Cross-Discipline Team Leader Review

Date	April 15, 2018
From	John R. Marler, MD
Subject	Cross-Discipline Team Leader Review
New Drug Application	NDA 022527 Supplement Number 24
Applicant	Novartis Pharmaceuticals Corporation
Date of Submission	November 10, 2017
PDUFA Goal Date	May 13, 2018
Proprietary Name	Gilenya
Established or Proper Name	Fingolimod
Dosage Forms	Capsules, 0.25 (new) and 0.5mg
Applicant Proposed Indication	(b) (4) • pediatric patients of 10 years and older of age and above with relapsing forms of multiple sclerosis.
Applicant Proposed Dosing Regimen	0.5 mg orally for those over 40kg and 0.25mg for those 40kg or less.
Recommendation For Regulatory Action	Approval
Recommended Indication	GILENYA is indicated for the treatment of relapsing forms of multiple sclerosis (MS) in patients of 10 years of age and older.
Recommended Dosing Regimens	*Same as applicant*
EDR Link	\\CDSESUB1\evsprod\NDA022527\0538
Related IND	IND 70139

1. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment
Prior to submission of this efficacy supplement, there was no treatment approved for the treatment of relapsing forms of multiple sclerosis in pediatric patients. The applicant submitted the results of a 215-patient clinical trial that clearly establishes the efficacy of fingolimod in pediatric patients 10 through 17 years of age. A robust reduction in the annualized relapse rate, a well-accepted and clinically relevant endpoint, was demonstrated in the trial. Serious adverse effects were observed in a small proportion of patients, but the safety risks associated with fingolimod treatment are clearly outweighed by the potential benefits and are well understood, generally preventable with careful monitoring, and consistent with the adverse event profile of fingolimod in adults. The application support expanding the fingolimod indication to include pediatric patients 10 through 17 years of age. This represents an important and needed advance in the care of pediatric patients with multiple sclerosis.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Pediatric multiple sclerosis represents approximately 5-10% of all cases of relapsing forms of MS (RMS).	Pediatric RMS is a serious disabling disease for which there is an unmet need.
Current Treatment Options	• Of fifteen different approved drugs for adult RMS, none are approved for use in children.	There is a significant unmet need for drugs to treat multiple sclerosis in children.
Benefit	• The applicant conducted a randomized, 24-week, double-blind, double-dummy, parallel-group clinical trial, using Avonex (a drug approved for the treatment of relapsing forms of MS in adults) as active control. The annualized relapse rate in fingolimod-treated patients (0.122) was significantly lower than that in Avonex-treated patients (0.675). Relapses are significant clinical events causing temporary disability early in the disease course. Relapses can last from a few weeks to several months or longer. In children, recovery from relapses is often, but not always, complete between episodes.	The benefit of fingolimod in pediatric patients is clearly established.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The safety profile of fingolimod is similar in pediatric patients and in adults.	Current labeling is appropriate to manage the risks of fingolimod treatment in pediatric patients.

2. Background

Fingolimod was approved for the treatment of relapsing forms of multiple sclerosis (MS) in adults in 2010, with a postmarketing requirement to perform a deferred study in children 10 through 17 years of age. FDA issued a Special Protocol Assessment agreement letter for the fingolimod pediatric trial (Study D2311) on December 26, 2012. A Pediatric Written Request (WR) was issued on March 20, 2013, and revised WR on March 8, 2016. Breakthrough Designation was granted on December 14, 2017, based on the topline results of Study D2311.

The supplement under review proposes to expand the indication of fingolimod to include children 10 through 17 years of age with RRMS, and add a 0.25 mg capsule.

The review team for this efficacy supplement is presented below.

Discipline	Reviewer
Product Quality	Richard Matsuoka Gurpreet Gill-Sangha David B. Lewis Parnali Chatterjee
Clinical	Paul Lee John Marler (CDTL)
Clinical Pharmacology	Angela Men (TL) Hristina Dimova Kevin Krudys
Statistics	Sharon Yan Kun Jin (TL)
Labeling	Tracy Peters (ADL) Aline Moukhtara Domenic D'Alessandro Marcia Williams (TL) Karen Dowdy Lolita White (TL) Chad Morris
Maternal Health/Pediatrics	Leyla Sahin Amy Taylor Hari Cheryl Sachs
Regulatory	Nahleen Lopez

3. Product Quality

The Office of Product Quality (OPQ) recommends approval of the new lower strength 0.25mg hard gelatin capsule intended for patients with body weight of 40 kg or less. An overall manufacturing inspection recommendation to approve was issued on January 26, 2018. I concur.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical information was submitted in support of this efficacy supplement.

5. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) recommends approval of this efficacy supplement. The primary focus of the OCP review was the evaluation of the weight-based dosing regimen proposed by the applicant. OCP agrees that dosing of fingolimod should be 0.25 mg once daily for patients weighing ≤ 40 kg, and 0.5 mg once daily for patients weighing over 40 kg. From a clinical pharmacology perspective, OCP concludes that the applicant has met the terms of the Pediatric Written Request. I concur.

6. Clinical Microbiology

Not Applicable.

7. Clinical/Statistical- Efficacy

This efficacy supplement proposes to expand the indication of fingolimod to include patients 10 years of age and older with relapsing forms of multiple sclerosis. In support of the expanded indication, the applicant submitted the results from Study D2311. Paul Lee, MD, performed the primary clinical review, and Sharon Yan, PhD, the statistical review of the application.

Study D2311 (NCT #01892722): Design

The core phase of Study D2311 was a 1:1 randomized, 24-week, double-blind, double-dummy, parallel-group, and active controlled clinical trial with a planned sample size of 95 patients in each of two arms (190 total). The primary outcome measure was the rate of confirmed relapses per patient and per year of treatment. The active control

was Avonex,[1] which is an FDA-approved treatment for RMS in adults (but not in children). The protocol had a double-dummy design because the route for Avonex is intramuscular injection weekly and that for fingolimod is oral capsules daily. The patient selection criteria were similar to those used in fingolimod adult studies, except for age. On entry, patients were 10 through 17 years of age, had pediatric MS as defined by consensus definitions, and had experienced at least two clinically apparent relapses within 2 years or at least one apparent relapse within 1 year prior to screening, or had evidence of one or more gadolinium enhancing lesions on MRI within 6 months prior to randomization.

The primary outcome event was a confirmed MS relapse. The operational definition of the primary outcome event used in the trial was built on a clinical description of an MS relapse: 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°C) or known infection."[2] A relapse was considered confirmed if there was an increase of at least 0.5 points on the EDSS score, or an increase of at least 1 point on two functional system (FS) scores or 2 points on one FS, excluding changes in the bowel or bladder FS or cerebral FS.

Study D2311 was originally designed with a fixed duration of 24 months for each patient in the double-blind phase. While the trial was ongoing, the applicant submitted a request on November 6, 2015, to modify the study duration from a fixed 24-month duration to a flexible duration of up to 2 years if certain conditions were met based on a blinded sample size re-estimation (BSSR). The justification for this change was a higher than anticipated relapse rate. FDA granted the request and issued an amendment of the Written Request on March 8, 2016. Dr. Yan describes the methodology of the BSSR in her review.[3]

Dose rationale. The daily pediatric fingolimod dose used in the study was 0.5 mg for patients with weights over 40 kg, and 0.25 mg for patients 40 kg or less (the 0.5 mg dose of fingolimod is the current approved dose for RMS in adults). The pediatric dosing was based on results from a pharmacokinetic (PK) study in children and PK modeling (see Clinical Pharmacology review for further details). For patients under

[1] This review refers to "Avonex" rather than "intramuscular interferon β-1a" or "interferon β-1a IM" because there are three approved forms of interferon β-1a (Avonex, Rebif, and Plegridy).
[2] Clinical Study Report page 3515 of 14939, Section 6.4.2, Final Protocol Study D2311.
[3] Dr. Yan Clinical Review, page 4 of 22.

40 kg at study entry, dosing was to increase to 0.5 mg if fingolimod blood levels were below targeted levels after one month, or when the patient's weight exceeded 40 kg.

The annualized relapse rate by 24 months was analyzed using a negative binomial regression model.

Study D2311: Efficacy Results

Baseline characteristics

The baseline demographics and RMS disease characteristics are well-balanced between the two treatment arms except for weight less than 40 kg and prepubertal status. Baseline characteristics are summarized in Table 1.

