05)
> 6 hours	61	0.4 (17.50)	47	-4.5 (18.38)	10	6.9 (17.02)	14	-1.7 (18.23)
QTc interval – Fridericia (ms)								
6 hours	834	8.8 (14.52)	826	7.6 (14.39)	413	2.5 (13.53)	420	-4.6 (14.75)
> 6 hours	61	9.7 (16.32)	47	6.5 (17.22)	10	6.3 (10.26)	14	-6.9 (17.27)
PR interval (ms)								
6 hours	834	11.3 (23.80)	825	4.5 (16.70)	413	-0.8 (12.17)	420	-3.2 (12.10)
> 6 hours	60	10.7 (25.25)	47	5.1 (16.19)	10	-4.2 (9.83)	14	-4.6 (10.99)
RR interval (ms)								
6 hours	835	172.6 (122.26)	826	122.8 (119.72)	413	11.3 (103.40)	420	-97.5 (123.49)
> 6 hours	61	131.1 (153.19)	47	153.4 (128.08)	10	-8.4 (144.15)	14	-67.2 (118.50)
QRS duration (ms)								
6 hours	835	1.0 (6.84)	826	1.3 (6.76)	413	0.3 (6.56)	420	0.0 (6.91)
> 6 hours	61	1.6 (7.06)	47	-0.1 (7.62)	10	3.5 (5.13)	14	0.6 (8.93)
Heart rate (bpm)								
6 hours	835	-12.0 (8.76)	826	-9.0 (8.87)	413	-1.1 (8.60)	420	9.6 (11.85)
> 6 hours	61	-9.1 (12.96)	47	-10.9 (9.54)	10	0.0 (13.40)	14	6.9 (12.69)

Source: ISS Table 4-52. ECG > 6 hours post dose were done only in patient who meet Day 1 protocol monitoring guidelines⁵

Upon initiation of FTY treatment, there was a decrease in mean heart rate on ECGs at 6 hours and > 6 hours after the first FTY dose (which was done only in subjects who met monitoring guidelines to stay > 6 hours⁷). This decrease in heart rate appeared to be dose dependent but was attenuated on chronic dosing.

There was a prolongation in the mean PR and RR intervals for both FTY groups in the 6 hours or longer post-dose ECGs, consistent with the observed AE of first and second degree AVB.

No relevant change was seen in the mean QRS duration upon first dose.

Mean QTc intervals by Bazett's correction show decreases from baseline (pre-dose) in both FTY

⁷ Patients might be discharged after 6 hours only if all of the following criteria were met: Heart rate at least 51 bpm; HR greater than 80% of baseline value; HR must not be the lowest hourly value measured during the observation period; patients must have no symptoms of bradycardia; ECG at 6 hours should not show any new significant abnormalities other than sinus bradycardia not observed at the pre-dose ECG)

groups on the 6 hours post-dose ECG. However, mean QTc intervals by Fridericia's correction, which provide a more accurate correction in subjects with heart rates below 60 bpm, show increases from baseline in both FTY groups on the 6 hours post-dose ECGs (8.8 msec, 7.6 msec and 2.5 msec in the FTY 1.25, FTY 0.5 and placebo groups). At >6 hours post dose, increases in QTc intervals adjusted with Fridericia's formula were seen in both FTY groups and placebo. (The FTY groups continued to show small increases in QTc intervals by Fridericia's correction on chronic dosing, although the increases from baseline were less than 4 ms at all timepoints.)

- ECGs with chronic use

ECG evaluations were done at baseline, 1 week, 1 month, 3 months, 6 months and 12 months for studies 2301 and 2302; plus at 18 and 24 months for study 2301; and baseline, 2 weeks, 1 month, and 6 months for 2201. Except data for week 1-2 and 3 months, ECG data was pooled for analysis in all pre-specified safety populations. I will present the data from safety pool D.

The most common abnormalities at baseline were conduction abnormalities (in particular first degree AV block and left anterior hemiblock) and T wave abnormalities (flat T waves). Four subjects had evidence of a prior myocardial infarction (2 on FTY 1.25, 1 on FTY 0.1 and one on placebo). The number of patients with abnormal ECGs in safety pool D is presented in the following table.

Table 71. Number of patients with abnormal ECG parameters in safety pool D by visit

		FTY 1.25 (N=943) n (%)	FTY 0.5 (N=854) n (%)	Placebo (N=511) n (%)	Interferon (N=431) n (%)
<i>Baseline</i>					
Number of patients with ECG		942	852	511	431
Any abnormality		62 (6.6)	63 (7.4)	40 (7.8)	36 (8.4)
Conduction		34 (3.6)	33 (3.9)	23 (4.5)	25 (5.8)
<i>Month 1</i>					
Number of patients with ECG		942	852	511	431
Any abnormality		68 (7.4)	65 (7.8)	38 (7.6)	33 (8.0)
Conduction		39 (4.3)	37 (4.4)	24 (4.8)	23 (5.6)
<i>Month 6</i>					
Number of patients with ECG		847	792	478	393
Any abnormality		71 (8.4)	64 (8.1)	35 (7.3)	44 (11.2)
Conduction		36 (4.3)	33 (4.2)	21 (4.4)	26 (6.6)
<i>Month 12</i>					
Number of patients with ECG		698	750	356	359
Any abnormality		64 (9.2)	69 (9.2)	32 (9.0)	37 (10.3)
Conduction		24 (3.4)	34 (4.5)	20 (5.6)	24 (6.7)
<i>Month 24</i>					
Number of patients with ECG		300	343	311	0
Any abnormality		33 (11.0)	39 (11.4)	34 (10.9)	0 (0.0)
Conduction		12 (4.0)	15 (4.4)	16 (5.1)	0 (0.0)

Source: ISS Post text table 7.3-4.

As seen in this table, the total number of patients with ECG abnormalities increased over time, but the percentage was similar in all treatment groups.

Analyses of number of patients with ECG changes over time did not reveal major differences between treatment groups in any of the areas that were evaluated (conduction, morphology, ectopy, ST changes, T wave abnormalities, U waves), however, by looking at the tables it is unclear if all the events observed at certain timepoint are the same as those at earlier timepoints, or not, as the pool of patients having ECGs changes (decreases) over time.

At the 1 month evaluation 6 subjects (instead of 4 observed at baseline) had ECG changes of MI (one additional in the FTY 1.25 mg group and another in the IFN group). This is of interest because one MI was reported as AE in the IFN group and one in the placebo group, but there was no adverse event of MI reported in the 1.25 mg group during the controlled studies. *(Information requested to identify this case)*

- Mean changes from baseline in PR and QRS intervals in safety pool D:

There were no relevant changes from baseline in PR and QRS duration for FTY 0.5 mg. At the one month ECG, there was a small increase from baseline in the point estimate for the PR interval (2 msec for FTY 5 and 1.25 mg), and a small decrease in the point estimate for the QRS interval (<1 msec for FTY 5 and 1.25mg), with large standard deviations. At the 12 month ECG and beyond, the duration of PR and QRS intervals was similar to that of placebo (data not shown).

- QT changes with chronic use

Evaluation of QT changes with chronic use did not show relevant differences among treatment groups. Again, it is unclear if some of the events observed at a certain timepoint are new or correspond to those observed at prior timepoints. Changes from baseline in QTc parameters by visit in safety pool D are presented in the following table.

Table 72. Changes from baseline in ECG parameters by visit for safety pool D

Parameter Visit	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 (%)	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
QTc interval (Bazett) (ms)										
Month 1	92	2.9 (16.84)	915	0.3 (18.27)	834	0.9 (17.80)	498	-1.3 (18.46)	414	-1.4 (19.92)
Month 6	82	4.7 (19.42)	845	1.5 (18.27)	792	1.5 (18.55)	478	-1.2 (19.46)	392	-1.0 (19.42)
Month 12			697	1.6 (18.81)	748	2.3 (18.32)	356	-1.1 (18.88)	358	0.9 (19.39)
Month 18			321	0.9 (17.75)	366	2.3 (19.25)	332	-2.1 (18.22)		
Month 24			299	-0.5 (17.53)	342	2.0 (19.32)	310	-2.0 (17.62)		
Treatment endpoint	93	3.1 (16.42)	912	1.1 (19.28)	841	1.8 (18.59)	502	-1.2 (19.64)	423	0.5 (19.73)
QTc interval (Fridericia) (ms)										
Month 1	92	6.1 (14.45)	915	2.1 (14.92)	834	3.2 (14.49)	498	0.9 (14.19)	414	0.2 (15.50)
Month 6	82	6.1 (15.06)	845	2.7 (15.30)	792	2.7 (15.34)	478	0.7 (15.63)	392	1.3 (15.09)
Month 12			697	3.0 (15.88)	748	3.8 (15.71)	356	0.5 (15.09)	358	3.2 (15.20)
Month 18			321	2.8 (14.88)	366	3.7 (15.88)	332	-0.1 (14.70)		
Month 24			299	1.4 (14.79)	342	3.0 (16.12)	310	0.1 (14.80)		
Treatment endpoint	93	5.6 (12.82)	912	2.9 (16.04)	841	3.5 (15.64)	502	0.9 (16.15)	423	2.5 (15.29)
Heart rate (bpm)										
Month 1	92	-3.6 (9.92)	915	-2.1 (8.94)	834	-2.6 (9.12)	498	-2.4 (9.81)	414	-1.5 (10.74)
Month 6	82	-1.7 (9.95)	845	-1.4 (9.32)	792	-1.4 (9.23)	478	-2.0 (10.88)	392	-2.3 (10.46)
Month 12			697	-1.6 (9.88)	748	-1.7 (9.44)	356	-1.7 (10.03)	358	-2.4 (10.16)
Month 18			321	-2.0 (8.85)	366	-1.7 (9.52)	332	-1.9 (10.39)		
Month 24			300	-2.2 (9.12)	342	-1.3 (9.57)	310	-2.2 (10.10)		
Treatment endpoint	93	-2.8 (10.12)	912	-2.0 (9.82)	841	-2.0 (9.44)	502	-2.2 (10.83)	423	-2.1 (10.64)

Change from baseline = timepoint – baseline. - Treatment endpoint includes the last non-missing value on treatment.
 - For each ECG, only patients with a value at both baseline and post-baseline are included. Source: [ISS PT-Table 7.3-2 and Table 22-1, ISS addendum 1]

Table 73. Outlier analysis of QT changes in safety pool D

		FTY720 5 mg (N=94) n %	FTY720 1.25 mg (N=943) n %	FTY720 0.5 mg (N=854) n %	Placebo (N=511) n %	Interferon (N=431) n %
Month 1						
No. of patients with any QT interval value		92	916	835	498	414
Bazett	Maximum increase from baseline					
Correction						
	< 30 msec	86 (93.5)	858 (93.7)	784 (93.9)	470 (94.4)	383 (92.5)
	30-60 msec	6 (6.5)	55 (6.0)	49 (5.9)	28 (5.6)	30 (7.2)
	> 60 msec	0 (0.0)	2 (0.2)	1 (0.1)	0 (0.0)	1 (0.2)
Number of patients with QTc values						
	> 450 ms (male) or 470 ms (female)	0 (0.0)	3 (0.3)	4 (0.5)	2 (0.4)	2 (0.5)
	> 500 ms (male) or 520 ms (female)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		FTY720 5 mg (N=94) n %	FTY720 1.25 mg (N=943) n %	FTY720 0.5 mg (N=854) n %	Placebo (N=511) n %	Interferon (N=431) n %
Bazett	Maximum increase from baseline					
Correction						
	< 30 msec	0	643 (92.1)	706 (94.4)	336 (94.4)	336 (93.9)
	30-60 msec	0	52 (7.4)	40 (5.3)	20 (5.6)	20 (5.6)
	> 60 msec	0	2 (0.3)	2 (0.3)	0 (0.0)	2 (0.6)
Bazett	Number of patients with QTc values					
Correction						
	> 450 ms (male) or 470 ms (female)	0	5 (0.7)	4 (0.5)	1 (0.3)	1 (0.3)
	> 500 ms (male) or 520 ms (female)	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fridericia	Maximum increase from baseline					
Correction						
	< 30 msec	0	661 (94.7)	707 (94.5)	349 (98.0)	345 (96.4)
	30-60 msec	0	35 (5.0)	40 (5.3)	7 (2.0)	12 (3.4)
	> 60 msec	0	1 (0.1)	1 (0.1)	0 (0.0)	1 (0.3)
Number of patients with QTc values						
	> 450 ms (male) or 470 ms (female)	0	0 (0.0)	3 (0.4)	0 (0.0)	0 (0.0)
	> 500 ms (male) or 520 ms (female)	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Month 24						
No. of patients with any QT interval value		0	300	342	310	0

Interim review, 5 12 10.

Lourdes Villalba, M.D

NDA 22-527. Fingolimod

Bazett Correction	Maximum increase from baseline					
	< 30 msec	0	286 (95.3)	316 (92.4)	297 (95.8)	0
	30-60 msec	0	13 (4.3)	25 (7.3)	12 (3.9)	0
	> 60 msec	0	0 (0.0)	1 (0.3)	1 (0.3)	0
Bazett Correction	Number of patients with QTc values					
	> 450 ms (male) or 470 ms (female)	0	0 (0.0)	3 (0.9)	0 (0.0)	0
	> 500 ms (male) or 520 ms (female)	0	0 (0.0)	0 (0.0)	0 (0.0)	0
Fridericia Correction	Maximum increase from baseline					
	< 30 msec	0	291 (97.0)	323 (94.4)	302 (97.4)	0
	30-60 msec	0	8 (2.7)	18 (5.3)	8 (2.6)	0
	> 60 msec	0	0 (0.0)	1 (0.3)	0 (0.0)	0
	Number of patients with QTc values					
	> 450 ms (male) or 470 ms (female)	0	0 (0.0)	1 (0.3)	0 (0.0)	0
	> 500 ms (male) or 520 ms (female)	0	0 (0.0)	0 (0.0)	0 (0.0)	0
Overall Worst Case *						
No. of patients with any QT interval value		94	931	848	505	426
Bazett Correction	Number of patients with QTc values					
	> 450 ms (male) or 470 ms (female)	0 (0.0)	13 (1.4)	13 (1.5)	6 (1.2)	4 (0.9)
	> 500 ms (male) or 520 ms (female)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Number of patients with QTc values					
Fridericia correction	> 450 ms (male) or 470 ms (female)	0 (0.0)	3 (0.3)	5 (0.6)	0 (0.0)	1 (0.2)
	> 500 ms (male) or 520 ms (female)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

* Overall Worst Case counts the worst case over all post-baseline visit timepoints per patient. Source: [ISS PT-Table 7.3-3]

Narratives of subjects with QTc Fridericia correction >450 msec (male) or 470 ms (female) were requested and are pending at the time of this review.

Of note, the TQTc study was not able to exclude the possibility of QTc prolongation >10 msec. The clinical database does not suggest an association with QTc prolongation.

7.4.5 Special Safety Studies

The following pre-scheduled special safety evaluations were incorporated into the phase 2 and 3 protocols:

1. 24-hour Holter monitoring
2. Echocardiogram
3. Chest high resolution computerized tomography (HRCT)
4. Pulmonary function tests
5. Ophthalmologic evaluations
6. Dermatologic evaluations

1) **24 hour Holter monitoring** ((2201, 2302 and 2309)

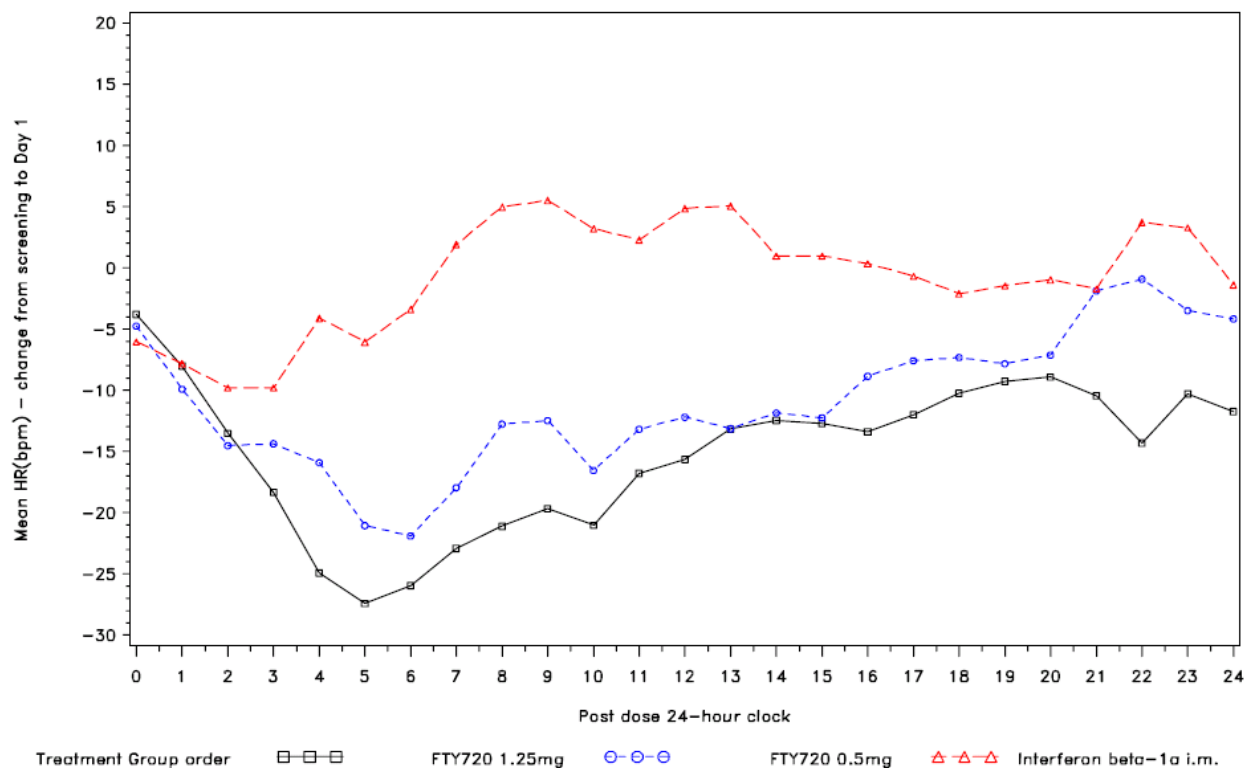
24-hour Holter ECGs were to be done at screening, Day 1 and Month 3 in all patients in study 2309 and at selected sites in study 2302 (all US sites and selected sites outside the US). The Holter ECGs data were collected and analyzed by a central reader. Holter was also done in study 2201 in some subjects. There was no Holter monitoring in study 2301.

- **Holter ECG in study D2302**

In total, 129 patients (42–45 per treatment group) participated in the 24-hour Holter monitoring. Consistent with the observations of pulse and heart rate on the 6-hour ECGs, a decline in mean hourly heart rate was observed in the FTY720 groups as early as 1 hour post-dose, reaching a maximum decrease at 5 hours post-dose in the FTY720 1.25 mg group (mean drop of approximately 28 bpm) and at 6 hours post-dose in the FTY720 0.5 mg group (mean drop of approximately 22 bpm). The corresponding mean heart rate at 5 hours post-dose was 67.4 bpm for the FTY720 1.25 mg and 67.6 bpm for the 0.5 mg groups. At the Month 3 Visit, the mean hourly heart rates were similar across the groups at all post-dose hours.

Graphical presentations of mean hourly heart rate by 24 hour Holter monitoring are as follows:

Figure 2. Line plot of change from screening to Day 1 in Holter hourly mean heart rate, study 2302



The most commonly reported finding was frequent ventricular premature complexes (4.8%, 4.8% and 2.2% in FTY 1.25, 0.5 and IFN, respectively) but in fewer patients at Day 1 than at screening in each group (7.1%, 4.8% and 6.7%, respectively).

Nonsustained ventricular tachycardia was observed in two patients, one in each FTY720 group. For patient 2302-0514-00001 receiving FTY 0.5 mg, the nonsustained ventricular tachycardia was also reported as an AE along with angina pectoris which resolved on the same day as onset. Patient 2302-0505-00010 receiving FTY 1.25 mg appeared to be asymptomatic, with no AEs reported on Day 1. Both patients had normal Holter findings at Month 3. Seven subjects had second degree AVB (4 had Mobitz I [9.5%] and 3 had 2:1 AVB [7.1%] in the FTY 1.25 mg group). There was also intermittent ectopic atrial rhythm in one subject in the 1.25 mg group (2.4%).

There were no cases of sustained supraventricular tachycardia, ventricular tachycardia, ventricular fibrillation or flutter, Torsades de Pointes, atrial fibrillation or flutter, high grade or complete AVB.

At the month 3 Holter, again, frequent PVCs and non sustained ventricular tachycardia (3-10 beats) were observed with FTY and IFN, without clinical complaints at the time of the event.

- Holter in study 2201

In study 2201, 96 patients had 24 hour Holter monitoring (approximately 30 subjects per treatment group). Mean hourly heart rate is presented as follows.

Table 74. Mean hourly rate (bpm) for 24 hour Holter in study 2201

Time Post-Dose	FTY720 5 mg (N=34) [†] mean (SD)	FTY720 1.25 mg (N=31) [†] mean (SD)	Placebo (N=31) [†] mean (SD)	P-value*	P-value*
00:00	72.3 (11.16)	78.7 (12.45)	79.9 (10.80)	a=0.710	b=0.015
01:00	66.0 (12.08)	75.0 (11.38)	83.4 (11.70)	a=0.011	b=<0.001
02:00	60.2 (11.28)	66.6 (9.80)	81.4 (10.32)	a<0.001	b<0.001
03:00	58.7 (9.85)	63.0 (10.21)	82.0 (10.86)	a<0.001	b<0.001
04:00	57.4 (7.93)	63.2 (10.58)	82.3 (9.24)	a<0.001	b<0.001
05:00	59.9 (8.28)	65.0 (9.22)	81.1 (10.07)	a<0.001	b<0.001
06:00	62.5 (10.85)	67.9 (8.51)	83.2 (13.02)	a<0.001	b<0.001
07:00	63.3 (15.37)	66.0 (9.09)	82.0 (11.23)	a<0.001	b<0.001
08:00	63.8 (14.15)	65.5 (9.53)	80.5 (11.93)	a<0.001	b<0.001
09:00	63.3 (14.67)	62.7 (9.10)	81.2 (13.72)	a<0.001	b<0.001
10:00	61.4 (14.75)	61.6 (9.59)	79.3 (12.13)	a<0.001	b<0.001
11:00	60.2 (13.85)	62.2 (9.07)	77.3 (11.13)	a<0.001	b<0.001
12:00	57.5 (12.04)	61.3 (9.34)	75.7 (10.13)	a<0.001	b<0.001
13:00	55.6 (10.17)	60.4 (8.29)	72.8 (9.48)	a<0.001	b<0.001
14:00	54.7 (9.33)	59.0 (9.14)	70.8 (9.24)	a<0.001	b<0.001
15:00	54.6 (9.68)	59.1 (11.06)	70.5 (9.88)	a<0.001	b<0.001
16:00	53.8 (9.65)	60.0 (11.61)	69.8 (9.43)	a=0.001	b<0.001
17:00	53.3 (9.42)	61.9 (13.31)	69.4 (10.88)	a=0.028	b<0.001
18:00	54.5 (9.65)	62.0 (11.19)	68.9 (10.86)	a=0.024	b<0.001
19:00	56.3 (9.69)	63.4 (11.20)	69.7 (9.30)	a=0.029	b<0.001
20:00	57.5 (9.36)	66.8 (11.99)	72.4 (10.70)	a=0.077	b<0.001
21:00	58.8 (9.75)	67.8 (13.82)	75.9 (12.84)	a=0.032	b<0.001
22:00	63.2 (11.74)	66.3 (11.64)	78.0 (12.14)	a=0.001	b<0.001
23:00	65.4 (13.79)	68.1 (11.92)	82.5 (13.47)	a<0.001	b<0.001
24:00	70.4 (10.16)	68.4 (14.75)	86.9 (18.81)	a=0.037	b=0.053
Overall	60.4 (8.22)	65.5 (7.68)	77.3 (7.10)	a<0.001	b<0.001

* P- values represent pairwise comparisons, a= FTY720 1.25mg vs Placebo; b= FTY720 5.0mg vs Placebo

[†] Patients are summarized if they are in the Holter Monitor population

Source: Table 4-23, ISS.

This table shows a dose-related response in decreased heart rate, with FTY 5 mg showing the most decrease. For the 5 mg dose there seems to be a dip at 4 hours, with a HR of 57.4 bpm, and another dip at 18 hours with HR of 53.3 bpm (overall HR over 24 hours= 60.4 bpm). For the FTY 1.25 mg dose, the maximum decrease was at 12 hours, with a mean HR of 59 bpm at that time (mean overall HR of 65.5 bpm). For placebo the maximum decrease was at 17 hours, with a HR of 69.4 bpm (mean overall HR = 77.3 bpm). The mean hourly HR by Holter from time post dose at Month 3 was no different from placebo.

Notable Holter findings in study 2201 are summarized in the following table.

Table 75. Summary of notable Holter findings, study 2201

Finding	FTY720 5 mg n (%)	FTY720 1.25 mg n (%)	Placebo n (%)
Baseline (n):	24	28	23
Sinus pause 2-3 seconds	0	0	0
Sinus pause >3 seconds	0	0	0
2 nd degree AV block	1 (4.2)	2 (7.1)	0
Sustained bradycardia	0	0	0
Day 1 (n):	28	27	31
Sinus pause 2-3 seconds	3	1	0
Sinus pause >3 seconds	0	0	0
2 nd degree AV block	5 (17.9)	3 (11.1)	0
Sustained bradycardia	1 (3.6)	0	0
Month 3 (n):	28	26	26
Sinus pause 2-3 seconds	0	0	0
Sinus pause >3 seconds	0	0	0
2 nd degree AV block	0	0	0
Sustained bradycardia	0	0	0

Source: ISS Table 4-25. Patients are summarized if they are in the Holter monitor population.

On Day 1 Holter monitoring, a sinus pause of a maximal duration of 3 seconds was reported in 1 FTY720 5 mg patient and sinus pauses of a maximal duration of 2 seconds were reported in 1 patient on FTY720 1.25 mg and 2 patients on FTY720 5 mg. No sinus pauses were observed during the Month 3 Holter monitoring. Further evaluation of the events showed that the reported sinus pauses were not “real” sinus pauses but non-conducting P waves in the context of a second degree AV block (3 events) or a sinus arrhythmia superimposed onto a sinus bradycardia (1 event). No sinus pauses lasting more than 3 seconds were reported.

There was no second degree AV block Mobitz II or third degree AV block on Day 1. Of the 8 patients with second degree AV block Mobitz I on Day 1, one patient in each of the FTY720 groups had a second degree AV block Mobitz I also in the baseline Holter. No patient had second or third degree AV block at Month 3 Holter monitoring. There were no findings in the Holters suggestive of ischemic events.

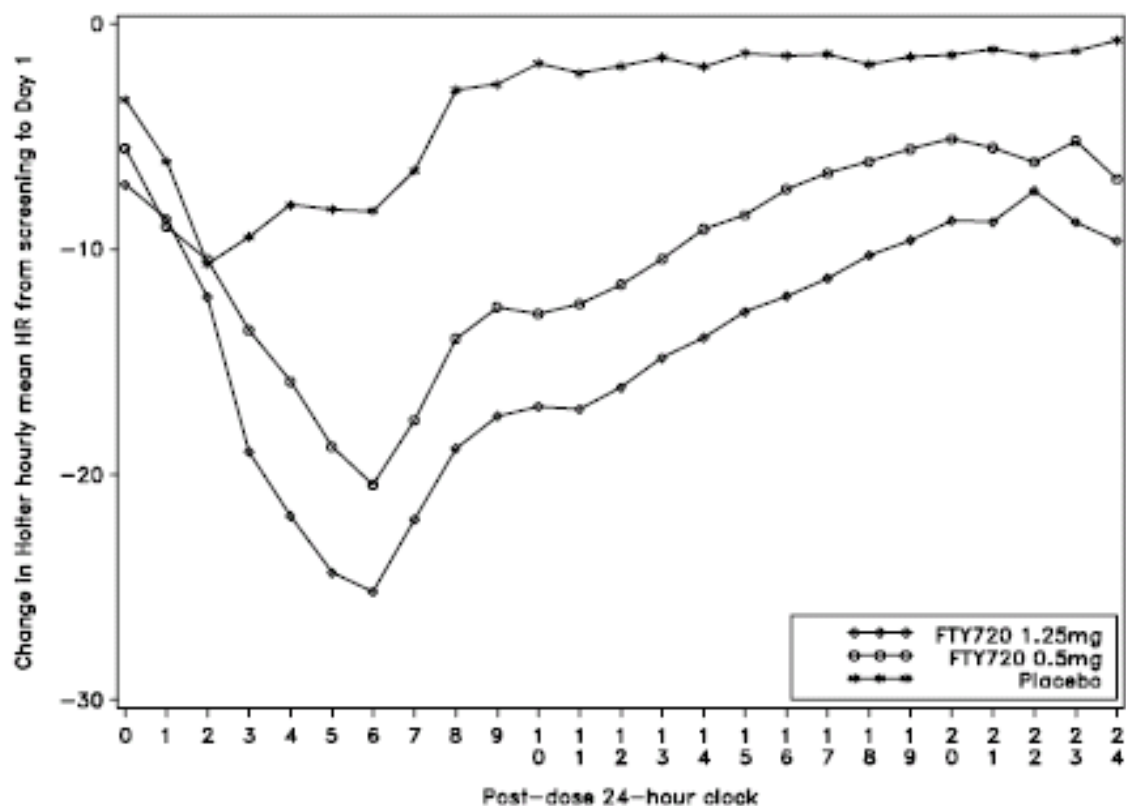
- Holter ECG in study D2309

Results of 24-hour Holter ECG evaluations are available for a total of 1075 patients (366 on FTY720 1.25 mg, 356 on FTY720 0.5 mg, 353 on placebo) from study D2309.

The line plot of change from baseline in hourly mean heart rate in study 2309 is presented as follows:

Figure 3. 24 hour Holter in study 2309

Figure 2-1 Line plot of change in Holter hourly mean heart rate (bpm) from screening to Day 1 by post-dose 24-hour clock (Holter ECG analysis set in study D2309)



Source: Special Safety Interim Report, original submission.

- Evaluation of Holter abnormalities

In study D2309, second degree AV blocks (Mobitz I only) were seen in approximately 1% of patients in all treatment groups during 24-hour monitoring before starting study drug. Upon treatment initiation, second degree AV blocks (Mobitz I or 2:1 blocks) were observed 6.6% of subjects on FTY 1.25, 3.4% of those on FTY 0.5 and 2.0% of those on placebo. For the majority of patients on FTY720, the second degree AV blocks were first seen within 6 hours post-first dose, whereas for the placebo-treated patients, these events first occurred >12 hours post-dose during the night.

Bradycardia, defined as average heart rate of 40 bpm for any one hour during 24-hour Holter monitoring, was observed in 1.4% of patients on FTY 1.25 mg, 0.3% of those on FTY 0.5 mg and none on placebo, after the first dose only.

Mobitz I, 2:1 AV block and bradycardia within 6 hours of the first dose of FTY 1.25 mg were reported as SAEs for 3 patients who were symptomatic and hospitalized for observation. They fully recovered by Day 2 and discontinued study drug.

One patient on FTY720 0.5 mg had ventricular tachycardia during Holter monitoring on Day 1 (scheduled) and Day 44 (unscheduled) which was reported as an SAE. The patient was asymptomatic, however study drug was discontinued on Day 65 due to this event. A repeat Holter 33 days after the last dose of study drug was normal.

At Month 3, neither Mobitz I nor 2:1 AV block was observed in the FTY720-treated patients, whereas Mobitz I occurred in 4 (1.1%) of patients on placebo. There was no evidence of newly occurring high grade AV blocks, torsades de pointes, ventricular fibrillation or flutter with FTY720 treatment.

Table 2-5 Number (%) of patients with predefined Holter ECG findings by finding, visit and treatment (Holter ECG analysis set in study D2309)

Predefined Holter ECG finding	Screening			Day 1			Month 3		
	FTY720 1.25 mg N=366 n (%)	FTY720 0.5 mg N=356 n (%)	Placebo N=353 n (%)	FTY720 1.25 mg N=366 n (%)	FTY720 0.5 mg N=356 n (%)	Placebo N=353 n (%)	FTY720 1.25 mg N=366 n (%)	FTY720 0.5 mg N=356 n (%)	Placebo N=353 n (%)
Frequent VPCs	28 (7.7)	31 (8.7)	30 (8.5)	29 (7.9)	30 (8.4)	25 (7.1)	24 (6.6)	27 (7.6)	29 (8.2)
Non-sustained VT 3-10 beats	4 (1.1)	2 (0.6)	3 (0.8)	6 (1.6)	6 (1.7)	4 (1.1)	6 (1.6)	2 (0.6)	5 (1.4)
Torsade de pointes	0	0	0	1 (0.3)*	0	0	0	0	0
Frequent short episodes of non-sustained SVT	0	1 (0.3)	2 (0.6)	2 (0.5)	2 (0.6)	4 (1.1)	0	0	2 (0.6)
Atrial fibrillation	0	0	1 (0.3)	0	0	0	0	0	0
Mobitz I (Wenckebach) 2nd degree AV block	4 (1.1)	4 (1.1)	4 (1.1)	24 (6.6)	12 (3.4)	7 (2.0)	0	0	4 (1.1)
2:1 AV block	0	0	0	12 (3.3)	6 (1.7)	0	0	0	0
High grade AV block	0	0	0	1 (0.3)*	0	0	0	0	0
Complete heart block	0	0	0	1 (0.3)*	0	0	0	0	0
Pause > 3.0 seconds	0	0	1 (0.3)	1 (0.3)	0	0	0	0	0
Average heart rate ≤40 for any one hour †	0	0	0	5 (1.4)	1 (0.3)	0	0	0	0
Marked sinus bradycardia (HR < 30)	0	1 (0.3)	0	0	0	0	0	0	0
Intermittent ectopic atrial rhythm	1 (0.3)	4 (1.1)	5 (1.4)	0	4 (1.1)	4 (1.1)	5 (1.4)	1 (0.3)	1 (0.3)
Intermittent junctional rhythm	1 (0.3)	0	1 (0.3)	2 (0.5)	0	1 (0.3)	0	0	0
Other	29 (7.9)	23 (6.5)	26 (7.4)	32 (8.7)	33 (9.3)	31 (8.8)	30 (8.2)	30 (8.4)	42 (11.9)
Nonsustained VT >10 beats, Sustained VT, Ventricular fibrillation, Ventricular flutter, Atrial flutter, Mobitz II AV block **	0	0	0	0	0	0	0	0	0

ECG = electrocardiogram; SVT = supraventricular tachycardia; VPC = ventricular premature complex; VT = ventricular tachycardia, HR = heart rate

* Patient 0537-00001: abnormalities occurred prior to study drug - refer to textual narrative in [Section 2.2.3](#).

** All predefined Holter ECG findings for which there were no cases at any time point.

† For Patient 0567-00018 in the FTY720 1.25 mg group, the Holter ECG finding on day 1 of "Average heart rate ≤40 for any one hour" is counted twice, once in the "Average heart rate ≤40 for any one hour" category of predefined findings and once in the "Other" findings, due to a data entry error in the clinical database.

Source: [PT-Table 14.3-2.6](#), [PT-Listing 14.3-2.1](#)

In summary, Holter monitoring from the three studies show a drop in heart rate that is dose related. For the FTY 0.5 mg dose, the maximum change from baseline was around 20-22 bpm at 6 hours post dose in both, 2302 and 2309. By the end of the 24 hour period, the mean HR was similar to that at pre-dose.

Average heart rate ≤40 bpm for any hour was observed in 5 (1.4%) and 1 (0.3%) of patients in the FTY 1.25 and FTY 0.5 during the first 24 hour Holter, but not at the 3 months Holter. The risk of second degree AV block (Wenckebach and 2:1 block) was higher in the FTY groups, with evidence of a dose response during the first 24 hour Holter, but not at the 3 months Holter. There were no cases of non-sustained VT > 10 bpm, sustained VT, ventricular fibrillation/flutter, atrial fibrillation/flutter, Mobitz II AV block or complete AV block.

2) Echocardiography evaluations

- Echocardiography (2302 and 2309)

Echocardiography (echo) assessments were performed in studies 2302 (1-year, IFN-controlled) and 2309 (2-year, placebo-controlled) at selected US sites at Screening Month 3, and Month 12. In 2309 there was also done at Month 24. They included assessment of myocardial function and estimation of pulmonary arterial pressure by echocardiography-doppler. Data were collected and analyzed by a central reader who was blinded to treatment. The original pooled echo analysis population included 183 subjects (152 subjects from study 2309 and 31 from 2302). At the time of the interim analysis data cut-off, there were 140 subjects with a Month 3, 84 with a Month 12 and 17 with a Month 24 echocardiography assessment. At the time of the Updated Special Safety interim report, the total number of patients with echocardiograms at Month 12 is 101 and at Month 24 is 31. Analyses were presented for the individual studies as well as pooled.

No clinically meaningful changes were found in the analyses of mean changes from baseline and outlier analyses in left ventricular ejection fraction, cardiac output, cardiac index, stroke volume, LV end diastolic and systolic volume, left posterior wall thickness or inter-ventricular wall thickness (data not shown). A small increase from baseline (approximately 10%) in Left atrial volume was observed. The clinical significance of this small change is unclear. The following table shows changes from baseline for the estimated pulmonary artery pressure (PaP) for the pooled echo analysis set (Updated report).

Table 76. Change from baseline for estimated pulmonary artery pressure (mm(Hg), pooled echo analysis set.

Visit Treatment	n*	Baseline Mean (SD)	Visit Mean (SD)	Change from baseline		
				Mean (SD)	Median	Range
Estimated pulmonary artery pressure (mmHg)						
Month 3 †						
FTY720 1.25 mg (N=71)	15	26.26 (2.951)	27.30 (3.415)	1.04 (3.364)	0.70	-4.8 - 7.4
FTY720 0.5 mg (N=69)	16	27.09 (3.705)	27.91 (4.307)	0.82 (4.465)	0.50	-7.0 - 13.3
Placebo (N=57)	9	30.30 (3.136)	28.16 (4.555)	-2.14 (2.468)	-2.10	-5.8 - 1.6
Interferon beta (N=11)	4	27.63 (4.033)	25.45 (3.389)	-2.18 (2.871)	-1.15	-6.4 - 0.0
Month 12 †						
FTY720 1.25 mg (N=71)	11	26.13 (3.593)	27.43 (7.692)	1.30 (6.787)	-1.00	-4.2 - 20.1
FTY720 0.5 mg (N=69)	13	27.42 (2.573)	27.70 (4.127)	0.28 (3.791)	-0.70	-5.6 - 9.3
Placebo (N=57)	5	26.04 (4.337)	24.82 (2.955)	-1.22 (4.209)	-0.80	-7.0 - 3.8
Interferon beta (N=11)	4	25.08 (4.472)	26.63 (2.611)	1.55 (2.791)	1.80	-1.7 - 4.3
Last post-baseline †						
FTY720 1.25 mg (N=71)	17	25.97 (2.956)	27.93 (6.837)	1.96 (5.863)	1.00	-4.2 - 20.1
FTY720 0.5 mg (N=69)	20	26.87 (3.635)	28.11 (3.975)	1.24 (3.993)	2.10	-7.0 - 9.3
Placebo (N=57)	11	28.81 (4.345)	27.28 (4.444)	-1.53 (2.111)	-1.30	-4.5 - 1.6
Interferon beta (N=11)	5	26.24 (4.668)	26.20 (2.453)	-0.04 (4.299)	0.20	-6.4 - 4.3

Source: Table 3-4, Special safety interim report update 4/21/10. Only patients with evaluable data at both baseline and the post-baseline visit are included in the summaries. † At month 3, month 12 and the last post-baseline assessment up to cut-off date of 10-Mar-2010, data from patients in study D2309 and D2302 are included. Only patients from study D2309 contributed data at month 24 (8 patients total, data not shown). Normal range for estimated systolic pulmonary artery pressure is 15 to 25 mmHg.

A small increase in mean values for systolic pulmonary artery pressure was observed in this database in the last post-baseline analysis, for both FTY 1.25 and FTY 0.5 mg, as compared to a small decrease on placebo (3 mmHg difference with placebo). The clinical significance of these small changes is unclear. Echocardiography only provides an estimate of the pulmonary pressure value and requires that some degree of tricuspid regurgitation be present. Pulmonary artery pressure could not be estimated in 2/3 of patients in this database.

One patient in the echo safety population discontinued from study 2309 because of pulmonary hypertension that seems to have improved after drug discontinuation (case was discussed under AE leading to drug discontinuation in the Cardiac SOC, study 2309).

A subject with a SAE of papillary muscle disorder was also identified from study 2309 during a non-scheduled echocardiogram done for evaluation of tachycardia (identified by Holter monitoring). The echo showed a questionable mass initially thought to be an atrial mixoma or lymphoma and later determined to be a prominent papillary muscle. The patient did not have a baseline echo because he was not part of the echo safety population, and was eventually discontinued from the trial because of a new diagnosis of asthma. There are no follow up echocardiograms in this patient.

Dr. Shari Targum, FDA cardiologist, concluded the following regarding echocardiogram data:

The available echocardiographic data do not reveal a large safety signal. Despite the preclinical signal of myocardial fibrosis, depressed left ventricular systolic function is not observed in this sample. However, the available echocardiographic evaluations are limited. The application did not include the actual echocardiograms. This reviewer is unable to comment on image quality of the images, or methods of calculation. We were not given the extent of intra-reader or inter-reader variability. In addition, no Doppler results or any evaluations of valve morphology were submitted. If one were concerned about papillary muscle fibrosis, one would have evaluated the mitral and tricuspid valves, including an assessment of regurgitation. Those examinations were not part of this application. If there were a large signal—for example, an imbalance in severe chronic mitral regurgitation in the FTY720 group—one would have expected consequences of chronic volume overload such as left ventricular and left atrial dilatation, in addition to a holosystolic murmur heard best at the apex. It is therefore somewhat reassuring that the 12 month left atrial volume, end-diastolic and end-systolic dimensions are not increased from baseline. However, one cannot exclude a smaller signal, or a signal appearing over a longer time period. Finally, since the study population excluded diabetics and subjects with significant heart disease, one cannot exclude safety signals that might surface in a more vulnerable population.

A retrospective evaluation of the morphology of the valves has been requested and is pending at the time of this review.

3) Pulmonary Function Tests (PFTs)

In studies D2301, D2302, and D2201, PFTs evaluating FEV1, FVC, and carbon monoxide

diffusing capacity (DLCO) were performed at the following time points:

- Study D2201: screening and Month 6
- Study D2301: screening, Month 1, 3, 6, 12, 18, and 24
- Study D2302: screening, Month 1, 3, 6, and 12

For the extension study D2201E1, PFTs were assessed every 3 months starting at Month 9.

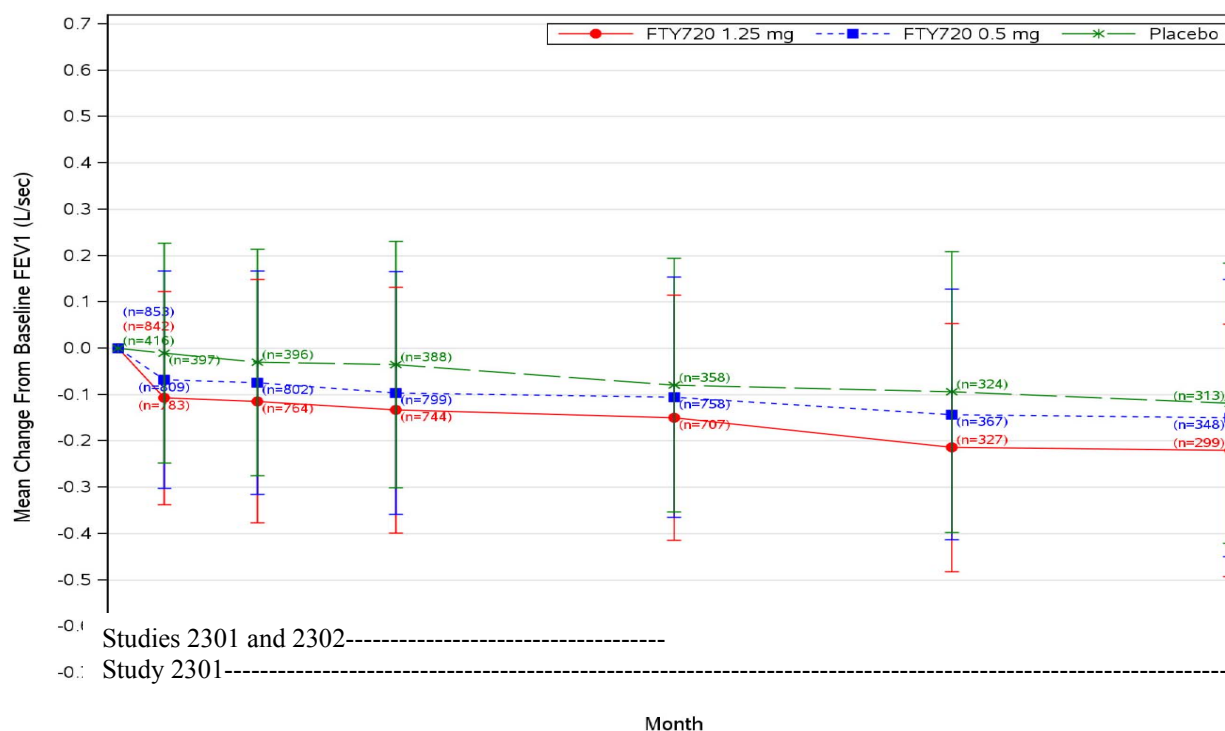
For the extension study D2302E1, PFTs were assessed at Month 13, 15, 18, and 24.

