U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22527 / Serial Number 0538
Drug Name:	Gilenya® (fingolimod)
Indication(s):	Multiple Sclerosis
Applicant:	Novartis
Date(s):	Submission Date: November 13, 2017
	PDUFA Due Date: May 13, 2018
Review Priority:	Priority Review
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1. EXECUTIVE SUMMARY

The purposes of this sNDA submission are to add the indication of Gilenya® (fingolimod) in pediatric patients 10 to <18 years of age with relapsing multiple sclerosis (MS) and to request pediatric exclusivity in response to the Pediatric Written Request.

Novartis has conducted a flexible-duration (up to 24 months) study, Protocol D2311, to compare the efficacy, safety, and tolerability of fingolimod in pediatric patients with relapsing forms of MS. Overall, the study D2311 has demonstrated superior efficacy of fingolimod over IFN β-1a on reduction of annualized relapse rate (ARR). The outcome of the pediatric study supports the application for fingolimod as the first MS treatment for pediatric MS patients aged 10 to < 18 years.

2. INTRODUCTION

2.1 Overview

The Core Phase of Study D2311 was a double-blind, double-dummy, randomized, active-controlled, parallel group, multicenter, flexible-duration (up to 24 months) study designed to evaluate the efficacy and safety of fingolimod compared to IFN β-1a in pediatric patients (10 to <18 years old) with a confirmed diagnosis of MS with relapsing remitting course.

The study D2311 demonstrated statistically superior efficacy of fingolimod vs. IFN β-1a in the treatment of pediatric patients aged 10 to <18 years with relapsing MS. Treatment with fingolimod for up to 24 months corresponds to a reduction of 81.9% in ARR compared with IFN β-1a ($p<0.001$). The robustness of the primary analysis results was confirmed with supportive and sensitivity analyses.

Table 1 List of All Studies Included in This Review

	Phase and Design	Treatment Period	Comparator	# of Subjects per Arm	Study Population
D2311	Phase 3, randomized, double-blind, 2-arm, active-controlled	Up to 24 months	IFNβ-1a	Fingolimod: 107 IFNβ-1a: 107	Pediatric patients 10 to < 18 years old

Source: Reviewer's summary

2.2 Data Sources

The path to CDER Electronic Document Room for documents of this NDA is listed below:

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3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The data quality was generally good and the reviewer was able to confirm the derived data and study results of the primary and key secondary endpoints.

3.2 Evaluation of Efficacy

3.1.1 Study Design

The primary objective of the study was to evaluate the efficacy of fingolimod relative to intramuscular interferon β-1a (IFN β-1a) in reducing the frequency of relapses as assessed by the annualized relapse rate (ARR) in pediatric MS patients aged 10 to less than 18 years treated for up to 24 months.

The study was divided into a Core Phase, which included the Pre-Randomization Period and the Double-Blind Treatment Period, and an Extension Phase in which all patients were treated with fingolimod.

The Core Phase was a double-blind, double-dummy, randomized, active-controlled, parallel-group multicenter study phase to evaluate the efficacy and safety of fingolimod compared to IFN β -1a in children/adolescent patients aged 10 to less than 18 years with MS. The end of the Core Phase of the study was determined by a blinded sample size re-estimation (BSSR).

The study was originally designed with a fixed duration of 24 months for the double-blind phase. While the trial was ongoing, Novartis submitted a request on November 6, 2015, to modify the study duration from a fixed 2-year duration to a flexible duration of up to 2 years if certain conditions were met based on a BSSR. Novartis stated that the change was because the study was overpowered due to the higher than anticipated observed relapse rate. The Agency granted the request and an amendment of the Written Request for the study was sent to Novartis on March 8, 2016.

The conditions to be met based on BSSR were as follows:

I. Under the condition that a further BSSR in the first quarter of 2017 indicates that the projected amount of information allows to take a decision to stop the trial in June 2017, while maintaining 80% power for the primary analysis, the study will stop earlier as planned.
II. If the blinded sample size re-estimation, based on the relapse rate observed, is below what is needed to maintain 80% power for the primary analysis, and does not allow to take the decision to stop the trial in June 2017, then the study will continue so that all patients are enrolled for a minimum of 2 years, as originally planned.

