CLINICAL REVIEW

Application Type	Supplemental NDA
Application Number(s)	NDA 22527 Pediatric Supplement (NCT 01892722) SDN 0538
Priority or Standard	Priority
Submit Date(s)	November 13, 2017
Received Date(s)	November 13, 2017
PDUFA Goal Date	May 13, 2018
Division/Office	Division of Neurology Products
Reviewer Name(s)	Paul R. Lee, M.D., Ph.D.
Review Completion Date	April 25, 2018
Established/Proper Name	Fingolimod
(Proposed) Trade Name	Gilenya
Applicant	Novartis
Dosage Form(s)	0.25 mg and 0.5 mg oral capsules
Applicant Proposed Dosing Regimen(s)	0.25 mg or 0.5 mg daily
Applicant Proposed Indication(s)/Population(s)	Gilenya is indicated for the treatment of pediatric patients ages 10 years and older with relapsing forms of multiple sclerosis (RMS)
Recommendation on Regulatory Action	Approval: Gilenya is indicated for the treatment of pediatric patients ages 10 years and older with relapsing forms of multiple sclerosis (RMS)
Recommended Indication(s)/Population(s) (if applicable)	Pediatric patients ages 10 years and older with Relapsing Forms of Multiple Sclerosis (RMS)

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BPM	Beats Per Minute
BRF	Benefit Risk Framework
BSSR	Blinded Sample Size Re-estimation
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CDP	Confirmed Disability Progression
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CNS	Central Nervous System
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DF	Degrees of Freedom
DMC	data monitoring committee
ECG	electrocardiogram
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
EOS	End of Study
EU	European Union
eCRF	Electronic Case Report Form
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FS	Functional System

GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IFN	Interferon
i.m.	Intramuscular
IND	Investigational New Drug Application
IR	Incidence Rate
IRB	Institutional Review Board
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LFT	Liver Function Test
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MMF	Mycophenolate Mofetil
MS	Multiple Sclerosis
msec	Millisecond
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
n/neT2	New/Newly Enlarged T2 lesions
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PFT	Pulmonary Function Test
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
RCT	Randomized Clinical Trial
REMS	risk evaluation and mitigation strategy
RMS	Relapsing Multiple Sclerosis

SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	System Organ Class
TEAE	treatment emergent adverse event
US	United States

1. Executive Summary

1.1. Product Introduction

Fingolimod (Gilenya, FTY720) is an orally active, first-in-class sphingosine-1-phosphate (S1P) receptor modulator. After oral dosing, fingolimod is phosphorylated to create the active moiety fingolimod-phosphate (fingolimod-P.) This active moiety has activity at four of the five G-protein coupled S1P receptors designated S1P1, S1P3, S1P4, and S1P5. At treatment doses, fingolimod-P binds as an agonist to S1P receptors but this initial agonism transforms into functional antagonism with subsequent internalization of the receptor. The net effect of chronic fingolimod administration is a decreased number of S1P receptors on cellular membrane surfaces. Lymphocytes utilize S1P1 receptor signaling to exit from lymph nodes. Thus, the key pharmacodynamic effect of fingolimod is a dose-dependent reduction of the peripheral lymphocyte count mediated by down modulation of the S1P1 receptors on lymphocyte membranes. Decreased S1P1 receptor function slows the egress of lymphocytes from the lymph nodes, thereby reducing the number of autoreactive lymphocytes available for circulating to central nervous system (CNS) tissues where they may cause inflammation and cellular injury.

Fingolimod is approved for the treatment of adults with relapsing multiple sclerosis (RMS.) The Sponsor (Novartis) developed fingolimod originally for the prevention of acute rejection after renal transplantation in adults but discontinued this development program while in Phase 3 trials due to an unfavorable risk benefit profile in comparison to other approved acute rejection treatments. Given the theoretical benefit of lowering circulating lymphocyte populations might have on autoimmune disease, Novartis initiated a clinical program to evaluate the treatment of RMS with fingolimod. This program yielded two clinical trials, submitted in NDA 22527, whose safety and efficacy data served as the basis for approval of 0.5 mg daily fingolimod for the treatment of RMS in adults. This supplement to NDA 22527 was the result of a pediatric study (D2311) required by the Pediatric Research Equity Act and seeks to expand the treatment population to include pediatric patients aged 10-18 years with RMS.

Fingolimod Drug Product is marketed currently as a hard gelatin capsule containing a (b) (4) composed of 0.5 mg of fingolimod hydrochloride with only two excipients, pharmaceutical grade mannitol (as a (b) (4)) and magnesium stereate (as a (b) (4)). The intended commercial formulation of 0.25 mg strength consists of a hard gelatin capsule containing fingolimod hydrochloride and the following excipients: mannitol ((b) (4)), hydroxypropylcellulose (b) (4)), hydroxypropylbetadex (b) (4)) and magnesium stearate (b) (4) . The capsule fill is produced by (b) (4) . Fingolimod 0.5 mg and 0.25 mg capsules were bioequivalent when administered at the same dose.

Reviewer Comment: Throughout this document when there is a reference to "fingolimod,"

it is assumed that "fingolimod" and "fingolimod-P" are interchangeable and equivalent terms.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Relapses

A single adequate and well-controlled clinical trial provides substantial evidence that daily oral doses of 0.25 mg or 0.5 mg fingolimod reduces the frequency of relapses in comparison to treatment with interferon β-1a in patients ≥ 10 years and < 18 years with relapsing forms of MS.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

An adequate and well-controlled trial in pediatric patients aged 10-18 years with RMS has provided substantial evidence that treatment with 0.25 mg or 0.5 mg fingolimod reduces the annualized relapse rate and reduces evidence of disease activity on magnetic resonance imaging in comparison to interferon β-1a. The observed benefits are clinically relevant, similar to those associated with fingolimod treatment in adult patients with RMS, and justify the previously known and newly observed safety risks. Though this efficacy finding represents the outcome from a single adequate and well-controlled trial in comparison to interferon β-1a, pediatric RMS is a rare disease without an approved treatment. Therefore, the fulfilment of an unmet medical need in a small recruitment population is relevant to the consideration of the adequacy of a single well-controlled study's data in this benefit-risk assessment. Based on the safety review, the risk of fingolimod in pediatric patients ages 10-18 years appears similar in both the affected organ systems and in the magnitude of the risks of fingolimod noted in adult patients. The most serious risks of fingolimod in pediatric patients can be managed with appropriate monitoring and are usually rectified by discontinuing the medication. The previous assessment of fingolimod risk in adult patients with RMS was determined to be acceptable with appropriate safety vigilance and accrual of additional post marketing safety information, and a similar conclusion is justified here. The benefit to risk comparison for fingolimod in pediatric patients with RMS in comparison to interferon β-1a justifies a recommendation of approval for the proposed indication.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• RMS in adults and children is a disease associated with periods of short-term neurological signs and symptoms due to relapses. RMS is also associated with periods of disability due in part to incomplete recovery from relapses. These periods of disability tend to last three to six months, approximately, with resolution thereafter. These acute deteriorations in neurological function attributed to RMS are generally thought to be caused by acute inflammation disseminated	• Treatment with fingolimod in patients aged ≥ 10 years to < 18 years with RMS results in a statistically significant and clinically meaningful reduction in the number of MS relapses. An adequate and controlled pediatric trial has demonstrated a reduction in the annualized relapse rate, an

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	over time in the most densely myelinated areas of the CNS and to a lesser extent in the neuropil and the meninges. However longer term and irreversible disability may also develop longitudinally due to neurodegeneration that appears to occur independently from relapses. The etiology of the neuronal pathology is not clearly understood and may be unrelated to the inflammatory process. RMS in the pediatric population differs from RMS in adults in that relapses occur more frequently. Pediatric patients with RMS acquire disability at a slower rate than adults with RMS. However, patients with an onset in childhood experience more years with the disease, and consequently their overall disability in adulthood is typically worse than individuals the same age who are diagnosed with RMS as adults. An adequate and well-controlled trial in patients aged 10-18 years with RMS provides substantial evidence that treatment with fingolimod reduces the frequency of relapses in a statistically significant and clinically relevant proportion of the pediatric patient population with RMS. There is minimal uncertainty regarding these clinical benefits.	endpoint considered a valid efficacy outcome measure in studies of patients with MS.
Current Treatment Options	• There are no therapies approved for RMS in patients younger than 18 years old. • There are fifteen approved agents for patients with RMS with reasonable certainty these agents are effective in reducing the	• The lack of an approved therapy for pediatric patients with RMS would justify approval of an effective therapy with known but manageable risks and uncertainty about long-term consequences of use. • Currently approved therapies for RMS are effective for the reduction of relapses

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	frequency of relapses. For all but two of the approved agents, the label indicates that safety and effectiveness have not been established in patients with RMS below the age of 18 years. The labeling for alemtuzumab and daclizumab states that they should not be used in pediatric patients because of serious associated risks.	based on studies performed in adults with RMS. These treatments have not previously been examined for effectiveness and safety in pediatric patients with RMS. Two of these products are explicitly not for pediatric use because of serious medical risks. There is a unmet medical need for an approved therapy with demonstrable efficacy and apparent safety in children and adolescents with RMS.
Benefit	• In patients aged 10-18 years old with RMS, treatment with fingolimod reduces the frequency of relapses. The results supporting this benefit in one adequate, well-controlled trial are robust.	• The benefits of treatment with fingolimod on relapses in pediatric RMS are persuasive and justify the risk.
Risk and Risk Management	Safety Database • The safety database submitted in support of this application includes safety data from the core phase of Study D2311, a Phase 3 study comparing fingolimod 0.25 mg and 0.5 mg daily to interferon β-1a in patients aged 10-18 years with RMS. There are supportive data from three controlled trials of fingolimod in adult patients with RMS, patients < age 18 in extension trials, and a pilot study of high dose fingolimod in renal transplant patients aged 11-18 years. Drug exposure is adequate for the 0.5 mg dose; there were too few patients enrolled at the 0.25 mg dose to reach definitive conclusions about safety at this dose. The demographics of the pediatric trial reflect the intended population for use.	• While the pediatric database from the controlled trial provides limited data, the safety findings are similar to those identified in the more extensive exposures from adult studies. The adult and pediatric safety data together provide an adequate basis for a safety analysis of 0.25 mg and 0.5 mg daily fingolimod in patients ages ≥ 10 years to < 18 years with RMS.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Safety Concerns • The most common AEs observed in the pediatric RMS study (at least 5% and at least as frequent as interferon β-1a) were as follows: Headache (HA, 25%), Upper respiratory tract infections (URI, 10%), and Influenza (6.9%). • There were no deaths in the pediatric RMS clinical trial. • There were more SAEs for epilepsy-related events (seizures), infections, and cardiac conduction disorders in the fingolimod treatment group compared to the interferon β-1a treatment group. Other Uncertainties • The risks of very long-term chronic treatment with fingolimod treatment starting in childhood or adolescence and continuing through adulthood are unknown.	• In patients ages ≥ 10 years to < 18 years, the risks of fingolimod are similar to those identified in adult patients. • The current labeling for fingolimod already highlights the risks of infections, bradycardia, atrioventricular block, increased blood pressure, macular edema, liver injury, and hypersensitivity reactions identified in pediatric patients. The labeling recommends first dose monitoring in a medical setting because of cardiovascular effects noted with initial dosing in adults. • There appears to be a specific risk of new onset seizures in pediatric patients taking fingolimod. An update to the labeling will help to mitigate this risk in the pediatric population with RMS.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

▪	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	▪ Clinical outcome assessment (COA) data, such as	[*e.g.*, Sec 6.1 Study endpoints]
	▪ Patient reported outcome (PRO)	Sec. 6.1.2 Other Relevant Benefits
	□ Observer reported outcome (ObsRO)	
	▪ Clinician reported outcome (ClinRO)	Sec. 6.1.2 Study Results
	□ Performance outcome (PerfO)	
	□ Qualitative studies (*e.g.*, individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[*e.g.*, Sec 2.1 Analysis of Condition]
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (*e.g.*, submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[*e.g.*, Current Treatment Options]
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Multiple Sclerosis (MS) is a chronic autoimmune disorder of the CNS characterized by recurrent episodes of neurologic deficits that are due to one of more areas of acute injury to myelin, oligodendrocytes, and neurons, specifically, the neuronal axon. Acute inflammation injury may occur in the subcortical white matter, brainstem, optic nerve, or the spinal cord. The diagnostic precepts used in establishing a diagnosis of MS require clinical or imaging evidence of a dissemination of neurological deficits and injuries "in space and time" (Polman *et al.*, 2011). This waxing and waning pattern of symptoms is the origin of the clinical subtyping of "relapsing and remitting" forms of MS as opposed to the rarer "progressive" forms of MS that typically do not have clearly identifiable periods of remission. Although early relapses in RMS may be followed by complete recovery, over time, there is an accumulation of residual deficits and increasing disability (Weinshenker *et al.*, 1989). Most patients diagnosed with MS experience an accrual of disability over the longitudinal course of the disease, and this disability progression is part of the natural history of MS, occurring in parallel and seemingly independent of acute exacerbations (Confavreux & Vukusic, 2014).

Up to 10% of patients experience an initial demyelinating event heralding a diagnosis of MS before age 18 years (Banwell, 2014). Pediatric MS is, like adult MS, an autoimmune disease and the neuropathological consequences of pediatric MS are similar to those noted in the CNS of adults with MS (Banwell *et al.*, 2007). The schematic process used by clinicians to diagnose pediatric MS requires the same dissemination in time and space of lesions or symptoms necessary for a MS diagnosis in adults (Krupp *et al.*, 2013). The natural history of pediatric MS is similar to adult MS in that children with MS overwhelmingly follow a relapsing-remitting course. Pediatric MS differs from its adult counterpart in that very few cases follow a progressive course at initial diagnosis (Banwell, 2014). Pediatric patients with MS experience more frequent relapses with less disability when compared with adult patients experiencing the same duration of disease (Giogio *et al.*, 2017). However, despite this apparent early resilience, when patients with pediatric-onset MS reach adulthood, they achieve irreversible disability a decade sooner than adult-onset patients acquire observable disabilities (Waldman *et al.*, 2016).

Given the apparent clinical similarity between pediatric and adult MS, the prevailing hypothesis driving drug development programs is that the same overall treatment goal of suppression of components of the immune system should be as successful in treating pediatric MS as it has proven to be in adult MS. However, given the rarity of the pediatric form of MS and the practical challenges inherent to pediatric trial design, there previously had been no adequate, well-controlled trials to establish safety and efficacy of any approved MS therapies in children. Case report and small case series have provided preliminary findings suggesting efficacy of treatments for adults in children, but any claims of effectiveness and safety following the use of all MS therapies in children remain anecdotal and without rigorous substantiation. Therefore, there is a significant unmet medical need for a treatment that has safety and efficacy data

generated via an adequately controlled, well-designed pediatric clinical trial.

2.2. Analysis of Current Treatment Options

There are no approved agents for patients less than 18 years of age with RMS. The sixteen approved agents for adult patients with RMS are listed below in Table 1. For all but two of the approved agents, the label indicates that safety and effectiveness have not been established in patients with MS below the age of 18 years. Daclizumab's labeling specifically states that it should not be used in patients under 17 years of age because of risks of hepatic injury and immune-mediated disorders. Alemtuzumab's labeling indicates it should not be used in pediatric patients due to the risks of autoimmunity, infusion reactions, and because it may increase the risk of malignancies (thyroid, melanoma, lymphoproliferative disorders, and lymphoma).

Table 1: FDA-approved treatments for Relapsing Forms of Multiple Sclerosis

Approved Drug	Product Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Major Safety Concerns	Other Comments
Beta interferon 1b	Betseron (Betaferon in EU)	Relapsing forms of MS	1993	subcutaneous every other day	32% reduction in ARR	None	
Beta interferon 1a	Interferon β-1a	Relapsing forms of MS	1996	IM weekly	32% reduction in ARR	hepatotoxicity	
Glatiramer acetate	Copaxone	Relapsing forms of MS	1996	subcutaneous daily	29% reduction in ARR	None	
Mitoxantrone	Novantrone	Relapsing forms of MS	2000	IV every 3 months	60% reduction in ARR 64% reduction in disability	Cardiotoxicity	
Beta interferon 1a	Rebif	Relapsing forms of MS	2002	subcutaneous three times weekly	32% reduction in ARR	hepatotoxicity	
Natalizumab	Tysabri	Relapsing forms of MS	2004	IV every 4 weeks	61% reduction in ARR	Progressive Multifocal Leukoencephalopathy	
Beta interferon 1b	Extavia	Relapsing forms of MS	2009	subcutaneous every other day	30% reduction in ARR	None	
Fingolimod	Gilenya	Relapsing forms of MS	2010	orally once daily	55% reduction in ARR	1st dose bradycardia, macular edema, impaired	

						pulmonary function tests, fetal risk	
Teriflunomide	Aubagio	Relapsing forms of MS	2012	orally once daily	31% reduction in ARR	black box warnings for hepatotoxicity and teratogenicity	
Dimethyl fumarate	Tecfidera	Relapsing forms of MS	2013	orally once daily	49% reduction in ARR	lymphopenia	
PEGylated Interferon β	Plegridy	Relapsing forms of MS	2014	subcutaneous every 2 weeks	36% reduction in ARR	None	
Alemtuzumab	Lemtrada	Relapsing forms of MS after inadequate responses to 2 or more other MS treatments	2015	2 courses 12 months apart	49% reduction in ARR	black box warning for serious/fatal autoimmune conditions thrombocytopenia and anti-glomerular basement membrane disease; serious and life-threatening infusion reactions, increased risk of malignancies	not indicated for use in patients less than 18 years of age due to safety concerns
Glatiramer acetate (generic)	various	Relapsing forms of MS	2015	subcutaneous daily	29% reduction in ARR	None	
Daclizumab	Zinbryta	Relapsing forms of MS after inadequate responses to 2 or more other MS treatments	2016	IV monthly	54% reduction in ARR	Black box warning for hepatic injury including autoimmune hepatitis, other immune-mediated disorders	not indicated for use in patients less than 18 years of age due to safety concerns
Ocrelizumab	Ocrevus	Relapsing and Progressive forms of MS	2016	IV every 2 weeks x 2 then IV every 6 months	46% reduction in ARR (RMS) 24% reduction in disability progression (progressive MS)	infusion reactions, increased risk of breast cancer	

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

FDA approved Gilenya for use in adults with RMS on September 22, 2010. Novartis markets Gilenya in the US for relapsing forms of MS in adults.

3.2. Summary of Presubmission/Submission Regulatory Activity

Initial Pre-IND (IND 70139) meeting: February 2, 2005

Original IND submission: May 9, 2005
The initial protocol was proposed as a double blind, randomized, multicenter, placebo-controlled, parallel group study comparing 1.25 mg of Gilenya to placebo.

FDA Approval: September 22, 2010 for treatment of RMS in patients ≥ 18 years old.
The approval letter required Novartis to perform a trial in patients aged 10 to 17 but waived the requirement for a trial in children ages 9 and younger (PMR 1679-1).

Pediatric Study SPA initial request and submission: February 11, 2011
Protocol CFTY720D2311 was for a two-year, open-label, rater-blinded randomized active-controlled study of Gilenya in comparison to interferon β-1a.

SPA No Agreement: November 1, 2011
Major reasons for no agreement were choice of MRI endpoint as opposed to a clinical endpoint, open-label design, and inadequate bradycardia evaluation.

SPA Request 2: December 1, 2011
Primary endpoint changed to ARR. Bradycardia evaluation changed in response to Agency feedback.

Information Request: March 19, 2012
Division requested clarifications regarding lack of blinding in study design and timing of PK analysis.

Response to Information Request: May 8, 2012
Resubmission of protocol as a double-blinded study design with requested clarifications of PK analysis.

SPA Agreement: November 29, 2012

3.3. Foreign Regulatory Actions and Marketing History

Gilenya is approved and marketed through the world as a treatment for adults with RMS. The first registration of Gilenya for the indication of multiple sclerosis occurred in Russia on August 17, 2010. The Australian Therapeutic Goods Administration approved Gilenya for RMS on January 19, 2011. The European Medicines Agency approved Gilenya for the treatment of RMS in adults, and the European Commission granted a marketing authorization valid throughout the European Union for Gilenya on March 17, 2011. Health Canada approved Gilenya for patients with RMS on March 10, 2011. The Japanese Ministry of Health, Labor, and Welfare approved Gilenya for RMS on September 27, 2011. Presently, Gilenya is registered as an approved treatment for adults with multiple sclerosis in over eighty-five countries. There are no approvals for pediatric patients.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Not applicable

4.2. Product Quality

See the review by the Chemistry, Manufacturing and Control (CMC) reviewers.

4.3. Clinical Microbiology

See the review by the CMC/microbiology reviewers.

4.4. Nonclinical Pharmacology/Toxicology

See the review by Drs. Freed and Siarey.

4.5. Clinical Pharmacology

See the review by Drs. Dimova, Krudys, and Men.

4.6. Devices and Companion Diagnostic Issues

Not Applicable

4.7. Consumer Study Reviews

Not Applicable

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 2: Reviewer Table: Clinical Trials Relevant to Pediatric RMS indication

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
D2311	01892722	RCT; Comparator interferon β-1a	0.25 or 0.5 mg by mouth daily	ARR; number of new/expanding T2 lesions	24 months	215	10 to <18 years old RMS	87 centers in 27 countries
		Studies to Support Safety						
D2301	NCT00289978	RCT; Comparator placebo	1.25 mg or 0.5 mg by mouth daily	ARR; CDP 24	24 months	1272	Patients 17 to 55 years old RMS	138 centers in 22 countries
D2302	NCT00340834	RCT; Comparator interferon β-1a 30 µg i.m. weekly	1.25 mg or 0.5 mg by mouth daily	ARR; number of new/expanding T2 lesions; CDP 12	12 months	1292	Adults 18 to 55 years old RMS	172 centers in 18 countries
D2309	NCT00355134	RCT; Comparator placebo	1.25 mg or 0.5 mg by mouth daily	ARR; percent brain volume change; CDP 24	24 months	1083	Adults 18 to 35 RMS	117 centers in 8 countries
		Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)						
A0115	N/A	Single dose, open label trial; Comparator none	0.07 mg/kg by mouth once	PK; PD	single dose	7	11 to 16 years old renal transplant patients	2 centers in 2 countries

5.2. Review Strategy

The review of efficacy for the indication of the treatment of pediatric RMS is limited to trial D2311. This trial was a randomized, double-blind, double-dummy study with an active control. The comparator in this trial was interferon β-1a. The treatment duration of up to 24 months is considered adequate to support an indication in reduction of relapse rate. In this review, I summarize information from Novartis's presentations and, when needed, I supplement Novartis's summaries with analyses that I conducted using the data from the data sets provided by Novartis. My review conclusions are predicated upon the pre-determined primary and secondary outcomes of the trial. Exploratory outcomes and *post hoc* analyses of trial findings were considered supportive of primary and secondary study outcomes and not as definitive outcomes in their own rights.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. D2311: Phase 3, double-blind, double dummy, randomized, multi-center, active controlled study evaluating efficacy/safety of fingolimod once daily (weight-based dosing; 0.25 mg ≤40 kg or 0.5 mg >40 kg) vs. interferon β-1a 30 µg i.m. once/week in pediatric patients with MS aged 10 to <18.

6.1.1. Study Design

Overview and Objective

Study D2311 ("PARADIGMS") was a randomized clinical trial (RCT) whose objective was to assess the efficacy and safety of fingolimod compared to Avonex (interferon β-1a) as treatment for relapsing forms of multiple sclerosis in patients aged 10 to <18 as measured by a reduction in the annualized relapse rate after two years of treatment.

> *Reviewer Comment: Throughout the document, when there is reference to "interferon β-1a," unless other specified, I am referring to Avonex, which is a 30 µg dose form of interferon β-1a that is administered i.m. once per week. The terms "interferon β-1a" and "Avonex" are synonymous in this text.*

Trial Design

Study D2311 was a 215-patient, randomized, 24 month flexible duration, double-blind, double-

dummy, active controlled Phase 3 study designed to evaluate the safety and efficacy of fingolimod in comparison to interferon β-1a in patients aged 10 to <18 years with RMS who had to have an Expanded Disability Status Scale (EDSS) score of 0 to 5.5, inclusive, and at least one MS relapse/attack during the previous year or two MS relapses in the two years prior to screening or evidence of one or more gadolinium-enhancing lesions on MRI within 6 months prior to randomization. The primary efficacy endpoint was annualized relapse rate (ARR) evaluated at up to 24 months.

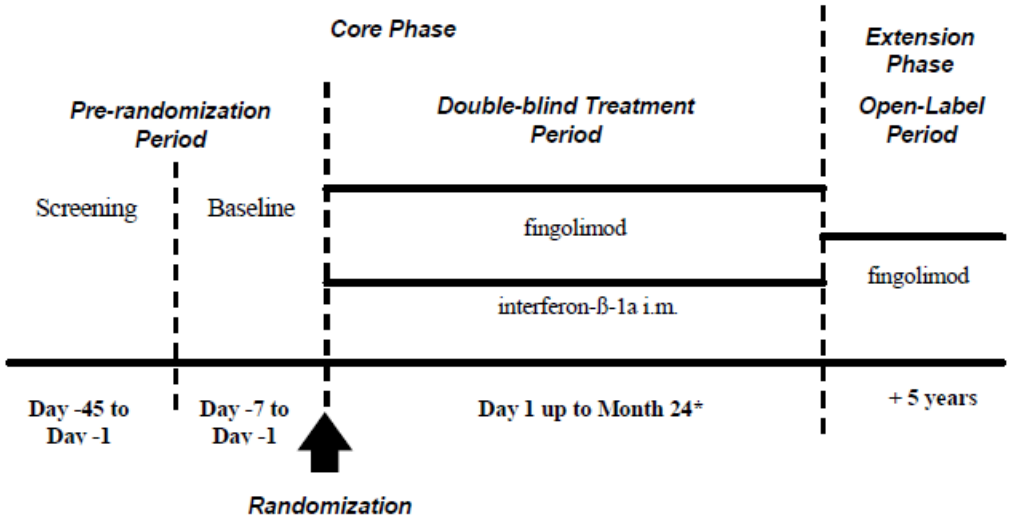
> *Reviewer Comment: Several adequately-controlled randomized clinical trials have shown that interferon β-1a given as a 30 µg intramuscular injection once weekly (Avonex) is superior to placebo in adults with RMS at reducing the number of MS relapses after 2 years of treatment (32% relative reduction) and at reducing the proportion of patients with confirmed disability (35% versus 22%). These pivotal trials were conducted in adults and there are no equivalent adequately controlled trial data for interferon β-1a in children with RMS. There is an expectation that interferon β-1a would be similarly effective in pediatric patients based on published case reports and small case series in the medical literature, but interferon β-1a is not approved for use in patients below age 18 years in the US (but is approved for use down to age 12 years by the EMA in the EU based on a review of the medical literature.) The lack of a placebo group in this pediatric trial limits the ability to confirm a benefit on relapses or disability of either treatment. Hence, any benefit claimed will be made relative to a treatment lacking an approval in the target population but with the reasonable assumption that this treatment, interferon β-1a, would be superior to placebo in the treatment of pediatric RMS.*

Patients who completed the initial 2-year core phase of the trial had the option to enter a single active treatment group with fingolimod 0.25 mg or 0.50 mg based on weight in an Open Label Extension (OLE) trial if the patients fulfilled the eligibility criteria for the OLE.

The study consisted for the following study periods:

- Screening (up to 45 days prior to randomization)
- Baseline (up to 7 days prior to randomization)
- 24-month double-blind, double-dummy comparative treatment
- Rebound or withdrawal follow-up: disease activity and lymphocyte counts were obtained from patients up to three months after study withdrawal or discontinuation of fingolimod.
- OLE (up to 5 years)

Figure 1: Sponsor Figure: Overview of Study Design, Study D2311



* The 3 months follow-up visit was required for those patients who did not continue into the Extension Phase.

Randomization was 1:1.

Blinding

This study had a double-blind, double-dummy design. Patients were randomized at Visit 3 to one of two possible treatment groups and given the following treatments:

Fingolimod Group: 0.25mg or 0.5 mg fingolimod capsule orally once daily + interferon beta-1a matching placebo i.m. injection once weekly

Interferon β-1a Group: interferon β-1a 30 µg i.m. injection once weekly (Avonex) + fingolimod matching placebo capsule orally once daily

All eligible patients were randomized via an Interactive Voice Response (IVR) system to one of the two treatment arms. The investigator or his/her delegate contacted the IVR system after confirming that the patient fulfilled all the trial's inclusion/exclusion criteria. The IVR system assigned a randomization number to the patient, which linked the patient to a treatment arm and specified a unique medication number for the first package of study drug to be dispensed to the patient. The randomization number was not communicated to the caller. The patient's treatment group assignment remained blinded until the entire double-blind treatment period elapsed and until the database lock for the trial occurred.

Patients, treating physician, site personnel, independent evaluating physician, First Dose Administrator and all Novartis personnel involved in the study, with the exception of Novartis Drug Supply Management (DSM), Novartis on-line PK analyst, Novartis independent statistician

and independent programmer for DMC, remained blinded to the identity of all treatment assignments from the time of randomization of the first patient until database lock. During this time, the treatment codes were accessible only to authorized personnel (those mentioned above and DMC members). The following measures were taken to protect the blinding of the Independent Evaluating Physician ("rater"):

- Prohibited access of "rater" to patient records, laboratory data etc.
- Separate binders of worksheets and electronic Case Report Form (eCRF) materials for "treating physician" and "rater"
- Prohibited cross-over of "treating physician" and "rater"
- Appropriate clothing for patients to cover potential injection sites during neurological examinations
- Limited interactions between evaluating physician and patients: permitting only a minimum required to perform the EDSS rating.

All patients received the same instructions regarding how to administer both the oral and injectable treatments. Patients randomized to fingolimod received a placebo dummy injector; patients randomized to interferon β-1a received a placebo capsule containing the same inert ingredients as fingolimod capsules.

Due to known cardiovascular-related safety concerns, monitoring of the initial dose of fingolimod was necessary. However, the particular fingolimod-related constellation of cardiovascular effects could have potentially unblinded the treating physician or site personnel. Therefore, all enrolled patients had the same first dose visit procedures with a First-dose Administrator and an independent monitoring team. The treating physician did not observe the first administration of study treatments and did not have access to any vital signs or initial findings unless such disclosure was medically warranted. The first dose procedure was required for any dose change in fingolimod/placebo pill, for study drug re-initiation per protocol criteria, and at Visit 6 for patients ≤40 kg (regardless of whether a dose change was implemented or not).

> *Reviewer Comment: Though the choice of a double-dummy study design was made to mitigate patient unblinding to treatment condition, there is a distinct possibility that patients or patients' caregivers could have observed the known symptoms associated with these treatments and made inferences regarding which treatment they or their child was receiving. During first dose administrations, without aggressive measures such as covering monitoring equipment or not noting vital signs publicly, patients could have noted the cardiovascular effects of fingolimod. There is no indication that the independent monitoring sites made an effort to obscure all clinical findings from observers. It is conversely possible that patients in the interferon active comparator arm noted the lack of such cardiovascular effects during first dose visits. Injection site*

reactions, or the subsequent flu-like illness that occurs with systemic interferon administration, could have allowed patients to deduce their treatment status. Maintaining a blind to these effects, particularly the subjective treatment experience of the patient, would have been technically difficult or impossible. A patient or caregiver post-first dose visit interview might have revealed any potential unblinding and allowed further intervention to restore blind status in some instances but was not attempted. It is therefore possible that patients in either of the treatment groups could have deduced their treatment status.

While fingolimod was dosed based on weight or PK evaluation, interferon β-1a treatment dose was not altered by weight throughout the study, but individual sites could initiate injectable study drug at ¼ or ½ volume per routine clinical practice at the site. Per protocol, full dose would have to be achieved by the fourth week of injections.

An Information Request was issued to Novartis on April 18, 2018 requesting clarification of which patients underwent dose titration for interferon β-1a and whether patients had relapses during dose titration. The response from Novartis is as follows:

"Novartis did not collect information regarding standard of care for titration of starting doses of IFN β-1a from the sites prior to the start of the study. Once the study started at a site we collected detailed information about IFN β-1a dose titration, including the dose administered and the duration for each dose was collected on eCRF pages. Per protocol, injectable study drug may have been initiated at ¼ or ½ volume per clinical practice at the individual sites. However, it was expected that full dose should be achieved by the 4th week of injections. Titration of the fingolimod treatment group was conducted by sites to maintain the blind as the study was double-blind, double-dummy design.... Of the 35 patients in the IFN β-1a treatment arm that had their initial dose of medication titrated, no confirmed relapses occurred during the titration period."

Reviewer Comment: An examination of the patients who underwent titration of interferon β-1a and subsequently experienced a confirmed relapse did not reveal any temporal correlation between initiation of titration and the onset of the relapse in comparison to patients who did not undergo titration. It does not appear that the idiosyncratic titration of interferon β-1a affected the onset or frequency of relapses.

Additional Blinding Procedures

To prevent unblinding, additional measures were implemented as explained below.

Disability Assessment

The EDSS was scored by an Independent Evaluating Physician who was blind with respect to the

patient's study condition and who spent only time with the patient sufficient to perform EDSS scoring. The Independent Evaluating Physician was involved in any other aspect of the patient's care and/or management. The study guidelines required that patients wear clothing that covered injection sites during all evaluation visits. To ensure consistency across sites, the Independent Evaluating Physician participated in the standardized training session on EDSS scoring prior to enrollment of subjects at their site. Re-certification was required annually. The communication of new findings on the neurological examination from the Independent Evaluating Physician to the Primary Treating Physician was permitted. The Independent Evaluating Physicians and Primary Treating Physicians had separate binders for case report forms and clinical study materials. The Primary and Evaluating Physicians were permitted access only to their own binders. The Independent Evaluating Physician could access prior EDSS ratings for a given patient in order to confirm a relapse. The roles of the Primary Treating Physician and the Independent Evaluating Physician, including their back-ups, were not interchangeable. The Independent Evaluating Physician remained blinded to adverse events, concomitant medications, laboratory data, and any other data that have the potential of revealing the treatment assignment. The patients and his/her parent/caregiver were instructed not to reveal any aspects of the patient's treatment to the Independent Evaluating Physician. It was strongly recommended that the Independent Evaluating Physician remain unchanged throughout the entire course of the study.

MRI

MRI scans were read blinded (with no information on treatment assignment) at the central MRI reading center. Prior to the start of the study, the neuroradiologist and MRI technician from each center received an MRI Manual, outlining technical implementation, image quality requirements and MRI administrative procedures. Each site was asked to program the MRI scanner that was designated for evaluation of the study patients and then to perform and to submit a dummy scan (so-called "dummy or dry run") to the MRI reading center to assess the image quality and to evaluate the compatibility of the electronic data carrier. Once the dummy run had been accepted, all the parameter settings for the study specific MRI sequences had to remain unchanged for the duration of the study.

Each MRI scan performed during the Core Phase was previewed by a local neuroradiologist. There was a mandate that the Primary Treating Physician be contacted in case of unexpected findings (*e.g.*, not consistent with MS) detected on the MRI scan.

During the study, the quality of each scan performed was assessed by the central blinded MRI reading center. The MRI scan was to be sent to the central MRI reading center within 3 working days, if possible. As soon as the scan was received by the central MRI reading center, it was evaluated for quality, completeness, and adherence to the protocol. Confirmation of MRI quality or a description of the quality problems, if detected, was communicated to the site. If a scan were incomplete or incorrectly performed, the study center would be asked to repeat it as

soon as possible. After completion of the quality check, all scans were analyzed according to the MRI protocol.

The central blinded MRI reading center provided MRI notifications during the Core Phase of the study if certain MRI activity criteria were met for a given patient. MRI notifications were based on combined unique active (CUA) lesion counts (gadolinium-enhancing lesions + new/enlarged T2 lesions not associated with gadolinium-enhancement).

Laboratory Studies

Laboratory tests that could lead to unblinding to treatment assignment such as the absolute total White Blood Cell Count (WBC), neutrophil and lymphocyte counts were measured at each visit by the central laboratory. These specific laboratory values were blinded from Novartis and from the investigator and were only communicated to the site in case of a notable abnormality from a pre-determined list of concerning laboratory abnormalities. For lymphocyte count this value was defined as $<0.2 \times 10^9$/L, in which case the lymphocyte count would be repeated in two weeks by the central lab to confirm the reading. If the repeat test confirmed the lymphocyte count was below 0.2×10^9/L or 200 cells/mm^3, the study drug had to be discontinued and the lymphocytes count needed to be monitored monthly until levels returned back to normal limits (by local laboratory for monitoring levels). If monthly site visits created a logistical burden for the patient, local lymphocyte testing was performed, and, ideally, an additional sample would be sent to central laboratory for analysis. In the event that central laboratory analysis was not available, the results of the local laboratory values (including reference ranges) were included in the eCRF to document recovery of values. The patient was evaluated and monitored for infections on a regular basis. Re-initiation of the study drug could only be considered once the lymphocyte counts are back within normal limits.

Dose Adjustment

Two doses of fingolimod (0.25 mg and 0.5 mg) were used in this study, and the dose chosen for pediatric patients was based on goal exposure at a given weight (see Dose Rationale). If a dose increase was necessary, it was performed in a blinded fashion. During the course of the study, any patient receiving the lower fingolimod dose of 0.25 mg who reached a weight of more than 40 kg (sustained over at least two visits, 3 months apart) was automatically switched to the 0.5 mg dose strength. Patients in the interferon β-1a arm whose bodyweight increased to above 40 kg during the Core Phase (sustained over at least 2 visits, 3 months apart), had blood samples drawn and would undergo subsequently a sham increase in their oral (placebo) dose. In patients ≤ 40 kg, the Month 1 PK assessment was evaluated by the Novartis on-line PK analyst to ensure an exposure of 65% of the target exposure. If the Month 1 PK assessment indicated an exposure below the target level, a dose change at the Month 2 visit would be communicated to the First-Dose Administrator by the IVR system. Dose adjustments of fingolimod for any other reason were not permitted.

If a patient elected to enter the Extension Phase prior to the Core Phase database lock, they would undergo the same initial dose procedure but would receive fingolimod. Whatever dose they received during the Core Phase (interferon or fingolimod) remained blinded until the Core Phase database had been locked. For any patient that was ≤ 40 kg when they started the Extension Phase, the Extension Phase dose of fingolimod was blinded. The dose remained blinded until the Core Phase database lock or until the patient had a dose increase to 0.5 mg (increase in body weight to >40 kg sustained at two consecutive visits at least 3 months apart). This blinding was required in order to maintain the blind of the Core Phase medication as some patients' may have had a dose increase during the Core Phase at the Month 2 visit based on the online PK results.

> *Reviewer Comment: Though Novartis made reasonable efforts to maintain the study's blinding, the scheduled dose change visit only for patients ≤ 40 kg at Month 2 is concerning as a potential source of unblinding to treatment status. While the treating physician remained blinded to the independent clinic events, this subset of patients had an additional scheduled opportunity to observe the cardiovascular effects of fingolimod that patients in the higher dose condition did not have. Since these cardiovascular effects are dose-related, bradycardia and heart block would be more likely to occur at a higher dose and therefore present another opportunity to reveal to a patient their treatment status. An examination of the subjective reporting data for this subset of patients does not suggest a systematic difference in their reports as compared to other patients in their treatment group. The objective findings used to determine efficacy such as MRI data should be insulated from patient unblinding. Nevertheless, given this potential bias, and how few patients in this study received the 0.25 mg dose, findings at the 0.25 mg dose are advanced with less confidence than those from the 0.5 mg dose.*

Key Eligibility Criteria

Key Inclusion Criteria

- Written informed consent must be obtained before any assessment is performed.
- Male and female patients aged 10-17 years old*, inclusive (*i.e.*, have not yet had their 18th birthday) at randomization.
- A diagnosis of MS as defined by the revised consensus definition for pediatric MS.
- Central review of the diagnosis of pediatric MS will be required for all patients prior to randomization.
- At least one MS relapse/attack during the previous year or two MS relapses in the previous two years prior to screening, or evidence of one or more Gadolinium

enhancing lesions on MRI within months prior to randomization (including screening MRI).

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

  *Exception: If, in a specific country, use of interferon-β-1a i.m. in children below a certain age is included in the Contraindications section of Avonex (interferon-β-1a i.m.) local product information, inclusion of such patients is not permitted in that country., *e.g.*, the Russian interferon β-1a product information lists use in children below the age of 12 years as a contraindication.

Key Exclusion Criteria

- Patients with progressive MS.
- Patients with an active, chronic disease (or stable but treated with immune therapy) of the immune system other than MS (*e.g.*, Sjögren's disease, systemic lupus erythematosus) or with a known immunodeficiency syndrome (AIDS, hereditary immune deficiency, drug induced immune deficiency) or tested positive for HIV.
- Patients with widespread and symmetric white matter alterations in the Screening MRI suggestive of other demyelinating disorders (*e.g.,* metabolic disorders, mitochondrial disorders).
- Patients meeting the definition of ADEM; patients meeting criteria for neuromyelitis optica or tested positive for aquaporin 4 (AQP4) at Screening.
- Patients treated with:
  - Systemic corticosteroids or adrenocorticotropic hormone (ACTH) in the 30 days prior to Screening MRI scan
  - High dose intravenous immunoglobulin within 2 months prior to randomization
  - Natalizumab within 3 months or teriflunomide within 3 ½ months prior to randomization
  - Immunosuppressive/immunomodulatory medications such as azathioprine, methotrexate, laquinimod, ofatumumab, ocrelizumab within 6 months prior to randomization.
  - Alemtuzumab, cladribine, cyclophosphamide, mitoxantrone, or rituximab at any time.

  - Fingolimod at any time.
  - The following antiarrhythmic drugs at Screening: Class Ia (*e.g.,* quinidine, disopyramide) or Class III (*e.g.*, amiodarone, sotalol) anti-arrhythmics.
  - Concurrently treated with heart-rate-lowering drugs at Screening *e.g.*, Beta blockers, heart-rate lowering calcium channel blockers (*e.g.,* verapamil, diltiazem or ivabradine), digoxin, anticholinesteratic agents, pilocarpine. Advice from a cardiologist should be sought regarding the switch to non-heart-rate lowering medicinal products.

- Patients diagnosed with macular edema during the pre-randomization phase.
- Patients with active systemic bacterial, viral, or fungal infections, including tuberculosis.
- Patients without acceptable evidence of immunity to varicella-zoster virus, mumps, measles, rubella, diphtheria, tetanus, and pertussis at Randomization.
- Patients who have received any live or live attenuated vaccines (including for varicella-zoster virus or measles) within one month prior to randomization.
- Patients with a history or presence of malignancy.
- Patients with any medically unstable condition, as assessed by the primary treating physician at each site.
- Patients with any severe cardiac disease or significant findings on the screening ECG, such as:
  - History of symptomatic bradycardia or recurrent syncope
  - Known ischemic heart disease
  - History of congenital heart disease (except conditions such as small patent ductus arteriosus, atrial septal defect, ventricular septal defect, or an ECG or rhythm abnormality, which have been assessed by a pediatric cardiologist and considered to be clinically insignificant).
- Cerebrovascular disease
- History of myocardial infarction
- Congestive heart failure

- History of cardiac arrest
- Uncontrolled hypertension despite prescribed medications
- Resting (sitting) heart rate <55 bpm (in patients 12 years or older) and <60 bpm (in patients below 12 years)
- Severe untreated sleep apnea
- Sick sinus syndrome or sino-atrial heart block

Reviewer Comment: The inclusion criteria are appropriate. Many of the exclusion criteria were not applicable to a pediatric population. The most commonly reported reason for a patient being excluded was lack of documentation of acceptable evidence of immunity to varicella-zoster virus, mumps, measles, rubella, diphtheria, tetanus, and pertussis.

Study Treatment-fingolimod

Rationale for dose selection

Novartis selected the doses of 0.5 mg (for patients ≥ 40 kg) and 0.25 mg (for patients <40 kg) based on a single pediatric study (A0115) and simulated modeling using the adult Phase 2 and 3 PK/PD data. As the adult studies had shown that exposure levels at the 0.5 mg dose were the best predictor of efficacy, the goal in the pediatric studies was to achieve a comparable systemic exposure that was safe and effective for patients across a range of ages and weights.

There is a paucity of clinical experience with fingolimod in pediatric patients. A single dose study (A0115) of high dose (5.0 mg equivalent) fingolimod in seven renal transplant patients ranging from 11-16 years of age had confirmed that a one-time oral dose of an equivalent of a 5.0 mg oral adult dose being used in adult transplant trials yielded comparable total exposure for fingolimod and its active metabolite fingolimod-P when accounting for the weight differences between the adolescents studied and pharmacokinetic data in adults taking the 5.0 mg dose. Novartis used these data along with the Phase 2 and Phase 3 elimination data in adults to simulate relationships between body weight, exposure, and elimination clearance of fingolimod-P at the 0.5 mg and 0.25 mg doses. Predictions from the simulation were then verified back against the data from the only pediatric study to suggest that a 0.25 mg daily dose in a patient weighing ≤ 40 kg would approximate the exposure of the approved 0.5 mg dose of fingolimod.

Thus, two doses were chosen for this trial as follows: 0.5 mg/day for all patients weighing more than 40 kg (at treatment initiation and/or during the study) and 0.25 mg/day for all patients

weighing 40 kg or less. The 0.5 mg dose of fingolimod is the current approved dose for RMS in adults. The 0.25 mg dose was increased based on the results of the Month 1 online pharmacokinetic analysis or if the patient had a sustained body weight increase to above 40 kg during the study (sustained over at least two visits that were three months apart). The 0.25 mg dose was necessary because the predicted body weight of patients aged 10 to <18 years would span a range 20-40 kg, with 5% of patients aged 10 years predicted to be <25 kg based on population normalized weight curves.

> *Reviewer Comment: The doses selected include the approved 0.5 mg dose of fingolimod that has established efficacy and safety in adult patients with RMS. The inclusion of a 0.25 mg dose was deemed necessary because of pediatric body weight variability and was justified based on simulated and observed exposures of fingolimod and its active metabolite fingolimod-P across a range of body weights. There were nine patients in Study D2311 who received the 0.25 mg dose at any time, and only two patients completed the Core Phase of the study taking the 0.25 mg dose throughout. Thus, any conclusions reached for the 0.25 mg dose of fingolimod in the pediatric population are based on limited data.*

First dose monitoring

Prior studies in adults had identified that the first dose of fingolimod can be associated with bradycardia, blood pressure changes, and potentially serious adverse events such as second or third degree heart block. To monitor for these events, and to maintain the investigators' blinding as the presence or absence of such symptoms could reveal treatment status, all patients were required to have their first intake/injection of study drug in the trial at an independent site with a first-dose administrator. The following testing was required or obtained in all patients at this initial visit:

- ECG must be obtained and evaluated prior to the first dose of study drug and 6 hours after.

- Baseline or pre-dose ECG should be available for comparison to the post-dose ECG. Sitting heart rate and blood pressure must be measured prior to the first dose of the study drug and then every hour for at least 6 hours thereafter.

- When obtaining the sitting heart rate, the patient should be allowed to rest for 5 minutes. Prior to the first dose of study drug, the sitting heart rate and blood pressure measurements should be repeated twice to produce three readings for both heart rate and blood pressure. Patients should receive the first dose of study drug before 12:00 PM (noon) at the site.

- Patients would be discharged after 6 hours only if the following discharge criteria were

met:

- Heart rate (sitting) at discharge must be at least 55 bpm (in patients 12 years or older) or 60 bpm (in children below 12).
- Heart rate (sitting) at discharge must not be the lowest hourly value measured during the observation period (which would be suggestive of a continuing progressive decline in heart rate).
- Patients must have no symptoms in sitting or standing position associated with decreased heart rate or received treatment for bradycardia.
- ECG at 6 hours should not show any new significant abnormalities, other than asymptomatic sinus bradycardia, not observed at the patient's pre-dose ECG (*e.g.,* prolongation of QT/QTcF interval, persistent new onset 2nd degree (Mobitz Type I (Wenkebach) or higher AV block, 3rd degree AV block at any time during monitoring.)
- If the above discharge criteria were not met, patients were observed until they are met (the observation must last for at least 2 hours even if the criteria are met earlier).
- However, patients experiencing any symptomatic event associated with reduction of the heart rate, a heart rate of < 45 bpm at the end of the 6-hour monitoring, received treatment for bradycardia, or had relevant changes on the ECG, not resolving by the end of the 6-hour monitoring (*e.g.,* ECG at 6 hours shows a QTcF interval ≥500 msec), must be hospitalized overnight. For those patients, the Day 2 dose of study drug should be given in the hospital according to monitoring and discharge criteria described above.
- If local product information required additional monitoring, this monitoring was performed in addition to above.

In case of bradycardia causing cardiorespiratory compromise (*e.g.*, hypotension or peripheral hypoperfusion), administration of atropine was recommended as the first line treatment of bradycardia. The initial recommended dose was 0.01 mg/kg (10 mcg/kg), up to a maximum dose of 1 mg. Furthermore, the region-appropriate common guidelines for treatment of bradycardia (*e.g.*, 2005 American Heart Association for cardiopulmonary resuscitation: pediatric advance support) were be followed as appropriate.

The trial protocol required this same monitoring protocol be applied to patients requiring re-initiation of study drug after interruption and at the time of individual dose increase based on weight or Month 1 PK assessment to maintain the study blind. An interruption requiring a

repeat first-dose observation was defined as follows:

- The treatment lasted for 14 days or less and was interrupted for 1 day or more, or
- The treatment lasted for more than 14 days and less than 29 days and was interrupted for more than 7 consecutive days, or
- The treatment lasting for 4 weeks or more and was interrupted for more than 14 consecutive days.

All patients received written instructions on when to return to the clinic and a 24-hour contact phone number to call in the event of any new or warranted symptoms (chest pain, dizziness, palpitations, syncope, nausea, vomiting, etc.) The fingolimod capsules (0.25 mg and 0.5 mg) and matching placebo capsules provided after the first dose administration were identical in appearance and were packaged in identical bottles.

The protocol included rules for permanent discontinuation after first dose or re-dose that included the following:

- Any hemodynamically compromising cardiac arrhythmias.
- Patients who meet the criteria requiring overnight hospitalization again on Day 2.
- Absolute QTcF ≥ 500 msec, confirmed by repeat ECG measurements (within 24 hours).
- New complete heart block (third degree AV block) or second degree AV block Mobitz type II.

Study Treatment-Interferon β-1a

Rationale for dose selection

The trial design employed interferon β-1a 30 µg weekly i.m. because of four considerations as follows: prior clinical trial experience, published clinical experience, ease of administration, and more favorable side effect profile. This Sponsor had used interferon β-1a 30 µg weekly i.m. as an active comparator in a prior study of adults with RMS (D2302) and wanted to ensure comparability of efficacy and safety results with the pediatric trial. This specific interferon formulation and dose are approved in the European Union for treatment of RMS in patients ages ≥ 12 years old and have safety and efficacy findings published in several international peer-reviewed journals. Other interferon formulations require more frequent administration schedules that might introduce compliance issues into the study. Finally, according to data supplied by the Sponsor, this particular formulation appears to be associated with fewer adverse events, especially infections, than other approved interferon variants.

First dose monitoring

The first dose of interferon β-1a i.m. at Day 1 was administered intramuscularly at the independent monitoring site by the First Dose Administrator or nurse. Site personnel provided training to the patients and to their parents/caregivers on the correct procedure for administration of i.m. injections. A patient leaflet and oral instructions were provided. The patient leaflet and/or oral instructions described information related to the i.m. study drug including storage information, precautions, and instructions for administering i.m. injections. This information was reviewed with the patient and his/her parents/caregivers to ensure that they understood the correct procedure. Injectable study drug could be initiated at ¼ or ½ volume per clinical practice at the individual sites. Full dose was, however, to be achieved by the fourth week of injections. Both the interferon β-1a and its matching placebo were provided in packages and supplied in pre-filled syringes.

Prophylaxis and treatment of flu-like symptoms with *e.g.*, paracetamol/acetaminophen was performed per clinical practice at the site.

> *Reviewer Comment: The use of medications containing acetaminophen was essentially equal between both treatment groups and so there was not a clear favoring of the interferon treatment arm with respect to use of this therapy. It does not appear that the clinical site fiat regarding use of acetaminophen favored a particular treatment group and could have revealed treatment status.*

Liver toxicity monitoring

Both study treatments have known associations with hepatotoxicity. The study protocol included monitoring of all patients for elevations in liver function studies.