As PFT data in study 2201 were collected differently from studies 2301 and 2302, data from 2201 and the extension study 2201E1 were not included in pooled analyses.

PFT evaluation over time showed an initial sharp decrease within the first month followed by a progressive decrease in FEV1 and DLCO over time, in both, the pooled phase 3 studies and in study 2309.

PFTs in pooled studies 2301 and 2302 (controlled, core studies) are presented as follows:

Figure 4. Changes from baseline in FEV1 in pooled studies 2301 and 2302 core studies



Source: Response to FDA request for information dated 4/8/10. FEV1=forced expiratory volume in 1 second (L/sec)

Table 77. Percentage change of predicted FEV1 in studies 2301 and 2302 core studies.

Visit Treatment Group	n	Baseline			Endpoint			Post-baseline		
		Mean	SD	Med	Mean	SD	Med	Change from baseline	SD	Med
Month 24										
FTY720 1.25 mg (N=849)	299	104.30	13.664	103.99	99.00	14.221	97.91	-5.30	8.431	-4.77
FTY720 0.5 mg (N=854)	348	103.65	14.451	104.00	100.59	14.350	99.73	-3.06	8.769	-3.74
Placebo (N=418)	313	105.16	13.906	105.98	103.20	12.919	103.03	-1.96	9.279	-0.82
Interferon (N=431)	0									

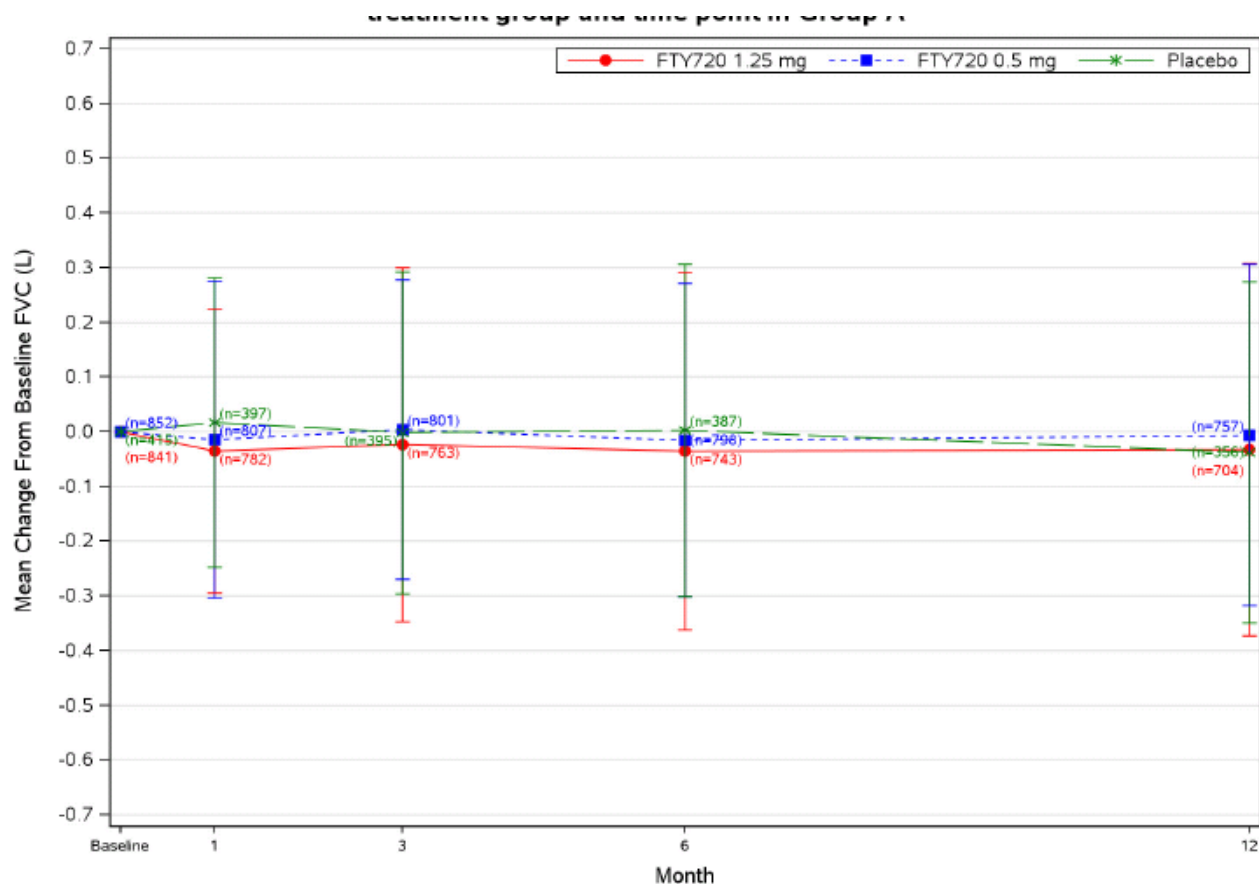
Source: Response to FDA request for information submitted 3/31/10

There is an overlap of confidence intervals and SDs, but the point estimates clearly show a decrease for FTY 1.25, and to a smaller extent for FTY 0.5, as compared to placebo for FEV1.

Dr. Porter, the FDA pulmonologist consultant noted that the change in FEV1 for FTY 0.5 was >100 ml at 6 months, which is greater than the annual decline in FEV1 seen in healthy patients, patients with COPD or MS patients in general. Also of note, PFTs did not correlate with symptoms; this may be due in part at the high percentage of predicted value for PFTs at baseline in these studies.

Changes in FVC are presented in the following figure and table.

Figure 5. Changes from baseline in FVC in pooled studies 2301 and 2302 core studies.



Interim review, 5 12 10.

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NDA 22-527. Fingolimod

Source: Response to FDA request for information submitted 4/8/10. FVC: forced vital capacity (L)

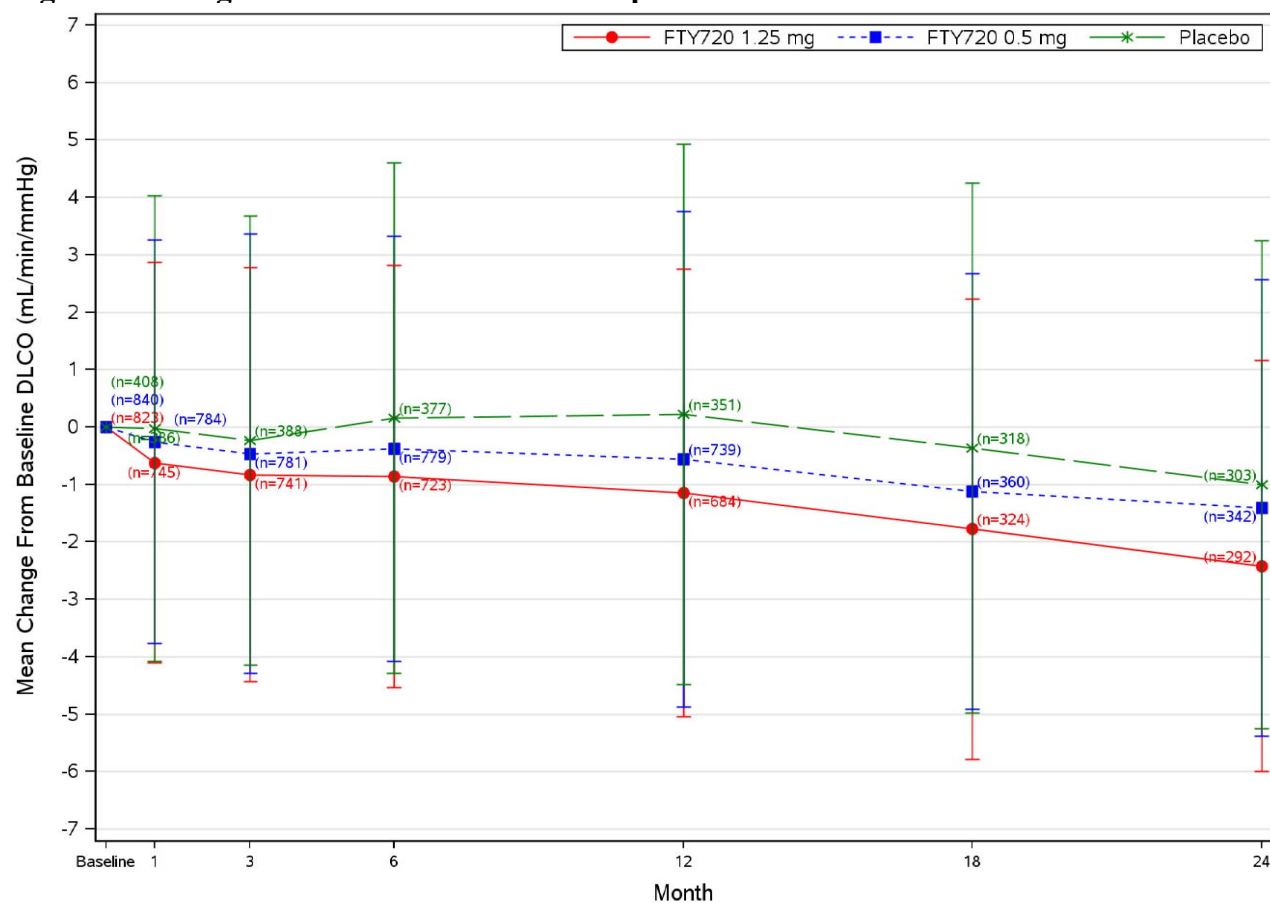
Table 78. Percentage of predicted FVC in 2301 and 2302 core studies

Visit	Treatment Group	n	Baseline			Endpoint			Post-baseline		
			Mean	SD	Med	Mean	SD	Med	Change from baseline		
									Mean	SD	Med
Month 24											
	FTY720 1.25 mg (N=849)	298	107.75	15.265	106.61	107.37	16.279	106.49	-0.38	11.659	-0.63
	FTY720 0.5 mg (N=854)	348	107.51	14.124	106.99	108.05	14.754	106.92	0.54	9.537	0.07
	Placebo (N=418)	312	108.25	14.795	107.49	107.91	14.725	107.53	-0.34	9.104	0.24
	Interferon (N=431)	0									

Source: Response to FDA submitted 3 31 10

There was no change from baseline in FVC in this database.

Figure 6. Changes from baseline in DLCO in pooled studies 2301 and 2302 core studies.



Source: response to FDA request submitted 4/8/10. DLCO=diffusion capacity for carbon monoxide.

Interim review, 5 12 10.
 Lourdes Villalba, M.D
 NDA 22-527. Fingolimod

Table 79. Percentage of predicted DLCO in studies 2301 and 2302 core studies

Visit Treatment Group	n	Baseline			Endpoint			Post-baseline		
		Mean	SD	Med	Mean	SD	Med	Change from baseline	SD	Med
Month 24										
FTY720 1.25 mg (N=849)	298	91.02	10.707	89.69	86.55	11.483	85.21	-4.47	6.130	-4.44
FTY720 0.5 mg (N=854)	348	90.58	10.978	88.67	87.27	11.677	85.79	-3.31	5.776	-3.42
Placebo (N=418)	312	91.25	10.363	89.65	89.55	10.407	87.78	-1.70	5.644	-1.99
Interferon (N=431)	0									

Source: FDA response for information submitted 3 31 10

There is a decrease in mean absolute and percentage values in DLCO in this database, with a suggestion of a dose response.

Table 80. PFT outlier analysis in studies 2301 and 2302 core studies

	FTY720 1.25 mg (N=849)		FTY720 0.5 mg (N=854)		Placebo (N=418)		Interferon (N=431)	
	n	(%)	n	(%)	n	(%)	n	(%)
<hr/>								
<80% of baseline PFT absolute values at any post-baseline visit								
FEV1	64	(7.5%)	39	(4.6%)	24	(5.7%)	15	(3.5%)
FVC	36	(4.2%)	23	(2.7%)	17	(4.1%)	11	(2.6%)
DLCO	157	(18.5%)	133	(15.6%)	50	(12.0%)	62	(14.4%)

Source: response to FDA request submitted 3/31/10.

The outlier analysis suggests a higher risk of decreased FEV1 and DLCO >20% for FTY 1.25 mg as compared to placebo, but not for FTY 0.5. There is no difference for FVC for any dose.

- PFT changes in safety pool E

The change from baseline in percent PFTs in safety pool E (all controlled and extension studies) in the safety update report is presented as follows.

Table 81. Percentage of PFT changes from baseline, safety pool E (SUR)

Variable Visit	FTY720 1.25 mg N=1168		FTY720 0.5 mg N=1176	
	n	Mean (SD)	n	Mean (SD)
FEV₁ (%)				
Month 1	1068	-3.15 (6.59)	1105	-1.97 (6.71)
Month 3	1008	-3.12 (7.76)	1059	-2.14 (6.88)
Month 6	953	-3.59 (7.56)	1014	-2.58 (7.65)
Month 12	860	-3.66 (7.99)	913	-2.38 (7.70)
Month 18	625	-4.46 (8.81)	695	-2.96 (8.09)
Month 24	557	-4.45 (8.24)	634	-2.66 (8.45)
Treatment endpoint	1107	-4.04 (8.37)	1151	-2.50 (8.08)
FVC (%)				
Month 1	1067	-1.01 (6.62)	1104	0.97 (49.24)
Month 3	1007	-0.54 (8.05)	1058	-0.03 (6.79)
Month 6	952	-0.65 (7.90)	1013	-0.33 (7.30)
Month 12	859	-0.34 (8.48)	914	0.29 (7.87)
Month 18	624	-0.35 (9.35)	695	0.02 (8.09)
Month 24	557	-0.09 (10.15)	634	0.96 (9.01)
Treatment endpoint	1106	-0.54 (9.07)	1150	1.45 (48.37)
D_LCO corrected for hemoglobin (%)				
Month 1	1027	-2.30 (12.69)	1078	-0.63 (11.40)
Month 3	979	-3.09 (12.26)	1031	-1.26 (12.44)
Month 6	929	-2.98 (13.08)	991	-0.83 (12.16)
Month 12	835	-3.18 (13.41)	893	-1.42 (14.08)
Month 18	603	-4.14 (13.30)	674	-2.71 (14.79)
Month 24	539	-5.12 (12.38)	619	-3.57 (14.00)
Treatment endpoint	1085	-4.47 (14.25)	1138	-2.62 (13.53)

Source: Table 4-7. Safety Update Report, 4/22/10. (There is no placebo in pool E)

The analysis indicates a small decrease from baseline in FEV₁ and DLCO (but not for FVC), for both, FTY 1.25 and FTY 0.5, with a suggestion for a dose response, which is consistent with the analyses in the core studies and in study 2309.

The outlier analysis of decreased PFTs for safety pool E is as follows (SUR)

Table 82. Outlier analysis, PFTs in safety pool E (SUR)

	FTY720 1.25 mg (N=1168) n (%)	FTY720 0.5 mg (N=1176) n (%)
<80% of baseline PFT absolute values at any post-baseline visit		
FEV ₁	94 (8.0)	63 (5.4)
FVC	49 (4.2)	32 (2.7)
D _L CO	262 (22.4)	223 (19.0)

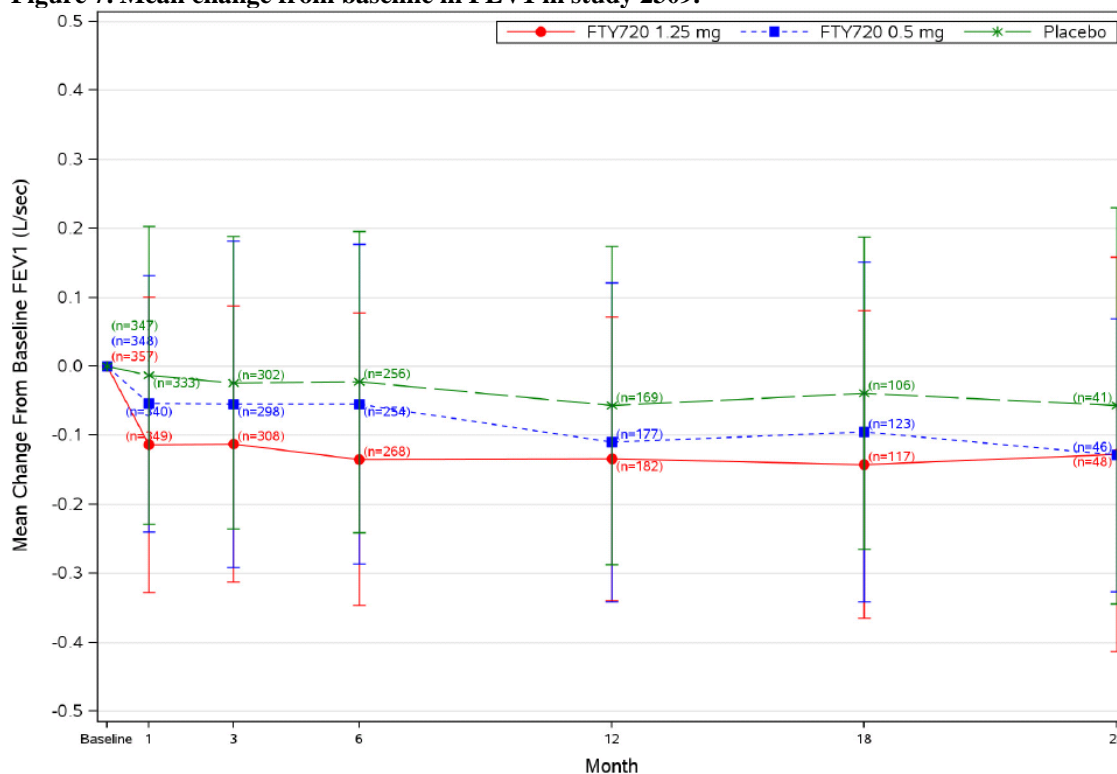
Source: Table 4-8, safety update report (4/22/10)

This analysis suggests that a slightly higher percentage of patients had decreased FEV1, FVC and DLCO in the FTY 1.25 mg group, as compared to FTY 0.5 mg (there is no placebo in pool E).

- PFT changes in study 2309

The following figures represent change from baseline in FEV1 and DLCO in study 2309. Consistent with the findings in the phase 3 studies, there is no decline in FVC in 2309 (data not shown).

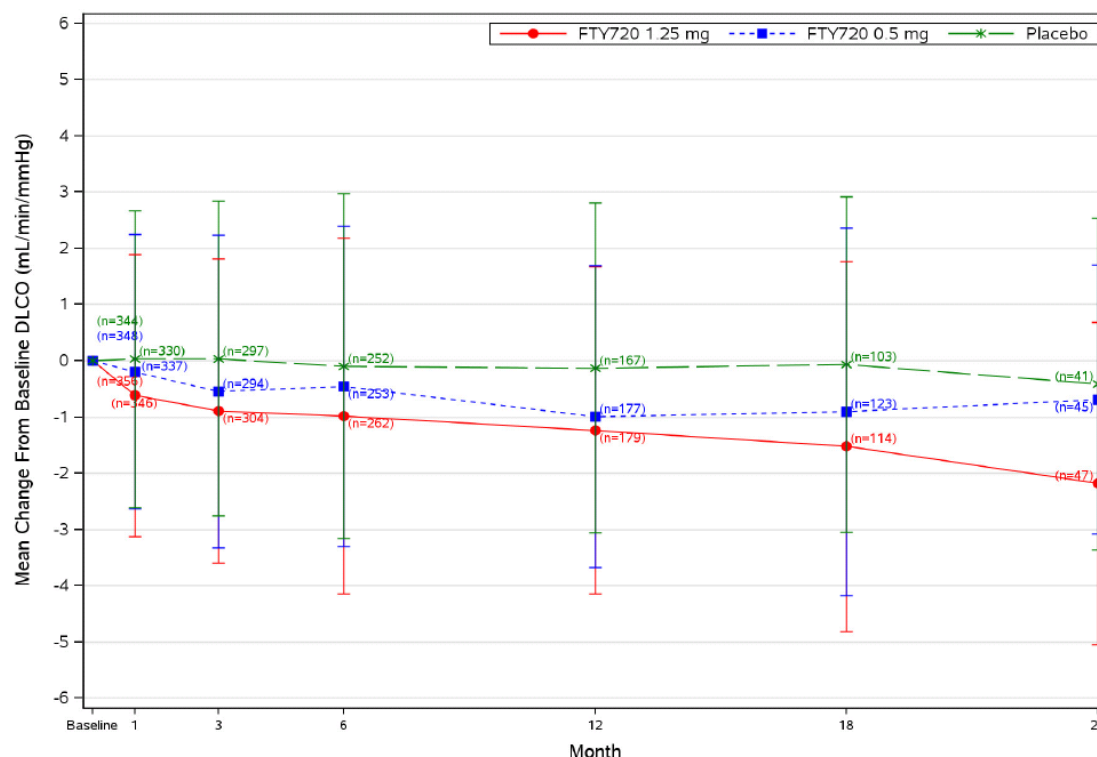
Figure 7. Mean change from baseline in FEV1 in study 2309.



Source: response to FDA request for information submitted 4/8/10

There is a decrease from baseline in mean FEV1 for FTY 1.25 mg and 0.5, as compared to placebo (of course, with wide confidence intervals). The change is observed already at the 1 month evaluation and it is maintained until the 24 month evaluation.

Figure 8. Mean change from baseline in absolute value DLCO in study 2309.



Source: response to FDA request for information submitted 4/8/10

The decrease in DLCO in study 2309 is consistent with the analysis in 2301 and 2302. There is a suggestion for some decline in DLCO over time particularly for the 1.25 mg dose.

Table 83. Outlier analysis of PFTs in study 2309, PFT analysis set.

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

Source: Response to FDA request for information submitted 2/9/10.

The PFT analyses (mean and outlier) indicate a decline in lung function for FTY 1.25 mg, particularly for FEV1 and DLCO, suggesting some degree of lung toxicity. This is observed in the phase 3 studies, pool E and study 2309.

The decrease in FEV1 may be in part explained by the known pharmacologic bronchoconstrictive effects of fingolimod. The reason for the decreased diffusion capacity observed in these studies is not clear.

It has recently been shown that prolonged S1P antagonist exposure increases the damage in mice with bleomycin - induced lung injury.⁸ The authors hypothesize that the increase in AE of dyspnea and decreased PFTs observed in study 2201 with FTY 5 mg dose as compared to placebo (from an article published in the NEJM in 2006) could be explained by “minor perturbations in lung endothelial barrier function” This is a very interesting hypothesis.

- Reversibility of effect on PFTs in safety pool E follow up population

A subset of patients in safety pool E (288 patients on FTY 1.25mg and 211 on FTY 0.5mg), was followed up after discontinuation (mean of 4 months). Change from baseline in FEV₁ and DLCO in this population are presented by visit and treatment as follows.

Table 84. Percentage of predicted FEV1 in E follow up population (SUR)

Visit Treatment Group	n	Baseline			Endpoint			Post-baseline		
		Mean	SD	Med	Mean	SD	Med	Change from baseline	SD	Med
TEP										
FTY720 1.25 mg (N=288)	248	102.08	14.871	101.00	98.11	14.467	98.30	-3.96	9.871	-3.69
FTY720 0.5 mg (N=211)	194	99.55	14.743	99.85	97.04	13.810	97.39	-2.51	8.316	-2.38
Day 1-45 after drug discontinuation										
FTY720 1.25 mg (N=288)	136	102.39	13.522	101.50	99.80	14.302	100.49	-2.58	8.371	-2.56
FTY720 0.5 mg (N=211)	92	103.00	15.191	104.12	101.76	14.372	101.84	-1.25	8.963	-0.70
Month 3 after drug discontinuation										
FTY720 1.25 mg (N=288)	163	101.92	14.671	100.87	100.55	14.364	99.79	-1.37	8.280	-2.16
FTY720 0.5 mg (N=211)	116	100.74	14.713	100.87	100.52	13.917	100.21	-0.22	7.547	-0.27

Source: post table 11.4-2 Safety Update Report (4/22/10). TEP: treatment endpoint; last non-missing value. Only patients with both, baseline and post-baseline are included.

Table 85. Percentage of predicted DLCO corrected for Hg in E follow up population (SUR)

Visit Treatment Group	n	Baseline			Endpoint			Post-baseline		
		Mean	SD	Med	Mean	SD	Med	Change from baseline	SD	Med
TEP										
FTY720 1.25 mg (N=288)	244	86.48	18.136	84.79	82.21	17.774	80.86	-4.27	16.449	-3.95
FTY720 0.5 mg (N=211)	193	83.57	17.742	81.97	80.46	15.521	80.01	-3.12	17.754	-1.96
Day 1-45 after drug discontinuation										
FTY720 1.25 mg (N=288)	134	86.37	17.558	85.86	79.58	15.079	79.14	-6.79	11.792	-5.76
FTY720 0.5 mg (N=211)	90	83.45	15.529	82.68	82.05	15.208	81.32	-1.40	10.904	-2.78
Month 3 after drug discontinuation										
FTY720 1.25 mg (N=288)	159	86.26	17.539	85.40	81.94	17.806	79.76	-4.31	15.120	-3.52
FTY720 0.5 mg (N=211)	115	84.23	19.028	80.85	80.63	14.018	79.66	-3.61	18.385	-1.62

Source: post table 11.4-2. Safety Update Report (4/22/10). TEP: treatment endpoint; last non-missing value. Only patients with both, baseline and post-baseline are included.

The analyses in the E follow up population suggest that the changes from baseline to the last available measurement in FEV1 are reversible, however, the DLCO changes do not appear to be reversible. Some patients were followed beyond 3 months but the numbers become too small (there were 56 patients at 6 months and 3 patients at 18 months). Additional analyses have been requested.

⁸ Shea et al. Prolonged S1P antagonist exposure may exacerbate vascular leak, fibrosis and mortality after lung injury. Am J. Resp.Cell.Mol. Biology. January 15, 2010.

s3) Chest high resolution computer tomography

- In 2201 Chest X-rays were done but HRCT were not part of the protocol.
- In 2301 chest X-rays were done at screening, month 12, 18 and 24. As per a protocol amendment (April 2006) chest HRCT were done instead of X-rays at screening and month 24 at selected sites. HRCT could be required at other visits in case of confirmed $\geq 20\%$ reduction of baseline PFTs (unscheduled HRCTs).
- In study 2302, chest X-rays were done at Screening and Month 12. HRCT were done instead of the X-rays at all US sites and selected sites outside the US where feasible, and interpreted by local radiologists. HRCT was to be done if PFT reduction of $\geq 20\%$.
- In 2309 HRCT was to be done in all subjects at screening and Month 24. Additionally, chest HRCT was to be performed at visit 14 (12 months) in the first 360 (approximately) randomized patients, and interpreted by a central reader.

Number of patients with month 24 chest HRCT in the NDA

Study	FTY720 0.5 mg	FTY720 1.25 mg	Placebo
2301	90	85	95
2309	45	40	36
Total	135	125	131

Source: ISS, original application

- Chest HRCT in study D2301

In total, 360 patients (one third of those randomized) had chest HRCT scans at screening in study 2301. Of these, 259 patients had the assessment at Month 24 visit, 34 patients had an end-of-study chest HRCT scan performed outside of the 24-month visit window and 67 had no post-baseline chest HRCT scan. Chest HRCT results in study D2301 as judged by the local radiologist at screening and at Month 24 are summarized the following table.

Table 86. HRCT abnormalities in 2301 by visit (does not include unscheduled tests)

	FTY 1.25 N=429 n (%)	FTY 0.5 N=425 n (%)	Placebo N=418 n (%)
Screening			
Number of patients	122	120	118
Abnormal findings	35 (28.7)	27 (22.5)	31 (26.3)
Clinically significant abnormality	0	1 (0.8)	0
Month 24			
Number of patients*	85	90	95
Abnormal	24 (28.2)	23 (25.6)	22 (23.2)
Abnormality compared to baseline:			
Unchanged	9 (10.6)	9 (10.0)	12 (12.6)
New or worsened	12 (14.1)	13 (14.4)	9 (9.5)
Clinically significant	4 (4.7)	4 (4.4)	2 (2.1)
Unscheduled			
Number of patients	8	11	10
Considered clinically significant	1	3	2

Source: Modified from ISS Table 4-35 and ISS text. * includes 11 patients (3 in FTY720 1.25 mg, 3 in FTY720 0.5 mg and 5 in placebo) who did not have baseline chest HRCT assessment

At screening, the proportion of patients with abnormal chest HRCTs was similar across the treatment groups. The majority of abnormal readings were related to prior-inflammatory events

or to small nodular changes. At Month 24, the percentage of patients with chest HRCTs showing new or worsened abnormalities compared to baseline was higher in the FTY groups than the placebo group (14.1% in the FTY1.25 mg, 14.4% in the FTY 0.5 mg, and 9.5% in the placebo group). Of those patients with new or worsened abnormalities, clinically significant pulmonary changes were seen in 2 patients on FTY 1.25 mg (benign cysts lower lobe, apical scarring and ground glass appearance), 3 patients on FTY0.5 mg (pneumofibrosis, suspected pneumonia, cysts/unknown abnormality) and 2 patients on placebo.

A similar number of patients had unscheduled HRCT (because of a clinical indication or because of decreased PFTs >20% from baseline). Among the 29 subjects with unscheduled chest HRCT, seven were considered clinically significant by the investigator: 1 (pericarditis/pleurisy/pneumonia) in the FTY 1.25 mg group, 3 (node enlargement, panbronchiolitis, and pneumonic infiltration) in the FTY 0.5 mg group and 2 (mild bronchial wall thickening in both lungs/bilateral glass appearance) in the placebo group.

Shifts from normal to abnormal on Month 24 chest HRCTs occurred slightly more frequently in the FTY 1.25 mg [8/56 (14.3%)] and FTY 0.5 mg [13/70 (18.6%)] than in the placebo group [8/67 (11.9%)]. Approximately half of the patients with an abnormal HRCT scan at baseline had a normal HRCT scan at Month 24 across the 3 treatment groups.

- Chest X-rays

The patients who did not have a chest HRCT assessment underwent a chest X-ray at Screening and Month 24 (read by local radiologist). At Screening, less than 10% of the patients had an abnormal chest X-ray in each group. At Month 24, there was a lower percentage of abnormal chest X-ray in all groups, lowest in the FTY 0.5 mg group; i.e. 8.4% in the FTY 1.25 mg group, 3.3% in the FTY 0.5 mg group, and 6.1% in the placebo group. There was no difference in the number of patients with clinically significant findings at Month 24 (2 patients in the FTY 1.25 mg group, 1 patient in the FTY 0.5 mg group, and 1 patient in the placebo group).

Therefore, evaluation of HRCT in this 2-years study suggests a slightly higher risk of pulmonary toxicity for FTY as compared to placebo, however, there was no particular pattern of toxicity and there was no evidence of pulmonary fibrosis.

- Chest HRCT in study 2302

In study D2302, chest HRCT was performed at all US sites and at sites outside the US where feasible and permitted per local regulations instead of chest X-ray. Chest HRCTs were performed in 478 patients at screening and 421 patients at Month 12. Chest HRCT results as judged by the local radiologist are presented by visit and treatment in the following table. The proportion of patients with chest HRCTs showing new or worsening abnormalities compared to baseline was similar across groups at each visit.

Table 87. Table Chest HRCT in 2302 by visit

FTY720 1.25 N=420	FTY720 0.5 N=429	Interferon N=431
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Baseline			
Number of patients	157	161	160
Abnormal findings	24 (15.3)	35 (21.7)	26 (16.3)
Clinically significant	0	0	1 (0.6)
Month 12			
Number of patients	135	139	147
Abnormal	24 (17.8)	25 (18.0)	25 (17.0)
Abnormality compared to baseline			
Unchanged	8 (5.9)	13 (9.4)	7 (4.8)
New or worsened	12 (8.9)	11 (7.9)	15 (10.2)
Not compared	4 (3.0)	1 (0.7)	3 (2.1)
Abnormality			
Clinically significant	3 (2.2)	1 (0.7)	3 (2.0)
Missing assessment	0	1 (0.7)	1 (0.7)
Unscheduled chest HRCTs			
Number of patients	9	14	6
Number of HRCT scans	10	15	9
Normal	7	13	2
Abnormal	3	2	7
Clinically significant	0	1	1
Abnormality compared to baseline:			
Unchanged	0	1	0
New or worsened	2	1	2
Not compared	1	0	5

Modified from ISS Table 4-36.

Seven subjects with HRCT abnormalities were considered to have clinically significant changes: 3 on FTY 1.25 (bronchopathy, atelectatic strias with tubular bronchiectasis, pulmonary nodules), one on 0.5 (pulmonary nodules, hepatic nodules) and 3 in the interferon group (pulmonary nodules, emphysema).

Among the 29 subjects who underwent unscheduled HRCT testing, 9 were in the FTY 1.25mg group, 14 in the TY 0.5 mg group and 6 in the IFN group. Only one in the FTY 0.5 mg and one in the IFN group were considered by the investigator be clinically significant changes.

Overall, there was no increased risk of pulmonary toxicity as compared to interferon, and there were no changes consistent with pulmonary fibrosis.

- HRCT in 2309

Results of HRCT in 2309 are presented in the following table.

Table 88. Chest high resolution CT in 2309 (original application)

	FTY720 1.25 mg N=88 n (%)	FTY720 0.5 mg N=88 n (%)	Placebo N=90 n (%)
Baseline chest HRCT			
Number of patients	87	87	87
Normal	49 (56.3)	49 (56.3)	56 (64.4)
Abnormal	38 (43.7)	38 (43.7)	31 (35.6)
Clinically significant	0	2 (2.3)	0
Clinically insignificant	38 (43.7)	36 (41.4)	31 (35.6)
End of study chest HRCT			
Number of patients	68	64	64
Missing	0	0	1 (1.6)
Normal	40 (58.8)	37 (57.8)	38 (59.4)
Abnormal	28 (41.2)	27 (42.2)	25 (39.1)
Clinically significant	2 (2.9)	3 (4.7)	5 (7.8)
Clinically insignificant	26 (38.2)	24 (37.5)	20 (31.3)
Abnormality compared to baseline			
Unchanged	13 (19.1)	9 (14.1)	9 (14.1)
Improved	0	0	0
New or worsened	10 (14.7)	16 (25.0)	12 (18.8)
Comparison not required	0	0	0
Not compared	4 (5.9)	2 (3.1)	4 (6.3)
Missing	1 (1.5)	0	0
Unscheduled chest HRCT			
Number of patients	9	10	10
Number of HRCT scans	11	14	10
Missing	1 (9.1)	0	0
Normal	2 (18.2)	9 (64.3)	7 (70.0)
Abnormal	8 (72.7)	5 (35.7)	3 (30.0)
Clinically significant	1 (9.1)	1 (7.1)	0
Clinically insignificant	7 (63.6)	4 (28.6)	3 (30.0)
Abnormality compared to baseline			
Unchanged	4 (36.4)	3 (21.4)	0
Improved	0	0	2 (20.0)
New or worsened	4 (36.4)	2 (14.3)	1 (10.0)
Comparison not required	0	0	0
Not compared	0	0	0

Source: Special safety interim report, original application.

The number of abnormal HRCT at the end of study is similar among treatment groups (40-42%) among scheduled studies. The percentage of abnormal HRCT among unscheduled tests is higher in the FTY 1.25 mg group, as compared to FTY 0.5 and placebo (and more than half of them are clinically significant). The number of new or worsened abnormalities as compared to baseline also is higher in FTY 1.25 as compared to FTY 0.5 and placebo, but the numbers are small. Review of Updated report is ongoing.

5) Ophthalmologic evaluations

A comprehensive ophthalmic examination was performed in all studies by an ophthalmologist at Screening and end of study, and regularly throughout the study, depending on the study. It included an eye history, visual acuity measurement and dilated ophthalmoscopy. For study 2309 ophthalmologic evaluations were at screening, month 1, 3, 6, 12, 18 and 24. For other studies, the original schedule of visits was less often, but a schedule similar to 2309 was implemented after the protocols were ongoing.

Study 2301 included OCT (optic coherence tomography) to determine central foveal thickness (CFT) at screening and Month 24. It could be required at other visits to evaluate macular thickness, if indicated.

In study 2302, OCT was done at screening and 12 months. Patients in the United States also had an OCT performed at Month 1, Month 3, Month 6, and if technically feasible, total macular volume and retinal nerve fiber layer (RNFL) thickness (requires OCT-3, done in US centers only). Patients with a medical history of uveitis or newly-diagnosed uveitis at Screening or after initiation of study drug required additional ophthalmic evaluations.

In study 2309, CFT and RNFL thickness by OCT was to be performed at each visit for the first 300 randomized patients and in all patients with history of uveitis or active uveitis, and at screening, Month 12 and Month 24 for the remaining randomized patients.

Results of CFT by OCT in study 2301 are presented as follows.

Table 89. Mean changes from baseline in CFT in Study 2301

Visit	Statistics	FTY720 1.25mg N=429	FTY720 0.5mg N=425	Placebo N=418
Baseline	n (eyes)	784	779	771
	Mean (SD)	169.2 (25.16)	168.7 (24.70)	169.5 (25.24)
Month 24	n (eyes)	566	637	557
	Mean (SD)	174.8 (31.16)	172.6 (30.41)	169.7 (30.78)
Change from baseline	n (eyes)	520	581	511
	Mean (SD)	5.45 (28.834)	4.08 (27.025)	0.85 (29.028)

Source: Table 4-41 ISS

Evaluation of mean changes in CFT indicates an increase in mean CFT for both FTY doses compared to placebo; however, more informative is the evaluation of the distribution of changes in study 2301 (2 year study) which shows a higher number of patients in the FTY 1.25 mg group had changes from baseline >40 microns at the 24 months evaluation.

Table 90. Distribution for change from baseline in central foveal thickness, study 2301

Table 14.3-6.6 (Page 1 of 2)
 Frequency (%) distribution for change from baseline in central foveal thickness, by visit and treatment
 Safety population

Visit		FTY720 1.25mg N=429	FTY720 0.5mg N=425	Placebo N=418
Month 24	Number of eyes with OCT performed at baseline and this visit	520	581	511
	Change from baseline in central foveal thickness			
	<-40	15 (2.9%)	20 (3.4%)	23 (4.5%)
	>=-40 to <=-21	40 (7.7%)	38 (6.5%)	33 (6.5%)
	>-21 to <=20	375 (72.1%)	417 (71.8%)	376 (73.6%)
	>20 to <=40	45 (8.7%)	69 (11.9%)	54 (10.6%)
	>40	45 (8.7%)	37 (6.4%)	25 (4.9%)
Last assessment on study drug *	Number of eyes with OCT performed at baseline and this visit	554	563	538
	Change from baseline in central foveal thickness			
	<-40	15 (2.7%)	19 (3.4%)	19 (3.5%)
	>=-40 to <=-21	43 (7.8%)	38 (6.7%)	35 (6.5%)
	>-21 to <=20	396 (71.5%)	415 (73.7%)	408 (75.8%)
	>20 to <=40	54 (9.7%)	57 (10.1%)	55 (10.2%)
	>40	46 (8.3%)	34 (6.0%)	21 (3.9%)

Source: PT table 14.3-6.6 CSR.

- The percentages are based on the number of eyes with OCT performed for each visit.
- The highest value is used if two or more unscheduled values exist for a patient.
- Only the worst case is counted in unscheduled visit.
- * The last central foveal thickness value taken at or before last day of study drug is summarized in row 'Last assessment on study drug'.

Analyses by gender and age are pending.

In study 2302 mean changes from baseline in CFT showed a slight increase in CFT for FTY 0.5 mg (2.5-4 microns) that was maximum at the 1 month evaluation, but not for FTY 1.25mg or IFN (data not shown). (Only US patients had measurement at 1, 3 and 6 months).

- OCT in 2309

As per the Updated Special safety interim report, the following number of AE of macular edema were reported in study 2309: 7 on FTY 1.25mg, 5 on FTY 0.5 and 2 on placebo. Macular edema was diagnosed within the first six months of treatment with FTY720 in all patients, except one. DSMB has confirmed macular edema for 8 of these 14 patients: 4 on FTY720 1.25 mg, 3 on FTY720 0.5 mg and 1 on placebo. Six of the 14 patients had absolute CFT >300 µm newly occurring, post-baseline (3 in each of the FTY720 groups). Out of the other 8 patients whose CFT data did not meet this notable CFT criterion, 3 had a change from baseline >40 µm, while 5 patients had only subtle changes in CFT.

Mean changes from baseline in central foveal thickness (microns), and distribution of changes in study 2309 is presented in the following tables (Updated Report).

Table 91. Change from baseline in central foveal thickness (microns), Ophtalmology analysis set, study 2309

Visit Treatment	n	Baseline Mean	Visit Mean	Change from baseline		
				Mean (SD)	Median	Range
Month 1						
FTY720 1.25 mg (N=359)	464	174.61	176.85	2.24 (23.858)	2.00	-83.0 - 150.0
FTY720 0.5 mg (N=350)	434	176.77	177.58	0.81 (25.642)	0.00	-121.0 - 257.0
Placebo (N=350)	426	176.86	175.96	-0.89 (20.840)	-1.00	-115.0 - 117.0
Month 12						
FTY720 1.25 mg (N=359)	392	175.33	180.23	4.90 (25.808)	4.00	-77.0 - 147.0
FTY720 0.5 mg (N=350)	388	173.44	178.08	4.63 (30.088)	2.00	-110.0 - 154.0
Placebo (N=350)	384	177.60	179.85	2.25 (28.886)	0.00	-119.0 - 137.0
Month 24						
FTY720 1.25 mg (N=359)	156	173.38	182.99	9.62 (31.638)	5.00	-73.0 - 108.0
FTY720 0.5 mg (N=350)	172	173.70	176.97	3.26 (34.082)	0.00	-99.0 - 175.0
Placebo (N=350)	158	175.20	177.70	2.51 (33.535)	1.00	-121.0 - 126.0

Table 5-1, Special safety interim report (Updated report). Source: N = number of patients in the OPH analysis set
 n = number of eyes evaluated by optical coherence tomography at baseline and the respective visit.
 Baseline assessment is the last ophthalmic assessment prior to initial dose of study medication.

Table 92. Distribution of change from baseline in central foveal thickness, study 2309

Visit	Change from baseline in CFT (µm)	FTY720 1.25 mg N=359, n (%)	FTY720 0.5 mg N=350, n (%)	Placebo N=350, n (%)
Month 1	n	464	434	426
	< -40	17 (3.7)	18 (4.1)	14 (3.3)
	≤ -40 to ≤ -21	24 (5.2)	33 (7.6)	27 (6.3)
	> -21 to ≤ 20	378 (81.5)	334 (77.0)	352 (82.6)
	> 20 to ≤ 40	26 (5.6)	34 (7.8)	22 (5.2)
	>40	19 (4.1)	15 (3.5)	11 (2.6)
Month 3	n	400	392	386
	< -40	16 (4.0)	16 (4.1)	21 (5.4)
	≤ -40 to ≤ -21	24 (6.0)	37 (9.4)	43 (11.1)
	> -21 to ≤ 20	308 (77.0)	294 (75.0)	288 (74.6)
	> 20 to ≤ 40	32 (8.0)	30 (7.7)	24 (6.2)
	>40	20 (5.0)	15 (3.8)	10 (2.6)
Month 24	n	156	172	158
	< -40	8 (5.1)	14 (8.1)	14 (8.9)
	≤ -40 to ≤ -21	11 (7.1)	12 (7.0)	14 (8.9)
	> -21 to ≤ 20	98 (62.8)	116 (67.4)	103 (65.2)
	> 20 to ≤ 40	24 (15.4)	14 (8.1)	13 (8.2)
	>40	15 (9.6)	16 (9.3)	14 (8.9)

Source: Updated Special safety interim report (submitted 4/22/10)

The number of patients with change from baseline in CFT >40 µm was higher for FTY 1.25 and 0.5 as compared to placebo at 1 month and 3 months. For other assessments (month 6, 12 and 18) and at the Month 24 visit, there was no difference. However, the number of eyes available for evaluation decreases with time, and patients with macular edema are withdrawn from the pool.

Several cases of macular edema were reported from study 2309. These cases were unblinded and narratives provided in the updated safety interim report. Evaluation of these cases is ongoing.

6) Dermatologic examination

Following the report of skin malignancies from the study 2201E1, dermatological exams performed by a dermatologist were implemented when studies 2301 and 2302 were ongoing. Thus, while a number of cases were detected on study, no pre-study assessment was available to determine that the lesions were not present prior to initiation of study medication. In study 2302, the majority of patients had only one exam in the study, in most cases at the end of the study. In study 2301, the mean time to the first assessment (1119 patients) was 10 months for all treatment groups. At this time, approximately 70% of patients had normal examinations. Of the abnormal findings, most were benign. Any finding of cancerous skin disorders resulted in permanent study drug discontinuation. Skin neoplasms have been discussed in the Other significant events, serious and non-serious neoplasms.

In study 2309 a complete dermatological examination is being performed at screening and Month 24 or end of study.

7.4.6 Immunogenicity

Immunogenicity was not evaluated.

7.4.7 Evaluation of safety in phase 1 studies

- SAE in the Phase 1 clinical pharmacology studies.

This database includes studies that were uncontrolled as well as crossover studies, therefore, comparisons of risk/rate between FTY and placebo in the overall database can not be done. Twelve subjects had SAE in this database. Five were in placebo treated subjects and seven in FTY treated subjects.