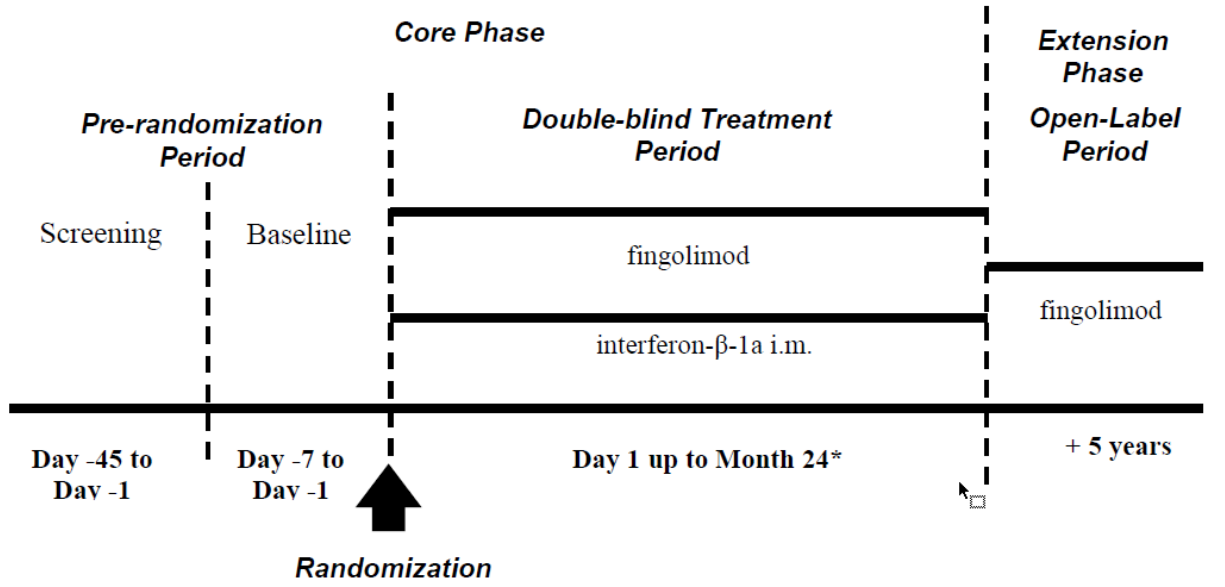
The criteria for stopping the Core Phase of the study was met with the BSSR conducted in the first quarter of 2017. The BSSR predicted that the study would maintain 80% power to detect a 50% relative treatment effect for the primary analysis if the study was stopped by the end of the first half of 2017. The study was subsequently stopped on 14-Jul-2017 (last patient last treatment).

On Day 1, the first visit in the double-blind treatment period, eligible patients were randomized to 1 of the 2 treatment groups (fingolimod or IFN β-1a) in a 1:1 ratio. Post-randomization visits were scheduled at 2 weeks, 1 month, 2 months, 3 months and then every 3 months during the double-blind treatment period.

The dose regimen yielding systemic exposure comparable to that obtained in MS adult patients was selected. The dose regimen chosen in this study, based on body weight, was:

- 0.5 mg/day for all patients weighing more than 40 kg (at treatment initiation and/or during the study);
- 0.25 mg/day for all patients weighing 40 kg or less.

The study was conducted in 87 centers in 26 countries worldwide.



*The 3-MFU visit will be required for those patients that do not go into the Extension Phase.

Figure 1 Study Design
Source: CSR

3.1.2 Efficacy Variables

3.1.2.1 Primary Efficacy Endpoint

The primary efficacy variable was the annualized relapse rate (ARR). For the primary analysis, the number of relapses was to include all the confirmed relapses experienced during the study.

3.1.2.2 Secondary Efficacy Endpoint

The key secondary variable was the annualized rate of the number of new/newly enlarged T2 lesions from baseline to end of the study, with duration up to 24 months.

Other secondary endpoints included time to first confirmed relapse, proportion of patients free of relapse, and number of T1 Gd-enhancing lesions per scan up to Month 24.

3.1.3 Statistical Analysis Methods

Unless otherwise specified, all efficacy analyses were to be based on the Full Analysis Set (FAS), defined as all randomized subjects with assigned treatments who took at least one dose of study medication.

3.1.3.1 Analysis of the Primary Efficacy Variable

As specified in the SAP, the primary efficacy variable, the aggregate annualized relapse rate (confirmed relapse), was to be analyzed using a negative binomial regression model adjusted by treatment group, region, pubertal status as main factors, and number of relapses within the previous two years as a covariate.

According to the SAP, the response variable for this analysis was the number of confirmed relapses, and the quadratic variance estimate was to be used. The natural log of time in study in years was to be used as an offset to account for the varying lengths of subjects' time in the study. Model-based estimates of the ARR was to be estimated with the OBSMARGINS (OM) option.

Supportive analysis on confirmed relapses **on study drug** (i.e., relapses counted only up to study drug discontinuation) and confirmed relapse on per-protocol set (PPS) were to be performed.

Supportive analysis using the same negative binomial model as in the primary analysis was to be performed on all relapses (i.e., confirmed and unconfirmed relapses) in the FAS and PPS, and at each quarterly time points Month 3, 6, ..., 24 in the FAS.

