Office of Clinical Pharmacology Review

NDA or BLA Number	22527
Link to EDR	\\CDSESUB1\evsprod\NDA022527\0538
Submission Date	November 13, 2017
Submission Type	Efficacy Supplement SE5
Brand Name	Gilenya
Generic Name	Fingolimod
Dosage Form and Strength	Hard Capsule (0.25 mg and 0.5 mg)
Route of Administration	Oral
Proposed Indication	Treatment of pediatric patients 10 years of age and above with relapsing forms of multiple sclerosis
Applicant	Novartis
OCP Review Team	Kevin Krudys, Ph.D., Hristina Dimova, Ph.D., Angela Men, M.D., Ph.D.
OCP Final Signatory	Ramana S. Uppoor, Ph.D.

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1. EXECUTIVE SUMMARY

In this supplemental New Drug Application submitted in response to FDA's Pediatric Written Request issued March 20, 2013 and amended March 8, 2016, Novartis is seeking approval of fingolimod for the treatment of relapsing forms of multiple sclerosis in pediatric patients ≥ 10 years of age.

Fingolimod, a sphingosine 1-phosphate receptor modulator, has been approved for the treatment of relapsing multiple sclerosis at a dose of 0.5 mg in adults. Fingolimod needs to be phosphorylated in vivo to fingolimod-phosphate (fingolimod-P, FTY720-P) to be pharmacologically active.

The submission contains one placebo controlled efficacy trial (Study D2311) to evaluate the safety and efficacy of fingolimod (0.5 mg/day or 0.25 mg/day based on body weight) versus interferon beta-1a once weekly in pediatric patients aged 10 to < 18 years with multiple sclerosis. Fingolimod was demonstrated to be superior to interferon beta-1a on the primary endpoint of annualized relapse rate. In addition, supportive data come from the bioequivalence study FTY20D2117.

The primary focus of this review is the evaluation of the proposed weight-based dosing regimen.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information submitted under NDA 22527 and recommends approval of fingolimod for the treatment of pediatric patients 10 years of age and older with relapsing forms of multiple sclerosis. From a clinical pharmacology perspective, the Applicant has also met the terms of the Pediatric Written Request. The dose of fingolimod should be 0.25 mg once daily for patients weighing ≤ 40 kg and 0.5 mg once daily for patients weighing greater than 40 kg.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The evidence of effectiveness of fingolimod in the pediatric population comes from one pivotal study (D2311) in patients 10 to less than 18 years of age with relapsing-remitting multiple sclerosis.
General dosing instructions	Pediatric patients 10 years of age and above: • Body weight ≤ 40 kg: 0.25 mg orally once daily, with or without food • Body weight > 40 kg: 0.5 mg orally once daily, with or without food
Dosing in patient subgroups (intrinsic and extrinsic factors)	Dosing in the pediatric population is adjusted by body weight (see general dosing instructions above)
Labeling	The review team does not agree with the Applicant's assertion in their proposed label that (b) (4) Instead, we recommend that the steady-state levels in pediatric patients be reported in the label.

Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed formulation was used in the pivotal trial.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Fingolimod is metabolized by sphingosine to the active metabolite, fingolimod-phosphate (fingolimod-P) which reduces the number of lymphocytes in peripheral blood. Steady-state fingolimod-P blood concentrations are reached within 1 to 2 months following once-daily administration and steady-state levels are approximately 10-fold greater than with the initial dose.

The pharmacokinetics of fingolimod in adults have been reviewed during the original, adult submission (Lai, DARRTS 8/4/2010) and are summarized in the product label.

Mean fingolimod-P concentrations in pediatric patients (1.10 ng/mL) were approximately 23% lower than the target concentration estimated from adult patients (1.35 ng/mL).

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The recommended dose in pediatric patients 10 years of age and above is based on body weight. Patients weighing ≤ 40 kg should receive a dose of 0.25 mg orally, once per day. Patients weighing greater than 40 kg should receive the adult dose of 0.5 mg orally, once per day. Similar to adults, pediatric patients should also undergo first dose monitoring for symptomatic bradycardia. Pediatric patients who start on the 0.25 mg dose and subsequently reach a stable body weight above 40 kg should be switched to the 0.5 mg dose and repeat first dose monitoring.

2.2.2 Therapeutic individualization

No therapeutic individualization is necessary for extrinsic/intrinsic factors other than body weight.