Table 1 Summary of Baseline Characteristics for Study D2311

Summary Table of Baseline Characteristics[4]		
Selected Baseline Characteristic	Study Arm	
	Fingolimod	Avonex
N	107	108
Age (Median Years)	16	16
10, 11, and 12 years	12.1%	8.3%
13 and 14 years	15.0%	17.6%
15 and 16 years	41.1%	41.7%
17 years	31.8%	29.6%
18 years	0%	2.8%
Proportion Female	65%	59%
Weight Less Than 40kg (N)	9	1
Prepubertal (N)	7	3
Mean Number or Relapses 2 years prior	2.4	2.5
Mean Years Since MS Onset	1.9	2.4
Mean Years Since RMS diagnosis	1.1	1.4
Prior MS Treatment (%)	35%	38%
Mean Gd Enhancing T1 lesions	2.6	3.1
Volume of T2 lesions (mm^3)	8902	11512

[4] CSR page 115-118 of 14939

Summary Table of Baseline Characteristics[4]		
Selected Baseline Characteristic	Study Arm	
	Fingolimod	Avonex
EDSS Mean	1.46	1.61
EDSS Max	11	9
EDSS Median	1.5	1.5
EDSS progression per year[5]	0.76	0.67
Proportion from US Center	25.5%	25.6%
*Prepubertal = Tanner Stage less than 2 using the higher score between breast development and pubic hair assessments for female and the higher score between genital stage and pubic hair assessments for male. A patient with missing Tanner staging score but a bone age >=16 years or menarche for females is considered pubertal.		

Completion Rate

Overall, there was an 87% completion rate. Dropout rate was 6.5% for fingolimod vs. 18.5% for Avonex. Dr. Yan notes that the reasons for discontinuation from the core phase of Study D2311 are generally comparable between the groups, with one exception: 6.5% of patients discontinued participation because of unsatisfactory therapeutic effect in the Avonex group compared to none in the fingolimod group.

Table 2 Completion Rate in Study D2311

Completion Rate in Study D2311		
	Avonex	Fingolimod
Subjects Randomized	108	107
Dropped Out	20	7
Completed	88	100
Completion Rate[6]	81.5%	93.5%
Dropout Rate[6]	18.5%	6.5%
Difference in completion rate[6]	12%	

[5] Calculated by CDTL: (mean EDSS at baseline)/(mean years since onset of MS)
[6] Calculated by CDTL

Trial D2311 Primary outcome results

Table 3, below, summarizes the applicant's primary clinical efficacy results for Study D2311. The results show a statistically significant reduction in the annualized relapse rate (ARR) in patients with relapsing MS. Dr. Yan notes that the positive results from the primary analysis are confirmed by all specified supportive and sensitivity analyses.[7] Relapses after study drug discontinuation are not included in this analysis.

Table 3 Primary Outcome -- Annualized Relapse Rate

Primary Outcome: Annualized Relapse Rate (ARR)[8]		
Treatment Arm	**Fingolimod**	**Avonex**
ITT (n)	107	108
Modified ITT (n)	107	107
Total number of relapses	37	138
Total number of confirmed relapses	25	120
Confirmation rate[9]	67.5%	87.0%
Total patient days followed	65575	59678
Mean time in study (years)[10]	1.68	1.53
Unadjusted ARR	0.139	0.734
Adjusted ARR*	0.122	0.675
(95% CI)**	(0.078, 0.192)	(0.515, 0.885)
Adjusted rate ratio		0.181
(95% CI)		(0.108, 0.303)
Risk Reduction		81.9%%
p-value		< 0.001

The ARR in fingolimod-treated patients (0.122) was one third the anticipated rate (0.36), while the ARR in Avonex-treated patients (0.675) is very close to that predicted (0.72). The sample size calculation for Study D2311 assumed a 50% relative reduction from 0.72 to 0.36 in the ARR over 24 months for fingolimod and Avonex, respectively, and predicted 80% statistical power to detect such a reduction at a two-sided alpha level of 0.05 with 95 subjects in each arm of the trial. A blinded sample size re-estimation study led to an early trial completion before all subjects had been in the study for 2 years.

[7] Dr. Yan's review, page 13 of 22.
[8] fty720d2311am1--legacy-clinical-study-report.pdf, Table 11.6, page 120 of 14939.
[9] Calculated by CDTL.
[10] Dr. Yan's review. Table 5, page 4 of 22.