3.1.3.2 Analysis of the Key Secondary Efficacy Variable

The key secondary endpoint of new or newly enlarging T2 lesions was to be analyzed based on a negative binomial regression model adjusted for treatment, pubertal status, region, and number of T2 lesions at baseline. The natural log of years in study was to be used as an offset. The model was to provide estimates of the annualized rate of new/newly enlarging T2 lesions up to Month 24.

3.1.3.3 Analysis of Other Secondary Efficacy Variables

The log-rank test of the treatment difference and the Kaplan–Meier estimates of the survival function of the time to first relapse were to be performed.

Cox's proportional hazards model adjusted for treatment, region, pubertal status, and number of relapses within the previous two year was to be performed as a supportive analysis for time to first relapse. Estimates of the hazard ratio and its 95% confidence intervals, and the p-value for treatment comparison from the Cox model were to be provided.

Number of T1 Gd-enhancing lesions per scan up to Month 24 was to be analyzed using a negative binomial regression adjusted by treatment, region, pubertal status and baseline T1 Gd-enhancing lesions. The number of scans was to be used as an offset. The response variable was the cumulative number of T1 Gd-enhancing lesions from each visit up to Month 24. The number of Gd-enhancing lesion data obtained less than 30 days after use of steroid for treatment of relapses was to be excluded from the analysis.

3.1.3.4 Missing data handling

1) Primary efficacy variable- confirmed relapse

The primary negative binomial model with an offset for the time in study was to adjust for various treatment duration and missing information (drop-out or censoring at the time of study completion) under the assumption of missing at random and constant relapse rate over time. According to the protocol, subjects who discontinued study treatment were to remain in the study and follow the assessment schedule. Relapses were to be counted regardless of whether a subject was on or off the study drug.

2) Key secondary efficacy variable – new/newly enlarging T2 lesions

Under the flexible duration study design, some patients did not complete the full 2-year follow-up due to the end-of-study censoring. This administrative censoring was unrelated to the treatment or the occurrence of relapse, so the number of censored patients and censoring times were expected to be balanced with respect to treatment. No imputation was planned for the end of study censoring.

3.1.3.5 Multiplicity adjustment

There was one primary endpoint and one key secondary endpoint. The key secondary endpoint was to be tested at 0.05 significance level if the hypothesis for the primary endpoint was statistically significant at 0.05.

3.1.4 Patient Results

3.1.4.1 Patient Disposition

A total of 215 patients were randomized into the study; 107 patients to the fingolimod group and 108 patients to the IFN β-1a group. One patient in the IFN β-1a group was randomized but not treated due to administrative problems (inability to swallow medication) and this patient was excluded from FAS.

More patients in the fingolimod group completed the Core Phase of the study (overall and while on study drug) than in the IFN β-1a group. The reasons for discontinuation from the Core Phase were generally comparable between the groups with one exception: 6.5% (7 patients) of patients discontinued from the Core Phase due to unsatisfactory therapeutic effect in the IFN β-1a group compared with none in the fingolimod group.

Three times as many IFN β-1a treated patients discontinued the study drug prematurely (patients could remain in the study) compared with the fingolimod treated patients. The primary reasons for discontinuation of study drug prematurely were generally comparable across both treatment groups, except for unsatisfactory therapeutic effect which was higher in the IFN β-1a group (12% [13 patients]) compared with none in the fingolimod group.

A summary of patient disposition is presented in Table 2.

Table 2 Patient Disposition – Randomized Set

	FTY720 N (%)	IFN β – 1a N (%)
Number of patients randomized	107	108
Number of patients treated	107 (100)	107 (99.1)
Completed core phase	100 (93.5)	88 (81.5)
Discontinued from the *core phase*	7 (6.5)	20 (18.5)
Withdrew consent	3 (2.8)	5 (4.6)
Unsatisfactory therapeutic effect	0	7 (6.5)
Adverse event(s)	3 (2.8)	2 (1.9)
Physician's decision	1 (0.9)	2 (1.9)
Patient/guardian decision	0	2 (1.9)
Administrative problems	0	1 (0.9)
Protocol deviation	0	1 (0.9)
Discontinued *study drug*	8 (7.5)	26 (24.1)
Withdrew consent	1 (0.9)	4 (3.7)
Unsatisfactory therapeutic effect	0	13 (12.0)
Adverse event(s)	4 (3.7)	2 (1.9)
Physician's decision	2 (1.9)	3 (2.8)
Patient/guardian decision	1 (0.9)	3 (2.8)
Protocol deviation	0	1 (0.9)
Patient's duration in study		
Mean (median) time in days	613 (649)	553 (561)
Duration interval, n (%)		
< 12 months	5 (4.7)	13* (12.0)
12 - < 18 months	29 (27.1)	36 (33.3)
18 - < 21 months	18 (16.8)	19 (17.6)
> 21 months	55 (51.4)	40 (37.0)

* Including one that was not treated
Source: CSR and reviewer's summary

3.1.4.2 Baseline demographic characteristics

The demographic characteristics of patients are summarized by treatment in Table 3. The groups were balanced for sex and race. As expected in a population typical of MS, the majority of patients were White and predominantly female (slight preponderance in the fingolimod group). The median age was 16 years. Among the subcategories of age ≤ 12 years old, weight ≤ 40 kg, and pre-pubertal status (based on Tanner staging scoring), there were slight differences between the treatment groups.