2.4 Summary of Labeling Recommendations

The review team does not agree with the Applicant's assertion in their proposed label that (b) (4) Instead, we recommend that the steady-state levels in pediatric patients be reported in the label.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

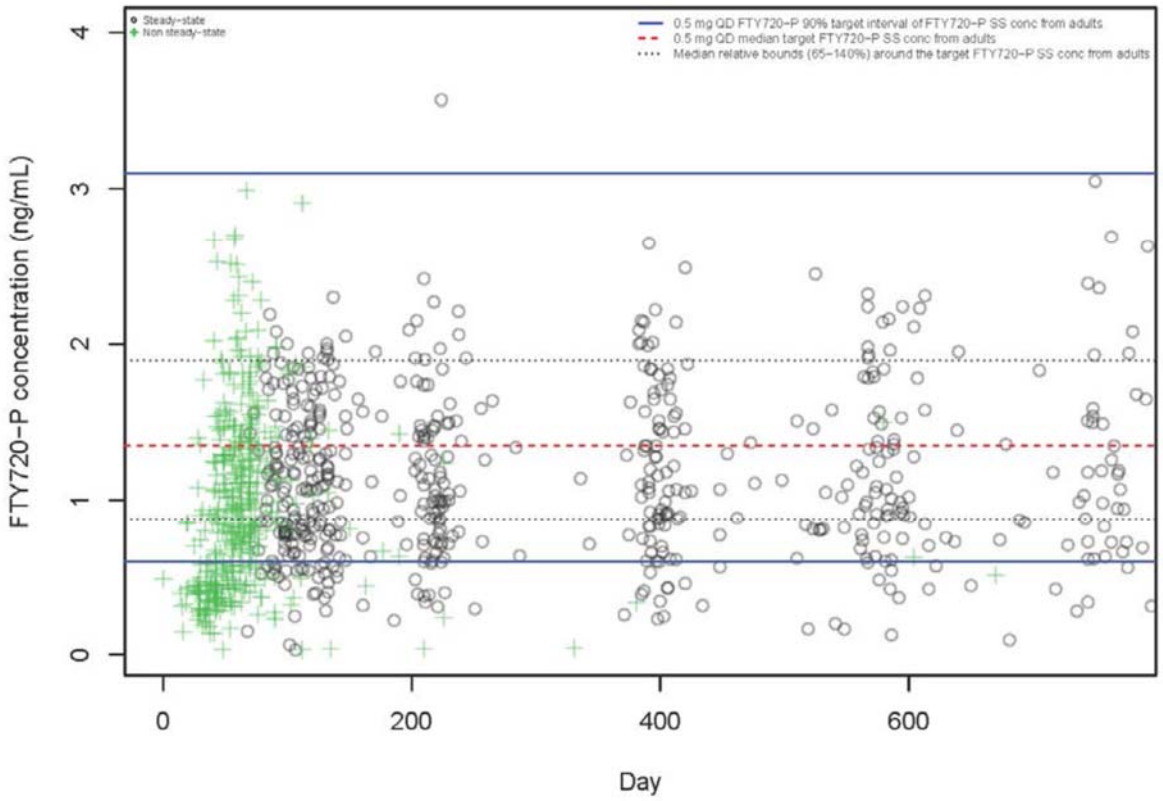
3.1 Overview of the Product and Regulatory Background

Fingolimod (Gilenya®) is an orally acting sphingosine-1 phosphate (S1P) receptor modulator that was approved at a daily dose of 0.5 mg for the treatment of relapsing multiple sclerosis (MS) in adults in September 2010. Based on the recommendation of OCP (Lai, DARRTS 8/4/2010), a post-marketing commitment to perform a controlled study of a lower dose (0.25 mg) was issued. In March 2013, a pediatric Written Request was issued (and later amended in 2016) and included a clinical trial to evaluate the efficacy and safety of fingolimod versus interferon beta-1a in pediatric patients (10 years of age and older) with MS.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Pharmacokinetic characteristics of fingolimod-P in the pediatric population are primarily derived from sparse sampling from the pivotal study D2311. Blood samples were obtained in the study at Day 1 and Day 30 pre-dose and 6 hours post dose and at any time on the following occasions: Day 15 and Months 2, 3, 6, 12, 18 and 24 or end of study. A total of 544 fingolimod-P concentrations (≥ 45 days after start of treatment or dose change) from 103 patients were available for analysis. The data suggested that steady state was reached by Month 2. Between-subject variability was large (72%), consistent with observations in adults. Overall, mean fingolimod-P concentrations in pediatric patients (1.10 ng/mL) were approximately 23% lower than the target concentration estimated from adult patients (1.35 ng/mL). These aspects are visualized in a plot of the data in Figure 1.

Figure 1: Observed Fingolimod-P Concentrations in Study D2311. Green circles correspond to non-steady-state data. Black circles correspond to steady-state data. The dotted red line is the median adult target concentrations. Black dotted lines correspond to 65%-140% bounds around the target and blue lines represent the 90%CI of the target.