Study D2311 rated relapses as severe, moderate, or mild using EDSS scale criteria (see Table 4, below).

Table 4 Criteria for Relapse Severity Rating in Study D2311

Criteria for Relapse Severity Rating[11]		
Mild Relapse	Moderate Relapse	Severe Relapse
EDSS increase of 0.5 point Or 1 point FS change in one to three systems	EDSS increase of 1 or 2 points Or 2-point FS change in one two systems Or 1-point change in four or more systems	Exceeding Moderate criteria

The occurrence of a severe relapses may be more likely to be accurately and completely reported than mild relapses; hence, despite the relatively high subjectivity of the relapse outcome event, the reporting of severe confirmed relapse events may be less subject to (but not free of) bias. There is a clear difference in the severe relapse rate in favor of fingolimod (see Table 5). Even though there may a difference in the rate of confirmation between treatment groups, the percentage of confirmed relapses that are severe was similar in both treatment groups.

Table 5 Severe Confirmed Relapses in Trial D2311

Severe Confirmed Relapses[12]		
	Fingolimod n=107	**Avonex n=107**
Number (%) of Patients with Severe Relapses	5 (4.7%)	23 (21.5%)
Number of Severe Relapses	6	32
Time in Study (days)	65575	59678
Raw Annualized Severe Relapse Rate (ARR) (time-based)	0.0278	0.1959
Percent raw ARR reduction	85.8%	
Number of relapses of all severity	25	120

[11] fty720d2311am1--legacy-clinical-study-report.pdf, Table 9-4, page 76 of 14939
[12] fty720d2311am1--legacy-clinical-study-report.pdf, Table 14/2-1.6b, page 293 of 14939

Severe Confirmed Relapses[12]		
	Fingolimod n=107	Avonex n=107
Percent of severe relapses	24.0%	26.7%

Study D2311: Secondary Outcomes

The protocol specifies one key secondary outcome and numerous other secondary and exploratory endpoints. Section 2.2 "Secondary Objectives" of the final protocol lists a key secondary objective, 5 secondary objectives, and 4 exploratory objectives, each of which includes multiple outcome measures. There was no hierarchy for the order of analysis of the non-key secondary and exploratory outcomes and no correction for multiplicity.

Table 6, below, shows the results of selected pre-specified secondary analyses.

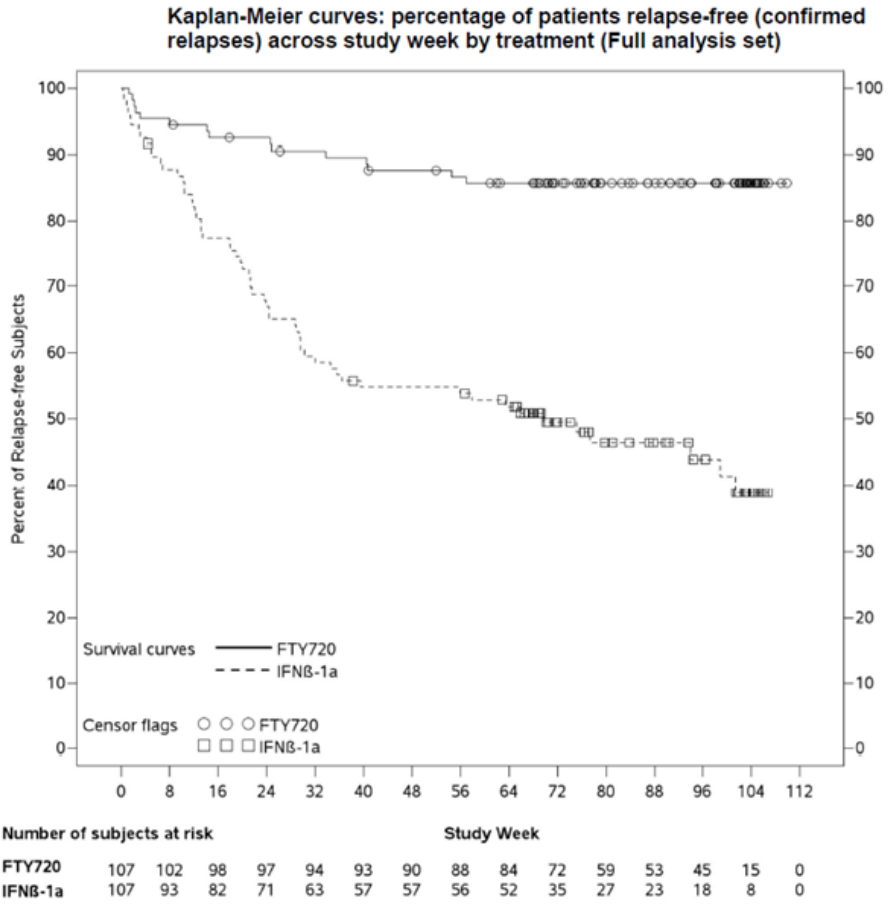
Table 6 Secondary Outcomes in Study D2311