Table 3 Demographic Summary (randomized set)

	FTY720 N=107	IFN β – 1a N=108
Age at randomization (years)		
Mean (SD)	15.2 (2.0)	15.4 (1.6)
Median	16.0	16.0
Age Group, n (%)		
>=10 to <=12	13 (12.1)	9 (8.3)
> 12 to <= 14	16 (15.0)	19 (17.6)
> 14 to <=16	44 (41.1)	45 (41.7)
> 16 to < 18	34 (31.8)	35 (43.4)
Sex, n (%)		
Female	70 (65.4)	64 (59.3)
Male	37 (34.5)	44 (40.7)
Race, n (%)		
White	100 (93.5)	97 (89.8)
Other	7 (6.5)	11 (10.2)
Weight Group, n (%)		
<=40 kg	9 (8.4)	1 (0.9)
> 40 kg	98 (91.6)	107 (99.1)
Pubertal status (Tanner), n (%)		
Pre-pubertal (<2)	7 (6.5)	3 (2.8)
Pubertal (>=2)	98 (91.6)	105 (97.2)

Source: CSR

3.1.1.4.3 Baseline disease characteristics

The average duration in years of MS since diagnosis was 1.1 for the fingolimod group and 1.4 for the IFN β-1a group. The mean baseline EDSS score was about 1.5.

Numerical differences in baseline MRI characteristics were shown in Table 4. Of note, a lower proportion of patients in the fingolimod group were free of Gd-enhancing T1 lesions but with slightly lower mean lesion numbers at baseline compared with the IFN β-1a group.

Overall, no substantial differences between the treatment groups in baseline disease or MRI characteristics were found.

Table 4 Summary of baseline characteristics (randomized set)

	FTY720 N=107	IFN β – 1a N=108
Duration of MS since diagnosis (years)		
Mean (SD)	1.1 (1.25)	1.4 (1.48)
Median	0.7	0.8
Duration of MS since first symptom (years)		
Mean (SD)	1.9 (1.70)	2.4 (2.11)
Median	1.2	1.8
Number of relapse past 24 months		
Mean (SD)	2.4 (1.44)	2.5 (1.32)
Median	2.0	2.0
EDSS		
Mean (SD)	1.5 (1.15)	1.6 (0.89)
Median	1.5	1.5
Number of Gd-enhancing T1 lesions		
Mean (SD)	2.6 (6.01)	3.1 (6.49)
Median	1.0	0
% of Patients free of GdE T1 lesions		
N (%)	47 (44.3)	59 (55.1)
Number of T2 lesions		
Mean (SD)	41.9 (30.33)	45.6 (33.85)
Median	31.0	32.0

Source: CSR

3.1.5 Efficacy Results

The efficacy results presented in this section represent the ones reported by the sponsor and confirmed by the reviewer unless noted otherwise. Additional analyses performed by the reviewer are noted where presented.

3.1.5.1 Efficacy Results of the Primary Endpoint

The primary efficacy endpoint was the annualized relapse rate (ARR) at the end of the study. Fingolimod demonstrated statistically significant superior efficacy in ARR over IFN β-1a with adjusted ARR estimate of 0.122 vs 0.675, respectively. This corresponded to a significant reduction of 81.9% in ARR for fingolimod-treated patients compared with IFN β-1a-treated patients ($p<0.0001$).

The positive results from the primary analysis were further confirmed by all specified supportive and sensitivity analyses. Analysis on all relapses (confirmed and unconfirmed), analysis on confirmed relapse while on treatment and analysis on PP population all produced similar reduction in ARR for patients treated by fingolimod. Analysis of time to first relapse showed a

significant delaying ($p < 0.0001$) in time to first confirmed relapse with risk reduction of 80% in the fingolimod group. The following table provides a summary of the analysis results.