In case of detection of (asymptomatic) elevated ALT/AST values >3 times the upper limit of the normal range (ULN), additional blood chemistry panel including ALT, AST, alkaline phosphatase, GGT, total and conjugated bilirubin should be performed within a week. If the elevation is confirmed, close observation of the patient and monitoring of liver function tests (LFTs) regularly at time intervals of 1 to 4 weeks (at investigator's discretion) should be initiated.

In case of detection of elevated ALT/AST values >3 times ULN which are accompanied by symptoms (general malaise, fatigue, abdominal pain, nausea or vomiting, rash with eosinophilia) study drug would need to be discontinued immediately. The patient would be hospitalized if clinically appropriate; establish causality. Further follow-up should include ALT, AST, total and conjugated bilirubin, albumin, PT/INR, alkaline phosphatase, and GGT until resolution (frequency of repeat testing at investigator's discretion).

In case of detection of elevated ALT/AST values ≥5 times the ULN, Blood chemistry liver panel

including ALT, AST, AP, GGT, Alb, PT/INR, total and conjugated bilirubin must be performed within 48 hours. If ALT/AST elevation persists for more than 2 weeks, study drug administration must be interrupted. The patient should be followed up bi-weekly, until no further increase in AST/ALT is observed. Further follow-up should include ALT, AST, total and conjugated bilirubin, albumin, PT/INR, alkaline phosphatase, and GGT until resolution (frequency of repeat testing at investigator's discretion).

If ALT/AST values reach 8 times the ULN, and the value is confirmed on a repeat lab within 48 hours, the study drug must be permanently discontinued. Follow-up should include ALT, AST, total and conjugated bilirubin, albumin, PT/INR, alkaline phosphatase, and GGT until resolution (frequency of repeat testing at investigator's discretion.)

Alkaline phosphatase monitoring

Isolated elevation of alkaline phosphatase would not necessarily require study drug discontinuation. Decisions regarding study drug discontinuation would be based on the investigator's discretion if the elevations were thought to be more serious in nature.

Bilirubin monitoring

In case of isolated elevation of bilirubin over 1.5 times ULN (in the absence of Gilbert's syndrome), the lab needs to be repeated within 48 hours. If elevation persists, the patient must discontinue the study drug; hospitalize if clinically indicated; establish causality. Additional evaluations may be performed at the discretion of the investigator.

In case of isolated elevation of bilirubin above 2x ULN (in the absence of Gilbert's syndrome), the patient must discontinue the study drug and be hospitalized if clinically indicated.

Follow-up on ALT, AST, total bilirubin, albumin, PT/INR, alkaline phosphatase, and GGT should continue until resolution (frequency of repeat testing at investigator's discretion) and testing for hemolysis (*e.g.*, reticulocytes, haptoglobin, and unconjugated/indirect bilirubin) should be performed.

Concomitant Medications

See page 65 for the use of medications concomitant with administrations of study drugs. Investigators instructed patients to notify the study site about any new medications and significant non-drug therapies initiated after start of the study drug. Patients were warned about any concomitant use of hepatotoxic agents and ketoconazole because administration with study drugs could lead to an increase risk of adverse events.

Patients already taking dimethyl fumarate, interferon β, or glatiramer acetate at Screening were allowed to continue drug intake up to the day before Day 1 without a washout period.

While patients were on trial therapy, uses of the following treatments were not permitted concomitantly with the study drug:

- Immunosuppressive medication (*e.g.,* cyclosporine, azathioprine, methotrexate, cyclophosphamide, mitoxantrone, cladribine, rituximab, alemtuzumab).
- Other concomitant medications: immunoglobulins, monoclonal antibodies (including natalizumab), interferon β, glatiramer acetate, teriflunomide, dimethyl fumarate, adrenocorticotropic hormone (ACTH).
- Class Ia (*e.g.,* quinidine, disopyramide) or Class III (*e.g.,* amiodarone, sotalol) antiarrhythmics
- Heart-rate-lowering drugs (*e.g.*, Beta blockers); heart-rate lowering calcium channel blockers (*e.g.,* verapamil, diltiazem or ivabradine)
- Digoxin, anticholinesterase therapies, pilocarpine

Treatment of MS relapses

The protocol allowed the following treatment regimen for treatment of a relapse: A standard short course of corticosteroids (methylprednisolone) on an inpatient or outpatient basis is allowed for treatment of relapses as clinically warranted. Steroid treatment should consist of 20-30 mg/kg/day or up to a maximum of 1,000 mg methylprednisolone i.v. for 3-5 days at the discretion of the treating physician. Standard of care was to be followed during treatment. Taper with oral steroids was not permitted. If a sign or symptom was unexpected for a MS relapse in the opinion of an investigator, an unscheduled MRI was permitted.

Assessments

The schedule of visits and assessments is summarized the following table.

Table 3: Sponsor Table, Schedule of Assessments, Study D2311

	Screen	Baseline	Double blind Double dummy Core Treatment Phase															
Visit	**1**	**2**	**3**	**4**	**5**		**6**	**7**			**8**	**9**	**10**	**11**	**12**	**13**	**14 EOS**	**FU**
Month				**0.5**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**+3**
Study Day	**-45**	**-7**	**1**	**15**	**30**	**51**			**71**	**72**								
Fingolimod daily			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Interferon β-1a weekly			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
First Dose Monitoring			X		X*	As needed												
Physical Exam	X	X		X	X		X	X			X	X	X	X	X	X	X	X
Bone Age/Tanner staging	X										X		X		X		X	
EDSS	X	X						X			X	X	X	X	X	X	X	X
ECG	X		X		X								X				X	
MRI	X										X		X		X		X	
PFTs	X			X				X			X		X		X		X	
Vital Signs	X	X	X	X	X		X	X			X	X	X	X	X	X	X	X
MS Relapses	X	X	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	X	X
Safety Labs	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS	X	X	X	X	X		X	X			X	X	X	X	X	X	X	X

*only for patients weighing 40 kg or less

Table 4: Sponsor Table: Abbreviated Schedule of Assessments, Study D2311

Phase	**Double Blind Treatment Phase**						
Visit Number	**8**	**9**	**10**	**11**	**12**	**13**	**14/EOS**
Study Month	**6**	**9**	**12**	**15**	**18**	**21**	**24**
Physical Exam	X		X		X		X
Skin Exam							X
Tanner Stage/Bone X-ray	X		X		X		X
Pulmonary Function Tests	X		X		X		X
MS Relapses	X	X	X	X	X	X	X
MS Treatment/Concomitant Meds/Steroids	X	X	X	X	X	X	X
EDSS	X	X	X	X	X	X	X
MRI	X		X		X		X
Peds QL			X				X
Cognitive Testing			X				X
Vital Signs	X	X	X	X	X	X	X
Hematology/Blood Chemistry	X		X		X		
Endocrine Lab Evaluations	X		X		X		X
Urinalysis	X		X				X
C-SSRS	X	X	X	X	X	X	X
AE/SAE reporting (if any)	X	X	X	X	X	X	X

Unscheduled Visits

Investigators would schedule a complete physical and neurological examination and a MRI as soon as possible for patients who developed new or worsening neurological symptoms regardless of the dates of their scheduled study visits.

Assessment of MS Relapses

The Primary Treating Physician performed the initial assessment, management, and made the report of any new or worsening neurological event concerning for a clinical relapse. The study definition of a *MS relapse* was 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. The abnormality must have been present for at least 24 hours and occurred in the absence of fever (< 37.5°C) or known infection."

Patients could report symptoms indicative of a relapse at a scheduled visit or at any other time. Patients were instructed to immediately contact the Primary Treating Physician if he/she developed any new, re-occurring, or worsening neurological symptoms. At each scheduled visit, the patient was also asked whether any such symptoms had occurred. If a patient reported new neurological symptoms or worsening of previous symptoms, an unscheduled visit was planned as soon as possible, ideally within 7 days. During this visit, the Primary Treating Physician would assess whether the new/worsening neurological abnormality is consistent with the definition of MS relapse above. If so, the standard neurological examination (for the EDSS score) would be performed by the Independent Evaluating Physician (EDSS rater). If there was any ambivalence on behalf of Primary Treating Physician regarding the relapse, the default was always to refer the case to the Independent Evaluating Physician to perform an EDSS rating.

Disability

Investigators used the EDSS instrument to assess disability in Study D2311. The EDSS is an ordinal scale based on findings from a neurological examination. It consists of scores in each of seven Functional Systems (FSs) that are then combined to determine the EDSS steps, ranging from 0 (normal) to 10 (death due to MS). The FSs are Visual, Brain Stem, Pyramidal, Cerebellar, Sensory, Bowel & Bladder, and Cerebral functions. EDSS is a widely used and accepted instrument to evaluate disability status at a given time and, longitudinally, to assess disability progression in clinical studies in MS.

Disability progression was defined by a sustained deterioration in EDSS present for more than 3 months during the study observation period. For patients with baseline EDSS score 5.0 or less: a change of ≤ −1 point was defined as improvement, a change from −0.5 to 0.5 was defined as stable, and a change of ≥1 point was defined as deterioration. For patients with a baseline EDSS

score > 5.0, a change of ≤−0.5 point was defined as improvement, zero change defined as stable, and change of ≥0.5 point was defined as deterioration.

> *Reviewer Comment: Confirmed disability progression was not a primary, secondary, nor an exploratory endpoint of this study.*

Procedure for Confirming a MS relapse

If a patient presented to a Primary Treating Physician during a scheduled or unscheduled visit with new or worsening neurological symptoms consistent with a potential relapse, the Primary Treating Physician was instructed to document the neurological symptoms and refer all potential relapses to the Independent Evaluating Physician for an EDSS rating. The default expectation per protocol was for treating physicians to refer all cases to the Independent Evaluating Physician for an EDSS rating, even those instances when there was doubt about the presence of a relapse. The definition of a confirmed MS relapse was one accompanied by a clinically relevant change in the EDSS performed by the Independent Evaluating Physician. A clinically relevant change was defined as "an increase of at least 0.5 points on the EDSS score, or an increase of 1 point on two FSs or 2 points on one FS, excluding changes involving bowel/bladder or cerebral FS compared to the previous available rating (the last EDSS rating that did not occur during a relapse)."

The main relapse-related analyses were based on confirmed relapses. All relapses, confirmed and unconfirmed, were recorded in the eCRF.

The severity of relapses was calculated centrally according to the criteria as indicated below.

Table 5: Sponsor Table: MS Relapse Severity Determination

Mild Relapse	Moderate Relapse	Severe Relapse
EDSS increase of 0.5 point	EDSS increase of 1 or 2 points	Exceeds Moderate Relapse criteria
or	or	or
1 point FS change in 1 to 3 systems	2 point FS change in 1 or 2 systems	Exceeds Moderate Relapse criteria

	or	or
	1-point change in ≥ 4 systems	Exceeds Moderate Relapse criteria

Reviewer Comment: Rating of relapses was not critical to trial outcomes because disability progression was neither a primary nor a secondary endpoint, but there were imbalances between the treatment groups with respect to relapse severity (see Section , and the use of clinically indistinct scoring is a potential source of bias and makes interpretation of ancillary outcomes suspect.

Brain Imaging

MRI scans of the brain were obtained in all patients at screening, Months 6, 12, 18, and 24. In addition, the study protocol required brain MRI scans for any patients withdrawn from the study if one had not been obtained during the previous 4 weeks prior to withdrawal.

Study Endpoints

Primary Efficacy Outcome

The primary efficacy endpoint was the frequency of relapses as assessed by the annualized relapse rate in pediatric patients with RMS treated for up to 24 months.

Key Secondary Outcome

The key secondary efficacy endpoint was the annualized rate of new/newly enlarging T2 (n/neT2) lesions in pediatric patients with RMS for up to 24 months.

Other Secondary Outcomes

- The time to onset of first relapse
- The proportion of patients relapse-free at 24 months
- The total number of T1 Gadolinium (Gd)-enhancing lesions as detected by brain MRI up to 24 months

Statistical Analysis Plan

Analysis population

The primary efficacy analysis for this study was performed using a modified intent-to-treat (mITT) population. The efficacy analyses were based on the Full Analysis Set (FAS) of patients who were randomized to an assigned treatment and took at least one dose of active medication (excluding a single enrolled study patient who was randomized but was unable to administer study treatments). Patients who prematurely withdrew from the study for any reason and for whom an assessment was not performed for any reason are included in the efficacy analyses. Patients who received a treatment that differed from what was intended were analyzed according to the actual treatment received following an intention-to-treat principle.

Relapses

The primary efficacy analysis for this trial compared the protocol-defined annualized relapse rate (ARR) at 24 months between the fingolimod group and the interferon β-1a group. The ARR was calculated as the number of confirmed relapses divided by the number of days on study and multiplied by 365.25. The ARR of a treatment group was the mean of ARRs of all patients in the group. The annualized relapse rates by 24 months were analyzed using a negative binomial regression model. Since eligible patients were randomized to treatment conditions stratified by region and pubertal status, all efficacy analyses were stratified by these two variables.

Sample Size Estimation

The sample size calculations were based on data from a previous RMS trial in adults (Study D2302) with the use of two-sided tests and an alpha of 0.05. The ARR among patients receiving fingolimod was predicted to be 0.18 as compared to 0.36 among patients receiving interferon β-1a. These values assumed a 50% relative reduction in ARR for fingolimod compared to the active comparator. For the ARR, the investigators used published methodology (Keene *et al.* 2007) to determine the sample size needed in each treatment group. This calculation predicted that a sample size of 95 patients per treatment group (190 patients total) would provide 80% power while maintaining a type I error rate of 0.05. The 80% prediction accounted for an assumed uniform drop-out rate of 15%.

For the key secondary efficacy endpoint, the rate of new or newly enlarged (n/ne) T2 MRI lesions, the investigators assumed that over 24-months patients in the fingolimod treatment group would accrue an average of 2.3 n/neT2 lesions, a 50% reduction compared to 4.6 in the interferon β-1a treatment group. Therefore, the 95-patient per treatment group (or 190 total) sample size would provide approximately 88% statistical power to detect a relative reduction of 50% (*i.e.*, from 4.6 to 2.3) in the fingolimod group compared to the interferon β-1a group. This sample size calculation assumed that the number of n/neT2 lesions over 24 months follows a negative binomial distribution. These estimates were based on the findings from the FREEDOMS I study (Study D2301) in adults.

The primary and key secondary efficacy endpoints were tested in a hierarchical order, all at an alpha level of 0.05. The key secondary efficacy endpoint was to be tested only if the primary efficacy endpoint achieved a significance level of 0.05. There was no correction for multiplicity in the other secondary and exploratory endpoints analyzed.

Based on the results of a blinded sample size re-estimations (BSSR) showing a retention of at least 80% power even if study was stopped early, the study duration was changed to a 24-month flexible duration study as opposed to a fixed-duration study.

There were two BSSRs in Study D2311. An Information Request was issued to Novartis on April 16, 2018 requesting a description of and rationale for the two BSSR processes. The reply from Novartis is as follows:

"BSSR- 1st Assessment (Data cut-off 28-Sep-2015)

"Recruitment for the study was slower than expected but due to the substantially higher blinded aggregate relapse rate than the one assumed in the protocol, it was anticipated that the study could be fully powered based on a reduced number of patients to be recruited or based on a reduced follow up time per patient being utilized or a combination of the two.

"Novartis confirms that the blinding was fully maintained and the treatment code was not revealed in the blinded data review. All analyses considered only blinded aggregate data (*i.e.*, all patients, regardless of their randomized treatment, were considered one single group).

"Novartis planned and conducted a BSSR on Study D2311 based on 28-Sept-2015 data cut-off to re-assess the power calculations which were in the original study protocol and initial statistical analysis plan. The method and procedure, including timing to perform the BSSR, were pre-specified and documented in the statistical analysis plan for the BSSR which was finalized before the blinded data transfer (28-Sept-2015) and the subsequent analysis.

"The timing of BSSR was determined based on simulations from negative binomial distribution under different recruitment projections and treatment effects assumptions, which showed that 28-Sept-2015 data cutoff gives good precision for the estimation of the blinded parameters (relapse rate and dispersion parameter) while allowing sufficient time for decision on study modification to be made without unnecessary delay.

"The aggregate blinded relapse data accumulated in Study D2311 as of the cut-off of 28-Sep-2015 showed that key assumptions made in the original protocol were overly conservative. The key findings are summarized in [FDA Briefing Book-amend WR; 04-Nov-2015] and [Revised WR; 08-Mar-2016] the briefing book and the amended WR.

"Based on this blinded analysis, it was agreed by FDA (08-Mar-2016) to amend the trial design to introduce a flexible duration without loss of power (compared to the original protocol) and to amend the Written Request accordingly.

"BSSR- 2nd assessment (Data cut-off 30-Jan-2017)

"Following the amended WR which stated that Novartis will conduct the 2nd (final) BSSR in the first half of 2017, Novartis conducted the 2nd BSSR based on the data cut-off of 30-Jan-2017. The reason was because this provided a good projection of the power of the study by the end of June 2017 and provided time to conduct all of the activities for a database lock. Results of the second BSSR were provided to FDA in the [Statistical Overview] included in the sNDA submission on 10-Nov-2017. The key findings are summarized below:

- "An estimated pooled ARR of 0.49, with a dispersion parameter of 1.8 was observed based on a negative binomial model which included covariates (number of relapses in last 2 years, pubertal status) selected according to pre-specified criteria. This leads to a projected 79.5% power for the primary analysis, if the study was stopped by 30-Jun-2017. Of note, the observed (blinded) dispersion of 1.8 from the second BSSR was much higher than that the original protocol assumed value (0.82) and first BSSR (0.53) likely due to high treatment effect. It was later confirmed after second study database lock and unblinding (actual dispersion = 0.83 from final unblinded data after Aug-2017database lock).

- "An 82.8% power was projected if the study was stopped by end of H1-2017 based on an additional analysis which adjusts for dispersion parameter based on the protocol assumed treatment effect of 50% relative ARR reduction by fingolimod vs IFN β-1a. This adjustment (which was based on simulation results) provided supportive information in line with the FDA/EMA request for power assessment under protocol-assumed treatment effect.

- "Since the 2nd BSSR results projected that the 80% study power requirement to stop the study early would be met by end of H1-2017, Novartis stopped the Core Phase of Study D2311 and locked the database on 11-Aug-2017.

"BSSR process steps:

1. Create a statistical analysis plan for the BSSR.
2. Define a cut-off point for data collection to use for the analysis (all data must be entered by a set date that includes all relapses, EDSS assessments and related efficacy and demographic endpoints up until the data cut-off time point).
3. Communicate data cut-off and cleaning timelines to the global Novartis clinical trial team and the Investigator sites.

4. Implement the data cleaning process with set timelines to complete data entry, query generation and query resolution with a primary focus on entering all efficacy endpoints in the clinical database and then clean the efficacy related endpoints.
Note: this data cleaning process was very similar to the regularly scheduled data cleaning timelines used when cleaning the safety data for the Data Monitoring Committee (DMC). Data cleaning was completed in a blinded fashion with no additional information provided to the sites that would potentially be unblinding.
5. Complete data review, query resolution, and finalization of database for all efficacy related endpoints by data management and Novartis clinical teams.
6. Take a snapshot of the database and extract the data for the blinded analysis.
7. Statistical team conducts the BSSR and provides summary tables and text description of the findings.
8. BSSR-1st: Findings were discussed with Novartis management and a proposal to amend the WR was created and provided to the FDA (06-Nov-2015) for approval.
9. BSSR-2nd: Results were reviewed by clinical trial team and then provided to Novartis management for approval to stop the study as the endpoint was met as agreed with the FDA and EMA.
Communicate to global Novartis clinical trial team that the study has met the BSSR endpoint and that the study will be stopping early as described in Amendment 7 of the protocol. All timelines were communicated to the global Novartis clinical trial team and the sites were informed.

"Personnel roles and involvement in BSSR:

1. Novartis Statistical Team: Prepared the statistical analysis plan for the blinded analysis. Members included the Trial Statistician, and the Project Statistician. The Functional Line Management Statistician was responsible for approvals to propose revision of the study design after the first BSSR and stopping the study after the second BSSR.
2. Novartis Clinical Team: Completed data review and query generation in support of the BSSR. Members included the Clinical Scientific Expert, Clinical Development Director, and Global Program Clinical Head. Senior Clinical Management was responsible for approvals to revise the study design after the first BSSR and decision to stop study after second BSSR.
3. Novartis Programming Team: Responsible for programming data outputs (*i.e.*, tables and listings) needed for the BSSR. Members included the Trial Programmer, Lead Trial Programmer, and Project Level Programmer.
4. Data Management Team: Responsible for all data cleaning activities needed for the BSSR. Members included Lead Trial Data Manager and supporting data managers.
5. Site Personnel: Completed study data entry at the site and answered queries. Personnel included the Principal Investigator, Study Coordinator, and other personnel at the site involved in study data entry.

Data Monitoring Committee role and involvement in BSSR:

A Data Monitoring Committee (DMC) was in place to oversee the study. The DMC was an external board comprised of various specialists (also relevant to the pediatric MS population being studied).

The DMC was primarily set up to monitor the safety of the patients. The protocol indicated that the DMC was responsible for on-going review of enrollment, safety and, if requested by the DMC, efficacy data. During the study, the DMC did not request any efficacy analysis for the study.

Novartis implemented the first BSSR without involvement of the DMC. The DMC was not provided with the results of the first BSSR and was not involved in the proposal to FDA to revise the study design.

The DMC was informed of the second BSSR process prior to its implementation and was provided with the results of the second BSSR. DMC agreed with the decision to stop the study early based on meeting the 80% power threshold to detect a 50% difference in the primary endpoint (ARR).

> *Reviewer Comment: The data integrity and protection of the study blinding appears to have been preserved throughout the two BSSRs. The BSSR leading to the discontinuation of the study appears appropriate.*

The annualized rate of new/newly enlarging T2 (n/neT2) lesions in pediatric patients with RMS for up to 24 months

The annualized rate of n/neT2 lesions was the cumulative sum of the number of new T2 lesions meeting the predetermined criteria for new or enlarging calculated from baseline to the end of the study's Core Phase with a duration up to 24 months. A negative binomial model was used to compare the difference between the fingolimod and interferon β-1a groups.

The Time to Onset of First Relapse

For patients with at least one event meeting the definition of a protocol-defined relapse, the time to event was calculated as (confirmed relapse start date – first dose date + 1). For patients who did not experience a relapse, their time to onset of first relapse was identical to their time in study used for their ARR calculation, or (final study phase visit date – 1st core dose date + 1).

Proportion of Relapse-Free Patients

A log-rank test of the treatment difference between fingolimod and interferon β-1a in the Kaplan–Meier estimates of the survival function of the time to first relapse was performed to assess the proportion of patients who had no relapses at 12 and 24 months. Kaplan-Meier (KM) estimates of the survival functions were constructed and reported by treatment group.

Number of T1 Gd-enhancing lesions per MRI scan up to Month 24

The number of T1 Gd-enhancing lesions was calculated from baseline to the end of the study's Core Phase with a duration up to 24 months. A negative binomial model was used to compare the difference between the fingolimod and interferon β-1a groups.

Protocol Amendments

There were seven protocol amendments to the original protocol FTY720D2311 released on November 24, 2011.

Table 6: Reviewer Table: Protocol Amendments, Study D2311

Protocol Version	Release Date	Notable Changes
Original	November 24, 2011	
Amendment 1	June 13, 2012	• Change in study design from open-label/rater-blinded to double-blind/double dummy to reduce potential bias. • On-line PK assessment of fingolimod concentration levels was specified to be conducted at Month 1 for all patients with a bodyweight of ≤ 40 kg in order to determine the need for an individual dose increase (from 0.25 mg to 0.5 mg) based on their individual concentration level rather than on PK results obtained from an initial subset of 6 patients in this weight group. • Aligned with the revised fingolimod label, (1) specific exclusion criteria, (2) the list of prohibited concomitant treatments, (3) selected safety monitoring guidance and (4) the potential for drug-drug interaction with concomitant use of systemic ketoconazole. • Additional first dose monitoring beyond 6 hours was implemented for patients meeting specific defined criteria at the end of the 6 hour observation period. Additional monitoring applied to: patients that had a heart rate (HR) of < 55 beats

		per minute (bpm) (in patients 12 years or older) or 60 bpm (in patients below 12 years), new onset second degree or higher AV block, HR at six hours post-dose was the lowest value post-dose, and/or QTc on the 6-hour ECG was 500 msec or greater.
Amendment 2	July 11, 2013	• modifications of first dose monitoring guideline with reference to local or regional product information for fingolimod in adults • follow up of adverse events of special interest (AESI) (cardiac, liver, lung, eye) until resolution or stabilization • inclusion of assessment of compliance • inclusion of puberty status as covariate in the statistical analysis • clarification of exclusion criteria, safety monitoring guidelines related to infections, first dose cardiac effects, liver functioning, assessments, and study drug discontinuation criteria • changes related to ECG/QTc findings, pregnancy and suicidality assessments • an optional, comprehensive cognitive testing battery as recommended by the International Pediatric MS Study Group (IPMSSG) was implemented
Amendment 3	July 14, 2014	• Inclusion criterion 2 modified to allow for countries to participate if interferon-β-1a was contraindicated for use below a certain age based on the local product information (Contraindication section) for that country.
Amendment 4	October 23, 2014	• Inclusion criterion for active disease based on prior relapses was expanded to additionally allow patients with evidence of active disease based on recent MRI activity alone (presence of Gd-enhancing lesions within 6 months prior to randomization) to be enrolled • The exclusion criterion for positive antibodies to varicella zoster virus (VZV), measles, mumps, rubella, diphtheria, pertussis, and tetanus was modified as acceptable evidence of immunity to determine a patient's immune status. • The exclusion criterion for patients testing positive for interferon-beta antibodies was removed. • The exclusion criterion for prior immunosuppressive/immunomodulatory

		treatments was revised to reduce the number of excluded prior treatments and to specify appropriate washout periods as needed. • The protocol exclusion of prior use of dimethyl fumarate was removed to allow dimethyl fumarate to be taken up to the start of study drug with no washout period required. • The exclusion criterion for liver enzymes was revised to align more closely with the clinical experience with fingolimod. • All 'must' criteria for permanent study drug discontinuation were provided in a single location in the protocol for clarity. • Appendix 3 safety monitoring guidelines were updated. • Notifications of sustained MRI activity by central MRI reader were added to allow Investigators to be notified if patients had significant MRI lesion activity during the course of the study. • The requirement for chest X-ray was removed due to concerns of unnecessary radiation exposure.
Amendment 5	June 16, 2015	• Details for the 5-year Extension Phase of the study, which was included as a phase of the overall study. Patients that complete the 2-year Core Phase (on or off from study drug) will be eligible to enter a 5-year Extension Phase. This amendment also included safety updates from the Investigator brochure (Edition 18) to provide additional guidance for safety monitoring of opportunistic infections (such as Cryptococcal meningitis) and basal cell carcinoma.
Amendment 6	August 22, 2016	• Clarification regarding study termination. It allowed the termination of the study as a whole (both Core and Extension Phases), or termination of only the Core Phase or the Extension Phase. The changes described in this amended protocol were non-substantial and did not require IRB/IEC approval prior to implementation.
Amendment 7	November 16, 2016	• Modified the study duration from fixed 2-year to an information-based flexible duration design study up to 2 years under the condition that blinded sample size re-estimation (BSSR) during early 2017 indicated that the projected amount of information

		would allow the trial to be stopped in June 2017, while maintaining 80% power for the primary analysis. If BSSR based on the relapse rate observed was below what was needed to maintain 80% power for the primary analysis, the study was to continue until all patients had been enrolled for a minimum of two years. • Assessment of Gd enhancement was no longer required at the Month 18 scan and for all MRI Extension Phase scans due to concerns of possible accumulation of Gd in the brain for patients with repeated MRI scans with Gd enhancement. Efficacy endpoints such as cumulative number of n/ne T2 lesions and number of Gd T1 lesions were modified to adjust for the variant study durations among patients.

6.1.2. Study Results

Compliance with Good Clinical Practices

In Section 5.1, Novartis stated that the research was conducted and reported "in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki." Novartis ensured all study investigators had training according to applicable Sponsor Standard Operating Procedures (SOPs). The Institutional Review Board (IRB) or Independent Ethics Committee (IEC) for each study center provided approval before the study commenced. After IRB/IEC approval, the study protocol could not be modified substantially without re-submission and a new approval. There were eight Investigator site audits conducted by Novartis or its designees. Novartis reported that no unsatisfactory audit findings were observed.

Financial Disclosure

Novartis provided Form 3454 indicating that there were no financial arrangements with investigators whereby the value of compensation could be affected by the outcome of the study as defined by 21 CFR 54.2(b). A list of investigators with any financial interest was provided in Module 1, Section 1.3.4. All disclosed financial interests were indicated as "significant payments of other sorts." Investigators with disclosable financial interests were recorded by 1 out of 995 (0.1%) investigators. This investigator was located as a (b) (6) site participating in the study. The number of patients in the study treated at this site represented (b) (6) % of the overall patients participating in the trial (b) (6) out of 214 or (b) (6) %). Any potential imp t of disclosed financial interest on overall efficacy or safety outcomes is therefore expected to be minimal.

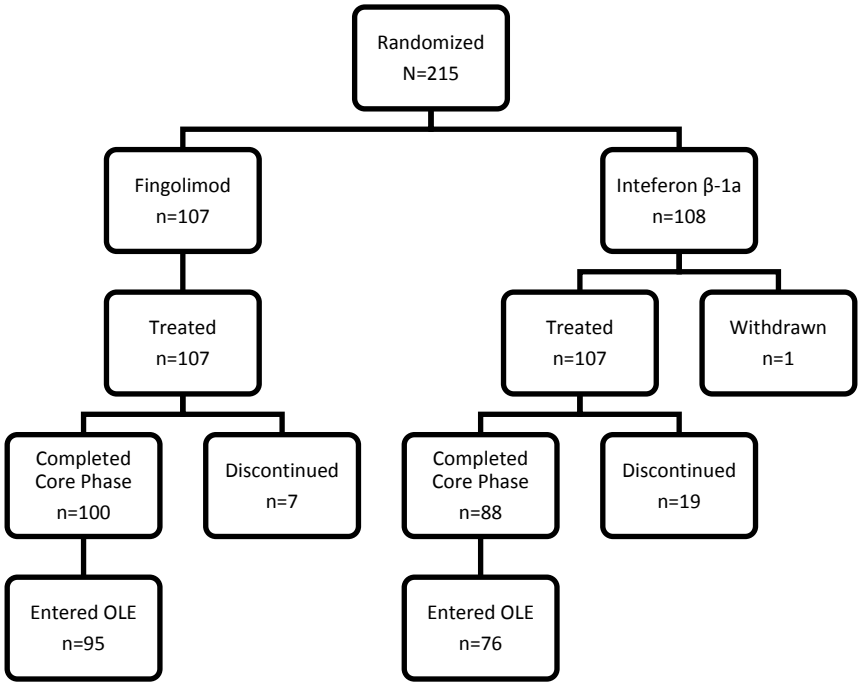
> *Reviewer Comment: Only a single investigator disclosed a relevant financial interest and though this investigator was a PI, the site at which they presided enrolled (b) (6) patients ((b) (6) % of the study population), and so any impact of bias on the overall study would be minimal.*

Patient Disposition

First patient randomized: November 25, 2013
Last patient randomized: August 29, 2016
Data cut-off date: July 14, 2017

348 patients were screened and 215 patients were enrolled and randomized to treatment. The primary analysis population was defined as all randomized patients who took at least one dose of study medication and analyzed following a modified ITT principle. A single patient was randomized but not treated; this patient was unable to swallow the study medication. The "Full Analysis Set" and safety population ("Safety Set") therefore consisted of the 214 randomized subjects who received a single study treatment.

Figure 2: Reviewer Figure: Disposition of Patients in Study D2311



More patients in the fingolimod arm (100/107 or 93.5%) completed treatment compared to the interferon β-1a arm (81.5%). Overall, the most common cited reason for discontinuing the study in either group was "withdrawal of consent." The most common reasons for discontinuation in the fingolimod arm were withdrawal of consent (3/107 or 2.8%) and adverse event (3/107 or 2.8%). The most common reason for discontinuation in the interferon β-1a treatment group was "unsatisfactory therapeutic effect" (7/108 or 6.5%).

> *Reviewer Comment: Of the patients who completed the Core Phase in either treatment arm, 17 patients total did not elect to continue in the Open Label Extension trial. None of the patients who discontinued or withdrew from either treatment condition entered the Open Label Extension trial.*

Table 7: Reviewer Table: Primary Reason for Study Withdrawal in Study D2311

	Fingolimod N=107 n (%)	**Interferon β-1a N=108 n (%)**	**Total Subjects N=215 n (%)**
Completed Core Phase of Study	100 (93.5%)	88 (81.5%)	188 (87.4%)
Discontinued Core Phase	7 (6.5%)	20 (18.5%)	27 (12.6%)
Withdrew Consent	3 (2.8%)	5 (4.6%)	8 (3.7%)
Adverse Event	3 (2.8%)	2 (1.9%)	5 (2.3%)
Unsatisfactory Therapeutic Effect	0 (0%)	7 (6.5%)	7 (3.3%)
Physician Decision	1 (0.9%)	2 (1.9%)	3 (1.4%)
Patient/Guardian Decision	0 (0%)	2 (1.9%)	2 (0.9%)
Unable to Administer Treatment	0 (0%)	1 (0.9%)	1 (0.5%)
Protocol Deviation	0 (0%)	1 (0.9%)	1 (0.5%)

Source: ACMP.xpt

Adverse events (AEs) leading to permanent discontinuation of study treatments were infrequent in both treatment groups. Over the course of the study, six patients in the fingolimod treatment group and five in the interferon β-1a treatment group had to discontinue study treatment permanently due to one or more AE. The most common AE leading to discontinuation in either study was multiple sclerosis relapse. No other AE leading to

discontinuation of treatment occurred in more than one patient in either treatment group. Note that six patients in the fingolimod treatment arm listed nine AEs and five patients in the interferon β-1a treatment arm listed seven AEs as reasons for discontinuation.

Table 8: Reviewer Table: Serious Adverse Events Leading to Drug Discontinuation, Safety Set, Study D2311

MedDRA System Organ Class MedDRA Preferred Term	**Fingolimod n=107 n (%)**	**Interferon β-1a n=107 n (%)**
Any primary system organ class	6 (5.6%)	5 (4.7%)
Blood and Lymphatic System Disorders	2 (1.9%)	0
Anemia	1 (0.9%)	0
Leukopenia	1 (0.9%)	0
Eyes Disorders	1 (0.9%)	0
Macular edema	1 (0.9%)	0
General Disorders and Administration Site Conditions	0	2 (1.9%)
Drug ineffective	0	1 (0.9%)
Influenza-like illness	0	1 (0.9%)
Investigations	0	1 (0.9%)
Alanine aminotransferase increased	0	1 (0.9%)
Aspartate aminotransferase increased	0	1 (0.9%)
Musculoskeletal and Connective Tissue Disorders	1 (0.9%)	0
Back pain	1 (0.9%)	0
Nervous System Disorders	2 (1.9%)	2 (1.9%)
Headache	1 (0.9%)	0
Multiple sclerosis plaque	1 (0.9%)	0
Multiple sclerosis relapse	1 (0.9%)	2 (1.9%)
Psychiatric Disorders	0	1 (0.9%)
Depression	0	1 (0.9%)
Skin and Subcutaneous Tissue Disorders	1 (0.9%)	0
Hypersensitivity vasculitis	1 (0.9%)	0
Injury, Poisoning, and Procedural Complications	1 (0.9%)	0
Maternal exposure during pregnancy	1 (0.9%)	

Source: AAEV.xpt

Unblinding

A total of twelve patients (eight in the fingolimod treatment group, four in the interferon β-1a treatment group) were suspected to have been unblinded during the study. A study site did not

follow proper blinding procedures for nine patients (seven patients in fingolimod treatment group, two patients in interferon β-1a treatment group). Three patients (one in the fingolimod and two in the interferon β-1a) were assumed to be unblinded in the most conservative statistical analysis set for protocol deviations because of an error in which the independent first dose monitoring site provided unblinded information regarding dose increase to the clinical investigator site that was seen by one member of the study team without any known further conveyance to other team members nor to the implicated patients.

Protocol Violations/Deviations

There were seven patients who did not meet all eligibility criteria, six treated with fingolimod, and one treated with interferon β-1a. One patient in the fingolimod treatment group did not meet the inclusion criterion for age (< 17 years old in a country contraindicated for interferon β-1a below age 18) and another patient was enrolled but did not satisfy the number of relapses prior to randomization stipulated in subsequent protocol revisions. Four patients were randomized in the fingolimod treatment group despite meeting exclusion criteria as follows: treatment with a corticosteroid within 30 days prior to enrollment, positive result for a hepatitis screening serology value, and two patients were missing lab values for a required screening lab result.

A single patient was randomized into the interferon β-1a treatment arm despite a positive aquaporin-4 antibody result, an exclusion criterion.

> *Reviewer Comment: The inclusion of patients failing to meet eligibility criteria is unlikely to have affected the efficacy results. While six out of seven patients with protocol deviations were randomized to the fingolimod treatment arm, all but one of the noted deviations were inconsequential (age consideration only applied if patient had been randomized to interferon β-1a) or rectified by subsequent lab value acquisitions. Of greater concern are the seven patients in the fingolimod treatment group who were potentially unblinded. However, efficacy analyses performed with these unblinded patients excluded yielded primary and key secondary outcome findings that were not significantly different from those performed on the FAS.*

<u>Eligibility/Screening Period</u>

The duration of time to establish eligibility should have been ≤ 45 days for all patients. The actual mean time between informed consent and randomization was 43.4 days for patients in the fingolimod arm and 44.9 days for patients in the interferon β-1a treatment arm. There were eleven patients with screening periods > 90 days, five in the fingolimod treatment group (range 91-163 days) and six in the interferon β-1a treatment group (range 91 to 147 days).

Table 9: Reviewer Table: Time from Consent to Randomization, Full Analysis Set, Study D2311

Treatment	Time from Consent to Randomization in days					
	N	**Mean**	**SD**	**Median**	**Min**	**Max**
Fingolimod	107	43.4	20.9	40	5	163
Interferon β-1a	108	44.9	22.08	41.5	15	147

Source: ARND.xpt

Table of Demographic Characteristics

The two treatment groups were balanced with respect to key demographic characteristics at baseline. The population was approximately 62% female as would be expected for the RMS population. The baseline age was greater than 14 years in over 70% of the population with only 22% enrollment ≤ 12 years old. Ten percent of the patients were pre-pubertal. Over 90% of the patients reported their race as “white” and over 66% of patients were recruited from European countries. Approximately 16% of enrolled patients were from the United States.

Table 10: Reviewer Table: Patient Demographic Characteristics, Randomized Set, Study D2311

Demographic Parameters	Treatment Group		
	Fingolimod (N=107) n (%)	IFN β-1a (N=108)[1] n (%)	Total (N=215) n (%)
Sex			
Male	37 (34.6)	44 (40.7)	81 (37.7)
Female	70 (65.4)	64 (59.3)	134 (62.3)
Age at randomization			
Mean years (SD)	15.2 (2.00)	15.4 (1.60)	15.3 (1.81)
Median (years)	16.0	16.0	16.0
Min, max (years)	10, 17	11, 17	10, 17
Age Group			
< 10 years	0 (0.0)	0 (0.0)	0 (0.0)
≥ 10 to ≤ 12 years	13 (12.1)	9 (8.3)	22 (10.2)
> 12 to ≤ 14 years	16 (15.0)	19 (17.6)	35 (16.3)
> 14 to ≤ 16 years	44 (41.1)	45 (41.7)	89 (41.4)
> 16 to ≤ 17 years	34 (31.8)	32 (29.6)	66 (30.7)
≥ 18 years[2]	0 (0.0)	3 (2.8)	3 (1.4)
Pubertal Status			
Pre-pubertal (Tanner stage <2)	7 (6.5)	3 (2.8)	10 (4.7)
Pubertal (Tanner stage ≥2 / bone age ≥ 16 years/menarche)	98 (91.6)	105 (97.2)	192 (94.4)[3]
Weight (kg), n (%)			
≤ 40 kg	9 (8.4)	1 (0.9)	10 (4.7)
> 40 kg	98 (91.6)	107 (99.1)	205 (95.3)
Race			
White	100 (93.5)	97 (89.8)	197 (91.6)
Black or African American	1 (0.9)	4 (3.7)	5 (2.3)
Asian	1 (0.9)	0 (0.0)	1 (0.5)
American Indian or Alaska Native	3 (2.8)	2 (1.9)	5 (2.3)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
Other[4]	2 (1.9)	5 (4.6)	7 (3.3)
Ethnicity			
Hispanic or Latino	9 (8.4)	11 (10.2)	20 (9.3)
Not Hispanic or Latino	98 (91.6)	97 (89.8)	195 (90.7)
Region			
United States	7	9	16 (7.4)
Rest of the World	100	99	199 (92.6)

Austria	1	2	3
Australia	2	2	4
Belarus	5	8	13
Brazil	1	4	5
Bulgaria	2	3	5
Canada	3	0	3
Croatia	0	2	2
Estonia	0	1	1
France	10	9	19
Germany	6	9	15
Italy	10	8	18
Latvia	0	1	1
Lithuania	4	4	8
Mexico	4	2	6
Netherlands	1	2	3
Poland	10	8	18
Romania	2	0	2
Russia	12	12	24
Serbia	3	4	7
Slovakia	3	0	3
Spain	4	3	7
Turkey	6	3	9
Ukraine	7	11	18
United Kingdom	3	2	5

Source: CSR, ADMG.xpt

[1]A patient randomized to the interferon β-1a treatment arm could not swallow the placebo capsule and therefore was withdrawn from the study without receiving any treatment.

[2]Patients were confirmed actual age of < 18 years at randomization but due to reporting restrictions only birth year could be used for demographic reporting purposes.

[3]Three patients had an undetermined baseline pubertal status

[4]Data on race and/or ethnicity were not collected at several sites because of local regulations.

Reviewer Comment: The characteristics of randomized patients in this study are consistent with the observed ethnic and age distributions reported for pediatric RMS (Jancic et al.*, 2016). Novartis achieved the protocol goal minimum enrollment of pre-pubertal patients (10%), but the small sample size in this group limits interpretability. There were thirteen patients under age 12, and this group was male predominant (eight males vs five females,) reflective of the observation in the literature of an absence of the usual female predominance in the RMS population below age 12.*

Other Baseline Characteristics (*e.g.*, disease characteristics, important concomitant drugs)

The two treatment groups were comparable for the clinical status of RMS at baseline (Table 9). The mean and median EDSS scores at baseline were not significantly different. Per enrollment criteria, all patients had one or two relapses in the past two years. Approximately half (49.8%) of the patients did not have a gadolinium-enhancing lesion at baseline. More than 60% of patients in either group had not used any prior treatment for MS.

Table 11: Reviewer Table: Baseline MS Characteristics, Randomized Set, Study D2311

	Fingolimod N=107	Interferon β-1a N=108
Baseline EDSS		
n	105	108
Mean (SD)	1.46 (1.145)	1.61 (0.894)
Median	1.50	1.50
Range	0.0 to 5.5	0.0 to 4.0
Duration since MS Symptom Onset (years)		
n	107	108
Mean (SD)	1.9 (1.7)	2.4 (2.1)
Median	1.2	1.8
Range	0 to 9	0 to 11
Relapses in previous 12 months		
n	107	108
Mean (SD)	1.5 (0.95)	1.5 (0.92)
Median	1.0	1.0
Range	0 to 4	0 to 7
Relapses in previous 24 months		
n	107	108
Mean (SD)	2.4 (1.4)	2.5 (1.3)
Median	2.0	2.0
Range	0 to 8	1 to 9
Baseline Number of Gadolinium-enhancing T1 Lesions*		
n	106	107
Mean (SD)	2.6 (6.0)	3.1 (6.5)
Median	1.0	0
Range	0 to 52	0 to 37
Volume of Gd-enhancing Lesions (mm^3)		
n	106	107
Mean (SD)	454.8 (1190.4)	412.3 (936.6)
Median	73.0	0

Range	0 to 9662	0 to 6160
Proportion of patients free of Gadolinium-enhancing lesions at baseline		
n (%)	47 (44.3)	59 (55.1)
Baseline Number of T2 lesions		
n	107	107
Mean (SD)	41.9 (30.3)	45.6 (33.9)
Median	31.0	32.0
Range	2 to 126	4 to 145
Volume of T2 Lesions (mm^3)		
n	107	107
Mean (SD)	8902.4 (13147.6)	11512.3 (15087.0)
Median	5245.0	6197.0
Range	52 to 116533	189 to 101099
Volume of T1 Hypointense Lesions (mm^3)		
n	107	107
Mean (SD)	1590.9 (3906.49)	2608.8 (5823.8)
Median	484.0	753.0
Range	0 to 35394	0 to 46893
Whole Brain Volume (cm^3)		
n	107	105
Mean (SD)	1154.3 (126.8)	1159.8 (121.5)
Median	1145.9	1135.9
Range	917 to 1633	910 to 1487
Any previous treatment for MS		
n (%)	38 (35.5)	41 (38.0)

Source: CSR Tables 11.-2 and 11-3, ADMG.xpt, AMRI.xpt

Reviewer Comment: The percentage of patients with no T1 Gd-enhancing lesions at baseline was lower in the fingolimod treatment group than in the interferon β-1a treatment group (44% vs. 59%) indicating potentially more radiologically apparent brain inflammation and perhaps more disease activity in the patients randomized to fingolimod before treatment initiation. There are no apparent consequences of this imbalance reflected in the baseline clinical data; the EDSS scores and number of relapses 12 and 24 months prior are statistically identical between groups. The concern with this imbalance would be that patients with more inflammation at baseline might have a diminished or delayed response to treatment and bias against a finding of efficacy in fingolimod, but the efficacy results for fingolimod indicate such was not the case. It may alternatively be the case that fingolimod reduces inflammation more effectively than interferon treatment. The volume of the T2 hyperintense and T1 hypointense lesions for the interferon β-1a treatment group are larger than the corresponding volumes in the

fingolimod group but with greater variability, and a statistical comparison of baseline T2 hyperintense and T1 hypointense lesions' characteristics revealed no significant difference between the treatment groups' T2 baseline lesion volumes. While it is concerning to have a difference between treatment groups with respect to lesion volumes, the baseline equivalency of the groups' baseline EDSS values replicates the often observed lack of correlation between MRI lesion burden and clinical appearance. Other baseline MRI measures were comparable between the two treatment groups.

Exposure

The duration of exposure to study treatments showed a difference between two treatment groups (Table 12). The duration of exposure for fingolimod (0.5 and 0.25 mg) on average was nearly 80 days longer than for exposure to interferon β-1a, and the median value difference was closer to 100 days. Nine patients total were exposed to the fingolimod 0.25 mg dose during the entire Core Phase.

Table 12: Reviewer Table: Duration of Exposure to Treatment by Treatment Group, Full Analysis Set, Study D2311

	Duration of Exposure during the double-blind treatment period (days)					
	n	Mean	SD	Median	Min	Max
Fingolimod (all doses)	107	602.4	159.9	647.0	9	767
Interferon β-1a	108	525.7	186.9	551.0	30	750

Source: ACMP.xpt DYLST1N by TGP1A

Reviewer Comment: The overall discrepancy in exposure between treatment groups reflects the fact that more patients completed the Core Phase of the study on study treatment in the fingolimod group (99/107) versus the interferon β-1a treatment group (81/108). The most often cited reason (in 7 out of 20 total withdrawals) for discontinuation in the interferon treatment group was "unsatisfactory therapeutic effect." In contrast, none of the seven patients who discontinued study treatment for fingolimod did so for "unsatisfactory therapeutic effect." This difference suggests there was both patient awareness of treatment assignment driving study completion and a differential expectation of therapeutic success between treatment groups.

Table 13: Sponsor Table: Duration of Exposure to Treatment in Pre-Pubertal Treatment Sub-groups, Full Analysis Set, Study D2311

	Duration of Exposure during the double-blind treatment period (days)					
	n	Mean	SD	Median	Min	Max
Fingolimod (all doses)	7	483.7	256.1	498.0	38	711

Fingolimod (0.25 mg)	9	280.7	265.7	183	38	724

Source: CSR Table 14.3-1.1a and AREL25.xpt STYDAY by TGP1A

Reviewer Comment: There were seven pre-pubertal patients randomized to fingolimod and *nine patients in total received 0.25 mg fingolimod, and only two of those patients remained on this treatment for the entire duration of the Core Phase of the study. Conclusions regarding pre-pubertal patients and those exposed to the 0.25 mg dose of fingolimod are limited by the small number of patients.*

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

Compliance with fingolimod or interferon β-1a was monitored by counting the medication dispensed and the used medication packages returned. Overall, percent compliance was similar in the two treatment groups.

Table 14: Sponsor Table: Percent Compliance for Fingolimod or Interferon β-1a, Safety Set, Study D2311

	Total Doses					
	Total	**Mean**	**SD**	**Median**	**Min**	**Max**
Fingolimod capsules	106	97.2	6.0	99.4	72.2	107.9
Interferon β-1a syringes	106	98.2	6.9	100.0	81.7	107.6

Source: CSR Table 14.3-1.2

Concomitant Medications

The most common concomitant medications used during the Core Phase of the trial were anti-inflammatory treatments, antibiotics, and vitamin supplements. The most common treatments in either group were ibuprofen and paracetamol. Methylprednisolone and other steroid treatments for MS relapses differed in use between the two treatment arms. Approximately 32% in both groups reported prior use of an interferon and approximately 7% reported prior use of glatiramer acetate. Despite similar exposures to corticosteroids, approximately 35% of patients in the interferon β-1a treatment arm used a proton pump inhibitor and/or a histamine antagonist for gastrointestinal prophylaxis versus less than 15% in the fingolimod group.

Table 15: Reviewer Table: Most Common Concomitant Medications During Treatment Phase, Full Analysis Set, Study D2311

Standardized Medication Name	Fingolimod N=107	Interferon β-1a N=107	Total N=214

Ibuprofen	41 (38.3%)	48 (44.9%)	89 (41.6%)
Paracetamol	39 (36.5%)	46 (43.0%)	85 (39.7%)
Corticosteroids (relapse-related)	18 (16.8%)	64 (59.8%)	82 (38.3%)
Vitamin D supplement (any)	27 (25.2%)	18 (16.8%)	45 (21.0%)
Corticosteroids (not relapse-related)	26 (24.3%)	17 (15.9%)	43 (20.1%)
Amoxicillin	13 (12.2%)	9 (8.4%)	22 (10.3%)
Omeprazole	9 (8.41%)	27 (25.3%)	36 (16.8%)
Amoxicillin w/Clavulanate	9 (8.41%)	5 (4.7%)	14 (6.5%)
Azithromycin	8 (7.5%)	1 (0.9%)	9 (4.2%)
Ambroxol	7 (6.5%)	6 (5.6%)	13 (6.1%)
Cetirizine	7 (6.5%)	5 (4.7%)	12 (5.6%)
Xylometazoline	7 (6.5%)	4 (3.7%)	11 (5.1%)
Dexibuprofen	6 (5.6%)	3 (2.8%)	9 (4.2%)
Mometasone	6 (5.6%)	3 (2.8%)	9 (4.2%)
Ranitidine	5 (4.7%)	12 (11.2%)	17 (7.9%)
Prednisolone/Prednisone	8 (7.5%)	5 (4.7%)	13 (6.1%)

Source: ACMDATC.xpt, ASTEROID.xpt, and Sponsor's submission Listing 16.2.5-1.6

Reviewer Comment: The increased use of corticosteroids for relapses, especially methylprednisolone, in the interferon β-1a group was anticipated given the relapse difference observed between the two treatment groups. The higher use of gastrointestinal prophylaxis agents in patients in the interferon β-1a arm logically parallels the increase in corticosteroid use. The use of any non-steroidal anti-inflammatory agents was approximately 6% higher in patients in the interferon β-1a arm. Higher use of analgesics in interferon-treated patients is an expected finding since myalgias/arthralgias are common side effects of interferon β-1a and the protocol stipulated treatment with non-steroidal anti-inflammatory agents for this specific indication would be implemented per individual site preference.