Secondary Outcomes[13]						
Hierarchy of Four Secondary Outcomes 24-Months or End-Of-Study Double-Blind Epoch	Fingolimod	Avonex	p-value	Rate Ratio	Absolute Difference[14]	NNT[14]
1. New or newly enlarging T2 lesions per patient	4.39	9.269	<0.001	0.526		
2. Proportion of Patients Relapse-Free Mean Time to First Relapse in Days	86.0% 150.9	45.8% 187.9	<0.001	0.26[15]	50.2%	2.0
3. New T1 Gd-enhancing lesions per scan	0.436	1.282	<0.001	0.66		
4. Mean Volume of T1 Gd-enhancing lesions (mm^3)	52.8	276.8	<0.001			
5. Mean T2 Lesion Volume	9345.5	13078.6	0.003			
6. Mean SDMT Improvement at EOS (correct items)[16]	4.0	6.2	0.08			
7. Trail Making Test at EOS(seconds)[17]	32.61	30.45	0.6			

Figure 1, below, is the Kaplan-Meier curve from the applicant's clinical study report showing time to first relapse listed in row 2 of Table 6, above.

[13] Data extracted from fty720d2311am1--legacy-clinical-study-report.pdf, Tables 11-7, 11-8, pp. 121-128
[14] Number needed to treat estimated by CDTL
[15] Represents reduction in number of patients with relapses compared to Avonex.
[16] CSR page 384 of 14939
[17] CSR page 402 of 14939

Figure 1 Kaplan-Meier Curves: Percentage Relapse Free



In Figure 2, above, FTY720 is fingolimod and IFNβ-1a is Avonex

Annualized Relapse Rate (ARR) in Patient Subgroups

For subgroups analyzed, the applicant reports that all point estimates of the annualized relapse rate in the application are similar and favor fingolimod (see Table 7, below), except for region. Because of the small number of patients in non-European sites, no definitive conclusion can be drawn from the subgroup analysis by region. Efficacy results from Western and Eastern European sites are applicable to the US population.

Table 7 Annualized Confirmed Relapse Rate by Subgroup in Study D2311

Annualized Confirmed Relapse Rate by Subgroup[18]			
Group	Annualized Relapse Rate		Reduction in ARR[19]
	Fingolimod	Avonex	
All	0.139	0.734	81%
Male	0.033	0.752	96%
Female	0.194	0.723	73%
Age 12 or less	0.095	0.721	87%
Age 13 and older	0.145	0.735	80%
Body Weight 40kg or less	0.234	0.000	---
Body Weight more than 40kg	0.132	0.740	82%
Prepubertal Tanner less than 2	0.195	1.494	87%
Pubertal Tanner 2 or more	0.133	0.720	81%
Hispanic	0.277	0.360	23%
Non-Hispanic	0.127	0.769	83%
East Europe[20]	0.102	0.887	89%[21]
West Europe[20]	0.159	0.688	77%[21]
All other regions including US[20]	0.145	0.161	10%[21]

Efficacy Review Considerations

Post-Hoc Analysis of 3-month sustained disease progression

The time to 3-month sustained disability progression was not a specified endpoint in Study D2311. However, in the Clinical Overview and Summary of Clinical Efficacy (SCE) (b) (4), the applicant presented a Kaplan-Meier plot for the 3-month CDP and a post-hoc analysis that shows a difference in the number of patients who experienced increased disability that lasted 3 months or longer. This analysis is not included in the final clinical study report for Study D2311.