Table 5 Primary analysis of ARR and supportive /sensitivity analysis

	FTY720 N=107	**IFN β – 1a N=107**
Descriptive Statistics		
Number (%) of patients with conf relapse	15 (14.0%)	58 (54.2%)
Total number of confirmed relapses	25	120
Mean time in study (year)	1.68	1.53
Primary analysis – confirmed relapse		
Adjusted ARR	0.122	0.675
95% CI	(0.078, 0.192)	(0.515, 0.885)
ARR ratio (% reduction)	0.181 (81.9%)	
p-value	<0.0001	
Supportive / Sensitivity analysis		
Confirmed relapses on Treatment*		
Adjusted ARR	0.123	0.727
95% CI	(0.078, 0.195)	(0.551, 0.960)
ARR ratio (% reduction)	0.169 (83.1%)	
p-value	<0.0001	
All Relapses (confirmed and unconfirmed) during Study		
Number (%) with any relapse	24 (22.4%)	67 (62.6%)
Adjusted ARR	0.181	0.802
95% CI	(0.125, 0.262)	(0.638, 1.009)
ARR ratio (% reduction)	0.226 (77.4%)	
p-value	<0.0001	
Time to first relapse		
p-value from log-rank test	< 0.0001	
Hazard ratio from Cox model	0.195	
p-value from Cox model	< 0.0001	

* Relapses after the study drug discontinuation while on core study are not included in this analysis.
Source: CSR and reviewer's analysis

The Kaplan-Meier curve for proportion of patients relapse-free (confirmed relapses) by treatment is shown in Figure 2.

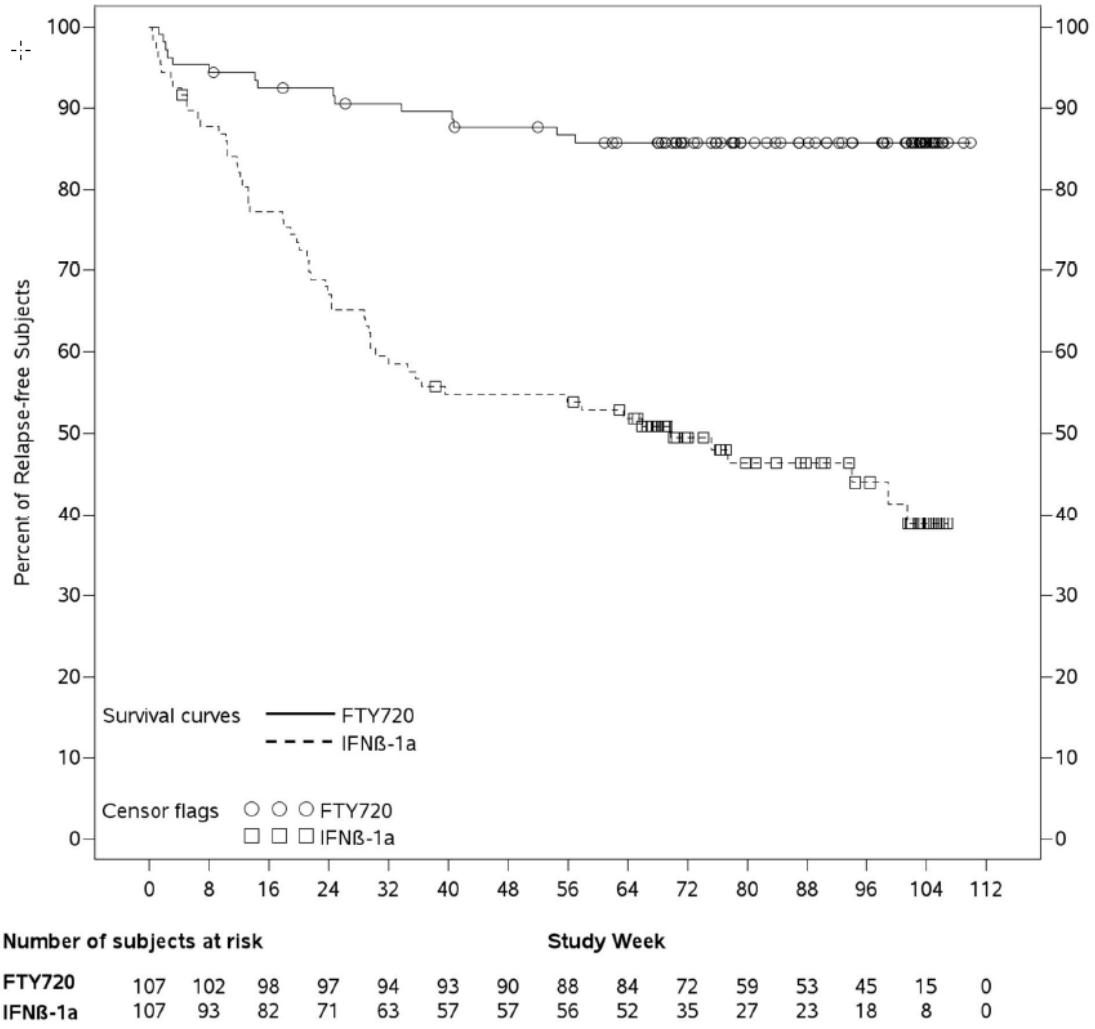


Figure 2 Kaplan-Meier curves: percentage of patients relapse-free (confirmed relapses) by treatment
Source: CSR

The study was stopped early after it met the stopping criteria at the blinded sample size re-estimation (BSSR). The primary negative binomial (NB) model with an offset for the time in study adjusted for various treatment duration and missing information under the assumption of missing at random and constant relapse rate over time.