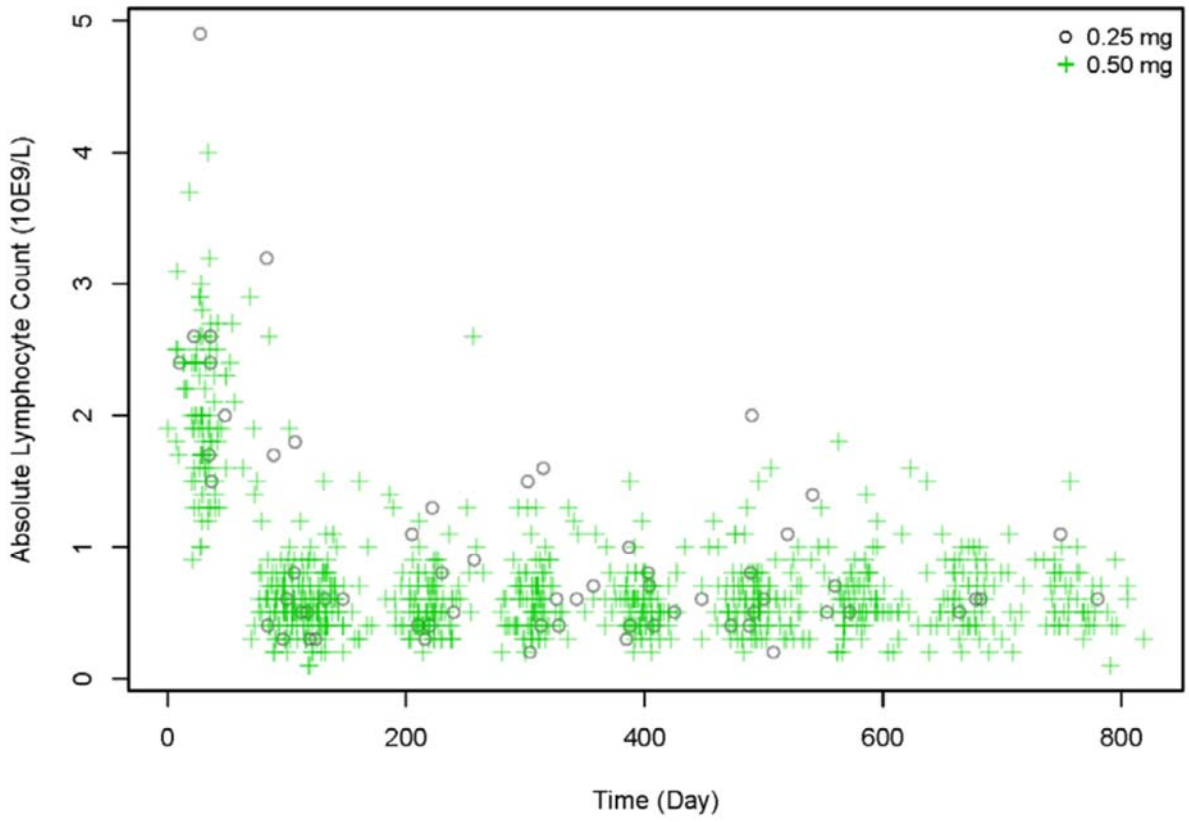
Source: Figure 9-3 on page 75 of Population PK Report (RA00500600)

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The evidence of effectiveness of fingolimod for the treatment of relapsing MS in pediatric patients is derived from a single, double-blind study to evaluate the safety and efficacy of fingolimod versus interferon beta-1a. The primary endpoint was the annualized relapse rate (ARR) of confirmed relapses. Fingolimod was demonstrated to be superior to interferon beta-1a (adjusted ARR of 0.122 vs 0.675, $p<0.0001$). Absolute lymphocyte count data provides supportive evidence that fingolimod had the intended pharmacodynamic effect of blocking the capacity of lymphocytes to egress from lymph nodes (Figure 2). The effect is consistent with that observed in the adult population, in which lymphocyte counts reached a nadir of approximately 0.5×10^9 cells/L with continued daily dosing.

Figure 2: Lymphocyte data from Study D2311



Source: Figure 9-10 on page 95 of Population PK Report (RA00500600)

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the dosing regimen was found to be safe and effective in pediatric patients greater than 10 years of age in Study D2311. The dose was selected to target concentrations observed in adults receiving the 0.5 mg dose, but median fingolimod-P concentrations in pediatric patients in Study 2311 were approximately 23% lower (1.10 ng/mL vs. 1.35 ng/mL). The reviewers explored potential explanations for this observation, including patient demographics, concomitant medications and bioanalytical methods, but none of them could sufficiently account for the discrepancy. Although of scientific interest, the lower observed concentrations in pediatric patients are not clinically relevant because the difference is modest, efficacy was established in Study D2311 at these concentrations and OCP previously concluded that it was likely that doses lower than 0.5 mg in adults would provide comparable effectiveness. The appropriateness of the 0.25 mg dose in patients weighing ≤ 40 kg is discussed in the following question.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