(b) (4)

. As described in Dr. Yan's review, disability progression was not an endpoint described in the study protocol, and there was no analysis of that endpoint described in the prospective statistical analysis plan. The applicant submitted an amendment to the statistical plan to analyze the effect of fingolimod on the incidence of disability progression dated one month after the

[18] Table 11-13, CSR page 129 of 14939.
[19] CDTL calculation
[20] Dr. Yan's review, page 21
[21] Calculated by reviewer.

database lock date. These late additions to the statistical plan used a different definition of 3-month progression than usual in adult MS studies. One important difference from the usual definition of 12-week progression in adult trials was that a progression event could begin with an increased EDSS score obtained in association with a relapse. Dr. Yan points out that it is known that a relapse episode could cause a temporary increase of EDSS score, and that a high percentage of 3-month disability progression events began on relapse visit in the IFN β-1a group. Because of these limitations, no definitive conclusion could be made about a fingolimod effect on disability progression.

Small number of patients with weights 40 kg or less.

Dr. Lee's expresses concern that the imbalance in the small number of patients weighing 40 kg or less (9 fingolimod to 1 Avonex) precludes any confident conclusion about the effectiveness of the 0.25 mg dose in that subgroup. However, the annualized relapse rate in patients weighing 40 kg or less (0.234) was similar to that observed in the overall population (0.139) (Table 7, above), and the subgroup of patients weighing 40 kg or less is too small to make meaningful conclusions. In addition, the clinical pharmacology review concludes that exposure to fingolimod was similar in patients under and above 40 kg. Overall, adequate evidence has been provided to support the effectiveness of fingolimod 0.25 mg in patients weighing 40 kg or less.

Data quality

Dr. Yan states that the data quality as submitted appears to be generally good. Using the data submitted with the application, she can confirm the derived data and study results of the primary and key secondary outcomes. The applicant's review of audit trail data reveals some delay in reporting relapse data and changes to the EDSS scale after initial reporting that suggest some limitations in data quality. There is no evidence that these limitations would alter the determination of effectiveness in Study D2311.

Blinding

Effective blinding in Study D2311 was important because the outcome is subjective requiring judgments from 4 different individuals: the child, the parent, the treating investigator, and the EDSS rater. The trial made significant efforts to ensure effective blinding, including an independent team to perform first-dose monitoring, prophylactic non-steroidal anti-inflammatory drugs to reduce injection site pain and

flu-like symptoms, centralized collection of ECG and leukocyte count data, masking injection sites for examination by the EDSS rater, and visually identical double dummy control drugs. The reported incidence of flu-like symptoms, injection site pain or reactions, and symptomatic bradycardia are all quite low compared to other trials in MS. If accurate, these low rates predict reasonably effective blinding of patients, parents, and treating physicians. The applicant did not evaluate the effectiveness of blinding.

Conclusion of efficacy review:

Dr. Yan concludes that the efficacy results support that fingolimod is effective in treating pediatric patients 10 through 17 years of age with relapsing forms of multiple sclerosis. She also concludes that Study D2311, on a statistical standpoint, met the terms of the Pediatric Written Request.

Dr. Lee concludes that the applicant provided substantial evidence of effectiveness of fingolimod in patients 10 through 17 years of age with relapsing forms of MS.
I agree with the conclusions of Drs. Lee and Yan.

8. Safety

Paul Lee, MD, performed the primary safety review. The primary source of safety information is from Study D2311. The applicant also provided pediatric data from 17 patients in other trials (for details on these other studies, see Dr. Lee's review).

Quality of Safety Data

In his review, Dr. Lee states that the safety data provided by the applicant appeared reliable and consistent. He replicated the key safety analyses in the clinical study report. For individual patients, he compared data across several sources and did not find discrepancies between datasets, narratives, care report forms, listings, or summary tables.

Exposure

Table 8 summarizes the duration of exposure in Study D2311. Exposure in Study D2311 is adequate to assess safety, and exceeded the Written Request requirement.