3.1.5.2 Missing Data Evaluation

More patients in the IFN β-1a group than in the fingolimod group discontinued the study (20[18.7%] vs. 7[6.5%]) or treatment (26[24.3%] vs. 8[7.5%]) prematurely. Among them, 21 of the 26 patients from the IFN β-1a group and 3 of the 8 patients from the fingolimod group discontinued treatment after one or more confirmed and/or unconfirmed relapses, indicating that higher discontinuation rate in the IFN β-1a group was largely due to lack of efficacy.

An additional sensitivity analysis was performed treating patients who discontinued study as having a confirmed relapse at the time of discontinuation. Both log-rank test and Cox model yielded a nominal p-value of < 0.0001. The hazard ratio estimated from the Cox model was 0.237, slightly higher than the one estimated without changing the censoring scheme. Hazard ratio with 95% confidence interval is plotted over time in Figure 3. There was little change in hazard ratio from Month 12.

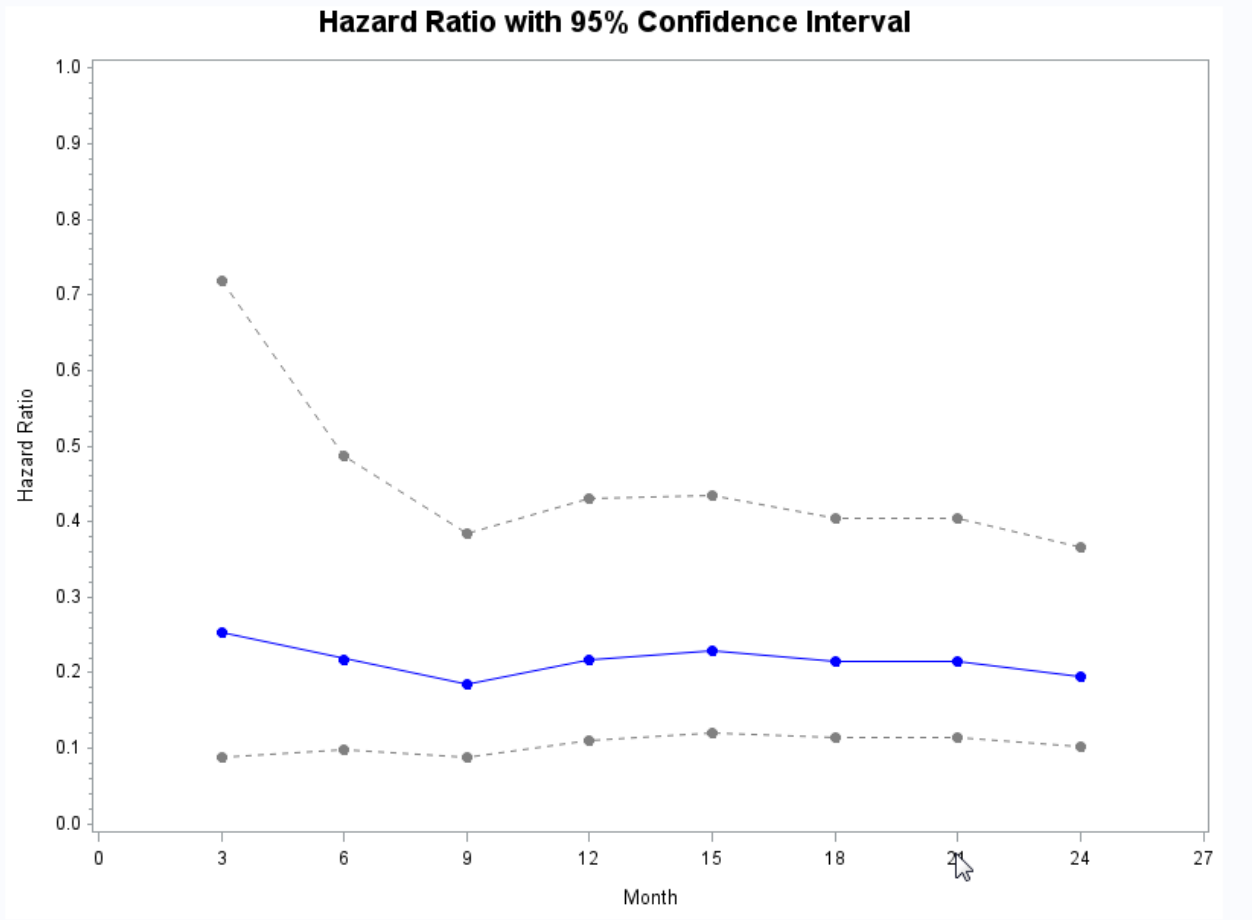


Figure 3 Hazard Ratio Over Time
Source: Reviewer's plot

3.1.5.2 Efficacy Results of Key Secondary Endpoints - New or newly enlarged T2 lesions

MRI scans were performed at screening, Months 6, 12, 18 and end of the study. Note that duration in study for each patient varied. The MRI data used in this analysis was the scan at the end of the study. The number of new/enlarging T2 lesions (compared to screening scan) for each patient varied scan by scan, but generally accumulated over time.

The annualized rate of the number of new or newly enlarged T2 lesions up to Month 24 was statistically significantly lower in patients treated with fingolimod compared to patients treated with IFN β-1a. Treatment with fingolimod resulted in a 52.6% reduction in the number of new or

newly enlarged T2 lesions compared with IFN β-1a (p<0.0001). The results are presented in Table 6.

Table 6 Annualized rate of the number of new or newly-enlarged T2 lesions compared to baseline up to Month 24

		FTY720 N=106		**IFN β-1a N=102**
Adjusted mean (SE)		4.393 (0.099)		9.269 (0.097)
95% CI		(3.617, 5.336)		(7.661, 11.214)
% Reduction		52.6%		
p-value		<0.0001		
By Visit	N	Mean (median)	N	Mean (median)
Baseline T2	107	41.9 (31.0)	107	45.6 (32.0)
New/enlarging T2				
Month 6	104	5.3 (2.5)	100	12.2 (6.0)
Month 12	98	5.9 (3.0)	90	13.3 (7.5)