Yes, the 0.25 mg dose is appropriate for pediatric patients weighing ≤ 40 kg. The 0.25 mg dose was included in Study D2311 based on PK considerations that pediatric patients weighing ≤ 40 kg would require a lower dose to match fingolimod-P exposures to heavier pediatric patients (and adults). In Study D2311 the Applicant conducted an online PK analysis of data in patients receiving the 0.25 mg dose at Month 1 to confirm the need for a lower dose in patients with body weight ≤ 40 kg. If concentrations at Month 1 were below 65% of the target exposure derived from adults, 0.9 ng/mL, the dose was to be increased to 0.5 mg. Only 9 patients in Study D2311 initially received the 0.25 mg dose (Table 1).

Table 1: Summary of Online PK Analysis in Patients Receiving the 0.25 mg Dose

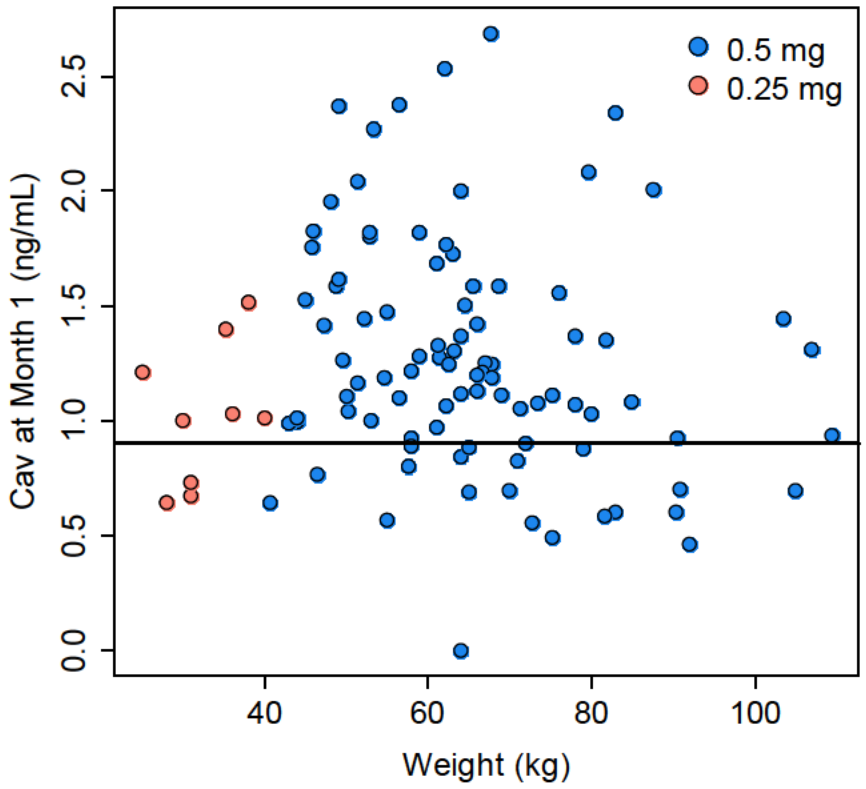
Individual fingolimod-P concentrations (Cav,ss; [(pre-dose concentration + 6 hour concentration) / 2])	Action taken with the study drug
0.675 ng/mL [(0.5+0.85)/2]	Dose was increased to 0.5 mg/day at Month 2
1.02 ng/mL [(0.831+1.2)/2]	Dose was kept at 0.25 mg/day at Month 2. Dose was increased to 0.5 mg/day at a later time during the study because body weight was above 40 kg.
0.643 ng/mL [(0.450+0.835)/2]	Dose was increased to 0.5 mg/day at Month 2
1.00 ng/mL [(0.887+1.12)/2]	Dose was kept at 0.25 mg/day at Month 2 and throughout the study duration.
0.735 ng/mL [(0.53+0.94)/2]	Dose was not increased to 0.5 mg/day at Month 2 due to an error at the online PK analysis (fingolimod concentrations instead of fingolimod-P concentrations were used). The patient and family declined the recommendation to increase the dose at a later time during the study once the error was discovered, and it was decided to maintain the current dose regimen at 0.25 mg/day.
1.52 ng/mL [(1.3+1.74)/2]	Dose was kept at 0.25 mg/day at Month 2. Dose was increased to 0.5 mg/day at a later time during the study because body weight was above 40 kg.
1.4 ng/mL [(1.29+1.51)/2]	Dose was kept at 0.25 mg/day at Month 2. Dose was increased to 0.5 mg/day at a later time during the study because body weight was above 40 kg.
1.02 ng/mL [(0.633+1.4)/2]	Dose was kept at 0.25 mg/day at Month 2 and throughout the study duration.
1.22 ng/mL [(1+1.43)/2]	Dose was kept at 0.25 mg/day. The patient withdrew from the study early.