Table 8 Duration of Exposure to Fingolimod in Study D2311[22]

Duration of Exposure to Fingolimod						
Treatment	Mean Exposure Days	Number of patients	At least **90 days**	At least **180 days**	At least **360 days**	At least **720 days**
Fingolimod	600.9	107	105	103	102	30
Avonex	517.1	107	105	99	88	19
Fingolimod 0.25 mg		9	6	3	2	2

Deaths

No deaths occurred during Study D2311.[23]

Serious adverse events (SAEs)

The analysis dataset submitted with this supplement shows that 19 fingolimod-treated patients had 33 serious adverse events, compared to 15 adverse events in 10 Avonex-treated patients (see Table 9 below). The 120-day safety update reports included two additional SAEs, fungal meningitis and endometriosis, unlikely to be related to treatment with fingolimod. Table 10, below, summarizes SAEs in fingolimod-treated patients by MedDRA class and notes whether Dr. Lee considers them unlikely to be related, already labeled, new and not labeled, or related to the disease. The events are overall consistent with the know safety profile of fingolimod. The seizure adverse events are discussed below under "common adverse events".

Table 9 Serious Adverse Events in Study D2311

Patients with Serious Adverse Events[24]			
	Fingolimod	**Avonex**	**Difference**
Number of Subjects	107	107	
Any SAE	19 (17.8%)	10 (9.3%)	8.5%
Drug Discontinuations	6.2%	3.5%	2.7%
All Adverse Events	83%	83%	0%

[22] Table 12-1 fty720d2311--legacy-clinical-study-report.pdf, page 141 of 14939 and Dr. Lee's review, Table 37 and 38
[23] fty720d2311--legacy-clinical-study-report.pdf, page 170 of 14939
[24] Table 12-9 fty720d2311--legacy-clinical-study-report.pdf, page 158 of 14939

Table 10 SAEs in Fingolimod-Treated Patients in Study D2311

Serious Adverse Events More Common in Fingolimod-Treated Group[25]			
MedDRA System Organ Class (MedDRA Preferred Term for Fingolimod Group)	Number of Patients		
	Fingolimod	Avonex	
Total number of patients with at least one SAE	**19**	**10**	**Labeling**
Infections	**4**	**2**	Labeled
Injury head injury and fracture	**2**	**0**	Not Related
Investigations ALT or GGT enzyme increased	**1**	**1**	Labeled
Nervous System Disorders Seizure	**4**	**0**	New
Nervous System Disorders Migraine	**2**	**0**	Not related
Nervous System Disorders MS Relapse or Plaque	**2**	**3**	Disease related
Blood Disorders Agranulocytosis	**1**	**0**	Not related
Blood Disorders Leukopenia (viral infection?)	**2**	**0**	Not related
Gastrointestinal Disorders	**3**	**1**	Not related
Musculoskeletal and Connective Tissue Disorders	**2**	**0**	Not related
Cardiac Disorders 2nd degree block	**1**	**1**	Labeled
Eye Disorders uveitis	**1**	**0**	Labeled
Skin Disorders hypersensitivity vasculitis	**1**	**0**	Labeled
Renal and Urinary Disorders bladder spasm and dysuria	**1**	**0**	Not related

Common adverse events

Common adverse events seen in at least 2 % of fingolimod-treated patients in Study D2311 are listed in Table 12. Overall, the safety profile in pediatric patients receiving fingolimod 0.25 mg or 0.5 mg daily was similar to that seen in adult patients.

Table 11 Common Adverse Events in Study D2311[26]

Common Adverse Events Trial D2311 Re-coded Adverse Events That Occurred in More Than 2% of Fingolimod-Treated Patients Sorted by Difference Between Fingolimod and Avonex Groups			
Preferred Term	Fingolimod	Avonex	Difference
	% of Patients	% of Patients	
Leukopenia	25.2%	2.8%	22.4%
Influenza	11.2%	3.7%	7.5%

[25] Table 12-9 fty720d2311--legacy-clinical-study-report.pdf, page 158 of 14939
[26] Derived from Dr. Lee's review Table 47, page 155.