Month 18	71	8.1 (4.0)	53	15.8 (11.0)
Month 24	35	8.0 (3.0)	24	21.8 (15.5)

(source: review's analysis)

3.1.5.3 Other Secondary Endpoint - Gd-enhancing T1 lesions

Treatment with fingolimod resulted in a reduction of 66.0% in the number of Gd-enhancing T1 lesions per scan compared with IFN β-1a up to Month 24 (Table 7). A higher proportion of patients in the fingolimod group were free of Gd-enhancing T1 lesions compared with the IFN β-1a group up to Month 24 (77.4% vs 53.5%).

Table 7 Summary of Gd-enhancing T1 lesions by treatment

	FTY720 N=106	**IFN β-1a N=101**
Adjusted mean (SE)	0.436 (0.170)	1.282 (0.161)
95% CI	(0.313, 0.608)	(0.934, 1.757)
% Reduction	66.0%	
Nominal p-value	<0.0001	
Free of Gd-enhancing T1		
N (%)	82 (77.4)	54 (53.5)

Source: Reviewer's analysis

3.1.5.4 Time to 3-month Confirmed Disability Progression (CDP)

In the adult studies of fingolimod, the results of 3-month CDP was positive in the 2-year study D2301 when fingolimod 1.25 mg and 0.5 mg were compared to placebo (p=0.012 and 0.026, respectively, from log-rank test). The 1-year adult study D2302 did not show positive efficacy when fingolimod 1.25 mg and 0.5 mg were compared to IFN β-1a (p=0.4979 and 0.2475, respectively, from log-rank test).

Time to 3-month CDP was not a specified endpoint in this pediatric study. In the Clinical Overview and Summary of Clinical Efficacy (SCE) of this supplement NDA, the sponsor presented a Kaplan-Meier plot for the 3-month CDP and a post-hoc analysis showing a p-value of 0.015 from a log-rank test and a hazard ratio of 0.23 with a p-value of 0.013 from a Cox regression, favoring fingolimod. These results were not included in the Clinical Study Report.

Since the variable was not an endpoint for the study, definition of 3-month disability progression and handling of varies censoring scenarios were not provided in the protocol or SAP. In the response to Division's Information Request for all versions of SAP, the sponsor included SAP for the core study as well as SAP and 3 amendments for SCE. In the last two amendments of SAP for SCE, both dated about one month after the core study database lock, definition and details of analysis for CDP as an exploratory analysis were added. The definition of CDP deviated from the one used in the adult study. The following table describe the difference.