Table 93. SAE in clinical pharmacology studies

Patient No.	Age/Sex	Study medication	Serious adverse event/infection	Day reported	Relationship to study medication
01-003	58/Male	FTY720 0.125 mg	Pneumonia	21	Not suspected
01-008	50/Female	FTY720 0.125 mg	Urinary tract infection	32	Not suspected
02-001	54/Female	FTY720 0.125 mg	Dyspnea	2	Suspected
04-001	21/Female	FTY720 0.25 mg	Gastroenteritis	33	Not suspected
01-032	50/Female	FTY720 5 mg	Herpes zoster	7	Not suspected
08-001	51/Female	FTY720 5 mg	Hepatic enzymes increased	3	Suspected
01-009	47/Female	Placebo	Cerebrovascular disorder	24	Not suspected
01-025	63/Female	Placebo	Tachycardia supraventricular	37	Not suspected
05-002	30/Male	Placebo	Gastroenteritis	4	Not suspected

Source: Table 2-98, ISS.

Findings in this dataset were consistent with those in the phase 2 and 3 studies, with events of bradycardia, AV Block, and hepatic enzyme increased (data not shown).

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There was a clear dose-response in terms of adverse events in this application, particularly for the serious events of macular edema, bradycardia and AV bloc as well as in liver enzyme elevations and decrease in pulmonary function tests.

7.5.2 Time Dependency for Adverse Events

Some events occurred immediately such as bradycardia and AV block. They were transient and mostly recovered without specific treatment, however, some required treatment or led to drug discontinuation. Other events tend to occur early, during the first few months of treatment, such as macular edema but they also occurred later (time to onset in ISS studies was mean 207 days, median 99 days). Some events are likely to occur with time and will need longer follow up (e.g. cardiac function, malignancies).

7.5.3 Drug-Demographic Interactions

Increased LFT was observed more in males as compared to female (See table below). Review of other AE drug-demographic interactions is ongoing.

Table 2-30 Number (%) of patients with liver enzyme elevation AEs by gender in Group A (12-month safety population)

Primary system organ class Preferred term	Male				Female			
	FTY720 1.25 mg (N=266) n (%)	FTY720 0.5 mg (N=277) n (%)	Placebo (N=120) n (%)	Inter- feron (N=139) n (%)	FTY720 1.25 mg (N=583) n (%)	FTY720 0.5 mg (N=577) n (%)	Placebo (N=298) n (%)	Inter- feron (N=292) n (%)
Investigations	90 (33.8)	102 (36.8)	24 (20.0)	14 (10.1)	108 (18.5)	99 (17.2)	57 (19.1)	24 (8.2)
ALT increased	41 (15.4)	42 (15.2)	4 (3.3)	4 (2.9)	25 (4.3)	19 (3.3)	7 (2.3)	4 (1.4)
GGT increased	23 (8.6)	17 (6.1)	1 (0.8)	1 (0.7)	23 (3.9)	11 (1.9)	2 (0.7)	0
Hepatic enzyme increased	17 (6.4)	22 (7.9)	1 (0.8)	2 (1.4)	6 (1.0)	8 (1.4)	0	1 (0.3)
AST increased	8 (3.0)	10 (3.6)	0	2 (1.4)	15 (2.6)	5 (0.9)	2 (0.7)	3 (1.0)
Transaminases increased	8 (3.0)	5 (1.8)	0	0	3 (0.5)	4 (0.7)	0	1 (0.3)
Liver function test abnormal	4 (1.5)	6 (2.2)	0	0	5 (0.9)	2 (0.3)	0	2 (0.7)

A patient with multiple AEs within a primary SOC is counted only once in the total row.

A patient with multiple occurrences of an AE under one treatment group is counted only once in the AE preferred term for that treatment group.

Source: ISS.

7.5.4 Drug-Disease Interactions

Of note, certain patient groups were excluded from the Phase III clinical studies in MS. Based on the known pharmacological effects occurring after the first dose of fingolimod, patients with relevant cardiac conditions (symptomatic bradycardia, sino-atrial heart block, second or

third degree AV block or vasovagal syncope, treatment with Class III antiarrhythmic drugs) were excluded. Based on previous clinical experience, patients with relevant pulmonary conditions, macular edema, diabetes mellitus and low white blood cell or lymphocyte counts were also excluded.

It is likely that these patients will have a greater risk of events than the healthy population included in this application. The proposed label recommends caution in use of fingolimod in such patients until experience is gained in those settings. I believe that fingolimod should be contraindicated in patients that were excluded from fingolimod studies, in particular, patients with diabetes and patients taking medications that were not allowed in the studies.

7.5.5 Drug-Drug Interactions

In the Phase III program, patients having used other MS therapies were allowed into the study, either directly after stopping prior therapy, or within a specified timeframe. However, no concomitant use of other currently approved immunosuppressants was allowed during the study. For results of drug-drug interaction studies the reader is referred to the Clinical pharmacology review.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Increased risk of lymphoma was observed in carcinogenicity studies in mice. See review by Pharmacology toxicology reviewer.

No evidence of increased risk of malignancy was observed in the MS database, except for a potential increase in basal cell carcinoma. However, exposure is relatively short. See SAE of Neoplasms in this review. This issue should be addressed in longer term postmarketing studies.

7.6.2 Human Reproduction and Pregnancy Data

As of 29-Jan-10, a total of 30 pregnancies were reported in FTY720-treated patients. Of these, 13 resulted in successful delivery, 5 in spontaneous abortions and 8 in elective abortions. Four pregnancies are still ongoing. The 13 term deliveries included 12 normal newborns and 1 with a congenital abnormality: One 29-year-old female, who had received FTY720 0.5 mg for approximately 9 months in Study D2301 before she became pregnant, gave birth to a premature baby with a congenital shortening of the right leg (congenital posteromedial bowing of the tibia).

7.6.3 Pediatrics and Assessment of Effects on Growth

Were not conducted in the application.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The assessment of abuse potential of fingolimod is being reviewed by the Controlled Substance Staff.

7.7 Additional Submissions

The DNP and FDA consultants requested several request for information and additional analyses. The applicant has responded in a timely manner to the FDA requests. Responses have been incorporated throughout this review up to April 26, 2010. The 4-month Safety Update Report was submitted on April 21, 2010. The SUR and SSIR have not been fully reviewed at the time of the completion of this interim review.

8 Postmarketing Experience

There is no postmarketing experience with fingolimod.

9 Appendices

9.1 Narratives

9.1.1 Additional details for selected narratives of Death.

- 2302-0212-00021: Herpes zoster disseminated, acute hepatic failure, multiorgan failure

29 year old female, randomized to FTY 1.25 mg in study 2302. She was diagnosed 1 year prior to study entry but symptoms had started 2 years before diagnosis. She had 3 relapses in the 2 years prior to study entry and 3 relapses in the year prior to study entry. She received the last course of steroids 1 year prior to study entry. The patient had been treated with INF β 1-a s.c (Rebif) at some point before study entry (date not reported). At baseline the EDSS score was 1. She worked as a teacher in a local nursery for children 0-3 years. (She had not have varicella as a child. She was VZV IgG negative).

On Day 212 she complained of 6-day history of progressive weakness of the limbs. Blood tests were performed. The investigator suspected a relapse and started treatment with intravenous (iv) methylprednisolone (MP) 1 g daily. On Day 231 she was reported to have complete recovery from MS relapse. On Day 272, at visit 9, she reported no symptoms.

On Day 300, 70 days after recovery from the previous relapse she was suspected to have another relapse. She had paresthesias and hypoesthesia in both feet. She received no treatment and continued working. On Day 306 she reported worsening symptoms. On Day 309, iv MP 1 g daily for five days was started. She continued to work at the nursery. (She subsequently reported that there was a varicella outbreak in the nursery at that time.) On Day 310 she reported epigastric pain, treated with omeprazole. On Day 314, after completing the 5-day iv MP course she continued oral steroid therapy 48 mg daily without the knowledge of the investigator.

On Day 317 she developed increasing epigastric pain and went to the emergency department. At that time she was found to have increased transaminases ("approx. 300") and was admitted to the hospital. Drug induced liver injury was suspected. Study medication was discontinued on Day

317 due to herpes zoster disseminated. In addition to increased liver enzymes (“approx 1200”), she was found to have vesicles in her throat and a vesicular eruption on the trunk. She was treated with intravenous Acyclovir. Later that evening she developed acute liver failure and disseminated intravascular coagulation. Serology for hepatitis viruses A, B and C were negative. Herpes virus serology and aspiration of skin lesions were performed and reported to be positive for varicella zoster virus (VZV). On Day 320 her condition deteriorated, with multiorgan failure. The cause of death was acute hepatic failure.

An autopsy showed massive hepatic necrosis with giant mononuclear cells with morphological alterations consistent with herpetic infection (possible VZV); non-alcoholic steatosis perivenular centrilobular fibrosis and neofibrillogenesis. Kidneys had signs of shock. Lungs revealed edema and endoalveolar hemorrhagic effusions. Heart had subendocardial and subpericardial hemorrhages and fibrinous pericarditis. The esophagus had subepithelial mucosal hemorrhages, “occasional aspect of viral esophagitis (possible herpes virus/VZV).” The diagnosis was reported as massive hepatic necrosis consistent with viral herpetic infection complicated by consumption coagulopathy in a patient with MS; viral esophagitis and steatotic non-alcoholic hepatopathy. The event was considered related to study medication.

Although drug toxicity was suspected at some point, she was found to have active disseminated VZV infection that could explain liver necrosis and multiorgan failure.

- 2302-0821-00007: Herpes simplex encephalitis, grand mal convulsion, coma

23 year-old Asian male, randomized to FTY 1.25 mg in study 3202. The patient had been diagnosed 2 ½ months prior to study entry. He had 3 relapses in the 2 years prior to study entry and 3 relapses in the year prior to randomization. His last relapse occurred 2 months prior to entry and was treated with steroids. He received INF beta 1b before entering the study. Baseline EDSS score was 3. He had no other significant medical history.

Approx. 11 months into treatment (Day 255) he experienced fever, headache and upper respiratory symptoms. Drug was permanently discontinued. The following day he developed sudden generalized tonic-clonic seizures and was hospitalized. Blood testing was unremarkable. CSF tests did not reveal any significant findings except for an increased opening pressure of 22 cmH₂O. In the CSF, microbiological analysis was negative. On Day 278, HSV 1 & 2, IgG was negative, IgG antibody to VZV was positive. A brain MRI scan showed diffuse low intensity lesion at the left temporal and parietal cortex and subcortical white matter. No specific diagnosis was made and the patient was treated with oxcarbazepine. He continued to have intermittent high fevers and partial seizures with secondary generalization, treated with phenobarbital. His level of consciousness rapidly deteriorated. A follow-up MRI revealed a markedly progressed confluent cortex and subcortical white matter lesion with extensive gyral swelling. The patient received antibiotics for aspiration pneumonia and high dose methylprednisolone. He was transferred to another hospital. A second CSF sample supported the diagnosis of a viral encephalitis (PCR was positive for HSV-1). He was treated with acyclovir. Additional CSF from this second sample was sent to the NIH and was negative for JC virus.

His condition deteriorated and he died 2 months after study drug discontinuation. An autopsy was not performed. Last available lymphocyte count was $0.43 \times 10^9/L$ on day 183 (nl 0.8 – 2.8). No additional values are available after this visit.

- **2302-0254-00011** – Acute Disseminated Encephalomyelitis (ADEM) and aspiration pneumonia

A 42 year old, Caucasian male (0254/00011) with RRMS was enrolled in study FTY720 D2302 and randomized to FTY 1.25 mg/day. He had been diagnosed with MS 2 and ½ years prior to study entry. He initially presented with quadriplegia. He had four additional relapses (two in the 2 years prior to randomization and two in the year prior to randomization) treated with steroids. Immunomodulators used prior to entering the study were INF β 1-a s.c (date not known), and azathioprine (two years prior to entry for about 2 months). No concomitant immunomodulators were taken at the time of the study. The last steroid course had been completed 9 months prior to entry. At the time of screening he had an EDSS of 5. The patient's VZV IgG antibody status was negative. No other medical history was reported for this patient.

On Day 348, approximately 11 months into FTY treatment he was hospitalized with fever, headache, cough, and mild hemoptysis. The hemoptysis initially reported by the patient was not persistent, not detected on examination and determined to be non-clinically significant. A chest x-ray revealed increased bronchovascular markings. AE was coded as chest infection. He was treated with paracetamol and antibiotics. The study medication was permanently discontinued.

On Day 351 he was transferred to the neurology department because of generalized tonic-clonic seizures associated with fever of 39.5C, hypertension (170/110), hyperglycemia (450 mg/dL) and hypocalcemia (3.31 mg/dL; nl 8.4-10.3). He was treated with phenytoin and seizures stopped. He regained consciousness but remained confused. A brain CT scan without contrast was reported as normal. A lumbar puncture was performed and the CSF was clear, colorless, with no cells; glucose 86 mg/dl (nl 60-90 mg/dl); protein 13 mg/dl (nl 15-45 mg/dl); LDH 35 U/L (nl 12-24 U/L); culture no growth; and cytology no cells. PCR for HSV-1, HSV-2, and JC virus testing (*not at NIH*) were negative. A brain MRI read by the local neuroradiologist showed bilateral deep and high parietal, bilateral frontal, basal ganglia and pontine foci of altered MRI signal surrounded by abnormal periventricular white matter signal intensity, suggestive of multiple demyelinating foci (MS) vs. ischemic foci (lacunar infarcts).

The central MRI reader subsequently reviewed the current MRI and compared it to the baseline MRI. On the current MRI scan, there was one new T2 lesion in the left frontal region, which could not readily explain the patient's clinical presentation. Otherwise, there were no remarkable findings, especially no evidence for infections. On both the baseline and current MRI scans, there were numerous T2 lesions in the periventricular region, deep white matter, and infratentorially. The distribution and appearance of most lesions was consistent with MS, but additional pathology, such as vascular lesions or metabolic disease, could not be ruled out.

On Day 353 the patient was transferred to the neurology intensive care unit. EEG showed diffuse slowing at theta rhythm. His level of consciousness appeared to improve, but on Day 359 started to deteriorate again. At that time he was found to have a urinary tract infection. On day 363 he again developed generalized tonic clonic seizures, with further deterioration in his level of consciousness. Glasgow Coma Scale (GCS) was 8-9. He was subsequently treated with MP 1 g/day for 5 days, followed by an oral steroid taper. On Day 366 he developed metabolic acidosis. On Day 367 he improved his GCS score to 11-12.

On Day 373 he was able to go to the bathroom on his own. Follow up tests performed as part of a vasculitis work-up were negative for autoantibodies (ANA, Ds-DNA, SM, SSA, and SSB). Viral serology tests suggested prior exposure to CMV and EBV IgG(+) , with CMV, EBV, HSV-1 and

HSV-2 IgM(-). As per the patient profile, on Day 369 IgG antibody to Varicella Zoster virus was 661 U/L. On Day 379 he was fully conscious with a mini mental status exam of 19/30. He had intermittent coarseness and emotional lability, but otherwise no changes in neuro exam. He was discharged from the hospital with a plan to be re-admitted after a holiday. He was able to stand but required assistance with walking. The patient was re-admitted to the hospital after the local holiday period. The diagnosis on the SAE follow-up form was 'acute disseminated encephalomyelitis (ADEM) on top of multiple sclerosis'. According to the investigator, the diagnosis was made according to the clinical picture: 1) disturbed consciousness level – delirious state and 2) convulsions.

On Day 395, a follow-up brain MRI showed no changes since the previous examination. On Day 425, while still hospitalized, the patient was noted by his wife to have mental and behavioral changes. He became more aggressive with her and others. He subsequently developed urinary and fecal incontinence. On Day 427 his medications were adjusted: reduction of prednisolone dose from 40mg to 30mg po daily, addition of risperidone to control his recent aggression and behavioral changes, discontinuation of SSRI antidepressant, and continuation of antiepileptic medication. A neurological examination revealed new findings of decreased attention and disorientation to place and time. On Day 435, the patient was discharged home at the request of his family.

On Day 530, the patient's caregiver reported to the investigator that the patient's movement was now difficult with weakness of both upper and lower limbs to the extent that he could not move without support. Superficial bed sores were present on the patient's back. Mental and behavioral changes were also noted in the form of aggression towards the patient's caregiver. The patient's orientation was not normal and he had bouts of confusion.

On Day 535 of the study, 187 days after fingolimod discontinuation, the patient died due to aspiration pneumonia. Prior to his death he was reported to be dehydrated and feverish and have bulbar symptoms. No autopsy was performed. According to the investigator, the events (acute disseminated encephalomyelitis, lower respiratory tract infection) required hospitalization, while the event (aspiration pneumonia) resulted in death, and all three were related to study medication.

This event was reviewed by an independent Data and Safety Monitoring Board (DSMB). According to the DSMB neurologists, although the patient's neurological history and baseline MRI scan may be consistent with a diagnosis of MS, there were atypical features in both the clinical presentation and baseline MRI scan. The normal CSF and a brain MRI at the time of the adverse event with no relevant changes do not support an infection and make a MS relapse unlikely as the cause of the events that started almost one year into fingolimod treatment. According to the DSMB neurologists, ADEM is not usually diagnosed in the context of already established MS. ADEM is a diagnosis of exclusion and is usually associated with large, often confluent new MRI abnormalities, with or without enhancement.

In summary this was a 42 year old male with a 3 year history of MS, who presented an ADEM-like clinical picture while on treatment with fingolimod 1.25 mg/day. The MRI showed a new T2 lesion that did not explain the extent of neurologic changes. JC virus testing done at a laboratory in Europe was negative. No samples remain for additional testing. The last available lymphocyte count in the patient profile on Day 105 was $0.4 \times 10^9/L$ (normal 0.18-2.8) but neurologic changes occurred on Day 348. This case was evaluated by Dr. Heather Fitter, DNP neurologist, who offered the following differential diagnoses: MS relapse in the setting of multiple infections, seizures and steroid induced encephalopathy, and PML.

- **2306-0362-0005:** rapidly deteriorating MS

46 year old male, enrolled in study 2306 (ongoing study). The patient reported first MS symptoms four years prior and was diagnosed with MS approximately 2 and ½ years prior to entering the trial, based on at least one year of disease progression, presence of at least nine T2 lesions in the brain MRI, at least two T2 lesions in the spinal cord MRI and oligoclonal bands in the CSF. The EDSS at baseline was 4.0 due to a visual acuity deficit (FS 2), a mild pyramidal deficit (FS 2), mild ataxia (FS 2), symptomatic mild sensory deficit (FS 2) and mild to moderate cognitive deficit or fatigue (FS 2) associated to restricted walking (>500 m). The patient was not treated with MS disease modifying therapies prior to study entry. Concomitant medications taken prior to randomization included: amantadine for fatigue, fesoterodine and tamsulosin for mictional urgency and citalopram for mood swings, all of them taken for approx 1 ½ years prior to study entry.

After 9 days on study drug, the patient presented with an AE of "muscle spasm left leg" that was treated with Baclofen (two days before the patient had been treated with Botulinium toxin for spasticity, location unknown). Approximately 1 month into study drug treatment, he was not able to walk 100 meters without assistance (EDSS 6). On Day 39 into study drug treatment, the patient presented with urinary tract infection treated with antibiotics.

On Day 49, the patient experienced "pain all over the body". The activities of daily living had become more difficult. There was frequent urinary incontinence. Spastic contraction of muscles of hand and feet were reported. No other relevant AE is reported in the clinical data base. Around this time, the patient started treatment with miconazole for "prevention of mucositis".

On Day 59, a neurological examination showed signs and symptoms of general deterioration that was considered to be consequence of the previous urinary tract infection and required hospitalization. However, the patient did not agree to an admission to hospital and wanted to stay at home. The investigational site advised the patient to stop study medication. The patient continued to take study medication until the supply was exhausted (unclear how many days).

The patient became gradually worse. A month after the neurology visit the patient experienced a severe lower respiratory infection. On Day 103 of the study, the patient died due to rapidly deteriorating MS. No autopsy was performed. The investigator indicated that the event was due to progression of underlying illness. The investigator did not suspect a relationship between the event and the study medication.

In summary, this was a 46 year old male with 2 and ½ years history of MS, who had not received immunomodulators for MS, who 9 days into fingolimod treatment developed muscle spasm and deterioration of neurologic status that was thought to be related to a urinary infection. Two months into fingolimod treatment he developed a severe respiratory tract infection. There was no autopsy, no following MRI, no adequate work up to rule out opportunistic infections, no information on level of immunosuppression achieved by this patient.

In my opinion, these two last cases may represent MS relapse/progression of disease but another cause, such a CNS opportunistic infection can not be ruled out. In one case, extensive work up was done and an infection was not identified (however, PML is not completely ruled out as JC virus PCR testing was not done

at the NIH). In the second case, there was worsening of the neurologic condition without any assessments to rule out causes other than MS progression. Both cases were complicated by fatal respiratory infections. No data on lymphocyte counts are available at the time of the deaths.

Deaths reported subsequent to the original submission

- **1201E-0005-00001:** Multiple sclerosis relapse, possible malignant kidney, lung, brain tumor, and lymphoma, coagulopathy, pancytopenia. Aspiration bronchopneumonia.

42 year old Japanese M, randomized to FTY 1.25 mg in study D1201. He completed the 6-month core study and received FTY 0.5 mg during the extension study. He was diagnosed with MS five years prior to entry and had had 6 relapses treated with steroids since diagnosis. He did not receive other immunosuppressants prior to randomization. Baseline EDSS score was 4. He had no significant medical history. At the end of the core study an MRI showed new T2 weighted lesions in the deep white matter of the anterior horn of the right lateral ventricle and left centrum semiovale. These lesions showed clear ring shaped enhancement on Gd-enhanced T1 weighted scan, suggesting the destruction of the blood brain barrier (BBB). These lesions were considered to be new MS lesions. He entered the extension study and continued taking FTY.

Approx. 1 ½ months into the extension study he was admitted for a course of steroid pulse (MP 1 g/day x 3 days) for MS relapse. MS symptoms deteriorated and he became unable to walk. He was admitted to the hospital with right hemiparesis and received a second course of steroid pulse. He was discharged from the hospital unable to walk, with decreased cognitive function and steroid psychosis, but readmitted a week later for worsening paresis. A repeat MRI showed spreading of the demyelinating lesion on the left parietal lobe with strong inflammation causing Blood Brain Barrier (BBB) destruction in the central area.

One month later, study drug was discontinued and the patient received three more courses of steroid pulse therapy. MRI was unchanged.

One month after drug discontinuation, based on the MRI scans, the possibility of brain malignant lymphoma in addition to MS was considered, however, CSF testing showed an extremely small quantity of lymphocytes with no malignant cells. Two more courses of IV pulse steroids were given (total of seven pulses within 2 ½ months), followed by oral prednisolone 60 mg/day for 3 more months.

Right after the seven IV steroid pulses, a brain MRI showed that the lesions “were disappearing to some extent”. Magnetic resonance spectroscopy (MRS) showed no increase in choline. At this time the probability of malignant lymphoma was considered to be low, although it could not be ruled out. A biopsy was not performed. In the investigator’s opinion the relationship to the event of MS progression and study drug could not be ruled out. *FDA reviewer’s comment: high dose steroid treatment may certainly have reduced the size/number of lesions and tumor activity if this were a malignant lymphoma.*

Seven months after drug discontinuation (two months after completing high dose oral steroids) the patient was readmitted to the hospital with suspected malignancy of the lungs, based on a chest X-ray with multiple irregularly shaped tumor lesions. The patient had concurrent aspiration pneumonia. A CT scan of the chest and abdomen showed multiple low absorption regions and nodules in both lungs and both kidneys, pleural effusions and atelectasies. Small scattered lymph

nodes were found in the pulmonary hilum, mediastinum, neck and axilla and paraaortic area along with hepatosplenomegaly. The findings suggested an atypical malignant lymphoma or metastases of malignant tumors. The patient was pancytopenic and lab tests showed abnormal coagulation.

A kidney biopsy was performed (8 months after study drug discontinuation). An Epstein-Barr (EB) virus related lymphoproliferative disorder was possible. However, the diagnosis could not be confirmed because tissue was not available for additional staining. Results of the kidney biopsy, as reported in MedWatch report):

Sample 1 tumour tissue showed cells with large irregular abnormally shaped cores with high solidity. The cell cytoplasm with either clear or acidophilic. In the inner portion of the tumour, tubule tissue that had been taken in was present. From hematoxylin and eosin (HE) staining, renal cell carcinoma G3 appeared most likely. In some areas, cells were also lymphoid. Sample 2 kidney tissue showed no clear invasion of tumour cells. Immunostaining of sample 1 showed negative keratin. It had been hypothesized that the structure originated in the epithelium but from HE staining, this appeared unlikely. Vimentin was positive, but desmin and alpha smooth muscle actin were negative. L26 was negative and CD3 was partially positive. However, it was not possible to make a clear determination. Ki-67, CD-68 and EB (Epstein-Barr) virus were positive. An EB virus related lymphoproliferative disorder was possible, but since only a small amount of biopsy tissue was available and additional staining was not possible, a determination could not be made.

An MRI of the brain showed demyelinating lesion was in remission after steroid therapy, although gliosis and hemosiderin deposits remained. Multiple nodular lesions with ring enhancement and micro hemorrhages were identified. A new, similar lesion with edematous changes was identified. A MR spectroscopy then revealed that the lesion showed an increase in choline and a decrease in N-acetyl aspartate (NAA). The ring enhancement and the fact that many lesions were in the cortical white matter was typical of metastases to the brain. So, the radiologist noted that it was possible that the lesions in either the chest or abdomen were the primary site. A repeat CT of the abdomen showed persistent kidney tumors and lymph node enlargement, and new multiple liver tumors. The finding was consistent with possible metastasis or malignant lymphoma.

An upper endoscopy was conducted and identified a possible tumor in the esophageal mucosa and multiple polyps in the stomach. A biopsy showed no malignancy, but tested positive for H pylori. A gallium scintigraphy showed increase in uptake to the upper left abdomen (probably the stomach) and to both kidneys. Suspected illnesses included interstitial pneumonia, malignant lymphoma of the kidneys and leukemia invasion of the kidneys. Possible determinations for the uptake to the stomach included gastritis and malignant lymphoma. Because of the low platelet count, a repeat biopsy or a bone marrow aspiration were not conducted. The investigator suspected a relationship between the ongoing events and study drug.

Eleven months after drug discontinuation and approximately 5 month after completion of high dose oral steroid treatment the patient showed invasive erythematous eruptions. A skin biopsy was "highly suspicious of T cell lymphoma" of the skin based on both immunostaining results and gene rearrangement using skin tissues. A CT scan showed that nodules in lung and kidney were increased in size/number (although at some point they had been reported to be somewhat decreased). The patient died approximately 1 year after drug discontinuation, after receiving FTY 0.5 mg daily for 8 ½ months.

Interim review, 5 12 10.
Lourdes Villalba, M.D
NDA 22-527. Fingolimod

Appendix 9.1.2. Brief narratives of SAEs in the Cardiac disorders SOC (Rhythm and conduction disorders), Safety pool D

Patient ID	Age /sex	Preferred term	Rel Study day		Comment
Placebo					
2301 0312_00004	31 M	AVB 2 nd degree sick sinus syndrome	DAY 684	-	History of Borrelia myocarditis; reported prior episodes of AVB 2 nd and 3 rd (not documented). No concomitant meds. On Day 684 admitted to pre-collapse ECG sinus rhythm, 52 /min. Chest Xray normal. During monitoring found to have intermittent 2 nd degree AVB, type 1 (Wenkebach). Asymptomatic during these episodes. Echo: mild mitral insuff. Recovered, completed core and entered extension.
2301 0909_00006	36 M	Palpitations Bradycardia Presyncope	121	dc	History of non-cardiac chest pain 7 years prior. History of orthostatic dizziness. Concomitant meds: tadalafil, gabapentin and citalopram. Baseline HR= 54-66 bpm. On Day 1 he had non-cardiac chest pain that recovered by Day 8. On Day 120 he had pre-syncopal episodes and bradycardia, with dizziness, sharp central chest pain and palpitations. Ten days before the event he had discontinued citalopram. ECG on Day 121, HR= 42 rpm, QT prolongation= 516ms and QTcB=430 ms. Study drug was discontinued. Repeat ECG: sinus bradycardia, otherwise normal. Echocardiography on Day 122 was normal. The event was not considered related to study drug.
FTY720 5 mg					
2201 0019_00006	26 F	Ventricular extrasystoles Bradycardia	1	dc	No CV history. ECG at 6 hours post dose showed arrhythmia; ventricular premature complexes. Bigeminism with moderate bradycardia. Drug was discontinued. No follow up.
2201 0025_00016	52 F	Bradycardia also chest pain & dyspnea	1	dc	History of intermittent dizziness with syncope. Baseline pulse: 73; BP 115/76. 2 hours after dose, pulse dropped to 47 bpm, BP 122/80. Lowest pulse was 43, 4 hours post dose. Six hours post dose, pulse was 48 and BP was 124/77. ECG showed sinus bradycardia. Symptoms: cold sensation, dizziness, flushing, oppression in chest. <u>On Day 4</u> patient presented sharp chest pain and dyspnea. Study drug was discontinued. No cardiac enzymes available. On day 31 she was still not feeling well but ECG and chest X-ray were normal.
2201 0066_00006	41 F	Bradycardia	2	-	No CV history. Baseline pulse: 68, BP 120/60. Day 1, 4 hours after dose, pulse: 54; BP 110/60. She went home after 6-hour observation. She had a Holter monitor. She woke up at 2 am with oppressive thoracic pain extending to both arms associated with nausea and vomiting that lasted for 5-6 hours. At the ER her BP was normal, pulse was 45 bpm. ECG showed sinus bradycardia. CK and troponin were normal.

					Cardiologist saw her within the first 24 hours, ECG sinus rhythm 55 bpm, otherwise normal. Echocardiography was normal. Stress test was submaximum, but negative. Diagnosed as non-anginal chest pain. Recovered. The Holter ECG recorded during the first 24 hours after study drug initiation showed no rhythm or conduction abnormalities. Mean HR decreased in the first 10 hours. The lowest HR registered was 34 bpm at 1:59 am. Drug was interrupted and re-started on Day 8, at 1.25 mg, and increased to 5 mg one week later. ECG at beginning of extension phase showed inverted T waves. She has remained in the study with no other cardiac symptoms. She is currently participating in the extension study. (updated narrative 4/22/10)
FTY720 1.25 mg					
2201 0018_00003	44 F	AVB first degree	1	-	History of HTN. Day one, baseline pulse= 81; BP 156/110; 4 hours post dose pulse dropped to 64, BP 147/75. ECG at 6 hours: 1 st degree AVB. Symptoms: chest pain at 3 hours post dose. Recovered. Drug not discontinued. She is still in the study.
2301 0101_00003	42 M	Bradycardia	1	dc	No CV history. Active smoker. Baseline HR 76 pm. He experience bradycardia with the lowest heart rate=49 bpm registered 13.5 hours after first dose. Hospitalized. Asymptomatic. ECG not performed at the time of event. Study medication was discontinued on Day 2. Pt recovered.
2301 0176_00001	45 F	Bradycardia & dyspnea	1 11 (1 st re-dose)	- dc	No CV medical history. Smoker. Day 1 pre dose, HR- 72-74, and BP 95/62 _ 112/48 mmHg. 2 hours post dose both variables started to decrease. Lower HR recorded was 52 bpm 5 hrs post dose. Lowest BP 94/52. Asymptomatic. Hospitalized. <u>On Day 2</u> , mild dyspnea and bradycardia. Drug interrupted. Events resolved on day 9. <u>Drug re-started on Day 11</u> noted to have other event of bradycardia and dyspnea which led to permanent drug discontinuation. All ECGs were normal. No change in PFTs. Pt discontinued study on day 12.
2301 0180_00007	53 M	Bradycardia	1	dc	No CV history. Smoker. Concomitant medications amitriptyline, ibuprofen. Baseline ECG: L anterior hemiblock. Day 1 Baseline HR= 64 bpm; BP 114/74. After first dose developed bradycardia. Lowest HR recorded was 38 bpm (4 hours post dose), lowest BP 96/54. Study drug permanently discontinued because of this event. Patient was asymptomatic. He was not hospitalized and did not undergo further monitoring. Even considered resolved the same day. Four days after drug discont, pulse was 58bpm.
2301 0404_00002	49 F	Bradycardia	1	-	History of HTN, MI (7 years prior) on captopril, HCTZ, thyroid replacement and venlafaxine. Non-smoker. Baseline HR 58-68 pm. 4 hours after first dose HR= 46 pm. Asymptomatic. Hospitalized. Recovered day 2 without specific treatment. No action taken with study drug
2301	25 F	AVB first	1	dc	No CV history. Non-smoker. Four days prior to randomization reported nausea. First

0405_00001		degree			dose, during first 6 hrs HR 56-64 bpm, BP 90/60-120/60. 1-2 hours post dose had nausea. At 6 hours HR=50 bpm. ECG post dose showed prolonged PR interval of 40 ms compared to pre-dose. She was hospitalized. At 7 hrs HR=45 bpm. Second ECG showed PR= 300 msec (First degree AVB). Patient transferred to ICU. She was given IV potassium. She complained of dizziness. The following morning HR=56 bpm at 7 am, with normalization of PR to 180 ms. At 10 am HR=60 bpm. Study drug was discontinued.
2301 0612_00002	46 M	Bradycardia	1	-	No history of heart disease. Smoker ½ pack daily for 3 years. No concomitant meds. Baseline HR before first dose= 80 bpm. Pt was hospitalized with asymptomatic bradycardia for overnight monitoring. Lowest HR= 48 bpm at 10 hrs post dose. Gradually recovered after 15 hrs post dose. Completely recovered on day 3. No action taken with study drug.
2301 0651_00016	27 F	Angina pectoris & AVB 2 nd degree	1 16	- dc	Symptomatic 1 st degree AV block” 4 years prior (as per narrative; not in patient profile). History of asthma (as per patient profile). Non smoker. Pre-dose HR=83 bpm; ECG: 1 st degree AVB, PR 208, QTc 448. Day 1: 3.5 hours after first dose developed shortness of breath, chest pain and irregular pulse. ECG showed first degree AVB (PR 344 ms). Repeat ECG 6 hrs post-dose showed 2 nd degree AVB (type 1). Pt hospitalized. At 9 hrs post-dose, she felt chest discomfort and dyspnea. She received treatment with atropine and symptoms improved. She recovered completely within 24 hrs. The following day she received 2 nd dose and did not have any symptoms. She continued taking fingolimod at home. On day 4 she was readmitted with “flashes” in the eyes and painful eye movements, dyspnea and overall feeling unwell. Symptoms resolved by Day 6 and she went home. <u>On Day 16</u> reported chest pain and pressure similar to those after first dose. An ECG done in an ambulance showed unspecified abnormalities. Admitted to hospital, ECG showed “increase in conduction disorder”. Cardiologist advised the patient to stop study medication. She was discharged home. On Day 17 again had chest pain but ECG showed no AVB. On Day 19 she was given low dose of nitrates IV and was discharged. DSMB cardiologist agreed with diagnosis of AVB 2 nd degree type 1 and thought that prior history of symptomatic first degree AVB may indicate chronic AV nodal disease or dysfunction. PFTs done on Day 62 showed decreased DLCO >20%. <i>(As per the patient profile drug was discontinued after the first dose. Upon FDA request for clarification the applicant confirmed that there was no interruption of treatment from Day 1 to Day 17. The AVB occurred one day after study drug dc).</i>
2301 0707_00049	55 M	Supraventricular extrasystoles	1	-	History of hypertension treated with cilazapril and metoprolol. Smoker 1 ½ pack for 30 years. Baseline ECG was normal. After first dose, 1 hr post-dose he had

Interim review, 5 12 10.
 Lourdes Villalba, M.D
 NDA 22-527. Fingolimod

		Arrhythmia	1		arrhythmia and supraventricular extrasystole. The same day he had a second run of paroxysmal ectopic supraventricular beats at an unspecified time. He was admitted to the hospital due to the event. He received oral calcium on Day 1, 2 and 3. He was completely recovered by Day 2. On Day 2 and 3 the ECG were normal. No action taken with study drug.
2302 0211_00003	41 F	Arrhythmia Bradycardia AVB 1 st degree	1 1 1	dc	No CV history. On Day 1 hospitalized with first degree AVB with bradycardia/arrhythmia. Medication was kept on hold and then discontinued due to these events. She recovered within 24 hours. No treatment details available.
2302 0219_00010	28 F	AVB 2 nd degree	1	dc	No CV history. On Day 1, six hrs after first dose she developed severe AVB 2 nd degree (Mobitz type 1) and was hospitalized. At the time she had chest discomfort. Drug was discontinued due to this event. Event recovered the same day without specific treatment.
2302 0307_00001	24 F	Sinus tachycardia Supraventricular extrasystoles Ventricular extrasystoles	344 344 344	- - -	No CV history. Smoked 3 cigarettes/day. Meds: aspirin for headaches and oral contraceptive. On Day 216 presented episode of dyspnea/hyperventilation. On Day 344 sinus tachycardia with extrasystoles and hyperventilation. Reported palpitations for 2 weeks. ECG on Day 353: sinus rhythm up to 150 bpm, rare SVES and many polytopic VES and one couplet. Drug interrupted til Day 362. Events resolved on Day 373 without specific treatment. <i>Patient is currently in extension study.</i>
2302 0326_00010	38 F	AVB 2 nd degree	1	-	No CV history. Smoker 20 cigarettes/day x 15 years. On Day 1, 4 hrs after first dose experienced chest discomfort, palpitations, bradycardia and decreased BP. Hospitalized with 2 nd degree AVB confirmed by ECG. She recovered without specific treatment. DSMB cardiologist stated ECG showed Wenkebach 3:2 AVB with narrow QRS. Patient is currently in extension study.
2302 0333_00007	29 F	Bradycardia	1	-	No CV history. HR at baseline was 89 bpm. On Day 1, hospitalized for arrhythmia, sinoatrial block and bigeminy. No action taken to study drug. Event resolved the next day. DSMB cardiologist noted that one of ECGs taken had shown atrial bigeminy (9/20 At 5:39); all others show right atrial rhythms with normal rates and some subtle shifts in P wave morphology that could be due to changes in posture or shift in the primary pacing site within the sinus node complex (usually of no clinical significance). Patient discontinued study drug in core phase, on Day 47.
2302 0361_00009	31 F	Bradycardia	1	-	No CV history. On Day 1, 6 hrs after first dose hospitalized due to asymptomatic bradycardia. Minimum HR 50 bpm. No specific treatment or action taken with study drug. Event resolved on Day 2.
2302 0361_00013	36 F	Bradycardia	1	-	History of depression and smoking. Conc meds: trazodone. On Day 1, after first dose, hospitalized for asymptomatic bradycardia. Lowest HR was 51 bpm at 10 hrs. (baseline HR was 84). No specific treatment or action taken with study drug. She

					recovered on Day 2. She discontinued on Day 140.
2302 0364_00007	44 F	Sinus bradycardia	1	N	History of diabetes, hypercholesterolemia and obesity. On Day 1, hospitalized with sinus bradycardia. Lowest HR= 55 bpm (baseline HR=82). No specific treatment or action taken with study drug. Patient recovered the same day.
2302 0364_00008	34 M	Sinus bradycardia	1	-	No CV history. Active smoker. On Day 1, hospitalized with sinus bradycardia. Lowest HR was 52 bpm after 4 hrs of first dose (baseline 82 No specific treatment or action taken with study drug. Event resolved same day.
2302 0381_00003	43 F	Bradycardia AVB 1 st degree	1	-	No CV history. Non smoker. On Day 1, hospitalized due to asymptomatic bradycardia. Lowest HR was 38 bpm after 8 hours of first dose (baseline was 56). ECG after 6 hours of first dose showed AVB “grade 1”. No action
2302 0443_00005	54 M	Bradycardia	1	-	No CV history. Non smoker. Concomitant med: baclofen. On Day 1 experienced low heart rate. 7 hrs after first dose, HR was 44 bpm. ECG showed no abnormalities. Hospitalized overnight for monitoring. No specific treatment or action taken with study drug. His HR on Day 2 was 60 bpm with normal ECG.
2302 0444_00003	48 F	AVB 1 st degree	1	-	No CV history. On Day 1, an ECG showed 1 st degree AVB that was asymptomatic. No action taken with study drug. No treatment details are available. Patient recovered the same day.
2302 0445_00006	43 M	Bradycardia	1	-	No CV history. Non smoker. On Day 1, 6 hours after first dose patient noted decrease in heart rate (47 bpm) (baseline was 69). Patient hospitalized with diagnosis of asymptomatic bradycardia confirmed by ECG. No action taken with drug. Treatment details are not available. He recovered the next day.
2302 0601_00009	41 M	AVB 2nd degree	1	dc	No CV history, On Day 1, 6 hrs after first dose he had irregular pulse, dizziness and shortness of breath. BP was 110/70. ECG showed HR 46 bpm with 2 nd degree AVB (Wenkebach). He received iv NaCl. At baseline HR was 74 bpm and systolic BP was 120-135 mmHg. By 7 hrs after dose he was back to sinus rhythm. He had two more 15-minute episodes of Wenkebach AVB 11 and 14 hours after first dosing. BP remained stable. No treatment was given. The patient decided to discontinue from the study.
2302 0903_00005	39 F	Bradycardia Bradycardia	1 12	- dc	No CV history. Smoker. On Day 1 patient experienced bradycardia requiring hospitalization. Drug was interrupted. The event resolved completely on Day 2. PR interval ranged from 204 to 209 msec. Drug was re-started on Day 12. The patient had an episode of asymptomatic sinus bradycardia. ECG showed borderline AVB. The patient discontinued from the study due to this event.

Source: original AE datasets submitted 12/18/09. Narratives (12/18/09) & patient profiles (2/16/10). Rel study day: relative day of study at onset of study day.
 Rel day FTY: relative day on fingolimod treatment during extension study. DC: drug discontinuation Y= yes; N= no.

Interim review, 5 12 10.
 Lourdes Villalba, M.D
 NDA 22-527. Fingolimod

SAE in Cardiac disorders SOC (Rhythm and conduction disorders related) in extension studies.

EXTENSION STUDIES						
Patient ID	Age /sex	Preferred term	Rel Study day	Rel day FTY	DC	Narrative
FTY 1.25 mg						
2302E 0141_00004	39 F	AVB 3 rd degree	372	1	dc	Received IFN during core. No cardiovascular history. Non smoker. Concomitant meds included oral contraceptive, magnesium-vitamin B. On Day 1, 2 hrs after first dose the patient had no complaints but her pulse went from 74 at baseline to 50 bpm, irregular. An ECG showed 1 st degree AVB, 59 bpm. One minute later, an ECG showed 2 nd degree AVB type I (wenckebach) with a heart rate of 55 bpm. No meds were given. Approx. 3 hours after the first dose the patient complained that she was not feeling well and reported having strange dreams. She lost consciousness. A heart monitor showed 3 rd degree AVB which lasted 30 seconds, followed by an escape rhythm for 19 seconds. She recovered spontaneously and hear rate returned to the 40's. Heart monitoring showed irregular rhythm with 2 nd degree AV B type II. BP was low. Atropine 0.125 mg was given because of low heart rate. Potassium was 3.4. She was transferred to ICU. 11 hours post dose, monitor showed 2 nd degree AVB type I. Few minutes later she was in sinus rhythm. An echo showed mild mitral valve insufficiency that was not considered to be significant. The drug was discontinued (she only received one dose) . The patient recovered completely and was discharged home the day after the event.
2302E 0211_00002	30 M	AVB 2 nd degree	376	1	dc	Received IFN during core. Prior history of first degree AVB for about 1 year. Concomitant med included lamotrigine. No history of diabetes. Non smoker. ECG pre-dose at 9:17am was 60, sinus rhythm first degree AVB; 6 hours after drug, at 15:43, sinus rhythm 56 bpm, 3:2 Wenckebach type 2 nd degree AVB; 8 hours after dose, sinus arrhythmia with both 2:1 AVB and variable ratio Wenckebach type, 2 nd degree AVB. QRS normal. At times HR was as low as 31 bpm. He was asymptomatic and did not receive medication for this event. The event of 2 nd degree AV B type I resolved on Day 3. An ECG before discharge showed 1 st degree AVB. A 24-hour Holter done 15 days after drug discontinuation showed bradycardia with mean HR of 68 (range 38 to 120 bpm), 1 st degree AVB and 4 nocturnal

Interim review, 5 12 10.
 Lourdes Villalba, M.D
 NDA 22-527. Fingolimod

						episodes of 2 nd degree AVB.
2302E_0426_00006	26 M	AVB 2 nd degree palpitations	361	1	dc	Received IFN during core. Prior history of optic neuritis. No CV history. Pre-dose, pulse was 57 bpm, ECG normal sinus, HR 65pm. There was no AVB but 1st degree AVB had been seen during core study. Six hour after receiving drug, he had palpitations. HR was as low as 37 bpm and BP was 100/60. ECG showed sinus bradycardia with occasional supraventricular premature complexes and second degree AVB Type I. No treatment was given. The event resolved completely the following day, and the patient was discharged home. Drug was discontinued.
2302E_0801_00009	39 M	Bradycardia	388	1	dc	Received IFN during core.
2201E_0025_00006	45 F	Extrasystoles Bradycardia palpitations	190	1	dc	Received placebo during core. First fingolimod dose: pre-dose pulse was 77, BP 119/90. Four hours post dose, pulse dropped to 54, BP 104/63. At 5 hours pulse was 35. 6 hrs post dose ECG showed ventricular rate of 30 bpm. Otherwise normal morphology. No further pulse/BP readings available. Symptoms: cold sensation, loss of heart beats, palpitations. Drug was discontinued.
FTY 0.5 mg						
2302E_0252_00002	42 F	Bradycardia	372	1	-	Received IFN during core. HR down to 36 bpm after 1 st dose. No narrative or pt profile available.