Rescue medication use

During the treatment phase, nineteen patients in the fingolimod treatment group received intravenous corticosteroids and sixty-four patients in the interferon β-1a group received methylprednisolone or oral equivalent corticosteroids indicating that corticosteroid treatments were given to all patients with confirmed MS relapses (fifteen and fifty-eight, respectively).

An information request was sent to Novartis on March 13, 2018 requesting clarification of steroids given for relapse and non-relapse reasons as the databases provided did not entirely reflect the steroid administrations noted on the patient CRFs. Novartis provided an updated data file with all steroid administrations and the following summaries to differentiate steroids given to patients for all MS relapses and for non-MS reasons.

Table 16: Sponsor Table: Summary of Corticosteroids Not for Relapse Treatment, Safety Set, Study D2311

Preferred term	FTY720 N=107 n (%)	IFNß-1a N=107 n (%)	Total N=214 n (%)
-Any medication	26(24.3)	17(15.9)	43(20.1)
MOMETASONE FUROATE	5(4.7)	2(1.9)	7(3.3)
FLUTICASONE PROPIONATE	3(2.8)	0(0.0)	3(1.4)
METHYLPREDNISOLONE SODIUM SUCCINATE	3(2.8)	1(0.9)	4(1.9)
PREDNISONE	3(2.8)	1(0.9)	4(1.9)
METHYLPREDNISOLONE ACEPONATE	2(1.9)	0(0.0)	2(0.9)
PREDNISOLONE	2(1.9)	1(0.9)	3(1.4)
PREDNISOLONE METASULFOBENZOATE SODIUM	2(1.9)	1(0.9)	3(1.4)
SERETIDE	2(1.9)	4(3.7)	6(2.8)
TIXOCORTOL PIVALATE	2(1.9)	0(0.0)	2(0.9)
TOBRADEX	2(1.9)	2(1.9)	4(1.9)
TRIAMCINOLONE ACETONIDE	2(1.9)	0(0.0)	2(0.9)
BECLOMETASONE DIPROPIONATE	1(0.9)	0(0.0)	1(0.5)
BETAMETHASONE	1(0.9)	1(0.9)	2(0.9)
BETAMETHASONE DIPROPIONATE	1(0.9)	0(0.0)	1(0.5)
BUDESONIDE	1(0.9)	2(1.9)	3(1.4)
BUDESONIDE W/FORMOTEROL FUMARATE	1(0.9)	0(0.0)	1(0.5)
DEXAMETHASONE	1(0.9)	6(5.6)	7(3.3)
METHYLPREDNISOLONE	1(0.9)	1(0.9)	2(0.9)
MOMETASONE	1(0.9)	0(0.0)	1(0.5)
TIXOCORTOL	1(0.9)	0(0.0)	1(0.5)
CORTISONE	0(0.0)	1(0.9)	1(0.5)
DIPROGENTA	0(0.0)	1(0.9)	1(0.5)
FLUOCINOLONE ACETONIDE	0(0.0)	1(0.9)	1(0.5)
FLUOROMETHOLONE	0(0.0)	1(0.9)	1(0.5)
MAXITROL	0(0.0)	1(0.9)	1(0.5)
POLYDEXA A LA PHENYLEPHRINE	0(0.0)	1(0.9)	1(0.5)
PREDNISOLONE SODIUM SUCCINATE	0(0.0)	1(0.9)	1(0.5)
RIMEXOLONE	0(0.0)	1(0.9)	1(0.5)
STER-DEX	0(0.0)	1(0.9)	1(0.5)

Source: Table 1.1, Appendix 2, Response to Information Request Received March 13, 2018

Table 17: Sponsor Table: Summary of Corticosteroids for Relapse Treatment, Safety Set, Study D2311

Preferred term	FTY720 N=107 n (%)	IFNß-1a N=107 n (%)	Total N=214 n (%)
-Any medication	19(17.8)	64(59.8)	83(38.8)
METHYLPREDNISOLONE	10(9.3)	45(42.1)	55(25.7)
METHYLPREDNISOLONE SODIUM SUCCINATE	10(9.3)	21(19.6)	31(14.5)
CORTISONE ACETATE	1(0.9)	0(0.0)	1(0.5)
GABAPENTIN	1(0.9)	0(0.0)	1(0.5)
PREDNISOLONE	1(0.9)	2(1.9)	3(1.4)
DEXAMETHASONE	0(0.0)	2(1.9)	2(0.9)
DEXAMETHASONE SODIUM PHOSPHATE	0(0.0)	1(0.9)	1(0.5)
PREDNISONE	0(0.0)	1(0.9)	1(0.5)
TRIAMCINOLONE ACETONIDE	0(0.0)	1(0.9)	1(0.5)

Source: Table 1.2, Appendix 4, Response to Information Request Received March 13, 2018

Reviewer Comment: The revised corticosteroid summaries and data accurately reflect the use of steroids in Study D2311. I removed the single use of "gabapentin" from my reviewer table as it is not a steroid treatment.

Efficacy Results – Primary Endpoint

Annualized Relapse Rate

New or worsening of a pre-existing neurological abnormalities were reported as a "Multiple Sclerosis Relapse" if the Primary Treating Physician determined that these symptoms met the initial protocol-defined criteria for a relapse. A relapse was confirmed by an EDSS performed by an Independent Evaluating Physician. If the Primary Treating Physician was unsure whether an abnormalities met the protocol standards for a clinical relapse, the protocol required that all patients with potential relapse events be referred to the Independent Evaluating Physician for an EDSS rating. A relapse was confirmed by a change in EDSS or by increases in the FS sub scores (see Section 6.1.1). All relapse events, confirmed and unconfirmed, were recorded in the eCRF.

Reviewer Comment: The lack of a clearly articulated algorithm for the MS relapse confirmation referral process is a concern as a source of bias. Leaving the ultimate decision regarding referral to the Primary Treating Physician's judgment means that patients could minimize new symptoms and thereby avoid a confirmatory referral for a relapse. The protocol stipulated that any "doubt" on behalf of the treating physician should default to a referral. This default favors the possibility of referrals that do not confirm a potential relapse but allows for a potential failure to refer a real relapse that would have been confirmed. One could imagine that a treating physician could eradicate subjective "doubt" despite the existence of clinical evidence suggestive of a relapse. Likewise, patients could trivialize complaints for any number of reasons in order to avoid a referral. A more systematic approach without reliance of Primary Treating Physician opinion, or a stipulation that all unscheduled visits would require an independent EDSS rating regardless, would have mitigated these concerns.

Using the AREL dataset, during the double-blind treatment period, there were 37 relapses (confirmed and unconfirmed) for 24 patients in the fingolimod treatment group and 138 relapses (confirmed and unconfirmed) for 66 patients in the interferon β-1a treatment group.

Reviewer Comment: On review of all the AEs reported under "Nervous System Disorders"

System Organ Class (SOC) there do not appear to be any AEs not counted as a relapse for the purposes of ARR calculations that could represent a potential MS relapse other than those MS relapses that were considered more severe than typical relapses and designated as SAEs that are discussed in Section 8.4.2.

Table 18: Reviewer Table: Number of All Confirmed and Unconfirmed Relapses During the Double-Blind Treatment Phase by Treatment Group, Full Analysis Set, Study D2311

Number of Relapses (Confirmed and Unconfirmed)	Number of Patients (%)	
	Fingolimod	Interferon β-1a
0	83 (77.6)	40 (37.4)
1	15 (14.0)	28 (26.2)
2	5 (4.7)	21 (19.6)
3-5	4 (3.7)	17 (15.9)
>5	0 (0)	1 (0.9)

Source: Clinical Study Report Table 14.2-1.7

When the MS relapse events were assessed using the protocol methodology for confirming a relapse described in Section 6.1.1, it was determined that 15 patients in the trial experienced twenty-five confirmed relapses. Novartis reported in Table 14.2-1.6b of the Clinical Study Report that there were thirty-seven total relapses, confirmed and unconfirmed, in the fingolimod treatment group, meaning that the confirmation rate for confirmed MS relapses was 25/37 or 68%. In the interferon β-1a group, fifty-eight patients had one hundred twenty confirmed relapses out of one hundred forty-one relapses for an 85% confirmation rate.

Reviewer Comment: A nearly 20% difference between the confirmation rates in the two groups could be suggestive of a systematic bias due to previously noted protocol violations that unblinded study personnel. If one excludes those patients in the fingolimod group with all protocol violations by using the per protocol data set provided by Novartis, the total number of confirmed and unconfirmed relapses drops to 31, and the confirmed number drops to 22. Thus, removing potentially unblinded patients from the analysis raised the confirmation rate from 68% to 22/31 or 71%. The lower confirmation rate in the fingolimod treatment group as compared to the interferon-treated group is therefore not entirely attributable to the patients potentially unblinded by deviations from the protocol. Patients in the fingolimod treatment arm did not report more neurological AEs to prompt unconfirmed referrals (see Section 8.4.4) nor did they utilize more corticosteroids that might have improved acute disability (see Concomitant Medications above.) It is therefore necessary to consider that there were more inappropriate referrals for confirmatory EDSS ratings in the fingolimod treatment group for an unclear reason, or the handling of relapse data introduced a difference into the confirmation rates between the two groups (see Data Quality and Integrity below).

The mean duration of exposure to assigned treatment during the double-blind treatment phase is shown in the table below.

Table 19: Sponsor Table: Mean Duration of Double-Blind Treatment by Treatment Group

Treatment	Twenty-four Month Exposure Duration (days)						
	N	Mean	SD	Median	Min	Max	Sum (patient-years)
Fingolimod	107	600.9	149.3	634.0	9	767	176.0
Interferon β-1a	107	523.7	187.3	547.0	30	750	154.4

Source: Clinical Study Report Table 14.3-1.1

The total number of days in trial for fingolimod treatment and interferon β-1a treatment were 65,575 and 59,678 days, respectively.

Based on the number of protocol-defined relapses and the sum of the total duration of time spent in the double-blind treatment Core Phase for each group, the unadjusted ARR by treatment group was as follows:

Table 20: Reviewer Table: Annualized Relapse Rate, Reviewer Calculation, Unadjusted

Treatment Group	Unadjusted ARR (see below for ARR calculation)
Fingolimod	0.139
Interferon β-1a	0.734

Source: AREL.xpt

The difference in ARR is statistically significant (Wilcoxon Signed Rank Test, S=908, p<0.0001). The relative reduction is 81.1%.

Novartis's report of the unadjusted and adjusted ARR is shown in the table below.

Table 21: Sponsor Table: Annualized Protocol-Defined Relapse Rate by Month 24 (Negative Binomial Model) Primary Analysis, Full Analysis Set, Study D2311

	Fingolimod n=107	Interferon β-1a n=107
Number (%) of Patients with Relapse	15 (14.0%)	58 (54.2%)
Number of Relapses	25	120
Time in Study (days)	65575	59678
Raw Annualized Relapse Rate (ARR)[1] (time-based)	0.139	0.734
Adjusted ARR (95% CI)[2]	0.122 (0.078,0.192)	0.675 (0.515,0.885)
Treatment Comparison of Fingolimod vs. Interferon β-1a		
ARR Ratio (95% CI)	0.181 (0.108,0.303)	
Percent ARR Reduction	81.9%	
p-value	p<0.001	

[1]Raw ARR (time-based) calculated by taking the total number of relapses observed for all patients within a treatment group, divided by the total number of days in study of all patients within the treatment group and multiplied by 365.25 days.
[2]Adjusted ARR, ARR ratio, percent rate reduction, and p-value are obtained by fitting a negative binomial regression model adjusted for treatment, region, pubertal status, and the number of relapses in the last 2 years (offset: time in study).
Source: AREL.xpt, Table 4-1 Clinical Overview

Reviewer Comment: This reviewer's calculation of the unadjusted ARR for all relapses falls within the 95% confidence interval for the ARR calculated by Novartis that adjusted for region, pubertal status, and number of relapses in prior 2 years. The ARR results from this pediatric study demonstrate a higher relative reduction in the ARR for pediatric patients with RMS (82%) compared to the reduction relative to interferon β-1a noted in adult patients with RMS (52%) in Trial D2302. This observed 30% difference between two studies' reductions is not necessarily indicative of greater efficacy of fingolimod in pediatric patients. The difference is more likely reflective of the fact that there are a higher number of relapses that occur on average in pediatric patients with RMS than in adult patients with RMS. It is also important to note that the ARR reductions in these studies are being made relative to an active comparator and not against a placebo. To provide further perspective, the largest prospective published study to define an ARR in pediatric patients with RMS found the ARR for pediatric patients was 1.13 (The ARR for patients in Study D2311 was approximately 1.20 before randomization) versus 0.40 in adults with RMS seen at the same institution in the same timeframe (Gorman et al., 2009). A theoretical fingolimod treatment reduction of 82% in these pediatric patients would yield an ARR of 0.20 which would be nearly equivalent to the ARR for adult MS patients (0.19) from the same study if they experienced their expected fingolimod treatment-related 52% reduction. To be more succinct, fingolimod treatment may

achieve the same approximate ARR in both adult and pediatric patients with RMS, preventing approximately 50% of annual relapses, but it is doing so in two populations with very different relapse rates.

ARR of Severe Relapses

Protocol Confirmed Relapses in Study D2311 were rated as "mild, moderate, or severe" based on pre-determined criteria (see Section 6.1.1). An ARR was generated using just "severe" relapses as indicated below.

Table 22: Reviewer Table: Annualized Protocol-Defined Severe Relapse Rate by Month 24, Full Analysis Set, Study D2311

	Fingolimod n=107	**Interferon β-1a 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%	

Source: AREL.xpt By (STYSID1A, ACTDSC1A, AEVSEV2C, INSTUDY1)

Reviewer Comment: Limiting the raw ARR analysis to just protocol-defined "severe" relapses changes the raw time-based ARR values but yields a similar percent reduction in the ARR between the treatment groups. Protocol defined "severe" relapses occurred much less frequently in the fingolimod treatment group than in the interferon β-1a treatment group.

Primary Endpoint by Subgroups

The reduction in ARR varied between several subgroups of interest. The largest difference was noted between those who participated at sites in the United States versus sites outside the United States. The percent reduction in ARR was just 37.6% for patients in the US whereas patients outside the US had reduction of 84.1%. There also appears to be a difference in male and female pediatric patients respond to fingolimod; male patients in the fingolimod treatment group had a ARR reduction of 95.6% relative to male patients in the interferon β-1a treatment group. Otherwise, the results comparing different subgroups confirmed an overall efficacy of fingolimod.

Table 23: Reviewer Table: Unadjusted Annualized Rate in Subgroups, Full Analysis Set, Study D2311

	Fingolimod N=107		Interferon β-1a N=107		
	N	**Unadjusted ARR**	**N**	**Unadjusted ARR**	**% Relative Reduction**
Full Analysis Set	107	0.139	107	0.734	81.1%
Subgroup					
Age Groups					
≥10 to ≤ 12 years	13	0.095	9	0.722	86.8%
> 12 to ≤ 18 years	94	0.145	98	0.735	80.3%
Sex					
Male	37	0.033	43	0.737	95.5%
Female	70	0.194	64	0.723	73.2%
Region					
United States	7	0.085	9	0.156	45.5%
Outside US	100	0.143	98	0.783	81.7%
Pubertal Status					

Pre-Pubertal	7	0.195	3	1.494	86.9%
Post-Pubertal	98	0.133	104	0.728	81.7%
Baseline Weight and Dose					
≤ 40 kg (0.25 mg dose)	9	0.234	1	0.000	--
> 40 kg (0.5 mg dose)	98	0.132	106	0.740	82.2%
Number of Relapses in Last 2 Years					
≤ 2	66	0.074	65	0.721	89.7%
> 2	41	0.263	42	1.067	75.4%
Previous Treatment for MS					
Yes	38	0.222	40	1.26	82.3%
No	69	0.104	67	0.616	83.1%
Presence of ≥ 1 Gadolinium-enhancing MRI Lesion at Baseline					
Yes	47	0.0485	58	0.676	92.8%
No	60	0.222	48	1.073	79.3%

Source: AREL.xpt merged with AMSHIS.xpt and AMRI.xpt

Reviewer Comment: While the patient numbers and number of relapses are small, 16 total patients and 5 total relapses, findings for patients randomized to fingolimod at sites in the

United States showing only a 45.5% risk reduction in ARR compared to interferon β-1a are of concern because these data were obtained in the population which will benefit from the potential approved indication. The apparent decreased efficacy for fingolimod is driven in large part by an ARR for interferon β-1a (0.156) that is a fraction of the ARR range (0.744-0.7947) reported for US pediatric patients using interferon β-1a in a recent paper by Krupp et al. *(2016). It is therefore unlikely given the consistent overall and subgroup findings for both treatments, as well as the ARR data gathered for both of these treatments in adequate controlled studies of thousands of adults, that the ARR findings in these sixteen US patients are accurately predictive of how either of these therapies will perform in a larger US pediatric patient population. The ARR reduction in patients taking fingolimod with ≥ 1 T1 Gd-enhancing lesion at baseline is informative in light of findings of a large reduction in T1 Gd-enhancing lesions noted at 6 months exclusively in the fingolimod treatment group. The ARR reduction in male pediatric patients compared to female pediatric patients in the fingolimod arm would represent a novel finding as studies of fingolimod in adult patients with MS have not noted a consistent difference in gender response to treatment. There is a paucity of data for the 0.25 mg dose of fingolimod in patients < 40 kg but there is a concern that the lower dose was not as effective in preventing relapses as the 0.5 mg dose. Patients receiving the 0.25 mg dose had an ARR 1.7-fold that of the overall fingolimod population and 1.8-fold that of the patients who took 0.5 mg fingolimod. Neither age nor puberty status demonstrated a similar discrepancy with overall ARR suggesting that weight alone, not hormonal or other age-related factors, was the most important determinant of this reduced efficacy.*

Data Quality and Integrity

Site monitoring visits for D2311 were conducted by two companies independent of Novartis, (b) (4), and (b) (4) at sites within the United States and by Novartis field monitors at sites outside the United States until database lock. Monitoring visits occurred regularly during the entire trial duration. The findings used to determine the ARR are entirely dependent on accurate identification and assessment of a potential relapse. The interval from patient symptom onset to a clinical assessment can affect whether a relapse is confirmed, or not confirmed, in a study.

On March 11, 2018, an Information Request was sent to Novartis requesting audit trail data related to all relapses, confirmed and unconfirmed. There were a specific queries regarding the durations between relapse onset and relapse data entry into the database, and the duration between relapse onset and confirmation. Novartis responded that "For the 181 relapses, the median duration of time between the start of a relapse and the recording of the first entry of data for the 'Summary of MS Relapse' CRF page was 28.0 days (mean 58.1 days; range 1 day to 595 days). Approximately half (56.4%) of the relapses were initially reported within 30 days and

the majority (87.3%) were reported within 90 days. A total of 11 relapses (6.1% of all relapses; 5 in fingolimod group and 6 in the IFNB-1a group) were reported more than 6 months after the start date of the relapse event." Regarding the other audit trail queries, Novartis replied, "[M]edian duration of time between the start of any relapse (confirmed or unconfirmed) and the recording of the first entry of data relating to the 'Y/N' confirmation in the CRF page was 28.0 days (mean 58.2 days; range 1 day to 595 days;). Approximately half (55.8%) of the relapses were initially reported within 30 days and the majority (87.3%) were reported within 90 days. Eleven relapses (6.1% of all relapses; five in fingolimod group and six in the IFNB-1a group) were reported more than 6 months after the start date of the relapse event.... [T]he median duration of time between the relapse confirmation date for confirmed relapses and the recording of data in the CRF page was 20.0 days (mean 45.3 days; range 1 day to 589 days). Approximately two thirds (67.1%) of the relapse confirmations were initially reported within 30 days of the confirmation date, and the majority (90.4%) were reported within 90 days. A total of 7 relapse confirmation dates (4.8% of confirmed relapses; 3 in fingolimod group and 4 in the IFNB-1a group) were recorded in the CRF more than 6 months after the actual confirmation date..... [T]he median number of days from the time of relapse start date until the date of relapse confirmation was 4.0 days (mean 6.7 days; range 1 to 50 days) which is in line with the study protocol for confirmation of relapses.... There are two roles (investigator and site user) able to enter data into the CRF and also to make data changes in the CRF. The data shows that both roles made changes to the CRFs with no apparent pattern observed and the percent of changes made across the key fields was highly variable (ranging from 11.1% to 76.5% for investigator changes and 23.5% to 100% for site user changes). The most common reason for making a change to relapse start date and to relapse confirmation date was 'derivation'. A derivation is the process for merging fields when a site made a change to either the 'day', 'month' or 'year' field for a given date entry. Once the change was made by the site then a derivation by the system was conducted to merge the 3 separate fields into a single derived date field containing all three of the fields. Other common changes across all key data fields included validation status changed, data entry errors, removed or response added. The majority of EDSS assessments that are used for confirmation of a relapse are not done at scheduled visits (typically conducted at unscheduled visits within a few days after the start date of a relapse), and... provides a summary of the number of changes to EDSS assessments by visit and treatment. The mean number of changes to the EDSS overall score at a given visit ranged from a low of 0.03 changes at Visit 10 to a high of 0.17 for unscheduled EDSS assessments. The data was generally comparable between treatment groups."

> *Reviewer Comment: The audit trail for the relapse data revealed latencies of up to 589 days between confirmation of a relapse and its recording in the CRF page. Novartis reported a lower rate of corrections in the fingolimod treatment group's EDSS data (9 vs. 25 total changes) and in the relapse severity assessment (38 vs 92 total changes). Given the concerns regarding the discrepancy between the fingolimod and interferon groups' relapse confirmation rates, the presence of long delays in data entry, and different data*

correction rates, introduce the possibility that the handling of the data from study site to database entry introduced potential bias that was manifested as a nearly 20% difference between the two treatments' relapse confirmation rates.

Table 24: Sponsor Table: Sensitivity Analysis of MS Relapses, Full Analysis Set, Study D2311

	Fingolimod		Interferon β-1a		
	N	**ARR (adjusted*)**	**N**	**ARR (adjusted*)**	**% reduction**
All Confirmed Relapses	107	0.122	107	0.675	81.9%
All Relapses (Confirmed & Unconfirmed)	107	0.181	107	0.802	77.4%
Confirmed Relapses (excluding patients with potentially unblinding protocol deviations)	94	0.123	101	0.729	83.1%
Confirmed Relapses (excluding Patients in interferon β-1a treatment arm with interferon-β neutralizing antibodies)	107	0.123	97	0.666	81.5%

Source: CSR Tables 14.2.-1.1a-d

*Obtained from fitting a binomial regression model adjusted for treatment, region, pubertal status, and number of relapses within prior two years

Reviewer Comment: The stability and sustained robustness in this sensitivity analysis mitigates some of the aforementioned concerns about data handling and the higher failure rate of confirmation in the fingolimod group.

Efficacy Results – Secondary and other relevant endpoints

New/Newly Enlarging T2 Lesions

The key secondary efficacy endpoint was the annualized rate of new/newly enlarging T2 (n/neT2) lesions in pediatric patients with RMS for up to 24 months. At baseline, there were no differences between the treatment arms with respect to T2 lesions.

Table 25: Reviewer Table: New or Newly Enlarging T2 Lesions, Full Analysis Set, Study D2311

	Fingolimod	**Interferon β-1a**	

	Baseline Lesion Data		Percent Rate Reduction in Annualized Rate of New Lesions
n	107	106	
Number of Lesions (baseline total)	4485	4832	
Mean (SD)	41.92 (30.33)	45.59 (34.01)	
Median	31.00	31.50	
Range	2-126	4-145	
New Lesions Month 0 to 6			
n	104	100	
Mean (SD)	5.31 (7.21)	12.23 (17.29)	
Median	2.50	6.00	
Range	0-45	0-104	
Adjusted Annualized Rate of New Lesions Mean (95% CI)*	9.29 (7.43-11.62)	17.80 (14.32-22.12)	47.8%
New Lesions Month 0 to 12			
n	98	90	
Mean (SD)	5.95 (7.75)	13.28 (15.01)	
Median	3.00	7.5	
Range	0-43	0-75	
Adjusted Annualized Rate of New Lesions Mean (95% CI)*	5.18 (4.24-6.33)	10.44 (8.57-12.72)	50.4%
New Lesions Month 0 to 18			
n	71	53	
Mean (SD)	8.10 (10.00)	15.83 (16.23)	

Median	4	11	
Range	0-55	0-80	
Adjusted Annualized Rate of New Lesions Mean (95% CI)*	5.14 (4.10-6.44)	8.48 (6.57-10.94)	39.4%
New Lesions Month 0 to 24			
n	35	24	
Mean (SD)	7.97 (8.50)	21.83 (21.64)	
Median	3	5	
Range	0-32	0-78	
Adjusted Annualized Rate of New Lesions Mean (95% CI)*	3.48 (2.49-4.85)	10.97 (7.46-16.13)	68.3%
New Lesions Month 0 to End of Study			
n	106	102	
Number of New Lesions (trial total)	867	1785	
Mean (SD)	8.18 (11.19)	17.50 (20.14)	
Median	3	10	
Range	0-65	0-104	
Unadjusted Annualized Rate of New Lesions Mean	4.05	8.75	53.7%
Adjusted Annualized Rate of New Lesions Mean (95% CI)*	4.39 (3.62-5.34)	9.27 (7.66-11.21)**	52.6%

Source: AMRI.xpt, CSR Table 14.2-3.1, Table 14.2-3.2, Table 14.2-3.3

*Obtained from fitting a binomial regression model adjusted for treatment, region, pubertal status, and number of relapses within prior two years
** $p<0.001$

Not all patients had assessments of new or enlarging T2 hyperintense lesions at baseline, 6, 12, 18, and 24 months. There were 58 patients in the fingolimod treatment group and 43 patients

in the interferon β-1a arm who had a complete sequence of scans at the five protocol-indicated time points. An analysis limited to population of patients who did have all five scans is provided below. The ARR generated in this analysis fall within the 95% confidence intervals for the ARR derived from Novartis's methodology.

Table 25: Reviewer Table: New or Newly Enlarging T2 Lesions, Full Analysis Set, Study D2311

New/Newly Enlarging T2 Lesions Months 6, 12, 18, and 24			
	Fingolimod	**Interferon β-1a**	
N	58	43	
Mean (SD)	9.35 (10.61)	15.69 (17.91)	
Median	6.00	8.50	
Range	0-65	0-80	**Percent Rate Reduction**
Unadjusted Annual Mean	4.68	7.85	40.4%

Source: AMRI.xpt By (STYSID1A.xpt, ACTDSC1A.xpt, RSLDCR1A.xpt, RSLVAL1N.xpt)

> *Reviewer Comment: In patients treated with fingolimod, Novartis results demonstrate that the number of new and enlarging T2 lesions and the T2 lesion ARR were reduced by at least 40% at all assessed time points and by approximately 50% overall. An ARR based on events and time alone agrees on a reduction of approximately 40%.*

Number of Gadolinium (Gd)-enhancing T1 lesions as detected by brain MRI up to 24 months

The number of Gd-enhancing T1 lesions was assessed at Months 6, 12, 18, and 24 months, respectively. The percentage of patients with a reduction in Gd-enhancing T1 lesions and the proportion free of Gd-enhancing T1 lesions was reduced by both treatments, with fingolimod showing significant reductions in both percentages and in proportion free of all Gd-enhancing T1 lesions. The observed effects of both treatments were sustained through Month 24. Gd-enhancing T1 data gathered within 30 days of treatment with corticosteroids was excluded from all analyses.

Table 26: Reviewer Table: Number of Gd-enhancing T1 Lesions by Time Point and Treatment, Full Analysis Set, Study D2311

	Fingolimod			Interferon β-1a		
	N	**Unadjusted Mean (SD)**	**Reduction Compared to Baseline**	**N**	**Unadjusted Mean (SD)**	**Reduction Compared to Baseline**
Baseline	106	2.6 (6.0)	--	106	3.2 (6.5)	--
Month 6	102	0.4 (1.7)	84.6%	92	1.7 (3.7)	46.9%
Month 12	95	0.5 (1.3)	80.8%	88	1.5 (2.9)	53.1%
Month 18	70	0.5 (1.2)	80.8%	49	1.5 (2.5)	53.1%
Month 24	35	0.3 (1.08)	88.5%	22	3.3 (5.5)	-3.2%
End of Study	106	0.5 (1.5)	80.8%	101	2.2 (4.6)	31.3%

Source: AMRI.xpt

Table 27: Sponsor Table: Number of Gd-enhancing T1 Lesions by Time Point and Treatment, Full Analysis Set, Study D2311

	Fingolimod		Interferon β-1a		
	N	**Adjusted Mean (95% CI)**	**N**	**Adjusted Mean (95% CI)**	**Relative Reduction**
Month 6	102	0.287 (0.171-0.485)	92	1.044 (0.683-1.597)	72.5% (p<0.001)
Month 12	95	0.457 (0.283-0.736)	88	1.025 (0.665-1.580)	55.5% (p<0.014)
Month 18	70	0.384 (0.223-0.661)	49	0.799-2.256)	71.4% (p=0.001)

Month 24	35	0.195 (0.070-0.542)	22	3.695 (1.621-8.423)	94.7% (p<0.001)
End of Study	106	0.436 (0.313-0.608)	101	1.282 (0.934-1.758)	66.0% (p<0.001)

Source: CSR Table 14.2-4.1

Reviewer Comment: Patients in the fingolimod group had a sustained relative reduction in the number of T1 Gd-enhancing lesions of at least 50% throughout the study. The analysis of the unadjusted means fall within the 95% confidence intervals of the means provided by Novartis using analyses adjusted for the stratification variables.

Table 28: Sponsor Table: Proportion of Subjects Free of Gd-enhancing T1 Lesions by Time Point and Treatment, Full Analysis Set, Study D2311

	Fingolimod	**Interferon β-1a**	
	Number of patients free of T1 Gd-enhancing lesions/number of patients with available scan		**Significance**
Baseline	47/106 (44.3%)	59/107 (55.1%)	
6 months	83/102 (81.4%)	57/92 (62.0%)	p=0.001
12 months	77/95 (81.1%)	48/88 (54.5%)	p<0.001
18 months	56/70 (80.0%)	25/49 (51.0%)	p<0.001
24 months	30/35 (85.7%)	10/22 (45.5%)	p=0.002
End of Study	82/106 (77.4%)	54/101 (53.5%)	p<0.001

Source: CSR Table 14.2-4.3

Review Comment: After six months of fingolimod therapy, the percentage of patients free of Gd-enhancing lesions nearly doubled. This improvement is especially noteworthy considering the imbalance in GD-enhancing lesions favoring interferon β-1a observed at baseline. Approximately half of the patients in the interferon β-1a treatment group were free of Gd-enhancing T1 lesions at baseline with little variance across the duration of

treatment; there was an apparent treatment effect of fingolimod on inflammatory lesions.

Time to Onset of First Protocol-defined Relapse and Proportion of Patients Without a Protocol-defined Relapse at 24 months

For patients with a protocol defined relapse, the time to first relapse was calculated as the start date of the relapse – 1st Core Phase dose date +1 day. If a patient did not have a relapse, their relapse interval was the same as their time in study interval used to calculate the ARR as above.

There were 15 patients (14%) in the fingolimod treatment group with at least one protocol-defined relapse, and there were 58 patients (54.2%) in the interferon β-1a treatment group with at least one protocol-defined relapse.

Table 29: Reviewer Table: Time to First Relapse, Full Analysis Set, Study D2311

	Time to First Relapse (Days)					
	n	**Mean**	**Standard Deviation**	**Median**	**Min**	**Max**
Fingolimod	107	549	214	608	9	769
Interferon β-1a	107	364	252	440	2	747

Source: AREL.xls, RELTM1

Table 30: Sponsor Table: Characteristics of First in Study MS Relapses, Full Analysis Set, Study D2311

	MS Relapse Characteristics	FTY720 N=107 n (%)	IFNß-1a N=107 n (%)
Confirmed relapses	Severity		
	Mild	3 (2.8)	7 (6.5)
	Moderate	7 (6.5)	27 (25.2)
	Severe	5 (4.7)	23 (21.5)
	Affecting daily activity		
	Yes	8 (7.5)	38 (35.5)
	No	7 (6.5)	20 (18.7)
	Hospitalization		
	Yes	3 (2.8)	20 (18.7)
	No	12 (11.2)	38 (35.5)
	Recovery as assessed by primary investigator		
	None	0 (0.0)	3 (2.8)
	Partial	4 (3.7)	20 (18.7)
	Complete	11 (10.3)	34 (31.8)
	Steroid treatment		
	Yes	13 (12.1)	56 (52.3)
	No	2 (1.9)	2 (1.9)

Source: Table 14.2-1.6a Clinical Study Report

Table 31: Sponsor Table: Characteristics of All Confirmed MS Relapses, Full Analysis Set, Study D2311

	MS Relapse Characteristics	FTY720 N=107 n/M (%)	IFNß-1a N=107 n/M (%)
Confirmed relapses	Severity		
	Mild	5/ 25 (20.0)	19/120 (15.8)
	Moderate	13/ 25 (52.0)	67/120 (55.8)
	Severe	6/ 25 (24.0)	32/120 (26.7)
	Missing	1/ 25 (4.0)	2/120 (1.7)
	Affecting daily activity		
	Yes	14/ 25 (56.0)	74/120 (61.7)
	No	11/ 25 (44.0)	46/120 (38.3)
	Hospitalization		
	Yes	6/ 25 (24.0)	38/120 (31.7)
	No	19/ 25 (76.0)	82/120 (68.3)
	Recovery as assessed by primary investigator		
	None	0/ 25 (0.0)	3/120 (2.5)
	Partial	5/ 25 (20.0)	27/120 (22.5)
	Complete	19/ 25 (76.0)	85/120 (70.8)
	Missing	1/ 25 (4.0)	5/120 (4.2)
	Steroid treatment		
	Yes	21/ 25 (84.0)	105/120 (87.5)
	No	4/ 25 (16.0)	15/120 (12.5)

Source: Table 14.2-1.6b

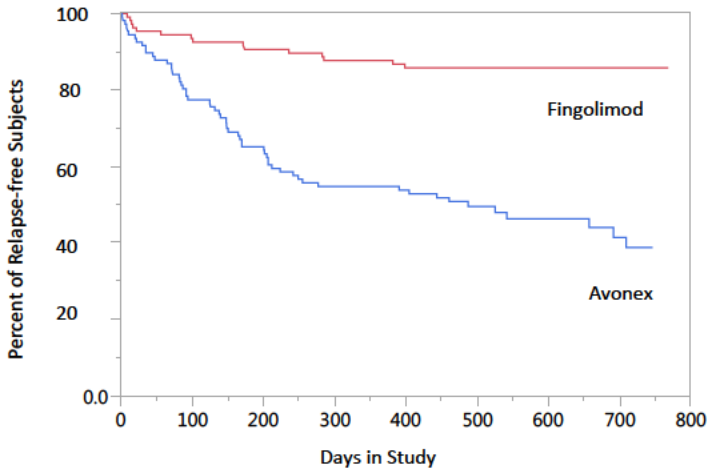
Reviewer Comment: The first relapses experienced by patients in the fingolimod

treatment group of Study D2311 occurred at a longer time after first treatment dose, in fewer patients, and with a lower proportion designated as "severe" (5/15 vs. 23/58) than first relapses experienced by patients in the interferon β-1a treatment arm. The first relapse in study for fingolimod patients were not different in major assessed characteristics from all confirmed relapses recorded in fingolimod-treated patients.

Kaplan-Meier Analysis

The proportion of patients without a relapse using a Kaplan-Meier model is shown in Figure 4. There is a statistically significant difference in the proportion of relapse-free patients between the treatment groups in favor of fingolimod. The result is comparable to the findings reported by Novartis.

Figure 3: Reviewer Figure: Kaplan-Meier Curve: Percentage of Subjects Relapse-Free (Confirmed Relapses) Across Study Week (RELTM1) by Treatment



Test	Chi Square	DF	Probability > Chi Square
Log-rank Test	39.0553	1	$p<0.0001$
Wilcoxon	33.2339	1	$p<0.0001$

	Confirmed Relapses		No Confirmed Relapses	
	n	% of total	n	%
Fingolimod	15	14.0%	92	86.0%
Interferon β-1a	58	54.2%	49	45.8%
Combined	73	34.1%	141	65.9%

Source: AREL.xpt analysis on RLCNFNUM, Clinical Study Report Table 16.1.9-1.6

Reviewer Comment: The separation between the curves for the treatment groups begins after 30 days of treatment and continues throughout the duration of study monitoring. This 30-day threshold of improvement was noted for the Gd-enhancing T1 lesion reduction. It is mechanistically plausible and evidently predictive that a reduction of active inflammatory lesions would precede a reduction in paroxysms of clinically-evident neurological deterioration.

Last EDSS Score

A comparison of the last EDSS value on treatment by treatment group is shown below. The last EDSS value for fingolimod patients is lower (difference -0.51, p<0.0006) than the last EDSS score for patients treated with interferon β-1a. At baseline, the two means were not statistically different (p<0.22).

Table 32: Sponsor Table: Last EDSS Score by Treatment Group, Full Analysis Set, Study D2311

	Month 24/End of Study EDSS Score					
	n	**Mean**	**Standard Deviation**	**Min**	**Max**	**Median**
Fingolimod	105	1.23	1.21	0	8.50	1.00
Interferon β-1a	107	1.84*	1.32	0	6.0	1.50

Source: Table 14.2-2.1
*p<0.0006, unpaired t-test

Table 33: Sponsor Table: EDSS Change from Baseline to End of Study/Last Recorded EDSS, Full Analysis Set, Study D2311

	Baseline EDSS Mean (SD)	**End of Study EDSS Mean (SD)**	**Change (SD)**	**% Change from Baseline**
Fingolimod (n=105)	1.46 (1.14)	1.23 (1.21)	-0.23 (0.89)	-15.8%
Interferon β-1a (n=107)	1.61 (0.89)	1.84 (1.32)	+0.22 (1.16)	+13.7%

Source: Table 14.2-2.1

Reviewer Comment: Treatment with fingolimod significantly reduced the mean EDSS value by 15.8% for patients compared to their baseline scores. This finding suggests that reducing the frequency of relapses may be associated with reduced disability and strengthens the post hoc finding of a 3-month confirmed disability improvement associated with fingolimod treatment.

Dose/Dose Response

This trial used two doses of fingolimod, 0.25 mg, and 0.5 mg. The evidence and justification or dose/dose response of the 0.5 mg dose was submitted with the original NDA. Formal dose response testing was not performed with the 0.25 mg dose because of limited data. There is an ongoing study of 0.25 mg compared to 0.5 mg fingolimod in adults with RMS (NCT01633112) that will provide additional findings for future consideration.

The key PD effect of fingolimod, established in prior adult trials, is a dose-dependent reduction in the peripheral lymphocyte count mediated by fingolimod's effects on the S1P receptors. The effects of fingolimod on lymphocyte count have been established 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 of 80-90% from baseline lymphocyte count is achieved in a multiple dose range from 2.5 mg to 40 mg. In prior MS studies in adults, dose-dependent reductions in the lymphocyte count were observed for doses ranging from 0.5 mg and 5 mg. These adult exposure dose- responses were used to create initial modeling of the potential pediatric dose-response with respect to lymphocyte count, as well as the Primary and key Secondary outcomes, the ARR, and new/newly enlarging T2 lesions, respectively.

The doses selected in Study D2311 were based on achieving the same fingolimod-P exposure as an adult receiving 0.5 mg daily who had a median fingolimod-P steady state concentration of 1.353 ng/mL. The pediatric PK model estimated fingolimod-P (the sole active metabolite of fingolimod) steady state concentration range (0.249, 1.96) ng/mL, which included the 0.25 mg treated pediatric patients, were mostly above the pediatric relapse and T2 lesions exposure-response model estimated IC50s (0.382 ng/mL and 0.197 ng/mL, respectively) as well as the lymphocyte IC50 (0.287 ng/mL).

> *Reviewer Comment: The small sample size precluded a thorough analysis of dose-response for the 0.25 mg dose. Analysis of this subset of patients' efficacy data suggested a decrease in ARR, and the fingolimod-P concentrations in three of the nine patients receiving this dose were below the targeted presumed effective serum level established at the 0.5 mg dose. The full extent of the pharmacodynamic and relevant clinical effects of the 0.25 mg dose is presently undetermined. Please refer to the Clinical Pharmacology review by Drs. Dimova, Krudys, and Men for further discussion of the 0.25 mg PK and PD data.*

Following administration of 0.5 mg per day of FTY720 in a pediatric population, the typical steady-state FTY720-P concentration for a body weight of 70 kg (0.978 ng/mL) was below the adult target FTY720-P steady-state concentration level (median: 1.35 ng/mL, (90% CI: 0.62, 3.1)) but within the 90% CI around the median of the adult target FTY720-P steady-state

concentration. On average, the concentrations following 0.25 mg in patients with body weight ≤ 40 kg was above 0.9 ng/mL (*i.e.,* 65% of the target exposure predicted from adult patients); the fingolimod-P concentrations were above 0.9 ng/mL in 6 of 9 patients at the Month 1 PK assessment. The typical steady-state FTY720-P concentration in pediatrics was also higher than the 65% relative bound (0.878 ng/mL) of the adult target FTY720-P steady-state concentration level. The steady-state FTY720-P concentrations were dose proportional following 0.25 mg and 0.50 mg capsule formulation of FTY720 in the pediatric population.

Since the serum lymphocyte count in children is known to be higher than in adults, the model used for estimation of effects account for the fact that the baseline (pre-treatment) lymphocyte count would be an estimated 17.2% higher in pediatric patients compared to the adult population. The values of Imax and IC50 in pediatric patients consequently were estimated with a large uncertainty but after adjustment using pediatric study data, these values were not found to be statistically different from the Imax and IC50 values found in adults. The magnitude of the observed differences was also not clinically relevant. The IC50 estimate from the model was predicted to be 12% lower in pediatric patients compared to adult patients; however, the maximum inhibition generated from the study results was estimated at 81% in adult male patients and 79% in pediatric male patients. Overall, the Imax estimate was 9.7% higher in females compared to males but the difference did not appear clinically relevant. The baseline lymphocyte count increased very slightly with increasing weight. A 10-kg increase in weight (*e.g.*, from 70 to 80 kg) would translate into a 2% increase in lymphocyte count. This effect of body weight on baseline lymphocyte count was not considered clinically significant.

The adult exposure-response model predictions of the pediatric ARR and mean new and newly enlarging T2 lesions at 12 months were higher and lower, respectively, than the observed pediatric ARR and mean T2 lesions from Study D2311, suggesting that the adult exposure-response models required updating to account for the differences. Updated exposure-response models based on pooled adult and pediatric data described the data better than the adult model alone. The revised modeling using all the Core Phase pediatric data showed results that there was little evidence of any difference in the exposure-response relationships between adult and pediatric patients after accounting for differences in the intercept parameters, *i.e.*, the intercept of the T2 lesion exposure-response model and the intercept transition rate from a relapse state to a non-relapse state.

Durability of Response

Patients who permanently discontinued study drug for any reason or who elected not to enter the OLE trial were required to return at 3 months for a safety examination and MRI scans (see Table 3). In the fingolimod treatment group, absolute lymphocyte count returned to within a normal range for 80% of patients within 90 days after study drug discontinuation. The data regarding relapses after last dose of study drug are limited due to there being few confirmed

relapses in either group (0 relapses in patients from the fingolimod treatment group, 2 confirmed, 4 unconfirmed in patients from the interferon β-1a treatment group). Novartis provided no statistical analysis of these results. A full account of data related to relapses and MRI findings in the follow-up patient population will be reported in the forthcoming OLE study report.

> *Review Comment: The small number of relapses after study drug discontinuation precludes a definitive comment on durability or rebound. Information about durable drug and rebound effects are of interest as there has been a suggestion of rebound, manifesting as more severe relapse with disability and markedly increased inflammatory MRI activity, in a subset of adult patients with RMS who discontinue fingolimod. The OLE trial data will provide more information regarding the possibility of these important effects in the pediatric RMS population.*

Persistence of Effect

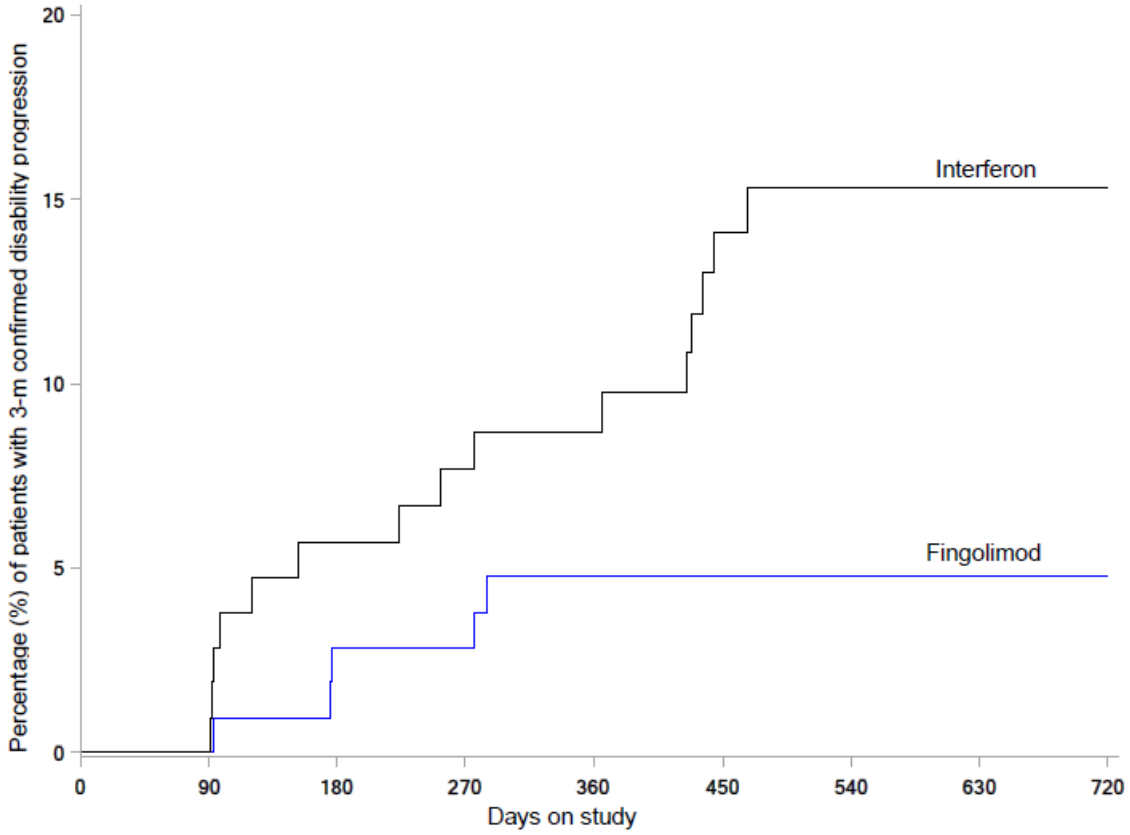
In trial D2311, the reduction in ARR for patients in the fingolimod treatment group was sustained throughout the course of the 24-month study. The reduction in new and newly enlarged T2 lesions and in Gd-enhancing lesions for patients in the fingolimod treatment group were observed at 6 months and persisted with small variation through Month 24. Additional information about the persistence of efficacy will be forthcoming when data from the 5-year OLE of this trial and data from trial NCT01633112 comparing 0.5 and 0.25 mg doses of fingolimod in adult RMS become available. Based on findings from the extension trials of 0.5 mg fingolimod taken for five years or longer in adult patients with RMS, if the pediatric population with RMS responds like adults with RMS, the expectation is that the benefits of reduced ARR and T2 lesion burden will persist in the approximately 70% of pediatric patients.

Additional Analyses Conducted on the Individual Trial

Kaplan-Meier Analysis of 3-month CDP

Novartis submitted a *post hoc* analysis result that fingolimod significantly delayed the time to 3-month confirmed disability progression (CDP) compared to interferon β-1a (log-rank test, p=0.015). The estimate of the percentage of patients free of 3-month CDP up to Month 24 of treatment was higher in the fingolimod treatment group (95.2%) compared to the interferon β-1a treatment group (84.7%). A Cox proportional hazard model indicated a risk reduction of 77.2% in 3-month CDP over 24 months for the fingolimod treatment group compared with the interferon β-1a treatment group (Hazard ratio=0.23, p=0.007).

Figure 4: Sponsor Figure: Kaplan-Meier Plot of Time to 3-month Confirmed Disability Progression, Full Analysis Set, Study D2311



Reviewer Comment: The 3-month CDP is considered a clinically meaningful and acceptable study endpoint in RMS trials. However, the 3-month CDP finding in this pediatric trial was based on a post hoc *analysis of Study D2311 data and was not a defined primary, secondary, or exploratory endpoint. However, there does appear to be a potential impact of reducing ARR on EDSS scores because I noted in my analysis a statistically significant reduction in final study EDSS for fingolimod-treated patients. Therefore, this reviewer would suggest that the 3-month CDP finding is supportive of the efficacy of fingolimod in treating pediatric RMS as defined by the statistically significant findings of the primary and secondary endpoints of the study as well as additional analysis performed by this reviewer. I therefore conclude that this disability finding should not be advanced with the same confidence and receive the same primacy as the pre-determined study endpoints. Pediatric patients with RMS accumulate disability at a slower rate than adult patients with RMS (Banwell, 2014); a three-month window may not be adequate time to assess treatment impact on long-term, permanent disability. Furthermore, there are additional concerns with the comparability of the EDSS thresholds used to define this 3-month CDP to those*

definitions used in adult RMS trials. Please refer to the Biostatistics review authored by Drs. Yan, Jin, and Hung for further discussion of this analysis.

Brain Volume Change

Treatment with fingolimod resulted in a significant reduction of the annual rate of brain atrophy in fingolimod-treated patients from baseline up to Month 24 (-0.48 VS -0.80) compared with interferon β-1a (p =0.014).

Reviewer Comment: Brain atrophy is not definitively correlated with how patients with RMS function, feel, or survive. The Division does not accept brain atrophy change as a valid endpoint for clinical trials because it does not describe a clinically meaningful outcome for patients with RMS. Furthermore, the brain volumes in the age ranges encompassed within this pediatric study are undergoing significant growth and development and are not static values. The dynamic nature of brain volumes in pediatric patients makes interpretation of brain volume changes in this study particularly problematic.

Cognitive Testing

Five cognitive tests, including the Symbol Digit Modalities Test (SDMT), Beery Visual- Motor Integration (VMI), Trail Making Test (TMT), Selective Reminding Test (SRT), Delis-Kaplan Executive Function System (DKEFS), were administered as part of the cognitive testing battery recommended for inclusion in pediatric MS clinical trials. At all sites, patients were administered the SDMT and VMI. In addition, per site agreement the TMT, SRT, and DKEFS were administered. Testing was performed at baseline, Month 12, and Month 24/EOS. The results of the cognitive testing battery showed no clinically meaningful differences at Month 12 or Month 24/EOS compared to baseline between the fingolimod and interferon β-1a groups when assessed using the SDMT, VMI, TMT, SRT, or the DKEFS.

Reviewer Comment: The cognitive results between the groups did not reveal statistically significant differences between groups. Over time, patients in both treatment arms demonstrated shorter (improved) SDMT and TMT performance times, indicating a possible learning effect. The fact that both treatment groups are able to improve their performance on different cognitive tasks may be evidence that the learning and memory impairments reported in adult patients with RMS are not as prominent in pediatric patients with RMS.

Pediatric Quality of Life Inventory

The Pediatric Quality of Life (Peds QL) parent or patient reported mean score values for all parameters improved *(i.e.*, numerically higher EOS value) in patients treated with fingolimod compared to worsening (*i.e.*, numerically lower value) for all parameters in patients treated with interferon β-1a. Consistent improvements from baseline to EOS visit were observed in the Peds QL scores, including Physical Health, Psychosocial Health, and Total Scale Summary Scores in the fingolimod-treated patients, compared to consistent worsening observed in the interferon β-1a treated patients, as assessed by parent and self-reported Peds QL score.

Reviewer Comment: The difference in the Peds QL scores between the two treatment groups is potential validation of the efficacy of fingolimod, but this discrepancy also provides potential evidence of patients and their caregivers being aware of their treatment condition and having differential expectations of treatment.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy across Trials

There was only one efficacy pivotal trial (D2311) under consideration in this application to support approval of fingolimod in the treatment of pediatric RMS. The prior basis for prior approval of fingolimod for the indication RMS was based on data from several controlled trials in adult patients with RMS.