Source: Summary of Clinical Pharmacology Studies, Table 2-2, Pages 16-17.

The results show that the dose was increased to 0.5 mg in two patients because of low concentrations at Month 1. An additional subject with low concentration at Month 1 remained on the 0.25 mg dose due to an error. A total of three subjects had their dose increased from 0.25 mg to 0.5 mg based on an increase

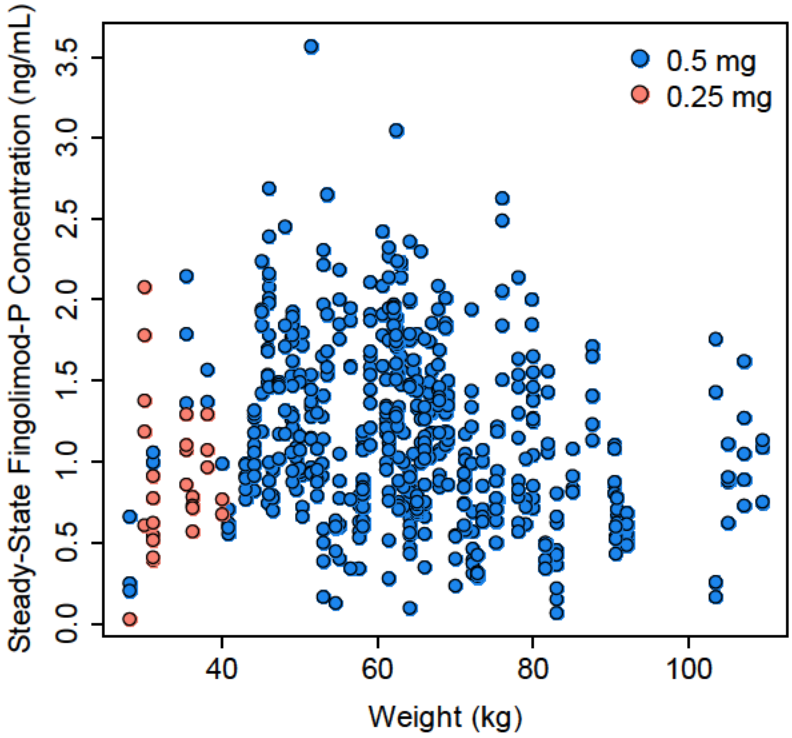
in body weight > 40 kg. Only 4 patients remained at a dose of 0.25 mg throughout the study. On face, it may appear concerning that 1/3 of patients receiving the 0.25 mg dose were deemed to have low concentrations, but it is important to view this observation in context of the overall population (Figure 3). The Month 1 concentrations in subjects receiving the 0.25 mg dose were visually comparable to Month 1 concentrations in heavier subjects receiving the 0.5 mg dose. In fact, if the same online PK analysis had been conducted in patients > 40 kg receiving the 0.5 mg dose, 22% of these patients would also have been deemed as having low concentrations.

Figure 3: Month 1 Concentrations in Study D2311. The horizontal black line is the cut off (0.9 ng/mL) used for determining the need for a dose increase in patients ≤ 40 kg.



To further evaluate the adequacy of the 0.25 mg dose, the reviewer plotted fingolimod-P concentrations at steady state in all patients (Figure 4). The results show that steady-state concentrations in patients ≤ 40 kg receiving the 0.25 mg dose are consistent with concentrations in patients > 40 kg who received the 0.5 mg dose. Therefore, the dose adjustment based on body weight is acceptable.

Figure 4: Steady-State Fingolimod-P Concentrations in Study D2311



4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Two formulations were used in the clinical trial in patients 10 to 18 years: a 0.5 mg fingolimod capsule (the approved strength for adult use) for patients with body weight greater than 40 kg and a new 0.25 mg fingolimod capsule for patients with body weight less than 40 kg. The 0.25 mg formulation used additional excipients to the ones used in the 0.5 mg capsule to improve the formulation stability and a modified manufacturing process ((b) (4)). An *in vivo* relative bioavailability study (study FTY720D2117) in healthy subjects was conducted to compare the new 0.25 mg formulation to the commercial 0.5 mg formulation.

Study FTY720D2117 was an open-label, randomized, single dose, two period, two sequence, crossover study. A total of 42 subjects were randomized in the study. Study drugs (2×0.25 mg and 0.5 mg capsules) were administered in the fasted state with a washout period of 36 days between dosing. Thirty eight (38) subjects completed the study. All 42 subjects were included for descriptive PK summary and safety analysis.

The results from this study conclude that the 0.25 mg capsule formulation is bioequivalent to the 0.5 mg capsule formulation, when administered at equal dose in the fasted state.