Several SAEs in the Cardiac disorders SOC have been reported from the ongoing blinded studies, including a case of 2nd degree AVB with nodal rhythm, summarized as follows:

2301 E_0707_00055 (BLINDED)	26 F	AVB 2 nd degree, bradycardia, nodal rhythm, blood pressure decrease	Received placebo during core study. Medical history of depression, optic neuritis, AVB first degree for 2 years. No other CV history. Non smoker. Baseline HR: 72 bpm. Six hours after first drug administration she developed bradycardia (46 bpm) and 2 nd degree AVB. After 14 hours, “ <u>the AVB seemed to progress to 3rd degree AVB.</u> ” Patient was asymptomatic and was treated with atropine for bradycardia. The AVB fully resolved 6 hours later. The DSMB cardiologist interpreted this ECG as 2:1 block with a competing junctional rhythm, which technically could not be interpreted as third degree AV block. The drug was reintroduced on Day 10 of the extension study, and the patient dropped the HR to 44 bpm (from 73 before drug). ECG showed 2 nd degree AVB, but there were no changes in BP. Drug was interrupted again. Drug was reintroduced 8 days later. Apparently the patient continued to take study medication without further episodes			
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Appendix 9.1.3. Brief narratives of subjects with serious AE of ischemic heart disease events in safety pool D

Placebo
2301 0703_00005. 45 M. Myocardial infarction, on Day 44. No history of ischemic heart disease. Depression and nicotine dependence. Smoker 25 pck/year. Meds: mianserin. On Day 44 symptoms suggestive of MI, found to have ECG consistent with acute MI and underwent angioplasty. No action taken with study drug.
2301_0309_00005. 42 M. MI occurred 50 days <u>after</u> drug dc. No previous history of heart disease. On day 729 discontinued because of hyperbilirubinemia. On day 775, 50 days after drug dc he had ventricular tachycardia and myocardial infarction .
IFN
2302 0314_00008. 55 M. Angina unstable on Day 337. Medical history of Myocardial infarction with stent 7 years prior to entry, HTN, hyperlipidemia, diabetes mellitus. On ramipril, metoprolol, simvastatin. On Day 337 had retrosternal chest pain and hospitalized with angina pectoris. ECG unchanged and echo was normal. No action taken with study drug.
FTY 1.25 mg
2301_0651_00016. 27 F. Angina pectoris & AVB 2 nd degree on Day 1. Recurrent event on Day 16. Drug discontinued (unclear if upon first or second event). <i>This case was also included in Table 16 of conduction disorders)</i>
FTY 0.5 mg
2301 0651_00005. 34 F. Angina pectoris on Day 573 (2 days after dc) History of pregnancy-induced HTN and palpitations. Non-smoker. On Day 573 of the study, two days after last dose of FTY 0.5 she was admitted to hospital with severe chest pain radiating to L arm. <u>Cardiac enzymes elevated and returned to normal within next 2 days</u> . Two days later, she had recurrent episode. On PExam, a cardiac murmur was noted. Cardiac catheterization found normal coronary arteries. There had not been ECG or PFT changes during the study. Review of labs indicate that she dropped her HTC from 41% at screening to 36% at end of study (nl 35 to 49%). In response to FDA informational request, the sponsor provided the following information on 3/4/10: Results of echocardiography were normal. Repeated ECG, ergometry and 24 hour Holter were normal. Other than MS, the patient had no complaints.
2301_0454-00002. 44 F. Dyspnea, chest pain, ventricular hypokinesia, myocardial ischemia on Day 449. Led to drug discontinuation. MS diagnosed 6 years prior to study entry. Prior treatments for MS included IFN and glatiramer acetate. Medical history included LDL elevated, febrile convulsion, optic neuritis and hepatitis. No history of heart disease or diabetes. No use of contraceptives. Active smoker (20 pack/year). On day 449 she had episode of “precordialgia” and dyspnea that lasted for 3 hours. Hospitalized, ECG showed T wave inversion in AVF and DIII. One month later echocardiography showed posterior wall hypokinesia consistent with coronary insufficiency (R coronary artery). This was considered to be the cause of the precordial pain. One week later she developed chest pain on exertion radiated to jaw, throat, arm and back. ECG showed isolated negative T waves and residual retrosternal oppression. Study medication was discontinued on Day 489. One month after drug discontinuation, a stress test was normal. The investigator suspected the event to be related to study drug. <i>44 year old female, no cardiovascular history but risk factors (smoking, elevated LDL) presented episode of chest pain associated with inverted T waves and posterior wall hypokinesia consistent with myocardial ischemia. There was no evidence of ischemia on stress test, one month after drug discontinuation.</i>

Interim review, 5 12 10.
 Lourdes Villalba, M.D
 NDA 22-527. Fingolimod
 Appendix 9.1.4.

Listing of SAES of MS or MS relapse in ISS

ID	Age Sex	PT	Verbatim	Rel day	dc
CONTROLLED					
Placebo					
2201_0074_00003	42 F	MS relapse	Relapse multiple sclerosis	26	Y
2301_0851_00010	23 F	MS relapse	Worsening of retrobulbar neuritis in the context of a MS relapse	43	Y
IFN					
2302_0331_00003	37 F	MS relapse	Frequent relapses [due to MS]	298	.
FTY 1.25		MS relapse			
2301_0409_00008	27 F	MS relapse	Unusual MS relapse	193	.
2301_0413_00001	43 F	MS relapse	Ms relapse	744	.
FTY 0.5					
2302_0310_00004	46 M	MS relapse	Ms relapse	222	Y
2301_0310_00009	44 F	MS relapse	Ms relapse	246	.
2301_0413_00005	20 F	MS relapse	Ms relapse	267	.
2301_0105_00007	36 F	MS	Worsening of MS	120	.
EXTENSIONS					
2201_0001_00012 FTY 1.25	42 F	MS relapse	Relapse	263	Y
2302_0202_00010 FTY 0.5	33 F	MS relapse	Unusually severe MS relapse	590	Y

Listing of as SAE of MS relapse after drug discontinuation.

After drug DC	Age sex	PT	Verbatim	Comment
2301_0412_00004	45 F	MS	Chronic progression of MS	Received FTY 0.5. Discontinued on Day 203 because of multiple basal cell carcinoma (at 3 sites). Relapsed 2 months after dc
2301_0407_00021	34 M	MS relapse	Unusually severe MS relapse	Received FTY 1.25. Discontinued because of lack of efficacy. Received Rebif for 5 months after FTY. Had unusually severe relapse after stopping Rebif.
2201_0051_00001	37 F	MS relapse	Ms relapse	Received FTY 5 during core, and 1.25 during the extension. Relapsed 3 months after drug dc
2201E1_0029_00008	33 F	MS relapse	Progression of MS	Received placebo during core and FTY 1.25 in the extension. Relapsed 57 days after last dose of study drug. Treated with acyclovir and steroids.

Serious ischemic/thrombotic events in the Nervous system disorders SOC

CONTROLLED STUDIES
<p># 2301_0108_00010. 40 F. Ischemic stroke. Cerebrovascular accident, on Day 393 of FTY 1.25 mg. MS diagnosed approx. 1 ½ years prior to entry. Her last relapse was 8 months prior to entry. She had received Betaseron until 3 months prior to entry. Medical history: obesity and depression. No history of HTN or DM. Non smoker. No family history of coronary disease. On Day 393 she collapsed in the dermatology clinic after undergoing a shaving biopsy of two nevus. She had global aphasia and paralysis of the right arm. Study drug was dc. During hospitalization she presented with a focal motor seizure in the right face/hand. One week later, a brain MRI was compatible with an extensive middle cerebral artery infarction in the subacute phase. An angiogram was negative for carotid artery dissection. Transthoracic echocardiography showed no evidence of embologenic source, with normal LV function and valves. Hypercoagulability work-up showed negative lupus anticoagulant, normal APC resistance, normal Protein C and S, normal antithrombin activity, anticardiolipin IgG and IgM negative, <u>elevated homocysteine 28 µmol/L (nl 5-15 µmol/L)</u>, other results pending. Other test results: normal lipid profile; negative hepatitis C serology; negative rheumatoid factor; ANA positive at 1/80 titer; ENA negative. The diagnosis provided by the investigator is “ischemic stroke of unknown origin”. He did not suspect a relationship between the study drug and this event. A Data Safety Monitoring Board (DSMB) neurologist reviewed this case. According to his review, the CT angiography done the day after the event, showed irregularity and narrowing of the M1 segment of the left middle cerebral artery with attenuation of flow distally. In his opinion, this abnormality could be due to an arteriopathy or residual thrombus following spontaneous thrombolysis. He concluded that the cause of the ischemic stroke is unknown, although the history and work-up are suggestive of an embolic stroke. Other possible causes include an arteriopathy/vasospasm disorder or unknown coagulopathy.</p>
EXTENSION
<p>#2302E1_0365_00002. 40 M. Carotid artery occlusion, Cerebral ischaemia on Day 682 of FTY 1.25 mg. Diagnosed with MS 7 years prior to randomization. Most recent relapse was 1 year prior to randomization. He had received Rebif and Betaseron in the past. History of optic neuritis, hypertriglyceridemia and depression. No history of HTN or DM. He was a smoker. On Day 532 he presented herpes zoster ophthalmicus L side, treated with IV acyclovir. He recovered on Day 681. On Day 682 of FTY 1.25 mg he presented with subacute loss of vision in the R visual field and hypesthesia in R arm, with R-sided homonymous hemianopsia. Patient was hospitalized with the diagnosis of left internal carotid artery dissection. The DSMB and an independent neuroradiologist with expertise in vascular disease felt that the arterial occlusion was due to an embolus or in situ thrombosis and not dissection, but source was not found. Study medication was discontinued after the event.</p>
<p>#2302E1_0142_00005. 25 F. Vascular disorder. Cerebral ischaemia on day 60 of FTY 1.25 mg. MS diagnosed 5 years prior. Last relapse 3 months prior to entry. She had received Avonex and Rebif in the past. Medical history optic neuritis, dysmenorrhea and headaches. No history of ischemic events, HTN or diabetes. Concomitant medications included ibuprofen and oral contraceptive. She received IFN during core study. On extension Day 60 she presented acute L sided headache with</p>

photophobia followed by tingling on R side of body, heavy limbs and dysarthria. Most symptoms resolved within 1 hour; mild headache persisted for some days. Drug was discontinued. A vascular event was suspected but MRI was negative for ischemic event and carotid ultrasound was negative for stenosis or dissection. MRA was negative for vascular stenosis. ECG was normal. Drug was re-started on Day 101. The case was reviewed by DSMB neurologist who concurred with “no evidence of infarction in the acute clinical phase” and concluded that event may have been “a complicated migraine”.

The following cases were reported from the ongoing study 2309:

- 2309 0567 00008- Stroke (Case recently unblinded: on FTY 1.25 mg)

41 year old Caucasian female (US 2309 567-8) diagnosed with MS approximately 3 ½ years prior to entry. Treated with Rebif one year prior to study entry. Medical history included severe migraine and meningioma, mitral and tricuspid valve incompetence. No history of HTN or diabetes. No previous ischemic event. Baseline EDSS score= 1.5. One month into FTY720 1.25 mg she had a severe headache, left hemiplegia and L homonymous hemianopia. MRI showed a 6.8 x 4.0 x 4.5 cm hemorrhagic stroke of the right occipital lobe. No immediate etiology was apparent but study medication was discontinued. A transesophageal echocardiogram showed no signs of left atrial appendage thrombus, atrial septum defect or patent foramen ovale; valves, chambers size all ok, no pericardial effusion and normal left and right ventricle. A work-up for hypercoagulable risk factors was negative. The DSMB neurologist evaluated the case and suspected embolic stroke affecting both the right and left posterior hemispheres with secondary hemorrhagic transformation in the right parietal lobe. No clear source of thromboembolism has been identified.

- 2309 0551 00022 IND report of TIA, IND report PHHO2009US08314, 4 9 10. (Case recently unblinded: on placebo)

40 year old woman with MS developed left side weakness, paresthesias of lip and hand and ataxia. Initially reported as stroke. An MRI and MRA of the brain and CT were done (and were apparently negative because the investigator changed the diagnosis to TIA). Carotid artery duplex examination showed less than 20% stenosis in the internal carotid arteries. ECG and echocardiogram showed normal sinus rhythm, normal size left ventricle, normal left ventricular systolic function, an ejection fraction (EF) between 60% and 65%, normal left atrium, normal right ventricle, normal aortic valve with no aortic regurgitation or stenosis, mild mitral regurgitation, mild tricuspid regurgitation, mild pulmonary hypertension, no pericardial effusion and no masses, thrombus or vegetations. Drug screen was negative for phencyclidine, benzodiazepines, cocaine, amphetamines, THC, opiates and barbiturates. The patient recovered 2 days after the onset of the event.

Interim review, 5 12 10.
 Lourdes Villalba, M.D
 NDA 22-527. Fingolimod

Appendix 9.1.6

Brief narratives of serious herpes viral infections in fingolimod trials

CONTROLLED studies
IFN
2302_0202_00016 - Herpes virus infection. 34 F. MS diagnosed 9 years earlier. Treated with Rebif until one month prior to study entry. On Day 187, herpes infection of mild intensity in the sacral area with a cutaneous lesion, treated with acyclovir. It resolved on Day 202. The patient reported the event at the 1 year visit. <i>It is unclear to me why this AE was coded as serious.</i>
FTY 1.25
2301_0303_00018 – herpes zoster genitalis 33 F. MS diagnosed 6 months prior to entry. She received corticosteroids before entering the study. On Day 106 she had eruption of herpes zoster genitalis. Hospitalized and treated with intravenous acyclovir. She recovered on Day 114.
2302_0318_00005 - Herpes zoster (polysegmental) 25 M. MS diagnosed approx 1 year earlier, treated with Rebif. On Day 230 he presented skin abnormalities that became painful. Patient was hospitalized with polysegmental herpes zoster (T12 & L1), treated with intravenous acyclovir. Drug was interrupted. Event resolved on Day 264. Drug re-started. Patient entered the extension.
2302_0212_00021 – herpes zoster disseminated. 29 F. Day 319 <i>Case described under Deaths.</i>
2302_0821_00007 – encephalitis viral. 23 M, Day 339. <i>Described under Deaths.</i>
FTY720 0.5 mg
2302_0442_00005 Herpes zoster ophthalmic 46 M, MS diagnosed 12 years earlier. Prior MS medications included Betaseron and Rebif. On Day 186 he had mild headache above L eye, followed by puffiness around both eyes. On Day 188 he presented vesicles above the left eye. Hospitalized with dx of ocular herpes zoster. He recovered on Day 212 and re-started drug.
2301_0652_00013 - Herpes simplex virus infection 48 F, Day 622. See narrative below, under Pneumonia and pneumococcal sepsis.
EXTENSION STUDIES
FTY 5 to 1.25 mg
2201E1_0038_00004 - Herpes zoster, facial paresis 42 F. MS dx 9 years prior. Treated with Rebif until 4 months prior to study entry. Received placebo during core. On Day 209 of FTY treatment she developed facial zona and external R otitis, hospitalized with facial paresis. She presented transient deafness and elevated transaminases. Skin lesions were confirmed by dermatologist, treated with acyclovir. Drug was dc due to the AE.
FTY 1.25 mg
2302E1_0365_00002 - Herpes zoster ophthalmic. 40 M. On Day 532 developed left side herpes zoster ophthalmicus that required hospitalization. He recovered with sequelae on Day 681. No action taken with study drug. (same patient who had cerebral ischemia on Day 682).

2302E1_0121_0000720 F. – Herpes zoster (possible reactivation). FTY 1.25 in core. On Day 388 developed herpes zoster with pulmonary lesions. DC due to AE (narrative provided as blinded IND report). Unclear if it is primary infection or reactivation. See text after table.
2302E1_0324_00019 – Herpes zoster 35 M. Treated with IFN beta 1a until one year prior to entry. Received FTY 1.25 in core. On Day 405 developed skin rash in left 5 th thoracic segment and neck pain. Hospitalized with herpes zoster. No action taken with study drug. Event considered resolved after 38 days.
2302E1_0212_00007 – herpes zoster ophthalmic 42 M. Received IFN during core. On Day 200 of FTY required hospitalization and iv acyclovir. Drug discontinued due to AE. Patient recovered after 18 days.
2302E1_0608_00012 – Herpes zoster L eye, arm and face. 33 F. On Day 87 of FTY treatment she had decreased lymphocyte and neutrophil counts. On Day 92: sinusitis. On Day 100: vaginal infection. All were non-serious. On Day 193 of FTY treatment she had pain under her left arm and spots extending from under her arm to her face, including the left eye, diagnosed as herpes zoster. The study medication was temporarily interrupted. The event was considered to be medically significant and serious. It is unclear how it was treated. There was no evidence of visceral involvement. In a follow up report, the investigator stated that the patient had a history of varicella infection (chicken pox) and the shingles were originally thought to be serious but had been downgraded to moderate in severity and non-serious.
FTY 0.5 mg
2302E1_0404_00001 – herpes zoster disseminated 47 F. Received IFN in core for 1 year. Six months into the extension, she presented with a fever of 38.8C and diarrhea diagnosed as gastroenteritis. Laboratory tests revealed low lymphocyte count. Two weeks later, the patient was admitted to the emergency department due to facial pain and vesicles on her face and eyelid as well as her trunk, arms and legs, typical of varicella zoster. She was lucid with normal vital signs. An ophthalmologist determined that there was no eye involvement. The patient was treated with intravenous acyclovir. Study drug was interrupted and then discontinued. Event lasted 30 days. There was not any evidence of visceral involvement and laboratory tests during the patient's hospitalization were normal (no hepatomegaly). Lumbar puncture was also normal-(white cells: 3, proteins: 31, glucose: 59). She did have a history of Varicella as a child. Laboratory testing 2 months after the episode revealed Varicella zoster IgG of 2.00 (positive > 1.10).

The following is a case of herpes zoster infection from the above table, in which viral reactivation is suspected.

- **Subject 2302E 0121 00007 (extension study) - Herpes zoster (VZ reactivation)**

20 year old female, Relative study day 388. (The narrative for this event was blinded in the original ISS.
 As per the AE datasets this event occurred on FTY 1.25 after receiving 1.25 during the core study. Relative days estimated from information in datasets.)

MS diagnosed 3 years prior, manifested as retrobulbar neuritis. She had 7 relapses treated with steroids. She received IFN until 1 year prior to study entry. She has not received varicella zoster vaccination but medical history included scattering of vesicles and red papules in small number which were possibly related to VZV (varicella zoster virus) when she was 9 years old.

On Day 386 of study treatment she presented weakness, dysarthria and shortness of breath, preceded by 1 week of asthenia. On Day 387, she experienced scattering of vesicles that started as red itchy papules, fever, headache and cold like symptoms. On day 390, neurologic exam was normal and the patient had no oropharyngeal or urogenital ulcers, but she had erythematous macules, papules, clear vesicles and pustules, intense pruritus and dyspnoea. The patient was hospitalized due to this event. The study medication was temporarily interrupted.

Laboratory results on day 390 showed neutropenia and Lymphopenia and mild transaminase elevation with normal bilirubin (BR). Immunological examination of CSF showed an intrathecal inflammatory process (positive IgG index at 88% with oligoclonal strips). Herpes group (VZV, HSF, CMV) PCR in CSF were negative. The patient was treated with intravenous Acyclovir 800mg three times daily for 10 days and Zovirax for 10 days. The patient's clinical condition improved. The patient's neurologic and pulmonary exams were normal since the first day of her hospitalization. On Day 391 (one day after drug discontinuation), a thoracic scan showed nodular and micronodular lesions in the pulmonary parenchyma, that evoked an acute viral disease. Arterial blood gases showed mild respiratory alkalosis consistent with hyperventilation. A control thoracic scan one week later showed that the number of lesions had decreased.

Plasma VZV serology showed that plasma VZV IgG was low positive on Day 391 and positive on Day 400. Plasma VZV IgM was reported as positive on both days. Ratio VZV IgG was 724.81 on Day 391 and 3541.3 on Day 400. Ratio VZV IgM was 1.1 on Day 391 and 4.57 on Day 400. IgG versus IgM was reported as IgG > IgM on both days. The serology report could not confirm a primary infection and concluded that the serum profile was in favor of a reactivation. The investigator did suspect a relationship between the event and the study medication.

The hospital report concluded that the patient experienced a spread vesicular cutaneous eruption in relation to a VZV reactivation. There was lung involvement with normal blood gases. There was no evidence of viral encephalitis. The patient recovered approximately 1 months after admission to the hospital.

On follow up report, Varizella zoster virus IgG tests on stored sera from a few months before this episode were negative (both less than 50 IU/L). In order to be positive, the IgG result should have been greater than or equal to 150 IU/L. The results indicated inadequate immune protection against varicella-zoster virus.

The case suggests that even patients who had prior immunity to VZ virus may have an increased risk of herpes infection.

Interim review, 5 12 10.
 Lourdes Villalba, M.D
 NDA 22-527. Fingolimod

Appendix 9.1.7.a. Brief narratives of cases of SAE of macular edema in the controlled studies with FTY 1.25 mg.

FTY 1.25 mg
<p>2302_0915_00006. 46 F. Macular edema on Day 54. Led to drug dc History of vitreous floaters for 10 years. Optic neuritis R eye 6 years prior. Blurred vision at entry. Dilated ophthalmoscopy at screening and 1 month: No hx of ME. Visual acuity (VA): 5/10, L; 10/10 R. Screening Central Foveal thickness (CFT) was 174/190 L/R. On Day 54 progressive deterioration in visual acuity R eye. On Day 72 OCT showed cystic macular edema with CFT of 182/418 L/R. Drug dc on Day 79 because of ME. 92 days after drug dc OCT showed CFT 188/193 L/R. However, Fluorescein Angiography (FA) showed capillary leakage R eye. Event was considered recovered with some decreased vision.</p>
<p>2301_0701_00033. 39 F. Uveitis on Day 52. Macular edema on Day 99, 33 days after drug discontinuation. No history of eye problems. No ME on dilated ophthalmoscopy. Screening: Visual acuity 0.8 L/0.9 R; CFT was 185/193 L/R. On Day 65 found to have elevated LFTs; drug discontinued. On Day 99 (end of study visit 33 days after last dose): visual acuity decreased: 0.6 L/ 0.7 R. Macular edema both eyes. CFT 483/355 L/R. <i>DSMB ophthalmologist thought it was MS-related uveitis based on pattern of fluorescein angiography.</i> Treated with dexamethasone and hydrocortisone iontophoresis. Macular edema reported as resolved on Day 150 (by OCT and ophthalmoscopy) but visual acuity still decreased as compared to screening (0.7/0.6 L/R).</p>
<p>2301_0708_00020. 21 M. Vitreo retinitis on Day 15. Macular edema on Day 90. Drug dc. No history of eye problems. MS dx 2 months prior to study entry. Most recent relapse 3 months prior to entry, treated with steroids. Screening CFT: 196/182 L/R; visual acuity: 0.9/1.0 L/R. On Day 13, decreased visual acuity L eye. On Day 15, dilated ophthalmoscopy showed <u>bilateral vitreoretinitis</u> with left ME which led to drug discontinuation. Visual acuity l eye was 0.1 as compared to 0.9 at screening; Events treated with iv MP, dexamethasone, topical depo-medrol, diclofenac. The PI thought this was ocular inflammation due to MS. A drug effect could not be excluded. FU exam 17 days after drug dc, visual acuity was 0.7/1.0 L/R. FA showed retinal capillary leakage in both eyes. The R eye had vasculitis in the lower part of the retina. End of study (D 46) CFT was 210/194 L/R. 92 days after last dose there was resolution of ME; visual acuity was decreased (0.7/0.9 L/R). DSMB ophthalmologist thought that this was MS-related uveitis.</p>
<p>2301_0904_0000377. 41 M. On Day 36, macular edema, retinal disorders, visual acuity reduced. Drug dc. MS diagnosed 11 years prior. No history of optic neuritis but intermittent double vision for 4 years. Visual acuity at screening: 1/1, L/R. Screening OCT FT: 187/192 L/R. On Day 36, macular edema. FA showed retinal capillary leakage of R eye. ME worse at R without reported symptoms of vision impairment. End of study OCT FT (D36): 203/259. Visual acuity on day 63: 1.0/0.6 L/R.; 66 days after drug dc, OCT CFT 175/200 L/R, visual acuity 1/1. As per DSMB ophthalmologist ME was consistent with pattern of FTY retinal toxicity.</p>

Interim review, 5 12 10.
 Lourdes Villalba, M.D
 NDA 22-527. Fingolimod

Appendix 9.1.7. b. Brief narratives of SAE of macular edema in extension studies in the fingolimod ISS, FTY 5-1.25 and FTY 1.25 mg dose groups

FTY 5- 1.25 mg
2201_E1_0052_00001. 38 F. Received FTY 5 mg during core study, and FTY 1.25 during extension. On day 476 diagnosed with ME. Duration 64 days. No dc.
FTY 1.25 mg
2201 E 0023_00003. 12 year diagnosis of MS. On Day 932 of study treatment he had 30 month ophthalmic assessment. Visual acuity was 20/30 R and 20/20 L. He had no visual complaints. Dilated ophthalmoscopy was indeterminate for ME both eyes. Retinal thickness by OCT-2 showed increased CFT as compared to month 24 (current 246/210 L/R), which led to the diagnosis of macular edema. Drug was discontinued due to the event. The event was considered resolved 28 days after the last dose, although no value for repeat OCT is available. A DSMB ophthalmologist opined that the change in CFT were within the range expected for noise. <i>(ME not confirmed)</i>
2201 E 0043_00001. 40 F. 13 years history of MS. No history of ocular problems with MS. She received FTY 1.25 during core study. On Day 575 as part of the protocol examination she underwent Retinal Thickness Analyzer (RTA) and dilated ophthalmoscopy and was diagnosed with macular edema R eye. Drug was discontinued. Two weeks after drug discontinuation a second ophthalmic assessment was done and no ME was detected. An OCT showed CFT < 160 in both eyes <i>(ME not confirmed)</i> .
2302E1_0145_00004. 53 F. 40 years history of MS. Previous history of uveitis of left eye 13 years prior, and uveitis right eye 5 years prior. History of depression. On gabapentin, oral contraceptive for menopausal complaints, trazodone and bupropion. She received IFN during the core study. On day 40 of FTY 1.25 during the extension study, at a scheduled visit, mild decreased visual acuity on right eye (from 0.6 to 0.5). An OCT showed CFT of 304 microns, from 156 microns at screening. Along with the use of FA, a diagnosis of <u>lamellar macular hole with surrounding cystic macular edema of the right eye</u> ” was made. Drug was discontinued. She was treated with acetazolamide, prednisolone and indomethacin for 2 months. 68 days after drug discontinuation, the patient had recovered from the macular edema in the right eye. The investigator suspected the event to be related to study drug. The DSMB ophthalmologist confirmed the diagnosis of macular edema, but not that of “lamellar macular hole”.
2302E1_0324_00008. 50 M. Received IFN during core study. MS dx 7 years prior. Five relapses treated with CS. Hx of HTN, strabismus and amblyopia in R eye since birth, uveitis since 3 years prior. No macular edema. No diabetes or retinopathy. Smoker (20 cigarettes/day). Screening visual acuity was 0.05 OD and 0.8 OS. On Day 312 of FTY therapy c/o blurred vision L eye. Visual acuity at that time not available. She was dx with macular edema by fundoscopy and OCT by local ophthalmologist. She also developed uveitis L eye. Drug was dc on Day 317 of FTY treatment. She was hospitalized, treated with acetazolamide, prednisone, MP and potassium bicarbonate. Two months later, visual acuity was 0.05 OD and 0.5 OS (decreased compared to screening). At time of last reporting she was considered recovered.
2302E1_0610_00001. 37 M. Diagnosed with MS 1 ½ years prior to entry. History of optic neuritis 7 years prior with <u>left</u> eye mild optic atrophy diagnosed 1 year prior. He received FTY 1.25 during core study. On Day 359, during the extension study he experienced blurred vision of the <u>right</u> eye. An examination a week later showed no change in visual acuity (20/20). An OCT showed intra-retinal cyst of the right eye (CFT not available). A FA showed bilateral cystoid macular edema. Drug was discontinued. No treatment was given. OCT done one month after drug dc showed persistent cyst. 59 days after the last dose of FTY, an ophthalmic assessment showed resolution clinical symptoms. Follow up OCT and FA were scheduled, results pending.

Appendix 9.1.8. a. Brief narratives of patients with SAE in the Respiratory, thoracic and mediastinal disorders SOC, safety pool D

Placebo
2301_0552_00006. 42 F. COPD dx on day 230. did not lead to drug dc.
2301_0307_00031. 53 F. Asthma on Day 493. History of asthma and optic neuritis. Non smoker. Presented two decompensations treated with bronchodilators. While in hospital also diagnosed with COPD. HRCT was not done.
2301_0304_00045. 52 M. Pulmonary embolism on day 657. Patient died of PE. Narrative included in table of deaths.
IFN
2302_0608_00004. 36 M. Pneumothorax, on Day 105 (motor vehicle accident, rib fracture and pneumothorax).
FTY 5 mg
2201_0025_00016. 52 F. Dyspnoea, chest pain and bradycardia on Day 5. Led to drug dc. She presented bradycardia on first day of treatment 2 hours after first dose, with dizziness and chest pain. <i>Case described under serious cardiac events.</i>
FTY 1.25 mg
2302_0521_00001. 51 F. Pleurisy, dyspnea. No significant medical history. On Day 116 she presented shortness of breath and chest pain and was diagnosed with severe pleurisy, treated with oxycodone. Chest Xray and labs were normal and stress test was negative. Event resolved on Day 126. On Day 198 the patient FEV1 was decreased from 2.44L at screening to 1.89 L. On Day 442 FEV1 was 1.77 L. HRCT at baseline and on Day 365 was normal. She discontinued from the study due to FEV decreased. Last dose of study drug was on Day 484 during extension study. 20 days after drug dc FEV1 was 1.58 L. <i>UNEXPLAINED DECREASE in FEV₁ on day 198. No HRCT or echocardiogram at time of the event or later.</i>
2302_0307_00001. 24 F. Hyperventilation and Dyspnoea No significant medical history. Smoker (3 cigarettes per day). Taking oral contraceptive. On day 216 of study presented dyspnea and hyperventilation. Treated with lorazepam, the event resolved on Day 220 and drug was re-started on Day 221. <i>Chest Xary, PFTs or HRCT are not available for this subject.</i>
2302_0125_00001. 34 F. Dyspnea, lung disorder on Day 1. Recurrent dyspnea on Day 140 led to drug dc. Smoker 10 cigarettes/day for 20 years. Baseline PFTs: FEV 4.34L, FVC 4.49 L, DLCO 69. On Day 1 the patient experienced dyspnea and dysgeusia, initially mild but worsening to the point of dyspnea on minimal exertion. One month into the study she had mild decreased DLCO (13% from baseline). On Day 139 she was hospitalized for dyspnea. An scintigraphy showed a non-specific pulmonary segmental dorsal defect compatible with pulmonary embolus (a definitive diagnosis was not made). Drug was dc on Day 140. 15 days after the last dose of study medication she experienced myocardial ischemia. 62 days after last dose of study drug, the event of dyspnea and dysgeusia completely resolved. A HRCT done 2 ½ months after drug dc was normal. The DSMB pulmonologist reviewed this case and found no etiologic cause, although the fact that it started after study drug initiation and improved after discontinuation suggests a causal relationship. <i>No HRCT available at time of the event. No echocardiogram or further cardiac workup available for this subject.</i>
2301_0601_00012. 24 F. Pneumonic infiltration. Pleurisy on Day 65. <i>Also associated with pericarditis. This case has been described under serious cardiac disorders and mentioned under infections. It was thought to be viral.</i>

FTY 0.5 mg
2302_0145_00003, 42 M. Pneumothorax. Day 85. No dc. History of hypertension and spontaneous pneumothorax. On Day 85 he was hospitalized due to spontaneous pneumothorax. Patient completed core phase and entered the extension.
2301_0454_00002, 44 F. Dyspnea Chest pain, myocardial ischemia on Day 449. No dc. Described under serious cardiac events.
2301_0408_00009, 21 F. Pulmonary oedema,(?myocardial ischemia) on Day 7. Led to drug dc. This cases was discussed under serious cardiac events because it was associated with LV dysfunction and increased cardiac enzymes. Etiology of the pulmonary edema is unclear, perhaps related to transient ischemia, confounded by the use of “varnish” prior to the event.

Appendix 9.1.8.b. Brief narratives of SAE in the Thoracic system disorders SOC in the extension studies, original ISS.

FTY 5 to 1.25 mg
2201E1_0003_00008, 44 F. Asthma on Day 349. Drug dc. MS symptoms for 4 years. No history of asthma. Non smoker. On Day 349 of FTY treatment she presented with asthma, treated with prednisone budesonide-formoterol, salbutamol and fluticasone. She returned to the ER the day after, and was hospitalized overnight for close monitoring. The event resolved on Day 351. Subject withdrew consent in discontinued from the study. PFTs not available. <i>NEW ONSET of ASTHMA.</i>
2201E1_0038_00010, 27 F. Asthma. Day 209. Drug dc. Medical history of asthma since 15 years prior to entry. On Day 27 he experienced mild dyspnea. On Day 209 of FTY treatment she experienced moderate exacerbation of asthma. She was hospitalized for 4 days and treated with prednisone, salbutamol, terbutaline. Study drug was interrupted from Day 241 to 275. Study drug was re-started on Day 276 but then discontinued on Day 278 due to the event of asthma. The investigator suspected a relationship between the event and the study medication. <i>EXACERBATION of ASTHMA.</i>
2201E1_0037_00013, 40 F. Bronchospasm on Day 8. Drug dc. MS diagnosed 5 years prior to entry. Non smoker. No history of asthma or respiratory disease. Concomitant medication: oral contraceptive. She received placebo during core study. On Day 8 of the extension she developed severe bronchospasm. PFT showed decreased FEV1 and DLCO. “Discrete obstructive syndrome” was diagnosed. Study drug was discontinued on extension day 183. A chest CT done on an unknown date showed no pleural or parenchymatous abnormalities. The event of bronchospasm resolved completely 63 days after last dose of study drug. <i>NEW ONSET BRONCHOSPASM, reversible upon drug discontinuation.</i>
FTY 1.25 mg
2302E1_0124_00001, 43 F. Dyspnea, hypoxia, lung disorder, day 570. Drug dc. Blinded narrative: Bilateral pneumopathy and mediastinal lesion/parenchymatous and <u>pleural lesions</u> . Study drug discontinued. There is no additional information about this event. One month later he presented fever and left lumbar pain and was diagnosed with pyelonephritis requiring hospitalization.
2302E1_0525_00002, 41 F. Pneumothorax (acinetobacter pneumonia), Day 400. Drug dc. R middle lobe “lung neoplasm” diagnosed by HRCT without biopsy. One month later, bronchoscopy + biopsy for evaluation of bronchiectasis. Culture from the day of bronchoscopy grew acinetobacter. Dx as acinetobacter pneumonia, complicated with pneumothorax during bronchoscopy <i>Case also described under infections.</i>

Interim review, 5 12 10.
Lourdes Villalba, M.D
NDA 22-527. Fingolimod

2302E1_0604_00010. 34 F. Asthma on day 494. No drug dc. Pt had history of mild asthma for 20 years, treated with fluticasone and salbutamol. One week prior to the event had common cold symptoms. On Day 118 presented asthma attack and was hospitalized with dyspnea & wheezing. Decreased FEV and FVC.
FTY 0.5 mg
2302E_0442_00012, 41 F. Pulmonary embolism 58. No dc. MS diagnosed 7 yrs prior to entry. Prior treatment with Avonex, Betaseron and Rebif. Medical history included varicose vein embolectomy, tachycardia, depression, optic neuritis. Family history of clots, stroke and heart attack. Active smoker. During study received perindopril for HTN, carbamazepine and pregabalin for MS pain, atorvastatin for high cholesterol and varenicline for cessation of smoking. On Day 58 of FTY 0.5 mg treatment she presented left sided chest pain and heaviness in her leg. ECG and blood tests, and computed tomography angiogram were done. She was treated with glyceryl trinitrate, morphine, aspirin. She improved and was discharged the next day with diagnosis of musculoskeletal chest pain. At home she continued with intermittent chest pain and dyspnea. On Day 62 of FTY treatment she was re-hospitalized. A VQ lung ventilation perfusion scan showed PE. She was treated with heparin followed by warfarin. At the time of last reporting, condition was improving. Drug was not discontinued. Follow up information is pending.

Appendix 9.1.9. Brief narratives of patients with SAE of chest pain, pool D

<p>Placebo</p> <p>2301_0206_00029 – 38 M. Non-cardiac chest pain on Day 561</p> <p>2301_0909_00006 – 36 M. Non-cardiac chest pain on Day 120</p>
<p>FTY720 5 mg</p> <p>2201_0025_00016. 57 F. Bradycardia on Day 1. Chest pain, dyspnea, tachycardia on Day 4. Patient had bradycardia on first day (<50 bpm), with dizziness and chest pain/pressure. HR back to normal 12 hours later. She continued treatment. On day 3 she had watery diarrhea; on day 4 she was tachycardic with sharp chest pain and dizziness and dyspnea and was withdrawn from the study. She recovered after 10 weeks. <i>Cardiology workup suggested non-anginal chest pain. This case was included in Table 16 among cases of bradycardia. Narrative updated 4/22/10.</i></p> <p>2201_0066_00006 – 41 F. Chest pain, bradycardia on Day 2. On 2nd day of treatment had unspecific thoracic pain spreading to arms, bradycardia, vomiting, normal CK and troponin. Chest pain though to be due to vomiting. Drug interrupted and restarted a week later. At 6 months, ECG showed inverted T waves. <i>Pt continues in the extension study as per 4/22/10 narrative update. Case is also included in Table 16.</i></p>
<p>FTY 1.25 mg</p> <p>2201_0018_00003 - 44 F. Chest pain, bradycardia, Day 1</p> <p>44 F. History of HTN. Had chest pain 3 hours after first dose. ECG showed first degree AVB. No symptoms with further doses. She received diazepam. Troponin level was normal. After the second dose, all subsequent ECGs were normal with no cardiac or respiratory symptoms. She is still in the study. She has have episodes of neck pain and anxiety but no cardiac chest pain. <i>Case included in Table 16. She is still in the extension study as per 4/22/10 updated narrative.</i></p>
<p>FTY720 0.5 mg</p> <p>2301_0459_00004 – 34 F. Chest pain on day 357</p> <p>Medical hx: Restless leg syndrome; Botallo's foramen ovale, atrial septal aneurysm. No hx of HTN or diabetes. Smoker ½ pack x 23 years. On Day 358 she had constrictive chest pain with palpitations that lasted 5 hours. Hospitalized. P exam, cardiac enzymes, troponin and ECG were normal. She recovered the same day and was discharged. Cause of pain was unknown. No further workup was done. <i>As per 4/22/10 follow up, she has no experienced further episodes of chest pain.</i></p> <p>2301_0413_00004 – 47 F. “Non-cardiac chest pain” and increased BP on Day 638.</p>

Interim review, 5 12 10.
Lourdes Villalba, M.D
NDA 22-527. Fingolimod

History of HTN. No diabetes or heart disease. Concomitant meds: carbamazepine, amantadine and estradiol-norethisterone. Prior to the study entry, the patient's blood pressure was 140/90 mmHg. On Day 638 had sudden onset of "non-anginal" thoracic pain. Hospitalized. Found to have high blood pressure. Treated with nitroglycerine and amlodipine. The event of chest pain and increased BP resolved on the next day. ECG, Echocardiogram and lab evaluations showed no evidence of myocardial infarction. *Subject still in the trial as per 4/22/10 follow up.*

2301_0651_00001 - 34 M, "Non-cardiac chest pain", day 514
History of varicose veins and thrombophlebitis. No HTN or diabetes. Non smoker. No concomitant meds. On Day 514 he had chest pain with radiation to R jaw and arm. Hospitalized, ECG and cardiac enzymes were normal. Nitroglycerin and unspecified analgesics were given. Over the ensuing 2 months he complained of intermittent light pressure. No additional work up was reported. *As per follow up on 4/22/10, the subject is still in the study.*

Interim review, 5 12 10.
 Lourdes Villalba, M.D
 NDA 22-527. Fingolimod

Appendix 9.1.10. Narrative of selected SAE in the Hepatobiliary disorders SOC and (hepatobiliary) Investigations SOC in fingolimod controlled studies.

FTY 1.25 mg
2201_0002_0001. 55 F. Hepatitis toxic on Day 36. Led to drug dc. MS diagnosed 1 year prior to entry. Previously treated with glatiramer. Medical history included type 2 diabetes mellitus, osteoarthritis, urinary frequency, HTN, intermittent cough, depression. Concomitant medications: methylsulfonylmethane, rofecoxib, oxytutynin, ramipril, triamterene for many years. Other prior meds were <i>Oenothera Biennis</i> oil, <i>Linum Usitatissimum</i> seed oil, erythromycin, but were discontinued within the first 10 days of the study. Baseline liver enzymes were normal (ALT 17 U/L –nl 1 to 30-, AST 19 U/L –nl-32-, BR 6.8 µmol/L –nl 1.7-18.8) and ALK Phos 94 U/L –nl 31-121-). On Day 36 she had an increase in ALT (123 U/L) associated with BR 5.1, ALK Phos 147 U/L. She was diagnosed with “chemical hepatitis”. Study medication was interrupted from Day 102 to Day 113 due to this event. Treatment was re-started on Day 114, and permanently dc on Day 119 due to this event. On Day 120, ALT rose again to 106 U/L. The toxic hepatitis resolved 41 days after drug discontinuation. The investigator did suspect a relationship between the event (toxic hepatitis) and the study medication.
2201_0074_00005. 30 M. ALT increased on day 148. Led to drug dc. (ALT baseline value: 32 U/L), presented with elevated ALT levels of 111 U/L on day 85, and 119 U/L after 4.5 months on study drug. A follow-up monitoring of the patient again showed raised ALT which was reported as a serious adverse event on day 148. Initially it was believed that this was due to the drug taken for body building, Norateen, which was discontinued. As ALT raised further to 474 U/L, the study drug was permanently discontinued on day 154. The patient was lost to follow-up.
2301_0152_00011. 40 M. ALT & GGT increased on Day 168. Led to drug dc. In accordance with protocol guidelines, drug dc on Day 175 due to ALT=217 (nl 0-45 U/L)(5x ULN). GGT was 2x ULN. BR was normal. Two months after drug dc, ALT was normal.
2301_0601_00012. 24 F. Liver function test abnormal on Day 65. Led to dc. On Day 65 she experienced chest pain, dyspnea, nausea and vomiting. Echocardiography showed pericarditis and pleuritis with mild pneumonic infiltrate. Labs showed ALT 122 (3xULN), AST 88 (2x ULN) and ALKP 446 (4x ULN). Drug was discontinued. Event was thought to be viral, but no definitive agent was identified.
2301_0903_00010. 29 F. Liver function test abnormal on Day 190. Concomitant meds included ibuprofen and oral contraceptive. On Day 190 during routine visit, ALT=96 U/L (2x ULN) with normal BR. On Day 281 liver enzymes continued to rise, with ALT 114 U/L (<3x ULN), AST 53 U/L and normal BR. Liver US was normal, hepatitis serology was negative. Drug was interrupted. On day 304 she had myalgias and arthralgias, upper limb weakness, sore throat and chest pain when breathing that lasted for five days. She was admitted to the hospital on Day 311. On day 316, ALT was 143 U/L; AST 79 U/L, with normal BR and ALK P. Study medication was resumed on Day 371.
2302_0145_00007. 46 F. Hepatic enzyme increased on Day 247. Led to dc. Medical history scoliosis, bronchitis and HTN. During the study she received nifedipine, ibuprofen and amoxicillin for periodonditis. At screening she had elevated ALT (104 U/L) and AST (53 U/L); at baseline, ALT,AST, GGT, BR and ALK P were normal. (Day 25), the patient was noted with elevated ALT (125 U/L, >2x ULN, AST (63 U/L > ULN), ALK P (112 U/L), total bilirubin (26 µmol/L > ULN) GGT 121 U/L > ULN). During the study ALT, AST, ALK P, total BR and GGT levels fluctuated. On Day 247 ALT= 252 U/L (>5x ULN), AST= 129 U/L (<3x ULN) AIK P= 177 U/L and GGT 282 U/L, <4x ULN). TBilirubin was within the normal range. Study drug was dc. Eleven days after last dose, GGT was still elevated (164 U/L) but other enzymes were normal.
FTY 0.5 mg
2302_0330_00004. 37 M. Hepatic enzyme increased on Day 19. Led to study dc. No concomitant medications. Liver enzymes at screening were normal. On Day 19 mild he was noted to have ALT =147 U/L (3xULN). BR and ALk P were normal. Drug was discontinued due to the event on day 36. Eleven days after last dose, ALT was 359 (>7xULN), AST was 147 U/L (>3xULN), and GGT was 224 (>3x ULN). Liver enzymes

normalized 69 days after drug dc.