Reviewer Comment: This pediatric trial demonstrated a larger reduction in ARR (82% versus 52%), in the mean number new and newly enlarged T2 lesions (55% versus 25%), and in the mean number of Gd-enhancing T1 lesions (67% vs. 55%) than the adult trial comparing fingolimod to interferon β-1a that supported approval of fingolimod for treating adults with RMS.

7.1.1. Primary Endpoints

See Section 6.1.2 for an assessment of the Primary Endpoint findings from Study D2311.

7.1.2. Secondary and Other Endpoints

See Section 6.1.2 for assessments of the Secondary endpoints' findings from Study D2311.

7.1.3. Subpopulations

See Section 6.1.2 for an analysis of subpopulations from Study D2311.

7.1.4. Dose and Dose-Response

See Section 6.1.2 for dose and dose-response assessments from Study D2311.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

See Section 6.1.2 for duration and durability assessments from Study D2311.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

There is a need to better characterize the efficacy of the 0.25 mg fingolimod dose. An ongoing active clinical trial comparing 0.25 mg to 0.5 mg fingolimod (NCT01633112) with an active comparator in adult patients with RMS should provide additional data regarding the 0.25 mg dose on preventing MS relapse and impact on MRI disease markers relative to the 0.5 mg dose.

The improvement in 3-month CDP claim generated by a *post hoc* analysis should be tested as a primary or secondary pre-determined efficacy endpoint in an adequate, controlled trial conducted in pediatric patients with RMS.

7.2.2. Other Relevant Benefits

See Section 6.1.2 for other relevant benefits.

7.3. Integrated Assessment of Effectiveness

A reduction in the Annualized Relapse Rate is noted in patients ages ≥ 10 years to < 18 years with RMS treated who were with fingolimod in a single adequate and well-controlled trial.

Reductions in several MRI measures of RMS disease activity are noted for patients ages ≥ 10 years to < 18 years with RMS who were treated with fingolimod within a single adequate and well-controlled pediatric trial.

8. Review of Safety

8.1. Safety Review Approach

Novartis is seeking approval for pediatric patients with RMS in a single adequate, controlled study submitted as a supplement to NDA 22527. Fingolimod has approval in adult patients for

the indication of RMS based on several adequate, controlled studies (D2301, D2302, and D2309) conducted in adult patients. Novartis presented these adult safety data along with safety findings from a single adequate, controlled study in pediatric patients.

This safety review will focus primarily on the experience with pediatric patients with RMS in Study D2311. The safety data from trials conducted for the indication of treatment of adult RMS are intended to support the pediatric RMS safety data. The data from the adult trials are robust but derived from a fundamentally different patient population with respect to age and MS disease characteristics (see Section 2.1).

Novartis seeks approval for the treatment of RMs in patients aged ≥ 10 years and < 18 years based on a results from a randomized, 24 month flexible duration, double-blind, double-dummy, active controlled Phase 3 study conducted in 214 patients aged ≥ 10 years to < 18 years. In this trial, 107 pediatric patients were exposed to fingolimod. After completion of the controlled phase of the trial, patients could enroll in an OLE trial. After completion or withdrawal, patients who did not enter the OLE were obligated to return for a 3-month safety follow-up.

Novartis provided a safety data set defined by the 214 patients in Study D2311 in the Core Phase who received at least one dose of study treatment. Novartis additionally provided a pooled set of safety data from three prior submissions (Studies D2301, 2302, and D2309) used to support the adult RMS application. These studies describe safety data from 1212 exposed adult patients. The adult data will be presented alongside the pediatric safety data, but the primary analysis will remain focused on the findings pediatric safety data set.

Fingolimod 1.25 mg was studied in a small (N=7) uncontrolled open-label study in adolescent patients for the indication of prevention of kidney allograft rejection (Study A0115). Study A0115 will not be discussed at length as Study A0115 was a prematurely discontinued study to assess pharmacokinetics in adolescents with renal transplants and did not produce substantial safety findings.

In this review, I summarize information from Novartis's presentations, and, when needed, supplement them with analyses that I conducted using data provided in Section 12 of the CSR, the Integrated Summary of Safety, the 120-day Safety Update, and the data sets provided by Novartis. I performed analyses using the JMP software program. For adverse events, the adult safety data are presented to demonstrate commonly reported events and infrequent events of potential concern to inform the presentation of adverse events from the pediatric trial.

Fingolimod is a first-in-class S1P receptor modulator that prevents lymphocyte egress from lymph nodes. This drug effect lowers the circulating lymphocyte count and presumably reduces the number of auto-reactive lymphocytes available to migrate to the CNS where they would

contribute to the inflammatory pathology associated with MS. The prior adult submission and post marketing experience have identified several adverse events and risks associated fingolimod use in adults. These risks include first dose bradycardia and cardiac conduction block, macular edema, reductions in pulmonary function test parameters (FEV1, DLCO), serious infections including opportunistic infections seen in immune compromised patients, and cutaneous malignancies. Additional general concerns with introducing this treatment into the pediatric population include impacts on growth and sexual maturity.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Safety Population Exposure

Novartis defined the Safety Population as "all patients who received at least one dose of study drug." The Safety Set therefore is identical to the Full Analysis set, which included all patients who were randomized and who received at least one dose of study drug. A single patient randomized into Study D2311 did not receive any study drug treatments and is excluded from both the Full Analysis and Safety sets.

Fingolimod was administered as a single oral dose with directions to be taken daily. Compliance with study treatment is discussed in Section 6.1.2. All patients in the fingolimod treatment group were exposed to one of the two daily doses (0.25 mg and 0.5 mg) of fingolimod for which Novartis is seeking approval. The 0.5 mg dose is approved currently for the treatment of RMS in adult patients.

The submitted patient exposure numbers demonstrate that exposure in Study D2311 met the ICH guidelines for chronically administered medications (*i.e.*, n=100 for 1 year). Novartis identified a total of 107 pediatric patients exposed to fingolimod at any dose, and 102 pediatric patients exposed to any dose for ≥ 360 days. The following table summarizes the exposure to fingolimod in this pediatric development program and in other studies conducted that included any patients < 18 years old.

Table 34: Reviewer Table: Safety Population, Size and Denominators, all Fingolimod Trials

Safety Database for Fingolimod N= 188 patients age <18 years old			
Clinical Trial Groups	Fingolimod (any dose)	Interferon β-1a	Placebo
Phase 3 Controlled Study for RMS indication in patients ages ≥ 10 to < 18 years old (Study D2311)	107	107	-

Phase 3 Open Label Extension Study for RMS indication in patients ages ≥ 10 to < 18 years old	171	-	-
Phase 3 Controlled Trials for RMS indication in adults (Studies D2301, D2302, and 2309)	1211 (adults) and 1 patient < 18 years*	431 (adults)	773 (adults)
Phase 3 Open Label Extension Trial for adults with RMS (Study D1401)	9**	-	-
Phase 3 Open Label PK and Safety Trial in pediatric renal transplant patients ages 11 to 17 years old (Study A0115)	7	-	-

*A patient in Study D2301 was randomized to treatment at age 17 and therefore is counted in the overall population for pediatric patients < 18 years old.
**A retrospective search of an extension trial database revealed nine patients who received fingolimod treatment who were < 18 years old.

The following table summarizes exposure by duration in Study D2311 and supports the assertion that drug exposure met ICH guidelines.

Table 35: Reviewer Table: Duration of Exposure, Safety Set, Study D2311

	Number of patients exposed to the study drug:					
Dosage	≥ 1 dose	≥ 90 days	≥ 180 days	≥ 360 days	≥ 540 days	≥ 720 days
0.25 mg	n=9	n=6	n=3	n=3	n=2	n=2
0.25 and 0.5 mg doses	n=107	n=105	n=103	n=102	n=74	n=30

The mean duration of fingolimod exposure for the overall population was 600.9 days (median 634 days) (see Tables 11 and 12).

In addition to a summary of the pediatric trial exposure, Novartis submitted person-time observation for the adult RMS population.

Table 36: Sponsor Table: Duration of Exposure to Study Drug by Treatment and Population, Safety Set, Study D2311

Duration of Exposure	**Fingolimod 0.25 mg and 0.5 mg Pediatric Population (D2311) n=107**	**Fingolimod 0.5 mg Adult Population (Studies D2301/D2302/D2309) n=1212**
Mean (SD)	600.9 (149.3)	517.1 (220.6)
Median	634.0	576.0
Patient-Years	176.0	1715.9

≥ 90 days	105 (98.1%)	1153 (95.1%)
≥ 180 days	103 (96.3%)	1110 (91.6%)
≥ 360 days	102 (95.3%)	949 (78.3%)
≥ 540 days	74 (69.2%)	618 (51.0%)
≥ 720 days	30 (28.0%)	374 (30.9%)
≥750 days	2 (1.9%)	41 (3.4%)

Source: Clinical Overview Table 5-2

120 Day Safety Update

Novartis updated the exposure in the trial in a 120-Day Safety Update. The overall exposure in pediatric RMS trials increased from 107 to 171 as patients enrolled in the Core Phase of Study D2311 transitioned into the OLE study. There were 95 patients from the fingolimod treatment arm and 76 from the interferon β-1a treatment arm who enrolled in the OLE study which increased the number of patients with a ≥ 90 day exposure to any dose of fingolimod to 171 patients.

Study A0115

Study A0115 was an open-label, single dose trial of fingolimod 1.25 mg. Seven patients aged 11-17 years old received one dose apiece of fingolimod 1.25 mg.

8.2.2. Relevant characteristics of the safety population:

While estimates vary, between 5-10% of MS presents before age 18 years, with a mean age of onset of approximately 15-16 years old (Jancic *et al.*, 2016). As is the case with most autoimmune diseases, in pediatric MS, there is a marked female preponderance (Renoux *et al.*, 2007). However, the female: male ratio approaches 1:1 below age 12 years (Ramagopalan *et al.*, 2008; Renoux *et al.*, 2007). There are few studies defining the race and ethnicity of pediatric MS cohorts, but it appears that the distribution of patients with pediatric MS mirrors the adult population with MS in that the majority (>70%) of patients with pediatric MS are white of Northern European descent, with Black and Asian children comprising the next most represented groups (Graves *et al.*, 2017).

The exposed population in the Safety set, further characterized by demographic subsets, is presented below.

Table 37: Reviewer Table: Summary of Exposure by Demographic Data, Safety Set, Study D2311

	All Exposure Fingolimod (n and % of total)	**Exposure (Patient-Years)**
All Patients (Safety Set)	107 (100%)	176.0
Age Groups		

Age ≤ 12 years	13 (12.1%)	20.0
Age > 12 years	94 (87.9%)	156.0
Gender		
Female	70 (65.4%)	117.4
Male	37 (34.6%)	58.6
Race		
White	100 (93.5%)	166.0
American Indian or Alaska Native	3 (2.8%)	3.9
Other	2 (1.9%)	3.1
Asian	1 (0.9%)	1.4
Black or African American	1 (0.9%)	1.6
Ethnicity		
Hispanic or Latino	9 (8.4%)	14.4
Not Hispanic or Latino	98 (91.6%)	161.6
Region		
United States	7 (6.5%)	11.7
Rest of the World	100 (93.5%)	164.3

Source: ADMG.xpt

Reviewer Comment: The demographic breakdown is also discussed in 6.1.1. The majority of the patient exposure data are derived from study participants who are over age 15, white, and female. The demographics of Study D2311 are thus adequately reflective of the approval population as pediatric RMS is diagnosed almost exclusively in female teenagers of Northern European descent.

8.2.3. Adequacy of the safety database:

The safety database for Study D2311 is smaller in size and patient number than a comparable database in adults because typically pediatric patients have fewer chronic conditions and because pediatric RMS is a rare disease representing less than 10% of the population of all patients with RMS. The demographic characteristics of the enrolled patients are similar to the intended treatment population although there are few patients who are below age 12, weigh < 40 kg, and are pre-pubertal. The results of the trial may therefore not be as generalizable to the youngest, least mature patients when marketed.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The safety data provided by Novartis appeared reliable and consistent. Novartis responded

appropriately to issues with the data sets in their responses to several Information Requests.

During the course of the review, I was able to replicate the analyses performed by Novartis as presented in the Safety Set. For individual patients, I compared data across several sources and did not find gross discrepancies between datasets, narratives, supplied CRFs, listing, or summary tables.

8.3.2. Categorization of Adverse Events

Novartis used common definitions of AEs and SAEs. Novartis's coding process for verbatim AE terms using MedDRA coded terms was adequate and allowed for accurate estimates of event risks. Novartis's assessment of AEs, and AEs of special interest were also adequate and appropriate.

The protocol defined an adverse event as "the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Study drug includes the investigational drug under evaluation and the comparator drug or placebo that is given during any phase of the study. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy." Novartis included all AEs reported during the Core Phase of the trial as well as events up through three months after last dose of study treatment. MS relapses were not typically noted as AEs. MS relapses which, in the judgment of the investigator, were unusually severe or had unexpected features, were reported as SAEs.

A Serious Adverse Event (SAE) was defined by the study protocol as an event which:

- "is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- is medically significant, *i.e.,* defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (*e.g.,* hospitalization for relapse treatment)
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start

of study drug
- treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- social reasons and respite care in the absence of any deterioration in the patient's general condition"

During the trial, AEs were elicited through open-ended, non-directive questioning. AE verbatim terms were coded to preferred terms using MedDRA v.20.0 for ISS and 120-day Safety Update presentation. AEs were graded in severity as mild, moderate, or severe according to the *National Cancer Institute Common Terminology Criteria fort Adverse Events, Version 4.1*. Novartis presented AE risks as percentages (number of events/number of patients x 100).

The relationship of AEs to the study drug was assessed by the Investigator as suspected or non-suspected.

Infections were analyzed using two definitions. The first definition considered all AEs coded to the medical dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) of infections and infestations. The second definition was broader in that it included all AEs coded to the MedDRA SOC of Infections and Infestations plus any AE from other MedDRA SOCs if a specific pathogen was provided by the investigator on the CRF. Infections were defined as SAEs if the investigator judged an event as serious or, more conservatively, if the infection required intravenous anti-microbial treatment. In addition to the presentation of data by MedDRA SOC, similar AEs were grouped using AE grouping terms and Standardized MedDRA Queries (SMQs). These pre-defined groupings included upper respiratory tract infections, herpes virus associated infections, infectious biliary disorders, sepsis/systemic inflammatory response syndrome (SIRS), and central nervous system (CNS) infections. There is no standard SMQ for opportunistic infections, and thus a set of preferred terms (PTs) was used to identify any potential opportunistic infections for more detailed review.

8.3.3. **Routine Clinical Tests**

General Lab Tests

During the Core Phase of Study D2311, hematology and chemistry lab tests were performed at screening, baseline, Months 0.5, 1, 2, 3, 6,9,12,15,18,and 24; urinalysis was obtained at the Month 6, 12, and 24. The hematology testing included complete blood cell count (CBC) analysis including red blood cell (RBC) count, total and differential white blood cell (WBC) count (basophils, eosinophils, lymphocytes, monocytes, neutrophils, WBC segments), platelet count, hemoglobin, hematocrit, MCV, MCH, MCHC and RBC morphology. Chemistry laboratory testing included sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen (BUN), uric acid, random glucose, albumin, alkaline phosphatase, creatinine, cystatin C, ALT, AST, GGT, amylase, total bilirubin, conjugated bilirubin, total cholesterol, triglycerides, HDL and

LDL. Abnormal laboratory parameters should be repeated for accuracy. A blood sample for liver function tests only (ALT, AST, GGT, alkaline phosphatase, total bilirubin, conjugated bilirubin) was performed at Months 1.5, 4, and 5.

Novartis provided summaries of abnormal laboratory values for each treatment group. Fingolimod lowers serum white blood counts, and Novartis therefore reported serum white blood cell counts relative to baseline (pre-treatment) values. Other chemistry values were assessed relative to baseline and compared to age appropriate pediatric normal values. The ALT and GGT values are interpreted relative to age appropriate baseline rather than comparison to baseline values because the normal range for these tests in children and adolescents increases with increasing age, and so a change from baseline could reflect an expected age-related increase and not a pathological response to treatment.

Table 38: Sponsor Table: Hematology, Chemistry, and Urinary Testing Abnormality Parameters, Study D2311

Hematology	Less Than	Greater Than
Hemoglobin	10 g/dL	20 g/dL
Hematocrit	30 vol%	60 vol%
RBCs	3,300,000/mm^3	6,800,000/mm^3
WBCs	3000/mm^3	15,000/mm^3
Granulocytes (Poly, neutrophils)	1000 mm^3	12000/mm^3
Lymphocytes	200 mm^3	8000 mm^3
Platelets	100,000/mm^3	600,000/mm^3
Chemistry		
Glucose	70 mg/dL	120 mg/dL (fasting) 200 mg/dL (random)
Calcium	7.5 mg/dL	11.6 mg/dL
Sodium	130 mEq/L	150 mEq/L
Potassium	3.0 mEq/L	5.2 mEq/L
Chloride	85 mEq/L	119 mEq/L
BUN	2 mg/dL	30 mg/dL
Creatinine	0.2 mg/dL	1.6 mg/dL
Total bilirubin	0 mg/dL	1.2 mg/dL
SGOT (AST)	0 U/L	100 U/L
SGPT (ALT)	0 U/L	110 U/L
GGT	0 U/L	120 U/L
LDH	0 U/L	500 U/L
Alkaline Phosphatase*		
10 -<13 years	42 U/L (m) / 51U/L (f)	362 U/L (m) / 332 U/L (f)
13 - < 16years	74U/L (m) / 50 U/L (f)	390 U/L (m) / 162 U/L (f)
16 -<18 years	52 U/L (m) / 47 U/L (f)	171 U/L (m) / 119 U/L (f)
18 years and above	37 U/L (m) / (f)	116 U/L (m) / (f)
Total Protein	4.0 g/dL	9.5 g/dL
Albumin	2.5 g/dL	6.0 g/dL
Uric Acid	1.5 mg/dL	10.0 mg/dL
*Normal ranges according to NIH Clinical Centre [http://cclnprod.cc.nih.gov/dlm/testguide.nsf; 10th May 2012		

Parameter	Abnormality
WBC	>5
RBC	>5
Protein	+ or greater*
Glucose	+ or greater*
* Trace should proceed +, otherwise ++ or greater	

Source: Table 13-1 Clinical Study Report

Submission Specific Tests

Fingolimod has a known association with macular edema. Ophthalmological testing including Optical Coherence Tomography was performed at Screening, Months 3, 6, and 24. If new complaints or physical exam findings raised suspicion of macular edema or other visual abnormality, ophthalmological examination could be performed at any visit.

Nonclinical findings and experience in adult patients with RMS revealed that fingolimod is associated with several pulmonary toxicities. Pulmonary function tests were performed at Baseline, Months 1, 3, 6, 12, 18, and 24 or at any visit when patients had new complaints or findings on physical examination that suggested a new respiratory symptom.

Study D2311 was the first controlled trial of fingolimod in children and adolescents. Evaluations of physical and sexual development, including assessment of pubertal changes according to Tanner staging and bone age analysis, were performed at Screening, Months 6, 12, 18, and 24. Serum endocrine evaluations for measures related to physical, insulin-like growth factor 1 (IGF-1) and insulin-like growth factor binding protein (IGFBP3) were obtained at Screening, Months 6, 12, 18, and 24. To monitor sexual development markers, in female patients, follicle stimulating hormone (FSH) and estradiol (E-2) were obtained, and in male patients, testosterone and luteinizing hormone (LH) were obtained in boys.

Vital Signs

In Study D2311, weight, height, sitting pulse rate, sitting systolic and diastolic blood pressures, and oral temperature were obtained at every visit; height and weight were obtained every 6 months. Radial pulse was assessed after 5 minutes of seated rest and measured just prior to blood pressure measurement. Because of fingolimod's known effects on heart rate and potential for inducing new heart conduction block, patients taking their first dose of study drug, taking their first dose of increased dose of study drug, or restarting after a protocol-defined lapse in treatment, were required to undergo first dose monitoring (see Section 6.1.1).

Table 39: Sponsor Table: Vital Signs Notable Values, Study D2311

Vital Sign	Age group	Notable criteria
Heart Rate	<12 years	>130 bpm or increase of ≥15 bpm from baseline Or <70 bpm or decrease of ≥15 bpm from baseline
	≥12 years	>120 bpm or increase of ≥15 bpm from baseline Or <50 bpm or decrease of ≥15 bpm from baseline
Systolic Blood Pressure	<12 years	≥125 mmHg or increase of ≥20 mmHg from baseline Or ≤70 mmHg or decrease of ≥20 mmHg from baseline
	≥12 years	≥160 mmHg or increase of ≥20 mmHg from baseline Or ≤90 mmHg or decrease of ≥20 mmHg from baseline
Diastolic Blood Pressure	<12 years	≥85 mmHg or increase of ≥15 mmHg from baseline Or ≤50 mmHg or decrease of ≥15 mmHg from baseline
	≥12 years	≥95 mmHg or increase of ≥15 mmHg from baseline Or ≤50 mmHg or decrease of ≥15 mmHg from baseline
Temperature		>38.3 °C or a change of 1.1 °C from baseline
Weight		≥7% decrease from baseline weight

Source: Table 13-3 Clinical Study Report

Electrocardiograms (ECGs)

In Study D2311, ECGs were performed at Screening, Day 1, and Months 1, 12, and 24. At any first dose monitoring visit, two ECGs were performed, one prior to administration of the study drug, and a second post-dose ECG after 6 hours of monitoring. Digital ECG devices were provided to each clinical site, and interpretations of ECG findings were performed by a central ECG reader throughout the Core Phase of the study. Abnormalities were reported as AEs. There were protocol-defined criteria for ECG findings that mandated permanent study drug

discontinuation.

8.4. Safety Results

8.4.1. Deaths

As of July 14, 2017, the original cut-off date of the application, there were no deaths reported in Study D2311. No deaths were reported in the 120-day safety follow-up to the original application.

8.4.2. Serious Adverse Events

In Study D2311, 19 patients in the fingolimod treatment group experienced 33 SAEs. The most common SAEs were related to infections, seizures, and MS relapses. There were no reported SAEs of aplastic anemia, cutaneous malignancies, drug reaction with eosinophilia and systemic symptoms (DRESS), encephalitis due to any herpes virus or any cause, pancytopenia, posterior reversible encephalopathy syndrome (PRES), progressive multifocal leukoencephalopathy (PML), or liver failure.

Overall, patients in the fingolimod treatment group had a higher incidence of reported SAEs (19 patients, 17.8%) than did patients in the interferon β-1a treatment group (10 patients, 9.3%). Individual SAEs were reported infrequently making broad grouping and one-to-one comparisons between treatments impractical, and so all SAEs are presented.

The most commonly reported SAEs were in the categories of infections and nervous system disorders. After examination of coding for all SAE cases in the fingolimod treatment group, five patients were noted to have infection-related SAEs. A multiple sclerosis relapse that was considered by the investigator to be more serious than a typical relapse was reported in four patients (one patient in the fingolimod treatment group and three patients in the interferon β-1a treatment group). Epilepsy and seizures were noted as an SAE in four patients in the fingolimod treatment group, but convulsions (due to seizures) were noted as AEs in six fingolimod-treated patients whereas only one patient in the interferon β-1a treatment group experienced convulsions (see Section 8.4.4.). Gastrointestinal disorders were noted in three patients in the fingolimod treatment group. Three patients reported SAEs defined as traumatic injuries (head injury, humerus fracture, and ankle fracture) in the fingolimod group. Leukopenia was reported as a SAE in two fingolimod-treated patients. No other SAE was reported for more than two patients in either treatment group.

To examine SAEs, I examined Novartis's presentations and tables. I reviewed the CRFs and narrative summaries for all SAEs. There were so few SAEs that this summary is inclusive of all events noted as SAEs in the Core Phase of Study D2311.

Analysis by subgroup recapitulated the finding of more SAEs in patients in the fingolimod treatment condition. In pre-pubertal children (Tanner stage <2), there were five SAEs reported in fingolimod-treated patients and one reported in an interferon β-1a-treated patient. For patients ≤ 12 years old, there were eight SAEs in the fingolimod treatment group versus two in the interferon β-1a treatment group. There was one study drug discontinuation and one study drug interruption for patients at the 0.25 mg fingolimod dose.

Table 40: Reviewer Table: All SAEs, Safety Set, Study D2311

	Safety Set Study D2311	
MedDRA System Organ Class MedDRA Preferred Term	**Fingolimod (n=107, 176.0 patient-years)**	**Interferon β-1a (n=107, 153.4 patient-years)**
Total with at least 1 SAE	19 (17.8%)	10 (9.3%)
Number/100 patient-years	11.6	7.0
Nervous System Disorders (total)	8 (7.5%)	5 (4.7%)
Multiple sclerosis relapse	1 (0.9%)	3 (2.8%)
Multiple sclerosis worsening plaque/lesion count	1 (0.9%)	0
Seizures[1]	4 (3.7%)	1 (0.9%)
Migraine[2]	2 (1.9%)	1 (0.9%)
Headache	0	1 (0.9%)
Sensory loss	0	1 (0.9%)
Optic neuritis	0	1 (0.9%)
Dizziness	0	1 (0.9%)
Infections and Infestations (total)	5 (4.7%)[3]	2 (1.9%)
Abscess (oral)	1 (0.9%)	0
Appendicitis	1 (0.9%)	0
Cellulitis	1 (0.9%)	0
Gastrointestinal infection[4]	3 (2.8%)	1 (0.9%)
Paronychia	0 (0.9%)	1 (0.9%)
Viral infection[5]	4 (3.7%)	0
Viral pharyngitis	1 (0.9%)	0
Blood and Lymphatic System Disorders	2 (1.9%)	0
Leukopenia	2 (1.9%)	0
Agranulocytosis	2 (1.9%)	0
Cardiac Disorders	1 (0.9%)	1 (0.9%)
Atrioventricular block (2nd degree)	1 (0.9%)	0
Supraventricular tachycardia	0	1 (0.9%)
Eye Disorders	1 (0.9%)	1 (0.9%)

Uveitis[6]	1 (0.9%)	1 (0.9%)
Gastrointestinal Disorders	3 (2.8%)	1 (0.9%)
Dyspepsia[7]	1 (0.9%)	
Gastroesophageal reflux	0	1 (0.9%)
Gastrointestinal necrosis	1 (0.9%)	0
Rectal tenesmus	1 (0.9%)	
Small intestinal obstruction	1 (0.9%)	0
General Disorders and Administration Site Conditions	0	2 (1.9%)
Fatigue	0	1 (0.9%)
Pyrexia	0	1 (0.9%)
Injury, Poisoning, and Procedural Complications	3 (2.8%)	0
Head injury	1 (0.9%)	0
Humerus fracture	1 (0.9%)	0
Ankle fracture[8]	1 (0.9%)	0
Investigations	1 (0.9)	1 (0.9%)
Alanine aminotransferase increased	1 (0.9%)	0
Gamma-glutamyltransferase increased	1 (0.9%)	0
Body temperature increased	0	1 (0.9%)
Musculoskeletal and Connective Tissue Disorders	2 (1.9%)	0
Arthralgia	1 (0.9%)	0
Muscular weakness	1 (0.9%)	0
Renal and Urinary Disorders	1 (0.9%)	0
Bladder spasm	1 (0.9%)	0
Dysuria	1 (0.9%)	0
Skin and Subcutaneous Tissue Disorders	1 (0.9%)	0
Hypersensitivity vasculitis	1 (0.9%)	0

Source: AAEV.xpt

[1]includes events coded to epilepsy, generalized tonic-clonic seizure, and seizures
[2]includes events coded to migraine with aura and migraine without aura
[3]there were five patients who experienced infectious events coded with multiple infection terms
[4]includes events coded to viral gastritis, viral infection when source was gastrointestinal, and dyspepsia syndrome in association with a gastrointestinal infection
[5]incudes all events coded as viral infection, viral pharyngitis, and viral gastroenteritis

[6]includes events coded to autoimmune uveitis and uveitis
[7]includes dyspepsia syndrome
[8]non-fatal SAE from extension trial added after data cut-off

> *Reviewer Comment: The SAEs in this pediatric study capture virtually all the SAEs that were identified in adult trials as having an association with fingolimod treatment, specifically infections, leukopenia, and heart block. The small number of patients and events in the 0.25 mg fingolimod treatment group precludes any definitive safety conclusions at this dose. A case of leukopenia and a case of second degree atrioventricular heart block occurred at the 0.25 mg dose, and thus it would appear the safety profile of this dose is similar to that of the 0.5 mg dose. The imbalance in bone fractures in the fingolimod treatment group is discussed below.*

120- Safety Update

Novartis noted a single SAE from the OLE, obtained after the data cutoff, an ankle fracture requiring surgical repair that was not treatment-related. Novartis submitted a 120-day safety update. The update added two patients with two SAEs to the previously identified list of SAEs. On review, one of the two SAEs, fungal meningitis, was noted in a setting of persistent leukopenia and was deemed by the investigator to be related to fingolimod treatment. The other SAE, endometriosis, does not appear to be treatment related. The patient narratives are included in Section 8.4.3.

Study D2301

A single patient randomized into Study D2301 was 17-years-old. She was treated with fingolimod 1.25 mg. She experienced no SAEs.

Study A0115

There were no SAEs reported for the seven randomized patients who received a single dose of 1.25 mg fingolimod.

Summary of SAE Narratives from Study D2311

Epilepsy, generalized tonic-clonic seizure, and seizures

Taken together, there was an imbalance (4 versus 1) of patients with SAEs of epilepsy, seizure, and generalized tonic-clonic seizure in the fingolimod treatment group. There are epidemiological observations suggesting that epilepsy occurs more often in patients with MS than in the general population.

A study in renal transplant patients taking doses of fingolimod ranging from 1.25 mg to 5 mg reviewed in the original NDA 22527 submission suggested a small dose-dependent increase in

seizures in this patient population, but the number of patients was small and the patients' significant comorbidities and concomitant medications represented additional risk factors.

Likewise, in the original ISS of NDA 22527, there were nine adult patients in the fingolimod arm with seizure-related SAEs, no patients in the interferon β-1a arm with seizure-related SAEs, and one patient with a seizure-related SAE in the placebo arm. The review suggested a potential increased seizure risk at the 1.25 mg, but not the 0.5 mg, fingolimod dose. Post-marketing surveillance for increased risk of seizure in adults with RMS has failed to identify an increased risk of seizures at the 0.5 mg dose.

In Study D2311, three of the four patients with epilepsy-related SAEs were female. The mean age of patients with a seizure-related SAE was 14.3 years (range 10-17). The mean duration of treatment with fingolimod on day of first seizure event was 407.5 days (range 99-655 days). The mean baseline EDSS was 2.25 (range 1-3.5). None of the patients had a prior seizure history. The edited clinical narratives of each pediatric patient are included below.

Patient (b) (6) A 16-year-old Caucasian female with multiple sclerosis was screened for the study on (b) (6) and received the first dose of study medication (fingolimod) on (b) (6) (Day 1). The patient was diagnosed with multiple sclerosis on (b) (6) . The patient did not have any history of seizure. On (b) (6) (Day 655) at 10:45 pm, the patient experienced an acute symptomatic seizure (severe in nature) which started with focal motor movements and then further evolved into a generalized (seemingly secondary generalized) epileptic tonic-clonic seizure. Symptoms included muscle rigidity, repetitive jerking movement, muscle stiffness, and local motor tonic phenomenon, and confusion. The patient had complete loss of consciousness and respiratory arrest lasting for several seconds. The patient was treated with magnesium sulfate on (b) (6) (Day 655), carbamazepine from (b) (6) (Day 655), and hopantenic acid from (b) (6) (Day 657). On (b) (6) (Day 655), the event (seizure) completely resolved. On (b) (6) (Day 664), the patient was evaluated by neurologist and there was no new physical abnormality or worsening or new neurological signs, or new seizure reported. On the same day ((b) (6) Day 664), an electroencephalogram results showed regional epileptiform activity, mainly in the left frontal, central and parietal leads with diffuse slowing of brain activity. A magnetic resonance imaging showed no clinically significant abnormalities except for typical multiple sclerosis lesions. The other contributory factor for the event was reported as progression of study indication. According to the investigator, the event (seizure) was considered life threatening and medically significant. The investigator did not suspect a relationship between the event (seizure) and the study medication. The investigator provided the rationale as although epileptic seizures were not frequent MS symptoms, they may be developed during the course of the disease in 4 to 5% of the patients. As per the Novartis safety physician, the event of seizure was possibly a manifestation of the underlying study indication of multiple sclerosis during the course of its clinical progression, and was hence assessed as not suspected.

Patient (b) (6) A 10-year-old Caucasian male with multiple sclerosis was screened for the study on (b) (6) and received the first dose of study medication (fingolimod) on (b) (6) (Day 1). The patient was diagnosed with multiple sclerosis on (b) (6) There was no [prior] history of seizure[s].

On (b) (6) (Day 99), the patient presented with a severe convulsion (tremor lasted for about 1 or 2 minutes) that resolved by itself but experienced another episode of the same after 10 minutes. The patient was admitted to local hospital. The patient had pre-seizure aura, visual disturbance, dizziness/light headedness, and a fall before seizure and became unconscious, and had tremor (right side body), hypersalivation, and problem with respiration about 2-3 minutes. The investigator reported that the convulsion was described by visual hallucination, eyes wide open, vomiting, and hypotonia. The patient had post-ictal confusion, headache, weakness, and somnolence. The patient was treated with Valium (diazepam) on the same day and Trileptal (oxcarbazepine) intermittently from (b) (6) A brain magnetic resonance imaging during the first episode showed ≥ 1 T2 bright lesion in brain, ≥ 1 T2 periventricular lesion, ≥ 1 T2 juxtacortical lesion, and ≥ 1 infratentorial T2 bright lesions, > 1 Gd (gadolinium) enhancing lesion and > 1 clinically silent Gd enhancing lesion. Clinical and laboratory examinations did not show any abnormality besides the neurological symptoms by the study disease. Study medication was temporarily interrupted on (b) (6) (Day 99) due to the event.

On (b) (6) (Day 100), the event (seizure) was considered resolved, and the patient was discharged from the hospital on the same day. On (b) (6) (Day 104), the patient's electroencephalography results were abnormal with slow waves particularly on the left centro-temporal region, and very slightly slow waves on right centro-temporal region secondary to diazepam administration. On (b) (6) (Day 111), the study medication was restarted.

On (b) (6) (Day 202), the patient presented with convulsions, loss of consciousness and spasms at 12:30 pm and generalized convulsions at 12:35 pm. On the same day at 12:40 pm, the patient partially recovered from the event after administration of midazolam, but his ambulation continued to be affected with no lateral imbalance. On (b) (6) (Day 251), the patient experienced convulsions, and was treated with midazolam. He recovered from convulsions on the next day ((b) (6) On an unknown date in February 2016, the patient had intermittent seizures.

On (b) (6) (Day 320), at 5:58 PM the patient had pain in right wrist and epileptic seizure, and at 6:00 pm, a generalized tonic-clonic seizure that resolved after 10 minutes on treatment with midazolam. At 6:12 pm, the patient vomited. He remained hemiplegic on the right side, post seizure.

On (b) (6) (Day 343), the patient was hospitalized for MS relapse. On (b) (6) (Day 344), at 08:50 pm, the patient had epileptic seizure and was treated with midazolam. At 9:15 pm, he had tremors, which was treated with diazepam. On the same day, convulsion stopped, and the patient was not able to talk but was able to move.

On an unknown date, the patient was discharged from the hospital. The patient completed the study with the last dose on (b) (6) (Day 722) and entered the extension phase of the study. According to the investigator, the event (seizure) led to hospitalization. The investigator did suspect a relationship between the event (seizure) and the study medication. As per the Novartis safety physician, the event of convulsions in this case was considered likely due to multiple sclerosis, and hence the causality was confounded by MS disease and not assessable due to incomplete information about therapy details.

Patient (b) (6) A 17-year-old Caucasian female with multiple sclerosis was screened for the study on (b) (6) and received the first dose of study medication (fingolimod) on (b) (6) (Day 1). The patient was diagnosed with multiple sclerosis on (b) (6) . The patient did not have any history of seizures, genetic disease, idiopathic seizures, brain tumor or other structural lesion, congenital brain defects, traumatic brain injury, stroke, peri- or post-partum brain injury, stopping alcohol after drinking heavily, sleep disorder, psychiatric disorder, emotional stress, migraine with focal symptoms or aura.

Event 1 (Epileptic seizure): On (b) (6) (Day 498), the patient fell out of bed due to mild epileptic seizure (epilepsy-first occurrence), which lasted for 3 minutes, and developed headache, vomiting (3 episodes), musculoskeletal pain in her left shoulder, and amnesia (all mild in nature). She also developed a hematoma over the left side of her head. Postictal symptoms included memory loss and weakness. The seizure was classified as a generalized tonic clonic seizure. No action was taken with the study medication due to the event, and no treatment was given for the event. On the same day (Day 498), the patient completely recovered from the events (vomiting and epilepsy-first occurrence). On (b) (6) (Day 499), the patient was hospitalized for epilepsy. Her electroencephalogram and a computerized tomogram results were normal. On the same day (Day 499), she completely recovered from the event (amnesia). On (b) (6) (Day 500), the event (headache) completely resolved, and the patient was discharged from the hospital. On (b) (6) (Day 501), the event (musculoskeletal pain) completely resolved, and it was reported that the patient was asymptomatic.

Event 2 (Epileptic seizure): On (b) (6) (Day 604), the patient had moderate epileptic seizures that was reported as an SAE (epilepsy-second occurrence), and was hospitalized. No action was taken with the study medication due to the event. On the same day (Day 604), the event (epilepsy-second occurrence) resolved. On (b) (6) (Day 606), the patient was discharged from the hospital and began treatment with lamotrigine 25 mg once daily (daily). On (b) (6) (Day 621), the dosage of lamotrigine was increased to 25 mg twice a day (every 12 hours). The dosage was further changed to 50 mg in the morning and 25 mg in the evening from (b) (6) (Day 636), to 50 mg bid from (b) (6) (Day 644), to 75 mg in the morning and 50 mg in the evening from (b) (6) (Day 651), and to 75 mg bid from (b) (6) (Day

658). The patient experienced additional epileptic seizures all mild in nature that were not considered to be SAEs on (b) (6) (Day 678), on (b) (6) (Day 707), and on (b) (6) (Day 714). The patient continued treatment with lamotrigine in the extension phase from (b) (6) for epileptic seizures. The patient completed the study with the last dose on (b) (6) (Day 714) and entered extension phase of the study. According to the investigator, the events (epilepsy-both occurrences) were considered medically significant and led to hospitalization. The investigator did not suspect a relationship between the events (epilepsy-both occurrences) and the study medication. As per the Novartis safety physician, the event musculoskeletal pain could be explained as a complication that occurred as a result of the trauma experienced due to fall. There was minimal information for the event of epilepsy (medical history, concomitant medication, event date, action taken with regards to study medication, outcome, and treatment given); the causality was kept as not suspected in agreement with the investigator and will be reassessed after follow up.

Patient (b) (6) A 14-year-old Caucasian female with multiple sclerosis was screened for the study on (b) (6) and received the first dose of study medication (fingolimod) on (b) (6) (Day 1). The patient was diagnosed with multiple sclerosis on (b) (6). The patient did not have any previous history of epilepsy. On (b) (6) (Day 378), the patient had severe generalized tonic-clonic seizures (2 episodes), and she was hospitalized. On the same day (Day 378), her blood chemistry and hematology reports were normal, and brain magnetic resonance imaging showed no new MS pathology. On an unspecified date, an electroencephalogram showed spikes. On the same day (Day 378), she was treated with diazepam, carbamazepine, dexamethasone, and furosemide for the event. Study medication was temporarily interrupted from (b) (6) (Day 378). The event (generalized tonic-clonic seizure) completely resolved on (b) (6) (Day 378). On (b) (6) (Day 379), treatment with study medication was restarted. The patient was discharged from the hospital on (b) (6) (Day 386). The patient completed the study with the last dose on (b) (6) (Day 591) and entered extension phase of the study. According to the investigator, the event (generalized tonic-clonic seizure) led to hospitalization. The investigator did not suspect a relationship between the event (generalized tonic-clonic seizure) and the study medication. The investigator reported the rationale for the event of epileptic seizures as one of the symptoms of pediatric MS. As per Novartis safety physician, the underlying indication of multiple sclerosis could provide a better explanation for the event of generalized tonic-clonic seizure in this pediatric patient.

Information Request

An Information Requested received by Novartis on February 28, 2018 requested additional context or data to explain the apparent discrepancy in the number of patients experiencing convulsions/seizures/epilepsy noted between the fingolimod and the interferon β-1a arm. The response from Novartis follows:

"Within [this response] the relevant pre-clinical data concerning seizures and central nervous system (CNS) effects from the pre-clinical studies conducted by Novartis are reviewed along with a review of the relevant pooled clinical trial data concerning seizures in adult patients with relapsing MS (as previously submitted in the Integrated Summary of Safety (ISS) in 2009 and 2012).

- "While there is no evidence from the fingolimod pre-clinical program to indicate a pro-convulsive effect (which could be relate to central nervous effects), a higher percentage of renal transplant patients who received fingolimod experienced a seizure, compared with patients in the control group: 31 patients (1.9%) of 1606 patients) who received fingolimod experienced a seizure, compared with 3 of 689 (0.4%) patients in the control group who received mycophenolate mofetil (MMF). However, this higher incidence of seizure-related AEs for fingolimod-treated patients compared to the reference drug MMF did not reach nominal statistical significance and was within the expected range for transplant patients. In addition, the finding was confounded by the fact that renal transplant patients have multiple co-morbidities, which pre-dispose this population to an increased risk of seizures (periods of critical illness and of various toxic, metabolic, electrolyte, and infectious abnormalities).

- "The pooled data of blinded placebo controlled randomized clinical trials in MS adult patients also showed higher IR (0.4%) of seizure in patients who received fingolimod, compared with patients in the placebo control group (0.2%). This produced an IRR of 1.77 (95% CI: 0.4 - 10.62) and 1.52 (95% CI: 0.22 - 16.79) for the Standardized MedDRA Query (SMQ) (broad) convulsions and PT Seizure, respectively, when comparing fingolimod 0.5 mg to the placebo control group.... The imbalance observed in MS adult patients did not reach nominal statistical significance.

- "In the recently concluded trial (Study D2311) in pediatric MS patients (aged 10 or more) an imbalance in the IR of seizures (Convulsions SMQ) was observed as well; the IRR for fingolimod 0.5 mg vs IFN was 5.37 (95% CI: 0.65, 247.15). The imbalance observed in this patient cohort did not reach nominal statistical significance. Overall, there was no conclusive evidence of causal association between use of fingolimod and the occurrence of seizures from pre-clinical data, post-marketing data, and no mechanistic plausibility could be identified. However, a preponderance of imbalances (although not reaching nominal statistical significance) was observed in the several clinical trials in the adult as well as the pediatric MS population. In addition, there is disproportionate reporting of fingolimod for convulsions in FDA-AERS database [Adverse Drug Reactions-Clinical Overview].

"Moreover, the IR of seizure in MS patients reported in the Swedish MS Registry (Sequence 0538;Seizure clinical-overview), adjusted approximately to the age distribution in the pediatric

Study D2311, while being similar to that seen in the IFN group, was higher than expected for fingolimod, suggesting that the risk for fingolimod may be greater than expected. Hence, Novartis considered it appropriate to update the "Adverse drug reactions" (ADR) sections of the USPI for adult as well as pediatric patients."

Reviewer Comment: The narratives do not suggest alternative diagnoses to new-onset of seizures in these patients. There is evidence that MS is a risk factor for a co-morbid diagnosis of epilepsy. An analysis of the entire Swedish MS Register suggests that risk of epilepsy is doubled in patients with MS (Burman & Zelano, 2017). Durmus et al. *(2013) observed in a cohort of pediatric patients with RMS a new onset seizure rate of 8 out of 146 (5.5%) though a more recent meta-analysis suggests a higher incidence of 7.6% (Gaspirini* et al.*, 2017). Thus, an increased rate of new onset seizures in this study would not be surprising were it not for the fact there was a marked discrepancy in the observed epilepsy rate between the treatment arms. When one adds the additional AE reports of convulsions (see Section 8.4.4) to the SAE reports of epilepsy-related events, the observed epilepsy rate in this study for patients in the fingolimod treatment group is 6/107 or 5.6% which is within the published incidence rate of seizures in pediatric patients with RMS, but the observed rate for interferon β-1a-treated patients was 0.9% which is below the rate of epilepsy predicted in the general population, approximately 1-2%. A treatment-related effect related to fingolimod could explain the difference between the epilepsy rates. In favor of this hypothesis is that an examination of the safety results submitted for the original NDA 22527 shows a difference in IR for seizures between adults treated with fingolimod and interferon β-1a. The onset of seizures in both the adult and pediatric trials did not occur at random as would be predicted for a true stochastic event. In the adult trials, the mean treatment duration at first epileptic event for adults in fingolimod studies was 319 days (range 33-678 days). In the pediatric study, the mean duration of exposure was 407.5 days* (range 99-655 days)*. In PSUR 29 Feb 2016-28 Feb 2017, Novartis identified 17 cases with new onset of seizures within first 3 months after first fingolimod intake. Thus, there is evidence of a temporal relationship between first intake of fingolimod and the onset of seizures within 1-3 months.*

An alternative hypothesis would be that interferon β-1a itself might prevent epileptogenesis in MS through an unknown mechanism. Finally, patients in the interferon β-1a treatment group had a markedly higher exposure to corticosteroids. This increased anti-inflammatory steroid exposure may have interrupted a component of the inflammatory process that is hypothesized to occur in the epileptic brain (van Vliet et al., *2018). Though a definitive mechanistic linkage between fingolimod and seizures is not clear, Novartis has proposed the addition of "seizures" to the labeling of adverse reactions for fingolimod. This label modification appears prudent. There are many hypothetical reasons for the observed discrepancy between treatment groups, and a definitive conclusion cannot be made in this small patient pool. Pediatric patients with RMS taking fingolimod will be at higher risk of seizures by virtue of their disease and providing a specific warning of seizures is the most*

conservative and safety conscious approach. Post-marketing reports should be monitored for epilepsy-related phenomena.

MS Relapses/Radiological Worsening of MS

Cases of serious MS relapses merit scrutiny because the prior experience with fingolimod in adults with RMS has suggested the possibility that severe MS exacerbations can occur in a subset of patients spontaneously due to treatment failure or when medication is discontinued.

Examination of the reported SAEs identified two patients in the fingolimod treatment group with a serious MS relapse and a patient with a significant worsening of disease on radiographic evaluation. I also include one additional patient with a constellation of neurological SAEs that upon review could be consistent in with a worsening in MS symptoms.

The two Sponsor-defined cases of relapse and MS worsening are consistent with the natural history of RMS in a setting of treatment failure. In one instance, a patient with multiple acute medical complaints had three new lesions documented on MRI, which is certainly consistent with MS relapse and MS progression despite adequate treatment. A second patient had several relapses on study treatment and MRI revealed a sizable cluster of more than five new lesions that prompted ending fingolimod treatment during the blinded Core Phase of the study. A third patient experienced new weakness within one day of discontinuing treatment and neurogenic bladder symptoms that became apparent nearly one month after discontinuing fingolimod suggestive of a rebound MS relapse. The edited patient narratives are below.

Patient (b) (6) A 16-year-old Caucasian female with multiple sclerosis was screened for the study on (b) (6) and received the first dose of study medication (fingolimod) on (b) (6) (Day 1). The patient was diagnosed with multiple sclerosis on (b) (6) . The patient experienced two relapses during the past 12 months and no relapses during the 12 to 24 months before study entry, and her last relapse prior to enrollment was on (b) (6) The patient was not treated with any MS disease-modifying drug prior to enrollment. At Screening, the patient's EDSS score was 0. The patient had no relevant prior medical history. No concomitant medications were taken prior to enrollment. On (b) (6) (Day 9), the patient had severe multiple sclerosis relapse and was treated with methylprednisolone sodium succinate 1000 mg intravenously for 5 days. The event (MS relapse) resolved on (b) (6) (Day 14). The patient again had MS relapse (moderate in nature) from (b) (6) (Day 502) to (b) (6) (Day 583). On (b) (6) (Day 718), a magnetic resonance imaging (MRI) showed a significant radiological worsening of multiple sclerosis lesions (multiple sclerosis; severe in nature). On (b) (6) (Day 720), the MRI showed five or more combined unique active lesions. The patient permanently discontinued study medication due to the event (MS plaque), but the patient completed the study as the event occurred after two full years in the study. The patient received the last dose of study medication on (b) (6) (Day 721). No treatment was given for the event. The patient's

condition was unchanged, and the event was ongoing at the time of the last available report. The other possible contributory factor for the event was lack of efficacy of study medication. The End of Study visit was completed on (b) (6) The patient did not enter the Extension Phase. According to the investigator, the event (multiple sclerosis relapse) was considered medically significant. The investigator did not suspect a relationship between the event (multiple sclerosis relapse) and the study medication. As per the Novartis safety physician, the aggravation of multiple sclerosis could be better explained by the progression and natural course of the underlying study indication rather than the study medication, and hence, causality was not suspected.

Patient (b) (6) A 17-year-old Caucasian female with multiple sclerosis was screened for the study on (b) (6) and received the first dose of study medication (fingolimod) on (b) (6) (Day 1). The patient was diagnosed with multiple sclerosis in July 2013. The patient experienced two relapses during the past 12 months and one relapse during the 12 to 24 months before study entry, and her last relapse prior to enrollment was in October 2015. The patient was treated with the following MS disease modifying drugs prior to enrollment: interferon β-1a (Rebif 44) until (b) (6) and interferon β-1a (Rebif 22) on an unknown date (not taken in past 6 months). No additional immunomodulatory or immunosuppressive drugs for MS were administered. At Screening, the patient's EDSS score was 2.0. The patient had no relevant prior medical history. During the study, the patient received vitamin B (ascorbic acid/tocopherol/vitamin B NOS) as a dietary supplement from (b) (6) to (b) (6) On (b) (6) (Day 399), the patient experienced right arm hyposthenia and speech difficulties, and was diagnosed with MS relapse (multiple sclerosis reactivation; severe in nature). On (b) (6) (Day 409), she was hospitalized and brain magnetic resonance imaging showed three new lesions. The patient was treated with Liometacen (indometacin meglumine) for MS related pain on the same day. On (b) (6) (Day 410), the patient experienced back pain (mild in nature) and was treated with paracetamol. On (b) (6) (Day 411), she had headache (mild in nature) and was treated with Toradol (ketorolac tromethamine) on the same day, paracetamol and codeine phosphate/guaifenasin from (b) (6) to (b) (6) She underwent plasmapheresis for MS reactivation and Valium (diazepam) for MS-related anxiety from (b) (6) to (b) (6) and her condition improved. On (b) (6) the laboratory results revealed mild anaemia (results not available). Study medication was permanently discontinued due to the events (multiple sclerosis relapse, back pain, headache, and anemia) with the last dose on (b) (6) (Day 409). She was treated with Lederfolin (calcium folinate/levofolinic acid) from (b) (6) to (b) (6) for anemia. She was also treated with 5 days of methylprednisolone therapy intravenously and was treated with paracetamol and codeine phosphate for headache on (b) (6) The patient was treated with Muscoril (thiocolchicoside) for back pain and ibuprofen sodium for headache from (b) (6) to (b) (6) The events (back pain and headache) resolved on (b) (6) (8 days after the last dose of study medication) and the event (anemia) was considered resolved on (b) (6) (12 days after the last dose of study

medication). The event (multiple sclerosis relapse) completely resolved on (b) (6) (13 days after the last dose of study medication), and subsequently, the patient was discharged from the hospital. The other possible contributory factor for the event was reported as progression of multiple sclerosis. The End of Study visit was completed on (b) (6) (13 days after the last dose of study medication). The patient did not enter the Extension Phase. According to the investigator, the event (multiple sclerosis relapse) led to hospitalization. The investigator did not suspect a relationship between the events (multiple sclerosis relapse, back pain, headache, and anemia) and the study medication. As per the Novartis safety physician, the reported event could be explained by the natural course and progression of underlying study indication multiple sclerosis and was assessed as not suspected.