Analyte	PK parameter	Adjusted geometric mean*		Geometric mean ratio*		
		New fingolimod formulation	FMI fingolimod formulation	Point estimates	90% Confidence limits	
					Lower	Upper
Fingolimod	Cmax (ng/mL)	0.465	0.424	1.10	1.07	1.13
	AUClast (ng·h/mL)	72	66.7	1.08	1.02	1.14
	AUCinf (ng·h/mL)	77.9	72	1.08	1.03	1.14

Analyte	PK parameter	Adjusted geometric mean*		Geometric mean ratio*		
		New fingolimod formulation	FMI fingolimod formulation	Point estimates	90% Confidence limits	
					Lower	Upper
Fingolimod-P	Cmax (ng/mL)	0.608	0.566	1.07	1.03	1.12
	AUClast (ng·h/mL)	38.3	34.8	1.10	1.04	1.17
	AUCinf (ng·h/mL)	44.5	41.1	1.08	1.02	1.15

*back-transformed from log scale.

New fingolimod formulation: 0.5 mg fingolimod (two 0.25 capsules)

FMI fingolimod formulation: 0.5 mg fingolimod (single 0.5 mg capsule)

Model: The log transformed PK parameter data were analyzed using a linear mixed effect model with treatment, sequence, period and subject as fixed effects.

Source: Study No FTY720D2117 CSR, PT-Table 14.2-1.1

No food effect for the 0.25 mg capsule was assumed based on no food effect for the 0.5 mg capsule. Fingolimod hydrochloride is a BCS class II compound based on its low solubility at physiological pH and the high apparent absolute oral bioavailability (93%) observed in humans. Due to the low solubility of Fingolimod in higher pH's, the 0.5 mg capsules dissolved no more than 63% in pH 4.5 and no more than 3% in pH 6.8 buffers. Therefore, the sponsor did not use *in vitro* dissolution comparison between the 0.5 mg and 0.25 mg strengths in pH 4.5 and pH 6.8 buffers (only in 0.1N HCl dissolution comparison was provided).

Dissolution Results of Fingolimod 0.5 mg (FMI) and 0.25 mg (New Pediatric Formulation) Capsules in 0.1N HCl

Time point (min)	% Fingolimod	
	0.5 mg lot H675FF	0.25 mg lot AEUS/2011-0143
10	96 (12)*	104 (12)
20	98 (12)	102 (12)
30	98 (12)	103 (12)

* In parentheses, number of units tested

Source: [FTY720 0.25 mg Analysis Report v5 2012] and [FTY720 0.5 mg Analysis Report 2009]

However, both the 0.25 and 0.5 mg capsules are immediate-release formulations and the additional excipients used in the 0.25 mg capsule (hydroxypropylcellulose, (b) (4) and hydroxypropylbetadex, (b) (4) are unlikely to cause a significant food effect. In addition, in the pediatric trial D2311, study drug was administered regardless of food. Therefore, the proposed dosage and administration of 0.25 mg Gilenya in pediatric patients with body weight ≤ 40kg "with or without food" is reasonable.

Analytical methods

An analytical method measuring simultaneously fingolimod and fingolimod-P (with citrate as anticoagulant) was developed and used for the analysis of studies D2117 and D2311 (Emotte et al 2012). The method consists of protein precipitation and solid phase extraction, evaporation of the supernatant to dryness, and analysis of the reconstituted sample residue by LC-MS/MS in multiple reaction monitoring (MRM) mode using electrospray ionization. The earlier pharmacokinetic samples from D2311 were analyzed at the bioanalytical laboratory (b) (4)), and later samples at a second bioanalytical laboratory, (b) (4)). The LLOQ of the bioanalytical method used at (b) (4) were set to 0.05 ng/mL and 0.0625 ng/mL for fingolimod and fingolimod-P [DMPK R1701101], respectively. The (b) (4) LC-MS/MS method had a LLOQ of 0.020 ng/mL and 0.025 ng/mL for fingolimod and fingolimod-P, respectively [DMPK R1100265a] and [DMPK R1100265a-01].

Summary of Analytical Methods Pertaining to the Pediatric Clinical Development of Fingolimod

Analyte	Matrix	Method	LLOQ	Method validation report	Clinical studies which used this method
fingolimod and fingolimod-P	Blood	LC-MS/MS	0.020 ng/mL (fingolimod) 0.025 ng/mL (fingolimod-P)	DMPK R1100265a DMPK R110265a-01 (b) (4)	CFTY720D2117 CFTY720D2311
fingolimod and fingolimod-P	Blood	LC-MS/MS	0.0500 ng/mL (fingolimod) 0.0625 ng/mL (fingolimod-P)	DMPK R1701101 (b) (4)	CFTY720D2311

Source: DMPK R110265a; DMPK R110265a-01; DMPK R1701101; CFTY720D2117; CFTY720D2311

Both methods were validated (accuracy, precision, selectivity, sensitivity, reproducibility and stability were demonstrated). Long term stability of fingolimod and fingolimod-P in human whole blood has been demonstrated for at least 189 days (about 6 months) in spiked human blood [DMPK R1100265-01] and for at least 783 days (about 26 months) [DMPK R1100265a-01] and 1291 days (about 43 months) in incurred samples when stored at −70°C.