Appendix 9.1.11a. Listing of SAEs in the Blood and Lymphatic system disorders SOC and Investigation (hematology related) SOC

FTY 1.25 mg
2301_0419_00001. 28 F. Leukopenia & Lymphopenia on Day 199. Per laboratory samples collected on Day 197 of FTY 1.25 mg, the patient presented with leucopenia $1.3 \times 10^9/L$ and lymphopenia 10.4% which were considered medically significant. The study medication was temporarily interrupted Day 244. The patient was treated with sulfamethoxazole 800mg and trimethoprim 160mg for a few days and did not have any signs/symptoms associated with the leucopenia and lymphopenia. The study medication was restarted on Day 351. On Day 393, laboratory tests showed normal values in all relevant samples.
2301_0459_00005. 26 F. Lymphopenia on Day 635. Led to drug dc. Diagnosed with MS 4 years prior. Received IFN B 1a s.c for 5 months, til 4 months prior to entry. On Day 635 of FTY 1.25 mg, the patient was noted to have decreased lymphocyte count to $0.19 \times 10^9/L$ ($0.85-4.10 \times 10^9/L$). and persistent, productive cough. Hospitalized due to productive cough and bronchitis. Found to have low CD4 (11 cells; normal above 490). Treated with bactrim for "toxoplasma prophylaxis." FTY interrupted for 3 weeks. Patient recovered from lymphopenia and cough. Drug re-started, and he entered extension study. On day 12 he developed Lymphopenia again and was discontinued from the study. He recovered from lymphopenia one month after drug discontinuation.
2302_0361_00007. 33 F. Lymphopenia on Day 124

Appendix 9.1.11. b. Listing of SAE in the Blood and lymphatic disorders SOC, extension studies

2201E_0002_00002. FTY 1.25. 37 F. Neutropenia on Day 309 of FTY treatment. Drug dc. Received FTY 5 mg during core.
1202E_0106_00009. FTY 1.25. 37 F. Lymphopenia on Day 302 of FTY treatment. Drug not dc. Received IFN during core.
2302E1-0316-00010. FTY 1.25 mg . 44 F Idiopathic thrombocytopenic purpura on Day 181 of FTY treatment. Received IFN during core study. MS dx 10 years prior to randomization. Hx of hyperthyroidism and menopause, taking levothyroxine and estrogens. During screening platelet count was $236 \times 10^9/L$. On day 487 it was $209 \times 10^9/L$. On day 181 of FTY treatment platelet count was $4 \times 10^9/L$. An hematologist diagnosed ITP. Drug was discontinued and patient was treated with steroids. At the time of last reporting, 5 months after drug dc the patient was considered completely recovered from ITP.
2302E_0510_00001. 50 F. On FTY 0.5. 50 F. Lymphadenopathy on Day 222 of FTY treatment. Received IFN during core. Left axillary lymph node enlargement. Drug not dc.
2302E_0303_00013. 48 F. Leukopenia on Day 548 of FTY treatment. On day 547 WBC was $1.6 \times 10^9/L$. Drug was interrupted for one week. WBC was $3.0 \times 10^9/L$. Drug re-started without further problems.

Source: AE datasets submitted 12/18/10 and selected patient narratives.

Appendix 9.1.12. Non-seriousAE leading to drug discontinuation in the EYE system disorders SOC

<p>FTY 1.25 mg</p>
<p>2301 0151_00003, 50 F. Macular edema on Day 19, duration 72 days. Prior history of Guillain Barre and optic neuritis 4 years prior. Screening CFT 125/186 microns L/R. On Day 19 c/o eye pain and blurred vision. One week later visual acuity decreased 20/40; macular edema Left eye; CFT 416/186 L/R. <u>Drug was discontinued</u>. 23 days after drug dc visual acuity was normal and ME had improved. 3 months after drug discontinuation FA demonstrated bilateral parafoveal dye leakage from the retinal capillaries R>L as well as mild bilateral dye leakage from the optic nerve heads.</p>
<p>2301 0651_00024, 38 M. Macular edema on Day 15, duration 40 days History of optic neuritis and uveitis prior to entry. At screening eye exam showed uveitis but no macular edema (CFT was 198/185 micron L/R). Visual acuity was 1.0 R and 0.8 L. He was treated with topical steroids. On Day 15 of FTY treatment, dilated ophthalmoscopy showed bilateral macular edema, confirmed with OCT and FA (bilateral leakage). CFT by OCT was 297/329 L/R. Visual acuity was normal. <u>On Day 17 drug was discontinued</u>. Ten days after drug discontinuation, visual acuity was 0.6 R, 0.8 L, ME still present. Event resolved 40 days after drug discontinuation. DSMB ophthalmologist confirmed that macular edema developed after drug started and thought could be related to therapy.</p>
<p>2301 0953_00007, 27 M, Macular edema on Day 173. Not recovered. May be not drug related. Prior history of optic neuritis Left eye and bilateral abnormal foveal thickness 2 months prior to entry. At screening pt already had significant reduction of visual acuity (0.05 both eyes) and increased thickness of paramacular area of L eye. Fluorescein angiography showed no leakage consistent with ME, then the patient was enrolled into the study. On Day 43 visual acuity was unchanged. No ME was detected by dilated ophthalmoscopy. OCT and FA were not done. On Day 173 ophthalmic examination by local ophthalmologist showed bilateral macular edema and drug was discontinued. The PI disagreed with the diagnosis of macular edema. The DSMB ophthalmologist reviewed all records and concluded that one month into treatment, the patient had bilateral papillitis and periphlebitis L>R. 9 months later, periphlebitis was less but still present, additionally there were two areas of retinal pigment epithelium (RPE) depigmentation inside the temporal arcades. He suspected that the patient had active uveitis at the time of enrollment and agreed that he should be off study drug. An uveitis specialist concluded that there was no doubt that the patient had cystoid macular edema of the left eye which would be typical of the intermediate uveitis seen in MS patients. Seven months after study drug discontinuation he withdrew from the study. At this visit, his visual acuity was “hand motion” both eyes, macular edema was present, assessed by dilated ophthalmoscopy, OCT showed normal CFT and FA showed no retinal capillary leakage. He showed no improvement after several months of discontinuation and local and systemic treatment for macular edema. At the end, the investigator suspected that it was not drug related.</p>
<p>2301 0952_00006. 42 F. Macular edema on Day 37. Duration 140 days. Prior history of uveitis for the last 2 years. No evidence of active retinopathy prior to study entry. At screening there was uveitis but no evidence of macular edema. A FA was normal with no retinal capillary leakage. On Day 37 of FTY 1.25 treatment a repeat OCT was still normal, but because of the uveitis a fluorescein angiogram was done which showed mild, very late, capillary leakage consistent with macular edema. The local ophthalmologist suggested that the leakage was related to the uveitis and not to the drug. The drug was discontinued on Day 85 due to macular edema. This date, opht evaluation showed improvement in the uveitis while the condition with respect to macular edema remained the same. She received topical treatment with dexamethasone and diclofenac. She had follow up opht evaluations. <u>She recovered completely from the event of macular edema 98 days after the last dose of study drug</u>. The DSMB ophthalmologist confirmed that the FA at screening was normal and on Day 37 showed bilateral perifoveal dye leakage in the late frames, and that the patient should stay off drug.</p>

Interim review, 5 12 10.
Lourdes Villalba, M.D
NDA 22-527. Fingolimod

2302 0106 00005, 37 F. Macular edema on Day 99 – no recovery date in dataset
2302 0251 00002. 32 M. Macular edema on Day 145 – no recovery date in dataset
2302 0524 00005 . 36 M. Macular edema on Day 98, lasted 33 days.
2302 0602 00005, 44 F. Macular edema on Day 99, lasted 85 days

Appendix 9.1.13.a. Listings and brief comments on non-serious events that led to discontinuation due to respiratory related symptoms are presented in the following table for the controlled studies.

Placebo
2301_0251_00002, 38 F. Dyspnea on Day 17; duration 17 days
2201_0025_00016, 31 F. Dyspnea on Day 12; duration 26 days
2301_0607_00009, 40 F. Spirometry (abnormal) on Day 555; duration 1 day. CT abnormal on day 576. Depression treated with amitriptyline. Other meds: tizanidine. Non smoker. No other significant history. During the study she had an upper respiratory tract infection. On Day 557 she was noted to have a decreased DLCO, from 23.7 mmol/min/Kpa at screening, to 17.6 mmol/min/KPa (less than 80% of screening value). HRCT showed bilateral ground glass areas. Drug was discontinued. No date of recovery.
2301_0751_00008, 28 M. DLCO decreased on Day 107; duration 202 days. Smoker, 1 pack day for 14 years. At screening DLCO was 0.68 mmol/min/KPa. On Day 107 DLCO was 6.52 (60% of predicted) but he did not have any respiratory symptoms. Drug was discontinued and DLCO improved after discontinuation. Chest Xrays and HRCT done 190 days after drug dc showed no significant abnormalities.
2301_0756_00004, 27 M. DLCO decreased on Day 548; no date of recovery. Non smoker, no hx of asthma, history of + antiphospholipid antibodies. During the study she had flu like symptoms and chest infection from day 503 to 527, treated with antibiotics. On Day 527 FEV1 was decreased 64%. Study drug was discontinued. 119 days after drug discontinuation the patient was diagnosed with asthma. Chest X-ray at screening and end of study visit (196 days after study dc) were normal.
IFN
2302_0220_00002, 43 F. DLCO decreased on Day 108; no date of recovery
2302_0220_00014, 43 F. DLCO decreased on Day 32; no date of recovery
FTY 5 mg
2201_0072_00003, 55 F. Dyspnea on Day 5; duration 16 days Baseline values of FEV1 2.58 L (110% of expected), FVC 3.29 L (119% of expected) and DLCO 24.78 ml/min/mmHg (108% of expected), presented with symptoms of moderate dyspnea on day 5. The investigator suspected a relationship with the study medication. Treatment with study medication was discontinued on day 16. The patient discontinued the study on day 63 after withdrawal of consent. There is no follow up PFT or HRCT for this patient.
FTY 1.25 mg
2301_0176_00001, 45 F. Dyspnea on Day 11; duration 2 days Smoker. No other significant medical history. On day 1, upon first FTY dose he presented asymptomatic bradycardia 6 hours post dose. The second day, he presented mild dyspnea. The patient adjusted his own dosing because of the AE. On Day 11 he had another event of bradycardia and dyspnea, which led to permanent drug discontinuation. <i>(In this case the dyspnea seems to be cardiac-related)</i>
2302_0311_00002, 49 F. Obstructive airways disorder on Day 178; no date of recovery
2302_0333_00008. Narrative was provided in NDA but case was not in AE datasets. 32 F, developed abnormal DLCO values on day 177. At screening DLCO was 10.07 mmol/min/KPa. On Day 177 DLCo was 6.19. No changes in FEV1 an FVC. HRCT not done at baseline. 72 days after drug discontinuation DLCO was 6.6. HRCT done 16 days after drug dc showed "residuals of outdated infiltration". <i>No fu HRCT available.</i>

Appendix 9.1.13.b. Discontinuations due to AE in Respiratory SOC in Extension studies

<p>2302E1-0307-00002 – Dyspnea. 42 F. Medical history included psoriasis, headache, intercostal neuralgia and migraine. No history of diabetes mellitus, HTN or cardiovascular disease. She received IFN during the cores study. On Day 109 of the extension study (DOSE?) she experienced mild dyspnea, asthenia, hypertension and diarrhea. She received last dose of study drug on extension Day 122. The event of dyspnea resolved 5 days after the last dose of study drug. The narrative does not provide any information about work-up conducted in this patient (<i>Additional information requested.</i>)</p>
<p>Patient 2302E1-0609-00006 –Fatigue, dyspnea, non-cardiac chest pain 41 F, MS diagnosed 14 years earlier. Medical history headaches, dysmenorrhea, seasonal allergy, optic neuritis, bronchitis. No diabetes or HTN. Smoker. She received IFN during core. On E Day 4 of FTY 0.5 mg, she experienced mild fatigue and dizziness. On E Day 14 increased fatigue and headache. On E Day 35 mild dyspnea and non-cardiac chest pain. Drug was discontinued on E Day 38. No treatment was given. The narrative has no information about work-up done in this patient. <i>Additional information requested.</i></p>
<p>Patient 2302E1-0543-00003 – Dyspnea 44 F, MS for 15 years. Medical history fibromyalgia, hypersensitivity to sulfa drugs, optic neuritis, sleep apnea syndrome, GERD. No history of diabetes or CV disease. She received IFN during core. On E day 58, while on FTY 1.25 mg she experienced dyspnea of moderate severity. Drug was discontinued on E day 68. Not treatment give. NEvent was ongoing at time of last available report. <i>Additional information requested.</i></p>
<p>Patient 2302E1-0222-00002 – Dyspnea 31 F. MS dx 2 years earlier. Medical history Gilbert. No other relevant history. On E day 22 she experienced moderate dyspnea. Drug discontinued on E Day 23. Dyspnea was ongoing at time of the last available report. <i>Additional information requested.</i></p>
<p>Patient 2302E1-0219-00002 – Carbon monoxide diffusing capacity decreased 19 F, MS diagnosed 7 years prior to randomization. No relevant medical history. Non smoker. No concomitant medications. At screening (Day – 37), the patient’s DLCO, FEV1 and FVC values were 22.12 mL/min/mmHg, 3.52 L and 4.01 L respectively. On Day 464 of FTY 0.5 mg, she was noted with a decreased DLCO value of 16.4 mL/min/mmHg. On Day 582 DLCO further decreased to severely low levels (15.41 mL/min/mmHg). FEV1 and FVC were mildly decreased as compared to screening. Drug was discontinued on Day 582. The event of DLCO decreased was ongoing at the time of last available report, 144 days after last dose. There is no information on chest Xray, HRCT, blood gases, ECG, laboratory evaluations. <i>Additional information requested.</i></p>

Appendix 9.1.14. Listing of subjects with serious and non-serious AE consistent with ischemic heart disease:

Placebo 2301_0703_00005	45 F	S	-	Serious Myocardial infarction on day 44
Placebo 2301_0309_00005	42 M	S	-	Serious Myocardial infarction on study day 775, 50 days after drug dc
Placebo 2301_0251_00010	46 F	-	-	Non-serious Angina pectoris, 1 month into study. History of heart murmur and intermittent chest pains/tightness for several years. No HTN or diabetes. Smoker. First report during the study was one month into treatment, when he reported that chest pains got worse since study medication started (from mild to moderate), but there was no chest pain with the first dose. The pain was considered to have cardiac origin but there is no documentation of a cardiac work up and there was no use of low dose aspirin. Concomitant meds included ibuprofen and paracetamol.
Placebo 2301_0402_00005	36 M	-	-	Non serious Angina pectoris, day 17. No hx of diabetes or HTN. Familial hyperlipidemia. Smoker. No concomitant meds. On day 1 he had asymptomatic first degree AV block by ECG at 6 hours post dose, with no decrease in HR. On Day 17 had “stenocardia” (angina pectoris) of moderate severity (chest pain/tightness). Stress test and cardiac ultrasound were normal. Cardiac enzymes not available. No action taken with study drug and no treatment given. Event resolved on Day 30. Other ECGs were normal, except first degree AVB again noted at Month 6 ECG.
Interferon 2302_0314_00008	55 M	S	-	Serious Angina unstable on day 337 (described under SAEs)
Interferon 2302_0253_00010	32 M	-	-	Non serious MI, day 204. No relevant medical Hx. No conc. meds. On Day 204 (6-mo ECG) had first degree AV block and suspected of mild anterior wall MI. No symptoms. A second ECG done a few days later showed no MI, just first degree AV block. The event of “acute MI” resolved on day 208. No action taken with study drug.
Interferon 2302_0407_00003	48 M	-	-	Non serious angina pectoris, day 383. No relevant medical Hx. Smoker. No conc. medications. 12 days after last dose in core study he had severe chest pain diagnosed as angina pectoris. No treatment given. ECG (ST elevation) and increased CK at the time suggested “cardiac ischemia” Echocardiogram was normal. He did not enter the extension because of abnormal ECG.
FTY 1.25 mg 2301_0651_00016	27 F	S	dc	Serious Angina pectoris on day 1 (described under SAEs)
FTY 1.25 mg 2302_0216_00013	30 M	-	dc	Non serious angina pectoris on day 56 and inverted T wave on day 62 leading to drug dc
FTY 1.25 mg 2302_0125_00001	34 F			Discontinued on Day 140 drug because of increasing dyspnea. Hypothyroidism. No diabetes or HTN. Smoker. On Day 1 had dyspnea and dysgeusia. Dyspnea increased progressively. At Month 1 DLCO had decreased by 13% and PEmax increased almost 3 fold. Scintigraphy was suggestive of P.E. Drug was dc. 13 days after drug dc she underwent multiple tests. Bronchial fibroscopy indicated a mild inflammation but the samples were negative; bronchial alveolar lavage revealed numerous macrophages and a transbronchial biopsy did not reveal any disorder. 15 days after drug dc she had an abnormal ECG.

		-	-	A cardiologist who saw the patient diagnosed sub-epicardial ischemia. The patient had no additional clinical symptoms. A HRCT done approx 2 months after drug dc was normal. The event of dyspnea resolved 62 days after last dose. Cause of dyspnea was not identified. The DSMB cardiologist reviewed the ECGs, persantin scan and echos and thought that the ECG changes were likely due to improper lead placements.
FTY 1.25 mg 2302 0382 00011	21 M	-	-	Non serious angina pectoris day 94. Hx of headaches, optic neuritis and abnormal chest X-ray. Smoker. No conc. meds. On Day 94 presented sharp pain in heart region, referred to a cardiologist who diagnosed angina pectoris of moderate severity. ECG and stress test showed no ischemic changes. The event resolved the same day. No action was taken with study drug. Patient entered the extension. Subsequent ECGs were normal.
FTY 1.25 mg 2302 0822 00005	37 F	-	-	Non serious angina pectoris on day 3. Medical Hx of HTN and optic neuritis. Mother had diabetes. Non-smoker. On Day 1, ECG showed transient first degree AV block. On Day 3 she had chest tightness and was dx with mild angina pectoris. No action taken with study drug. No treatment given. ECG on Day 3 showed bradycardia. Subsequent ECGs were normal. 2 weeks later, BP was 150/100 mmHg. On Day 35 she had 24 hour Holter, that showed no specific findings. On Day 36 BP was 150/100. She was treated with amlodipine and HCTZ. 2-D Doppler echo was done on Day 30 but results are not available. Event of angina resolved the same day that it started. HTN was ongoing. Pt completed the core phase and entered the extension.
FTY 0.5 mg 2301 0402 00010	29 F	-	-	Non serious angina pectoris on day 68. Hx of headaches, thrombocytosis, and "stenocardia" (angina pectoris), No diabetes, HTN or smoking. During study was taking oral contraceptives and multiple analgesics. On day 68 she had one episode of chest tightness with pain in left arm (angina pectoris) and elevated blood pressure (150/90 mmHg) that resolved spontaneously. No ECG or cardiac enzymes available at the time of the event. Subsequent ECGs were normal. No treatment given for angina pectoris. No further work up was done. Patient withdrew consent on Day 497.
FTY 0.5 mg 2301 0652 00008	44 F	-	-	Non serious angina pectoris on day 327. Hx of knee surgery and hip replacement. HTN and hypercholesterolemia were diagnosed after randomization, before initiation of study drug, HTN treated with HCTZ, metoprolol, amlodipine, lisinopril, irbesartan; high chol. treated with simvastatin. During study received oral contraceptive and tramadol. On Day 179 reported palpitations that lasted until Day 183. At Month 6 and 9 visits, BP was 157/103 and 158/91, respectively. On Day 327 experienced cardiac pain during cycling, diagnosed as angina pectoris. One month later saw a cardiologist, ECG and angiography were normal. No action taken with study drug. Event was resolved by Day 450 (Month 15 visit) without specific treatment. The patient withdrew consent because of HTN.
FTY 0.5 mg 2302 0514 00001	43 F			Non serious angina pectoris on day 1. Hx of ADHD, depression, GERD, restless legs syndrome, treated with multiple medications. No diabetes or HTN. At screening mild abnormality on valves on echocardiogram. At randomization visit, Day 1, Holter revealed 4 beat episode of non-sustained VT and 13 VPCs approximately 3.5 hours after start of monitoring. ECG showed first degree upon first dose. Events resolved the same day. On Day 8 pt experienced mild chest discomfort. ECG showed bradycardia. No action taken with drug. Cardiac workup included normal cardiac enzymes and normal continuous cardiac monitoring. A week later a stress echo was within normal. On Day 98, echo showed mild abnormalities on valves, similar to screening echo. No action taken with drug. Pt completed core phase and

Interim review, 5 12 10.
 Lourdes Villalba, M.D
 NDA 22-527. Fingolimod

		-	-	entered the extension.
FTY 0.5 mg 2302 0535 00002	39 M	-	-	ECG ST segment elevation on day 1, with bradycardia and dizziness. Treated with aspirin and lisinopril. No cardiac workup available.
FTY 0.5 mg 2301 0651 00005	34 F	S	-	Angina pectoris (day 573, 2 days after dc)
FTY 0.5 mg 2301 0454 00002	44 F	S	dc	Dyspnea, chest pain day 449. Recurrent chest pain/pressure radiated to jaw (led to dc) Echo posterior wall hypokinesia.

Source: AE datasets. S= serious. Dc= led to discontinuation

Appendix 9.1.15. Brief narratives of cases of seizure in the fingolimod controlled studies

ID	AGE SEX	PT_TXT	DAY	Ser	DC	
FTY 5 mg						
2201_0062_00010	21 M	Epilepsy	112	N	.	
FTY 1.25 mg						
2301_0104_00007	31 M	Epilepsy	430	N	.	Ms dx 14 years prior. Hx of epilepsy for 18 years, treated with lamotrigine. During the study also received carbamazepine for trigeminal neuralgia. No action taken with study drug.
2301_0304_00005	28 F	Epilepsy	62 77	N N	. .	Ms dx 1 ½ years prior. Medical history included epilepsy diagnosed 8 years prior to entry, treated with lamotrigine. No action taken with study drug.
2301_0657_00019	34 F	Epilepsy Epilepsy Epilepsy	45 176 177	Y Y Y	. dc dc	MS dx 10 year prior. No hx of seizures. Most recent relapse 2 months prior to entry, treated with steroids. On day 45 had decreased consciousness and motor abnormalities c/w seizure. EEG showed varying epileptic activity. NO MRI or CT scan done during hospitalization. On Day 176 she had 2 epileptic attacks and developed a fever treated with paracetamol. She was treated with IV methylprednisolone x3 and drug was discontinued. MRI showed active MS lesions. Investigator stated that epileptic attack could be drug related but was probably 2 nd to active MS. No additional work up provided for this patient.
2301_0707_00007	43 F	Grand mal convulsion Epilepsy Epilepsy Epilepsy	678 789 789 789	Y N N Y	MS dx 8 years prior to entry. No hx of epilepsy. Most recent relapse was 3 months prior to randomiz, treated with steroids. Hx of optic neuritis and HTN. On Day 678 had grand mal Sz with nystagmus, ataxia and left sided hemiparesis. EEG showed “sharp waves of general nature, mostly in posterior regions bilaterally.” She was found to have leukocytes & bacteria in urine, and she was treated for UTI. On Day 760 during extension phase she had 3 grand mal seizures. A CT scan showed cortical-subcortical brain and cerebellum atrophy and lesions with symmetric dilatation of the ventricular system and extracerebral fluid space. Also regions of reduced density around lateral ventricles associated with “chronic ischaemic processes” She was started on valproic acid. Final diagnosis was epilepsy and MS. The investigator stated that the reason for the seizure was not known and that there was <u>no evidence to suggest an MS relapse.</u>
2302_0253_00003	34 M	Grand mal convulsion Status epilepticus	33 358	N Y	. .	MS dx 13 years prior. Last relapse prior to random. Was 7months prior, treated with steroids. Patient also received IFN beta 1a in the past. No history of seizures. No concomitant meds. He had two relapses during the study, the second one on Day 118 was associated with generalized tonic clonic seizure and was treated with steroids and carbamazepine. On Day 369 he was hospitalized with status epilepticus. MRI was not done. The cause of status was thought to be non-compliance with his antiepileptic medication. The patient remains in the study.

Interim review, 5 12 10.
 Lourdes Villalba, M.D
 NDA 22-527. Fingolimod

2302_0821_00007	23 M	Grand mal convulsion Epilepsy Epilepsy	339 311 312	Y N N	dc . .	No history of seizures. Patient had fatal herpes simplex encephalitis. Case describe in more detail under deaths.
FTY 0.5 mg						
2301_0108_00002	42 F	Petit mal epilepsy	723	N	.	Ms dx 9 years prior. Last relapse prior to random was 4 months prior to random. Hx of temporal lobe epilepsy not ongoing at the time of study entry. On Day 723 experienced episodes of absence epilepsy. No action taken with study drug.
2301_0453_00003	19 M	Partial Sz Partial Sz Partial Sz w 2 nd .generaliz.	483 496 308	N N Y	. . .	No history of seizures. Had 1 relapse in 2 yrs prior and one relapse in the year prior to randomization. Most recent relapse was 6 mo. prior to randomization. Treated with IFN and glatiramer up to 6 mo. prior to random. Hx of optic neuritis. Smoker. On Day 308 of FTY 0.5 mg he had partial seizure with secondary generalization. CT scan showed subarachnoidal bleeding thought to be due to head trauma during seizure. He recovered from the event. On Day 365 MRI showed an active MS lesion very close to the cortex. It was suggested that this lesion could be the cause of the seizure. This was considered an MS relapse and was treated with Methylprednisolone. The event did not lead to drug dc. The clinical course was favorable with recurrent partial seizures but no new neurological symptoms.

Source: AE datasets and patient profiles

9.2 Labeling Recommendations

Pending

9.3 Advisory Committee Meeting

To be held on June 10, 2010.

9.4 Information from the transplant population

- Studies conducted in the transplant population.

For completeness of this safety review, I am including relevant information from studies in the transplant population. We need to keep in mind that the renal transplant population is a sicker population than the MS population, includes post-surgical patients with end stage renal disease, with multiple co-morbidities and concomitant medications (cyclosporine A and corticosteroids) with their own set of complications. Interpretation of safety in these trials is complex. More importantly, the doses of fingolimod used in this program (5 and 2.5 mg/day) were higher than in the MS program (1.25 and 0.5 mg/day), therefore one can not extrapolate these findings to the MS population. Still, some patterns of toxicity may be of help in trying to identify potential safety issues in the MS population. In fact, the transplant studies preceded the MS studies and led

Interim review, 5 12 10.
 Lourdes Villalba, M.D
 NDA 22-527. Fingolimod

to discontinuation of development in the transplant population, to the use of lower doses in the MS population and to the identification of AE that needed to be monitored in MS studies.

Studies contributing to safety in the renal transplant population are presented in the following table.

Table 94. Phase 2 & 3 studies of fingolimod in the transplant population

Study No.	Study design	Patients randomized	Treatment Duration	Study medication maintenance dose/day
Key controlled trials:				
0124	Phase III, randomized, partially-blinded efficacy/safety study in de novo adult renal Tx patients	682	1 year	*FTY720 5 mg + RDN + corticosteroids FTY720 2.5 mg + FDN + corticosteroids MMF 2 g + FDN + corticosteroids
†0124E1	Two-year, open-label extension to patients who completed one year study 0124	374	†2 years	*FTY720 5 mg + RDN + corticosteroids FTY720 2.5 mg + FDN + corticosteroids MMF 2 g + FDN + corticosteroids
†0125	Phase III, randomized, partially-blinded efficacy/safety study in de novo adult renal Tx patients	696	†1 year	*FTY720 5 mg + RDN + corticosteroids FTY720 2.5 mg + FDN + corticosteroids MMF 2 g + FDN + corticosteroids
†0125E1	Two-year, open-label extension to patients who completed one year study 0125	373	†2 years	*FTY720 5 mg + RDN + corticosteroids FTY720 2.5 mg + FDN + corticosteroids MMF 2 g + FDN + corticosteroids
Other controlled trials				
B201	Phase IIa, randomized, open-label dose-finding safety, tolerability, and efficacy study in de novo renal transplant recipients	208	12 weeks (+12 weeks FU)	FTY720 0.25 mg FTY720 0.5 mg FTY720 1.0 mg FTY720 2.5 mg MMF 2 g (all groups + FDN + corticosteroids)
A121	Phase II, randomized, partially-blinded efficacy/safety study in de novo adult renal Tx patients	270 (269~)	1 year	*FTY720 5 mg + RDN + corticosteroids *FTY720 2.5 mg + RDN + corticosteroids FTY720 2.5 mg + FDN + corticosteroids MMF 2-3 g + FDN + corticosteroids
A121E1	Two-year, partially-blinded, extension to patients who completed one year study A121	116	2 year	*FTY720 2.5 mg + RDN + corticosteroids *FTY720 5 mg + RDN + corticosteroids FTY720 2.5 mg + FDN + corticosteroids MMF 2-3 g + FDN + corticosteroids
†A121E2	Two-year, open-label second extension to patients who completed one year study A121 and two year A121E1	59	†2 year	*FTY720 5 mg + RDN + corticosteroids FTY720 2.5 mg + FDN + corticosteroids MMF 2 g + FDN + corticosteroids

Interim review, 5 12 10.
 Lourdes Villalba, M.D
 NDA 22-527. Fingolimod

[†] A121E2	Two-year, open-label second extension to patients who completed one year study A121 and two year A121E1	59	[†] 2 year	[‡] FTY720 5 mg + RDN + corticosteroids FTY720 2.5 mg + FDN + corticosteroids MMF 2 g + FDN + corticosteroids
A2216	24 hr Holter monitoring and observational ECG study in stable adult renal transplant patients maintained on Neoral [®] or MMF	308 [‡]	2 day	Maintenance treatment: Neoral + MMF with or without corticosteroids
[†] A2218	Phase IIb, randomized, double-blind, double-dummy, efficacy/safety study in de novo adult renal Tx patients (including Japanese patients)	271	[†] 1 year	FTY720 5 mg + FDN + corticosteroids FTY720 2.5 mg + FDN + corticosteroids MMF 2 g + FDN + corticosteroids
[†] A2218E1	Two-year, extension to patients who completed one year study A2218	121	[†] 2 year	FTY720 5 mg + FDN + corticosteroids FTY720 2.5 mg + FDN + corticosteroids MMF 2 g + FDN + corticosteroids
[†] A2302	Phase III, randomized, open-label safety/efficacy study in combination with tacrolimus in de novo adult renal Tx patients	103	[†] 1 year	FTY720 2.5 mg + tacrolimus + corticosteroids MMF 2 g + tacrolimus + corticosteroids
[†] A2302E1	Two-year, open-label extension to patients who completed one year study A2302	4	[†] 2 year	FTY720 2.5 mg + tacrolimus + corticosteroids MMF 2 g + tacrolimus + corticosteroids
Other non-controlled trials				
A2202	Phase II, open-label safety/tolerability and efficacy study in de novo adult renal Tx patients at increased risk of DGF	56 (53*)	1 year	FTY720 2.5 mg + RAD 2 mg bid + corticosteroids
A2202E1	Two-year, open-label extension to patients who completed one year study A2202	27**	2 year***	FTY720 2.5 mg + RAD 2 mg bid + corticosteroids
[†] A2307	Phase III, randomized, open-label safety/efficacy study in combination with antibody induction in de novo adult renal Tx patients	9	[†] 1 year	FTY720 5 mg + RDN + corticosteroids FTY720 2.5 mg + FDN + corticosteroid (in both groups + antibody induction)

Table 96. cont.

treatment arm was discontinued by protocol amendment & patients switched to center-specific standard care

[†]Study medication terminated by protocol amendment and patients switched to center-specific standard care. For Study 0125 at time of implementation only 2 MMF patients had not reached 12 months on study and were discontinued.

*Study A2202 was single-arm (non-randomized study) 56 patients were enrolled and treated but only 53 patients were transplanted and included in the safety analyzable population for the CSR.

~ Study 121 enrolled 270 patients who all took study drug but only 269 were randomized.

** Study A2202E1 was a single-arm (non-randomized study) 27 patients were included in the extension safety population

***Two year Study 2202E1 was stopped after 12 months.

[‡]Study A2216 was a non randomized study Data from A2216 (308 MMF patients) was combined with data from A121E1 (94 FTY720 patients and 19 MMF patients). Study A2216 was not included in the pooled populations.

Source: Table 2-1 of Transplant ISS

- Populations pooled for safety analyses in the transplant population.

- **The Key Safety population** included data from the two large, pivotal, Phase III

transplantation trials 0124 and 0125, combined with their respective study extensions (0124E1 and 0125E1).

- **The Overall Safety population** pooled safety data from the 8 completed transplantation trials including 0124, 0125, A121, A2202, A2218, A2302, A2307 and B201 with core and extension phases combined.
- **The Ophthalmic population** included patients from all trials in which ophthalmic data were collected, including Studies 0124, 0125, A121, A2218, A2302, and A2307, with core and extension phases combined. All patients enrolled in these trials and who received study medication were included.

- Exposure in Transplant population

Approximately 1600 subjects were exposed to fingolimod in renal transplant studies. Approximately 1000 subjects were exposed to doses of 5 mg and 2.5 mg daily for at least 6 months and 670 were exposed for at least a year, in the Key safety transplant population (controlled studies, up to 2 years); and approximately half that number was exposed to MMF. FTY and MMF were added to background Cyclosporin A and corticosteroids. Less than 10% of patients in any treatment group experienced 24 months or more cumulative exposure (source: table submitted on 12 2 09 at the FDA request).

Table 95. Key safety population (controlled data). Cumulative duration of exposure

	FTY720 5 mg (N=461) n (%)	FTY720 2.5 mg (N=456) n (%)	MMF (N=461) n (%)
Duration of exposure*	PYRs= 357.8	PYRs= 447.5	PYRs= 500.3
≥ 1 week	431 (93.5)	422 (92.5)	431 (93.5)
≥ 1 month	389 (84.4)	388 (85.1)	402 (87.2)
≥ 6 months	279 (60.5)	310 (68.0)	337 (73.1)
≥ 12 months	168 (36.4)	260 (57.0)	289 (62.7)
≥ 18 months	75 (16.3)	140 (30.7)	166 (36.0)
≥ 24 months	17 (3.7)	26 (5.7)	45 (9.8)
≥ 30 months	0	0	0
≥ 36 months	0	0	0

*any exposure (at least 1 dose)

Note: A patient is counted in the maximum category of duration which fits and in each lower category

Source: response to FDA request for information , December 2009.

Overall Renal transplant Safety Population. Cumulative duration of exposure

Duration of exposure*	FTY720 (N=1606) n (%)	MMF (N=689) n (%)
≥ 1 week	1506 (93.8)	652 (94.6)
≥ 1 month	1386 (86.3)	607 (88.1)
≥ 6 months	962 (59.9)	484 (70.2)
≥ 12 months	670 (41.7)	386 (56.0)
≥ 18 months	324 (20.2)	194 (28.2)
≥ 24 months	113 (7.0)	63 (9.1)
≥ 30 months	56 (3.5)	16 (2.3)
≥ 36 months	51 (3.2)	16 (2.3)

*any exposure (at least 1 dose)

Note: A patient is counted in the maximum category of duration which fits and in each lower category

Source: response to FDA request for information. December 2009.

- Adverse Events in the renal transplant population

Adverse events summaries are based on treatment emergent adverse events (events started or worsened on or after the first date of study medication or within 7 days after the last study medication). The adverse events tables that were based on all events, not only treatment emergent, are summaries of malignant neoplasm, deaths, and the incidence of macular edema.

- Deaths in the transplant program

Deaths in the Key Safety Population

Deaths as the primary cause of discontinuation was reported in 3.5% of patients in the key safety population (3.5% in each treatment group: fingolimod 5mg, fingolimod 2.5 mg and MMF). The most commonly reported causes of death in the key safety population were infections and infestations, in all treatment groups. Deaths in the cardiac SOC occurred in 7 patients in the FTY720 5 mg (4 MI and 3 cardiac arrest). For most of these patients, the cardiac event leading to death was part of a wider pattern of symptoms, and all the patients had pre-existing cardiac risk factors. Additionally, two patients in the fingolimod 2.5 mg/day were found dead at home and are categorized as death or unknown reason, however, they should probably be categorized as sudden death. There were no cardiac deaths in the MMF group. There were no GI deaths in the fingolimod group. Otherwise, incidence of death by SOC is similar to those on MMF.

Table 96. Deaths in the renal transplant Key safety population

	FTY720 5 mg (N=461)	FTY720 2.5 mg (N=456)	MMF (N=461)
No. (%) who died	16 (3.5)	16 (3.5)#	15 (3.5)#
System organ class Preferred term	n (%)	n (%)	n (%)
Cardiac disorders	7 (1.5)	0	0
Cardiac arrest	3 (0.7)	0	0
Myocardial infarction	4 (0.9)	0	0
Gastrointestinal disorders	0	0	3 (0.7)
Intra-abdominal haemorrhage	0	0	1 (0.2)
Pancreatitis	0	0	1 (0.2)
Pancreatitis acute	0	0	1 (0.2)
General disorders and administration site conditions	2 (0.4)	4 (0.9)	1 (0.2)
Multi-organ failure	1 (0.2)	0	1 (0.2)
Catheter related complication	0	1 (0.2)	0
Death [unspecified]*	0	3 (0.7)	0
Sudden death	1 (0.2)	0	0
Infections and infestations	4 (0.9)	7 (1.5)	6 (1.3)
Septic shock	1 (0.2)	1 (0.2)	2 (0.4)
Brain abscess	0	0	1 (0.2)
Dengue fever	0	0	1 (0.2)
Sepsis	1 (0.2)	3 (0.7)	1 (0.2)
Urosepsis	0	0	1 (0.2)
Bronchopneumonia	1 (0.2)	0	0
Infection	1 (0.2)	1 (0.2)	0
Pneumonia cytomegaloviral	0	2 (0.4)	0
Injury, poisoning and procedural complications	0	1 (0.2)	0
Procedural complication	0	1 (0.2)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.4)	1 (0.2)	1 (0.2)
Central nervous system lymphoma	0	0	1 (0.2)
Lung neoplasm	1 (0.2)	0	0
Myelodysplastic syndrome	0	1 (0.2)	0
Neoplasm malignant	1 (0.2)	0	0
Nervous system disorders	1 (0.2)	1 (0.2)	2 (0.4)
Anoxic encephalopathy	0	0	1 (0.2)
Cerebral haemorrhage	1 (0.2)	0	1 (0.2)
Cerebral ischaemia	0	1 (0.2)	0
Respiratory, thoracic and mediastinal disorders	0	1 (0.2)	1 (0.2)
Respiratory failure	0	0	1 (0.2)
Acute pulmonary oedema	0	1 (0.2)	0
Unspecified deaths during follow-up#	0	1 (0.2)	1 (0.2)

- one patient died following a traumatic fall and 2 deaths occurred at home of unknown cause.

Sixteen (3.5%) FTY720 5 mg, 15 (3.3%) FTY720 2.5 mg and 14 (3.0%) MMF patients died as reported on the CRF study completion form. A further 1 patient each in the FTY720 2.5 mg and MMF groups were reported to have died during follow-up of unknown cause: FTY720 2.5 mg patient [124/0086/00017] died on Day 239 having discontinued study medication on Day 0 and

MMF patient [124/0052/00010] died on Day 311 having discontinued study medication on Day 14. Source: Table 4-8 of Transplant ISS.

- Deaths in Overall Transplant Population

Deaths in the overall transplant safety population occurred in 0.6% of fingolimod patients and 0.4% of MMF patients. As for AEs, cause of deaths were pooled according to groupings of studies which used the same version of the MedDRA dictionary. Deaths in two of these subpopulations are summarized here (data not shown).

- The analysis of death from studies 0124, 0125, A2218, A2302 and A2307 and their respective extension periods shows that the most common cause of death in this study was infections and infestations (1% of fingolimod, 1.3% of MMF patients) followed by cardiac disorders (0.7% of fingolimod and 0.2% of MMF patients). Fatal infections and infestations in the fingolimod group included 2 cases of septic shock, 4 of sepsis, one bronchopneumonia and 2 cytomegaloviral pneumonia.
 - The analysis of deaths in study A121 and extension also showed infections and infestations (one bacterial sepsis, one lung infection and one mycotic spsis), one cardiac arrest, one respiratory arrest and one cardiogenic shock). No such cases occurred with MMF.
- Serious AES in the transplant Key Safety population

Serious AE in the transplant Key Safety population are presented in the following table.

Table 97. SAE in the Renal transplant Key Safety population by SOC

	FTY720 5 mg (N=461)	FTY720 2.5 mg (N=456)	MMF (N=461)
No. (%) with SAE(s)	278 (60.3)	273 (59.9)	249 (54.0)
No. (%) with SAEs leading to discontinuation	123 (26.7)	101 (22.1)	75 (16.3)
System organ class	n (%)	n (%)	n (%)
Blood and lymphatic system disorders	19 (4.1)	16 (3.5)	21 (4.6)
Cardiac disorders	36 (7.8)	25 (5.5)	18 (3.9)
Congenital, familial and genetic disorders	1 (0.2)	0	0
Ear and labyrinth disorders	1 (0.2)	2 (0.4)	2 (0.4)
Endocrine disorders	0	0	2 (0.4)
Eye disorders	23 (5.0)	22 (4.8)	8 (1.7)
Gastrointestinal disorders	30 (6.5)	28 (6.1)	43 (9.3)
General disorders and administration site conditions	25 (5.4)	29 (6.4)	21 (4.6)
Hepatobiliary disorders	5 (1.1)	3 (0.7)	5 (1.1)
Immune system disorders	36 (7.8)	21 (4.6)	16 (3.5)
Infections and infestations	71 (15.4)	80 (17.5)	116 (25.2)
Injury, poisoning and procedural complications	63 (13.7)	63 (13.8)	67 (14.5)
Investigations	40 (8.7)	47 (10.3)	27 (5.9)
Metabolism and nutrition disorders	27 (5.9)	26 (5.7)	20 (4.3)
Musculoskeletal and connective tissue disorders	7 (1.5)	4 (0.9)	9 (2.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9 (2.0)	11 (2.4)	10 (2.2)
Nervous system disorders	20 (4.3)	22 (4.8)	10 (2.2)
Pregnancy, puerperium and perinatal conditions	0	1 (0.2)	0
Psychiatric disorders	3 (0.7)	5 (1.1)	5 (1.1)
Renal and urinary disorders	72 (15.6)	72 (15.8)	60 (13.0)
Reproductive system and breast disorders	3 (0.7)	8 (1.8)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	28 (6.1)	34 (7.5)	10 (2.2)
Skin and subcutaneous tissue disorders	3 (0.7)	6 (1.3)	2 (0.4)
Social circumstances	0	1 (0.2)	0
Surgical and medical procedures	0	2 (0.4)	3 (0.7)
Vascular disorders	34 (7.4)	56 (12.3)	26 (5.6)

Note deaths specifically reported as SAEs i.e. preferred terms "death" or "sudden death" are not included.

Source: Table 4-14, Transplant ISS (SN 002)

Selected Serious AEs in the transplant Key Safety population are presented in the following tables (from Post-Text Table 4.4-2 of ISS):

Blood and lymphatic system disorders, renal transplant Key safety population

Body System	Preferred term	FTY 5mg (N=461) n (%)	FTY 2.5mg (N=456) n (%)	MMF (N=461) n (%)
-ANY BODY SYSTEM	-TOTAL	278 (60.3)	273 (59.9)	249 (54.0)
-Patient disc. drug due to SAE(s)		123 (26.7)	101 (22.1)	75 (16.3)
Blood and lymphatic system disorders	-TOTAL	19 (4.1)	16 (3.5)	21 (4.6)
	Leukopenia	8 (1.7)	3 (0.7)	8 (1.7)
	Anaemia	2 (0.4)	2 (0.4)	7 (1.5)
	Agranulocytosis	0	0	2 (0.4)
	Thrombocytopenia	2 (0.4)	2 (0.4)	2 (0.4)
	Coagulopathy	0	0	1 (0.2)
	Microangiopathic haemolytic anaemia	0	0	1 (0.2)
	Neutropenia	3 (0.7)	1 (0.2)	1 (0.2)
	Fancytopenia	0	0	1 (0.2)
	Polycythaemia	0	0	1 (0.2)
	Anaemia haemolytic autoimmune	1 (0.2)	1 (0.2)	0
	Haemolysis	1 (0.2)	1 (0.2)	0
	Haemolytic anaemia	0	3 (0.7)	0
	Haemolytic uraemic syndrome	4 (0.9)	2 (0.4)	0
Blood and lymphatic system disorders	Haemorrhagic anaemia	1 (0.2)	0	0
	Lymphopenia	0	1 (0.2)	0
	Splenomegaly	1 (0.2)	0	0
	Thrombotic microangiopathy	1 (0.2)	2 (0.4)	0

This table indicates that in addition to the expected leukopenia, there are other AEs such as thrombocytopenia and 6 cases of hemolytic uremic syndrome. These AEs are of interest, however, the relevance of this information at doses of 5 and 2.5 mg is unclear to the MS population (for which the only proposed dose for marketing is 0.5 mg). This comment applies to all tables shown below as well.

SAEs in Cardiac disorders SOC, renal transplant Key safety population.