Table 8 Deviation in Definition of Disability Progression

	Adult Studies	**SCE Amendments 2 and 3**
Disability progression by increase in EDSS	$\geq$ 1.0 if baseline EDSS $\leq$ 5.0 $\geq$ 0.5 if baseline EDSS > 5.0	$\geq$ 1.5 if baseline EDSS = 0 $\geq$ 1.0 if baseline EDSS > 0 and $\leq$ 5.0 > 0.5 if baseline EDSS > 5.0

Source: Reviewer's summary

The difference was the definition when baseline EDSS=0. An 1-point increase was required for progression in the adult studies while an 1.5-point increase was required in this pediatric study in the definition.

A total of 7 patients (5 in the fingolimod group and 2 in the IFN β-1a group) who had baseline EDSS=0 were censored in this study and would have met the criteria of disability progression by the adult study definition. The following table presents the difference in results based on two different versions of definition of disability progression.

Table 9 Analysis of Disability Progression by Different Definitions of CDP

	FTY720 N=107	IFN β – 1a N=107
Number of CDP – sponsor's data		
N (%)	5 (4.7)	15 (14.0)
Nominal p-value (log-rank)*	0.0151	
Hazard ratio (Cox model)	0.224	
Nominal p-value (Cox model)**	0.0071	
Number of CDP – adult study definition		
N (%)	10 (9.4)	17 (15.9)
Nominal p-value (log-rank)*	0.1319	
Hazard ratio (Cox model)	0.418	
Nominal p-value (Cox model)**	0.0431	
Number of CDP occurred on relapse	3	13
% of total number of CDP	30%	76.5%

*Log-rank test was the primary analysis in the adult studies and in SAP for SCE.
**Cox model is a supportive analysis in the adult studies and in SAP of SCE.
Source: Reviewer's analysis

The onset of disability progression was allowed on a relapse assessment, as long as the confirmation was made on a regular scheduled visit. It is commonly known that relapse rate is higher in pediatric MS patient population than it is in adult MS patient population. It is also known that a relapse episode could cause a temporary increase of EDSS score. Given the large effect of fingolimod on relapse rate (81.9% reduction in ARR) and given the high percentage of CDP occurred on relapse visit in the IFN β-1a group (76.5%), it is not clear any treatment difference would represent an effect of fingolimod on CDP or it is an effect on "acute" CDP due to relapse.

3.2 Evaluation of Safety

Refer to Clinical Review by Dr. Paul Lee for Evaluation of Safety.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Table 10 presents the estimated ARR by sub-population analyzed. 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 number of patients with pre-pubertal status at baseline were too few, so analysis by age group cut at 14 years old was performed instead. The data did not suggest a gender or age difference in relapse rate.

Table 10 ARR by gender and age group

Adjusted ARR	**FTY720 N=107**	**IFN β-1a N=107**
Sex		
Male		
n	37	43
ARR	0.028	0.691
Female		
n	70	64
ARR	0.168	0.671
Age		
10 to ≤ 14 years		
n	29	28
ARR	0.056	0.723
> 14 to ≤ 18 years		
n	78	79
ARR	0.147	0.657

Source: Reviewer's analysis

4.2 Other Special/Subgroup Populations

The study was conducted in 87 centers in 26 countries worldwide. For the purpose of efficacy analysis, centers were pooled into 3 regions: East Europe, West Europe and Rest of the Regions. The Rest of the Regions consisted of countries of Australia, Brazil, Canada, Mexico, and US, with a total of 34 patients (16 of them US patients). The number of patients in each of the individual regions that pooled to the Rest of Regions was too small to allow a meaningful subgroup analysis.

Table 11 Analysis of ARR by region

Region	FTY720 N=107	IFN β-1a N=107
East Europe		
n	55	56
ARR	0.102	0.887
West Europe		
n	35	34
ARR	0.159	0.698
Rest of the Regions		
n	17	17
ARR	0.145	0.161

Source: Reviewer's analysis

Only 10 patients were in the $\leq$ 40 kg by weight group and received lower dose of 0.25 mg/day fingolimod. The subgroup analysis by dose was not performed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Although the amount of missing data was not balanced and the assumption of missing at random was not likely to be true, the large number of IFN β-1a treated patients discontinued the treatment due to unsatisfactory therapeutic effect and discontinued after relapse episodes nevertheless suggested that the study drug was effective. No major statistical issues were identified.

The evidence shown in the results of study D2311 suggested that fingolimod was effective in reducing the relapse rate significantly in pediatric patients with relapsing form of MS.

5.2 Conclusions and Recommendations

The efficacy results obtained from the analyses of study D2301 supports the conclusion that fingolimod is effective in treating pediatric patients aged 10 to < 18 years with relapsing form of multiple sclerosis.

The study was designed and conducted following the specifications of pediatric Written Request (WR).

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/s/

XIAORONG YAN
04/18/2018

KUN JIN
04/18/2018
I concur with the review.

HSIEN MING J HUNG
04/18/2018