Patient (b) (6) A 16-year-old Caucasian female with multiple sclerosis was was screened for the study on (b) (6) and received the first dose of study medication (fingolimod) on (b) (6) (Day 1). The patient was diagnosed with multiple sclerosis on (b) (6) . The patient experienced one relapse during the past 12 months and no relapses during the 12 to 24 months before study entry, and her last relapse prior to enrollment was on (b) (6) The patient was not treated with any MS disease-modifying drug prior to enrollment. At Screening, the patient's EDSS score was 2.0. The patient had no relevant prior medical history. Concomitant medication taken prior to enrollment included Uvedose (colecalciferol) for vitamin-D deficiency from (b) (6) During the study, the patient additionally received Efferalgan (paracetamol) from (b) (6) for headache, Solupred (prednisolone metasulfobenzoate sodium) from (b) (6) to (b) (6) and amoxicillin from (b) (6) to (b) (6) both for otitis media, paracetamol for abdominal pain form (b) (6) to (b) (6) and was treated with interferon β-1a from (b) (6) for multiple sclerosis after completing the study and stopping the study medication.

Event 1 (Muscular weakness): On (b) (6) (Day 618), the patient developed brief intermittent tonus with moderate weakness of the right superior limb (muscular weakness). On (b) (6) (Day 623), the patient was hospitalized for further evaluation. Magnetic resonance imaging (MRI) of the brain showed no significant change from the previous MRI and no acute lesions. An electroencephalogram was also normal. No action was taken with the study medication and no treatment was given for the event. The patient completed the study with the last dose on (b) (6) (Day 713) and the End of Study visit was on (b) (6) (Day 714). The patient did not enter the Extension Phase. The events (muscular weakness) completely resolved on (b) (6) (Day 714). Other possible contributory factor to the event (muscular weakness) was reported as intermittent weakness linked to the subtle sequelae from first relapse prior to the trial.

Event 2 (Bladder Spasm, Dysuria and rectal tenesmus): On (b) (6) (13 days after the last dose of study medication), the patient developed bladder spasm, dysuria, and two episodes of rectal tenesmus (all events mild in nature). On (b) (6) (42 days after the last dose of study

medication), the patient was hospitalized for these events. The patient was treated with Solumedrol (methylprednisolone) for a day. On the same day, renal function tests were normal. The patient also had anxiety. On (b) (6) (43 days after the last dose of study medication), urine analysis and spine MRI were also normal. The events (bladder spasm, rectal tenesmus, dysuria) resolved on (b) (6) (44 days after the last dose of study medication), and the patient was discharged from the hospital. According to the investigator, the events (bladder spasm, muscular weakness, dysuria, and rectal tenesmus) were considered medically significant and led to hospitalization and the event (bladder spasm) led to hospitalization. The investigator did not suspect a relationship between the events (muscular weakness, dysuria, bladder spasm, and rectal tenesmus) and the study medication. As per the Novartis safety physician, considering the nature of the underlying disease and etiopathogenesis of the event, the events of muscular weakness and bladder spasm could be attributed to multiple sclerosis rather than the suspect drug. It was considered possibly to be the sequelae of the relapse that occurred before the trial initiation, and was assessed as not suspected. The causality for both the events of dysuria and tenesmus was assessed as not suspected, as the risk factors for the events were anxiety due to school with other alternative explanations present.

Reviewer Comment: In Event 1, the patient appears to have some residual weakness in the right upper extremity from an earlier pre-trial relapse event that waxes and wanes throughout the trial. What is of particular interest is Event 2, the onset of the bladder spasms and rectal tenesmus beginning two weeks after discontinuation of study drug with a hospitalization for these symptoms 42 days after fingolimod. Rebound of MS symptoms after discontinuation of fingolimod remains a topic of ongoing debate and investigation, but descriptions of this putative rebound after ending fingolimod treatment suggest that symptoms and radiology findings worsen 4-6 weeks after last dose. This event falls within that temporal window. It is therefore possible that this case could represent a rebound MS relapse related to discontinuing fingolimod. A single case is not sufficient basis for declaring a drug-related rebound effect exists, but this case would join others in the extant literature that suggest fingolimod discontinuation can be followed by a rebound MS relapse. It would be appropriate to monitor safety reports to determine whether discontinuation of fingolimod is associated with rebound phenomena in children and adolescents.

Infections

Cases of infections, particularly those due to atypical or known opportunistic pathogens only causing disease in immune compromised patients, are concerning events because fingolimod's mechanism of action is due to inhibition of white blood cell egress from lymph nodes that could theoretically lead to significant immune compromise. The current labeling of fingolimod includes risk of infections as a general warning because infections were noted as one of the most common AEs in the adult RMS trial. The pre- and post-marketing experiences with fingolimod in adults have informed label warnings regarding the specific risks of herpes viral

infections, Cryptococcus infections, and progressive multifocal leukoencephalopathy due to reactivation of latent John Cunningham (JC) virus.

There were no clearly "opportunistic" infections documented as SAEs in the Core Phase of Study D2311.

The five cases with infection-related SAEs are summarized below and include cellulitis with an oral abscess, pharyngitis, appendicitis, several cases of gastroenteritis with one complicated by intussusception with bowel necrosis. The cases required hospitalizations and in all but two cases, intravenous antimicrobials to resolve. Two of the SAEs involved a surgical intervention. Infections are the most commonly reported AE in pediatric studies, and gastrointestinal disorders are the third most commonly reported AE preferred system organ class in a meta-analysis of pediatric clinical trials (Luo *et al.*, 2016). Appendicitis is the most common acute surgical condition in children with a peak incidence between ages 10-19 years old (Addiss *et al.*, 1990). Thus, while pharyngitis, cellulitis, appendicitis, and gastroenteritis can be considered relatively common medical events in the pediatric population, intussusception following a viral gastrointestinal infection is extremely uncommon outside of infancy. Considering the report of intussusception represents a single case without a clear tie to fingolimod, there does not appear to be a need for labeling adjustment at this time. Safety reports documenting any intussusception should be monitored to ascertain whether this example is an isolated event or representative of a uniquely pediatric risk. Otherwise, the existing labeling is adequate. The edited narratives follow.

Patient (b) (6) A 10-year-old Caucasian female with multiple sclerosis was screened for the study on (b) (6) and received the first dose of study medication (fingolimod) on (b) (6) (Day 1). The patient was diagnosed with multiple sclerosis on (b) (6) . The patient experienced 2 relapses during the past 12 months and 2 relapses during the 12 to 24 months before study entry, and her last relapse prior to enrollment was on (b) (6) At Screening, the patient's EDSS score was 2.5. The patient had no relevant prior medical history. Concomitant medication taken prior to enrollment included Brufen (ibuprofen) 400 mg from (b) (6) to (b) (6) for acute viral pharyngitis. During the study, the patient additionally received paracetamol for acute rhinitis on (b) (6) paracetamol on (b) (6) as prophylaxis; paracetamol on (b) (6) for worsening of bronchitis; and Clorura De Sodiu (sodium chloride-0.9%) on (b) (6) and Ventolin (albuterol) and Flixotide (fluticasone propionate) for bronchial asthma from (b) (6) and Emeset (ondansetron) for nausea on (b) (6) On (b) (6) (Day 12), the patient experienced mild upper abdominal pain. No action was taken with the study medication. The patient was treated with Dicarbocalm (calcium carbonate and magnesium carbonate), and the event resolved on the same day (Day 12). On (b) (6) (Day 64), the patient experienced nausea, vomiting, diarrhea, and pyrexia, and was diagnosed with dyspeptic syndrome (dyspepsia; moderate in nature). The patient was reported to have had improper food intake and inadequate nutrition prior to the symptoms. No

action was taken with the study medication. On (b) (6) (Day 65), the patient was hospitalized for dyspepsia and was treated with drotaverine hydrochloride on the same day, ranitidine hydrochloride, trimebutine, ringer, ondansetron hydrochloride, sodium chloride, and paracetamol for dyspeptic syndrome from (b) (6) (Day 65) to (b) (6) (Day 66). On (b) (6) (Day 66), the event (dyspepsia) resolved and the patient was discharged from the hospital. The other possible contributory factor for dyspepsia was reported as malnutrition and viral infection. The patient completed the study with the last dose on (b) (6) (Day 708) and entered extension phase of the study. According to the investigator, the event (dyspepsia) led to hospitalization. The investigator did not suspect a relationship between the event (dyspepsia) and the study medication. As per the Novartis safety physician, although the patient developed dyspepsia on the same day of the most recent dose of study medication, the event could be better explained by malnutrition and viral infection, hence the event was assessed as not suspected.

Patient (b) (6)] An 11-year-old Caucasian female with multiple sclerosis was screened for the study on (b) (6) and received the first dose of study medication (fingolimod) on (b) (6) (Day 1). The patient was diagnosed with multiple sclerosis on (b) (6) . The patient had experienced one relapse during the past 12 months and one relapse during the 12 to 24 months before study entry; and her last relapse prior to enrollment was on (b) (6) The patient was not treated with any MS disease-modifying drug prior to enrollment. At Screening, the patient's EDSS score was 1.0. The patient had no relevant prior medical history. No concomitant medications were taken prior to enrollment. During the study, the patient received paracetamol as pre-treatment on (b) (6) On (b) (6) (Day 6), the patient experienced vomiting and abdominal pain, and was diagnosed with acute gastrointestinal infection (mild in severity). On the same day (Day 6), she was hospitalized. The patient also experienced hyperpyrexia and diarrhea. No action was taken with the study medication due to the event. On the same day, the patient received glucosaline as a hydration therapy for the event. The investigator reported that the patient was infected by her brother, who also had similar symptoms 3 days prior to this event. The event (gastrointestinal infection) completely resolved on (b) (6) (Day 7). The patient was discharged from the hospital on (b) (6) (Day 8). The patient completed the study with the last dose on (b) (6) (Day 721) and entered extension phase of the study. According to the investigator, the event (gastrointestinal infection) led to hospitalization. The investigator did not suspect a relationship between the event (gastrointestinal infection) and the study medication.

> *Reviewer Comment: The two cases above appear to be viral gastroenteritis complicated by an inability to take adequate fluids by mouth requiring hospitalization for dehydration. The dyspepsia syndrome description used for one case was re-coded in the reviewer SAE table to depict more clearly the clinical picture described. A relationship of fingolimod to severe gastroenteritis is possible due to the known increased risk of infection with fingolimod treatment. Dehydration due to protracted vomiting is a*

common reason for hospitalization in previously healthy children and is not attributable directly to fingolimod.

Patient (b) (6) A 15-year-old Caucasian male with multiple sclerosis was screened for the study on (b) (6) and received the first dose of study medication (fingolimod) on (b) (6) (Day 1). The patient was diagnosed with multiple sclerosis on (b) (6) The patient was not treated with any MS disease-modifying drug prior to enrollment. At Screening, the patient's EDSS score was 1.5. The patient's relevant medical history included varicella on (b) (6) During the study, the patient additionally received Augmentin (amoxicillin and clavulanate); metamizole sodium from (b) (6) to (b) (6) and Mucosolvan (ambroxol hydrochloride) from (b) (6) to (b) (6) for upper respiratory tract infection. On (b) (6) (Day 164), the patient experienced facial pain, edema, erythema, and increased body temperature (up to 38°C), and was diagnosed with severe facial cellulitis. The patient was hospitalized on (b) (6) (Day 166). No action was taken with the study medication. On the same day (Day 166), the laboratory test results showed white blood cell (WBC) count of 7.2×10^9/L (normal range: 4.0-10.7 × 10^9/L), neutrophil count of 5.95 × $10^3/mm^3$ (normal range not reported), and neutrophil of 82.6% (normal range: 43%-74%). The urine dipstick test showed trace amount of ketone and protein. Urine culture was positive for Candida albicans. On (b) (6) (Day 167), he underwent skin excision and was treated with tobramycin on (b) (6) and fluconazole, amikacin sulfate, metronidazole, and ceftriaxone sodium from (b) (6) to (b) (6) for the event. On (b) (6) (Day 167), microbiological examination of wound secretion was negative. On (b) (6) (Day 173), a repeat laboratory test results showed WBC count of 5.481×10^9/L, neutrophil count of 3.86 × $10^3/mm^3$, and neutrophil of 70.5%. On (b) (6) (Day 173), the event (cellulitis) completely resolved, and the patient was discharged from the hospital. On (b) (6) (Day 174), the patient developed severe abscess in the left mandibular-lingual region (oral abscess). On the same day, he was hospitalized. His X-ray of facial bones was normal. No action was taken with the study medication. On the same day (Day 174), he underwent incision and drainage, and was treated with cefazolin sodium, gentamicin, and metronidazole from (b) (6) to (b) (6) and clindamycin from (b) (6) to (b) (6) On (b) (6) (Day 176), the event (oral abscess) completely resolved, and the patient was discharged from the hospital on the same day (Day 176). The patient completed the study with the last dose on (b) (6) (Day 494) and entered extension phase of the study. According to the investigator, the events (cellulitis and oral abscess) led to hospitalization. The investigator did suspect a relationship between the events (cellulitis and oral abscess) and the study medication. The investigator reported that the study medication could probably cause lower immunity that increased the risk of infections. As per the Novartis safety physician, the role of study medication in the events (cellulitis and oral abscess) could not be excluded.

Reviewer Comment: While cellulitis and oral abscesses are not uncommon in children, the presence of both simultaneously in a patient with a lower than expected white blood

cell count in the setting of a large abscess are strongly suggestive of sequelae related to the known capability of fingolimod to reduce lymphocyte counts in serum and impair immune response.

Patient (b) (6) A 15-year-old Caucasian male with multiple sclerosis was screened for the study on (b) (6) and received the first dose of study medication (fingolimod) on (b) (6) (Day 1). The patient was diagnosed with multiple sclerosis in November 2013. The patient experienced one relapse during the past 12 months and one relapse during the 12 to 24 months before study entry; and his last relapse prior to enrollment was in August 2014. The patient was treated with the following MS disease-modifying drug prior to enrollment: Avonex (interferon β-1a) until (b) (6) No additional immunomodulatory or immunosuppressive drugs for MS were administered. At Screening, the patient's EDSS score was 1.5. The patient's relevant medical history included seasonal allergy. Concomitant medications taken prior to enrollment included Uvedose (cholecalciferol) from (b) (6) for vitamin D deficiency and Advil (ibuprofen) from November 2014 as a prophylaxis. During the study, the patient additionally received ibuprofen from (b) (6) to (b) (6) for cephalalgia, Solumedrol (methylprednisolone) on (b) (6) for muscle weakness, and amitryptiline and ibuprofen from (b) (6) to (b) (6) for cephalgia during MS relapse.

Event 1 (Viral pharyngitis): On (b) (6) (Day 65), the patient presented with fever of 38.2°C to 38.5°C, nausea, ataxia, vertigo, and cephalgia. The investigator suspected that these symptoms might be due to a new demyelinating lesion (multiple sclerosis), but cerebral and spinal magnetic resonance imaging did not show any new lesions. On (b) (6) (Day 66), the patient recovered from fever. On (b) (6) (Day 67), the C-reactive protein (CRP) was 89 mg/L (normal range: < 5 mg/L), and he was hospitalized. On (b) (6) (Day 68), his white blood cell count (WBC) was 3800 × 10^6/L (normal range: 4000-10700 × 10^6/L) and lymphocyte count was 280 × 10^6/L (normal range: 1000-4000 × 10^6/L). On (b) (6) (Day 69), his CRP was 57 mg/L, WBC count was 4400 × 10^6/L, lymphocyte count was 360 × 10^6/L, and quantiFERON test was negative; the investigator concluded the final diagnosis as viral pharyngitis (severe in nature) with an onset date of (b) (6) (Day 65). No action was taken with the study medication. The patient was treated with Profenid (ketoprofen) for headache, and ondansetron for nausea from (b) (6) (Day 67) to (b) (6) (Day 68), Laroxyl (amitriptyline) for headache from (b) (6) (Day 67) to (b) (6) (Day 72), and metopimazine for nausea from (b) (6) (Day 68) to (b) (6) (Day 72). The patient recovered from vertigo on (b) (6) (Day 70) and from nausea, ataxia, and headache on (b) (6) (Day 71). The event (viral pharyngitis) completely resolved on (b) (6) (Day 72), and the patient was discharged from the hospital on the same day. The other possible contributory factor included banal viral disease.

Event 2 (Appendicitis): On (b) (6) (Day 390), the patient experienced fever and abdominal pain. On (b) (6) (Day 391), an abdominal ultrasonography showed appendicitis (moderate

in nature; onset date of (b) (6) and he was hospitalized on the same day. No action was taken with the study medication. On (b) (6) (Day 392), the patient underwent coelioscopic appendectomy without complication and was treated with ketoprofen LP from (b) (6) (Day 392), to (b) (6) (Day 393). The event (appendicitis) completely resolved on (b) (6) (Day 393), and the patient was discharged from the hospital on the same day.

Event 3 (Migraine): On (b) (6) (Day 658), the patient was diagnosed with migraine (moderate in nature). No action was taken with the study medication. On (b) (6) (Day 659), the patient was hospitalized and a brain magnetic resonance imaging was stable. The patient was treated with Solumedrol (methylprednisolone sodium succinate) for 3 days and Laroxyl (amitriptyline hydrochloride) from (b) (6) (Day 660) to (b) (6) (Day 662). The event (migraine) completely resolved on (b) (6) (Day 662), and the patient was discharged from the hospital on the same day. The patient completed the study with the last dose on (b) (6) (Day 726) and entered extension phase of the study. According to the investigator, the event (viral pharyngitis) was considered medically significant, led to hospitalization, and disability; the events (appendicitis and migraine) led to hospitalization. The investigator did not suspect a relationship between the events (viral pharyngitis, appendicitis, and migraine) and the study medication. As per the Novartis safety physician, the available information did not allow for a comprehensive causality assessment, and hence the causality for the events of viral pharyngitis and migraine was kept as reported by the investigator with plans to reassess the case upon the receipt of follow up information.

> *Reviewer Comment: Viral pharyngitis is a common occurrence in pediatric patients but rarely requires hospitalization. The neurological symptoms accompanying the acute viral infection in this patient appear to be recrudescent MS symptoms and would not meet protocol criteria for a true clinical relapse that requires persistence of symptoms 30 days after fever resolution. This severe viral infection is possibly related to fingolimod. The patient experienced a third SAE, migraine, and this SAE is discussed below. As stated above, this patient is within the peak age range when appendicitis occurs. Fingolimod treatment is broadly associated with increased risk of infection. In the adult safety data set there was not a notable increase in appendicitis risk, and so there does not appear to be an even greater risk of the abdominal infections associated with appendicitis.*

Patient (b) (6) An 11-year-old Caucasian male with multiple sclerosis was screened for the study on (b) (6) and received the first dose of study medication (fingolimod) on (b) (6) (Day 1). The patient was diagnosed with multiple sclerosis on (b) (6) The patient experienced one relapse during the past 12 months and two relapses during the 12 to 24 months before study entry, and his last relapse prior to enrollment was on (b) (6) He was not treated with any MS disease-modifying drug prior to enrollment. At Screening, the patient's EDSS score was 3.0. The patient had no relevant prior medical history.

The patient did not have any birth defects or history of chronic constipation. Concomitant medications taken prior to enrollment included paracetamol for muscle pain and headache from (b) (6) and vitamin D for MS from (b) (6) During the study, the patient additionally received influenza vaccine on (b) (6) as prophylaxis and ibuprofen for MS symptoms from (b) (6)

Event 1 (Viral infection): On (b) (6) (Day 42), the patient presented with tiredness, weakness, and fever. On the same day (Day 42), a viral infection (severe in nature) was suspected. On (b) (6) (Day 43), a magnetic resonance imaging scan revealed new lesions and decrease in size of a few lesions. On (b) (6) (Day 44), he was hospitalized for this event. No action was taken with study medication. On an unspecified date, a lumbar puncture was negative and laboratory investigations showed a white blood cell count of 0.4 mm^3 (normal range not provided). It was reported that the patient's family members had a viral flu-like illness and all of them had recovered, except for the patient who remained unwell with lethargy, dizziness, high temperature, and inability to get out of bed. The patient was treated with intravenous ceftriaxone and acyclovir from (b) (6) (Day 44) to (b) (6) (Day 50). The event (viral infection) completely resolved on (b) (6) (Day 50) and the patient was discharged from the hospital on the same day. A possible contributory factor was the patient's family members also having a viral illness.

Event 2 (Small intestinal obstruction, gastrointestinal necrosis): On (b) (6) (Day 481), the patient experienced vomiting and abdominal pain (both moderate in nature), constipation (mild in nature), and dehydration. The investigator reported that the patient felt sick and had vomiting after intake of food. On (b) (6) (Day 482), the patient had oliguria (moderate in nature), and he was hospitalized for rehydration and blood tests. He was given dextrose and sodium chloride injection on (b) (6) (Day 482). Study medication was temporarily interrupted from (b) (6) (Day 477) to (b) (6) (Day 519). On (b) (6) (Day 484), the patient had abdominal distension (moderate in nature), and nasogastric tube output showed high bilious aspirate (gastric fluid analysis abnormal; moderate in nature). The patient was treated with ranitidine for high bilious aspirate and mucosal protection from (b) (6) (Day 483) to (b) (6) (Day 497), ondansetron as an anti-emetic from (b) (6) (Day 483) to (b) (6) (Day 498), cefotaxime on (b) (6) and metronidazole from (b) (6) (Day 484) to (b) (6) (Day 490) as antibiotics, and Oromorph (morphine sulfate pentahydrate) on (b) (6) (Day 484) for analgesia. On the same day (Day 484), oliguria resolved. The patient was diagnosed with intussusception and small intestinal obstruction (onset date of (b) (6) severe in nature). On (b) (6) (Day 485), the patient was transferred to another hospital, and underwent emergency laparotomy and bowel resection for small intestinal obstruction and gastrointestinal necrosis (severe in nature). The parts of the intestine that were affected were caecum, transverse colon, and small bowel to the right of the abdomen. He received clonidine, fentanyl, atracurium, and propofol on (b) (6) (Day 485) for sedation. Urinary catheter insertion was done (from (b) (6) to (b) (6) to

monitor urinary output. The events of abdominal pain, vomiting, small intestinal obstruction, and gastrointestinal necrosis were considered resolved on the same day (Day 485), but the patient developed moderate post procedural pain and decreased blood calcium. The patient was treated with morphine from (b) (6) to (b) (6) paracetamol from (b) (6) to (b) (6) and ketamine from (b) (6) to (b) (6) as analgesics; piperacillin/tazobactam from (b) (6) to (b) (6) amikacin from (b) (6) to 11-Apr-2017, and Co-amoxiclav (amoxicillin/clavulanate potassium) from (b) (6) to (b) (6) as antibiotics, and hyoscine butylbromide from (b) (6) to (b) (6) as an anti-spasmodic. Additionally, he was treated with plasmalyte/5% glucose from (b) (6) to (b) (6) and 0.9% sodium chloride from (b) (6) to (b) (6) for hydration and replacement of fluid loss. On (b) (6) (Day 489), the event of abdominal distension resolved. On (b) (6) (Day 490), he presented with moderate dysuria, and on (b) (6) (Day 491), he had mild right lower back pain. On (b) (6) (Day 491), the patient underwent peripherally inserted central catheterization and had total parenteral nutrition (TPN) from (b) (6) to (b) (6) Vitamin D supplement was added to the TPN. On the same day (b) (6)), the event of decreased blood calcium resolved. On (b) (6) (Day 492), constipation resolved, but the patient had right flank pain and diarrhoea (both moderate in nature). On (b) (6) (Day 493), the patient had fluid collection in his right flank (intra-abdominal fluid collection; moderate in nature), and underwent drain insertion with levobupivacaine, propofol, fentanyl, and atracurium. On the same day ((b) (6) the patient received tranexamic acid for prolonged coagulation time. On (b) (6) (Day 494), the patient recovered from mild right lower back pain and right flank pain. On (b) (6) (Day 497), the event of intra-abdominal fluid collection resolved, and the drain was removed. On an unknown date, the patient was discharged from the hospital. The events of diarrhoea were ongoing at completion of the Core Phase. Other possible contributory factor for the event was unclear if it was predisposition to intussusception or if it was related to medication and lymphoid hyperplasia. The investigator stated that intussusception in teenage population was rare, but could be caused by lymphadenopathy. No obvious lymph node hyperplasia was noted, and no unusual condition was seen. On (b) (6) (Day 524), the event of post procedural pain resolved. The patient completed the study with the last dose on (b) (6) (Day 567) and entered extension phase of the study. According to the investigator, the events (viral infection, small intestinal obstruction, and gastrointestinal necrosis) led to hospitalization. The investigator did suspect a relationship between the events (viral infection, small intestinal obstruction, and gastrointestinal necrosis) and study medication. As per the Novartis safety physician, infections are known adverse events with fingolimod, and hence the role of study medication in the event of viral infection could not be excluded. The patient presented with vomiting and resultant dehydration and was diagnosed with bowel obstruction secondary to malrotation and volvulus. In the absence of information around risk factors for small intestinal obstruction, the role of study medication in the event could not be ascertained.

Reviewer Comment: Event 1 appears to be a viral gastroenteritis as the patient's symptoms, and the history of family members with similar symptoms, strongly argue for this diagnosis. Fingolimod increases infection risk so it is related plausibly to the acquisition and potential worsening of this serious viral infection. The Second Event, intussusception leading to bowel necrosis, has a possible relationship to fingolimod therapy. Intussusception is rare in patients outside the first year of life (Jiang et al., 2013), and while intussusception is a known complication of viral gastroenteritis, the peak incidence of this complication occurs before age 2 years (Restivo et al., 2017). However, the patient does not appear to have had an antecedent gastrointestinal infection immediately prior to Event 2 (Event 1 ended 431 days before Event 2). The Investigator advanced intestinal lymphoid hyperplasia as a possible cause of the intussusception; the pathology from the excised tissue was negative for anatomical abnormalities. The absence of lymphoid hyperplasia on the surgical pathology specimens is not necessarily reassuring as the patient had paused taking study drug on Day 477, and thus the lymphoid tissue may have regressed by Day 485, when surgery was performed. The relationship between fingolimod and intussusception risk is uncertain. Monitoring for intussusception cases in the pediatric population is indicated.

Leukopenia/Agranulocytosis

Below are the summaries of the three cases identified with SAEs of leukopenia. One case had concurrent agranulocytosis. The relationship of reduced serum white count to fingolimod is established and is noted in the current fingolimod labeling with monitoring recommendations.

Patient (b) (6) A 15-year-old Caucasian female with multiple sclerosis was screened for the study on (b) (6) and received the first dose of study medication (fingolimod) on (b) (6) (Day 1). The patient was diagnosed with multiple sclerosis on (b) (6) The patient experienced one relapse during the past 12 months and one relapse during the 12 to 24 months before study entry, and her last relapse prior to enrollment was on (b) (6) The patient was not treated with any MS disease modifying drugs prior to enrollment. At Screening, the patient's EDSS score was 0.0. The patient had no relevant medical history. No concomitant medications were taken prior to enrollment. During the study, the patient received Lymecyclinum (tetracycline) from (b) (6) to (b) (6) for acne and alprazolam from (b) (6) to (b) (6) for anxiety. On (b) (6) (Day 182), the patient's laboratory tests showed absolute basophil count of 0, absolute eosinophil count of 0, absolute monocyte count of 0.3 (units and normal ranges not provided), and white blood cell count of 12× 10^9/L (normal range: 4.0-10.7 × 10^9/L). On the same day (Day 182), an event of severe leukopenia was reported. On (b) (6) (Day 183), the patient's neutrophil count was 0.5 × 10^9/L (normal range: 1.6-7.4 × 10^9/L). The patient did not have any concurrent symptoms consistent with the abnormal laboratory results. On the same day (Day 183), an event of severe agranulocytosis was reported. Subsequently, she was hospitalized due to these events. Study

medication was temporarily interrupted on (b) (6) (Day 188) due to the events of leukopenia and agranulocytosis. After interruption, an improvement was noted. Study medication was restarted on (b) (6) (Day 223). The event (agranulocytosis) completely resolved on (b) (6) (Day 312). The event (leukopenia) completely resolved on (b) (6) (Day 375). The patient completed the study with the last dose on (b) (6) (Day 748) and entered extension phase of the study. According to the investigator, the event (agranulocytosis) was considered medically significant and the events (agranulocytosis and leukopenia) led to hospitalization. The investigator did suspect a relationship between the event (agranulocytosis and leukopenia) and the study medication. As per the Novartis safety physician, the recent administration of tetracycline provided a more likely explanation for the event in this patient who had tolerated the study medication for approximately 6 months.

> *Reviewer Comment: The combination of tetracycline and fingolimod may have precipitated the agranulocytosis. The timing of onset of agranulocytosis within one month of initiating tetracycline, the rapid resolution off tetracycline therapy, and the patient otherwise tolerating fingolimod therapy are further evidence of a limited concomitant medication effect.*

Patient (b) (6) An 11-year-old Caucasian male (b) (6)) with multiple sclerosis was screened for the study on (b) (6) and received the first dose of study medication (fingolimod) on (b) (6) (Day 1). The patient was diagnosed with multiple sclerosis on (b) (6) The patient experienced one relapse during the past 12 months and no relapses during the 12 to 24 months before study entry, and his last relapse prior to enrollment was on (b) (6) The patient was not treated with any MS disease-modifying drug prior to enrollment. At Screening, the patient's EDSS score was 0.0. The patient had no relevant prior medical history. No concomitant medications were taken prior to enrollment. During the study, the patient received ibuprofen for common cold from (b) (6) to (b) (6) The patient also received psychotherapy for depression from (b) (6) On (b) (6) (Day 46), the patient was run over by a car, resulting in hospitalization due to severe head injury. After admission, he remained unconscious for one day. He had headache, concentration problems, and remained very sleepy. A computerized tomogram report showed hematoma of soft tissues in orbital localization and mild concurrent hemorrhage in the right frontal lobe, and pubic bone fracture. His neurological examination was normal. No action was taken with the study medication. He was treated with paracetamol, cefazolin sodium, and metamizole from (b) (6) to (b) (6) for head injury. Additional treatment included ketoprofen, mannitol, furosemide, cefuroxime, and Losec (omeprazole). The event (head injury) resolved on (b) (6) (b) (6) (Day 59), and the patient was discharged from the hospital on the same day. On (Day 60), the laboratory test results showed increased gamma-glutamyltransferase (GGT) of 187 U/L (normal range: 3-22 U/L), and increased alanine aminotransferase (ALT) of 156 U/L (normal range: 5-30 U/L) (both severe in nature), total bilirubin of < 3 (normal range: 2-21 µmol/L), direct bilirubin of 1 µmol/L (normal range: 0-7

µmol/L), increased alkaline phosphatase (ALP) of 305 U/L (normal range: 0-299 U/L), increased aspartate aminotransferase of 82 U/L (normal range: 0-41 U/L). No action was taken with the study medication due to these events. No concomitant medications were administered to treat these events. The event (ALT increased) completely resolved on (b) (6) (Day 69). The event (GGT increased) completely resolved on (b) (6) (Day 95). The patient experienced frequent headache post trauma and was treated with metamizole from (b) (6) to (b) (6) for headache; magnesium, vitamin B6 (pyridoxine hydrochloride), carbamazepine, and piracetam for post traumatic headache/headache from (b) (6) On (b) (6) (Day 181), the patient was diagnosed with mild leukopenia. On the same day, his laboratory tests showed white blood cell count of 2.3 × 10^9/L (normal range: 4-10.7 × 10^9/L). He also had sore throat probably due to viral infection. No action was taken with the study medication due to the event of leukopenia. The other possible contributory factor for the event of leukopenia was reported as viral infection. The event (leukopenia) completely resolved on (b) (6) (Day 195). The patient completed the study with the last dose on (b) (6) (Day 286) and entered extension phase of the study. According to the investigator, the event (head injury) was considered life threatening and led to hospitalization and the event (leukopenia, ALT increased and GGT increased) was considered medically significant. The investigator did not suspect a relationship between the event (head injury) and the study medication, but did suspect a relationship between the events (leukopenia, ALT increased, and GGT increased) and the study medication. As per the Novartis safety physician, the event of head injury could be attributed to car accident (blindsiding), and was assessed in concurrence with the investigator's assessment as not suspected. The role of study medication in the events of leukopenia, gammaglutamyl transferase increased and alanine aminotransferase increased could not be ruled out.

> *Reviewer Comment: Leukopenia in this instance appears plausibly related to fingolimod treatment. The ALT, AST, and GGT elevations will be discussed below. The head trauma appears wholly unrelated to fingolimod treatment. Pedestrian injury is not an uncommon occurrence in children. The 2015 United States National Highway Traffic Safety Administration Data Sheet for Pedestrians (the most recent year available with injury statistics) states that 5% of pedestrians injured in a car collision were children ≤ 14 years old and that the fatality rate for male pedestrians ≤ 14 years old was estimated at 0.47 per 100,000. There are no data in the adult exposure data to support a claim of increased risk of experiencing traumatic injuries while taking fingolimod.*

Patient (b) (6) A 10-year-old Caucasian male ((b) (6)) with multiple sclerosis was screened for the study on (b) (6) and received the first dose of study medication (fingolimod) on (b) (6) (Day 1). The patient was diagnosed with multiple sclerosis on (b) (6) . The patient experienced one relapse during the past 12 months and two relapses during the 12 to 24 months before study entry, and his last relapse prior to enrollment was on (b) (6) The patient was not treated with any MS disease-modifying drug prior to

enrollment. At Screening, the patient's EDSS score was 1.5. The patient's relevant medical history included thyroid mass since April 2014. No concomitant medications were taken prior to enrollment. During the study, the patient did not receive any concomitant medications.

Event 1 (Leukopenia): On (b) (6) (Day 35), at Visit 5 the patient's white blood cell (WBC) count was decreased (moderate in nature) at 1.9×10^9/L (normal range: 4.0-10.7 × 10^9/L). Study medication was permanently discontinued due to the event of leukopenia and the patient received the last dose of study medication on (b) (6) (Day 38). On (b) (6) (32 days after the last dose of study medication), the event (leukopenia) completely resolved.

Event 2 (Humerus fracture): On (b) (6) (4 days after the last dose of study medication), the patient fell from his bike and experienced a sharp pain in his left hand that resulted in hospitalization. On (b) (6) (5 days after the last dose of study medication), an X-ray results showed closed proximal left humerus fracture (moderate in nature) with dislocation with an onset date of (b) (6) On (b) (6) (5 days after the last dose of study medication), he was hospitalized and underwent surgery of the fractured humerus with plaster casting. The patient was also treated with Ketonal (ketoprofen) and ceftriaxone from (b) (6) to (b) (6) On (b) (6) (7 days after the last dose of study medication), the patient discharged from the hospital. The patient also received ibuprofen from (b) (6) to (b) (6) On (b) (6) (32 days after the last dose of study medication), the plaster cast was removed and the function of the left hand was restored with no pain during the movement. On the same day, the event (humerus fracture) completely resolved. The End of Study visit was completed on (b) (6) (32 days after the last dose of study medication), and the patient completed the Follow-up visit on (b) (6) (109 days after the last dose of study medication). The patient did not enter the Extension Phase. According to the investigator, the event (humerus fracture) led to hospitalization. The investigator did not suspect a relationship between the events (humerus fracture and leukopenia) and the study medication. As per the Novartis safety physician, the event of humerus fracture was due to fall; hence, the causality was in concurrence with the investigator's assessment as not suspected.

> *Reviewer Comment: The patient's leukopenia can be plausibly linked to drug treatment with fingolimod. Overall, humerus fractures are among the most common fractures children experience (Pasco* et al.*, 2015). Fractures of the proximal humerus are less frequent in children than in adults, but there is no evidence from safety analyses of the adult RMS trials with fingolimod to support an increased risk of falls or fractures in any bone that can be reasonably attributed to fingolimod. Though there are three traumatic injury cases described in this data set, the mechanisms of the injuries are sufficiently common in children and adolescents so as not to be concerning for a safety signal, but monitoring of safety reports for unusual mechanisms or overrepresentations of common traumas should continue. There were equal numbers of fractures reported as AEs in both treatment groups, which favors the SAE imbalance being due to chance and not*

treatment-related. Alternatively, if fingolimod treatment is improving pediatric patients' daily function, then it is also possible that the increased risk of bone fractures and traumatic injury will approach that of the general population as these children and adolescents resume activities typical of their healthy peers.

Cardiac Effects

Below I provide the summary report of atrioventricular block in a pediatric patient in the fingolimod treatment group. New onset of heart block with fingolimod initiation is a known SAE with fingolimod. The label elaborates this risk and provides recommendations regarding first dose monitoring in adults that Novartis proposes to be extended to pediatric patients.

Patient (b) (6) A 10-year-old Asian female with multiple sclerosis was screened for the study on (b) (6) and received the first dose of study medication (fingolimod) on (b) (6) (Day 1). The patient was diagnosed with multiple sclerosis on (b) (6) The patient experienced one relapse during the past 12 months and no relapses during the 12 to 24 months before study entry, and her last relapse prior to enrollment was on (b) (6) The patient was treated with the following MS disease-modifying drug prior to enrollment: Rebif (interferon β-1a) until (b) (6) and Copaxane (glatiramer acetate) until (b) (6) No additional immunomodulatory/immunosuppressive drugs for MS were administered. At Screening, the patient's EDSS score was 0.0. The patient had no relevant prior medical history. The patient did not have any history of electrocardiogram (ECG) abnormalities, valvular disease, or congenital heart disease. No concomitant medications were taken prior to enrollment. During the study, the patient additionally received fish oil from (b) (6) to March 2017 and vitamin D NOS from (b) (6) On (b) (6) (Day -27), the patient's baseline heart rate was 76 beats per minute (bpm). The patient was enrolled on (b) (6) (Day 1) and received the low dose of study medication (0.25 mg/day) due to body weight below 40 kg. On (b) (6) (Day 1), the patient's weight was 28.0 kg (7th percentile). On the same day (Day 1), the patient underwent the first dose administration. The patient's pre-dose ECG was normal (8:49 AM). The patient had the 6 hours post-dose ECG conducted at 2:54 PM and it revealed a first degree AV block with prolonged QTc. The patient underwent extended monitoring and had repeat ECGs conducted at 5:05 PM (~8 hours post first dose), 5:06 PM, 6:07 PM and 6:12 PM (~9 hours post first dose) and all revealed a first degree AV block. The patient was discharged from the clinic and went home. On (b) (6) (Day 31), at Visit 5 (Month 1), no first degree AV block was present on the ECG. On (b) (6) (Day 64), at Visit 6 (Month 2), the patient underwent dose up titration (full dose) based on pharmacokinetic results and was monitored in the clinic. On the same day (Day 64), the patient's weight was 28.5 kg (6th percentile). On (b) (6) (Day 64), at 08:53 am, an ECG prior to administration of study medication was normal (PRT axes of 76 to 18, PR interval of 178 ms, QRS duration of 100 ms, QT/QTc of 341/394 ms, average RR of 627 ms, QTcB of 430 ms, and QTcF of 398 ms). Following administration of study medication, during the sixth hourly monitoring, the patient had a Mobitz I cardiologic abnormality (second degree atrioventricular block; severe in nature), which, subsequently

changed to a first degree atrioventricular (AV) block during the ninth hourly monitoring. On the same day (Day 64), her sitting blood pressure was 104/65 mmHg and sitting pulse rate was 87 bpm. The patient's systolic blood pressure and heart rate on the same day was as follows:

Vital Signs:

Examination date	Time	Sitting pulse (bpm)	Mean Systolic blood pressure (mmHg)	Mean Diastolic blood pressure (mmHg)
(b) (6)	Pre-dose	74	109	60
(Visit 3 Day 1)	10:06 (Hr 1)	91	116	64
	11:04 (Hr 2)	87	112	59
	12:09 (Hr 3)	74	106	54
	12:58 (Hr 4)	69	99	54
	14:01 (Hr 5)	75	107	67
	14:53 (Hr 6)	68	100	56
	15:59 (Hr 7)	73	107	56
	17:05 (Hr 8)	68	103	57
	18:15 (Hr 9)	73	108	55
(b) (6)	Pre-dose	89	104	65
(Visit 6 Day 64)	10:04 am (Hr 1)	90	110	65
	11:10 am (Hr 2)	77	107	65
	12:01 pm (Hr 3)	81	106	63
	01:01 pm (Hr 4)	97	106	65
	02:10 pm (Hr 5)	97	104	66
	03:02 pm (Hr 6)	95	112	69
	05:10 pm (Hr 8)	99	110	72
	05:58 pm (Hr 9)	99	109	70
(b) (6)	Pre-dose	103	114	65
(Visit 6 Day 65)	9:53 (Hr 1)	102	107	62
	10:55 (Hr 2)	90	115	64
	11:45 (Hr 3)	92	109	63
	12:53 (Hr 4)	88	118	64
	13:51 (Hr 5)	73	106	62
	14:51 (Hr 6)	86	106	60

She was asymptomatic and hemodynamically stable during hospitalization and her ECG was monitored continuously. An ECG at 05:02 pm showed ventricular rate of 99 bpm, PRT axes of 999, PR interval of 0 ms, QRS duration of 81 ms, QT/QTc of 329/386 ms, average RR of 601 ms, QTcB of 424 ms, and QTcF of 389 ms. No action was taken with the study medication. No concomitant medications were administered to treat the event. An ECG at 06:03 pm showed

ventricular rate of 101 bpm, PRT axes of 68, PR interval of 262, QRS duration of 85 ms, QT/QTc of 356/414 ms, average RR of 594 ms, QTcB of 461 ms, and QTcF of 423 ms. The event (atrioventricular block second degree) completely resolved on (b) (6) (Day 64). The patient was hospitalized overnight for safety monitoring. On (b) (6) (Day 65), the patient underwent Day 2 of the dose increase monitoring as required per protocol. The pre-dose ECG showed sinus tachycardia and conduction prolonged QTc (ventricular rate of 151 bpm, PRT axes of 78, PR interval of 156, QRS duration of 81 ms, QT/QTc of 329/397 ms, average RR of 520 ms, QTcB of 456 ms, and QTcF of 409 ms). The patient's 3 hour ECG was normal and the 6-hour ECG showed conduction prolonged QTc. On (b) (6) (Day 65), she was discharged from the hospital. The patient completed the study with the last dose on (b) (6) and entered extension phase of the study. According to the investigator, the event (atrioventricular block second degree) led to hospitalization. The investigator did suspect a relationship between the event (atrioventricular block second degree) and the study medication. The investigator provided rationale for causality assessment as the events occurred following oral dosing of study medication during 6 hours post-dose observation period and there were no other contributory factors. As per the Novartis safety physician, AV blocks are known adverse events to occur at the initiation of fingolimod and were hence assessed as suspected.

Vital signs:

Visit	Examination date	Weight (kg)	Sitting pulse (bpm)	Mean systolic blood pressure (mmHg)	Mean diastolic blood pressure (mmHg)
Visit 1	(b) (6)	28.6	77	105	62.33
Visit 2		28.0	88	98	60.33
Visit 3 (see above)					
Visit 5		28.6	77	104.67	57.33
Visit 6 (see above)					
Visit 10		32.8	85	106	57.33

Reviewer Comment: This case illustrates that both the 0.25 mg and 0.5 mg doses of fingolimod can induce cardiac conduction block in pediatric patients and reinforces the need for first dose monitoring at initial intake of any dose of fingolimod, even after prior treatment at a lower dose, in all patients ≥ 10 years to < 18 years old.

Liver Injury

The current label for fingolimod advises that elevations of liver enzymes may occur and provides counseling regarding monitoring. The case summarized below had a transient transaminase elevation in setting of a traumatic injury. This case was discussed above in regards to the SAE of leukopenia.

Patient [(b) (6) An 11-year-old Caucasian male (b) (6) with multiple sclerosis was screened for the study on (b) (6) and received the first dose of study medication (fingolimod) on (b) (6) (Day 1). The patient was diagnosed with multiple sclerosis on (b) (6) The patient experienced one relapse during the past 12 months and no relapses during the 12 to 24 months before study entry, and his last relapse prior to enrollment was on (b) (6) The patient was not treated with any MS disease-modifying drug prior to enrollment. At Screening, the patient's EDSS score was 0.0. The patient had no relevant prior medical history. No concomitant medications were taken prior to enrollment. On (b) (6) (Day 46), the patient was run over by a car, resulting in hospitalization due to severe head injury. After admission, he remained unconscious for one day. He had headache, concentration problems, and remained very sleepy. A computerized tomogram report showed hematoma of soft tissues in orbital localization and mild concurrent hemorrhage in the right frontal lobe, and pubic bone fracture. His neurological examination was normal. No action was taken with the study medication. He was treated with paracetamol, cefazolin sodium, and metamizole from (b) (6) to (b) (6) for head injury. Additional treatment included ketoprofen, mannitol, furosemide, cefuroxime, and Losec (omeprazole). The event (head injury) resolved on (b) (6) (Day 59), and the patient was discharged from the hospital on the same day. On (b) (6) (Day 60), the laboratory test results showed increased gamma-glutamyltransferase (GGT) of 187 U/L (normal range: 3-22 U/L), and increased alanine aminotransferase (ALT) of 156 U/L (normal range: 5-30 U/L) (both severe in nature), total bilirubin of < 3 (normal range: 2-21 µmol/L), direct bilirubin of 1 µmol/L (normal range: 0-7 µmol/L), increased alkaline phosphatase (ALP) of 305 U/L (normal range: 0-299 U/L), increased aspartate aminotransferase of 82 U/L (normal range: 0-41 U/L). No action was taken with the study medication due to these events. No concomitant medications were administered to treat these events. The event (ALT increased) completely resolved on (b) (6) (Day 69). The event (GGT increased) completely resolved on (b) (6) (Day 95). The patient completed the study with the last dose on (b) (6) (Day 286) and entered extension phase of the study. According to the investigator, the event (head injury) was considered life threatening and led to hospitalization and the event (leukopenia, ALT increased and GGT increased) were considered medically significant. The investigator did not suspect a relationship between the event (head injury) and the study medication, but did suspect a relationship between the events (leukopenia, ALT increased, and GGT increased) and the study medication. As per the Novartis safety physician, the event of head injury could be attributed to car accident (blindsiding), and was assessed in concurrence with the investigator's assessment as not suspected. The role of study medication in the events of leukopenia, gammaglutamyltransferase increased and alanine aminotransferase increased could not be ruled out.

LFT laboratory values:

Visit Visit date	ALT (normal range: 5-30 U/L)	AST (normal range: 0-41 U/L)	Total bilirubin (normal range: 2-21 µmol/L)	Direct bilirubin (normal range: 0-7 µmol/L)	Alkaline phosphatase (normal range: 0-299 U/L)	Gamma-glutamyltransferase (normal range: 3-22 U/L)
V2 (b) (6)	13	28	6	2	292	14
Unscheduled (b) (6)	14	27	7	3	245	14
V4 (b) (6)	11	23	3	2	**317**	13
V5 (b) (6)	19	32	7	-	**340**	12
V6 (b) (6)	**156**	82	<3	1	**305**	**187**
Unscheduled (b) (6)	**54**	**43**	6	-	236	**105**
V7 (b) (6)	13	23	6	2	251	30
V51 (b) (6)	12	25	7	3	329	15
V71 (b) (6)	10	21	4	2	**300**	16
V72 (b) (6)	17	23	6	3	**331**	15

Reviewer Comment: The transaminase elevations' concurrence with a traumatic event involving a crush soft tissue injury (being run over by a motor vehicle) suggests an alternate etiology, post-traumatic muscle release of transaminases. Since muscle-specific transaminase isoforms were not obtained, there is no way to ascertain whether the AST/ALT elevations occurred in liver- or muscle-specific isoforms. The GGT elevation might suggest a liver-specific origin and drug-induced liver toxicity, but it is also possible that the motor vehicle-induced trauma the patient experienced could have involved direct injury to the liver or kidney, which would cause serum elevations in AST, ALT, and GGT levels. The absence of a parallel rise in either serum bilirubin marker suggests that the liver's metabolic insult was either absent or mild. Therefore, the relationship of this patient's transaminase elevations to fingolimod is unclear.

Other SAE Narratives

Leukoclastic Vasculitis

Below I describe a single case of SAE of hypersensitivity vasculitis reaction. The current labeling for fingolimod includes warnings regarding both hypersensitivity reactions and vascular events, and this vasculitis event would identify under either of these risks. No additional label changes appear necessary to address this known risk.

Patient [(b) (6)] A 17-year-old Caucasian female [(b) (6)]) with multiple sclerosis was screened for the study on [(b) (6)] and received the first dose of study medication (fingolimod) on [(b) (6)] (Day 1). The patient was diagnosed with multiple sclerosis in March 2012. The patient experienced no relapses during the past 12 months, but experienced two relapses during the 12 to 24 months before study entry; and her last relapse prior to enrollment was on [(b) (6)] The patient was treated with the following MS disease modifying drug prior to enrollment: interferon β-1a i.m from [(b) (6)] to [(b) (6)] interferon β-1a until [(b) (6)] and Avonex (interferon β-1a) until [(b) (6)] No additional immunomodulatory/immunosuppressive drugs for MS were administered. At Screening, the patient's EDSS score was 1.0. The patient's relevant medical history included tonsillitis on [(b) (6)] (not active at the start of study medication; treated with Golamixin (benzocaine/cetrimonium bromide/tyrothricin), ketoprofen (ketoprofen lysine), and Macladin (clarithromycin) from [(b) (6)] to [(b) (6)] Other concomitant medication taken prior to enrollment included Yasmine (drospirenone/ethinyl estradiol) for contraception from [(b) (6)] During the study, the patient additionally received Lanzox (lansoprazole) for gastritis from [(b) (6)] paracetamol as prophylaxis on [(b) (6)] and Pineal as a prophylaxis for insomnia from [(b) (6)] On [(b) (6)] (Day 1), the patient's physical examination was normal. On [(b) (6)] (Day 2), the patient presented to the emergency department with symmetrical rash on her legs, and was diagnosed with urticaria (mild in severity). The patient was treated with chlorpheniramine maleate and Urbason (methylprednisolone) for the event on [(b) (6)] The event (urticaria) resolved on [(b) (6)] (Day 3). On [(b) (6)] (Day 9), the patient was hospitalized due to widespread papular rash and erythema. On the same day, she was diagnosed to have hypersensitivity vasculitis with arthralgia (both moderate in severity). A skin biopsy was performed and results confirmed vasculitis. C-reactive protein was elevated at 1.31 mg/dL (cut off was < 0.5 mg/dL). Hemochrome and other blood tests (glucose, creatinine, total bilirubin, sodium, potassium, alanine aminotransferase, and aspartate aminotransferase) were normal. Study medication was permanently discontinued due to the event (hypersensitivity vasculitis), and she received the last dose on the same day (Day 9). The patient was treated with Urbason (methylprednisolone) and Unasyn (ampicillin/sulbactam) for the events from [(b) (6)] to [(b) (6)] The event (arthralgia) resolved on [(b) (6)] (8 days after the last dose of study medication), and the patient was discharged from the hospital on the same day. The event (hypersensitivity vasculitis) was considered to have improved from moderate to mild in severity on [(b) (6)] (9 days after the last dose of study medication); de-challenge was positive. The patient received amoxicillin/clavulanic acid from [(b) (6)] to [(b) (6)] and Medrol (methylprednisolone) from [(b) (6)] to [(b) (6)] The event (hypersensitivity vasculitis) completely resolved on [(b) (6)] (27 days after the last dose of

study medication). In the investigator's opinion, the other possible contributory factors for hypersensitivity vasculitis were tonsillitis and the concomitant medications of benzocaine/cetrimonium bromide/tyrothricin, ketoprofen, and clarithromycin. The patient was discontinued from the study due to the event (hypersensitivity vasculitis). The End of Study visit was completed on (b) (6) According to the investigator, the events (hypersensitivity vasculitis, arthralgia) led to hospitalization. The investigator did suspect a relationship between the events (hypersensitivity vasculitis, arthralgia) and the study medication. In the investigator's opinion, the other possible contributory factor was tonsillitis. As per the Novartis safety physician, the event was unexpected according to the Investigator's Brochure. The information provided in this individual case did not warrant a change to the Investigator's Brochure, although it would be monitored closely. The causality of the event was assessed as suspected.