Cardiac disorders	-TOTAL	36 (7.8)	25 (5.5)	18 (3.9)
	Myocardial infarction	10 (2.2)	1 (0.2)	5 (1.1)
	Angina pectoris	1 (0.2)	2 (0.4)	2 (0.4)
	Cardiac arrest	3 (0.7)	2 (0.4)	2 (0.4)
	Cardiac failure	2 (0.4)	1 (0.2)	2 (0.4)
	Cardiac failure acute	0	0	1 (0.2)
	Cardiac failure congestive	5 (1.1)	4 (0.9)	1 (0.2)
	Cardio-respiratory arrest	0	0	1 (0.2)
	Coronary artery insufficiency	0	0	1 (0.2)
	Coronary artery occlusion	0	0	1 (0.2)
	Myocarditis	0	0	1 (0.2)
	Pericarditis	2 (0.4)	1 (0.2)	1 (0.2)
	Sinus bradycardia	1 (0.2)	0	1 (0.2)

Cardiac disorders	Supraventricular tachycardia	1 (0.2)	1 (0.2)	1 (0.2)
	Tachyarrhythmia	0	0	1 (0.2)
	Ventricular hypertrophy	0	0	1 (0.2)
	Ventricular tachycardia	0	0	1 (0.2)
	Acute coronary syndrome	1 (0.2)	0	0
	Acute myocardial infarction	0	1 (0.2)	0
	Angina unstable	1 (0.2)	0	0
	Atrial fibrillation	2 (0.4)	3 (0.7)	0
	Bradycardia	7 (1.5)	9 (2.0)	0
	Brugada syndrome	0	1 (0.2)	0
	Cardiac aneurysm	0	1 (0.2)	0
	Coronary artery disease	2 (0.4)	0	0
	Coronary artery stenosis	0	1 (0.2)	0
	Coronary artery thrombosis	1 (0.2)	0	0
	Hypertensive heart disease	1 (0.2)	1 (0.2)	0
	Mitral valve incompetence	0	1 (0.2)	0
	Myocardial ischaemia	2 (0.4)	0	0
	Pericardial effusion	0	1 (0.2)	0
	Ventricular fibrillation	0	1 (0.2)	0

There is a signal for myocardial infarction for the fingolimod 5mg dose and for bradycardia for both 2.5 and 5 mg doses as compared to MMF. Of note, ECG and Holter monitoring were extensively conducted in the MS population. The DNP also requested that echocardiogram be conducted in a subset of patients.

SAE in Eye disorders SOC, renal transplant Key safety population

Eye disorders	-TOTAL	23 (5.0)	22 (4.8)	8 (1.7)
	Macular oedema	19 (4.1)	18 (3.9)	7 (1.5)
	Diabetic retinal oedema	1 (0.2)	1 (0.2)	1 (0.2)
	Blindness unilateral	0	1 (0.2)	0
	Glaucoma	0	1 (0.2)	0
	Maculopathy	1 (0.2)	0	0
	Retinal haemorrhage	0	1 (0.2)	0
	Retinal oedema	1 (0.2)	2 (0.4)	0
Eye disorders	Retinal telangiectasia	1 (0.2)	0	0
	Visual acuity reduced	0	2 (0.4)	0

There is a signal for increased macular edema for both doses of fingolimod 5mg and 2.5 mg as compared to MMF. Extensive ophthalmologic evaluations were conducted in the MS program.

Immune system disorders, renal transplant Key safety population)

Immune system disorders	-TOTAL	36 (7.8)	21 (4.6)	16 (3.5)
	Transplant rejection	31 (6.7)	18 (3.9)	14 (3.0)
	Kidney transplant rejection	4 (0.9)	2 (0.4)	2 (0.4)
	Anaphylactic reaction	1 (0.2)	1 (0.2)	0
	Serum sickness	1 (0.2)	0	0

There were a total of two cases of anaphylactic reactions and one serum sickness in the transplant key safety population in the fingolimod group and no such cases in the MMF group.

An increased risk of infections and infestations is expected with agents that cause immuno-suppression. In fact, 15.4% of fingolimod 5 mg treated patients and 17.5% of fingolimod 2.5mg treated patients had serious infections or infestations. Of note, 25% of those treated with MMF also had serious infections and infestations (data not shown).

In the Investigations SOC, the risk of SAEs was 8.7%, 10.3% and 5.9% in the fingolimod 5, fingolimod 2.5 and MMF groups, respectively, mostly related to blood creatinine increased in 7.4%, 8.6% and 3.9% of patients in the fingolimod 5, fingolimod 2.5 and MMF, respectively. (data not shown).

In the Neoplasms SOC, the overall risk of SAEs was similarly distributed among treatment groups (0.9%, 0.9 % and 0.7% for fingolimod 5, 2.5 and MMF, respectively). Of interest, there was one case of B-cell lymphoma, one T-cell lymphoma and one lymphoproliferative disorder among 456 patients in the fingolimod 2.5 mg. No such cases were observed in the fingolimod 5 mg or MMF groups, but there was a case of CNS lymphoma in the MMF group (data not shown). Fingolimod is supposed to inhibit peripheral circulation and it is not supposed to affect lymphocyte proliferation. These disorders were not observed in the higher fingolimod dose group. It is unclear if these events are related to fingolimod.

Regarding the Nervous system disorders SOC, overall, there were more SAEs in the fingolimod groups (4.3% and 4.8%, for the 5 and 2.5 mg doses, respectively) as compared to the MMF group (2.2%). A summary of these events is presented in the following table.

Serious AEs in the Nervous system disorders SOC. Renal transplant Key safety population.

Body System	Preferred term	FTY 5mg (N=461) n (%)	FTY 2.5mg (N=456) n (%)	MMF (N=461) n (%)
Nervous system disorders	-TOTAL	20 (4.3)	22 (4.8)	10 (2.2)
	Headache	1 (0.2)	3 (0.7)	2 (0.4)
	Cerebral haemorrhage	1 (0.2)	0	1 (0.2)
	Cerebrovascular accident	2 (0.4)	3 (0.7)	1 (0.2)
	Convulsion	5 (1.1)	6 (1.3)	1 (0.2)
	Dizziness	0	2 (0.4)	1 (0.2)
	Drop attacks	0	0	1 (0.2)
	Femoral nerve lesion	0	0	1 (0.2)
	Hypotonia	0	0	1 (0.2)
	Neurological symptom	0	0	1 (0.2)
	Transient ischaemic attack	1 (0.2)	0	1 (0.2)
	Benign intracranial hypertension	1 (0.2)	0	0
	Cerebral haematoma	0	1 (0.2)	0
	Cerebral ischaemia	2 (0.4)	0	0
	Cerebrovascular spasm	0	1 (0.2)	0
	Cognitive disorder	0	1 (0.2)	0
	Depressed level of consciousness	0	1 (0.2)	0
	Diabetic coma	1 (0.2)	0	0
	Dysarthria	0	2 (0.4)	0
	Encephalitis	2 (0.4)	0	0
Nervous system disorders	Encephalopathy	0	2 (0.4)	0
	Grand mal convulsion	2 (0.4)	0	0
	Haemorrhage intracranial	1 (0.2)	0	0
	Hypertensive encephalopathy	3 (0.7)	1 (0.2)	0
	Ischaemic cerebral infarction	0	1 (0.2)	0
	Locked-in syndrome	1 (0.2)	0	0
	Migraine	1 (0.2)	0	0
	Nervous system disorder	0	1 (0.2)	0
	Neurotoxicity	1 (0.2)	1 (0.2)	0
	Partial seizures	0	1 (0.2)	0
	Somnolence	1 (0.2)	0	0
	Subarachnoid haemorrhage	0	1 (0.2)	0
	Syncope	3 (0.7)	1 (0.2)	0
	Tremor	1 (0.2)	0	0

Source, Post-text Table 4.4-2, Transplant ISS.

Of note, SAEs of convulsions were reported by 5 (1.1%) and 6 (1.3%) of patients in the fingolimod 5mg and 2.5mg groups, as compared to 1 (0.2%) of the MMF group; grand mal convulsion was reported in 2 (0.4%) of the fingolimod 5mg and partial seizures in 1 (0.2%) of the fingolimod 2.5mg group. Additionally, one patient had a “locked-in syndrome” (I suspect it could have been post-ictal) and 2 (0.4%) reported encephalitis in the fingolimod 5mg group.

These events are of concern. It is unclear what the total number of events is. Additional information will be requested from these patients. This finding suggests that fingolimod, at the doses of 5 and 2.5 mg/day may be associated with seizures.

With regard to the Renal and Urinary disorders SOC, the risk of SAEs was slightly higher in the fingolimod groups (15.6% and 15.8% in the fingolimod 5 and 2.5 mg, respectively), as compared to the MMF treated group (13%). The difference seems to be driven by events of hydronephrosis and renal impairment, renal tubular necrosis, renal vein thrombosis and proteinuria in the fingolimod groups. Renal adverse events are very difficult to assess in the setting of failing transplanted kidneys. I have not conducted a full review of these cases.

In the Respiratory, thoracic and mediastinal disorders, the risk of SAEs was higher in the fingolimod groups. See table below.

SAEs in the Respiratory, thoracic and mediastinal disorders SOC. Renal transplant Key safety population.

Body System	Preferred term	FTY 5mg (N=461) n (%)	FTY 2.5mg (N=456) n (%)	MMF (N=461) n (%)
Respiratory, thoracic and mediastinal disorders	-TOTAL	28 (6.1)	34 (7.5)	10 (2.2)
	Cough	1 (0.2)	0	2 (0.4)
	Dyspnoea	6 (1.3)	6 (1.3)	2 (0.4)
	Non-cardiogenic pulmonary oedema	0	0	2 (0.4)
	Pharyngolaryngeal pain	2 (0.4)	0	2 (0.4)
	Respiratory failure	2 (0.4)	1 (0.2)	2 (0.4)
	Interstitial lung disease	2 (0.4)	2 (0.4)	1 (0.2)
	Pleuritic pain	0	0	1 (0.2)
	Respiratory distress	0	0	1 (0.2)
	Acute pulmonary oedema	1 (0.2)	3 (0.7)	0
	Acute respiratory distress syndrome	1 (0.2)	0	0
	Acute respiratory failure	1 (0.2)	0	0
	Alveolitis	1 (0.2)	0	0
	Asthma	0	4 (0.9)	0
	Atelectasis	1 (0.2)	1 (0.2)	0
	Bronchopneumopathy	0	2 (0.4)	0
	Bronchospasm	1 (0.2)	0	0
	Chronic obstructive pulmonary disease	1 (0.2)	0	0
	Dysphonia	0	1 (0.2)	0
Respiratory, thoracic and mediastinal disorders	Epistaxis	1 (0.2)	0	0
	Haemoptysis	0	1 (0.2)	0
	Hypoxia	1 (0.2)	1 (0.2)	0
	Laryngeal granuloma	0	1 (0.2)	0
	Obstructive airways disorder	1 (0.2)	0	0
	Orthopnoea	0	1 (0.2)	0
	Pneumonitis	0	1 (0.2)	0
	Pulmonary congestion	0	1 (0.2)	0
	Pulmonary embolism	2 (0.4)	1 (0.2)	0
	Pulmonary oedema	6 (1.3)	10 (2.2)	0
	Sleep apnoea syndrome	1 (0.2)	1 (0.2)	0

Of note, the risk of SAEs in the Respiratory, thoracic and mediastinal disorders was higher in the fingolimod 5 and 2.5 mg groups (6.1% and 7.5%, respectively) as compared to MMF (2.2%). Dyspnea was reported by 6 (1.3%), 6 (1.3%) and 2 (0.4%) of patients in the fingolimod 5 mg, 2.5 mg and MMF groups, respectively. Pulmonary edema was reported by 6 (1.3%) and 10 (2.2%) of patients in the fingolimod 5 and 2.5 mg groups, as compared to 0 in the MMF group. Acute pulmonary edema was reported by 1 (0.2%), 4 (0.9%) and 0% in the fingolimod 5, 2.5 and MMF groups. Additionally acute respiratory failure, acute respiratory distress syndrome and alveolitis

(one case each) were reported in the fingolimod 5 mg group. It is possible that a single patient may have reported more than one of these events. Still, there is a clear signal of lung or may be cardiac toxicity for fingolimod in this database, at the 5 and 2.5 mg doses. This is consistent with the findings in non-clinical studies. Because of these findings, the sponsor conducted extensive lung assessments (including PFTs and HRCT) in the MS program. A small number of patients also underwent echocardiography.

Of note, S1P1 receptor modulators are expected to affect bronchoconstriction. In the key renal transplant database there is one case of bronchospasm in the fingolimod 5 mg group and 4 of asthma in the fingolimod 2.5 mg group, with no such cases in the MMF group.

With regards of the Vascular disorders SOC, the risk of SAEs was higher in the fingolimod groups (7.4% and 12.3% for the 5 and 2.5 mg doses, respectively) as compared to the MMF group (5.6%). The listing of SAEs in this SOC is presented as follows:

SAEs in the Vascular disorders SOC, renal transplant Key safety population.

Body System	Preferred term	FTY 5mg (N=461) n (%)	FTY 2.5mg (N=456) n (%)	MMF (N=461) n (%)
Vascular disorders	-TOTAL	34 (7.4)	56 (12.3)	26 (5.6)
	Lymphocele	9 (2.0)	17 (3.7)	11 (2.4)
	Deep vein thrombosis	2 (0.4)	3 (0.7)	4 (0.9)
	Hypertension	6 (1.3)	11 (2.4)	3 (0.7)
	Shock haemorrhagic	0	1 (0.2)	3 (0.7)
	Extremity necrosis	0	1 (0.2)	1 (0.2)
	Hypertensive crisis	2 (0.4)	3 (0.7)	1 (0.2)
	Hypotension	5 (1.1)	7 (1.5)	1 (0.2)
	Hypovolaemic shock	0	1 (0.2)	1 (0.2)
	Orthostatic hypotension	3 (0.7)	2 (0.4)	1 (0.2)
	Steal syndrome	0	0	1 (0.2)
	Arterial disorder	0	1 (0.2)	0
	Arterial occlusive disease	0	1 (0.2)	0
	Arterial thrombosis	2 (0.4)	0	0
	Blood pressure fluctuation	1 (0.2)	0	0
	Haematoma	1 (0.2)	0	0
	Hypertensive emergency	0	1 (0.2)	0
	Iliac artery stenosis	1 (0.2)	1 (0.2)	0
	Iliac artery thrombosis	0	1 (0.2)	0
	Intermittent claudication	0	1 (0.2)	0
Vascular disorders	Lymphoedema	0	1 (0.2)	0
	Lymphorrhoea	0	1 (0.2)	0
	Peripheral artery dissection	1 (0.2)	0	0
	Phlebitis	1 (0.2)	0	0
	Subclavian vein thrombosis	0	1 (0.2)	0
	Vascular pseudoaneurysm	1 (0.2)	0	0
	Venous stenosis	0	1 (0.2)	0
	Venous thrombosis	0	2 (0.4)	0
	Venous thrombosis limb	0	1 (0.2)	0

As seen in this table, SAEs related to changes in blood pressure were more common in the fingolimod groups. Hypertension was reported in 6 (1.3%), 11 (2.4%) and 3 (0.7%) of patients in the fingolimod 5, fingolimod 2.5 and the MMF groups, respectively. Hypotension was reported by 5 (1.1%), 7 (1.5%) and 1 (0.2%) of patients in the fingolimod 5, fingolimod 2.5 and MMF groups respectively. Overall, arterial ischemic and thrombotic events as well as venous thrombotic events appear to be somewhat more frequent in the fingolimod groups, but the number of individual events are small and some of them may have occurred in the same patient. No definitive conclusions can be drawn from this table of vascular events.

Laboratory evaluations

Larger mean increases for total cholesterol, triglycerides and sodium levels, a larger mean decrease for calcium, and lower mean decreases for magnesium and potassium occurred for the FTY720 5 mg group compared to the MMF group. However, mean values for sodium, potassium and calcium remained within normal range for all treatment arms at visits through Month 12 and Month 24. Some of the findings in the FTY720 5 mg group may be explained by the increased incidence of rejections in this treatment arm which were treated with steroids.

Table 5-7 Number (percent) of patients with at least one notable clinical chemistry abnormality – Key Safety Population

Variable (unit)	Notable criteria	FTY720 5 mg (N=461) n (%)	FTY720 2.5 mg (N=456) n (%)	MMF (N=461) n (%)
Alpha Amylase (Serum) (U/L)	High: $\geq 2 \times$ ULN	108 (23.4)	128 (28.1)	123 (26.7)
Lipase (Blood) (U/L)	High: $\geq 2 \times$ ULN	121 (26.2)	147 (32.2)	131 (28.4)
Cholesterol (total) (mmol/L)	High: ≥ 9.051	10 (2.2)	9 (2.0)	4 (0.9)
Triglycerides (mmol/L)	High: ≥ 8.5	3 (0.7)	5 (1.1)	5 (1.1)
Alkaline phosphatase, serum (U/L)	High: $\geq 3 \times$ ULN	14 (3.0)	13 (2.9)	7 (1.5)
Bilirubin (total) (umol/L)	High: ≥ 34.2	11 (2.4)	49 (10.7)	31 (6.7)
AST (SGOT) (U/L)	High: $\geq 3 \times$ ULN	22 (4.8)	26 (5.7)	19 (4.1)
ALT (SGPT) (U/L)	High: $\geq 3 \times$ ULN	88 (19.1)	95 (20.8)	70 (15.2)
Calcium (mmol/L)	Low: ≤ 1.5	5 (1.1)	10 (2.2)	5 (1.1)
	High: ≥ 3.2	4 (0.9)	3 (0.7)	2 (0.4)
Glucose (mmol/L)	Low: < 2.5	36 (7.8)	41 (9.0)	44 (9.5)
	High: > 13.9	53 (11.5)	57 (12.5)	51 (11.1)
Glycosylated hemoglobin (HbA1c) (%)	High: > 6.4	82 (17.8)	94 (20.6)	100 (21.7)
Magnesium (mmol/L)	Low: < 0.4	1 (0.2)	1 (0.2)	4 (0.9)
	High: > 1.5	6 (1.3)	11 (2.4)	9 (2.0)
Potassium (mmol/L)	Low: ≤ 3	22 (4.8)	20 (4.4)	23 (5.0)
	High: ≥ 6	121 (26.2)	136 (29.8)	125 (27.1)
Sodium (mmol/L)	Low: ≤ 130	70 (15.2)	71 (15.6)	63 (13.7)
	High: > 145	72 (15.6)	75 (16.4)	70 (15.2)
Creatinine (umol/L)	High: $> 30\%$ above value from preceding visit or Day 1 to Week 4 > 354 or After Week 4 > 265	394 (85.5)	379 (83.1)	381 (82.6)
Uric Acid (umol/L)	High: Male ≥ 714 or Female ≥ 535	103 (22.3)	120 (26.3)	74 (16.1)

Source: PT-Table 5.2-2a

Source: Renal transplant ISS. SN 002.

This analysis suggests a higher risk of markedly abnormal increase in cholesterol, ALT, and uric acid as compared to MMF.

In summary, review of tables of deaths and serious AEs in the renal transplant population indicates an increased risk of cardiac events (MI, cardiac arrest), eye toxicity (macular edema), respiratory events (pulmonary edema) (or is it cardiac failure?) and neurologic events (seizures) for the fingolimod at the doses of 5 and 2.5 mg/day as compared to MMF. Additionally there is a suggestion for increased renal toxicity, lymphoproliferative disease and allergic reactions in fingolimod-treated patients as compared to MMF.

In the renal transplant controlled key safety population there was an excess of cardiovascular death with FTY 5mg and increase risk of SAE in the cardiac, vascular, respiratory, neurologic and eye disorders SOC's with both FTY 5 and 2.5 mg as

compared to MMF. There was also higher risk of Investigations, blood creatinine increased AE as compared to MMF, but there was also a higher rate of transplant failure as compared to MMF. Again, it is hard to extrapolate these findings to other population and to lower fingolimod doses.

9.6 Sponsor's proposed REMS

The sponsor proposes to address three safety issues:

1. Bradycardia/bradyarrhythmia
2. Infections
3. Macular edema
4. Teratogenicity
5. Liver toxicity (added 5/11/10)

It proposes to have a MedGuide a Communication plan consisting on a Dear HCP letter and product Brochure, with no elements of safe use.

The applicant also proposes to conduct a 5,000 patient, 5-year postmarketing registry (PASS= post-authorization safety study to investigate the incidence of selected safety-related outcomes in patients with MS receiving fingolimod under conditions of routine clinical practice.

CLINICAL REVIEW

Application Type	NDA
Application Number	22-527
Priority or Standard	P

Submit Date	12-21-2009
Received Date	12-21-2009
PDUFA Goal Date	6-21-2010
Division / Office	FDA/ODE1

Reviewer Name	Heather D. Fitter
Review Completion Date	Draft: May 7, 2010

Established Name	Fingolimod
(Proposed) Trade Name	Gilenia
Therapeutic Class	S1P receptor modulator
Applicant	Novartis

Formulation(s)	Oral tablets
Dosing Regimen	0.5 mg
Indication(s)	To reduce the frequency of relapses and delay the progression of disability in relapsing MS

Intended Population(s)	Relapsing Multiple Sclerosis
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Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	6
1.1	Recommendation on Regulatory Action	6
1.2	Risk Benefit Assessment.....	7
2	INTRODUCTION AND REGULATORY BACKGROUND	7
2.1	Product Information	8
2.2	Table of Currently Available Treatments for the Proposed Indication.....	8
2.3	Availability of Proposed Active Ingredient in the United States	11
2.4	Important Safety Issues With Consideration to Related Drugs.....	11
2.5	Summary of Presubmission Regulatory Activity Related to Submission	11
3	ETHICS AND GOOD CLINICAL PRACTICES.....	14
3.1	Submission Quality and Integrity	14
3.2	Compliance with Good Clinical Practices	15
3.3	Financial Disclosures.....	15
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	16
4.1	CHEMISTRY MANUFACTURING AND CONTROLS	16
4.3	Preclinical Pharmacology/Toxicology	16
4.4	Clinical Pharmacology	18
4.4.1	Mechanism of Action.....	18
4.4.2	Pharmacodynamics.....	19
4.4.3	Pharmacokinetics.....	20
5	SOURCES OF CLINICAL DATA.....	22
5.1	Tables of Clinical Trials	22
5.2	Review Strategy	22
5.3	Discussion of Clinical Trials.....	23
5.3.1	Protocol CFTY720D2301	23
5.3.2	Protocol CFTY720D2302	37
5.3.3	Protocol CFY720D2201	47
5.3.4	Protocol FTY720D2201E1	48
5.3.5	Protocol FTY720D2309.....	48
6	REVIEW OF EFFICACY	49
6.0	Efficacy Summary.....	49
6.1	Indication	50
6.1.1	Method.....	50
6.1.2	Demographics.....	51
6.1.3	Subject Disposition.....	56

6.1.4	Analysis of Primary Endpoint	57
6.1.5	Analysis of Key Secondary Endpoints.....	60
6.1.5	Other Secondary Endpoints	68
6.1.7	Subpopulations	70
6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations	72
6.1.9	Discussion of Persistence of Efficacy and/or Withdrawal/Rebound Effects	77
8	POSTMARKET EXPERIENCE.....	78
9	APPENDICES	78
9.2	Labeling Recommendations	78
9.3	Advisory Committee Meeting.....	78

Table of Tables

Table 1: Table of Currently Available Treatment for Proposed Indications'	9
Table 2: Summary of studies providing efficacy data	22
Table 3: Assessment schedule: Protocol D2301	26
Table 4: Abbreviated schedule of assessments for patients discontinuing study drug	29
Table 5: Assessment schedule: Protocol D2302	40
Table 6: Abbreviated schedule of assessments for patients discontinuing study drug: D2302	41
Table 7: Demographic characteristics-trials D2301 and D2302 (randomized population)	51
Table 8: MS disease baseline characteristics: trials D2301 and D2302 (randomized population)	52
Table 9: MS medication history of previous disease-modifying agents- trials D2301 and D2302 (randomized population)	53
Table 10: Multiple Sclerosis MRI baseline parameters- Trial D2301 and D2302 (randomized population)	54
Table 11: Dr. Yan's Analysis of ARR by region- trial D2302	55
Table 12: Study participation and discontinuation- studies D2301 and D2302 (randomized population)	57
Table 13: Summary of clinical efficacy for the primary outcome measure, aggregate annualized relapse rate for protocol D2301 and D2302	58
Table 14 : Sensitivity analysis of the ARR up to 24 month- study D2301	59
Table 15: Sensitivity analyses of the ARR up to month 12- trial D2302	60
Table 16: Time to 3 month confirmed disability progression up to month 24- trial D2301 (ITT population)	61
Table 17: Time to 3 month confirmed disability progression up to month 12-trial D2302 (ITT population)	62
Table 18: change from baseline in EDSS at month 12 and month 24- trials D2301 and D2302	63
Table 19: Change from baseline in MSFC z-score	65
Table 20: Number of new or newly enlarged T2 lesions at month 12 in D2302: Original analysis sent in clinical study report	66
Table 21: Number of new or newly enlarged T2 lesions at month 12- trial D2302 (ITT population)	67
Table 22: New or newly enlarged T2 lesions up to month 24- trial D2301	68
Table 23: Gd-enhancing lesions-Trial D2301 and D2302	68
Table 24: Time to first confirmed relapse- trials D2301 and D2302	69
Table 25: Percent Brain Volume Change from baseline: trials D2301 and D2302	70
Table 26: Aggregated ARR (confirmed relapses) by age and gender and treatment (pooled ITT population)	71
Table 27: Aggregate ARR (confirmed relapses) by baseline EDSS and treatment (pooled ITT population)	72

Table of Figures

Figure 1: Study Outline for Protocol D2301	24
Figure 2: Study design D2302	39
Figure 3: Predicted potency of FTY720-P to reduce the lymphocyte count at steady state	74
Figure 4: Predicted potency of FTY720-P to reduce the number of new T2 lesions at month 12	75
Figure 5: ARR versus predicted FTY720-P steady state concentration model with no covariates and approximate 95% confidence band.....	76

1 Recommendations/Risk Benefit Assessment

This is a preliminary efficacy review of fingolimod (also referred to as FTY720 in this review). Final recommendations will be made following the Advisory Committee meeting on June 10, 2010.

1.1 Recommendation on Regulatory Action

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

The primary endpoint for both pivotal efficacy trials was the aggregate annualized relapse rate (ARR). D2301 was a 24 month multi-center randomized placebo controlled double blind trial in 1272 RRMS patients comparing FTY720 at two doses (1.25 mg and 0.5 mg) to placebo. Trial D2302 was a superiority 12 month study comparing two FTY720 doses (1.25 and 0.5 mg) to interferon β - 1a in 1292 RRMS patients. Both trials had robust findings for the primary endpoint of aggregate annualized relapse rate, with p values < 0.001 for both doses compared to control. There was approximately a 50% reduction in the relapse rate of FTY 720 0.5 mg compared to placebo and approximately a 30% reduction compared to IFN β - 1a. Although the intent to treat population included patients that remained in the study but were off study drug, the proportion of patients that were off study drug in each group was comparable, with the exception of the high dose FTY720 group in D2301. In addition, the supportive analysis in the per protocol population (on treatment with no major protocol violations) also provided consistent evidence that FTY720 is effective in reducing the aggregate ARR in patients with RRMS (p<0.001) as compared to control.

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

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

The next key secondary endpoint (pre-specified only in trial D2302) was the number of new or newly enlarged T2 lesions at month 12. While a statistically significant effect for that endpoint was clearly demonstrated for fingolimod 1.25 mg compared to placebo (mean of 2.51 vs. 4.86, p=0.017), the 0.5 mg group only trended in favor of fingolimod 0.5mg, compared to placebo (mean of 3.5 vs. 4.86, p=0.053), using the original pre-

planned analysis. The sponsor submitted an alternative analysis for this endpoint with their justification for why a new analysis was warranted. This alternative analysis method yielded a nominally significant contrast ($p=0.004$), but the validity of the alternative method is still under review at the time of redaction of this document. Trial D2301 demonstrated a nominally significant contrast ($p<0.001$) for both fingolimod 1.25 mg (mean of 2.5 vs. 9.8) and 0.5 mg (mean of 2.5 vs. 9.8) as compared to placebo for new or newly enlarged T2 lesions up to month 24.

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

1.2 Risk Benefit Assessment

Multiple safety signals are present with this product, and will be discussed in detail in the safety review. Final risk benefit assessment will be provided upon consideration of the safety review findings, and advice by the advisory committee panel.

2 Introduction and Regulatory Background

Multiple Sclerosis (MS) is a progressive neurologic illness with a distinctly variable phenotype and course in different individuals. The etiology remains unknown, although several factors, such as genetic susceptibility, autoimmune mechanisms, viral infection and sun exposure especially up to adolescence are thought to contribute to the development of MS in an individual. This illness is thought to trigger an autoimmune response that leads ultimately to demyelination in the Central Nervous System. More recently, data is accumulating to suggest that there also is a significant degree of gray matter involvement. Treatment for MS is generally directed in three areas 1) reduction of acute exacerbations, 2) reduction of relapses/disability progression or 3) symptomatic relief. The development program for fingolimod has explored this medication's utility to reduce relapses and disability progression. Currently there are several other first or second line therapies with this target, but all require either IV, i.m or s.q. administration. Fingolimod is distinct from these other agents, in that its mode of administration is oral and it is the first sphingosine 1 phosphatase receptor modulator seeking marketing authorization in the United States.

2.1 Product Information

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

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

2.2 Table of Currently Available Treatments for the Proposed Indication

Table 1: Table of Currently Available Treatment for Proposed Indications^{1,2}

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

¹annualized exacerbation rate

²acute myelogenous leukemia

³progressive multifocal leukoencephalopathy

*32% reduction in proportion of Rebif patients who experienced relapses compared to Avonex

1 Continuum, Multiple Sclerosis, Volume 10, Number 6, December, 2004, p. 120-163

2 Most recent approved labels for all products in table above

Two classes of agents are approved as first line treatment for the prevention of clinical relapses in relapsing forms of MS. The first class is recombinant interferon-b (IFN-b), which includes three formulations, specifically Avonex, Betaseron and Rebif. IFN-b is hypothesized to exert many effects at critical points in MS pathogenesis. It induces the expression of a number of genes and effects major histocompatibility complex (MHC) gene expression, antiviral and antiproliferative actions and monocyte activation in vitro. The exact mechanism that leads to improvement in MS patients is not well understood. Some of the effects hypothesized to be important are inhibition of leukocyte proliferation, the decrease of antigen presentation by microglia, a modulatory effect on the IgG synthesis of plasma cells, the reduction of T cell matrix metalloproteinase (MMPP) expression as well as the down regulation of adhesion molecules that allow T cell migration into the brain³. Another first line compound is glatiramer acetate (GA), which is a random polypeptide made up of four amino acids in a specific molar ratio that resembles myelin basic protein. This compound is thought to exert its immunomodulatory effect due to altered T cell activation and differentiation⁴.

Mitoxantrone (Novantrone), an alkylating chemotherapeutic agent, is considered a second line treatment option because of its potential cumulative cardiotoxicity, which limits the individual maximum dose. Mitoxantrone intercalates into DNA, resulting in cross links and strand breaks⁵. In addition, this product interferes with the enzyme topoisomerase II that forms double strand breaks when DNA is altered during replication. Therefore, mitoxantrone is thought to affect replication predominantly in rapidly dividing cells. As a result of this effect, there are secondary effects on the immune system, including interference with antigen presentation, proinflammatory cytokines and attenuation of leukocyte migration⁶.

Natalizumab (Tysabri) is another second line treatment option. Because of a risk for progressive multifocal leukoencephalopathy (PML), natalizumab is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate MS therapy. Natalizumab binds to the $\alpha 4$ -subunit of $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrins expressed on the surface of all leukocytes except neutrophils, and inhibits the $\alpha 4$ -mediated adhesion of leukocytes to their counter-receptors. Disruption of these molecular interactions prevents transmigration of leukocytes across the endothelium into inflamed parenchymal tissue. The specific mechanism by which Tysabri exerts its effects in multiple sclerosis has not been fully defined. Progressive multifocal leukoencephalopathy (PML) occurs in approximately 1/1000 patients treated

3 Markowitz, CE. Interferon-beta: mechanism of action and dosing issues. *Neurology* 2007;68:S8-11.

4 Menge T et al, Disease-Modifying agents for Multiple Sclerosis: Recent advances and future prospects. *Drugs* 2008; 68: 2445-2468.

5 Durr FE, Wallace RE, Citarella RV. Molecular and biochemical pharmacology of mitoxantrone. *Cancer Treat Rev* 1983; 10 Suppl. B 3-11.

6 Neuhaus O, et al. Multiple sclerosis: mitoxantrone promotes differential effects on immunocompetent cells in vitro. *J Neuroimmunol* 2005; 168: 128-137.

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

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

2.3 Availability of Proposed Active Ingredient in the United States

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

2.4 Important Safety Issues With Consideration to Related Drugs

See 2.3.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

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

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

After the third hold cycle regarding the safety monitoring for the proposed study D2301, the Agency received a package (**April 5, 2006**) for Dr. Temple’s review specifically requesting input on three key areas of disagreement 1) overnight admission after initial dosing for holter monitoring, 2) Optical coherence tomography (OCT) frequency and stopping rules, and 3) the need to conduct chest HRCT in all patients at baseline and end of treatment. During the arbitration process, the company sent a submission (**April**

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

Ophthalmology:

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

Pulmonary:

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

Cardiac:

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

An EOP2 meeting was held on **March 26, 2007**. Important points made in this meeting were as follows: 1) Although 15% or less of the patients were to be from the U.S, the division did not feel this would be unacceptable. 2) The sponsor said that safety data would be presented from studies D2301, D2302 and D2309 and FDA said that would be

acceptable if similar patient populations were enrolled and monitoring was identical. 3) FDA also stated that in order to describe disability progression in labeling, there would have to be independent substantiation of this endpoint. FDA noted that study D2309 was not powered for this endpoint and 4) Discussion about possible filing for accelerated approval under Subpart H was addressed. FDA stated the conditions under which this could be acceptable.

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

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

On **December 7, 2009** a pre-NDA teleconference was held. The sponsor briefly summarized information about the disability endpoint in their pivotal clinical trials of MS. FDA restated that this is a review issue and there should be no expectation that we can come to an agreement in this meeting. There was additional discussion about whether there would be insufficient data submitted from trial D2309 on the special safety issues. The sponsor stated that there should be approximately 180 echocardiograms, which includes 150 coming from study 2309. There should be approximately 30 echocardiograms per dose arm. FDA restated that this is less than what was originally requested, and that whether this would be a sufficient number was a review issue. The sponsor stated that they were considering transitioning study 2309 to an open label safety extension study from a placebo controlled trial. FDA expressed concerns that although it would not affect the filing of the NDA it may affect approval, as less controlled data on special safety issues would become available if this study was changed to an open label design.

On **September 8, 2009**, the DSMB sent a letter to Novartis recommending that the FTY720 1.25 mg dose be stopped in all MS trials unless review of the efficacy data from D2301 showed improved efficacy of the 1.25 mg dose over the 0.5 mg dose. The basis of their recommendation was largely based on six unexplained vascular events, all on treatment with FTY720 1.25. Several serious adverse events all occurring in the FTY 1.25 mg dose group also contributed to this recommendation, although the DSMB felt these were not as concerning as the cluster of vascular events. The serious adverse events included one highly unusual MS relapse case (2301 409-8 Germany), two viral infections (2302 212-21 Italy, 2302 821-07 Korea) and one 3rd degree heart block (2302E1 141-4 Belgium). On **December 1, 2009**, FDA was informed of this decision to

discontinue the FTY720 1.25 mg dose in several of their ongoing studies due to the DSMB recommendation.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

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

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

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

The correct statistical analyses plans (SAPs) for the pivotal trials dated prior to the database lock were not provided with the original submission. The first time they were

requested, the SAPs that came were dated after the database lock. The second time they were requested, the correct SAPs arrived.

An addendum was provided to the SAP, predominantly to present an alternate analysis for the variable new or newly enlarged T2 lesions at month 12 (trial D2302) That revised analysis is under review.

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

3.2 Compliance with Good Clinical Practices

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

3.3 Financial Disclosures

The sponsor provided sufficient information about the processes used to collect financial disclosure information. Financial disclosure information for the MS program was obtained or requested for all Principal Investigators, Co-Investigators and Sub-Investigators. In addition, in the MS program, the sponsor also collected financial disclosure information for physicians in the following categories since the information obtained from these clinicians were directly related to study outcomes: EDSS/EDSS rater (EDSSR); 1st dose administrator/independent first dose administrator (IFDA), Back up Treating Neurologist (BU TN), Examining Neurologist (EN); Back up Examining Neurologist (BU EN).

There were twenty one investigators identified as receiving > \$25,000 , yet only three were investigators included in the pivotal efficacy trials. Details provided for these three Investigators are as follows:

- 1) (b) (6) (b) (6) (b) (6)
(b) (6)
- 2) (b) (6) (b) (6)
- 3) (b) (6)

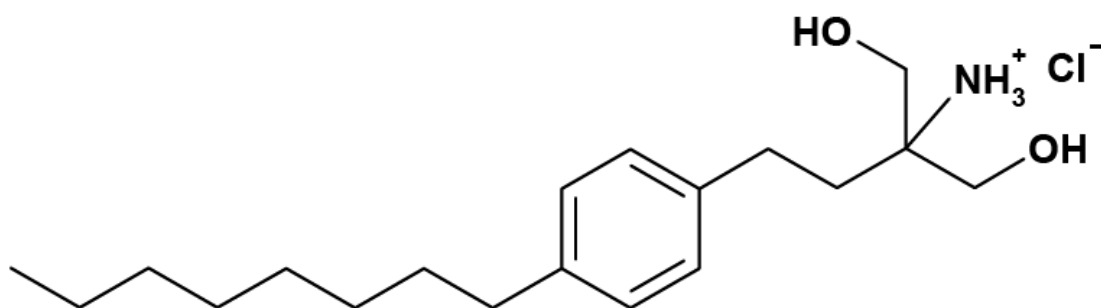
Information was obtained on 97-99% of the Investigators involved in the trials D2301 and D2302.

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

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

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



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

Please see the Agency Chemistry review for further details.

4.3 Preclinical Pharmacology/Toxicology

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

In safety pharmacology studies several potential safety signals were identified. A potential for bronchoconstriction and increased sensitivity induced by agents known to induce bronchoconstriction was found in experimental settings. In addition, FTY720 induced a transient decrease in heart rate and increase in blood pressure, both of which were not associated with relevant findings in long-term toxicology studies, although histopathological findings in the heart in dogs at high doses in chronic toxicity studies were seen. Effects on heart rate were characterized further and are related to an effect

of FTY720-phosphate on GIRK channels at the level of the sinoatrial (SA) node. Although a slight inhibition of hERG channel activity at the solubility limit (0.5 μM) of FTY720 or FTY720-phosphate was seen, there was no indication of QT prolongation in a series of in vitro or in vivo studies up to high concentrations and/or doses. FTY720 treatment resulted in a decrease in motor coordination in mice and a mild depressive activity in the central nervous system in rats at high dose levels. A transient decrease in renal function was seen in rats and dogs at high oral doses, and kidney changes, consisting of basophilic tubuli or increased incidence of interstitial inflammation was found in toxicity studies with rats and mice. No effects on platelet activation or coagulation were found in preclinical in vitro or in vivo studies.

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

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

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

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

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

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

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

4.4 Clinical Pharmacology

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

4.4.1 Mechanism of Action

Fingolimod is phosphorylated by sphingosine kinase in vivo to form the active metabolite fingolimod phosphate (fingolimod-P). Fingolimod-P binds four of the five G protein-coupled sphingosine 1-phosphate (S1P) receptors, namely S1P1, S1P3, S1P4 and S1P5. With initial dosing there is agonism of S1 receptors, manifested as decreased heart rate, however with continued fingolimod dosing, functional antagonisms occurs with internalization of S1P receptors.

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

autoimmune encephalomyelitis (EAE), fingolimod administration (resulting in S1P1 deletion from neural cells) reduced astrogliosis, demyelination and axonal loss.

4.4.2 Pharmacodynamics

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

Lymphocytes

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

Heart

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

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

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

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

Lung

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

Overdose

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

4.4.3 Pharmacokinetics

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

Absorption

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

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

Metabolism

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

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

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

Excretion

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

Pharmacokinetics in special patient populations

Ethnic origin, age, weight nor gender have a clinically relevant effect on the pharmacokinetics of fingolimod and fingolimod-P.

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

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

5 Sources of Clinical Data

5.1 Tables of Clinical Trials

Table 2: Summary of studies providing efficacy data

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

5.2 Review Strategy

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

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

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

5.3 Discussion of Clinical Trials

5.3.1 Protocol CFTY720D2301

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

Objectives:

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

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

Other secondary objectives were:

- To evaluate the safety and tolerability of FTY720 compared to placebo in patients with RRMS treated up to 24 months
- To evaluate the effect of FTY720 1.25 mg and 0.5 mg compared to placebo in patients treated for up to 24 months with respect to MRI parameters of inflammatory disease activity, burden of disease, and brain volume (atrophy)
- To evaluate the effect of FTY720 1.25 mg and 0.5 mg compared to placebo in patients treated for up to 24 months with respect to relapse-related parameters:
 - time to the first relapse
 - proportion of relapse-free patients
- To evaluate the effect of FTY720 1.25 mg and 0.5 mg compared to placebo in patients treated for up to 24 months on disability progression with respect to:
 - time to 6-month confirmed disability progression as measured by EDSS

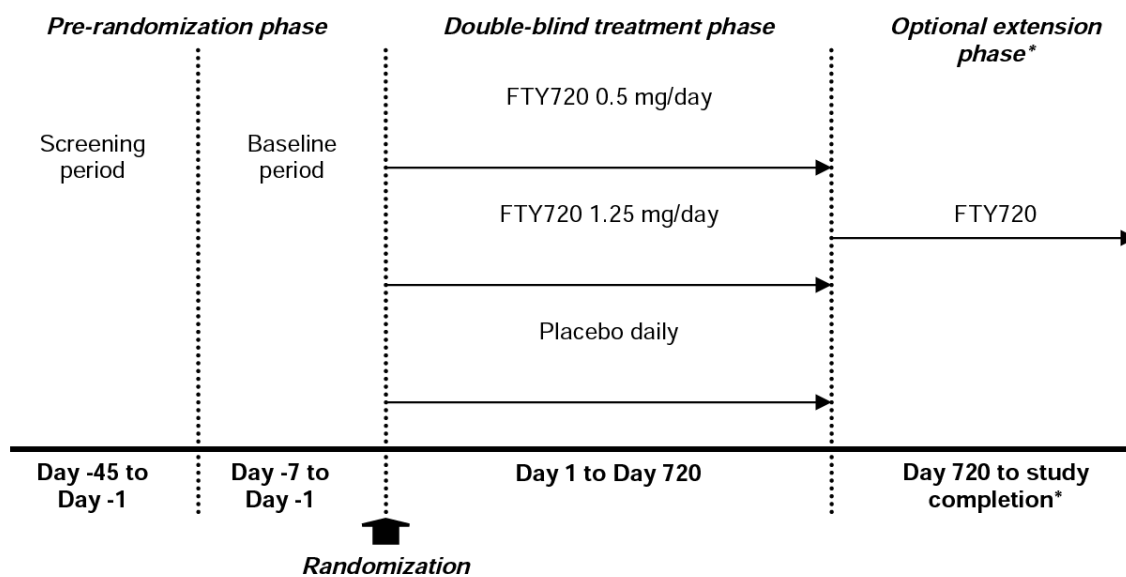
- proportion of patients with confirmed disability progression
- change from baseline to the end of the study on the Multiple Sclerosis Functional Composite (MSFC) z-score
- To evaluate the effect of FTY720 1.25 mg and 0.5 mg compared to placebo on multidimensional health status as measured by the Patient Utility Index derived from patients responses on the EuroQoL (EQ-5D)
- To evaluate the pharmacokinetics of FTY720
- To evaluate the pharmacokinetic/pharmacodynamic relationship of FTY720 1.25 mg and 0.5 mg for main efficacy and safety outcomes in patients with RRMS

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

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

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

Figure 1: Study Outline for Protocol D2301



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

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

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

All MRI scans was evaluated by a blinded reader at the central MRI Evaluation Center.

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

Table 3: Assessment schedule: Protocol D2301

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

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

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

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

Key Inclusion criteria:

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

Key Exclusion criteria

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

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

10. Any of the following pulmonary conditions:

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

11. Any of the following hepatic conditions:

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

12. Any of the following abnormal laboratory values:

- Serum creatinine > 1.7 mg/dL (150 µmol/L)
- White blood cell (WBC) count < 3,500/mm³ (< 3.5 x 10⁹/ L)
- Lymphocyte count < 800/mm³ (< 0.8 x 10⁹/ L)

Removal of patients from therapy or assessments:

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

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

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

Premature patient withdrawals and study drug discontinuations

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

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

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

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

Treatments administered

Investigational drug:

FTY720 0.5 mg capsules for oral administration once daily

FTY720 1.25 mg capsule for oral administration once daily

Reference therapy:

Matching FTY720 placebo in capsules for oral administration once daily

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

Concomitant therapy

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

Prohibited medication

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

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

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

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

Efficacy Outcome Measures

Primary efficacy outcome measure

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

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

Key secondary efficacy outcome measure

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

Analysis plan:

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

1. FTY720 1.25 mg vs. placebo testing treatment difference for aggregate ARR (using negative binomial model with covariates treatment, country, number of relapses in previous 2 years, and baseline EDSS);
2. FTY720 0.5 mg vs. placebo testing treatment difference for aggregate ARR (using negative binomial model with covariates treatment, country, number of relapses in previous 2 years, and baseline EDSS);
3. FTY720 1.25 mg vs. placebo testing treatment difference for time to 3-month confirmed disability progression (using log-rank test);
4. FTY720 0.5 mg vs. placebo testing treatment difference for time to 3-month confirmed disability progression (using log-rank test).

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

Primary endpoint analysis

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

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

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

Key secondary endpoint analysis

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

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

Populations definitions

- Randomized population (RND): All patients who were assigned randomization numbers. This population was used to summarize patient disposition, demographic and baseline characteristics, and protocol deviation information.
- Intent-to-treat population (ITT): All patients who were randomized and received at least one dose of study medication. Patients were grouped according to the assigned treatment. Efficacy analyses were performed on the ITT population.
- Per-protocol population (PP): All patients in the ITT population without any major protocol deviations. Major protocol deviations were determined before unblinding the treatment according to the pre-defined protocol deviation criteria, which have been specified prospectively. Any efficacy data after study drug withdrawal were excluded. This population was used for the supportive analyses of the primary efficacy endpoint and key secondary endpoints.
- Safety population (SAF): All patients who received at least one dose of study medication. Patients were analyzed according to the treatment received. Safety and tolerability analyses were performed on the safety population. Some of the safety assessment, such as chest HRCT (baseline and month 12 scheduled assessments), OCT (month 1, 3 and 6 serial collection), and 24-hour holter were

only done on a subgroup of patients. The analysis on these safety assessments was performed on the subgroup of the safety population.