Common Adverse Events Trial D2311 Re-coded Adverse Events That Occurred in More Than 2% of Fingolimod-Treated Patients Sorted by Difference Between Fingolimod and Avonex Groups			
Preferred Term	Fingolimod	Avonex	Difference
	% of Patients	% of Patients	
Viral Infection	44.9%	39.3%	5.6%
Seizure	5.6%	0.9%	4.7%
Depression/Depressed Mood	8.4%	3.7%	4.7%
Hypercholesterolemia	3.7%	0.0%	3.7%
Constipation	3.7%	0.0%	3.7%
Anorexia	3.7%	0.0%	3.7%
Dyspnea/SOB/Respiratory Distress	4.7%	0.9%	3.7%
Gastroenteritis	7.5%	3.7%	3.7%
Anxiety	8.4%	4.7%	3.7%
Headache	36.4%	32.7%	3.7%
Urticaria	2.8%	0.0%	2.8%
Eczema	2.8%	0.0%	2.8%
Memory Loss or Impairment	2.8%	0.0%	2.8%
Migraine	4.7%	1.9%	2.8%
Fungal Infection	6.5%	3.7%	2.8%
Falls	7.5%	4.7%	2.8%
Fatigue	13.1%	10.3%	2.8%
Nausea/Vomiting	16.8%	14.0%	2.8%
Paresthesia	2.8%	0.9%	1.9%
Dysuria	2.8%	0.9%	1.9%
Anemia	2.8%	0.9%	1.9%
Asthma	2.8%	0.9%	1.9%
Tachycardia	3.7%	1.9%	1.9%
Pre-syncope/Syncope	3.7%	1.9%	1.9%
Bronchitis/Bronchiolitis	4.7%	2.8%	1.9%
Dermatitis	4.7%	2.8%	1.9%
Urinary Tract Infection	5.6%	3.7%	1.9%
Insomnia/Sleep Disturbance	5.6%	3.7%	1.9%
GOT, GPT, GGTP, LFTs	7.5%	5.6%	1.9%
Arrhythmia	3.7%	2.8%	0.9%
Chest Pain (non-cardiac or unknown)	3.7%	2.8%	0.9%
Rash	5.6%	4.7%	0.9%
Abdominal Pain	12.1%	12.1%	0.0%
Back Pain	5.6%	5.6%	0.0%
Bleeding	4.7%	4.7%	0.0%
Fracture	3.7%	3.7%	0.0%
Herpes Virus Infection	2.8%	2.8%	0.0%
Allergic/Hypersensitivity Reaction	4.7%	5.6%	-0.9%
Diarrhea	7.5%	9.3%	-1.9%
Cough	9.3%	11.2%	-1.9%
Fever/Rigors	8.4%	23.4%	-15.0%

Common Adverse Events Trial D2311 Re-coded Adverse Events That Occurred in More Than 2% of Fingolimod-Treated Patients Sorted by Difference Between Fingolimod and Avonex Groups			
Preferred Term	Fingolimod	Avonex	Difference
	% of Patients	% of Patients	
Upper respiratory tract infection	65.4%	81.3%	-15.9%

In Study D2311, 5.6% (6) of fingolimod-patients experienced seizures, compared to 0.9% (1) in those treated with Avonex. In adult clinical trials, the rate of seizures was 0.9% in fingolimod-treated patients and 0.3% in placebo-treated patients. Dr. Lee considers the association of seizures with fingolimod in Study D2311 to be weak, because there was increased use of corticosteroids in the Avonex group that might have reduced the seizure rate, and because there is no apparent pathogenic mechanism of epileptogenesis attributable to fingolimod. In addition, the number of events is small, and seizures are known to occur in MS patients, so that it remains unknown whether the seizure events are related to the effects of multiple sclerosis alone, to fingolimod, or to a combination of both.

Need for Risk Evaluation and Mitigation Strategy (REMS) after Approval

A REMS is not necessary for fingolimod, as the safety profile in pediatric patients is similar to that seen in adults.

9. Advisory Committee Meeting

An advisory committee meeting was not necessary for this efficacy supplement.

10. Pediatrics

The September 21, 2010, Approval Letter for Gilenya included a postmarketing requirement (1679-1) to perform a deferred pediatric study under PREA. A Pediatric Written Request was issued on March 20, 2013, and revised Written Request on March 8, 2016. The review team has confirmed that the conditions of the revised Written Request have been met. The applicant was notified on April 17, 2018, that pediatric exclusivity has been granted.

11. Other Relevant Regulatory Issues

There are no other regulatory issues.

12. Labeling

There are no outstanding labeling issues. The Division of Medication Error Prevention and Analysis review team has recommended revisions to the applicant-proposed prescribing information and other labeling to ensure the safe and effective use of fingolimod in children 10 through 17 years of age.

13. Postmarketing Recommendations

There are no postmarketing recommendations or requirements.

14. Recommended Comments to the Applicant

None.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN R MARLER
05/11/2018

ERIC P BASTINGS
05/11/2018
I concur.