> *Reviewer Comment: The timing of this reaction, following just a single dose of fingolimod, is consistent with a hypersensitivity vasculitis due to treatment. In drug hypersensitivity vasculitis or so-called "leukoclastic" vasculitis, the predominant driver of the drug-induced vasculitis response is an inflammatory process involving inflammation of the vascular endothelium and complement deposition within small-caliber vessels. Separately, there is a known association between fingolimod and several vasculopathic processes such as PRES, ischemic strokes, and peripheral arterial occlusive disease. The etiopathology underlying these vascular SAEs is not clear but is potentially inflammatory, but, unlike drug-induced vasculitis, these vascular SAEs would be confined to large- and medium-caliber vessels. Finally, it would not be implausible that a vasculitis due to autoantibody (ANA, ANCA) complex formation could emerge as a consequence of fingolimod treatment in medium- or small-caliber vessels. An autoimmune vasculitis mediated by antibody complexes would require that a patient begin producing auto-reactive antibodies. In order to promote the conditions necessary to foster auto-reactive antibody production, a substantial sequestration of inhibitory white blood cells and release of circulating B-lymphocytes from regulatory control would need to occur to make such an etiology possible. A single dose of fingolimod would not be sufficient to create this degree of immune dysregulation. Given the timing and obtained pathology, of these three etiologies, the most reasonable hypothesis for this patient's vasculitis is a drug induced "leukoclastic" vasculitis which is drug related but can occur with any newly introduced exogenous substance. Continued monitoring of safety reports for all events listed as "vasculitis" is warranted, however, given the theoretical concerns discussed above.*

<u>Uveitis</u>

Below is an edited summary of a single pediatric patient who developed uveitis while taking fingolimod. Uveitis is a rare complication of MS, occurring in <1% of diagnosed cases (Kaya *et al.*, 2014). The current labeling for fingolimod advises of an increased risk of macular edema in patients with a history of uveitis, but there is no stated risk of developing uveitis *de novo*.

Patient [(b) (6)] A 16-year-old Caucasian female ((b) (6)) with multiple sclerosis was screened for the study on (b) (6) and received the first dose of study medication (fingolimod) on (b) (6) (Day 1). The patient was diagnosed with multiple sclerosis in May 2015. The patient experienced three relapses during the past 12 months and no relapses during the 12 to 24 months before study entry; and her last relapse prior to enrollment was in December 2015. The patient was not treated with any MS disease-modifying drug prior to enrollment. At Screening, the patient's EDSS score was 1.0. The patient's relevant prior medical history included worsening of vision in the left eye in form of negative scotoma. The patient did not have any hereditary diseases. Concomitant medications were taken prior to enrollment included methylprednisolone for MS relapse from (b) (6) to (b) (6) During the study, the patient received ibuprofen for menstrual discomfort on (b) (6) and for headache on (b) (6) and, pantoprazole as a gastric prophylaxis from (b) (6) to (b) (6) On (b) (6) (Day 399), the patient experienced blurriness and black spots in the left eye. On (b) (6) (Day 400), she visited the site and underwent a computerized visual field examination and an optical coherence tomography, which showed no macular oedema. On (b) (6) (Day 401), she was diagnosed with autoimmune uveitis (moderate in nature). On the same day, she was hospitalized for this event. The concomitant medications administered to treat the event included methylprednisolone (date not reported) and prednisone from (b) (6) to (b) (6) No action was taken with the study medication due to the event. The patient was discharged from the hospital on (b) (6) (Day 407). The event (autoimmune uveitis) completely resolved on (b) (6) (Day 483). Other possible contributory factor was progression of study indication. The patient completed the study with the last dose on (b) (6) (Day 483) and entered extension phase of the study. According to the investigator, the event (autoimmune uveitis) led to hospitalization. The investigator did not suspect a relationship between the event (autoimmune uveitis) and the study medication. Other possible contributory factor for the event was reported as progression of study indication. As per the Novartis safety physician, considering the autoimmune etiology of the event, it could be better attributed to the underlying disease indication rather than the study medication, and was hence assessed in concurrence with the investigator's assessment as not suspected.

Reviewer Comment: A review of the published literature suggests a complex relationship between fingolimod and uveitis. There are reports that fingolimod-induced macular edema occurs at a higher rate in patients with a prior history of uveitis (Zarbin et al*., 2013) and as a result, the fingolimod label advises patients with a history of uveitis of this increased risk. What is not clear is if fingolimod treatment confers any increased risk of uveitis. There is a case report describing an adult patient who developed uveitis five days after initiation of fingolimod treatment (Mack* et al*., 2016), but given the published rarity of uveitis in the RMS population, there is a prediction that uveitis will occur infrequently in RMS regardless of which treatment is used, and a single reported case out of thousands of exposed adult patients is well below even*

the most optimistic projected population rate. Of particular note, there was a case of uveitis reported in the interferon β-1a treatment group in this pediatric study. If the estimates of uveitis in MS are accurately estimated at <1% (Kaya et al.*, 2014), then the observed 2 out of 214 (0.9%) rate is consistent with the expected rate of uveitis in the population with MS and does not compel a change in labeled adverse risks.*

Migraines

Below I provide two narratives for patients reported with migraines as SAEs. Migraines are a very common condition in pediatric patients. One epidemiologic study estimated that the prevalence of headaches in individuals through age 20 years old is 58% with an incidence of 7.7% (Jacobs & Gladstein, 2012). With an event this frequent, it can be difficult to ascertain whether such an event is treatment-related or occurring frequently but at the expected background rate. In the approval studies submitted for NDA 22527, headache was the most reported adverse reaction (25%) in the fingolimod treatment groups (as compared to 24% of placebo-treated patients), and migraines were common, occurring in 6% of patients taking fingolimod and 4% of patients taking placebo. These migraine and headache figures are on the current fingolimod label. Headaches and migraines are a common medical complaint. Given the predicted frequency in children and adolescents, two patients with SAEs coded as migraines in the fingolimod treatment group with one SAE report of headache in the interferon β-1a treatment group are within the expected reporting range for any pediatric clinical trial.

Patient [(b) (6)] A 12-year-old Caucasian male with multiple sclerosis was screened for the study on (b) (6) and received the first dose of study medication (fingolimod) on (b) (6) (Day 1). The patient had height of 163 cm, weight of 53 kg, and Tanner staging of 4 at Visit 1. The patient was diagnosed with multiple sclerosis in March 2015. The patient experienced one relapse during the past 12 months and no relapses during 12 to 24 months before study entry, and his last relapse prior to enrollment was in November 2014. The patient was not treated with any MS disease-modifying drug prior to enrollment. At Screening, the patient's EDSS score was 0.0. The patient had no relevant prior medical history. No other concomitant medications were taken prior to enrollment. During the study, the patient received salicylic acid (Guttaplast) from (b) (6) to unspecified date in 2015 for verruca (left hand) and ibuprofen from (b) (6) to (b) (6) for common cold. On (b) (6) (Day 67), the patient experienced a non-serious event of mild headache (oppressive pain on head). He was treated with ibuprofen on (b) (6) and his headache improved. On (b) (6) (Day 68), the patient experienced a strong headache associated with feeling of sickness and three episodes of vomiting (moderate in nature) after taking the study medication, which resulted in hospitalization. He was diagnosed with migraine without aura (severe in nature) with an onset date of (b) (6) (Day 67). On (b) (6) (Day 68), laboratory investigation showed neutrophil of 84.6% (normal range: 43.0%-57.0%). The patient did not have fever, diarrhea, dizziness, or any neurological symptoms. No action was taken with the study

medication due to this event. The patient was treated with metamizole on (b) (6) and electrolytes infusion with 5% glucose from (b) (6) to (b) (6) for the event. The event (migraine without aura) completely resolved on (b) (6) (Day 70) and the patient was discharged from the hospital. The patient completed the study with the last dose on (b) (6) (Day 707) and entered extension phase of the study. According to the investigator, the event (migraine without aura) led to hospitalization. The investigator did not suspect a relationship between the event (migraine without aura) and the study medication. As per the Novartis safety physician, the available information did not permit the causality assessment of event; hence, the causality of event migraine was kept as reported by the investigator at this point with plan to reassess upon the receipt of follow up information.

Patient [(b) (6)] A 15-year-old Caucasian male with multiple sclerosis was screened for the study on (b) (6) and received the first dose of study medication (fingolimod) on (b) (6) (Day 1). The patient was diagnosed with multiple sclerosis in November 2013. The patient experienced one relapse during the past 12 months and one relapse during the 12 to 24 months before study entry; and his last relapse prior to enrollment was in August 2014. The patient was treated with the following MS disease-modifying drug prior to enrollment: Avonex (interferon β-1a) until (b) (6) No additional immunomodulatory or immunosuppressive drugs for MS were administered. At Screening, the patient's EDSS score was 1.5. The patient's relevant medical history included seasonal allergy. Concomitant medications taken prior to enrollment included Uvedose (cholecalciferol) from (b) (6) for vitamin D deficiency and Advil (ibuprofen) from November 2014 as a prophylaxis. During the study, the patient additionally received ibuprofen from (b) (6) to (b) (6) for cephalalgia, Solumedrol (methylprednisolone) on (b) (6) for muscle weakness, and amitriptyline and ibuprofen from (b) (6) to (b) (6) for cephalgia during MS relapse.

Event 1 (Viral pharyngitis): see discussion above

Event 2 (Appendicitis): see discussion above

Event 3 (Migraine): On (b) (6) (Day 658), the patient was diagnosed with migraine (moderate in nature). No action was taken with the study medication. On (b) (6) (Day 659), the patient was hospitalized and a brain magnetic resonance imaging was stable. The patient was treated with Solumedrol (methylprednisolone sodium succinate) for 3 days and Laroxyl (amitriptyline hydrochloride) from (b) (6) (Day 660) to (b) (6) (Day 662). The event (migraine) completely resolved on (b) (6) (Day 662), and the patient was discharged from the hospital on the same day. The patient completed the study with the last dose on (b) (6) (Day 726) and entered extension phase of the study. According to the investigator, the event (viral pharyngitis) was considered medically significant, led to hospitalization, and disability; the events (appendicitis and migraine) led to hospitalization. The investigator did not suspect a relationship between the events (viral pharyngitis, appendicitis,

and migraine) and the study medication. As per the Novartis safety physician, the available information did not allow for a comprehensive causality assessment, and hence the causality for the events of viral pharyngitis and migraine was kept as reported by the investigator with plans to reassess the case upon the receipt of follow up information.

> *Reviewer Comment: These reports conform to the accepted clinical definition of a migraine with and without aura. The migraines do not have unusual symptoms to suggest an alternative or more serious diagnosis. Aside from a severity requiring hospitalizations, the only atypical feature of these reports is that the patients reporting migraines are both post-pubertal males. Migraines are reported 50% more often in post-pubertal females than in males (Jacobs & Gladstein, 2012). Headache was the most common AE in the adult trials of fingolimod (IR=24.6), but there was no difference in incidence rate for headache when compared to the rate in patients treated with interferon β-1a (IR=26.0) and no discrepancy between females and males when the trials' inherent demographic skew towards females was accounted for.*

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

For Study D2311, the protocol mandated that investigators discontinue study drug if they felt continuing would pose a significant risk to the patient. The protocol allowed investigators to consider an individualized decision to discontinue study drug under the following conditions:

- Serious adverse event (*e.g.*, diagnosed malignancy)
- Abnormal laboratory value(s) or abnormal test result(s) with protocol-defined safety monitoring
- Sexual activity in girls who do not agree to the protocol-defined adequate use of contraception
- Use of protocol-defined prohibited medications (see 6.1.1 Exclusion Criteria)
- Adverse events
- Protocol deviation
- Unsatisfactory therapeutic effect
- Patient's condition no longer requires study treatment
- Administrative problems (*e.g.*, patient's non-compliance)

The protocol mandated study drug discontinuation for following conditions:

- Hepatic
    - Increase in ALT or AST >8 x ULN (with confirmed value on a repeat lab within 48 hours) or
    - "Hy's law" criterion is met or
    - The occurrence of new elevations greater than 5x the ULN for ALT/AST in patients where study drug was re-initiated after drug stoppage for liver enzyme elevations.

- Ophthalmic
    - Diagnosis of macular edema.
    - If systemic immunosuppressive treatment (other than corticosteroids) is required for treatment of uveitis.
- First/Re-dose Criteria
    - Any hemodynamically compromising cardiac arrhythmias.
    - Patients who meet the criteria requiring overnight hospitalization again on Day 2.
- ECG abnormalities (all visits including first/re-dose)
    - Absolute QTcF > 500 msec, confirmed by repeat ECG measurements (within 24 hours).
    - New complete heart block (third degree AV block) or second degree AV block Mobitz type II.
- ECG abnormalities (non-first/re-dose visits)
    - Resting heart rate < 40 or > 120 bpm observed after 1st dose monitoring and confirmed on repeat measure.
    - Increase in QRS duration > 25% from Baseline (Day 1 pre-dose) observed after 1st dose monitoring and confirmed on repeat ECG measure (within 24 hours).
- Pregnancy
- Withdrawal of consent

Patients who prematurely discontinued study treatment for any reason were encouraged to remain in the study. These patients would complete the Visit 14 assessments (as end of treatment assessments) followed by a 3-month follow-up prior to following the abbreviated schedule of assessments (see Section 6.1.1).

In Study D2311, six patients (5.6%, 6/107) in the fingolimod treatment group and five patients (4.7%, 5/107) in the interferon β-1a treatment group permanently discontinued study treatment due to AEs. Of the six patients who discontinued fingolimod treatment, five patients were at the 0.5 mg dose. No single AE was reported for more than one patient as a reason for discontinuing fingolimod in Study D2311. Three AEs listed on the current label, macular edema, leukopenia, and hypersensitivity reaction, were reported as permanent discontinuation reasons for fingolimod. Patients taking fingolimod discontinued interferon β-1a most often because of multiple sclerosis relapses (n=2, 1.9%). The following table summarizes all AEs leading to study drug discontinuations.

Table 41: Reviewer Table: Adverse Events Causing Permanent Study Drug Discontinuation, Regardless of Study Drug Relationship, by Primary System Organ Class, Preferred Term, and Treatment, Safety Set, Study D2311

MedDRA System Organ Class MedDRA Preferred Term	Fingolimod n=107 n (%)	Interferon β-1a n=107 n (%)
Any primary system organ class	6 (5.6%)	5 (4.7%)
Blood and Lymphatic System Disorders	2 (1.9%)	0
Anemia	1 (0.9%)	0
Leukopenia	1 (0.9%)	0
Eyes Disorders	1 (0.9%)	0
Macular edema	1 (0.9%)	0
General Disorders and Administration Site Conditions	0	2 (1.9%)
Drug ineffective	0	1 (0.9%)
Influenza-like illness	0	1 (0.9%)
Investigations	0	1 (0.9%)
Alanine aminotransferase increased	0	1 (0.9%)
Aspartate aminotransferase increased	0	1 (0.9%)
Musculoskeletal and Connective Tissue Disorders	1 (0.9%)	0
Back pain	1 (0.9%)	0
Nervous System Disorders	2 (1.9%)	2 (1.9%)
Headache	1 (0.9%)	0
Multiple sclerosis plaque	1 (0.9%)	0
Multiple sclerosis relapse	1 (0.9%)	2 (1.9%)
Psychiatric Disorders	0	1 (0.9%)
Depression	0	1 (0.9%)
Skin and Subcutaneous Tissue Disorders	1 (0.9%)	0
Hypersensitivity vasculitis	1 (0.9%)	0
Injury, Poisoning, and Procedural Complications	1 (0.9%)	0
Maternal exposure during pregnancy	1 (0.9%)	

Source: AAEV.xpt

Reviewer Comment: The table above includes a pregnancy report that was not incorporated into the clinical database (see Section 8.8.2). The overall rate of SAEs leading to permanent discontinuation of study treatment was equal between groups. The SAEs associated with discontinuations revealed no new safety findings associated with fingolimod treatment. Several of the AEs causing drug discontinuation such as leukopenia, increased liver transaminases, macular edema, and hypersensitivity reactions were established as risks in prior trials in adults, and their presence in this

pediatric study confirms that these serious known AEs exist in pediatric patients as well. The serious AEs leading to discontinuation noted in the pediatric study with clear relationship to fingolimod treatment therefore are listed currently on the current labeling with one exception, seizures. Novartis has proposed adding seizures as an adverse reaction based in part on the observations from this study, and though it is unclear how much of a greater risk of seizures exists (see Section 8.4.3.) an additional warning of seizures appears justifiable. Due to the small number of patients and events, definitive conclusions cannot be reached about the relative safety of the 0.25 mg dose.

120 Safety Update

In the 120 Day Safety Update, Novartis reported two non-fatal SAEs and one patient discontinuation due to an adverse event in Study D2311. The SAE leading to discontinuation was fungal meningitis. The meningitis diagnosis was suspected by the investigator to be related to fingolimod-induced persistent leukopenia. The narrative of the discontinuation SAE is included below.

Patient [(b) (6)] A 14-year old male patient received the first dose of fingolimod in the core phase of Study D2311 on (b) (6) (Day 1) and entered the fingolimod open-label extension phase on (b) (6) On (b) (6) (2 years 1 month after start of core phase and 3.5 months after start of extension phase), at the age of 16, the patient experienced an SAE of meningitis (serous meningitis). Prior to the event the patient had persistent leukopenia and experienced intermittent symptoms of headache, vomiting, and increasing fever (38 up to 40 degrees Celsius). Subsequently, the patient was diagnosed with meningitis (based on clinical findings), was hospitalized, and study drug was discontinued. Non-serious influenza and ear infection were also reported. The patient underwent multiple lumbar punctures for diagnostic purposes from (b) (6) to (b) (6) No specific infectious agent was identified, in spite of repeated microscopy, microbiology, and PCR testing (including PCR for Cryptococcus, Candida, Enterovirus, and Herpes Type I and II). The lumbar puncture on (b) (6) showed some 'fungi metabolites' (*i.e.*, mannose 115; normal range: less than 50). However, as no specific infectious agent was clearly identified, the final diagnosis was reported as 'serous meningitis.' Treatment medications included fluconazole, azithromycin, acetazolamide, imidazolyl ethanamide pentandioic acid, magnesium aspartate, potassium aspartate, and vinpocetine. The patient completely recovered from meningitis on (b) (6) (one month after diagnosis). The meningitis was suspected by the investigator to be related to study treatment.

8.4.4. **Significant Adverse Events**

AEs leading to Treatment Interruptions

In Study D2311, there were more patients with study drug interruptions in the fingolimod treatment group (n=12, 11.2%) than in the interferon β-1a treatment group (n=3, 2.8%). The

most common reasons for study drug interruption in the fingolimod treatment group, reported in two patients each, were leukopenia, vomiting, and seizures. The most common reason for interrupting interferon β-1a, reported by two patients, was vomiting. No other AE was reported by more than one patient in either treatment group.

Table 42: Sponsor Table: Adverse Events Causing Study Drug Interruption, Regardless of Study Drug Relationship, by Primary System Organ Class, Preferred Term, and Treatment Study D2311

MedDRA System Organ Class MedDRA Preferred Term	Fingolimod n=107 n (%)	Interferon β-1a n=107 n (%)
Any primary system organ class	12 (11.2%)	3 (2.8%)
Blood and Lymphatic System Disorders	2 (1.9%)	0
Leukopenia	2 (1.9%)	0
Agranulocytosis	1 (0.9%)	0
Lymphopenia	1 (0.9%)	0
Gastrointestinal Disorders	2 (1.9%)	2 (1.9%)
Vomiting	2 (1.9%)	2 (1.9%)
Small bowel obstruction	1 (0.9%)	0
General Disorders and Administration Site Conditions	2 (1.9%)	1 (0.9%)
Non-cardiac chest pain	1 (0.9%)	0
Pyrexia	1 (0.9%)	1 (0.9%)
Asthenia	0	1 (0.9%)
Investigations	4 (3.7%)	0
Alanine aminotransferase abnormal	1 (0.9%)	0
Aspartate aminotransferase increased	1 (0.9%)	0
Blood pressure increased	1 (0.9%)	0
Lymphocyte count decreased	1 (0.9%)	0
White blood cell count decreased	1 (0.9%)	0
Nervous System Disorders	3 (2.8%)	0
Seizure	2 (1.9%)	0
Generalized tonic-clonic seizure	1 (0.9%)	0
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnea	1 (0.9%)	0

Source: Table 12-11 Clinical Study Report

Reviewer Comment: The imbalance in SAEs leading to treatment interruptions between treatment arms reflects the difference in monitoring due to the severity of the AEs associated with fingolimod relative to the AEs associated with interferon β-1a treatment.

120 Day Safety Update

In the 120 Day Safety Update, Novartis provided two new SAEs as indicated in Section 8.4.3, and one SAE is discussed above because it led to permanent discontinuation of fingolimod treatment. The second SAE, endometriosis, led to temporary study drug discontinuation but was not deemed related to fingolimod. The narrative follows below.

Patient [(b) (6)] A 17-year old female patient received the first dose of fingolimod in the core phase of Study D2311 on (b) (6) (Day 1) and entered the extension phase on (b) (6) On (b) (6) (3 years and 4 months after start of core phase and 1 year and 4 months after start of extension phase), at the age of 21, the patient experienced an SAE of endometriosis. Previous medical history included abdominal pain and dysmenorrhea. An abdominal ultrasound was performed on (b) (6) (unknown with CTCAE grade 1) and an abdominal pelvic MRI on (b) (6) (unknown with CTCAE grade 1). On (b) (6) study medication was temporarily interrupted and the patient was hospitalized for laparoscopy confirming endometriosis CTCAE grade 2. The subject was treated with desogesterol, paracetamol and codeine. On (b) (6) the patient completely recovered and study drug was resumed. The event was not suspected by the investigator to be related to the study treatment.

Study D2302

The following narrative encapsulates the entire safety data collected for the single patient < 18 years old randomized into Study D2302.

Patient (b) (6)] A 17-year-old Caucasian female with multiple sclerosis was randomized to 1.25 mg/day fingolimod at the age of 17 years and 11 months, one month short of her 18th birthday. The date of birth for this patient was (b) (6) while the date of first dose in the study was (b) (6) The inclusion criteria for this study stated that patients must be 18 to 55 at time of randomization and thus this randomization was reported as a protocol deviation (FTY2301 CSR Listing 16.2.2-1.1). The patient was allowed to continue in the study. The patient was diagnosed with multiple sclerosis on (b) (6) The patient experienced two relapses since diagnosis with two relapses during the past year and two relapses during the past 2 years before study entry. Both relapses required steroid treatment. Her last relapse prior to enrollment was on (b) (6) (FTY2301 CSR Listing 16.2.4-1.4). The patient had multiple sclerosis symptoms of numbness/ on both lower extremities (FTY2301 CSR Listing 16.2.4-1.5). The patient did not receive any MS disease modifying therapies prior to enrollment in the study (FTY2301 CSR Listing 16.2.4-1.6). The patient's last dose of corticosteroids prior to enrollment in the study was on (b) (6) (FTY2301 CSR Listing 16.2.4-1.7). At Screening, the patient's EDSS score was 2.0 (FTY2301 CSR Listing 16.2.6- 1.1). At baseline the patient weighed 68.0 kg was 172 cm in height and had a BMI of 23.0 (FTY2301 CSR Listing 16.2.4-1.1). The patient was not an active smoker, had no history of COPD, asthma or other respiratory disorders (FTY2301 CSR Listing 16.2.4-1.2). The patient's relevant prior medical history included amblyopia (amblyopia right eye) starting on (b) (6) that was ongoing at the start of the study. The patient did not

take any concomitant medications prior to the start of the study. During the study, the patient received coricidin (A-Ferin (Paracetamol)) for the flu from (b) (6) to (b) (6)

During the study, the patient experienced two adverse events of mild influenza (flu) from (b) (6) to (b) (6) (Day 237 to 239) and (b) (6) to (b) (6) (Day 249-251) {(FTY2301 CSR Listing 16.2.7-1.1 and Listing 16.2.7-1.2). Both adverse events were not suspected to be related to study drug. No serious adverse events were experienced by this patient during the study. The patient had normal dermatologic exams at screening, Month 12 and end of study (FTY2301 CSR Listing 16.2.9-1.16). The patient had a clinically notable decrease in weight (>7% change from baseline) from 68 kg at baseline to 63 kg at month 6, 12, 18, 21 and end of study with a decrease in weight to 62.5 kg at Month 15. The patient also had a clinically notable value (≤ 90 mmHg) and decrease (≥20 mmHg) in systolic blood pressure from a baseline value of 110 to a post-baseline value of 90 at 2 hours, Month 1, 2, 9, 15 and 21 (FTY2301 CSR Listing 14.3-3.1). A clinically notable increase (change of ≥15 mmHg) in diastolic blood pressure was observed at 5hrs post first dose (change from 60 to 80 mmHg) and a clinically notable decrease (change of ≥ 15 bpm) in pulse from 83.7 to 68, 64, and 68 at 3 hours, 4 hours and 1 Month post first dose. The patient had no clinically notable abnormal laboratory values (FTY2301 CSR Listing 14.3.4-1.1), no absolute lymphocyte values less than 0.2 x 10E9/L (FTY2301 CSR Listing 14.3.4-1.2), no liver enzyme values for SGPT (ALT) (U/L) greater or equal to 5xULN (FTY2301 CSR Listing 14.3.4-1.3) during the study The patient completed study D2301 (Core Phase) on study drug with the last dose on (b) (6) (Day 759; FTY2301 CSR Listing 16.2.1-1.1) At the completion of the Core Phase the patient entered the Extension Phase. During the Extension Phase, the patient did not experience any adverse events (FTY2301-E1 CSR Listing 16.2.7-1.1). The patient completed the Extension Phase on (b) (6) (Day 1456; FTY2301-E1 CSR Listing 16.2.1-1.1).

> *Reviewer Comment: This patient's AE of influenza was noted at high frequency in Study D2311. No additional new AEs or risks are evident with inclusion of this case.*

Study A0115

The table below describes the AEs reported for patients with renal transplants (n=7) in a trial using single dose exposures of fingolimod 1.25 mg for indication of prevention of allograft kidney rejection. The AEs noted that appear reasonably related to a single administration of fingolimod include the most common AE reported, bradycardia (n=7, 100% of patients), and hypotension (2 patients, 28.6%).

Table 43: Sponsor Table: Adverse Events, All Patients, Study A0115

System organ class and event	Number of patients (%)
Blood and lymphatic system disorders	
Lymphadenitis	1 (14.3)
Cardiac disorders	
Bradycardia	7 (100)
Eye disorders	
Visual disturbance	1 (14.3)
Gastrointestinal disorders	
Diarrhea	2 (28.6)
Vomiting	1 (14.3)
Infections and infestations	
Nasopharyngitis	1 (14.3)
Injury, poisoning and procedural complications	
Procedural site reaction	3 (42.9)
Nervous system disorders	
Headache	1 (14.3)
Respiratory, thoracic and mediastinal disorders	
Cough	1 (14.3)
Pharyngeal erythema	1 (14.3)
Skin and subcutaneous tissue disorders	
Acne	2 (28.6)
Vascular disorders	
Hypotension	2 (28.6)

Source: Table 7-1 Clinical Study Report, Study A0115

Reviewer Comment: A review of these AEs does not identify any new AEs or safety risks not already previously identified.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The overall incidence of AEs in the fingolimod treatment group was 88.8% and was 95.3% in the interferon β-1a treatment group. The exposure adjusted IR for the fingolimod treatment group was 247.5 per 100 patient-years and was 559.6 per 100 patient-years for the interferon β-1a treatment group.

Novartis reported both the absolute number of AEs and odds ratios but based conclusions on

the odds ratios. Novartis explained that due to the small sample size in Study D2311 and the study's variable duration study design, a larger number of AEs for fingolimod occurred because more patients in the fingolimod-treatment group remained in the trial longer than did interferon β-1a-treated patients. Therefore, a greater number of fingolimod-treated patients had more monitored time in which to report AEs than did interferon β-1a-treated patients. I will report absolute numbers and IRs and generate conclusions based on a totality of the evidence approach.

Severity of AEs

Almost 75% of the AEs reported in both treatment groups were rated as "mild" or "moderate" by the investigators using the protocol-defined rating criteria (see Section 6.1.1). There was overall a lower incidence of "mild" AEs but a higher incidence of "severe" AEs in fingolimod-treated patients compared to interferon β-1a-treated patients as indicated in the table below.

Table 44: Sponsor Table: Adverse Event Severity, Safety Set, Study D2311

Severity Rating	Fingolimod n=107 n (%)	Interferon β-1a n=107 n (%)
All Rated Events	95 (88.8%)	102 (95.3%)
Mild	41 (38.3%)	57 (53.3%)
Moderate	38 (35.5%)	35 (32.7%)
Severe	16 (15.0%)	10 (9.3%)

Source: Table 2-3, Summary of Clinical Safety

> *Reviewer Comment: The imbalance between groups in observed severe AEs was expected based on the known serious risks of fingolimod and mirrors the SAE findings in adult MS trials comparing fingolimod to interferon β-1a.*

Adverse Events

The most commonly reported AEs in Study D2311 were headache, infections, leukopenia, and fatigue. As shown in the table below, these AEs are entirely consistent with the AEs reported in a trial conducted in adult patients with RMS comparing fingolimod 0.5 mg to interferon β-1a. Events most often came from the Infections and Infestations and Nervous System Disorders SOC

Table 45: Sponsor Table: Common AEs in All Treatment Groups, Pediatric Study D2311 and Adult Trials D2301/D2302/D2309

	Pediatric Population (D2311)		Adult Population (D2301/D2302/D2309)		
Preferred term	FTY720 N=107 n (IR)	IFN ß-1a N=107 n (IR)	FTY720 0.5mg N=1212 n (IR)	IFN ß-1a N=431 n (IR)	Placebo N=773 n (IR)
Any preferred term	95 (247.5)	102 (559.6)	1122 (391.9)	396 (625.4)	730 (380.2)
Headache	34 (24.6)	32 (27.0)	286 (19.7)	88 (26.0)	174 (16.0)
Viral upper respiratory tract infection	23 (14.2)	26 (18.5)	252 (16.4)	80 (21.5)	177 (16.0)
Upper respiratory tract infection	17 (10.1)	5 (3.1)	191 (12.2)	27 (6.7)	159 (14.2)
Leukopenia	15 (8.7)	3 (1.8)	20 (1.1)	1 (0.2)	1 (0.1)
Influenza	12 (6.9)	4 (2.5)	118 (7.0)	32 (8.1)	65 (5.2)
Fatigue	10 (5.7)	6 (3.7)	116 (7.0)	45 (11.8)	72 (5.9)
Cough	10 (5.6)	12 (7.7)	116 (7.0)	16 (3.9)	87 (7.2)
Rhinitis	10 (5.6)	9 (5.7)	41 (2.3)	11 (2.7)	31 (2.4)
Nausea	9 (5.1)	5 (3.1)	142 (8.8)	29 (7.4)	90 (7.5)
Oropharyngeal pain	9 (5.0)	5 (3.0)	75 (4.4)	15 (3.7)	62 (5.0)
Abdominal pain	9 (4.9)	9 (5.8)	43 (2.4)	7 (1.7)	32 (2.5)
Diarrhoea	8 (4.4)	10 (6.4)	131 (7.9)	19 (4.7)	74 (6.1)
Pyrexia	8 (4.4)	22 (16.1)	40 (2.3)	77 (22.0)	28 (2.2)
Influenza like illness	5 (2.8)	40 (36.8)	36 (2.0)	159 (59.2)	15 (1.1)
Chills	1 (0.5)	11 (7.4)	10 (0.6)	21 (5.3)	6 (0.5)

- N=Number of patients in the Analysis Set; n=Number of patients who experienced at least one AE in this category; IR=the incidence rate expressed per 100 patient-years of the at-risk population. - All AEs with onset date on or after start of study drug to 45 days after last dose of study drug and all SAE (irrespective of time after last dose of study drug) are included.
- Preferred terms are sorted in descending frequency, as reported in the FTY720 column from the pediatric population.
- Incidence rate: The number of patients experiencing at least one event in this category, over the total patient-years of the "at-risk" population for that event. An underlying Poisson process for incidence rate within treatment arm is assumed.

Source: Table 5-3 Clinical Study Overview

In the table below, Novartis describes AEs reported in at least 2% of patients.

Table 46: Sponsor Table: AEs Noted in >2% in Fingolimod Group by Preferred Term, Safety Set, Study D2311

Preferred term	FTY720 N=107 n (%)	IFN β-1a N=107 n (%)
Any preferred term	95 (88.8)	102 (95.3)
Headache	34 (31.8)	32 (29.9)
Viral upper respiratory tract infection	23 (21.5)	26 (24.3)
Upper respiratory tract infection	17 (15.9)	5 (4.7)
Leukopenia	15 (14.0)	3 (2.8)
Influenza	12 (11.2)	4 (3.7)
Cough	10 (9.3)	12 (11.2)
Fatigue	10 (9.3)	6 (5.6)
Rhinitis	10 (9.3)	9 (8.4)
Abdominal pain	9 (8.4)	9 (8.4)
Nausea	9 (8.4)	5 (4.7)
Oropharyngeal pain	9 (8.4)	5 (4.7)
Diarrhoea	8 (7.5)	10 (9.3)
Nasopharyngitis	8 (7.5)	5 (4.7)
Pyrexia	8 (7.5)	22 (20.6)
Vomiting	8 (7.5)	7 (6.5)
Anxiety	7 (6.5)	2 (1.9)
Back pain	6 (5.6)	6 (5.6)
Toothache	6 (5.6)	2 (1.9)
White blood cell count decreased	6 (5.6)	0 (0.0)
Abdominal pain upper	5 (4.7)	4 (3.7)
Cystitis	5 (4.7)	3 (2.8)
Depressed mood	5 (4.7)	0 (0.0)
Depression	5 (4.7)	3 (2.8)
Influenza like illness	5 (4.7)	40 (37.4)

Lymphopenia	5 (4.7)	0 (0.0)
Rhinitis allergic	5 (4.7)	0 (0.0)
Alanine aminotransferase increased	4 (3.7)	5 (4.7)
Constipation	4 (3.7)	0 (0.0)
Decreased appetite	4 (3.7)	0 (0.0)
Dizziness	4 (3.7)	5 (4.7)
Dyspnoea	4 (3.7)	1 (0.9)
Gamma-glutamyltransferase increased	4 (3.7)	0 (0.0)
Pain	4 (3.7)	4 (3.7)
Pharyngitis	4 (3.7)	5 (4.7)
Rash	4 (3.7)	4 (3.7)
Respiratory tract infection viral	4 (3.7)	2 (1.9)
Sinusitis	4 (3.7)	3 (2.8)
Anaemia	3 (2.8)	1 (0.9)
Asthenia	3 (2.8)	3 (2.8)
Blood cholesterol increased	3 (2.8)	0 (0.0)
Dry eye	3 (2.8)	0 (0.0)
Dysmenorrhoea	3 (2.8)	3 (2.8)
Dysuria	3 (2.8)	1 (0.9)
Epilepsy	3 (2.8)	0 (0.0)
Hypovitaminosis	3 (2.8)	0 (0.0)
Insomnia	3 (2.8)	2 (1.9)
Low density lipoprotein increased	3 (2.8)	0 (0.0)
Migraine	3 (2.8)	2 (1.9)
Non-cardiac chest pain	3 (2.8)	1 (0.9)
Pain in extremity	3 (2.8)	5 (4.7)
Paraesthesia	3 (2.8)	1 (0.9)
Syncope	3 (2.8)	1 (0.9)
Tachycardia	3 (2.8)	0 (0.0)
Urticaria	3 (2.8)	0 (0.0)
Viral infection	3 (2.8)	3 (2.8)

Source: Table 12-3 Clinical Study Report

A review of all AEs using MedDRA search terms grouped using logical clinical associations of disorders yielded substantially similar findings for all AEs reported in Study D2311. Events subsumed under the SOC heading of “Infections and Infestations” were the most commonly reported events overall in either treatment group.

Table 47: Reviewer Table: Re-coded AEs in > 2% of Fingolimod Treatment Group, Safety Set, Study D2311

MedDRA Preferred Term	All Exposure to Fingolimod n=107; 176.0 PY	All Exposure to Interferon β-1a n=107; 153.4 PY
Parients with at least 1 AE (n, %)	95 (88.8%)	102 (95.3%)
Number AEs/100 patient years	406.3	519.8

Upper respiratory tract infection[1]	70 (65.4%)	87 (81.3%)
Viral Infection	48 (44.9%)	42 (39.3%)
Headache	39 (36.5%)	35 (32.7%)
Leukopenia[2]	27 (25.2%)	3 (2.8%)
Nausea/Vomiting[3]	18 (16.8%)	15 (14.0%)
Fatigue[4]	14 (13.1%)	11 (10.3%)
Abdominal Pain[5]	13 (12.1%)	13 (12.1%)
Influenza	12 (11.2%)	4 (3.7%)
Cough	10 (9.3%)	12 (11.2%)
Fever/Rigors	9 (8.4%)	25 (23.4%)
Anxiety[6]	9 (8.4%)	5 (4.7%)
Depression/Depressed Mood	9 (8.4%)	4 (3.7%)
Diarrhea	8 (7.5%)	10 (9.3%)
GOT, GPT, GGTP, LFTs[7]	8 (7.5%)	6 (5.6%)
Falls[8]	8 (7.5%)	5 (4.7%)
Gastronenteritis[9]	8 (7.5%)	4 (3.7%)
Fungal Infection	7 (6.5%)	4 (3.7%)
Back Pain	6 (5.6%)	6 (5.6%)
Rash	6 (5.6%)	5 (4.7%)
Urinary Tract Infection[10]	6 (5.6%)	4 (3.7%)
Insomnia/Sleep Disturbance	6 (5.6%)	4 (3.7%)
Seizure[11]	6 (5.6%)	1 (0.9%)
Allergic/Hypersensitivity Reaction	5 (4.7%)	6 (5.6%)
Bleeding	5 (4.7%)	5 (4.7%)
Bronchitis/Bronchiolitis	5 (4.7%)	3 (2.8%)
Dermatitis	5 (4.7%)	3 (2.8%)
Migraine	5 (4.7%)	2 (1.9%)
Dyspnea/SOB/Respiratory Distress	5 (4.7%)	1 (0.9%)
Fracture[12]	4 (3.7%)	4 (3.7%)
Arrhythmia	4 (3.7%)	3 (2.8%)
Chest Pain (non-cardiac or unknown)	4 (3.7%)	3 (2.8%)
Tachycardia	4 (3.7%)	2 (1.9%)
Pre-syncope/Syncope	4 (3.7%)	2 (1.9%)
Hypercholesterolemia	4 (3.7%)	0
Constipation	4 (3.7%)	0
Anorexia	4 (3.7%)	0
Herpes Virus Infection[13]	3 (2.8%)	3 (2.8%)
Paresthesia	3 (2.8%)	1 (0.9%)
Dysuria	3 (2.8%)	1 (0.9%)

Anemia	3 (2.8%)	1 (0.9%)
Asthma	3 (2.8%)	1 (0.9%)
Urticaria	3 (2.8%)	0
Eczema	3 (2.8%)	0
Memory Loss or Impairment	3 (2.8%)	0
Influenza-like Illness	2 (1.9%)	34 (31.8%)

Source: AAEV.xpt joined with AAEV.xpt, Clinical Study Report Table 14.3.1-1.12

[1]includes events coded to upper respiratory tract infection, sinusitis, pharyngitis, nasopharyngitis, rhinitis, viral upper respiratory tract infection, laryingitis, tonsillitis, acute tonsillitis, acute sinusitis, pharyngitis streptococcal, chronic sinusitis, pharyngitis bacterial, pharyngotonsilitis, upper respiratory tract infection bacterial, tonsillitis bacterial, viral rhinitis, viral tonsillitis, viral pharyngitis
[2]includes events coded to lymphopenia, leukopenia, neutropenia
[3]includes events coded to nausea, vomiting, indigestion, epigastric pain, dyspepsia, duodenitis
[4]includes events coded to asthenia, fatigue, malaise, weakness
[5]incudes events coded to abdominal discomfort, abdominal pain, abdominal pain upper, abdominal pain lower, abdominal tenderness, epigastric discomfort, gastrointestinal pain
[6]includes events coded to anxiety, panic attack, phobia
[7]includes events coded to transaminases abnormal, AST raised/abnormal, ALT raised/abnormal, GGT raised/abnormal, GOT raised/abnormal, raised LFTs
[8]includes events coded to falls, dizziness, balance disorder, gait disturbance, difficulty standing
[9]includes events coded to gastroenteritis, colitis, enteritis, proctitis, C-difficile colitis
[10]includes events coded to urinary tract infection, pyelonephritis, pyelonephritis acute, bacterial pyelonephritis, urosepsis, cystitis, E. coli urinary tract infection, kidney infection, urinary tract infection bacterial, and urinary tract infection fungal
[11]includes events coded as seizure, convulsion, epilepsy, partial seizure, partial seizure with secondary generalization, generalized tonic-clonic seizure
[12]incudes events coded to ankle fracture, clavicle fracture, facial bones fracture, femoral neck fracture, femur fracture, fibula fracture, foot fracture, hand fracture, humerus fracture, lower limb fracture, spinal compression fracture, stress fracture, tibia fracture, thoracic vertebral fracture, upper limb fracture, wrist fracture
[13]includes events coded to genital herpes, genital herpes simplex, herpes ophthalmic, herpes simplex, herpes zoster, herpes virus infection, ophthalmic herpes simplex, oral herpes, varicella

Reviewer Comment: The re-coded list of AEs confirms that upper respiratory tract and viral infections were very common in patients in both treatment groups. The re-coding does not reveal a significant new safety concern for fingolimod in pediatric patients. Anxiety and depression were seen in twice as many patients in the fingolimod group as compared to the interferon β-1a group. These psychiatric conditions are common co-morbidities in patients with MS. A prospective study of MS patients conducted by Wood

> et al. *(2012) estimated anxiety and depression prevalences 44.5% and 18.5%, respectively, and Goretti* et al. *(2010) surveyed pediatric patients with RMS and reported a 30% rate of anxiety and affective disorders. The observed event rates for anxiety and depression fall below these estimates. A suicidal behavior and ideation assessment tool was administered to all patients in the trial and yielded no marked differences between the groups.*

Adverse Events Requiring Additional Therapy or Treatment

More patients in the interferon β-1a treatment group (88.8%) required additional medications or therapies for AEs than in the fingolimod treatment group (76.6%).

Influenza-like illness was the most common AE in any treatment group (31.8% in interferon β-1a arm versus 1.9% in the fingolimod arm) that required additional treatment.

The most common AE requiring additional therapy overall in both groups was headache (23.4% for fingolimod and 22.4% for interferon β-1a). Viral upper respiratory infections were the next most often reported AE in both treatment groups that required additional therapy (17.8% and 14.0%).

Adverse Drug Reactions

In Study D2311, an Adverse Drug Reaction (ADR) was defined as an undesirable event that could be reasonably associated with the use of a drug. For fingolimod, ADRs were identified based on the safety knowledge and observations garnered from trials of fingolimod in adult patients with RMS.

The most common AEs rated as study drug related by investigators were leukopenia (11.2%) for fingolimod and headache (22.4%) for interferon β-1a. There were fewer AEs ascribed to study drug for fingolimod (46.7%) compared with interferon β-1a (66.4%).

In the table below, Novartis identifies all AEs reported with a difference greater than 2% between groups.

Table 48: Sponsor Table: AEs Reported ≥ 2% Difference between Treatments by Preferred Term, Safety Set, Study D2311

Preferred term	FTY720 N=107 n (%)	IFN β-1a N=107 n (%)
Viral upper respiratory tract infection	23 (21.5)	26 (24.3)
Upper respiratory tract infection	17 (15.9)	5 (4.7)
Leukopenia	15 (14.0)	3 (2.8)
Influenza	12 (11.2)	4 (3.7)
Fatigue	10 (9.3)	6 (5.6)
Nausea	9 (8.4)	5 (4.7)
Oropharyngeal pain	9 (8.4)	5 (4.7)
Pyrexia	8 (7.5)	22 (20.6)
Nasopharyngitis	8 (7.5)	5 (4.7)
Anxiety	7 (6.5)	2 (1.9)
Toothache	6 (5.6)	2 (1.9)
White blood cell count decreased	6 (5.6)	0 (0.0)
Influenza like illness	5 (4.7)	40 (37.4)
Depressed mood	5 (4.7)	0 (0.0)
Lymphopenia	5 (4.7)	0 (0.0)
Rhinitis allergic	5 (4.7)	0 (0.0)
Dyspnoea	4 (3.7)	1 (0.9)
Constipation	4 (3.7)	0 (0.0)
Decreased appetite	4 (3.7)	0 (0.0)
Gamma-glutamyltransferase increased	4 (3.7)	0 (0.0)
Blood cholesterol increased	3 (2.8)	0 (0.0)
Dry eye	3 (2.8)	0 (0.0)
Epilepsy	3 (2.8)	0 (0.0)
Hypovitaminosis	3 (2.8)	0 (0.0)
Low density lipoprotein increased	3 (2.8)	0 (0.0)
Tachycardia	3 (2.8)	0 (0.0)
Urticaria	3 (2.8)	0 (0.0)
Acne	2 (1.9)	5 (4.7)
Myalgia	2 (1.9)	5 (4.7)
Chills	1 (0.9)	11 (10.3)
Glomerular filtration rate decreased	1 (0.9)	6 (5.6)
Aspartate aminotransferase increased	0 (0.0)	5 (4.7)
Body temperature increased	0 (0.0)	4 (3.7)
Nasal congestion	0 (0.0)	4 (3.7)
Hypothyroidism	0 (0.0)	3 (2.8)
Muscle rupture	0 (0.0)	3 (2.8)
Optic neuritis	0 (0.0)	3 (2.8)

Source: Table 12-5 Clinical Study Report

Respiratory AEs

Fingolimod has a specific known risk of respiratory-related symptoms such as dyspnea or cough and fingolimod treatment is associated with reduced pulmonary function tests. The respiratory and chest-related AEs are listed below.

Table 49: Sponsor Table: Respiratory, Thoracic, and Mediastinal Disorders AEs by Preferred Term, Safety Set, Study D2311

Preferred term	FTY720 N=107 n (%)	IFN β-1a N=107 n (%)
Total	**27 (25.2)**	**25 (23.4)**
Cough	10 (9.3)	12 (11.2)
Oropharyngeal pain	9 (8.4)	5 (4.7)
Rhinitis allergic	5 (4.7)	0 (0.0)
Dyspnoea	4 (3.7)	1 (0.9)
Asthma	2 (1.9)	1 (0.9)
Obstructive airways disorder	2 (1.9)	0 (0.0)
Bronchospasm	1 (0.9)	0 (0.0)
Catarrh	1 (0.9)	2 (1.9)
Diaphragmalgia	1 (0.9)	0 (0.0)
Dyspnoea exertional	1 (0.9)	0 (0.0)
Epistaxis	1 (0.9)	0 (0.0)
Paranasal cyst	1 (0.9)	0 (0.0)
Rhinorrhoea	1 (0.9)	1 (0.9)
Vasomotor rhinitis	1 (0.9)	0 (0.0)
Wheezing	1 (0.9)	0 (0.0)
Dysphonia	0 (0.0)	2 (1.9)
Laryngospasm	0 (0.0)	1 (0.9)
Nasal congestion	0 (0.0)	4 (3.7)
Nasal septum deviation	0 (0.0)	1 (0.9)
Oropharyngeal discomfort	0 (0.0)	1 (0.9)

AE PTs within MedDRA SOC 'Respiratory, thoracic and mediastinal disorders' were included in this table.
A patient may appear in more than one row in the table.
Preferred terms are sorted by descending frequency in the FTY720 group.

Source: Table 12-15 Clinical Study Report

Reviewer Comment: Dyspnea is more frequently reported in fingolimod-treated patients. Respiratory symptoms do not appear as prominent in pediatric patients with RMS treated with fingolimod (see Section 8.5.1).

Cardiac AEs

Fingolimod treatment is associated with several cardiac AEs. The cardiac disorders noted in Study D2311 are noted below.

Table 50: Sponsor Table: Cardiac Disorder AEs by Preferred Term, Safety Set, Study D2311

Preferred term	FTY720 N=107 n (%)	IFN β-1a N=107 n (%)
Total	6 (5.6)	3 (2.8)
Tachycardia	3 (2.8)	0 (0.0)
Atrioventricular block second degree	1 (0.9)	0 (0.0)
Defect conduction intraventricular	1 (0.9)	0 (0.0)
Palpitations	1 (0.9)	0 (0.0)
Atrioventricular block	0 (0.0)	1 (0.9)
Atrioventricular block first degree	0 (0.0)	1 (0.9)
Bradycardia	0 (0.0)	1 (0.9)
Supraventricular tachycardia	0 (0.0)	1 (0.9)

AE PTs within MedDRA SOC 'Cardiac disorders' were included in this table. A patient may appear in more than one row in the table. Preferred terms are sorted by descending frequency in the FTY720 group.

Source: Table 12-16 Clinical Study Report

Reviewer Comment: Cardiac disorders are noted more frequently in the fingolimod treatment group in this pediatric study just as they were in the studies of adults with RMS. The observations of bradycardia and conduction abnormalities confirm that the presence of these AEs in pediatric patients. Tachycardia is noted in fingolimod-treated patients at a higher rate, but this finding is at odds with the first dose monitoring and scheduled visit vital sign data showing overall reductions in heart rates during treatment.

AEs after Study Drug Discontinuation

Few AEs were reported in patients after permanent discontinuation of study treatments. Eight patients (34.8%) in the interferon β-1a treatment group reported an AE within 45 days of ending treatment versus one patient (14.3%) in the fingolimod treatment. The AEs reported by the patient who discontinued fingolimod were asthenopia (deemed unrelated to study drug) and an upper respiratory tract infection (deemed possibly related to study drug.)

8.4.6. **Laboratory Findings**

Hematology

Fingolimod lowers the serum lymphocyte count by inhibiting leukocyte egress from lymph nodes. In adult patients, fingolimod treatment is associated with a 75% decrease in absolute lymphocyte count and a nearly 20% decrease from baseline in absolute neutrophil counts. Basophil counts were reduced by 80% in adult patients.

In pediatric patients, there was a sustained decrease in the absolute lymphocyte and neutrophil counts for patients in the fingolimod treatment group as compared to their baseline values. In the second week of treatment, the mean lymphocyte count for patients in the fingolimod treated patients was reduced by 67% from baseline and remained reduced by over 70% of baseline across the duration of treatment through 24 months. The mean neutrophil count of the fingolimod group was reduced by approximately 8% following one week of treatment, and the mean neutrophil count remained reduced by approximately 20% from baseline throughout the remainder of treatment. These reductions were similar in all ages studied (see Figures 8 and 9). The mean lymphocyte count in interferon β-1a-treated patients declined by less than 1% at Week 2 and ranged from a 1.5% to a 3% decrease through the end of study. The mean of the absolute neutrophil count was reduced 13% at Week 2 but returned to baseline by Month 24.