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

Relapse and disability progression definitions

MS relapses

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

Confirmed relapse

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

Disability progression

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

Confirmed disability progression

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

Other secondary efficacy analyses

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

MRI inflammatory measures

MRI efficacy variables included the following:

Inflammatory activity up to 24 months:

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

Burden of disease up to 24 months:

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

Brain volume up to 24 months:

- Percent change from baseline in brain volume (atrophy)

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

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

MRI analysis method

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

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

Lesions were identified as follows:

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

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

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

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

Health-related quality of life

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

Relapse variables

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

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

Additional endpoints that are described in this report are 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), hospitalizations due to relapse, severity of relapses, impact on daily activities, recovery status, and duration of relapse were summarized by treatment arm. The treatment arms were compared using Fisher's exact test (for categorical variables) or Wilcoxon rank sum test (for continuous variables).

Disability progression-related variables

Other secondary disability progression endpoints included:

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

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

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

Interim analysis

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

Determination of sample size

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

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

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

5.3.2 Protocol CFTY720D2302

Study Title: A 12-month double-blind, randomized, multicenter, active-controlled, parallel-group study comparing the efficacy and safety of 0.5 mg and 1.25 mg

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

fingolimod (FTY720) administered orally once daily versus interferon β -1a (Avonex) administered i.m. once weekly in patients with relapsing-remitting multiple sclerosis with optional extension phase

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

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

Objectives:

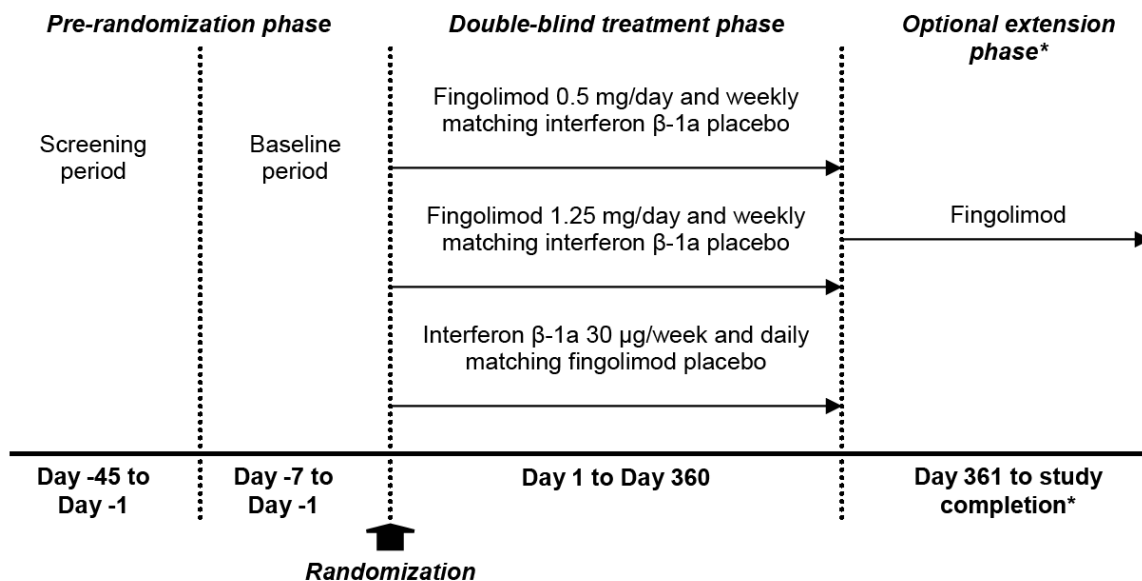
The primary objective was to compare two doses of FTY720 (1.25 mg and 0.5 mg) with IFN β -1a i.m. to demonstrate that at least 1.25 mg FTY720 is superior to IFN β -1a i.m. in terms of annualized relapse rate (ARR) in patients with relapsing-remitting multiple sclerosis (RRMS) treated for up to 12 months.

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

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

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

Figure 2: Study design D2302



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

Table 5: Assessment schedule: Protocol D2302

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

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

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

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

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

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

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

Treatments administered

Investigational drug

FTY720 1.25 mg capsules for oral administration once daily

FTY720 0.5 mg capsules for oral administration once daily

Control therapy

IFN β -1a 30 μ g in pre-filled syringes for i.m. injection once weekly

Reference therapy

Matching FTY720 placebo in capsules for oral administration once daily

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

Patients were randomized 1:1:1

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

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

Efficacy Variables

Primary Outcome Measure

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

Key Secondary Outcome Measure:

Two key secondary variables were tested:

1. MRI key secondary efficacy endpoint: This endpoint determined the effect on inflammatory disease activity as measured by the number of new/newly enlarged T2 lesions at 12 months.
2. Disease progression key secondary efficacy endpoint: This endpoint determined the time to 3-month confirmed disability progression as measured by EDSS during 12 months.

Statistical Analysis Plan

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

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

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

Primary efficacy variable

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

The identical methods for primary analysis evaluations and handling of discontinuations were used as that in D2301. Please refer to this section in my review.

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

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

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

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

There were two treatment comparisons for the time to 3-month confirmed disability progression: 1.25 mg FTY720 vs. IFN β -1a i.m. and 0.5 mg FTY720 against IFN β -1a i.m.

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

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

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

Determination of sample size

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

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

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

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

Based on historical data, it was assumed that the mean (SD) for the number of new or newly enlarged T2 lesions at month 12 for the IFN β -1a i.m. group is 2.4.⁸ It was

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

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

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

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

Changes in the conduct of planned analyses

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

1. The primary analysis method of the primary endpoint, ARR, was changed to negative binomial regression analysis method. Rank ANCOVA replaced Poisson regression with GEE as the supportive analysis method for the ARR.
2. The key secondary efficacy endpoints 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.
3. Multiplicity adjustment was extended from primary endpoint only to one primary endpoint and two key secondary endpoints for two doses. For the hypothesis testing, the hierarchical approach was adjusted.

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

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

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

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

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

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

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

The validity of that reanalysis is under review.

5.3.3 Protocol CFY720D2201

Study objectives:

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

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

Study design: D2201 was a 6 month, double-blind, randomized, placebo-controlled, parallel-group multicenter study evaluating safety, tolerability and effect on MRI lesion parameters of FTY720 versus placebo in patients with relapsing MS.

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

Method of Magnetic Resonance Imaging

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

Definition of MS relapse: The definition of a relapse was similar to the definition used in D2301 and D2302, but in D2201 only 14 days of stability or improvement were required between relapses. In addition, the definition of confirmed relapse allowed for a 0.5 point change on the EDSS and/or 1 point in 1 or more functional systems of the EDSS (excluding bowel/bladder and mental FS).

Statistical Methods

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

5.3.4 Protocol FTY720D2201E1

Study objective

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

Study design

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

Efficacy assessments

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

Statistical Analysis

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

Patient Disposition

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

5.3.5 Protocol FTY720D2309

A 24 month double blind, randomized, multicenter, placebo controlled, parallel-group study comparing the efficacy and safety of 0.5 mg and 1.25 mg fingolimod administered orally once daily versus placebo in patients with relapsing-remitting multiple sclerosis. This study is almost identical in design to D2301 except it also

incorporates special safety studies, to address safety concerns identified during development program. This trial includes in the study schedule ophthalmologic testing for the first 300 randomized patients, HRCT for the first 360 randomized patients and echocardiography between month 3 and 5. Pulmonary function tests were followed on all patients. 1089 patients have been enrolled into this study which is currently ongoing. Safety but not efficacy data has been provided in this new drug application.

6 Review of Efficacy

6.0 Efficacy Summary

Relapse rate

Substantial evidence of effectiveness for the reduction of relapses was provided in this application from the two pivotal efficacy trials, D2301 and D2302. Both trials had robust findings for the primary endpoint of aggregate annualized relapse rate, with p values < 0.001 for both doses compared to control. There was approximately a 50% reduction in the relapse rate of FTY 720 0.5 mg compared to placebo and approximately a 30% reduction compared to IFN β - 1a. In addition, the supportive analysis looking at the per protocol population (on treatment with no major protocol violations) also provided consistent evidence that FTY720 is effective in reducing the aggregate ARR in patients with RRMS (p<0.001).

Disability progression

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

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

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

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

Number of new or newly enlarged T2 lesions

The next key secondary endpoint pre-specified only in trial D2302 was the number of new or newly enlarged T2 lesions at month 12. The initial analysis provided by the sponsor with this application, was not supportive of efficacy of this endpoint for the low dose group ($p=0.053$), although there was evidence of efficacy at the high dose group ($p=0.017$) compared to placebo. An addendum to the statistical analysis was sent which included a reanalysis of this endpoint based on two issues identified by the sponsor. The sponsor reanalyzed the data without 18 patients that did not have a 12 month MRI to compare to the baseline and with revised data that resulted from recounting the new and newly enlarged T2 lesion variable. The sponsor claimed that the method prespecified in the protocol for counting these lesions was not adhered to by the central MRI reader. Essentially, all new or newly enlarged T2 lesions were counted only if there was not Gd enhancement on T1 by the central MRI reader for the original analysis, but the lesions should have been counted as T2 lesions whether or not there was Gd enhancement. The sponsor proposed adding the T2 lesion variable with the Gd-enhanced variable to yield the new "T2 lesion variable". FDA requested that the sponsor go back to the MRIs or the data collection sheets and recount the lesions directly rather than adding the variables. In addition, FDA suggested including the 18 patients without the 12 months MRI scans by using data from the last MRI scan obtained using the last observation carried forward method. No conclusions can be made about this endpoint until the new analysis is submitted.

6.1 Indication

Treatment of patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.

6.1.1 Method

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

6.1.2 Demographics

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

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

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

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

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

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

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

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

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

Abbreviation: IFN = interferon

¹ Treatment-naïve patients were defined as those not receiving any of MS disease-modifying drugs, approved or not (excluding symptomatic therapies).

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

MS MRI baseline characteristics

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

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

D2301	FTY720 1.25 mg N = 429	FTY720 0.5 mg N = 425	Placebo N = 418	Total N = 1272
Proportion of patients free of Gd-enhancing lesions – n (%)				
n	424	424	416	1264
n (%)	257 (60.6)	263 (62.0)	262 (63.0)	782 (61.9)
Number of Gd-enhancing lesions				
n	424	424	416	1264
Median (mean)	0.0 (1.8)	0.0 (1.6)	0.0 (1.3)	0.0 (1.6)
Total volume of T2 lesions (mm³)				
n	425	424	416	1265
Median (mean)	3556.5 (6828.7)	3303.4 (6127.7)	3416.3 (6162.4)	3453.3 (6374.6)
Normalized brain volume (cc)				
n	423	424	414	1261
Median (mean)	1514.7 (1510.5)	1528.5 (1520.8)	1514.8 (1512.2)	1520.2 (1514.5)
D2302	FTY720 1.25 mg N = 426	FTY720 0.5 mg N = 431	IFN β-1a i.m. N = 435	Total N = 1292
Proportion of patients free of Gd-enhancing lesions – n (%)				
n	412	427	425	1264
n (%)	270 (65.5)	288 (67.4)	268 (63.1)	826 (65.3)
Number of Gd-enhancing lesions				
n	412	427	425	1264
Median (mean)	0.0 (1.5)	0.0 (1.0)	0.0 (1.1)	0.0 (1.2)
Total volume of T2 lesions (mm³)				
n	413	428	425	1266
Median (mean)	3095.9 (5085.4)	2381.8 (5169.6)	2901.1 (4923.6)	2786.6 (5059.5)
Normalized brain volume (cc)				
n	409	421	420	1250
Median (mean)	1527.8 (1526.2)	1526.2 (1524.1)	1533.3 (1526.7)	1529.5 (1525.7)

Applicability of Foreign Data

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

patterns from the patients from the US who enrolled in D2302 are similar to that of the overall study population. The US patients tended to be slightly older, with a lower proportion of Caucasian (85% vs. 95%) and had higher body mass indexes (BMIs). 3) Practice patterns in MS have become considerably more homogeneous than in the past, as more therapies have become available to treat this disorder. In addition, International attendance at major MS meetings have encouraged standardization of disease management. 4) Although the number of US patients included in the fingolimod trials were proportionately small compared to the overall program, many other marketed products for MS had equally small numbers of US patients at the time of marketing approval. These include Rebif (339 patients), Betaseron (207 patients), Copaxone (251 patients) and Mitoxanthrone (no US patients- 188 patients overall). 5) At a meeting with the sponsor, FDA agreed that on face, although it appeared that only 15% or less of patients would be from the US in this marketing application this would probably be acceptable.

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

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

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

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

6.1.3 Subject Disposition

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

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

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

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

6.1.4 Analysis of Primary Endpoint

Annualized relapse rate

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

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

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

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

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

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

*indicates two-sided statistical significance at 0.05 level

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

Sensitivity analyses of the ARR

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

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

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

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

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

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

6.1.5 Analysis of Key Secondary Endpoints

Disability Progression

In both Phase III studies a key secondary objective was to compare the effect of FTY720 1.25 mg and 0.5 mg to control (placebo in D2301 and IFN β -1a in D2302) on disability progression as measured by the time to 3 month confirmed disability progression, measured by the EDSS in patients with RRMS. The EDSS is a widely accepted standardized test to evaluate disability in MS patients. A 3-month confirmed disability progression required onset EDSS, 3-month confirming EDSS, and all EDSS in between to meet the disability progression criteria. The EDSS rater used for confirmation of the disability progression was blinded to all information about the patient's treatment.

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

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

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

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

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

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

The second pivotal efficacy trial (D2302) did not provide independent substantiation of a delay in time to 3 month confirmed disability progression on FTY720 vs. control as was seen in trial D2301. Other secondary measures of disability progression were collected in these two Phase III pivotal trials. Although these were not key secondary measures and did not have a prespecified analysis plan, I will discuss these measures to determine if any confirmatory evidence exists to support the finding seen in trial D2301 of a reduction of disability progression.

Disability Scales

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

EDSS

At month 24 in study D2301, there was a slight decrease from baseline in EDSS for the 1.25 mg dose; there was no change for the 0.5 mg dose while an increase was observed in placebo. Although the difference between FTY720 and placebo was nominally significant at the 0.05 level for both FTY720 doses, the absolute mean differences were small. Please refer to Table 18 for the specific values.

Consistently, in study D2302 a slight decrease in EDSS was observed in FTY720 1.25 mg and FTY720 0.5 mg as compared to a slight increase in the IFN β -1a group. In study D2302, the difference in mean EDSS change from baseline to Month 12 was nominally significant for FTY720 1.25 mg when compared to IFN β -1a (p = 0.016) but not for FTY720 0.5 mg (refer to sponsor Table 18). Interestingly at Month 12 in study D2301 (the 24 month study), the difference in mean EDSS change from baseline was nominally significant for FTY720 0.5 mg vs. placebo but not for FTY720 1.25 mg.

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

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

Abbreviation: IFN = interferon

Results are presented for ITT patients who had EDSS values at both baseline and Month 12 (or Month 24).

P-value was calculated using rank ANCOVA with covariates of treatment, country, the corresponding baseline value, and age.

Reviewer's comment: *The difference in the mean change from baseline in the EDSS in D2301 for 0.5 mg compared to placebo was 0.13. Although the mean difference is so low, this trial demonstrated statistically significant results for three month confirmed disability progression. Data from trial D2302 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, but not the FTY 0.5 mg treatment group vs. active control. The mean change between FTY 1.25 mg and IFN β -1a was 0.12.*

Multiple Sclerosis Functional Composite

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

external reference population. The PASAT-3 is considered the least specific test of the three subscales due to the effect of learning over time on the scale⁹.

At month 24 in study D2301, there was slight decrease in the mean MSFC z-score values over time in the placebo group, while in the FTY720 1.25 mg and FTY720 0.5 mg groups a slight increase was observed. The nominal p value (unadjusted for multiple comparisons) for the drug vs. placebo difference in MSFC z-score change from baseline was under 0.05 for both doses of fingolimod (see sponsor Table 19). Regarding MSFC subscales, nominal p values (unadjusted for multiple comparisons) were under 0.05 for the drug vs. placebo difference in 9HPT (both doses), and in 25'TWT change from baseline (0.5 mg dose), while p values were above 0.05 for the PASAT-3 contrasts.

At month 12 in study D2302, the mean change from baseline in the MSFC z-score showed a slight increase for both FTY720 treatments (1.25 mg and 0.5 mg) versus a decrease for IFN β -1a. The nominal p value for the contrast of MSFC z-score changes between both doses of FTY720 and IFN β -1a was under 0.05 (unadjusted for multiple comparisons). Regarding MSFC subscales, nominal p values (unadjusted for multiple comparisons) under 0.05 were observed between the FTY720 groups and IFN β -1a only for the PASAT-3 (both doses) and the 9HPT (1.25 mg dose) contrasts. No significant differences were observed in 25'TWT.

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

Table 19: Change from baseline in MSFC z-score

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

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

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

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

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

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

New and newly enlarged T2 lesions

The first key secondary endpoint in trial D2302 was the number of new or newly enlarged T2 lesions at 12 months. Procedures were implemented to decrease bias when evaluating MRI variables as follows: 1) MRI efficacy measures followed standardized MRI scan technical procedures and 2) MRI images were centrally evaluated by blinded raters. In an addendum to the clinical study report, treatment with both FTY720 doses resulted in a statistically significant lower number of new or newly enlarged T2 lesions at month 12 compared to IFN β -1a. In the original clinical study report for D2302, this key secondary endpoint was only statistically significant for the 1.25 mg dose (refer to Table 20 below).

Table 20: Number of new or newly enlarged T2 lesions at month 12 in D2302: Original analysis sent in clinical study report

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

n=the number of patients with evaluable MRI at baseline and Month 12

P-value is calculated using a negative binomial model adjusting for treatment, country, baseline number of relapses in the previous 2 years, and baseline EDSS.

* Indicates two-sided statistical significance at 0.05 level.

The sponsor sent in an addendum to the clinical study report on 11-22-2009 to correct the statistical analysis for the key secondary endpoint “new and newly enlarged T2 lesions” and other related efficacy endpoints. This correction was described in this review (p. 46) refer to Table 21 below for the amended analysis, which the sponsor considers the official analysis of this key secondary outcome measure from D2302. This new analysis now shows that there is a statistically significant difference between numbers of new or newly enlarged T2 lesions at month 12 compared to IFN β -1a in both FTY720 dose groups. The validity of that revised analysis is under review.

Table 21: Number of new or newly enlarged T2 lesions at month 12- trial D2302 (ITT population)

	FTY720 1.25mg N=420	FTY720 0.5mg N=429	Interferon beta-1a i.m. N=431
As Intended per Protocol			
n**	350	372	361
Mean (SD) #	1.5 (2.73)	1.7 (3.92)	2.6 (5.81)
Median	1.0	0.0	1.0
Range	0 – 26	0 - 38	0 - 63
P-value for treatment comparison of FTY720 vs. Interferon beta-1a i.m. (negative binomial regression with covariates)	<0.001*	0.004	–
As analyzed by MRI Central reader			
n**	350	372	361
Mean (SD)	1.4 (2.51)	1.5 (3.52)	2.1 (4.89)
Median	1.0	0.0	1.0
Range	0 - 22	0 - 32	0 - 60
P-value for treatment comparison of FTY720 vs. Interferon beta-1a i.m. (negative binomial regression with covariates)	0.017*	0.041	–
n**	356	380	365
Mean (SD)	1.4 (2.51)	1.5 (3.50)	2.1 (4.86)
Median	1.0	0.0	1.0
Range	0 – 22	0 – 32	0 – 60
P-value for treatment comparison of FTY720 vs. Interferon beta-1a i.m. (negative binomial regression with covariates)	0.017*	0.053	–

n=the number of patients with evaluable MRI at baseline and Month 12

P-value is calculated using a negative binomial model adjusting for treatment, country, baseline number of relapses in the previous 2 years, and baseline EDSS.

* Indicates two-sided statistical significance at 0.05 level.

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

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

In trial D2301, the 24 month pivotal controlled trial of FTY720 1.25mg and 0.5 mg vs. placebo in patients with RRMS, the variable “number of new or newly enlarged T2 lesions” was not identified as a key secondary endpoint. Yet, there were robust nominal p values associated with strong differences in the number of T2 lesions in FTY720 treated patients compared to placebo (see sponsor Table 22).

Table 22: New or newly enlarged T2 lesions up to month 24- trial D2301

	FTY720 1.25 mg N ^{**} = 337	FTY720 0.5 mg N ^{**} = 370	Placebo N ^{**} = 339
Number of lesions¹			
Median (mean)	0.0 (2.5)	0.0 (2.5)	5.0 (9.8)
p-value vs. placebo (negative binomial regression with covariates)	< 0.001*	< 0.001*	
Proportion (%) of patients free of lesions	51.9	50.5	21.2
p-value vs. placebo	< 0.001*	< 0.001*	

¹ Number of lesions at Month 24 were obtained by adding the Month 0 - 12 results to the Month 12 - 24.
p-value for number of lesions is calculated using a negative binomial model adjusted for treatment and country. p values for proportion of patients free of lesions was calculated using the logistic regression model adjusting for treatment and country

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

** Results are presented for ITT patients who had a T2-weighted scan at both baseline and Month 24.

6.1.5 Other Secondary Endpoints

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

Gd-enhancing lesions

In study D2301, treatment with both FTY720 doses, 1.25 mg and 0.5 mg significantly reduced the number and volume of Gd-enhancing lesions at month 24 compared to placebo. In study D2302, treatment with FTY720 significantly reduced the number and volume of Gd-enhancing lesions at month 12 compared to placebo or IFN β-1a. Please refer to Table 23.

Table 23: Gd-enhancing lesions-Trial D2301 and D2302

Gd-enhancing lesions at 2 years				
D2301		FTY720 1.25 mg n = 343	FTY720 0.5 mg n = 369	Placebo n = 332
Number of lesions	Median (mean)	0.0 (0.2)	0.0 (0.2)	0.0 (1.1)
	P-value vs. placebo	< 0.001*	< 0.001*	---
Total volume of lesions (mm³)	Median (mean)	0.0 (28.9)	0.0 (39.5)	0.0 (149.1)
	P-value vs. placebo	< 0.001*	< 0.001*	---
Proportion of patients free of lesions	% lesion-free	89.8	89.7	65.1
	P-value vs. placebo	< 0.001*	< 0.001*	---

Gd-enhancing lesions at 1 year

D2302		FTY720 1.25 mg n = 352	FTY720 0.5 mg n = 374	IFN β -1a i.m. n = 354
Number of lesions	Median (mean)	0.0 (0.1)	0.0 (0.2)	0.0 (0.5)
	P-value vs. IFN β -1a	< 0.001*	< 0.001*	---
Total volume of lesions (mm ³)	Median (mean)	0.0 (19.5)	0.0 (22.6)	0.0 (50.7)
	P-value vs. IFN β -1a	< 0.001*	< 0.001*	---
Proportion of patients free of lesions	% lesion-free	91.2	90.1	80.8
	P-value vs. IFN β -1a i.m.	< 0.001*	< 0.001*	---

Time to first relapse

In both phase III trials D2301 and D2302, there was a significant prolongation in the time to confirmed relapse with fingolimod 1.25 mg and 0.5 mg groups as compared to the control group. Refer to Table 24 below.

Table 24: Time to first confirmed relapse- trials D2301 and D2302

Time to first confirmed relapse

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

Brain Volume Change

In both pivotal efficacy trials, there was a nominally significant lower reduction in brain volume from baseline in both treatment groups as compared to placebo. In study D2301, there was a 30% reduction relative to placebo for both FTY720 doses, and in trial D2302, there was a 50% reduction compared to IFN β -1a. The sponsor suggests that this reduction in brain volume represents less atrophy, although they acknowledge that there is no pathological confirmation that this represents true tissue loss. They also suggest that the greater effect size seen in trial D2302 (refer to Table 25) in brain volume change may reflect the “pseudo-atrophy” effect that has been observed with interferon within the first year.

Table 25: Percent Brain Volume Change from baseline: trials D2301 and D2302

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

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

6.1.7 Subpopulations

ARR by age and gender

In a pooled analysis of trials D2301 and D2302, there were no clear differences in the effect of FTY720 on ARR by gender or age (refer to Table 26). A higher overall ARR was seen in the subgroup of patients that were younger, which is consistent with published data on the natural history of MS.

Table 26: Aggregated ARR (confirmed relapses) by age and gender and treatment (pooled ITT population)

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

ARR by baseline EDSS

In a pooled analysis of trials D2301 and D2302, there were no clear differences in the effect of FTY720 on ARR by baseline EDSS. There is a higher ARR in both treatment groups and control patients that entered the study with higher baseline EDSS as would be expected. Please refer to Table 27 below.

Table 27: Aggregate ARR (confirmed relapses) by baseline EDSS and treatment (pooled ITT population)

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

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

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

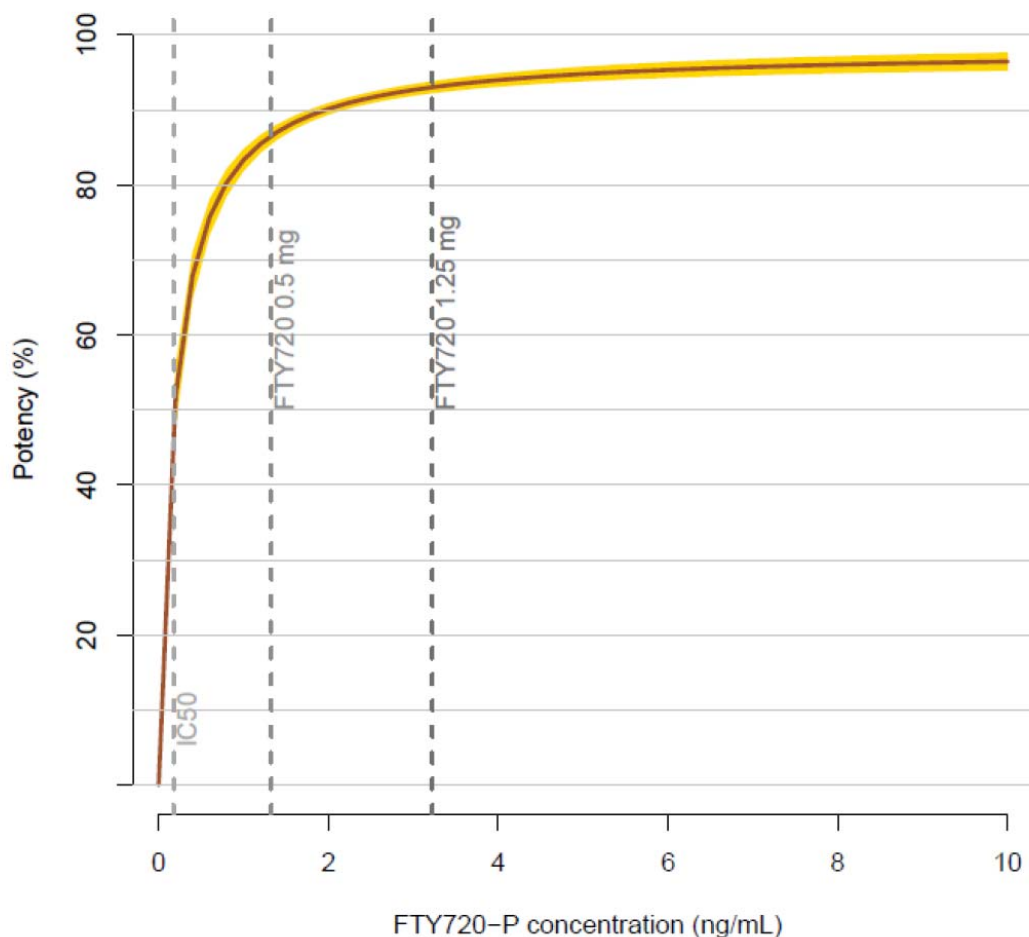
Within the MS studies a dose span of 0.5-5.0 mg FTY720 was studied.

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

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

Modeling of the exposure-response relationship in patients from the Phase III studies D2301 and D2302 showed that lymphocyte counts decrease with increasing FTY720-P concentration with an estimated maximum reduction of 85% in female and 80% in male patients. The 0.5 mg dose is on the shoulder of the response curve while the 1.25 mg dose is on the plateau (refer to sponsor Figure 3).

Figure 3: Predicted potency of FTY720-P to reduce the lymphocyte count at steady state



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

Further modeling was done by the sponsor to predict potency of FTY720 in relation to reduction of new T2 lesions counts and annualized relapse rate and in both cases the 0.5 mg dose was at the shoulder of the curve with a steep exposure response predicted for lower FTY720 concentrations (see Figure 4 and Figure 5).

Figure 4: Predicted potency of FTY720-P to reduce the number of new T2 lesions at month 12

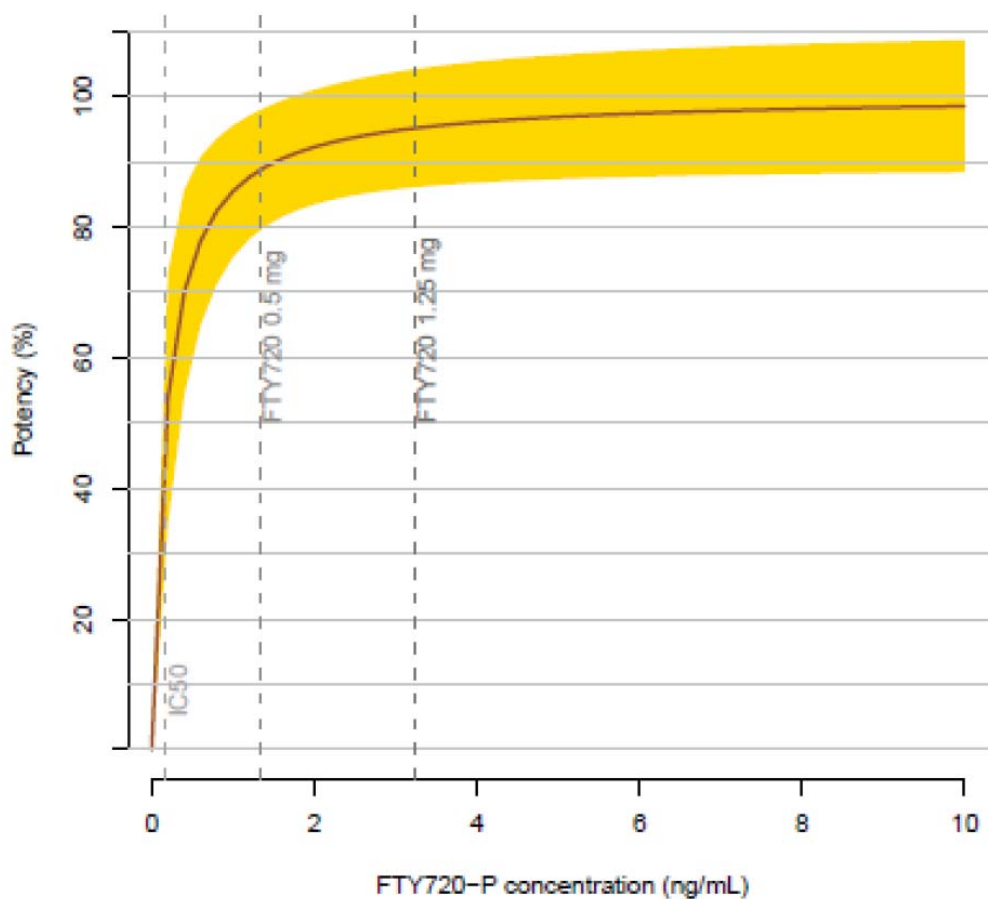
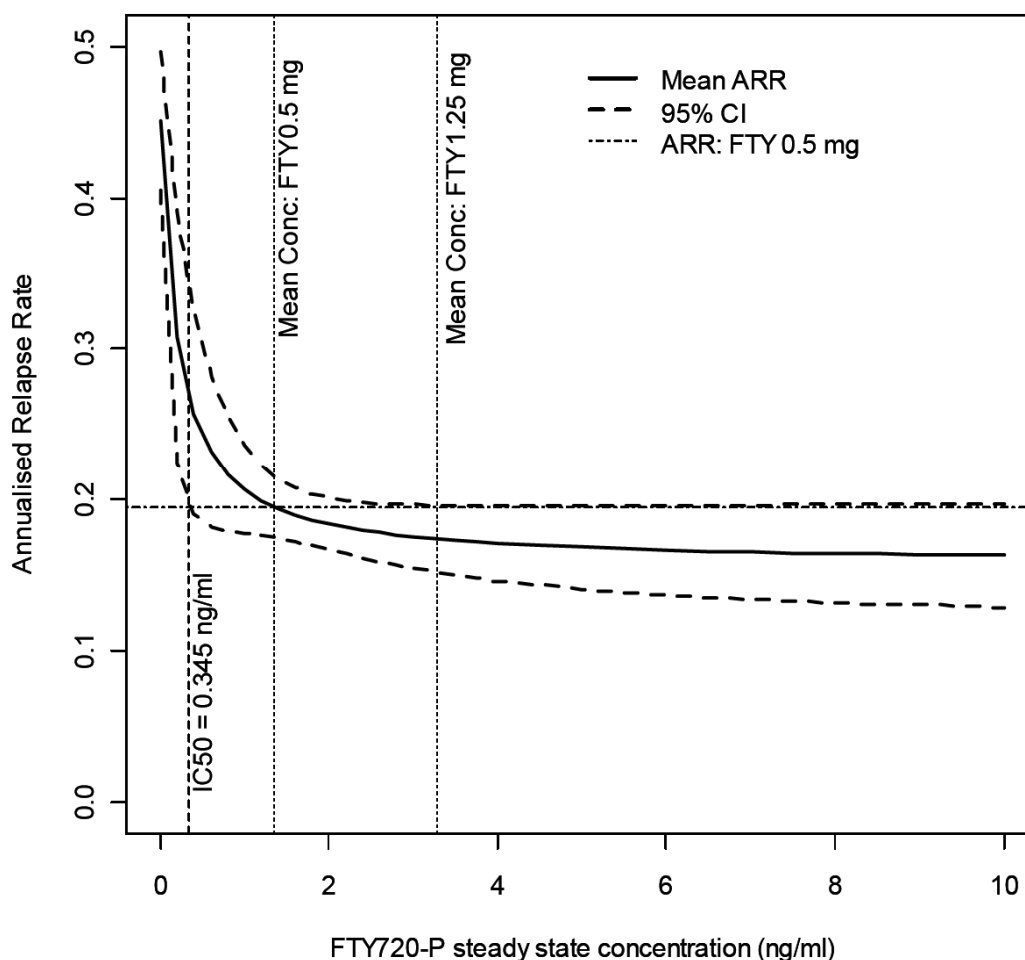


Figure 5: ARR versus predicted FTY720-P steady state concentration model with no covariates and approximate 95% confidence band



The 0.5 mg dose was selected to explore the presence of a lower efficacious dose with an improved safety profile. According to the sponsor, FTY 720 was shown to exhibit dose proportional exposure (for C_{max} and area under the concentration time curve) at steady state over the dose range of 0.125-5.0 mg. The 0.5 mg dose represented the next lower dose offering adequate separation from the 1.25 mg dose in terms of PK exposure.

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

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

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

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

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

Persistence of efficacy

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

Withdrawal/Rebounds effects on efficacy

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

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

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

8 Postmarket Experience

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

9 Appendices

9.1 Literature Review/References

Literature references were incorporated in the review

9.2 Labeling Recommendations

Pending

9.3 Advisory Committee Meeting

To be held on June 10, 2010



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoeconomics and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 22527 / Serial Number 000-
Drug Name: FTY720 (Fingolimod Hydrochloride)
Indication(s): Multiple Sclerosis
Applicant: Novartis
Date(s): Rolling Submission Completion Date: 12/21/2009
PDUFA Due Date: 6/21/2010
Review Priority: Priority Review
Biometrics Division: Division of Neurology
Statistical Reviewer: Sharon Yan
Concurring Reviewers: Kun Jin
Kooros Mahjoob
Medical Division: Neurology
Clinical Team: Heather Fitter, M.D., Clinical Reviewer
Lourdes Villalba, M.D., Safety Reviewer
Eric Bastings, M.D., Deputy Director
Russell Katz, M.D., Director
Project Manager: Hamet Toure, Pharm.D., Lt., Project Manager

DRAFT

Table of Contents

1. EXECUTIVE SUMMARY	3
1.1 CONCLUSIONS AND RECOMMENDATIONS	3
1.2 BRIEF OVERVIEW OF CLINICAL STUDIES	3
1.3 STATISTICAL ISSUES AND FINDINGS	3
2. INTRODUCTION	3
2.1 OVERVIEW	3
2.2 DATA SOURCES	4
3. STATISTICAL EVALUATION	5
3.1 EVALUATION OF EFFICACY	5
3.1.1 Study D2301	5
3.1.1.1 Description of the Study	5
3.1.1.2 Efficacy Variables	5
3.1.1.2.1 Primary Efficacy Endpoint	5
3.1.1.2.2 Secondary Efficacy Endpoint	6
3.1.1.3 Statistical Analysis Methods	6
3.1.1.3.1 Analysis of the Primary Efficacy Variable	6
3.1.1.3.2 Analysis of the Key Secondary Efficacy Variable	7
3.1.1.3.3 Multiplicity Adjustment	7
3.1.1.4 Patient Results	8
3.1.1.4.1 Patient Disposition	8
3.1.1.4.2 Baseline demographic characteristics	9
3.1.1.4.3 Baseline disease characteristics	9
3.1.1.4.4 Medications taken prior to the start of study drug treatment	11
3.1.1.5 Efficacy Results	12
3.1.1.5.1 Efficacy Results of the Primary Endpoint	12
3.1.1.5.2 Efficacy Results of Secondary Endpoints	14
3.1.2 Study D2302	16
3.1.2.1 Description of the Study	16
3.1.2.2 Efficacy Variables	17
3.1.2.2.1 Primary Efficacy Variable	17
3.1.2.2.2 Key Secondary Variables	17
3.1.2.3 Statistical Analysis Methods	17
3.1.2.3.1 Analysis of Primary Efficacy Variable	17
3.1.2.3.2 Analysis of Key Secondary Efficacy Variables	18
3.1.2.3.3 Multiplicity Adjustment	18
3.1.2.4.1 Disposition of patients	19
3.1.2.4.3 Baseline Disease Characteristics	21
3.1.2.5 Efficacy Results	24
3.1.2.5.1 Efficacy Results of the Primary Endpoint	24
3.2 EVALUATION OF SAFETY	29
4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS	29
4.1 GENDER, RACE AND AGE	29
4.2 OTHER SPECIAL/SUBGROUP POPULATIONS	31
5. SUMMARY AND CONCLUSIONS	33
5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE	33
5.2 CONCLUSIONS AND RECOMMENDATIONS	33

1. EXECUTIVE SUMMARY

This NDA submission is to obtain marketing authorization for FTY720 (fingolimod hydrochloride) in the treatment of relapsing multiple sclerosis (MS). The proposed recommended dose is 0.5 mg once-daily administered orally. 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 accumulation of physical disability.

1.1 Conclusions and Recommendations

The two Phase III studies in patients with relapsing MS presented evidence that FTY720, at once daily oral doses of 1.25 mg and 0.5 mg, is efficacious for the treatment of relapsing MS based on reduction in annual relapse rate. Patients in both of the FTY720 dose groups in the 2-year study D2301 were also found having significantly slower progression of disability, but such result was not replicated in the 1-year study D2302.

1.2 Brief Overview of Clinical Studies

The Phase III clinical development program of FTY720 in relapsing MS included 3 Phase III studies (D2301, D2302, D2309), all evaluating the efficacy and safety of FTY720 at once daily oral doses of 0.5 mg and 1.25 mg. Two of the studies (D2301, D2302), which constitute the pivotal program, are completed and included in the current submission. The third one is still ongoing at time of submission of this NDA.

1.3 Statistical Issues and Findings

No major statistical issues were found.

2. INTRODUCTION

Two large adequate and well-controlled Phase III studies contributed the bulk of the efficacy data in this submission; one 2-year, placebo-controlled study, and a one-year, active-controlled study employing interferon β -1a (IFN β -1a, Avonex®) as the active comparator. Another 6-month, Phase II placebo-controlled study is also submitted but not included in this review.

2.1 Overview

The Phase III clinical development program of FTY720 in relapsing MS included 3 Phase III studies (D2301, D2302, D2309), all evaluating the efficacy and safety of FTY720 at once daily oral doses of 0.5 mg and 1.25 mg. Two of these studies (D2301, D2302), which constituted the pivotal program, are completed and are included in the current submission:

- D2301: a 2-year, double-blind, placebo-controlled study in 1272 patients with relapsing remitting MS (RRMS) conducted globally (outside of the USA). The primary endpoint was annualized relapse rate. The aggregate ARR was significantly lower in both FTY720 groups compared with the placebo group. The magnitude of treatment effect (relapse reduction relative to placebo) was 60% for the 1.25 mg group and 54% in the 0.5 mg group with no significant difference between the two FTY720 doses.
- D2302: 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. The primary endpoint was annualized relapse rate. The ARR was significantly lower in both FTY720 groups compared with the IFN β-1a group, resulting in a relative reduction in the ARR of 38% for 1.25 mg and 52% for 0.5 mg, with no significant difference between the two FTY720 doses.

The third, still ongoing study (D2309), is a 2-year, double-blind, placebo-controlled study in approximately 1080 patients with RRMS, conducted mainly in the USA (completed recruitment).

All three studies included a long-term extension phase, which are still on-going. A phase II, 6-month placebo controlled MRI study is also included in the submission.

2.2 Data Sources

All documents reviewed for this NDA submission are in electronic form. The path to CDER Electronic Document Room for documents of this NDA is listed below:

<\\Cdseubl\evsprod\NDA022527>

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study D2301

3.1.1.1 Description of the Study

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 annualized relapse rate (ARR) in patients with RRMS treated for up to 24 months. The key secondary objective was to evaluate the effect of FTY720 1.25 mg and 0.5 mg relative to placebo on time to 3-month confirmed disability progression as measured by EDSS in patients treated for up to 24 months.

This was a 24-month, double-blind, randomized, multicenter, placebo-controlled, parallel-group study. Patients were randomized 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 centers in 22 non-US countries. A total of 1250 patients were planned and 1272 patients were actually randomized. Patients enrolled in this study were diagnosed of MS based on 2005 revised McDonald criteria, were treatment naïve or previously treated, had a relapsing-remitting course with at least one documented relapse during the previous year or two documented relapses during the previous 2 years, prior to randomization, and had Expanded Disability Status Scale (EDSS) score of 0 to 5.5 inclusive.

3.1.1.2 Efficacy Variables

3.1.1.2.1 Primary Efficacy Endpoint

The primary endpoint was the aggregate annualized relapse rate (ARR) at 24 months, which was defined as the number of relapses per year. Only confirmed relapses were considered for the primary analyses.

Relapse was defined as an appearance of a new neurological abnormality or worsening of previously stable or improving pre-existing neurological abnormality, separated by at least 30 days from the onset of a preceding clinical demyelinating event. The abnormality must have been present for at least 24 hours and have occurred in the absence of fever ($< 37.5^{\circ}\text{C}$) or infection.

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), and it was confirmed by the Independent Evaluating Physician (examining neurologist).

The average ARR was calculated in two ways.

1. Group level (aggregate ARR)

The ARR of the treatment group was calculated by taking the total number of confirmed relapses for all 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.

2. Patient level

The ARR for each patient was calculated as the total number of confirmed relapses divided by total number of days on study, multiplied by 365.25. The ARR for each treatment group was the mean of ARRs from all patients in the group.

3.1.1.2.2 Secondary Efficacy Endpoint

The key secondary endpoint was the time to 3-month confirmed disability progression assessed at 24 months.

Confirmed disability progression was defined as 1 point EDSS increase from baseline or 0.5 point increase if baseline EDSS was ≥ 5.5 , confirmed 3 months later. A 3-month confirmed progression was defined as a 3-month sustained increase from baseline EDSS score. It means that every EDSS score obtained (scheduled or unscheduled) within a 3-month duration after the first progression should also meet the progression criteria.

Disability progression could only be confirmed at a scheduled visit in the absence of a relapse.

If a patient died due to MS after the start of a tentative disability progression event, then it would be considered as a confirmed 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.

3.1.1.3 Statistical Analysis Methods

Efficacy analyses were to be performed on the ITT population. ITT patient population consisted of all patients who were randomized and received at least one dose of study medication. Patients were grouped according to the assigned treatment.

3.1.1.3.1 Analysis of the Primary Efficacy Variable

The primary null hypotheses to be tested were: 1) there was no difference in the aggregate annualized relapse rate (ARRs) between patients treated with the FTY720 1.25 mg versus placebo, and 2) there was no difference in the aggregate ARRs between patients treated with the FTY720 0.5 mg versus placebo.

The test of the null hypotheses was to be based on a negative binomial regression model using treatment group, country, number of relapses in previous 2 years, and baseline EDSS as covariates. Number of relapses in the previous 2 years and baseline EDSS were to be treated as continuous covariates in the model. Individual countries with small number of patients were to be pooled for analysis.