In Study D2311 in pediatric patients, the steady state of fingolimod-P concentration was achieved between month 1 and 2 of daily administration of fingolimod. The geometric mean of concentrations of fingolimod-P at month 1 (online PK analysis) was 0.984 ng/mL and 1.22 ng/mL for patients at 0.25 mg/day and 0.5 mg/day respectively, below 1.35 ng/mL that was the target exposure predicted from

adult patients. The sponsor suggests that this difference might be due to two different analytical methods being used to measure the fingolimod-P concentrations in the phase 3 studies in adult MS patients (Studies CFTY720D2301 and CFTY720D2302) and in Study D2311 in pediatric MS patients. However, this is an unlikely reason, as all bioanalytical methods were properly validated and performed adequately during the analysis of study samples.

Note: The concentrations of fingolimod and fingolimod-P in whole blood in adults MS patients ([Study CFTY720D2301] and [Study CFTY720D2302]) were determined using two LC-MS methods, one for each analyte, with LLOQ of 0.08 ng/mL for fingolimod and 0.100 ng/mL for fingolimod-P. Those methods were described in the original NDA for fingolimod in adults MS patients (NDA22527).

Also, two different bioanalytical methods (and sites) were used to quantify fingolimod-P plasma samples in study D2311, however no significant difference in fingolimod-P concentrations were observed, see table below.

Summary of Fingolimod-P Concentrations by Bioanalytical Sites

Visit	N	Mean (CV%)	Geomean (CV%)	Median (Min-max)
Lab= (b) (4)				
3, pre-dose	13	0	0 (NC)	0 (0-0)
3, 6 hr sample	14	0.482 (33.5)	0.462 (29.8)	0.424 (0.300-0.912)
4	17	1.05 (24.8)	1.02 (25.1)	1.02 (0.700-1.47)
5, pre-dose	18	1.18 (41.6)	1.08 (45.5)	1.00 (0.474-2.03)
5, 6 hr sample	18	1.65 (37.2)	1.52 (45.0)	1.74 (0.698-2.67)
6	22	1.14 (37.7)	1.03 (58.1)	1.12 (0.151-1.77)
7	31	1.12 (36.0)	1.00 (65.9)	1.12 (0.0640-1.97)
8	32	1.20 (51.4)	1.06 (55.9)	1.10 (0.221-3.57)
10	30	1.16 (51.6)	0 (NC)	1.13 (0-2.49)
12	22	1.11 (53.6)	0.935 (74.1)	0.927 (0.128-2.24)
777	81	1.09 (58.9)	0 (NC)	0.982 (0-3.05)
Lab (b) (4)				
3, pre-dose	88	0 (NC)	0 (NC)	0 (0-0)
3, 6hr sample	88	0.365 (35.8)	0 (NC)	0.369 (0-0.649)
4	87	1.01 (41.8)	0 (NC)	0.943 (0-2.53)
5, pre-dose	80	1.05 (43.5)	0.962 (46.0)	1.01 (0.321-2.68)
5, 6 hr sample	77	1.44 (36.2)	1.35 (37.2)	1.36 (0.450-2.99)
6	79	1.11 (44.4)	0.971 (66.6)	1.09 (0.0304-2.19)
7	70	1.09 (48.7)	0.938 (71.7)	0.996 (0.0375-2.30)
8	67	1.14 (47.6)	0.976 (72.2)	1.03 (0.0382-2.42)
10	67	1.18 (47.1)	1.03 (61.9)	1.07 (0.230-2.65)
12	40	1.22 (42.4)	1.11 (48.3)	1.12 (0.368-2.32)
777	16	1.04 (72.2)	0.708 (154)	0.913 (0.0337-2.69)

Source: [FTY720K PopPKPD-PK-lymphocytes report Table 4-4]

NC = Not Calculated

Visit 3 was on Day 1; Visit 4 was on Day 15; Visit 5 was at Month 1; Visit 6 was at Month 2; Visit 7 was at Month 3; Visit 8 was at Month 6; Visit 10 was at Month 12; Visit 12 was at Month 18; Visit 777 was the end of study visit

4.3 Population PK and or PD Analyses

4.3.1 Population PK Analysis

The objectives of the Applicant's population PK analyses were to develop a model of steady-state fingolimod-P concentrations in Study D2311 and to assess if those concentrations achieved the adult target level. Blood samples were obtained in the study at Day 1 and Day 30 pre-dose and 6 hours post dose and at any time on the following occasions: Day 15 and Months 2, 3, 6, 12, 18 and 24 or end of study. Measurements that met any of the following conditions were considered not to be at steady-state and therefore were excluded from the analysis:

- ≤ 45 days from starting treatment
- After > 7 days without any dose
- ≤ 45 days after a treatment interruption that lasted > 7 days
- ≤ 45 days after the switch from 0.25 mg to 0.5 mg if pediatric patient gained weight or had a dose increase

The final dataset included 544 fingolimod-P concentrations from 103 patients. A summary of the observed steady-state concentrations is displayed in Table 2. Concentrations following the 0.25 mg dose tended to be slightly (10% to 20%) lower on average than concentrations following the 0.5 mg dose, but there was considerable overlap in the distribution.

Table 2: Summary of Fingolimod-P Concentrations at Steady-State by Actual Dose

Visit	N	Mean (CV%)	Geometric mean (CV%)	Median (Min-Max)
Overall				
6	101	1.11 (42.8)	0.983 (64.5)	1.09 (0.0304-2.19)
7	99	1.12 (43.6)	0.992 (58.6)	1.07 (0.0640-2.30)
8	97	1.17 (47.8)	1.03 (55.1)	1.07 (0.221-3.57)
10	95	1.20 (46.2)	1.05 (58.4)	1.10 (0.230-2.65)
12	60	1.19 (46.1)	1.05 (58.6)	1.08 (0.128-2.32)
777	92	1.13 (56.1)	0 (NC)	0.988 (0-3.05)
Dose=0.25 mg				
6	8	0.707 (49.3)	0.517 (173)	0.774 (0.0304-1.19)
7	6	0.822 (24.4)	0.803 (24.1)	0.754 (0.608-1.07)
8	5	0.975 (42.6)	0.886 (56.3)	1.10 (0.391-1.38)
10	2	1.10 (88.4)	0.855 (139)	1.10 (0.411-1.78)
12	1	0.911 (NC)	0.911 (NC)	0.911 (0.911-0.911)
777	3	1.09 (78.9)	0.900 (83.4)	0.619 (0.566-2.08)
Dose=0.5 mg				
6	93	1.15 (41.1)	1.04 (51.3)	1.17 (0.151-2.19)
7	93	1.13 (43.5)	1.01 (60.1)	1.10 (0.0640-2.30)
8	92	1.18 (48.0)	1.04 (55.2)	1.06 (0.221-3.57)
10	93	1.20 (45.9)	1.06 (57.7)	1.10 (0.230-2.65)
12	59	1.19 (46.3)	1.05 (59.1)	1.09 (0.128-2.32)
777	89	1.14 (55.9)	0 (NC)	0.989 (0-3.05)

Source: mt24135.csv, Visit 6=2 months, Visit 7=3 months, Visit 8=6 months, Visit 10=12 months, Visit 12=18 months and Visit 777=24 months, NC: Not calculated, CV: Coefficient of variation, Min: Minimum, Max: maximum

Source: Table 4-2 on page 32 of Population PK Report (RA00500600)

The previously developed linear mixed effects model developed in adults (reviewed in Lai, DARRTS 8/4/2010) served as the starting point for the pediatric PK analysis. Age, body weight, gender, race and dose group were evaluated as potential covariates. The final model included effects of weight and dose on intercept. The Applicant concludes that following 0.5 mg, the typical steady-state fingolimod-P concentration was estimated to be 0.978 ng/mL for a body weight of 70 kg, which is below the adult target level (1.35 ng/mL) but within the 90% CI around the median and within the median 65%-140% bounds around the adult target. This difference was not considered clinically relevant and the Applicant considered steady-state concentrations to be similar between adult and pediatric patients.

4.3.2 Population PKPD Analyses

The previously developed PKPD model between fingolimod-P concentration and lymphocyte count derived in adults was used as a starting point for analysis in the pediatric population. Lymphocyte count data were collected in Study D2311 at screening, baseline, Day 15 and Months 1, 2, 3, 6, 9, 12, 15, 18, 21 and 24 months (or end of study) and a follow-up sample after 3 months in patients who prematurely discontinued study drug or who did not enter the extension phase. The data are illustrated in Figure 2. A visual predictive check (VPC) was performed to assess whether the adult model could adequately

describe the pediatric data. The VPC showed that the adult model predicted lower lymphocyte levels than the observed pediatric data. The PKPD model was then re-estimated using pooled adult and pediatric data and a binary covariate to describe differences in the two populations. The updated model showed that baseline lymphocyte count was 17.2% higher in children compared to adults. Differences in I_{max} and IC50 were estimated with poor precision, but did not reveal clinically relevant differences between populations. The maximum reduction in lymphocytes from baseline was estimated to be 81% in adult patients and 79% in pediatric patients.

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