Table 51: Reviewer Table: Change in Absolute Lymphocyte and Neutrophil Counts, Safety Set, Study D2311

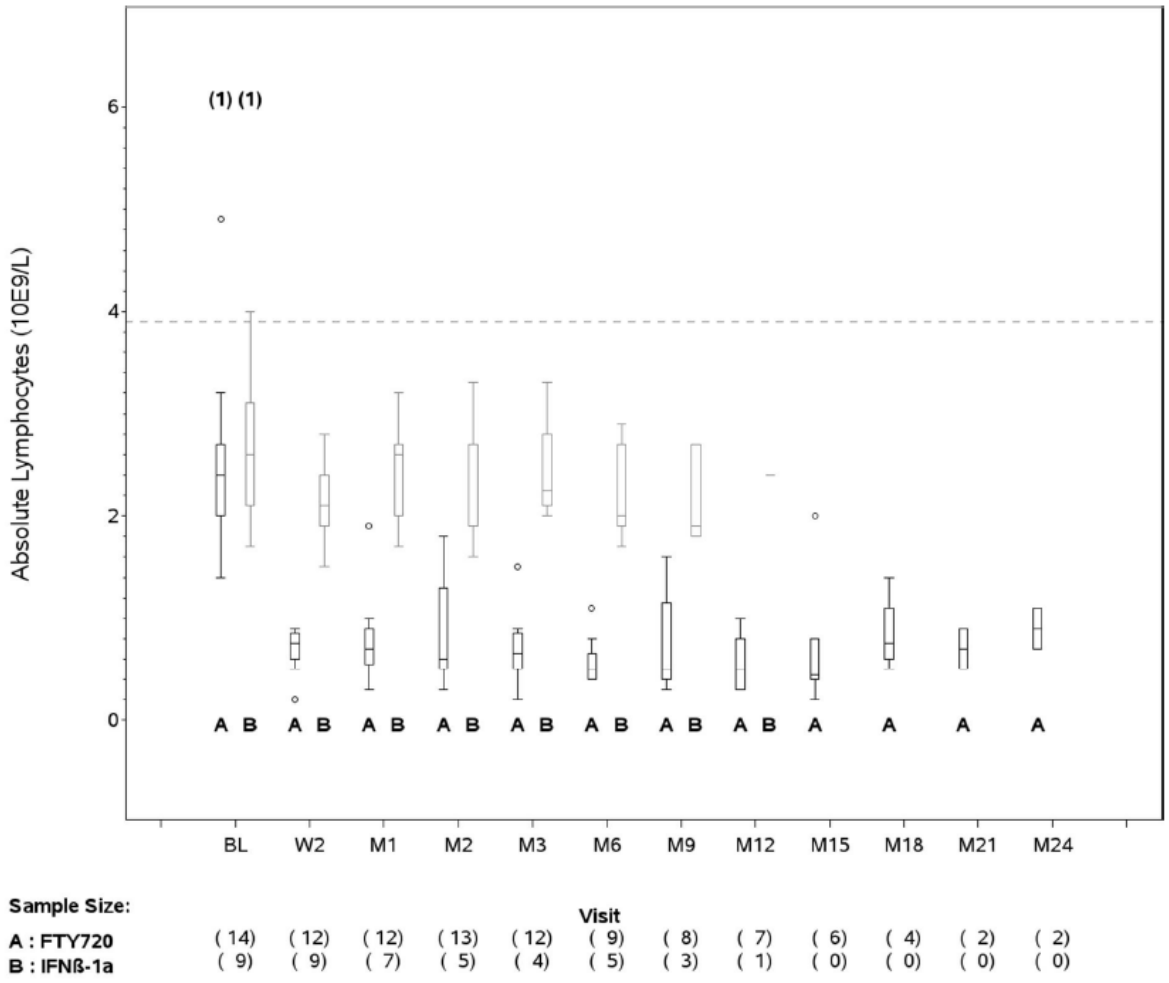
Parameter	**Fingolimod 0.25 and 0.5 mg n=107**	**Interferon β-1a n=107**	**Fingolimod 0.5 mg n=854 (adults)**
Absolute Lymphocytes (10^9/L)			
n	101	106	
Baseline Mean (SD)	2.059 (0.624)	1.971 (0.540)	
Week 2 Mean (SD)	0.675 (0.328)	1.896 (0.589)	
Change from Baseline Mean (SD)	-1.385 (0.621)	-0.075 (0.637)	
Percent Change Baseline to Week 2	-67.22%	-0.38%	
n	94	99	785
Baseline Mean (SD)	2.080 (0.656)	1.958 (0.510)	1.82 (0.59)
Month 1 Mean (SD)	0.621 (0.2852)	1.928 (0.5628)	0.49 (0.24)
Change Baseline to Month 1 Mean (SD)	-1.459 (0.666)	-0.029 (0.573)	-1.33 (0.56)
Percent Change Baseline to Month 1	-70.14%	-1.48%	-73.1%
n	101	98	772
Baseline (SD)	2.071 (0.640)	1.984 (0.548)	1.81 (0.58)
Month 6 Mean (SD)	0.585 (0.249)	1.947 (0.586)	0.49 (0.29)
Change Baseline to Month 6 Mean (SD)	-1.474 (0.636)	-0.036 (0.642)	-1.33 (0.56)
Percent Change Baseline to Month 6	-71.59%	-1.82%	-73.5%

n	100	90	736
Baseline (SD)	2.061 (0.645)	1.968 (0.582)	1.82 (0.58)
Month 12 Mean (SD)	0.582 (0.238)	1.880 (0.593)	0.49 (0.32)
Change Baseline to Month 12 Mean (SD)	-1.480 (0.672)	-0.076 (0.682)	-1.33 (0.55)
Percent Change Baseline to Month 12	-71.81%	-3.86%	-73.1%
n	50	31	
Baseline (SD)	2.210 (0.6425)	1.784 (0.353)	
Month 24 Mean (SD)	0.628 (0.234)	1.742 (0.503)	
Change Baseline to Month 24 Mean (SD)	-1.582 (0.609)	-0.042 (0.621)	
Percent Change Baseline to Month 24	-71.58%	-2.35%	
Absolute Neutrophil Count (10^9/L)			
n	101	106	
Baseline Mean (SD)	3.893 (2.031)	3.662 (1.558)	
Week 2 Mean (SD)	3.575 (2.273)	3.170 (1.132)	
Change from Baseline Mean (SD)	-0.318 (2.477)	-0.492 (1.396)	
Percent Change Baseline to Week 2	-8.17%	-13.44%	
n	94	99	786
Baseline Mean (SD)	3.969 (2.143)	3.672 (1.565)	4.00 (1.45)
Month 1 Mean (SD)	3.407 (1.510)	3.260 (1.668)	3.39 (1.36)
Change Baseline to Month 1 Mean (SD)	-0.562 (2.135)	-0.412 (1.710)	-0.61
Percent Change Baseline to Month 1	-14.16%	-11.22%	-15.25%
n	101	98	
Baseline (SD)	3.861 (2.018)	3.781 (1.617)	
Month 6 Mean (SD)	3.079 (1.329)	3.484 (1.501)	
Change Baseline to Month 6 Mean (SD)	-0.782 (1.953)	-0.296 (1.808)	
Percent Change Baseline to Month 6	-20.25%	-7.82%	
n	100	90	739
Baseline (SD)	3.819 (1.997)	3.612 (1.501)	3.99 (1.44)
Month 12 Mean (SD)	3.058 (1.457)	3.349 (1.525)	3.26 (1.45)
Change Baseline to Month 12 Mean (SD)	-0.761 (1.928)	-0.263 (1.737)	-0.73 (1.49)
Percent Change Baseline to Month 12	-19.93%	-7.28%	-18.30%
n	50	31	
Baseline (SD)	3.782 (1.562)	3.758 (1.324)	

Month 24 Mean (SD)	3.015 (1.143)	3.800 (1.636)	
Change Baseline to Month 24 Mean (SD)	-0.767	+0.042	
Percent Change Baseline to Month 24	-20.28%	+1.12%	

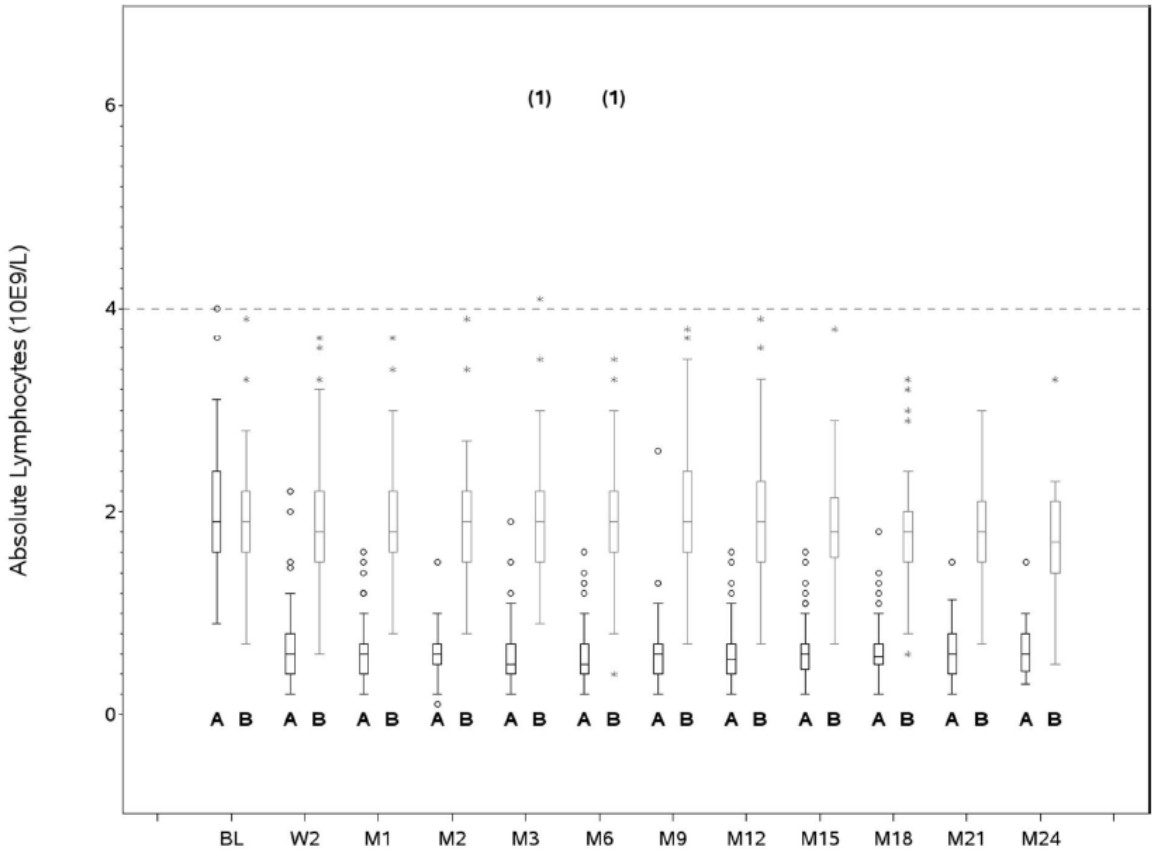
Source: Table 14.3-2.1 Clinical Study Report and Safety Review of NDA-22527

Figure 5: Sponsor Figure: Box and Whisker Plot of Absolute Lymphocyte Count for Ages 10 to <13 years, Safety Set, Study D2311



(k) = the number of patients with Absolute Lymphocytes (10E9/L) > 3.9 (10E9/L), i.e., 1 × ULN as shown by the reference line; ULN: Upper Limit of Normal.
-BL: baseline; W2: Week 2; M#: Month #, e.g. M3 is Month 3.

Figure 6: Sponsor Figure: Box and Whisker Plot of Absolute Lymphocyte Count for Ages ≥ 13 to 18, Safety Set, Study D2311



(k) = the number of patients with Absolute Lymphocytes (10E9/L) > 4 (10E9/L), i.e., 1 × ULN as shown by the reference line; ULN: Upper Limit of Normal.
-BL: baseline; W2: Week 2; M#: Month #, e.g. M3 is Month 3.

While there were sustained reductions in lymphocyte and neutrophil counts, there were no significant changes in eosinophil or in monocyte counts during the Core Phase of Study D2311 (data not shown).

In adult patients, fingolimod was associated with an 80% reduction in basophil counts after 12 months. A reduction in basophil counts of almost 90% was observed in Study D2311 after 24 months of fingolimod treatment as shown in the table below.

Table 52: Reviewer Table: Absolute Basophil Count Changes, Safety Set, Study D2311

Parameter	Fingolimod	Interferon β-1a

	n=107	n=107
Absolute Basophil Count (10^9/L)		
n	100	90
Baseline (SD)	0.040 (0.053)	0.032 (0.049)
Month 12 Mean (SD)	0.013 (0.034)	0.036 (0.051)
Change Baseline to Month 12 Mean (SD)	-0.027 (0.051)	0.004 (0.055)
Percent Change Baseline to Month 12	-67.50%	+12.50%
n	50	31
Baseline (SD)	0.036 (0.485)	0.035 (0.551)
Month 24 Mean (SD)	0.004 (0.020)	0.029 (0.046)
Change Baseline to Month 24 Mean (SD)	-0.032 (0.051)	-0.006 (0.063)
Percent Change Baseline to Month 24	-88.89%	-17.14%

Source: Table 14.3-2.1 Clinical Study Report

Reviewer Comment: A reduction in the serum absolute basophil count is of unclear clinical significance. The most concerning potential consequence of a low basophil count would be an increased risk of parasitic, particularly helminthic, infections, but an increased rate of parasite infections has not been observed in either the adult or pediatric fingolimod-treated populations.

Platelets

Adult patients in the fingolimod treatment group were noted to have a 3-5% reduction in platelet counts at Month 12. A reduction of 1.73% was noted in pediatric patients in the fingolimod treatment condition at Month 12. The mean platelet count for pediatric patients in the fingolimod treatment group returned to baseline by Month 24.

Table 53: Reviewer Table: Platelet Count Changes, Safety Set, Study D2311

Parameter	**Fingolimod n=107**	**Interferon β-1a n=107**
Platelet Count (10^9/L)		
n	100	89
Baseline (SD)	243.4 (47.84)	254.2 (58.27)
Month 12 Mean (SD)	239.2 (55.21)	247.7 (64.10)
Change Baseline to Month 12 Mean (SD)	-4.2 (38.78)	-6.4 (42.37)
Percent Change Baseline to Month 12	-1.73%	-2.52%
n	50	29
Baseline (SD)	243.5 (45.86)	243.8 (50.97)
Month 24 Mean (SD)	243.5 (49.40)	239.3 (55.43)
Change Baseline to Month 24 Mean (SD)	+0.1 (33.93)	-4.5 (47.91)
Percent Change Baseline to Month 24	+0.04%	-1.85%

Source: Table 14.3-2.1 Clinical Study Report

Reviewer Comment: A platelet reduction of less than 2% is of no clinical significance. Bleeding diatheses were not observed in any fingolimod trial. In the pediatric study, as in the adult studies, the standard deviations for these values are quite large. The restoration of baseline platelet values by Month 24 further confirms this change as being inconsequential.

Other hematologic parameters

There were no significant changes in the red blood cell count, hemoglobin and hematocrit values for fingolimod-treated patients during the Core Phase of Study D2311 (data not shown).

Follow-up

A subset of patients (n=47) in the fingolimod treatment group had follow-up values of absolute lymphocyte and absolute neutrophil counts after discontinuing fingolimod. The lymphocyte counts appeared to need more than 45 days to return to a normal range value, but the neutrophil counts returned to a normal value range within 45 days of discontinuing fingolimod as indicated below.

Table 54: Sponsor Table: Absolute Lymphocyte and Neutrophil Counts After Discontinuation of Study Treatments, Study D2311

Parameter			FTY720 N=47 n (%)	IFNß-1a N=58 n (%)
Absolute Lymphocytes (10E9/L)	Days 1-45 after drug discontinuation	Total	22	29
		> ULN	0 (0.0)	0 (0.0)
		Normal	7 (31.8)	27 (93.1)
		< 1.0 x 10E9/L	15 (68.2)	2 (6.9)
		< 0.8 x 10E9/L	12 (54.5)	1 (3.4)
		< 0.6 x 10E9/L	11 (50.0)	0 (0.0)
		< 0.4 x 10E9/L	3 (13.6)	0 (0.0)
		< 0.2 x 10E9/L	0 (0.0)	0 (0.0)
		< 0.1 x 10E9/L	0 (0.0)	0 (0.0)
	>45 days after drug discontinuation	Total	5	21
		> ULN	0 (0.0)	3 (14.3)
		Normal	4 (80.0)	13 (61.9)
		< 1.0 x 10E9/L	1 (20.0)	5 (23.8)
		< 0.8 x 10E9/L	1 (20.0)	4 (19.0)
		< 0.6 x 10E9/L	0 (0.0)	3 (14.3)
		< 0.4 x 10E9/L	0 (0.0)	1 (4.8)
		< 0.2 x 10E9/L	0 (0.0)	0 (0.0)
		< 0.1 x 10E9/L	0 (0.0)	0 (0.0)

Parameter			FTY720 N=47 n (%)	IFNß-1a N=58 n (%)
Absolute Neutrophils (Seg. + Bands) (10E9/L)	Days 1-45 after drug discontinuation	Total	22	29
		> ULN	2 (9.1)	1 (3.4)
		Normal	20 (90.9)	27 (93.1)
		< 1.6 x 10E9/L	0 (0.0)	1 (3.4)
		< 1.0 x 10E9/L	0 (0.0)	0 (0.0)
		< 0.5 x 10E9/L	0 (0.0)	0 (0.0)
	>45 days after drug discontinuation	Total	5	21
		> ULN	1 (20.0)	2 (9.5)
		Normal	4 (80.0)	18 (85.7)
		< 1.6 x 10E9/L	0 (0.0)	1 (4.8)
		< 1.0 x 10E9/L	0 (0.0)	0 (0.0)
		< 0.5 x 10E9/L	0 (0.0)	0 (0.0)

Source: Table 14.3-2.9 Clinical Study Report

Reviewer Comment: In adult studies, the lymphocyte counts of most patients returned to within approximately 5% of patient baseline at 3 months after discontinuing fingolimod. The pediatric data are more limited in number and duration, but it appears that the majority of pediatric patients' lymphocyte count recoveries are completed outside the 45-day (5 half-lives) period whereas neutrophil counts rectify within the 45-day period that is consistent with the adult recoveries.

Analysis of outliers for hematologic abnormalities

Outlier analysis of the Safety Set of Study D2311 is presented in the following table:

Table 55: Sponsor Table: Outlier Analysis of Hematologic Abnormalities, Safety Set, Study D2311

Parameter	Criterion	FTY720 N=107 n (%)	IFN β-1a N=107 n (%)
Leukocytes (WBC) (10E9/L)	Total	107	107
	< 3 x 10E9/L	59 (55.1)	7 (6.5)
	> 15 x 10E9/L	1 (0.9)	2 (1.9)
Absolute Lymphocytes (10E9/L)	Total	107	107
	< 0.2 x 10E9/L	3 (2.8)	0 (0.0)
	> 8 x 10E9/L	0 (0.0)	0 (0.0)
Absolute Neutrophils (Seg.+Bands) (10E9/L)	Total	107	107
	< 1 x 10E9/L	5 (4.7)	3 (2.8)
	> 12 x 10E9/L	3 (2.8)	3 (2.8)
Erythrocytes (RBC) (10E12/L)	Total	107	107
	< 3.3 x 10E12/L	1 (0.9)	0 (0.0)
	> 6.8 x 10E12/L	0 (0.0)	0 (0.0)
Haemoglobin (g/L)	Total	107	107
	< 100g/L	1 (0.9)	0 (0.0)
	> 200g/L	0 (0.0)	0 (0.0)
Platelet count(direct) (10E9/L)	Total	107	107
	< 100 x 10E9/L	0 (0.0)	1 (0.9)
	> 600 x 10E9/L	0 (0.0)	0 (0.0)
Haematocrit (1)	Total	107	107
	< 0.3(1)	1 (0.9)	0 (0.0)
	> 0.6(1)	0 (0.0)	0 (0.0)

Source: Table 12-18 Clinical Study Report

Reviewer Comment: Analysis of outliers for hematologic parameters did not suggest a safety signal other than the previously identified effects of fingolimod on lymphocyte and neutrophil counts.

Table 56: Sponsor Table: Frequency Distribution of Notable Hematologic Parameters, Safety Set, Study D2311

Parameter	Criterion	FTY720 N=107 n (%)	IFN β-1a N=107 n (%)
Leukocyte (WBC) (10E9/L)	Total	107	107
	> ULN	6 (5.6)	15 (14.0)
	Normal	14 (13.1)	55 (51.4)
	< 3.0 x 10E9/L	59 (55.1)	7 (6.5)
	< 1.5 x 10E9/L	2 (1.9)	0 (0.0)
	< 1.0 x 10E9/L	0 (0.0)	0 (0.0)
Absolute Lymphocytes (10E9/L)	Total	107	107
	> ULN	0 (0.0)	3 (2.8)
	Normal	3 (2.8)	78 (72.9)
	< 1.0 x 10E9/L	104 (97.2)	26 (24.3)
	< 0.8 x 10E9/L	103 (96.3)	7 (6.5)
	< 0.6 x 10E9/L	87 (81.3)	2 (1.9)
	< 0.4 x 10E9/L	45 (42.1)	0 (0.0)
	< 0.2 x 10E9/L	3 (2.8)	0 (0.0)
	< 0.1 x 10E9/L	0 (0.0)	0 (0.0)
Absolute Neutrophils (Seg. + Bands) (10E9/L)	Total	107	107
	> ULN	13 (12.1)	16 (15.0)
	Normal	67 (62.6)	69 (64.5)
	< 1.6 x 10E9/L	27 (25.2)	22 (20.6)
	< 1.0 x 10E9/L	5 (4.7)	3 (2.8)
	< 0.5 x 10E9/L	0 (0.0)	0 (0.0)
Platelet count (direct) (10E9/L)			
Patient ≤14 yrs at the time of assessment	Total	29	28
	> ULN	1 (3.4)	1 (3.6)
	Normal	23 (79.3)	22 (78.6)
	< 175 x 10E9/L	5 (17.2)	5 (17.9)
	< 150 x 10E9/L	2 (6.9)	4 (14.3)
	< 125 x 10E9/L	0 (0.0)	1 (3.6)
	< 100 x 10E9/L	0 (0.0)	0 (0.0)
	<25 x 10E9/L	0 (0.0)	0 (0.0)
Patient > 14 yrs at the time of assessment	Total	93	96
	> ULN	10 (10.8)	14 (14.6)
	Normal	72 (77.4)	73 (76.0)
	< 150 x 10E9/L	11 (11.8)	10 (10.4)
	< 125 x 10E9/L	2 (2.2)	4 (4.2)
	< 100 x 10E9/L	0 (0.0)	1 (1.0)
	<25 x 10E9/L	0 (0.0)	0 (0.0)

Source: Table 12-19 Clinical Study Report

Shift Analysis of Hematologic Values

Table 57: Sponsor Table: Shift Analysis of Absolute Lymphocyte Counts, Safety Set, Study D2311

Absolute Lymphocytes (10E9/L)

Treatment		Baseline n (%)	Extreme lab value: Low n (%)	Normal n (%)	High n (%)	Low & high n (%)
FTY720 (N=107)	Low	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
	Normal	104 (98.1)	102 (96.2)	2 (1.9)	0 (0.0)	0 (0.0)
	High	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	106 (100)	104 (98.1)	2 (1.9)	0 (0.0)	0 (0.0)
IFNß-1a (N=107)	Low	1 (0.9)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
	Normal	105 (98.1)	26 (24.3)	76 (71.0)	3 (2.8)	0 (0.0)
	High	1 (0.9)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
	Total	107 (100)	26 (24.3)	78 (72.9)	3 (2.8)	0 (0.0)

Source: Table 14.3-2.1

Table 58: Sponsor Table: Shift Analysis Absolute Neutrophils, Safety Set, Study D2311

Absolute Neutrophils (Seg. + Bands) (10E9/L)

Treatment		Baseline n (%)	Extreme lab value: Low n (%)	Normal n (%)	High n (%)	Low & high n (%)
FTY720 (N=107)	Low	3 (2.8)	2 (1.9)	1 (0.9)	0 (0.0)	0 (0.0)
	Normal	98 (92.5)	25 (23.6)	61 (57.5)	12 (11.3)	0 (0.0)
	High	5 (4.7)	0 (0.0)	4 (3.8)	1 (0.9)	0 (0.0)
	Total	106 (100)	27 (25.5)	66 (62.3)	13 (12.3)	0 (0.0)
IFNß-1a (N=107)	Low	5 (4.7)	4 (3.7)	1 (0.9)	0 (0.0)	0 (0.0)
	Normal	99 (92.5)	18 (16.8)	65 (60.7)	16 (15.0)	0 (0.0)
	High	3 (2.8)	0 (0.0)	3 (2.8)	0 (0.0)	0 (0.0)
	Total	107 (100)	22 (20.6)	69 (64.5)	16 (15.0)	0 (0.0)

Source: Table 14.3-2.1

Reviewer Comment: The shift analyses for absolute lymphocytes and absolute neutrophils demonstrate four findings. First, over 92% of patients in the fingolimod treatment group entered the study with a normal baseline count for the lymphocyte and neutrophil parameters. Second, most patients in the study who took fingolimod did not ever register an absolute lymphocyte nor neutrophil value at an extreme high or low value. Third, over 98% of patients in the fingolimod treatment group registered a hematology value consistent with lymphopenia. Fourth, a lab value consistent with neutropenia was noted in on over 25% of patients in the fingolimod treatment group. The frequency distribution of abnormal values confirms the significant reductions in lymphocytes and neutrophils without significant effects on other bone marrow originating cells such as platelets. The shift analyses confirm that fingolimod therapy is

associated with significant lymphopenia, an expected finding that was anticipated based on the mechanism of action of fingolimod, the prevention of the egress of these lymphocytes from the lymph nodes.

Chemistry Evaluations

As indicated in Sections 6.1.1 and 8.3.3, patients enrolled in Study D2311 had routine chemistry and urinalysis testing during the Core Phase of the study. The overall evaluation was guided by knowledge of the chemistry changes observed in the adult studies of fingolimod that had identified increased liver transaminases and concern for proteinuria.

Overall, as indicated in the table below, there were no significant changes noted in most serum chemistry values.

There were notable changes in serum alkaline phosphatase and total bilirubin in fingolimod-treated patients relative to the interferon β-1a-treated patients.

There was more variability observed for serum alkaline phosphatase in the fingolimod treatment group. Serum alkaline phosphatase values are difficult to interpet in the pediatric population because normal ranges for alkaline phosphatase vary considerably across pre- and post-puberty due to growth and bone maturity (Turan *et al.*, 2011). The alkaline phosphatase shifts in the fingolimod treatment group are of unclear significance, especially since there were nearly an equivalent number of patients with abnormal values in the interferon β-1a treatment group.

Reviewer Comment: The mean alkaline phophatase in adult patients was also elevated approximately 10% without a clear pathological and no observed clinical significance.

Five patients (4.7%) in the fingolimod treatment group elevated serum glucose values of > 6.661 mmol/L versus only two patients in the interferon β-1a treatment group. In a trial of adults treated with fingolimod 0.5 mg, four patients (0.5%) had serum glucose outliers in this range. The significance of the elevated value in adult patients was unclear, as is the significance in this small subset of pediatric patients.

Reviewer Comment: A review of the abnormal high values revealed no systematic pattern in glucose elevation suggestive of a durable, treatment-related effect. The values were distributed as single outlier findings in patients who otherwise had glucose values within the normal range.

Sixteen pediatric patients (15%) had increased total bilirubin values (> 20.52 µmol/L). In an adult trial with 0.5 mg fingolimod, 11% had abnormal total bilirubin values greater than twice

upper limit of normal. On review of the pediatric cases, most elevated total bilirubin values occurred as isolated outliers among otherwise normal range readings for the patient. Four patients (b) (6)) in the fingolimod treatment group had consistent elevations in bilirubin during the randomized treatment period that suggested a treatment-related impairment of hepatic synthetic capability. Five patients (b) (6)) had elevated readings in pre-treatment values testing suggesting undiagnosed Gilbert's syndrome or an explanation independent of fingolimod treatment. One patient's elevated bilirubin value ((b) (6)) appeared to originate from a hemolyzed sample as the sample had unusually elevated potassium consistent with hemolysis.

Table 59: Sponsor Table: Clinically Notable Chemistry Abnormalities, Safety Set, Study D2311

Parameter	Criterion (units)	FTY720 N=107 n (%)	IFN β-1a N=107 n (%)
Albumin	Total	107	107
	< 25 g/L	0 (0.0)	0 (0.0)
	> 60 g/L	0 (0.0)	0 (0.0)
Alkaline phosphatase, serum*	Total	107	107
	< (42,51) (74,50) (52,47) 37 U/L	11 (10.3)	14 (13.1)
	> (362,332) (390,162) (171,119) 116 U/L	17 (15.9)	9 (8.4)
Blood Urea Nitrogen (BUN)	Total	107	107
	< 0.714 mmol/L	0 (0.0)	0 (0.0)
	> 10.71 mmol/L	0 (0.0)	1 (0.9)
Calcium	Total	107	107
	< 1.871 mmol/L	1 (0.9)	0 (0.0)
	> 2.894 mmol/L	0 (0.0)	0 (0.0)
Chloride	Total	107	107
	< 85 mmol/L	0 (0.0)	1 (0.9)
	> 119 mmol/L	0 (0.0)	0 (0.0)
Creatinine	Total	107	107
	< 17.68 µmol/L	0 (0.0)	0 (0.0)
	> 141.44 µmol/L	0 (0.0)	0 (0.0)
Gamma Glutamyltranferase	Total	107	107
	> 120 U/L	1 (0.9)	0 (0.0)
Glucose**	Total	107	107
	< 3.886 mmol/L	27 (25.2)	21 (19.6)
	> 6.661 (11.102) mmol/L	5 (4.7)	2 (1.9)
LDH	Total	107	107
	> 500 U/L	0 (0.0)	1 (0.9)
Potassium	Total	107	107
	< 3 mmol/L	0 (0.0)	0 (0.0)
	> 5.2 mmol/L	17 (15.9)	17 (15.9)
SGOT (AST)	Total	107	107
	> 100 U/L	1 (0.9)	4 (3.7)
SGPT (ALT)	Total	107	107
	> 110 U/L	4 (3.7)	3 (2.8)
Bilirubin (total)	Total	107	107
	> 20.52 µmol/L	16 (15.0)	4 (3.7)
Sodium	Total	107	107
	< 130 µmol/L	0 (0.0)	0 (0.0)
	> 150 µmol/L	1 (0.9)	1 (0.9)
Total Protein (Serum)	Total	107	107
	< 40 g/L	0 (0.0)	0 (0.0)
	> 95 g/L	0 (0.0)	0 (0.0)
Uric Acid	Total	107	107
	< 89.22 µmol/L	0 (0.0)	1 (0.9)
	> 594.8 µmol/L	0 (0.0)	0 (0.0)

Source: Table 12-21 Clinical Study Report

Shift analyses revealed there were no clinically relevant mean changes from baseline in amylase, blood urea nitrogen, calcium, chloride, cystatin C, conjugated bilirubin, LDH, magnesium, inorganic phosphate, potassium, sodium, total protein, triglycerides, uric acid, creatinine, age adjusted estimated creatinine clearance (Schwartz), or albumin in the Safety Set for Study D2311.

> *Reviewer Comment: Studies in adult patients taking fingolimod had suggested a dose-dependent association with elevated serum sodium that was not noted in this study. In the four patients whose elevated bilirubin values appeared related to treatment with fingolimod because of coincidental elevated transaminases, none of the elevated serum total bilirubin values were > 2x ULN. Transaminase changes are discussed below. No other relevant changes emerged from the biochemistry laboratory value review.*

Shift analyses revealed two possible trends in cholesterol for fingolimod treated patients, an elevation in total cholesterol among some fingolimod treated patients and a reduction in serum HDL.

Table 60: Sponsor Table: Total Cholesterol Shift Analysis, Safety Set, Study D2311

Cholesterol (total) (mmol/L)

		Baseline	Extreme value			
			Low	Normal	High	Low & high
Treatment		n (%)	n (%)	n (%)	n (%)	n (%)
FTY720 (N=107)	Low	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Normal	99 (92.5)	0 (0.0)	73 (68.2)	26 (24.3)	0 (0.0)
	High	8 (7.5)	0 (0.0)	0 (0.0)	8 (7.5)	0 (0.0)
	Total	107 (100)	0 (0.0)	73 (68.2)	34 (31.8)	0 (0.0)
IFNß-1a (N=107)	Low	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Normal	100 (93.5)	0 (0.0)	89 (83.2)	11 (10.3)	0 (0.0)
	High	7 (6.5)	0 (0.0)	2 (1.9)	5 (4.7)	0 (0.0)
	Total	107 (100)	0 (0.0)	91 (85.0)	16 (15.0)	0 (0.0)

Table 61: Sponsor Table: HDL Cholesterol Shift Analysis, Safety Set, Study D2311

Cholesterol (HDL) (mmol/L)

Treatment	Baseline n (%)	Extreme value: Low n (%)	Normal n (%)	High n (%)	Low & high n (%)
FTY720 (N=107)	Low 12 (11.2)	10 (9.3)	2 (1.9)	0 (0.0)	0 (0.0)
	Normal 95 (88.8)	21 (19.6)	74 (69.2)	0 (0.0)	0 (0.0)
	High 0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total 107 (100)	31 (29.0)	76 (71.0)	0 (0.0)	0 (0.0)
IFNß-1a (N=107)	Low 15 (14.0)	14 (13.1)	1 (0.9)	0 (0.0)	0 (0.0)
	Normal 92 (86.0)	36 (33.6)	56 (52.3)	0 (0.0)	0 (0.0)
	High 0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total 107 (100)	50 (46.7)	57 (53.3)	0 (0.0)	0 (0.0)

An Information Request was sent received by Novartis on February 28, 2018 requesting clarification of the observed trends and comparison to any relevant cholesterol value findings from the adult trials with fingolimod 0.5 mg.

Novartis replied as follows:

“In the clinical study report (CSR) Table 14.3-2.1 provides details about a change from baseline in laboratory values. However, it is important to take the following facts about lab collections into consideration while reviewing the reported results: the study lab manual did not specify fasting requirements and, therefore, lab samples were collected both ways, fasting or not fasting, which lead to potential variability and made interpretation of the findings difficult. Also, the study design incorporated flexible study duration, contributed to a fewer patients with samples collected at the later time points of 18, 21 and 24 months which may confound the study results collected at these time points. In fact, significantly more patients collected lab samples in FTY720 group compare to IFN β-1a group due to high dropout rate in IFNß-1a group (85, 65 and 50 patients were collected blood samples at18/21/24 months compare to 64, 46 and 30 in IFN β-1a group). As a consequence, FTY720 group has approximately 6% more cholesterol total and LDL assessments after randomization than IFN β-1a group due to higher dropout rate in IFNß-1a group (Number of cholesterol total assessments: FTY720: 1084 vs. IFN β-1a: 1018; number of LDL assessments: FTY720: 1083 vs IFN β-1a: 1019). Patients in the FTY720 group had an increase compared to baseline in mean total cholesterol of 3.7% at Month 12 (N=102), with a 6.0% increase at Month 18 (N=85), 6.9% increase at Month 24 (N=50) and subsequent reduction to a 4.5% increase at the end of study visit (N=106). In contrast, patient[s] in IFN β-1a group had an unexplained initial decrease of 5.5% in mean total cholesterol at Week 2 (N=106), following by a gradual increase (though values appear to be decreased compared to baseline) in mean total cholesterol throughout the study (3.7% decrease Month 12 (N=91), 4.1% decrease Month 18 (N=64), 1.1% decrease Month 24 (N=30)

and 3.6% decrease at end of study assessment (N=107)). Similar results were seen for percent change from baseline in mean LDL but of lesser magnitude. No study drug interruptions, discontinuation or cases of premature study discontinuation were reported in association with elevated total cholesterol or LDL results."

Reviewer Comment: The lack of specification of fasting cholesterol testing in the protocol precludes any meaningful interpretation of LDL, HDL, and total cholesterol values in Study D2311.

Liver Transaminases

Prior studies of fingolimod identified a rise in liver transaminases, particularly ALT and GGT that occurred after treatment initiation. While most patients in the two treatment groups in Study D2311 had normal range values for AST, GGT, and total bilirubin, there was a subset of patients with abnormal values suggesting that pediatric patients behave similarly with respect to liver enzymes and liver-related laboratory testing results as adult patients.

No patient in the pediatric study met Hy's law crtieria. As in adults treated with fingolimod, a larger proportion of patients with an elevated AST or an elevated ALT were from the fingolimod treatment group. Patients with elevated transaminases had normal alkaline phophastase and the majoirty had normal total bilurubin values. Two patients in the fingolimod treatment group versus four patients in the interferon β-1a treatment group had ALT values ≥ 5x ULN. A single patient from the interferon β-1a treatment group had a ALT > 10X ULN; no patient in the fingolimod treatment group had an ALT > 8x ULN. There was two patients with a GGT ≥5 x ULN in the fingolimod treated group and none in the interferon β-1a treatment group. The table below summarizes the frequency of liver transaminase elevations in the study.

Table 62: Reviewer Table: Distributions of Patients with Liver-related Laboratory Abnormalities, Safety Set, Study D2311

Parameter	Criterion	Fingolimod 0.25 and 0.5 mg n=107 n (%)	Interferon β-1a n=107 n (%)	Fingolimod 0.5 mg n=854 (adults) n (%)
ALT (U/L)	n	107	107	851
	No abnormalities	32 (29.9%)	53 (49.5%)	461 (54.2%)
	> ULN	74 (69.2%)	47 (43.9%)	390 (45.8%)
	≥ 2 x ULN	31 (29.0%)	11 (10.3%)	148 (17.4%)
	≥ 3 x ULN	8 (7.5%)	6 (5.6%)	72 (8.5%)

	≥ 5 x ULN	2 (1.9%)	4 (3.7%)	14 (1.6%)
	≥ 10 x ULN	0	1 (0.9%)	1 (0.1%)
	≥ 20 x ULN	0	0	0
AST (U/L)	n	107	107	851
	No abnormalities	86 (80.4%)	93 (86.9%)	636 (74.7%)
	> ULN	21 (19.6%)	14 (13.1%)	215 (25.3%)
	≥ 2 x ULN	5 (4.7%)	4 (3.7%)	36 (4.2%)
	≥ 3 x ULN	0	3 (2.8%)	17 (2.0%)
	≥ 5 x ULN	0	2 (1.9%)	2 (0.2%)
	≥ 10 x ULN	0	0	0
	≥ 20 x ULN	0	0	0
GGT (U/L)	n	107	107	851
	No abnormalities	65 (60.7%)	93 (86.9%)	580 (68.2%)
	> ULN	42 (39.3%)	14 (13.1%)	271 (31.8%)
	≥ 2 x ULN	12 (11.2%)	4 (3.7%)	119 (14.0%)
	≥ 3 x ULN	2 (1.9%)	2 (1.9%)	56 (6.6%)
	≥ 5 x ULN	2 (1.9%)	0	15 (1.8%)
	≥ 10 x ULN	0	0	0
	≥ 20 x ULN	0	0	0
Bilirubin (total) (µmol/L)	n	107	107	851
	No abnormalities	72 (67.3%)	67 (62.6%)	763 (89.7%)
	> ULN	19 (17.8%)	5 (4.7%)	88 (10.3%)
	≥ 2 x ULN	0	0	8 (0.9%)

Source: Table 12-22 Clinical Study Report and Safety Review NDA 22527

Reviewer Comment: The frequency distributions in pediatric patients grossly resemble those observed in adult patients in fingolimod trials. A smaller percentage of patients in the pediatric trials had normal range ALT and GGT values, but the majority of ALT and GGT abnormalities in pediatric patients were confined to < 2 x ULN. The AST elevations in the pediatric patients were not as pronounced as in the adult patient population treated with fingolimod. The timetable for the transaminase changes is also similar in the pediatric population as the onset of abnormalities occurs within 6 months of treatment initiation. The existing label information regarding liver transaminase monitoring for adults appears appropriate for the pediatric population.

Urinalysis

In adult studies, there had been concern for a dose-dependent shift from normal to 3+ proteinuria in fingolimod treated patients. There were no significant changes in urine dipstick parameters in the pediatric study. There were no patients in the fingolimod treatment group in the pediatric study with 3+ proteinuria measured at any visit.

Table 63: Sponsor Table: Shift Analysis of Urine Protein Dipstick Test Values, Safety Set, Study D2311

Urine Protein Dipstick test

Treatment		Baseline n (%)	Extreme value: NEG n (%)	+ n (%)	2+ n (%)	3+ n (%)	4+ n (%)
FTY720	(N=107)	NEG 100 (94.3)	67 (63.2)	29 (27.4)	4 (3.8)	0 (0.0)	0 (0.0)
		+ 3 (2.8)	1 (0.9)	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)
		2+ 3 (2.8)	2 (1.9)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
		3+ 0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		4+ 0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Total 106 (100)	70 (66.0)	31 (29.2)	5 (4.7)	0 (0.0)	0 (0.0)
IFNß-1a	(N=107)	NEG 96 (92.3)	70 (67.3)	21 (20.2)	4 (3.8)	1 (1.0)	0 (0.0)
		+ 5 (4.8)	4 (3.8)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
		2+ 3 (2.9)	1 (1.0)	2 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)
		3+ 0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		4+ 0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Total 104 (100)	75 (72.1)	24 (23.1)	4 (3.8)	1 (1.0)	0 (0.0)

Source: Table 14.3-2.6c

More than twice as many patients in the fingolimod treatment group had a notable post-baseline urinary white blood cell finding (23 patients, 21.5%) than did patients in the interferon β-1a treatment group (10 patients, 9.3%). There was an increase of approximately 1.5 white blood cells per high power field in quantitative urinalysis testing for fingolimod treatment patients in Study D2311.

Table 64: Sponsor Table: Number of Urinary White Blood Cells at Month 24 and End of Study, Study D2311

Urinalysis
Urinary WBC (Quantitative) (/hpf)

Visit Window	Statistics	FTY720 N=107 Base	FTY720 N=107 Post	FTY720 N=107 Change	IFNß-1a N=107 Base	IFNß-1a N=107 Post	IFNß-1a N=107 Change
Month 24	n	72	72	72	52	52	52
	Mean	1.4	2.9	1.5	1.4	1.2	-0.2
	SD	3.08	6.23	6.29	3.41	3.14	4.75
	Minimum	0	0	-13	0	0	-17
	Median	0.0	0.0	0.0	0.0	0.0	0.0
	Maximum	16	33	31	17	19	18
Last assessment on study drug *	n	101	101	101	98	98	98
	Mean	1.2	2.6	1.4	0.9	1.1	0.1
	SD	2.69	5.91	5.84	2.58	2.75	3.80
	Minimum	0	0	-14	0	0	-17
	Median	0.0	0.0	0.0	0.0	0.0	0.0
	Maximum	16	33	31	17	19	18

Source: Table 14.3-2.1

Reviewer Comment: The glomerular surface expresses S1P1 receptors. There were adult patients in the fingolimod 1.25 mg treatment group who had onset of proteinuria, and the possibility of a change in glomerular filtration was offered as a potential explanation for those earlier findings. Pediatric patients and adults treated with 0.5 mg fingolimod did not have proteinuria. There are no published studies with relevant data to determine whether fingolimod can promote translocation of white blood cells into urine by acting on S1P1 receptors along the glomerular surface. An increase from 1.2 to 2.6 white blood cells per high power field is unlikely to be of any clinical significance. The pediatric normal range for white blood cells per high power field in spontaneously voided urine can be as high as 50 cells, and void volume variability from pediatric samples can make quantitative cell counts of urine samples obtained from children and adolescents unreliable (Utsch & Klaus, 2014).

8.4.7. Vital Signs

The evaluation of vital signs in Study D2311 focused on acute changes after initial dose of fingolimod and any changes after chronic administration. Previous studies in adults had identified that, with administration of the first dose of fingolimod to a patient, there is a decline in heart rate and blood pressure noted within the first six hours after the initial dose. Therefore, to monitor for the expected heart rate and blood pressure changes in pediatric patients, and to maintain blinding, all patients in this study were mandated by protocol to undergo monitoring at an independent monitoring site (see Section 6.1.1) of their first dose, of a restart dose after a medication pause, or of a first dose of an increased dose.

As in adults, the first dose of fingolimod in pediatric patients was associated with a decline in heart rate. The maximal decline from pre-dose heart rate observed in the fingolimod treated patients was an average of 7.53 beats per minutes at five hours post-dose. In adults receiving their initial dose of fingolimod 0.5 mg, the average heart rate decrease was 9 bpm at six hours. As shown in the figures below, the trend in reduction in the heart rate was comparable between patients ages 10-12 and patients ≥ 12 years old.

Figure 7: Sponsor Figure: Box and Whisker Plot of Sitting Pulse (BPM) during 6 Hours Post First Dose Administration, Age < 12 years old, Safety Set, Study D2311

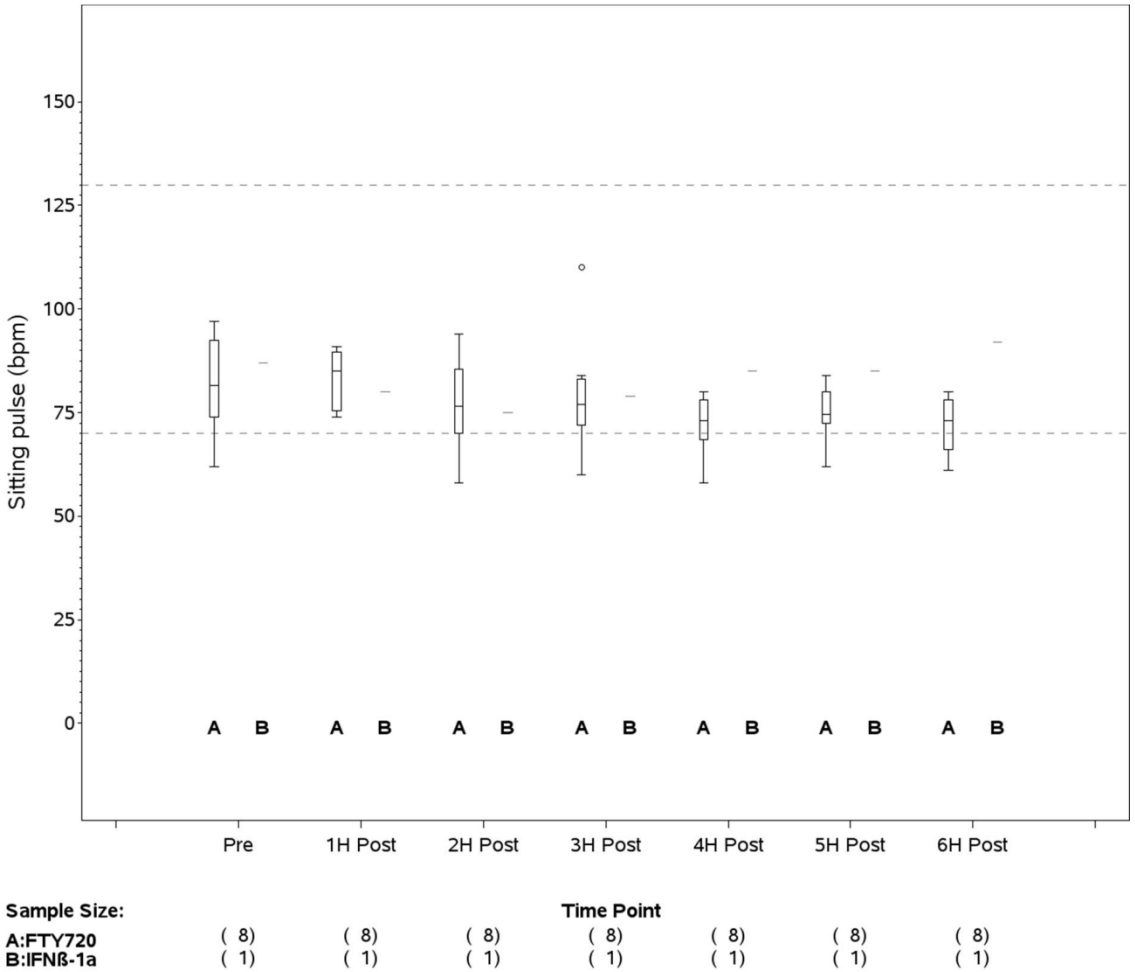
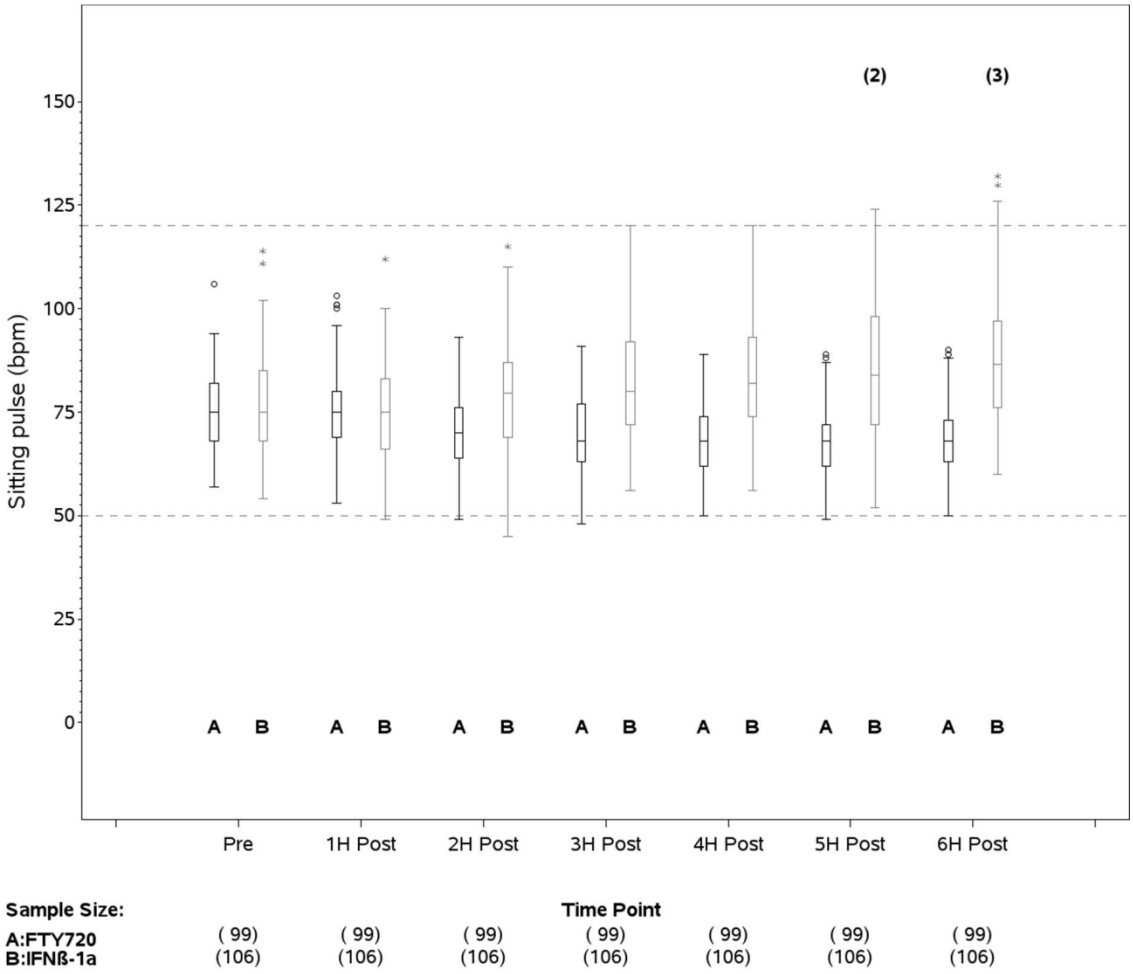


Figure 8: Sponsor Figure: Box and Whisker Plot of Sitting Pulse (BPM) during 6 Hours Post First Dose Administration, Age ≥ 12 years old, Safety Set, Study D2311



Source: Figures 12-3 and 12-4 Clinical Study Report

A decline in post dose systolic and diastolic blood pressure was noted in the fingolimod treatment group. As indicated in the tables below, the declines began 2 hours after the dose and peaked at hour 5.