For the negative binomial regression, the response variable was the number of relapses for each patient and quadratic variance estimate was to be used. Log of time on study in years was to be used as the offset variable to account for the varying lengths of patients' time in the study. The ARR and its 95% confidence interval for each treatment group were to be estimated from the model.

For patients who prematurely discontinued study drug, the relapses collected after the study drug discontinuation were to be included in the analysis.

3.1.1.3.2 Analysis of the Key Secondary Efficacy Variable

The treatment groups were to be compared for time to disability progression using a log-rank test.

A patient was to be censored if the patient prematurely withdrew from the study or completed the study before the onset of a disability progression or before the progression could be confirmed if an onset had occurred. Therefore, any disability progression onset occurred after the 21 month visit was to be treated as censored in the analyses.

3.1.1.3.3 Multiplicity Adjustment

To control the overall type-I error rate of the study, a multiplicity adjustment was to be applied to the primary and key secondary endpoints.

There was one primary endpoint and one key secondary endpoint with two doses, which yielded a total of four comparisons. The testing was to be done in a hierarchical order as follows:

1. FTY720 1.25 mg vs. placebo testing treatment difference for aggregate ARR;
2. FTY720 0.5 mg vs. placebo testing treatment difference for aggregate ARR;

3. FTY720 1.25 mg vs. placebo testing treatment difference for time to 3-month confirmed disability progression;
4. FTY720 0.5 mg vs. placebo testing treatment difference for time to 3-month confirmed disability progression.

Each testing was to be performed at a significant level of 0.05 for these four ranked comparisons. However, the lower-ranked testing was to be performed only when every higher-ranked testing preceding it was statistically significant at 0.05.

3.1.1.4 Patient Results

3.1.1.4.1 Patient Disposition

A total of 1564 patients were screened for participation in this study. Of the 1272 patients who were randomized, 1033 (81.2%) completed the study, with the highest percentage of patients completing in the FTY720 0.5 mg group (86.8%) compared with 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. Patient disposition for the randomized population is presented in Table 1.

Table 1 Patient Disposition

	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.

Discontinuations from study drug were mostly common for safety reasons, i.e., 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 vs. the 0.5 mg group. Patients in the FTY720 0.5 mg treatment group discontinued from study drug due to withdrawal of consent less often compared with the FTY720 1.25 treatment group and placebo. Patients in the placebo group discontinued study drug due to unsatisfactory therapeutic effect at least twice as often compared with patients in the two FTY720 treatment groups.

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.

3.1.1.4.2 Baseline demographic characteristics

The study population was consistent with a population of RRMS patients in that approximately two thirds were female (69.9% female vs. 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 these baseline demographic characteristics.

3.1.1.4.3 Baseline disease characteristics

Baseline MS disease characteristics were consistent with a RRMS patient population and were balanced across the treatment groups (Table 2). 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).

Table 2 Clinical MS baseline characteristics

	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

Baseline MRI measures for the FTY720 1.25 mg group were worse than the ones of the other 2 groups. Approximately 40% of the patients showed active lesions on MRI (Table 3).

Table 3 MRI baseline characteristics

	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 (mm³)				
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 (mm³)				
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 (mm³)				
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

3.1.1.4.4 Medications taken prior to the start of study drug treatment

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 4. 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 4 Prior use of MS disease-modifying drug

	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)

3.1.1.5 Efficacy Results

The efficacy results presented in this section represent the ones reported by the sponsor and confirmed by the reviewer as well as the results from additional analyses performed by the reviewer.

3.1.1.5.1 Efficacy Results of the Primary Endpoint

The primary analysis of ARR included 1271 patients. One patient in the FTY720 0.5 mg group did not have prior 2-year relapse number, and was not included in the primary analysis. The patient was included in the calculation of unadjusted ARR and other analyses that did not require baseline number of relapses.

The primary analysis of ARR with negative binomial model was performed, and the results reported by the sponsor were confirmed. Analysis of all relapses during the study and confirmed relapses while on treatment were performed using the same model. The following table presents the results from these analyses.

Table 5 Results from analysis of ARR – Study D2301

Annualized Relapse Rate (ARR)	FTY720 1.25 mg N=429	FTY720 0.5 mg N=425	Placebo N=418
Confirmed relapses during Study			
Unadjusted (observed)	0.19	0.21	0.47
Adjusted (estimated from model)	0.16	0.18	0.40
95% CI	(0.13, 0.19)	(0.15, 0.22)	(0.34, 0.47)
p-value	<.001	<.001	
Hazard ratio from Cox model	0.38	0.48	
% free of confirmed relapse	75.52	71.06	47.85
Confirmed relapses on Treatment			
Unadjusted (observed)	0.16	0.21	0.48
Adjusted (estimated from model)	0.14	0.18	0.43
p-value	<.001	<.001	
All Relapses during Study			
Unadjusted (observed)	0.26	0.31	0.65
Adjusted (estimated from model)	0.24	0.29	0.62
p-value	<.001	<.001	
Relapse rate at patient level (mean)			
Confirmed relapses on study	0.24	0.23	0.56
Confirmed relapses on Treatment	0.30	0.36	1.12
All relapses	0.32	0.32	0.77

Treatment with both FTY720 1.25 mg and FTY720 0.5 mg resulted in lower aggregate ARR compared to treatment with placebo, with ARR estimates of 0.16 and 0.18 vs. 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, which were statistically significant relative to placebo ($p < 0.001$ for both comparisons). The difference between the two FTY720 dose groups was not statistically significant ($p = 0.238$) from the primary analysis.

Results from analyses of ARR for all relapses, confirmed and non-confirmed, and ARR while patients were on treatment are consistent with the results of confirmed relapse (Table 5) in terms of between-group treatment difference. Results from analysis of ARR on per-protocol (PP) population were similar.

The difference between the adjusted and unadjusted relapse rate is largely contributed by countries of Hungary and Slovakia, which were pooled with Estonia and had a total of 30 patients. Without this pooled country, the estimates of ARR would be 0.17, 0.20, and 0.44 for FTY720 1.25 mg, 0.5 mg, and placebo group, respectively. More details of subgroup analysis can be found in Section 4.

The relapse rate at patient level was higher than the relapse rate at group level in all forms of relapses and in all treatment groups. This was because most patients had 0 relapse, and their relapse rate was 0 regardless how long they had stayed in the study. Most of these patients stayed in the study until completion.

Other Analysis Related to the Relapse Rate

Time to first confirmed relapse is plotted in the following graph. Treatment difference in time to first confirmed relapse was analyzed using a log-rank test. The difference between each of the FTY720 dose groups and placebo group yielded a nominal p-value of less than 0.001. Median time to first confirmed relapse could not be obtained because more than half of the patients did not have confirmed relapse at study completion or early withdrawal. Hazard ratio, which measures the relative risk of having a relapse, was estimated from the Cox proportional hazard model, included terms of treatment, country, baseline number of relapses and baseline EDSS scores. The estimated hazard ratio for FTY720 1.25 mg and 0.5 mg group relative to the placebo group was 0.38 and 0.48, respectively, with nominal p-values of less than .001 for comparisons of each of the FTY720 dose groups versus placebo.

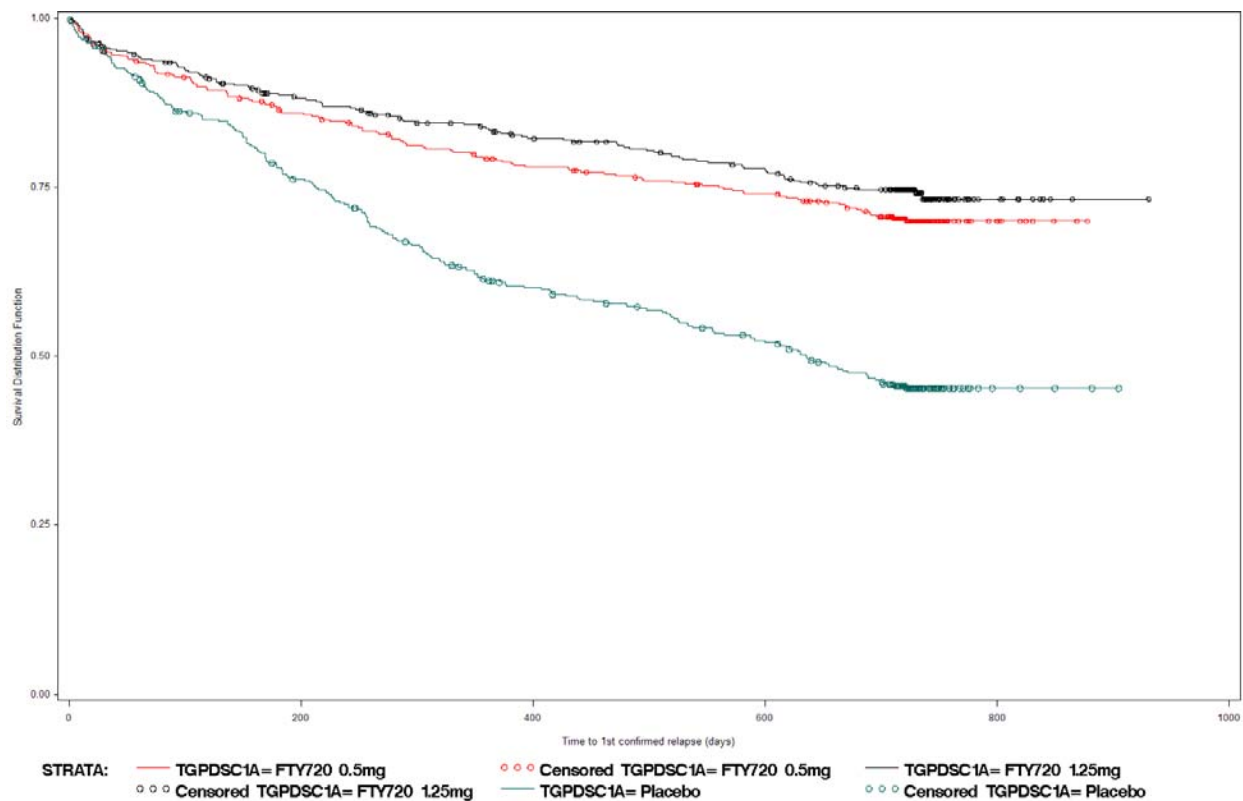


Figure 1 Time to first confirmed relapse - ITT population (D2301)

3.1.1.5.2 Efficacy Results of Secondary Endpoints

The key secondary efficacy endpoint was time to 3-month confirmed disability progression up to Month 24. Time to disability progression curves for each treatment group were generated by the Kaplan–Meier method and compared by means of the log-rank test.

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; nominal $p=0.012$ and $p=0.026$, respectively) (Figure 2). The two FTY720 dose groups were not statistically significantly different ($p=0.7427$). Results from analysis of time to 6-month confirmed disability were similar, with nominal p -values of 0.0044 and 0.0112 for the comparisons of FTY720 1.25 mg and 0.5 mg versus placebo, respectively.

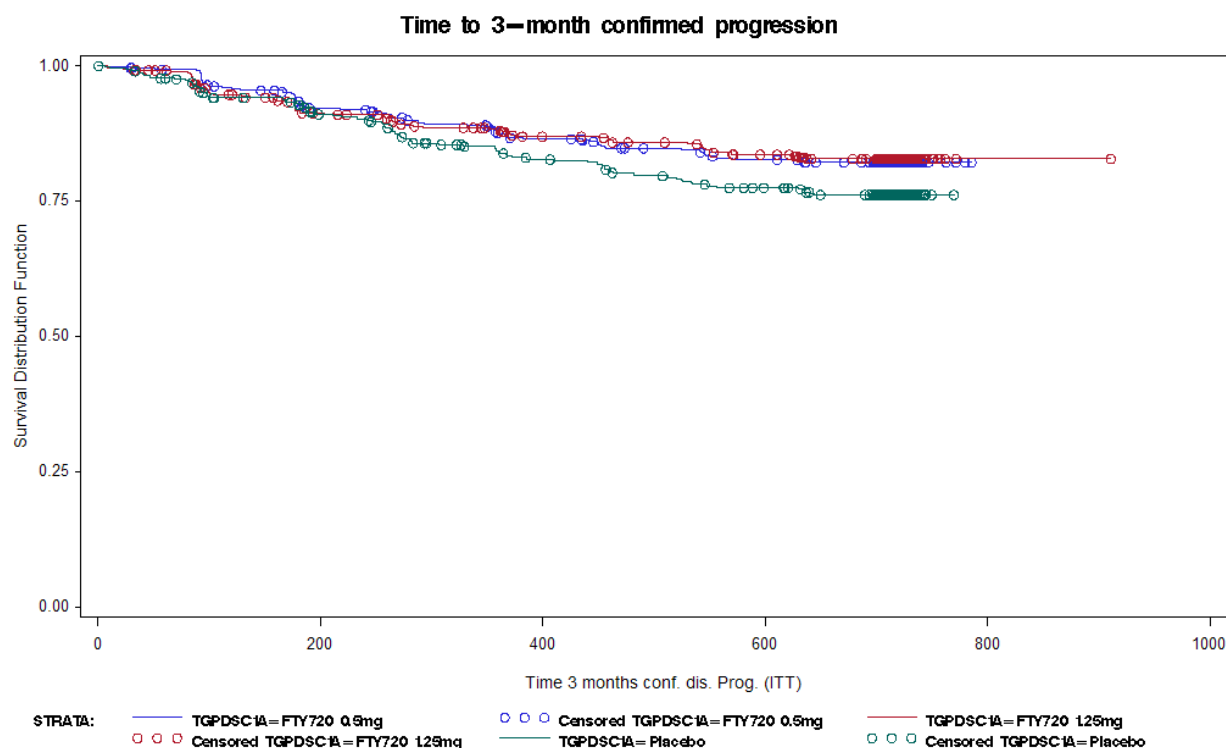


Figure 2 Time to 3-month confirmed disability progression (ITT population)

The median time to 3-month disability progression could not be estimated because more than 50% of patients in each treatment group were censored. The means of time to disability progression are therefore underestimated due to high censoring, and are not reported here.

The percentage of patients without 3-month confirmed disability progression at Month 24 was higher in both FTY720 treatment groups (84.62% and 83.06% for 1.25 mg and 0.5 mg, respectively) compared with placebo (77.51%). The pairwise comparisons yielded nominal p -values of 0.008 and 0.043 for FTY720 1.25 mg and 0.5 mg versus placebo, respectively.

Analyses of change from baseline in EDSS scores were performed for ITT patient population. After excluding the EDSS assessments that were performed during a relapse or assessments from unscheduled visit for safety reasons, 1254 had at least one valid EDSS score during the study. Post-hoc analyses using an ANOVA model adjusted for baseline EDSS score and country were performed. Note that some patients discontinued treatment but stayed in the study, and their last assessment of EDSS score represented the one when they were off study drug. Patients who

discontinued study drug but stayed in the study were allowed to take alternative MS disease modifying drug. Therefore, analysis of change in EDSS from baseline to last on-treatment score was also performed. The following table presents the results.

Table 6 Change from baseline in EDSS score (D2301)

	FTY720 1.25 mg	FTY720 0.5 mg	Placebo
During Study , mean (SD)			
N	420	422	411
Baseline	2.410 (1.358)	2.302 (1.287)	2.468 (1.271)
Change	0.007 (0.888)	0.002 (0.887)	0.135 (0.957)
Nominal p-value	0.0282	0.0144	
On treatment , mean (SD)			
N	387	411	397
Baseline	2.413 (1.343)	2.293 (1.283)	2.448 (1.272)
Change	-0.031 (0.852)	-0.036 (0.859)	0.092 (0.910)
Nominal p-value	0.0369	0.0126	

It appeared that EDSS scores were little changed during the study or while patients were on treatment. However, the nominal p-values without multiplicity adjustment were below 0.05 for all comparisons of FTY720 dose groups versus placebo, which had a small increase in EDSS scores.

3.1.2 Study D2302

3.1.2.1 Description of the Study

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

Key secondary objectives were to demonstrate superiority of FTY720 1.25 mg and 0.5 mg over IFN β -1a 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; and 2) the effect on disability progression as measured by the time to 3-month confirmed disability progression as measured by EDSS.

This was a 12-month, randomized, multicenter, double-blind, double-dummy active-controlled, parallel-group study in patients with RRMS. Patients were randomized to receive an oral fixed dose of FTY720 0.5 mg/day or 1.25 mg/day, or IFN β -1a i.m. 30 μ g/week i.m. in a double dummy design.

The study consisted of three phases: a pre-randomization phase lasting for up to 45 days, a 12-month double-blind treatment phase, and an optional extension phase, which is expected to last until FTY720 is commercially available or development is stopped.

The study was conducted in 172 centers in 18 countries, including US. A total of 1275 patients were planned and 1292 patients were actually randomized. The study enrolled patients who were treatment-naïve or previously treated, had diagnosis of MS by 2005 revised McDonald criteria with a relapsing-remitting course, had at least one documented relapse during the previous year or two documented relapses during the previous 2 years prior to randomization, and had Expanded Disability Status Scale (EDSS) score of 0 to 5.5 inclusive.

3.1.2.2 Efficacy Variables

3.1.2.2.1 Primary Efficacy Variable

The primary endpoint was the ARR, which was defined as the number of relapses in a year. Only confirmed relapses were considered for the primary analyses. Refer to Section 3.1.1.2 for definition of confirmed relapse and calculation of relapse rate.

3.1.2.2.2 Key Secondary Variables

There were two key secondary efficacy variables: number of new or newly enlarged T2 lesions on MRI scan at Month 12 and time to 3-month confirmed disability progression at Month 12.

MRI was to be performed at screening, Month 12, and follow-up visit 3 months after the discontinuation of study drug.

Refer to Section 3.1.1.2 Efficacy Variables for definition of 3-month confirmed disability progression.

3.1.2.3 Statistical Analysis Methods

Efficacy analyses for the primary and secondary efficacy endpoints were to be applied to the intent-to-treat population (ITT), which is defined as all patients who were randomized and received at least one dose of study medication. Patients were grouped according to the assigned treatment.

3.1.2.3.1 Analysis of Primary Efficacy Variable

The primary null hypotheses to be tested were: 1) there is no difference in the ARRs between patients treated with the FTY720 1.25 mg and IFN β -1a, and 2) there is no difference in the ARRs between patients treated with the FTY720 0.5 mg and IFN β -1a.

The test of the hypotheses was to be based on a negative binomial regression model for the aggregate ARR adjusting for treatment group, country, baseline number of relapses in previous 2 years, and baseline EDSS as covariates. For the negative binomial regression, the response variable was the number of relapses for each patient. Log of time on study in years was to be used as the offset variable to account for the varying lengths of patients' time in the study. The ARR and its 95% confidence interval (CI) for each treatment group were to be estimated from the model.

For patients who prematurely discontinued study drug, the intent-to-treat approach was to use all relapse data, i.e. relapse data collected after the study drug discontinuation were included in the analyses.

3.1.2.3.2 Analysis of Key Secondary Efficacy Variables

The first key secondary efficacy endpoint was the number of new or newly enlarged T2 lesions at Month 12. Between-treatment comparisons of FTY720 with IFN β -1a were to be performed using a negative binomial model adjusting for treatment group, country, baseline number of relapses in the previous 2 years, and baseline EDSS.

The second key secondary efficacy endpoint was the time to 3-month confirmed disability progression as measured by EDSS during 12 months.

Time-to-event curves for each treatment group were to be generated by the Kaplan–Meier method and compared by means of the log-rank test.

Cox proportional hazard model was a secondary analysis for the time to 3-month confirmed disability progression. The model was adjusted for treatment, country, baseline EDSS and age. Hazard ratios and p-values were to be obtained.

If a patient died due to MS after the start of tentative progression, then the time to disability progression was to be 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 to be censored if follow-up ended before a confirmed progression occurred. The disability progression occurred after the 9 month visit could not be confirmed due to the 12-month study duration. Hence, they were to be treated as the censoring data in the analysis.

3.1.2.3.3 Multiplicity Adjustment

To control the overall type-I error rate of the study, a multiplicity adjustment was to be applied to the primary and key secondary endpoints. There was one primary endpoint and two key secondary endpoints with two doses, which yielded six FTY720 (1.25 mg and 0.5 mg)

comparisons vs. IFN β -1a. The testing of FTY720 comparisons vs. IFN β -1a was to be done in a hierarchical order according to as follows:

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

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

3.1.2.4 Study Patients

3.1.2.4.1 Disposition of patients

A total of 1573 patients were screened for participation in this study. Of the 1292 patients who were randomized, 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 IFN β -1a group). A total of 1123 patients (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 IFN β -1a 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 IFN β -1a), 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 IFN β -1a). Of the 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 7 presents the disposition of patients.

Table 7 Patient disposition – Study D2302

	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.

Source: [PT-Tables 14.1-1.1](#) and [14.1-1.2](#)

The ITT patient population included 1280 subjects. Overall, 12 patients were excluded from both ITT and safety population because they were randomized in error and did not receive study drug.

The PP population included all ITT patients who did not have any major protocol deviations, and 34 subjects were excluded from the PP population. The three most common protocol deviations which excluded patients from the PP population were: 1) patient took the wrong treatment medication for less than 3 months (i.e., wrong randomization was inadvertently dispensed to the patient at one of the study visits by the study staff) (0.9% of all patients); 2) unblinding through MRI (i.e., MRI information was inadvertently shared between the local neuroradiologist and investigator) (0.8% of all patients); and 3) not following per protocol blinding procedures (PI accidentally saw hematology results) (0.7% of all patients).

3.1.2.4.2 Baseline Demographic Characteristics

The groups were balanced for age, sex, and race. Approximately two-thirds of patients were female (67.3% female vs. 32.7% male) and the majority (94.1%) of patients in all groups were Caucasian. The median age was 36 years.

3.1.4.2.3 Baseline Disease Characteristics

Across all treatment groups the mean duration of MS since first symptoms was 7.4 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 IFN β -1a group. The MS disease characteristics of patients at baseline are summarized by treatment group in Table 8.

Table 8 Clinical MS baseline characteristics - Study D2302

	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 mean number and the volume of Gd-enhanced T1-weighted lesions at baseline was higher in the FTY720 1.25 mg group (1.5 and 147.5, respectively) than in the FTY720 0.5 mg group (1.0 and 93.9, respectively) and the IFN β -1a group (1.1 and 100.7, respectively), and the difference (vs. the IFN β -1a group) carried a p-value of 0.068. The total volume of T2 lesions as well as all other baseline MRI characteristics was comparable among treatment groups. MRI characteristics for patients at baseline are summarized by treatment group in Table 9.

Table 9 MRI baseline characteristics - Study D2302

	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

About 40-45% of the patients were treatment-naïve. 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 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. Table 10 presents the information of prior use of MS disease-modifying drug.

Table 10 Prior use of MS disease-modifying drug - Study D2302

	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](#)).

Source: [PT-Table 14.1-3.10](#)

3.1.2.5 Efficacy Results

3.1.2.5.1 Efficacy Results of the Primary Endpoint

One patient in the IFN β -1a group did not have prior 2-year relapse number, and was not included in the primary analysis. The patient was included in the calculation of unadjusted ARR and other analyses that did not require baseline number of relapses. Another patient in the FTY720 0.5 mg group had 40 relapses during the 2 years prior to study entry, and the patient baseline relapse number was changed to 24, the maximum possible in a 2-year period. This change did not result in different estimates of ARR from the ones obtained by the sponsor in the primary analysis. The results for the primary efficacy analysis (aggregate ARR analyzed using negative binomial regression), analysis of all relapses during the study and confirmed relapses while on treatment are shown in the following table.

Table 11 Results from analysis of ARR – Study D2302

ARR	FTY720 1.25 mg N=420	FTY720 0.5 mg N=429	IFN β-1a N=431
Confirmed relapses during Study			
Unadjusted (observed)	.26	.21	.43
Adjusted	.20	.16	.33
95% CI	(.16, .26)	(.12, .21)	(.26, .41)
p-value	<.001	<.0001	
Hazard ratio from Cox model	.63	.52	
% free of confirmed relapse	80.48	82.52	70.07
Confirmed relapses on Treatment			
Unadjusted	.25	.21	.43
Adjusted	.20	.16	.34
p-value	.0002	<.0001	
All Relapses			
Unadjusted	.33	.30	.63
Adjusted	.28	.24	.51
p-value	<.0001	<.0001	
Relapse rate at patient level (mean)			
Confirmed relapses on study	0.26	0.21	0.43
Confirmed relapses on Treatment	0.25	0.21	0.43
All relapses	0.33	0.30	0.63

Treatment with both FTY720 1.25 mg and FTY720 0.5 mg resulted in a significantly lower ARR compared to treatment with IFN β -1a with ARR estimates of 0.20 and 0.16 vs. 0.33, respectively. This corresponded to reductions of 38% and 52% in ARR estimates, respectively, which were statistically significant ($p < 0.001$ for both comparisons). The difference between the two FTY720 dose groups was not statistically significant ($p = 0.152$) from the primary analysis.

Results from analyses of ARR for all relapses, confirmed and non-confirmed, and ARR while patients were on treatment are consistent with the results from analysis of confirmed relapse.

Three countries had a large effect on estimates of the relapse rate: Korea with 18 patients, Greece with 31 patients and Switzerland with 22 patients. More details of subgroup analysis including difference between US and non-US patient population can be found in Section 4.

Time to first confirmed relapse is plotted in the following graph. Treatment difference in time to first confirmed relapse was analyzed using a log-rank test and hazard ratios were estimated from the Cox proportional hazard model. The difference between each of the FTY720 dose groups and placebo group yielded a nominal p-value of less than 0.001 from the log-rank test. Median time to first confirmed relapse could not be obtained because more than half of the patients did not have confirmed relapse at study completion or early withdrawal.

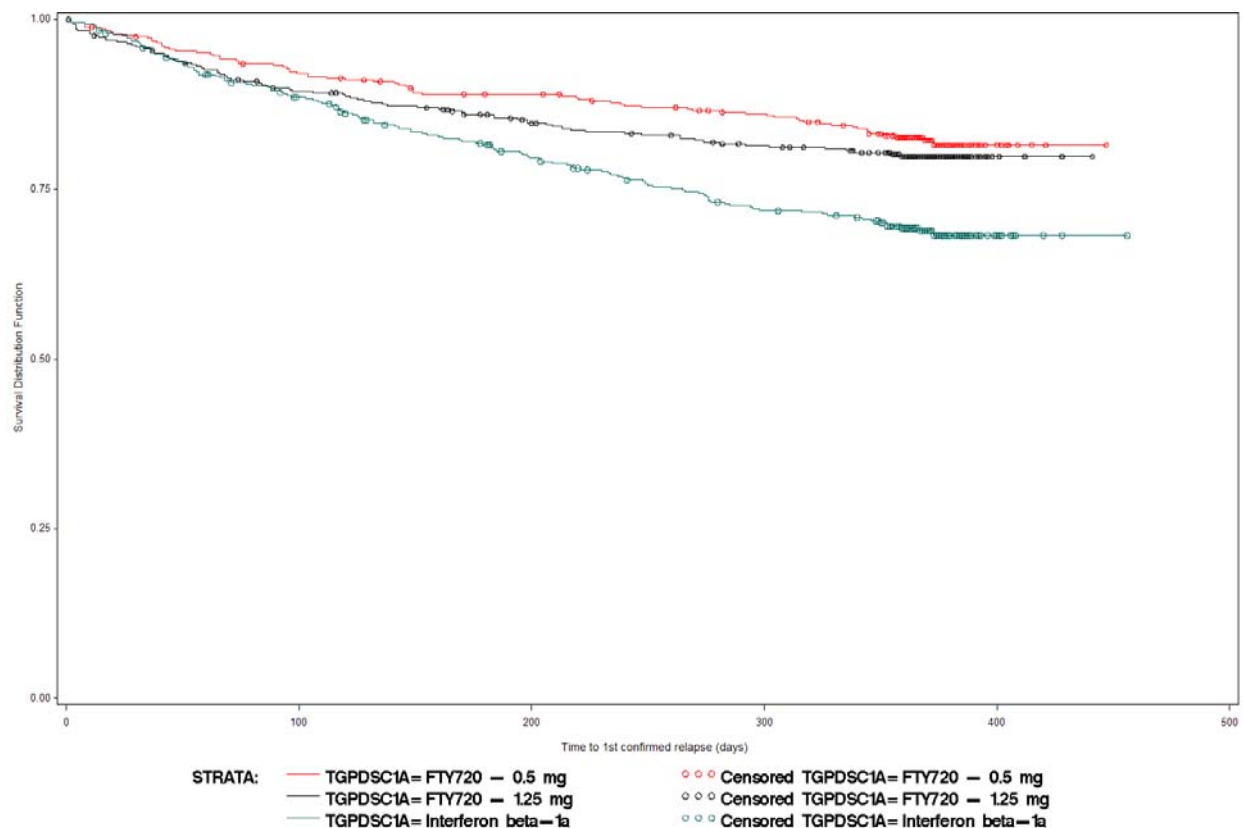


Figure 3 Time to confirmed relapse - ITT population (D2302)

Results from analyses of ARR on PP population and ARR at the patient level were consistent with the results from the primary analysis.

3.1.2.5.2 Efficacy Results of Key Secondary Endpoints

New or newly enlarged T2 lesions at Month 12

The results in this section were reported from the sponsor. I will analyze the MRI data when scans of 18 patients are re-read. The sponsor filed an amendment with new analysis in which 18 patients were excluded.

The number of new or newly enlarged T2 lesions at Month 12 was compared between 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 12.

Table 12 Mean number of new or newly enlarged T2 lesions at Month 12 - D2302

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

n=the number of patients with evaluable MRI at baseline and Month 12

P-value is calculated using a negative binomial model adjusting for treatment, country, baseline number of relapses in the previous 2 years, and baseline EDSS.

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 IFN β -1a group, which reached statistical significance for the FTY720 1.25 mg group ($p=0.017$) and did not reach statistical significance for the FTY720 0.5 mg group ($p=0.053$). In the PP population, the mean number of new or newly enlarged T2 lesions at Month 12 compared to the IFN β -1a group, did not reach statistical significance for the FTY720 1.25 mg group ($p=0.067$) or the FTY720 0.5 mg group ($p=0.052$).

As described in [Section 9.8.3](#), a sensitivity analysis for this efficacy endpoint was performed using the same negative binomial regression model pre-specified in the analysis plan on all available data (two FTY720 arms and IFN β -1a) to fully assess the effect of the covariates on treatment responses. Analysis results showed that both FTY720 1.25 mg and 0.5 mg treatment groups were superior to IFN β -1a ($p=0.007$ and 0.038 , [PTTable 16.19-1.7](#)). The analysis details are reported in [Appendix 16.1.9-Statistical document](#)).

Time to 3-month confirmed disability progression at Month 12

There was no difference between either of the two FTY720 treatment groups and the IFN β -1a group in the time to 3-month confirmed disability progression based on log-rank test (p -values are 0.4979 and $.2475$ for FTY720 1.25 mg and 0.5 mg versus IFN β -1a, respectively).

Altogether, 85 patients had confirmed disability progression, 27 in the 1.25 mg FTY720 group, 25 in the 0.5 mg FTY720 group, and 33 in the placebo. The proportion of patients who were free of disability progression were 94.20% and 92.41% for FTY720 1.25 mg and 0.5 mg groups, respectively, compared to 93.66% for the IFN β -1a group. The Kaplan-Meier curve for the time to 3-month confirmed disability progression at Month 12 is shown in Figure 4.

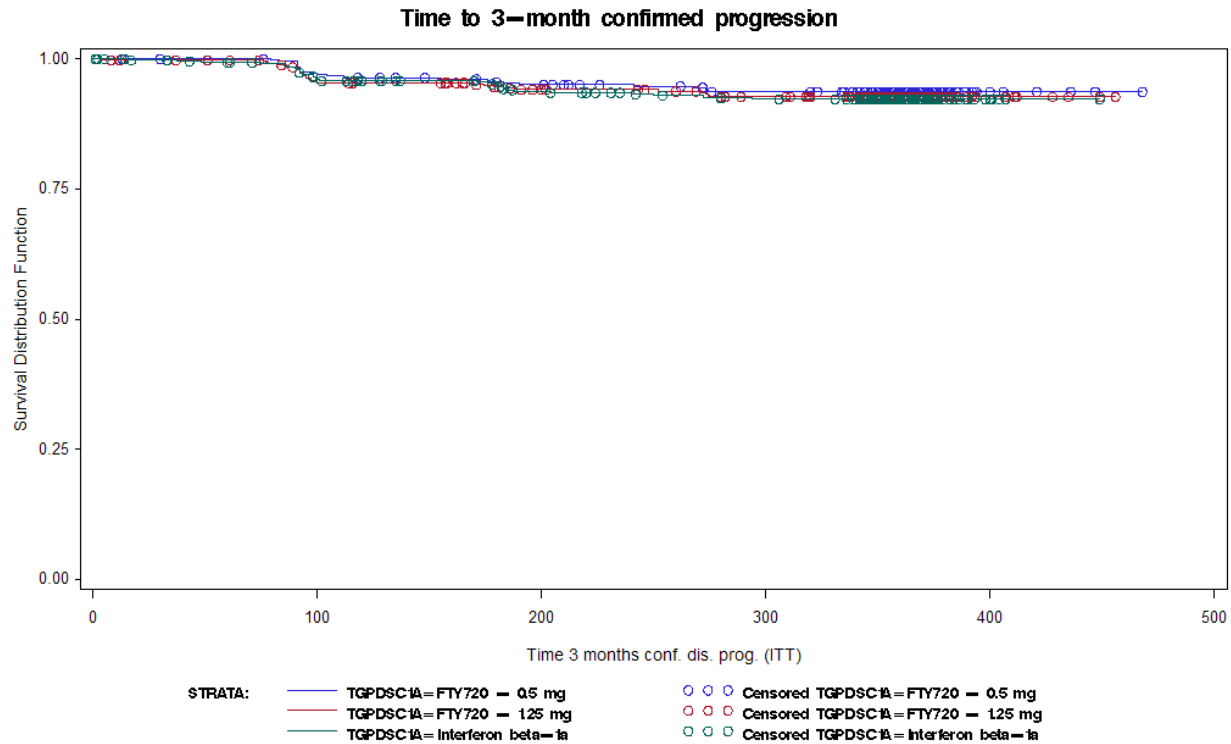


Figure 4 Time to 3-month confirmed disability progression - ITT population (D2302)

In order to examine whether or not the lack of treatment difference in disability progression was due the short length of this study as compared to Study D2301, which was a 2-year study, the first year data of D2301 was analyzed for disability progression and compared to results of D2302. Note that patients who had onset of disability progression after 9 months could not be confirmed in Study D2302. Therefore, the analysis of data in Study D2301 used cutoff time of 290 days, which approximated 9 months plus 14 days of window period. Patients in Study D2301 who did not have onset of disability progression by 290 days were censored.

Table 13 Comparison of disability progression rate for D2301 and D2302

D2301 first 9 months	FTY720 1.25 mg N=429	FTY720 0.5 mg N=425	Placebo N=418
Number (%) progressed	66 (15.38%)	72 (16.94%)	94 (22.49%)
p-value	P=0.1024	P=0.0590	
D2302	FTY720 1.25 mg N=420	FTY720 0.5 mg N=429	IFN β -1a N=431
Number (%) progressed	27 (6.43%)	25 (5.83%)	33 (7.66%)
p-value	0.4979	0.2475	

Difference in time to 3-month disability progression for Study D2301 did not reach statistical significance level for either of the FTY720 dose groups but had much smaller p-value compared to Study D2302: p=0.1024 for comparison of FTY720 1.25 mg versus placebo and p=0.0590 for comparison of FTY720 0.5 mg versus placebo. In Study D2302, p-values from comparisons of FTY720 1.25 mg and 0.5 mg versus IFN β -1a were 0.4979 and 0.2475, respectively.

Change from baseline in EDSS scores were performed for ITT patient population. After excluding the EDSS assessments that were performed during a relapse or assessments from unscheduled visit for safety reasons, 1248 patients had at least one valid EDSS score during the study. Post-hoc analyses using an ANOVA model adjusted for baseline EDSS score and country were performed. Note that some patients discontinued treatment but stayed in the study, and for those patients their last assessment of EDSS score represented the one when they were off study drug. Patients who discontinued study drug but stayed in the study were allowed to take alternative MS disease modifying drug. Therefore, analysis of change in EDSS from baseline to last on-treatment score was also performed. The following table presents the results.

Table 14 Change from baseline in EDSS score (D2302)

	FTY720 1.25 mg	FTY720 0.5 mg	IFN β-1a
During Study , mean (SD)			
N	408	423	417
Baseline	2.212 (1.299)	2.243 (1.334)	2.159 (1.249)
Change	-0.103 (0.862)	-0.084 (0.778)	0.016 (0.798)
Nominal p-value	0.0421	0.1005	
On treatment , mean (SD)			
N	394	412	407
Baseline	2.206 (1.290)	2.239 (1.332)	2.154 (1.257)
Change	-0.126 (0.806)	-0.108 (0.800)	0.010 (0.781)
Nominal p-value	0.0182	0.0504	

There was a small decrease in EDSS scores in both of the FTY720 dose groups and small increase in the IFN β -1a group. The nominal p-values without multiplicity adjustment for the treatment difference in this post-hoc analysis were below 0.05 in the comparison between FTY720 1.25 mg group versus placebo group, but were above 0.05 for the comparison between FTY720 0.5 mg group versus placebo group.

3.2 Evaluation of Safety

Refer to Clinical Review by Dr. Heather Fitter and Safety Review by Dr. Lourdes Villalba for Evaluation of Safety.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Analyses of relapse rate by gender and age group were performed. The majority of patients were Caucasians, and analysis by race was not performed. The following table presents the estimated relapse rate and the p-value for the comparison between each of the FTY720 dose group and the control group in the subgroup population. Due to the large number of countries and relatively small number of patients in each sub-population, accurate estimate of relapse rate from the negative binomial model could not be obtained, and unadjusted relapse rates are presented. In both studies, the data did not suggest gender or age difference in relapse rate.

Table 15 ARR by gender and age group – Study D2301

Study D2301 Unadjusted relapse rate	FTY720 1.25 mg	FTY720 0.5 mg	Placebo
Overall Population			
N	429	425	418
ARR	0.19	0.21	0.47
Sex			
Male, n	134	129	120
ARR	0.21	0.18	0.54
Female, n	295	296	298
ARR	0.18	0.23	0.44
Age			
≤ 37 years, n	204	237	215
ARR	0.19	0.20	0.53
> 37 years, n	225	188	203
ARR	0.19	0.23	0.40

Table 16 ARR by gender and age group - Study D2302

Study D2302 Unadjusted relapse rate	FTY720 1.25 mg	FTY720 0.5 mg	IFN β-1a
Overall Population			
N	420	429	431
ARR	0.26	0.21	0.43
Sex			
Male, n	132	148	139
ARR	0.29	0.21	0.34
Female, n	288	281	292
ARR	0.24	0.21	0.47
Age			
≤ 37 years, n	232	226	244
ARR	0.25	0.18	0.48
> 37 years, n	188	203	187
ARR	0.28	0.24	0.36

4.2 Other Special/Subgroup Populations

Both studies were conducted in a large number of countries globally. Study D2301 was conducted outside of US in 22 countries. A few countries with small number of patients were pooled together to form larger pooled countries: UK and Ireland were pooled, Greece and Israel were pooled, and Estonia, Hungary and Slovakia were pooled. The effect from the pooled countries of Estonia, Hungary and Slovakia was so big that the estimates of ARR and confidence intervals could not be obtained if the pooling was not formed. Among the 3 countries, Hungary and Slovakia belonged to the same region while Estonia was a single country separated from others and had little effect. Altogether, 30 patients were from these 3 countries: 5 in Estonia, 12 in Hungary, and 13 in Slovakia. The following table presents the ARR estimates with the p-values in the overall patient population and in patient population without these 3 countries.

Table 17 Analysis of ARR by region - Study D2301

D2301	FTY720 1.25 mg N=429	FTY720 0.5 mg N=425	Placebo N=418
Overall Patient Population			
Adjusted ARR	0.16	0.18	0.40
95% CI	(0.13, 0.19)	(0.15, 0.22)	(0.34, 0.47)
p-value	<.001	<.001	
Excluding patients in 3 countries			
n	417	416	409
Adjusted ARR	0.17	0.20	0.44
95% CI	(0.14, 0.21)	(0.17, 0.24)	(0.37, 0.51)
Nominal p-value	<.001	<.001	

Although these 30 patients constituted only less than 2.5% of the total patient population, the estimates of ARR were quite different without them. The p-values were little changed.

Study D2302 was conducted in 18 US and non-US countries. ARR was estimated by sub-populations of US and non-US patients. Korea was the only country in Asia and Greece was the only country in East Europe. These two countries had small number of patients, 18 and 31, respectively, but had large effect in the estimation of ARR. Therefore, estimates of ARR from non-US countries excluding these two countries are also provided. The results are presented in the following table.

Table 18 Analysis of ARR by resion - Study D2302

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

The number of patients in US sites was about 10% of the total patient population, and the estimates of ARR were quite different from the estimates of the non-US patient population. The estimated ARR for FTY720 0.5 mg group and the placebo group were the same (0.28), and estimated ARR for FTY720 1.25 mg group was much smaller (0.16) than the estimate from the overall patient population (0.20). The following table breaks down in the number of relapse for US and Italy, which had the largest number of patients.

Table 19 Number of relapse in US and Italy by treatment group - Study D2302

	Number of Relapses				
	0	1	2	3	4
USA					
FTY720 1.25 mg (n=42)	36 (85.71%)	5 (11.90%)	1 (2.38%)	0 (0%)	0 (0%)
FTY720 0.5 mg (n=42)	30 (71.43%)	11 (26.19%)	1 (2.38%)	0 (0%)	0 (0%)
IFN β -1a (n=45)	34 (75.56%)	9 (20.00%)	1 (2.22%)	1 (2.22%)	0 (0%)
Italy					
FTY720 1.25 mg (n=79)	70 (88.61%)	7 (8.86%)	2 (2.53%)	0 (0%)	0 (0%)
FTY720 0.5 mg (n=88)	75 (85.23%)	12 (13.64%)	0 (0%)	0 (0%)	1 (1.14%)
IFN β -1a (n=83)	65 (78.31%)	13 (15.66%)	5 (6.02%)	0 (0%)	0 (0%)

The estimates of ARR from overall non-US countries were lower than those from non-US countries without Korea and Greece across all treatment groups, though the p-values were little changed.

Annual relapse rate in subgroups with respect to prior MS-drug use, baseline EDSS score and baseline number of Gd-enhancing lesions were reported by the sponsor. The data suggests that treatment-naïve and less severe patients had lower relapse rate than the more severe patients, which was normally expected (results not shown).

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The two pivotal studies collectively provided sufficient evidence that FTY720 at doses 1.25 mg or 0.5 mg is effective in treating patients with relapsing form of multiple sclerosis. No major statistical issues were identified.

5.2 Conclusions and Recommendations

The efficacy results obtained from the analyses of the two pivotal studies D2301 and D2302 support the conclusion that FTY720 is effective in treating patients with relapsing form of multiple sclerosis.

Risk Evaluation and Mitigation Strategy (REMS)

Information about risk evaluation and mitigation strategy (REMS) is available in the draft Guidance for Industry: Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications.

Typically, product safety issues are managed through a product's package insert, sponsor-provided communications, post-marketing studies, and routine post-marketing safety surveillance. However, if the seriousness of the risks associated with the product make it necessary to require and enforce risk management beyond these measures, the Food and Drug Administration Amendments Act of 2007 (FDAAA) provides FDA authority to require (REMS). Accordingly, REMS may be required if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks (Section 505-1(a)). Before requiring a REMS, FDA must consider the following: the estimated size of the population likely to use the product, the seriousness of the disease or condition that is to be treated with the product, the expected benefit of the product with respect to such disease or condition, the expected or actual duration of treatment with the drug, the seriousness of any known or potential adverse events related to the drug and the background incidence of such events in the population likely to use the drug, and whether the drug is a new molecular entity.

REMS may include one or more of the following: A Medication Guide or patient package insert for patients, a communication plan for healthcare providers, and elements to assure safe use (ETASU). The statute [Section 505-1(d)] also requires that all approved REMS for NDA and BLA products have a timetable for submission of assessments of the REMS. These assessments are prepared by the sponsor and reviewed by FDA.

A Medication Guide provides FDA approved patient labeling. A Medication Guide can be required if FDA determines one or more of the following apply:

- Patient labeling could help prevent serious adverse events.
- The product has serious risks that could affect a patient's decision to use or continue to use the drug.
- Patient adherence to directions is crucial to product effectiveness.

A communication plan consists of FDA approved materials used to aid a sponsor's implementation of the REMS and/or inform healthcare providers about serious risk(s) of an approved product. For example, "Dear Healthcare Professional" letters, collaboration with professional societies, brochures focusing on the important risk messages, and other educational materials have been required to alert prescribers to serious risks associated with the use of certain drugs and biologics.

ETASU can include one or more of the following requirements:

- Prescriber training or certification
- Certification of dispensers
- Drug administration restricted to certain health care settings
- Documentation of safe-use conditions prior to dispensing
- Monitoring of patients
- Enrollment of patients in a registry

Because ETASU can impose significant burdens on the healthcare system and reduce patient access to treatment, ETASU are required only if FDA determines that the product could be approved only if, or would be withdrawn unless, ETASU are required to mitigate a specific serious risk listed in the labeling. Accordingly, the statute [FDCA 505-1(f)(3)] specifies that ETASU:

- Must be commensurate with specific serious risk(s) listed in the labeling.
- Cannot be unduly burdensome on patient access to the drug.
- To minimize the burden on the healthcare delivery system, must, to the extent practicable, conform to REMS elements for other drugs with similar serious risks and be designed for compatibility with established distribution, procurement, and dispensing systems for drugs.