Table 65: Summary First Dose Administration Vital Signs by Hour and Treatment, Safety Set, Study D2311

First Dose
Sitting Systolic Blood Pressure (mmHg)

Time point	Statistics	FTY720 N=107			IFNß-1a N=107		
		pre-dose	Post	Change	pre-dose	Post	Change
Pre-dose	n	107			107		
	Mean	111.99			112.36		
	SD	11.255			10.377		
	Minimum	86.0			89.0		
	Median	111.00			110.00		
	Maximum	155.0			140.0		
Hour 1	n	107	107	107	107	107	107
	Mean	111.99	112.59	0.60	112.36	113.09	0.73
	SD	11.255	11.366	8.277	10.377	11.041	8.328
	Minimum	86.0	88.0	-27.0	89.0	90.0	-23.0
	Median	111.00	113.00	0.00	110.00	112.00	1.00
	Maximum	155.0	146.0	27.0	140.0	142.0	30.0
Hour 2	n	107	107	107	107	107	107
	Mean	111.99	110.97	-1.02	112.36	112.29	-0.07
	SD	11.255	11.819	9.096	10.377	11.911	9.128
	Minimum	86.0	76.0	-27.0	89.0	69.0	-32.0
	Median	111.00	111.00	0.00	110.00	112.00	0.00
	Maximum	155.0	144.0	18.0	140.0	152.0	21.0
Hour 3	n	107	107	107	107	107	107
	Mean	111.99	111.46	-0.53	112.36	112.05	-0.32
	SD	11.255	11.746	7.862	10.377	12.402	9.989
	Minimum	86.0	81.0	-34.0	89.0	77.0	-26.0
	Median	111.00	111.00	0.00	110.00	112.00	0.00
	Maximum	155.0	140.0	17.0	140.0	150.0	22.0
Hour 4	n	107	107	107	107	107	107
	Mean	111.99	111.56	-0.43	112.36	112.32	-0.05
	SD	11.255	12.184	8.633	10.377	11.921	10.382
	Minimum	86.0	87.0	-34.0	89.0	80.0	-30.0
	Median	111.00	110.00	0.00	110.00	111.00	-1.00
	Maximum	155.0	145.0	22.0	140.0	149.0	30.0
Hour 5	n	107	107	107	107	107	107
	Mean	111.99	110.67	-1.32	112.36	113.25	0.89
	SD	11.255	11.407	7.614	10.377	10.998	9.978
	Minimum	86.0	81.0	-36.0	89.0	79.0	-34.0
	Median	111.00	110.00	-1.00	110.00	112.00	1.00
	Maximum	155.0	139.0	15.0	140.0	150.0	23.0

		FTY720 N=107			IFNß-1a N=107		
Time point	Statistics	pre-dose	Post	Change	pre-dose	Post	Change
Hour 6	n	107	107	107	107	107	107
	Mean	111.99	112.74	0.75	112.36	115.50	3.13
	SD	11.255	11.327	7.413	10.377	12.277	10.287
	Minimum	86.0	79.0	-18.0	89.0	87.0	-33.0
	Median	111.00	112.00	1.00	110.00	115.00	4.00
	Maximum	155.0	151.0	20.0	140.0	150.0	31.0

Source: Table 12.3-8.2a Clinical Study Report

The frequency observed distribution of pulse values during first dose monitoring confirmed the pharmacodynamic effect of fingolimod as most of the heart rates recorded below 70 beats per minute were from patients in the fingolimod treatment group.

Table 66: Sponsor Table: Frequency (%) distribution of lowest pulse (bpm) during first dose monitoring, Safety Set, Study D2311

	FTY720 N = 107 n (%)			IFN β-1a N = 107 n (%)		
Criterion	**< 12 years**	**≥ 12,< 18 years**	**≥ 18 years**	**< 12 years**	**≥ 12,< 18 years**	**≥18 years**
< 40 (bpm)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
≥ 40-< 50 (bpm)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	2 (1.9)	0 (0.0)
≥ 50-< 60 (bpm)	1 (12.5)	31 (31.3)	0 (0.0)	0 (0.0)	13 (12.6)	0 (0.0)
≥ 60-< 70 (bpm)	4 (50.0)	47 (47.5)	0 (0.0)	0 (0.0)	28 (27.2)	0 (0.0)
≥ 70-< 90 (bpm)	3 (37.5)	20 (20.2)	0 (0.0)	1 (100)	53 (51.5)	3 (100)
≥ 90-< 120 (bpm)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (6.8)	0 (0.0)
≥ 120-< 130 (bpm)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
≥ 130 (bpm)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	8 (100)	99 (100)	0 (0.0)	1 (100)	103 (100)	3 (100)

Note: Pulse values are from the first 6 hours of monitoring.
Total: number of patients with pulse data for the corresponding age group.

Source: Table 12-23 Clinical Study Report

Analysis of clinically notable changes in vital signs noted a clear difference in the magnitude and direction of post dose changes sitting pulse rates and both systolic and diastolic blood pressure readings between the fingolimod and interferon β-1a treatment groups as shown below.

Table 67: Sponsor Table: Clinically Notable Vital Sign Abnormalities during First Dose Administration Monitoring, Safety Set, Study D2311

Vital Signs (units)	Criterion	FTY720 N = 107 n (%)	IFN β-1a N = 107 n (%)
Sitting pulse (bpm)	Low:< 50 (70,50)	6 (5.6)	2 (1.9)
	High: > 120 (130, 120)	0 (0.0)	3 (2.8)
Sitting pulse (bpm) change from predose	≥ 15 decrease	40 (37.4)	15 (14.0)
	≥ 15 increase	12 (11.2)	54 (50.5)
Sitting systolic BP (mmHg)	Low:≤ 90 (70,90)	4 (3.7)	10 (9.3)
	High: ≥ 160 (125, 180)	0 (0.0)	1 (0.9)
Sitting systolic BP (mmHg) change from predose	≥ 20 decrease	6 (5.6)	7 (6.5)
	≥ 20 increase	2 (1.9)	15 (14.0)
Sitting diastolic BP (mmHg)	Low:≤ 50	14 (13.1)	15 (14.0)
	High: ≥ 95 (85, 105)	0 (0.0)	2 (1.9)
Sitting diastolic BP (mmHg) change from Predose	≥ 15 decrease	24 (22.4)	14 (13.1)
	≥ 15 increase	9 (8.4)	12 (11.2)

- A patient can be counted in every category.
- When the notable criteria is different between the age groups of <12 years, >=12 and <18 years, and >=18 years, the notable criteria will be expressed as criteria for the age group of >=12 and <18 years (criteria for the age group of <12 years, and criteria for the age group of >=18 years.

Source: Table 12-24 Clinical Study Report

Restart of study drug, and first dose of an increased dose of study drug, revealed that these changes were well tolerated by patients, with fewer but similar findings of heart rate and blood pressure changes as those found during first dose monitoring as indicated below.

Table 68: Sponsor Tables: Incidence of Notable Abnormalities of Vital Signs After Actual Dose Increase or After Restart of Fingolimod, Study D2311

		Dose administration monitoring for	
		dose initiation at randomization visit	dose increase*
Vital Signs	Notable Criteria	N=5, m=3 n (%)	N=5, m=3 n (%)
Systolic BP (mmHg)	Low: <=90 (70, 90)	0 (0.0)	0 (0.0)
	High: >=160 (125, 180)	0 (0.0)	0 (0.0)
Systolic BP change from predose(mmHg)	>=20 increase	1 (33.3)	0 (0.0)
	>=20 decrease	0 (0.0)	0 (0.0)
Diastolic BP (mmHg)	Low: <=50	1 (33.3)	0 (0.0)
	High: >=95 (85, 105)	0 (0.0)	0 (0.0)
Diastolic BP change from predose(mmHg)	>=15 increase	1 (33.3)	0 (0.0)
	>=15 decrease	0 (0.0)	0 (0.0)
Pulse (bpm)	Low: <50 (70, 50)	1 (33.3)	0 (0.0)
	High: >120 (130, 120)	0 (0.0)	0 (0.0)
Pulse (bpm)change from predose	>=15 increase	2 (66.7)	0 (0.0)
	>=15 decrease	2 (66.7)	0 (0.0)
Temperature	>38.3 °C or a change of 1.1 °C or more from baseline	0 (0.0)	0 (0.0)

Vital Signs	Notable Criteria	FTY720 N=107, N'=7, m=8 n (%)	IFNß-1a N=107, N'=1, m=1 n (%)
Sitting systolic BP (mmHg)	Low: <=90 (70, 90)	1 (12.5)	0 (0.0)
	High: >=160 (125, 180)	0 (0.0)	0 (0.0)
Sitting systolic BP change from predose(mmHg)	>=20 increase	0 (0.0)	0 (0.0)
	>=20 decrease	0 (0.0)	0 (0.0)
Sitting diastolic BP (mmHg)	Low: <=50	3 (37.5)	0 (0.0)
	High: >=95 (85, 105)	0 (0.0)	0 (0.0)
Sitting diastolic BP change from predose(mmHg)	>=15 increase	1 (12.5)	1 (100)
	>=15 decrease	2 (25.0)	0 (0.0)
Sitting pulse (bpm)	Low: <50 (70, 50)	0 (0.0)	0 (0.0)
	High: >120 (130, 120)	0 (0.0)	0 (0.0)
Sitting pulse (bpm) change from predose	>=15 increase	1 (12.5)	0 (0.0)
	>=15 decrease	2 (25.0)	0 (0.0)
Temperature	>38.3 °C or a change of 1.1 °C or more from baseline	0 (0.0)	0 (0.0)

- N'=No. of subjects with dose restart, m = the total number of monitored study drug restarts (not subjects); %=n/m.
- No second dose assessment is available for analysis.
- A subject can be counted in every category.
- Only post-dose data is counted. Vital signs data collected from the Bradycardia CRF is also counted.
- When the notable criteria is different between the age groups of <12 years, >=12 and <18 years, and >=18 years, the notable criteria will be expressed as criteria for the age group of >12 and <18 years (criteria for the age group of <12 years, and criteria for the age group of >=18 years).

Source: Tables 14.3-8.3b and 3c Clinical Study Report

Chronic administration of fingolimod 0.5 mg in adults is associated with increases in systolic (+2 mmHg) and in diastolic (+1 mmHg) blood pressure. Pediatric patients exhibited a higher increase in both readings over the 24 months of treatment, with an average increase of approximately +3 mmHg and +2 mmHg, systolic and diastolic, respectively. Pediatric patients

also had a net decrease of over 1 bpm over the course of treatment as noted in the table below.

	Vital signs		
Time-point **Treatment group**	**N**	**Mean**	**SD**
Sitting pulse (bpm)			
Change from baseline to Week 2			
FTY720 (N = 107)	105	−2.49	9.018
IFN β-1a (N = 107)	105	−0.30	10.477
Change from baseline to Month 1			
FTY720 (N = 107)	106	−0.77	9.414
IFN β-1a (N = 107)	105	−0.37	10.627
Change from baseline to Month 2			
FTY720 (N = 107)	105	0.84	10.062
IFN β-1a (N = 107)	105	−1.76	11.278
Change from baseline to Month 3			
FTY720 (N = 107)	105	−0.90	9.566
IFN β-1a (N = 107)	106	−1.49	12.326
Change from baseline to Month 6			
FTY720 (N = 107)	104	0.19	9.942
IFN β-1a (N = 107)	100	0.98	11.682
Change from baseline to Month 9			
FTY720 (N = 107)	103	0.26	11.165
IFN β-1a (N = 107)	95	−0.74	10.602
Change from baseline to Month 12			
FTY720 (N = 107)	102	−1.67	10.852
IFN β-1a (N = 107)	92	−0.70	12.202
Change from baseline to Month 15			
FTY720 (N = 107)	100	−0.76	10.115
IFN β-1a (N = 107)	83	1.39	10.222
Change from baseline to Month 18			
FTY720 (N = 107)	84	−1.12	10.712
IFN β-1a (N = 107)	65	−0.49	9.302
Change from baseline to Month 21			
FTY720 (N = 107)	65	−1.20	10.922
IFN β-1a (N = 107)	46	0.23	12.653
Change from baseline to Month 24			
FTY720 (N = 107)	50	−2.78	10.426
IFN β-1a (N = 107)	31	3.45	9.821
Last assessment on study drug			
FTY720 (N = 107)	106	−1.20	10.928
IFN β-1a (N = 107)	107	1.61	11.162
Sitting systolic blood pressure (mmHg)			

Change from baseline to Week 2			
FTY720 (N = 107)	105	1.30	8.760
IFN β-1a (N = 107)	105	−0.01	9.168
Change from baseline to Month 1			
FTY720 (N = 107)	106	2.57	8.092
IFN β-1a (N = 107)	105	0.90	9.333
Change from baseline to Month 2			
FTY720 (N = 107)	105	2.98	9.488
IFN β-1a (N = 107)	105	−1.59	8.907
Change from baseline to Month 3			
FTY720 (N = 107)	105	2.49	8.684
IFN β-1a (N = 107)	106	−0.37	8.833
Change from baseline to Month 6			
FTY720 (N = 107)	104	2.11	8.833
IFN β-1a (N = 107)	100	1.24	9.291
Change from baseline to Month 9			
FTY720 (N = 107)	103	2.79	9.149
IFN β-1a (N = 107)	95	1.68	9.431
Change from baseline to Month 12			
FTY720 (N = 107)	101	3.13	9.479
IFN β-1a (N = 107)	92	1.64	9.630
Change from baseline to Month 15			
FTY720 (N = 107)	100	4.08	8.977
IFN β-1a (N = 107)	83	2.22	9.216
Change from baseline to Month 18			
FTY720 (N = 107)	84	3.13	9.626
IFN β-1a (N = 107)	65	0.90	8.658
Change from baseline to Month 21			
FTY720 (N = 107)	65	4.95	9.683
IFN β-1a (N = 107)	46	1.59	8.060
Change from baseline to Month 24			
FTY720 (N = 107)	50	2.86	9.651
IFN β-1a (N = 107)	31	0.65	8.143
Last assessment on study drug			
FTY720 (N = 107)	106	3.33	9.127
IFN β-1a (N = 107)	107	1.79	9.820
Sitting diastolic blood pressure (mmHg)			
Change from baseline to Week 2			
FTY720 (N = 107)	105	1.69	8.898
IFN β-1a (N = 107)	105	1.18	7.782

Change from baseline to Month 1			
FTY720 (N = 107)	106	1.20	8.383
IFN β-1a (N = 107)	105	1.12	8.320
Change from baseline to Month 2			
FTY720 (N = 107)	105	2.10	8.876
IFN β-1a (N = 107)	105	0.24	7.957
Change from baseline to Month 3			
FTY720 (N = 107)	105	2.04	9.180
IFN β-1a (N = 107)	106	1.02	7.401
Change from baseline to Month 6			
FTY720 (N = 107)	104	1.51	8.832
IFN β-1a (N = 107)	100	1.25	8.179
Change from baseline to Month 9			
FTY720 (N = 107)	103	2.42	8.748
IFN β-1a (N = 107)	95	1.58	8.616
Change from baseline to Month 12			
FTY720 (N = 107)	101	2.34	8.715
IFN β-1a (N = 107)	92	1.67	8.054
Change from baseline to Month 15			
FTY720 (N = 107)	100	2.08	8.433
IFN β-1a (N = 107)	83	1.90	8.598
Change from baseline to Month 18			
FTY720 (N = 107)	84	1.95	8.852
IFN β-1a (N = 107)	65	0.83	8.202
Change from baseline to Month 21			
FTY720 (N = 107)	65	2.95	9.507
IFN β-1a (N = 107)	46	2.35	7.040
Change from baseline to Month 24			
FTY720 (N = 107)	50	2.30	10.477
IFN β-1a (N = 107)	31	2.29	7.699
Last assessment on study drug			
FTY720 (N = 107)	106	2.10	9.702
IFN β-1a (N = 107)	107	1.48	8.386

Source: Table 12-25 Clinical Study Report

Follow-up

In the small pool of follow-up data provided, notable increases in pulse rate appear in patients at > 45 days after discontinuation of fingolimod.

Table 69: Sponsor Table: Incidence of Clinically Notable Abnormalities of Vital Signs for Subjects with Follow-up data, Study D2311

Vital Signs		Notable Criteria	FTY720 N=47 n (%)	IFNß-1a N=58 n (%)
Sitting systolic BP (mmHg)	Days 1-45 after drug discontinuation	m	19	30
		Low: <=90 (70, 90)	0 (0.0)	0 (0.0)
		High: >=160 (125, 180)	0 (0.0)	0 (0.0)
		>=20 increase from baseline	1 (5.3)	1 (3.3)
		>=20 decrease from baseline	0 (0.0)	0 (0.0)
	>45 days after drug discontinuation	m	7	21
		Low: <=90 (70, 90)	0 (0.0)	0 (0.0)
		High: >=160 (125, 180)	0 (0.0)	0 (0.0)
		>=20 increase from baseline	0 (0.0)	3 (14.3)
		>=20 decrease from baseline	0 (0.0)	0 (0.0)
Sitting diastolic BP (mmHg)	Days 1-45 after drug discontinuation	m	19	30
		Low: <=50	0 (0.0)	0 (0.0)
		High: >=95 (85, 105)	0 (0.0)	0 (0.0)
		>=15 increase from baseline	2 (10.5)	2 (6.7)
		>=15 decrease from baseline	0 (0.0)	0 (0.0)
	>45 days after drug discontinuation	m	7	21
		Low: <=50	0 (0.0)	0 (0.0)
		High: >=95 (85, 105)	0 (0.0)	0 (0.0)
		>=15 increase from baseline	0 (0.0)	5 (23.8)
		>=15 decrease from baseline	0 (0.0)	0 (0.0)
Sitting pulse (bpm)	Days 1-45 after drug discontinuation	m	19	30
		Low: <50 (70, 50)	1 (5.3)	0 (0.0)
		High: >120 (130, 120)	0 (0.0)	0 (0.0)
		>=15 increase from baseline	0 (0.0)	2 (6.7)
		>=15 decrease from baseline	2 (10.5)	3 (10.0)
	>45 days after drug discontinuation	m	7	21
		Low: <50 (70, 50)	1 (14.3)	0 (0.0)
		High: >120 (130, 120)	0 (0.0)	0 (0.0)
		>=15 increase from baseline	2 (28.6)	5 (23.8)
		>=15 decrease from baseline	1 (14.3)	3 (14.3)

Reviewer Comment: The acute first administration decrease in heart rate and blood pressure changes with fingolimod 0.5 mg are similar in magnitude and duration of onset to those noted in adult patients. The blood pressure changes with initial dose do not appear to be as pronounced in children as adults. Though there were only a few patients who had an increase from 0.25 mg to 0.5 mg fingolimod, the findings suggest there is no accommodation to fingolimod from being treated with a lower dose of fingolimod and justify the need for first dose monitoring in children with any change in dose. The results in younger patients implies a larger decrease from 0.25 mg than patients did at 0.5 mg but the resting heart rate of patients < 12 years old will be higher than those older patients by 6-10 bpm so the decreases in heart rate noted between the age groups are proportional when this higher resting heart rate is considered. The proposed labeling reflects this suggestion. The chronic dose effects of fingolimod are slightly more evident

than in adults, but an increase of 3 mmHg in systolic blood pressure, 2 mmHg in diastolic blood pressure, and a decrease in heart rate by approximately 1 bpm do not appear clinically significant. There are increases in pediatric patient heart rates noted > 5 half-lives after fingolimod discontinuation suggesting return to baseline cardiac status with drug withdrawal.

8.4.8. Electrocardiograms (ECGs)

Due to previous adult experience with fingolimod a risk of acute first dose potential cardiac conduction block abnormalities, the protocol mandated first dose pre- and post-dose ECGs and other monitoring during the trial. To avoid unblinding investigators, all enrolled patients had the same first dose visit procedures with a First-dose Administrator and an independent monitoring team. The treating physician did not observe the first administration of study treatments and did not have access to any vital signs or initial findings unless such disclosure was medically warranted. The first dose procedure was required for any dose change in fingolimod/placebo, for study drug re-initiation per protocol criteria, and at Visit 6 for patients ≤40 kg (regardless of whether a dose change was implemented or not). The monitoring duration was six hours minimum post dose with provisions for an extension in monitoring or hospitalization pre-defined per protocol guidelines. Finally, a remote independent monitor performed ECG reviews.

Data recorded as part of the first dose administration monitoring included hourly vital signs, ECG, and summaries of bradycardia events, symptoms reported by patients and observed by site personnel, and medications given to rectify any abnormalities. Bradycardia was defined as < 55 bpm for patients 12 years and older and < 60 bpm for children younger than 12 years old.

Overall, over 90% of pediatric patients tolerated the first dose of fingolimod at any dose with a discharge at six hours; in comparison, 82% of adult patients in a trial of 0.5 mg were discharged at six hours. In Study D2311, more patients in the fingolimod treatment group (10 patients) required extended monitoring as compared to interferon β-1a treatment group patients (3 patients). The outcomes from the first dose monitoring are summarized in the table below.

Table 70: Sponsor Table: First Dose Administration Experience, Safety Set, Study D2311

	FTY720 N=107 n (%)	IFN β-1a N=107 n (%)
Discharged at 6 hours	98 (91.6)	105 (98.1)
Required extended monitoring after 6 hours	10 (9.3)	3 (2.8)
Hospitalized	3 (2.8)	2 (1.9)
Required Day 2 monitoring in the local clinic	0 (0.0)	0 (0.0)
Study drug permanently discontinued	0 (0.0)	0 (0.0)

Source: Table 2-32 Clinical Study Report

Table 71: Sponsor Table: ECG Abnormalities at 6 Hours Post First Dose Fingolimod, Safety Set, Study D2311

ECG Evaluation type ECG Finding	FTY720 N = 107 n (%)	IFN β-1a N = 107 n (%)
Number of patients with ECGs	105	107
Number of patients with any ECG Abnormality	17 (16.2)	20 (18.7)
Conduction	15 (14.3)	18 (16.8)
Intraventricular conduction delay (IVCD)	9 (8.6)	7 (6.5)
Prolonged QTc	5 (4.8)	8 (7.5)
First degree AV block*	3 (2.9)	3 (2.8)
Right bundle branch block (RBBB)	0 (0.0)	1 (0.9)
Incomplete right bundle branch block (IRBBB)	0 (0.0)	6 (5.6)
Rhythm	5 (4.8)	6 (5.6)
Sinus bradycardia	5 (4.8)	0 (0.0)
Sinus tachycardia	0 (0.0)	6 (5.6)

*Patient (D2311-0201-00002) in the fingolimod treatment group experienced a second degree AV block Mobitz I after dose increase on Month 2 visit (Day 64), which had subsequently changed to a first degree AV block during the ninth hourly monitoring without any pharmacological treatment.
Percentages for ECGs relate to the total number of patients with ECGs at given visit.

Source: Table 12-27 Clinical Study Report

All but one patient who required a re-dose after temporarily discontinuing study drug or who started a new higher dose of fingolimod were discharged at 6 hours (a single patient with a drug restart visit required extended monitoring before discharge.) There were no hospitalizations in the restart or new dose escalation groups.

> *Reviewer Comment: The overall incidence of post-dose ECG abnormalities was higher in the interferon β-1a treatment group. This finding was unexpected based on prior first dose ECG changes observed with fingolimod administration in adults that demonstrated more post-dose ECG abnormalities in patients administered fingolimod than patients who received interferon β-1a. The adult labeling for interferon β-1a does not note any ECG abnormalities as known risks inviting speculation that these findings potentially unmask a cardiac safety issue in the initial pediatric exposure to interferon β-1a. However, this pediatric study does confirm the presence of the most frequently observed findings in fingolimod patients, cardiac conduction interruptions and rhythm slowing. These disturbances were the most common changes seen in adult patients who received first dose 0.5 mg fingolimod. One pediatric patient* (b) (6) *who underwent dose increase from 0.25 to 0.5 mg based on PK findings had a second degree Mobitz I block that converted after 9 hours of observation to a first degree AV block. Findings in the table above are consistent with the SAE reporting (see Section 8.4.4). The current adult labeling adequately describes the pediatric cardiovascular conduction risks.*

Changes from baseline QTc interval after first dose in all treated patients are presented in the following table:

Table 72: Sponsor Table: Frequency (%) Distribution of QTc Interval at Six Hours during First Dose Monitoring, Safety Set, Study D2311

Correction		FTY720 (N = 107) n (%)	IFN β-1a (N = 107) n (%)
Bazett	Maximum increase from baseline	N' = 105	N' = 107
	< 30 msec	100 (95.2)	96 (89.7)
	30-60 msec	5 (4.8)	11 (10.3)
	> 60 msec	0 (0.0)	0 (0.0)
	Number of patients with QTc values	N' = 105	N' = 107
	> 450 msec (Male) or 460 msec (Female)	3 (2.9)	2 (1.9)
	> 500 msec	0 (0.0)	0 (0.0)
Fridericia	Maximum increase from baseline	N' = 105	N' = 107
	< 30 msec	100 (95.2)	106 (99.1)
	30-60 msec	5 (4.8)	1 (0.9)
	> 60 msec	0 (0.0)	0 (0.0)
	Number of patients with QTc values	N' = 105	N' = 107
	> 450 msec (Male) or 460 msec (Female)	0 (0.0)	0 (0.0)
	> 500 msec	0 (0.0)	0 (0.0)

N': number of patients with evaluable records; % = n/N'
QTc intervals are from ECG evaluations during the first dose monitoring.

Source: Table 12-28 Clinical Study Report

As noted in Section 8.4.7., after initial dose, there was a decrease in patients' heart rates by over 7 beats per minute, but over 95% of evaluated pediatric patients had a QTc change less than 30 msec. Analysis of QTc changes using Bazett's correction revealed 3 patients with prolongations > 450 msec but this incidence was not noted using Fridericia's correction.

> *Reviewer Comment: Adult patients in the 0.5 mg treatment group had an average prolongation of 6-7 msec so the pediatric prolongation results appear similar. The patients with prolongations > 450 msec by Bazett's correction did not have associated AEs.*

Chronic Effects

Chronic dosing with fingolimod led to attenuation of the observed decrease in heart rate, and the same attenuation was noted in QTc interval prolongations. After baseline and first dose, routine ECGs were performed at the Month 1, 12, 24, and finale study visits. Most patients in the study, regardless of treatment, had normal ECGs at each visit as shown in the table below.

Table 73: Sponsor Table: Incidence Rates of Abnormal ECG Findings, Safety Set, Study D2311

ECG Evaluation type ECG Finding	FTY720 (N = 107) n (%)	IFN β-1a (N = 107) n (%)
Baseline		
Number of patients with ECGs	107	107
Any finding	15 (14.0)	22 (20.6)
Conduction	15 (14.0)	22 (20.6)
IVCD	10 (9.3)	8 (7.5)
Prolonged QTc	4 (3.7)	5 (4.7)
First degree AV block	1 (0.9)	4 (3.7)
IRBBB	1 (0.9)	6 (5.6)
RBBB	0 (0.0)	1 (0.9)
Rhythm	0 (0.0)	2 (1.9)
Sinus bradycardia	0 (0.0)	1 (0.9)
Sinus tachycardia	0 (0.0)	1 (0.9)
Month 1		
Number of patients with ECGs	104	105
Any finding	21 (20.2)	23 (21.9)
Conduction	20 (19.2)	23 (21.9)

IVCD	11 (10.6)	13 (12.4)
Prolonged QTc	7 (6.7)	6 (5.7)
First degree AV block	1 (1.0)	5 (4.8)
IRBBB	1 (1.0)	1 (1.0)
RBBB	0 (0.0)	2 (1.9)
Rhythm	4 (3.8)	6 (5.7)
Sinus bradycardia	4 (3.8)	6 (5.7)
ST segment	1 (1.0)	0 (0.0)
Elevated ST segment	1 (1.0)	0 (0.0)
Month 12		
Number of patients with ECGs	99	93
Any finding	10 (10.1)	16 (17.2)
Conduction	10 (10.1)	13 (14.0)
IVCD	7 (7.1)	4 (4.3)
Prolonged QTc	4 (4.0)	3 (3.2)
First degree AV block	1 (1.0)	2 (2.2)
IRBBB	0 (0.0)	3 (3.2)
RBBB	0 (0.0)	2 (2.2)
Rhythm	1 (1.0)	8 (8.6)
Sinus bradycardia	0 (0.0)	8 (8.6)
Sinus tachycardia	1 (1.0)	0 (0.0)
Ectopic Supraventricular Rhythm	0 (0.0)	1 (1.1)
Month 24		
Number of patients with ECGs	72	53
Any finding	2 (2.8)	7 (13.2)
Conduction	2 (2.8)	6 (11.3)
IVCD	2 (2.8)	3 (5.7)
First degree AV block	0 (0.0)	3 (5.7)
RBBB	0 (0.0)	1 (1.9)
Rhythm	1 (1.4)	2 (3.8)
Sinus bradycardia	1 (1.4)	2 (3.8)
Last assessment on study drug		
Number of patients with ECGs	107	105
Any Finding	7 (6.5)	18 (17.1)
Conduction	7 (6.5)	15 (14.3)
IVCD	5 (4.7)	6 (5.7)
First degree AV block	2 (1.9)	3 (2.9)
RBBB	0 (0.0)	2 (1.9)
IRBBB	0 (0.0)	2 (1.9)
Prolonged QTc	0 (0.0)	4 (3.8)
Rhythm	1 (0.9)	5 (4.8)
Sinus bradycardia	1 (0.9)	5 (4.8)

- A patient with multiple occurrences of a finding is counted only once in the corresponding category.
- A patient with multiple findings within a finding type is counted only once in the total row of this finding type.
- The ECG monitoring for study drug starts, restarts, and dose increase are not included.
- Percentages for ECGs relate to the total number of patients with ECGs at given visit.

Source: Table 12-29 Clinical Study Report

The changes in QTc interval observed in pediatric patients decreased from a mean prolongation of 7.8 msec to 1.1 msec over the 24-month duration of the study.

		QTc interval (Fridericia's correction)		
Treatment		**n**	**Mean (SD)**	**Median**
Day 1 6h post-dose				
FTY720	(N = 107)	100	7.8 (13.73)	8.0
IFN β-1a	(N = 107)	106	−5.5 (15.47)	−6.0
Month 1				
FTY720	(N = 107)	104	3.6 (14.48)	2.5
IFN β-1a	(N = 107)	105	−0.6 (16.67)	−2.0
Month 12				
FTY720	(N = 107)	97	3.1 (15.12)	3.5
IFN β-1a	(N = 107)	93	−6.7 (27.16)	−6.5
Month 24				
FTY720	(N = 107)	72	1.3 (15.97)	1.0
IFN β-1a	(N = 107)	53	−5.8 (18.71)	−8.0
Last assessment on study drug *				
FTY720	(N = 107)	107	1.1 (14.65)	2.0
IFN β-1a	(N = 107)	105	−3.5 (19.04)	−7.0

* The last value taken at or before last day of study drug is summarized in row 'Last assessment on study drug'.

Source: Table 12-30 Clinical Study Report

Table 74: Sponsor Table: Frequency (%) of Distribution of QTc Interval during Chronic Dosing, Safety Set, Study D2311

Correction		FTY720 (N = 107) n (%)	IFN β-1a (N = 107) n (%)
Bazett	Maximum increase from baseline	N' = 105	N' = 107
	< 30 msec	92 (87.6)	95 (88.8)
	30-60 msec	12 (11.4)	11 (10.3)
	> 60 msec	1 (1.0)	1 (0.9)
	Number of patients with QTc values	N' = 105	N' = 107
	> 450 msec (Male) or 460 msec (Female)	3 (2.9)	2 (1.9)
	> 500 msec	0 (0.0)	0 (0.0)
Fridericia	Maximum increase from baseline	N' = 105	N' = 107
	< 30 msec	91 (86.7)	100 (93.5)
	30-60 msec	14 (13.3)	6 (5.6)
	> 60 msec	0 (0.0)	1 (0.9)
	Number of patients with QTc values	N' = 105	N' = 107
	> 450 msec (Male) or 460 msec (Female)	0 (0.0)	1 (0.9)
	> 500 msec	0 (0.0)	0 (0.0)

- N': number of patients with evaluable records; % = n/N'
QTc intervals are from post baseline ECG evaluations excluding those from the first dose monitoring.

Source: Table 12-31 Clinical Study Report

Reviewer Comment: As noted in Section 8.4.7, the heart rate decrease attenuated over the course of treatment. The proportion of patients with a prolongation between 30-60 msec as measured using Bazett's correction however increased during the study duration for both treatment groups, with the change for fingolimod patients shifting from 4.8% to 11.4% in this interval. In the adult trial, the proportion of patients from the fingolimod 0.5 mg treatment group who were in the 30-60 msec group increased from 5.3 to 7.5% over the same 24 month observation interval. The Fridericia's correction QTc values seem to confirm a significant shift in the proportion of patients from < 30 msec to 30-60 msec prolongation. The significance of this shift is unclear as there was not an accompanying increase in AEs related to cardiovascular conduction late in the trial and mean heart rates were increased, not decreased, relative to the Month 1 mean value at 24 months. The effects of fingolimod on conduction are believed to be a direct result of fingolimod acting at cardiac S1P1 receptors. Cardiac S1P1 expression is dynamic during early heart development; a paucity of research exists in S1P1 after embryogenesis. The findings regarding QTc suggest the pediatric cardiac response to fingolimod involves a larger fraction of the exposed population than was observed in adults. A long-term concern with fingolimod administration in the pediatric population would be the unknown impact of chronic antagonism on S1P1 receptors from childhood or

adolescence through adulthood. Further study of cardiac parameters in pediatric patients taking fingolimod long-term should be considered but may require significant observation periods before definitive conclusions can be made.

8.4.9. QT

A thorough QT trial was not required for Study D2311. A thorough QT study had been submitted with the original approval submission of NDA 22527. The thorough QT study's findings were considered negative for QT interval changes by Novartis, the Agency's reviewer disagreed with Novartis's conclusions and recommended that all patients be monitored for at least 6 hours after their first dose of fingolimod with monitoring to include a pre- and post-dose ECG with periodic ECG follow-up.

8.4.10. Immunogenicity

Fingolimod is a small molecule with low antigenicity potential. In the original approval submission for NDA 22527, Novartis included studies conducted to assess fingolimod's impact on neoantigen immunogenicity and recall immunogenicity. The findings of this neoantigen study revealed that fingolimod would impair vaccination response in a dose-dependent fashion. The labeling advises of this impairment and recommends against the use of live attenuated vaccinations during and for up to two months after discontinuing fingolimod. The current adult label advises that patients without prior vaccination against varicella or a documented medical history of chickenpox infection be vaccinated for varicella before beginning fingolimod. We are suggesting the additional label caution that all patients be up-to-date on recommended vaccinations before initiating fingolimod therapy.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Decreased FEV1 and DLCO

In adult studies, patients in the fingolimod treatment groups experienced ≥15% reductions in FEV1 and DLCO without a change in FVC. In Study D2311, pediatric patients had pulmonary function testing including FVC, FEV1, and DLCO at Screening, Months 1, 3, 6, 12, 18, and 24. The results are presented below.

Table 75: Sponsor Table: Frequency Distribution of Decreased Pulmonary Function Tests, Safety Set, Study D2311

		FTY720 N=107 n (%)	IFN β-1a N=107 n (%)
<80% of baseline PFT percent predicted values at any post-baseline visit	FEV1	9 (8.7)	5 (4.8)
	FVC	6 (5.8)	5 (4.8)
	D_LCO	38 (38.4)	33 (32.4)
<80% of baseline PFT percent predicted values at 2 consecutive post-baseline visits	FEV1	5 (4.8)	1 (1.0)
	FVC	1 (1.0)	2 (1.9)
	D_LCO	14 (14.1)	14 (13.7)
<60% of baseline PFT percent predicted values at any post-baseline visit	FEV1	0 (0.0)	1 (1.0)
	FVC	0 (0.0)	1 (1.0)
	D_LCO	1 (1.0)	6 (5.9)
<60% of baseline PFT percent predicted values at 2 consecutive post-baseline visits	FEV1	0 (0.0)	0 (0.0)
	FVC	0 (0.0)	0 (0.0)
	D_LCO	0 (0.0)	2 (2.0)

Source: Table 12-33 Clinical Study Report

Table 76: Sponsor Table: Change from Baseline in Percent of Predicted DLCO by Selected Visit, Safety Set, Study 2311

	Statistics	FTY720 N=107	IFN β-1a N=107
Month 12	n	94	85
Baseline	Mean (SD)	95.23 (19.626)	92.45 (17.953)
Post	Mean (SD)	87.88 (19.433)	84.63 (17.524)
Change from baseline	Mean (SD)	-7.35 (14.602)	-7.82 (15.673)
Month 24	n	46	30
Baseline	Mean (SD)	96.84 (21.772)	94.64 (18.612)
Post	Mean (SD)	84.68 (19.188)	82.14 (16.624)
Change from baseline	Mean (SD)	-12.16 (17.570)	-12.50 (15.969)
Last assessment on study drug*	n	100	102
Baseline	Mean (SD)	94.93 (19.342)	92.00 (17.716)
Post	Mean (SD)	84.98 (18.786)	84.01 (18.381)
Change from baseline	Mean (SD)	-9.94 (16.013)	-7.98 (14.864)

*The last value taken at or before last day of study drug is summarized in row "last assessment on study drug.

The percent decrease in FEV1 at Month 24 relative to baseline for patients in the fingolimod treatment group was 1.63%. No patients in the fingolimod treatment group with an assessment at 24 months (53 out of 107) had a FEV1 less than 80% of predicted.

The percent decrease for DLCO at Month 24 was 12.16% relative to baseline. At 24 months, 23 of 49 (46.9%) patients assessed had a DLCO below 80% of predicted in the fingolimod treatment group as compared to 14 of 32 (43.8%).

Reviewer Comment: The fingolimod treatment-related 15% or more reductions in FEV1 noted in adults were not seen in pediatric patients in this study, because the observed net mean reduction in FEV1 was less than 2%. Respiratory complaints were uncommon in this pediatric study. Dyspnea was reported by less than 5% of patients in the fingolimod treatment condition, and cough was reported by approximately 10% of patients in both treatment groups (see Section 8.4.4). With respect to DLCO, both groups had a longitudinal reduction in DLCO. There was a high degree of variability in pulmonary function testing values; many potentially significant findings were noted as isolated events and not replicated at subsequent visits. Thus, there appears to be an effect on DLCO capacity in pediatric patients treated with fingolimod, but unlike adults, the effect is small and not predictably persistent throughout treatment.

8.5.2. Macular Edema

Macular edema occurs in association with fingolimod treatment and labeling has explicit warnings regarding the need to monitor for eye findings related to macular edema in all patients. Ophthalmological examinations were mandated by protocol at Months 3, 6, and 24. As indicated in Section 8.4.3, a single case of macular edema was identified in Study D2311 leading to permanent drug discontinuation.

8.5.3. Suicidal Ideation and Suicidal Behavior

The Columbia Suicide Severity Rating Scale (C-SSRS) was administered to patients at most scheduled and unscheduled visits to elicit patient responses regarding possible suicidal ideation and suicidal behaviors. The results of this structured interview survey are presented below.

Table 77: Sponsor Table: Columbia Suicide Severity Rating Scale Overall Assessment, Safety Set, Study D2311

Category	FTY720 N=107 n (%)	IFN β-1a N=107 n (%)
C-CASA code/category		
1. Complete suicide	0 (0.0)	0 (0.0)
2. Suicide attempt	0 (0.0)	0 (0.0)
3. Preparatory actions towards imminent suicidal behavior	1 (0.9)	3 (2.8)
4. Suicidal ideation	9 (8.4)	9 (8.4)
7. Self-injurious behavior without suicidal intent	3 (2.8)	1 (0.9)
Suicidal behavior	1 (0.9)	3 (2.8)
Suicidality	10 (9.3)	10 (9.3)

Suicidal behavior is defined as response 'Yes' for actual, interrupted, or aborted suicidal attempts or any preparatory actions toward imminent suicidal behavior during the study treatment period.
Suicidality is defined as response "yes" for any suicidal behavior and/or response "yes" for any ideation at least once during the study treatment period.
If data from two sources collected on the same day have different responses all data was considered for analysis. In case of discrepant data values (yes/no) for any answer, the 'yes'-answer-result has been accounted for in the table.

Source: Table 12-32 Clinical Study Report

In patients who discontinued study treatment, there was 1 (3.4%) patient in the fingolimod treatment group and 2 (4.7%) patients in the interferon β-1a treatment group who reported a "yes" response any suicidal behavior or ideation.

Reviewer Comment: Though there were more patients reporting AEs related to depression and anxiety in the fingolimod treatment group, the number of patients reporting suicidal ideation and behaviors in either treatment condition were essentially equal. There were no

reported patient deaths for any reason, including suicide, during the Core Phase or ongoing OLE study.

8.5.4. Dermatology Assessment

Because of the known risk of basal cell carcinoma and other skin malignancies in association with fingolimod treatment, dermatological examinations were mandated by the pediatric study protocol at 24 months.

Most patients in either treatment arm had normal dermatological examinations (85.0% for fingolimod treatment group, 81.9% for the interferon β-1a treatment group.) The end of study dermatological examination identified 16 patients in the fingolimod treatment group with concerning new skin lesions. None of the lesions in the fingolimod treatment group was considered pre-cancerous or cancerous upon further investigation.

8.6. Safety Analyses by Demographic Subgroups

Novartis provided limited analyses of several demographic subgroups. Study D2311 featured a small patient pool and little diversity with respect to most demographic variables. In most instances, there are too few patients or events to permit a robust assessment of risk by demographic variable.

Table 78: Frequency of AE and SAE by Subgroup, Safety Set, Study D2311

	Fingolimod N=107 n (%)	**Interferon β-1a** N=107 n (%)
Female	**70 (65.4%)**	**64 (59.8%)**
Any AE	58 (82.9%)	59 (92.2%)
Any SAE	10 (14.3%)	7 (10.9%)
SAE leading to drug discontinuation	4 (5.7%)	4 (6.3%)
SAE leading to drug interruption	5 (7.1%)	3 (4.7%)
Male	**37 (34.6%)**	**44 (41.1%)**
Any AE	37 (100%)	43 (97.7%)
Any SAE	9 (24.3%)	3 (6.8%)
SAE leading to drug discontinuation	2 (5.4%)	1 (2.3%)
SAE leading to drug interruption	7 (18.9%)	0
Pre-Pubertal Patients (Tanner Stage < 2)	**7 (6.5%)**	**3 (2.8%)**
Any AE	7 (100%)	3 (100%)

Any SAE	5 (71.4%)	1 (33.3%)
SAE leading to drug discontinuation	1 (14.3%)	0
SAE leading to drug interruption	1 (14.3%)	0
Patients ≤ 12 years old	**13 (12.1%)**	**9 (8.4%)**
Any AE	11 (84.6%)	9 (100%)
Any SAE	8 (61.5%)	2 (22.2%)
SAE leading to drug discontinuation	1 (7.7%)	0
SAE leading to drug interruption	2 (15.4%)	0

Source: Clinical Study Report, Table 12-8

8.7. Specific Safety Studies/Clinical Trials

Not applicable

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

In the original submission for NDA 22527, an increased risk of lymphoma was observed in carcinogenicity studies in mice and has been observed in clinical trials and the postmarketing setting.

The original submission noted a potential increased risk of basal cell carcinoma. Postmarketing studies confirmed the initial observation. The current labeling states the specific risk of basal cell carcinoma in Section 5.10 and recommends surveillance.

8.8.2. Human Reproduction and Pregnancy

Fingolimod is a known teratogen class "C" medication with an identified association with fetal cardiac abnormalities. Fingolimod does not have known effects on fertility. Novartis maintains a pregnancy registry for fingolimod and the approved label and patient materials advise women of childbearing age to use effective contraception to avoid pregnancy while taking fingolimod and for 2 months after stopping fingolimod.

Pregnancy was an exclusion criteria and adequate birth control was required for entry into Study D2311. Females of childbearing potential were defined as all females physiologically capable of becoming pregnant. This included female children and adolescents who were post-menarche at trial enrollment or who achieved menarche during the study.

Serum pregnancy tests were performed by the central laboratory and home pregnancy tests were collected for all females of childbearing potential according to the visit schedule.

Female patients of childbearing potential were informed of the potential teratogenic risk with fingolimod and the need for highly effective contraception to prevent pregnancy while on study drug and for 2 months after stopping study drug if they became sexually active. The decision on the contraceptive method was reviewed at least every three months to evaluate the individual need and compatibility of the method chosen. Hence, female patients of childbearing potential who were sexually active underwent a urine pregnancy test (*e.g.*, via a home pregnancy test kit) monthly (in the months between clinic visits and serum pregnancy testing). In the event of a positive urine pregnancy test, the patient was required to contact the investigator immediately. Additional pregnancy tests were performed at the investigator's discretion during the study. Patients becoming pregnant had to discontinue study treatment.

A patient did report a pregnancy during the trial. For unclear reasons, this report was not incorporated into the clinical database as an AE leading to permanent drug discontinuation. The edited narrative is included below.

Patient (b) (6)] A 16-year-old Native American female (b) (6)) with multiple sclerosis was enrolled in Study FTY720D2311 (an up to two-year, double blind, randomized, multicenter, active-controlled study to evaluate the safety and efficacy of fingolimod administered orally once daily versus interferon β-1a once weekly in pediatric patients with multiple sclerosis). The patient was screened for the study on (b) (6) and received the first dose of study drug (fingolimod) on (b) (6) (Day 1). The patient had a height of 160 cm, a weight of 95.6 kg, and a Tanner staging of 4 at Visit 1. The patient was diagnosed with multiple sclerosis in March 2014. The patient experienced one relapse during the past 12 months and one relapse during the 12 to 24 months before study entry; and her last relapse prior to enrollment was in May 2015. The patient was treated with the following MS disease-modifying drug prior to enrollment: interferon β-1A. No additional immunomodulatory or immunosuppressive drugs for MS were administered. At screening, the patient's EDSS score was 5.5. The patient's relevant medical history included Cushing's syndrome since 2014 and elevated hepatic transaminases and hypertension since (b) (6) No other concomitant medications were taken prior to enrollment. During the study, the patient received enalapril for hypertension from (b) (6) to (b) (6) ursodeoxycholic acid for elevated hepatic transaminases from (b) (6) to (b) (6) and tizanidine for spasticity due to MS relapse from (b) (6) to (b) (6) On (b) (6) (Day 519), the patient's pregnancy was confirmed through positive pregnancy test. The patient discontinued from the study and received the last dose of study medication on (b) (6) (Day 519). On (b) (6) (3 days after the last dose of study medication), she consulted a physician and uterine curettage was solicited. On (b) (6) (20 days after the last dose of study medication), she underwent uterine dilation and curettage without complications and was advised to take rest for 15 days. The abortion was considered as therapeutic.

8.8.3. Pediatrics and Assessment of Effects on Growth

Physical development was assessed throughout the Core Phase of Study D2311. Overall, there were no significant differences at baseline or during the study in key physical development endpoints.

The majority of patients in the fingolimod treatment group had a normal body weight percentile (67.3%) and a normal BMI percentile (66.4%) at baseline. At last assessment in the study, the majority of fingolimod-treated patients maintained a normal body weight percentile (67.0%) and had a normal BMI percentile (67.9%).

In terms of pubertal development, most of the male and female patients in both the treatment groups were pubertal at baseline (Tanner stage ≥ 2), and the mean change in Tanner staging score was similar at each visit between the treatment groups for both male and female patients as indicated below.

Table 79: Sponsor Table: Tanner Staging Scale Change from Baseline, Safety Set, Study D2311

Gender	Visit window	Baseline Tanner staging score	FTY720 N=107 n	Mean(SD)	Median	(Min,Max)
Both	Last assessment on study drug*	1	7	1.7(1.11)	2.0	(0, 3)
		2	4	0.5(0.58)	0.5	(0, 1)
		3	3	0.7(0.58)	1.0	(0, 1)
		4	18	0.6(0.51)	1.0	(0, 1)
		5	10	0.0(0.00)	0.0	(0, 0)

Source: Clinical Study Report Table 14.3-11.2

Table 80: Sponsor Table: Number (%) of Subjects with Bone Age, Safety Set, Study D2311

Gender	Time point		FTY720 N=107	IFNß-1a N=107
Female	Baseline	n	69	64
		Bone age <16 years	16 (23%)	17 (27%)
	Month 6	n	29	24
		Bone age <16 years	10 (34%)	5 (21%)
	Month 12	n	18	15
		Bone age <16 years	3 (17%)	2 (13%)
	Month 18	n	11	6
		Bone age <16 years	1 (9%)	1 (17%)
	Month 24	n	6	3
		Bone age <16 years	2 (33%)	0 (0%)
	Last assessment on study drug*	n	34	25
		Bone age <16 years	5 (15%)	3 (12%)

Gender	Time point		FTY720 N=107	IFNß-1a N=107
Male	Baseline	n	37	43
		Bone age <16 years	15 (41%)	22 (51%)
	Month 6	n	21	29
		Bone age <16 years	9 (43%)	12 (41%)
	Month 12	n	16	20
		Bone age <16 years	7 (44%)	4 (20%)
	Month 18	n	8	7
		Bone age <16 years	4 (50%)	2 (29%)
	Month 24	n	3	0
		Bone age <16 years	3 (100%)	0 (0%)
	Last assessment on study drug*	n	21	32
		Bone age <16 years	9 (43%)	8 (25%)

Source: Table 14.3-11.3 Clinical Study Report

Reviewer Comment: There are no obvious differences between treatment groups to raise concern of a treatment effect on somatic growth or sexual maturity. Pre- and post-pubertal patients appeared similar in physical growth. There were no unexplained delays in Tanner stage

advancement or lasting discrepancies in bone growth estimation of age through the duration of the study. However, a two-year observation period may not be sufficient time in which to see a subtle effect on growth or sexual maturation. Study D2311 randomized only seven pre-pubertal patients to the fingolimod treatment group and thus had only a few observations of exposure effects in patients transitioning through pubertal onset. Because of the small pool of data, continued examination of patient growth parameters in the postmarket setting would be advised.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The assessment of abuse potential of fingolimod was reviewed by the Controlled Substance Staff. There does not appear to be a potential for abuse with fingolimod. There has been no evidence to date in the postmarket experience of fingolimod abuse.

Novartis states that there has been an extensive analysis of potential rebound effect after discontinuation of fingolimod without evidence to suggest such an effect exists. There are published reports suggesting a rebound phenomenon with discontinuation of fingolimod that is characterized by a more severe disease activity both in lesion number and size as measured by MRI and in acute disability that is seen within 3-6 months of discontinuation of fingolimod. The current label for fingolimod does not describe rebound.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Study D1401 is an ongoing postmarketing study in Japan. Novartis did a search of all SAEs for patients below age 18 years in the database of Study D1401 with a cut-off-date matching of February 28, 2017. The search identified nine SAEs, seven of which had been downgraded to "not serious" upon further review. The seven re-categorized events were four cases of "MS relapse" and three cases of "lymphocyte count decreased." The two SAEs retained as "serious" were "optic neuritis" and "MS relapse."

> *Reviewer Comment: The addition of these nine SAEs does not alter any prior conclusions. Lymphopenia is a known treatment effect associated with fingolimod. MS relapses and optic neuritis are MS disease-related events.*

8.9.2. Expectations on Safety in the Postmarket Setting

The expectation for fingolimod in the postmarket setting with respect to pediatric patients is that the previously identified and confirmed safety issues and risks will continue to be noted in pediatric patients.

8.9.3. Additional Safety Issues From Other Disciplines

At the time of completion of this review, I am not aware of any safety issues from other disciplines.

8.10. Integrated Assessment of Safety

1. Seizures

Seizure/convulsion risk with fingolimod is an area of uncertainty with significant implications. During the pediatric trial 5.6% (n=6) of patients in the fingolimod treatment group experienced a new onset of seizure/convulsion as compared to 0.9% (n=1) of patients in the interferon β-1a treatment group. Similar concerns of a potential increased risk of seizures had been raised based on findings from a trial of high dose fingolimod in renal transplant patients and in fingolimod trials in adult patients with RMS but were dismissed for plausible alternative explanations.

Evidence Supporting an Association

The evidence supporting an association between fingolimod and increased risk of new onset of seizures is the quantitative difference in risk observed during randomized controlled trials. Overall, in this trial, 5.6% of fingolimod-treated patients and 0.9% of comparator patients had a seizure/convulsion diagnosed during the treatment phase of the study. In controlled trials of adult patients with RMS, seizures were noted to occur twice as frequently in the fingolimod treatment group than in the IFN β-1a treatment group. An increased risk was noted in patients receiving high dose fingolimod in a trial for prevention of kidney allograft rejection. There is also the general observation that patients with RMS in clinical trials have many fewer seizures than would be predicted for unknown reasons. The patients in the fingolimod and comparator arms of this pediatric study were matched on many MS-related variables and therefore entered the treatment trial at theoretically equal risk of developing seizures/convulsions. There were neither clearly epileptogenic exposures nor any known anticonvulsant medication exposures unique to either group to explain the observed difference in the new onset seizure IR. Thus, a significant divergence in IR between the two groups is strong evidence of a treatment association even in the absence of a clear mechanism.

Evidence against an Association

Published natural history data suggest that patients with MS are at higher risk of seizures than the general population and that over 5% of pediatric patients with MS develop seizures. The observed rate of seizures/convulsions in this pediatric study is not different from the rate predicted by the extant published literature. The only potential exposure difference between the two treatment groups providing a possible explanation would be the disproportionate use of corticosteroids in the IFN β-1a treatment group. One

hypothetical impact of more exposure to potent corticosteroids would be an interruption of the processes believed to underlie the development of epilepsy in pediatric patients, but this hypothesis remains a theory in need of empirical proof.

Novartis has proposed that the totality of the evidence justifies adding seizures to the "Adverse drug reactions" section of the core data sheet. This addition appears appropriate given the evidence submitted by Novartis and my own interpretation of the data presented in this supplemental NDA.

2. Anxiety and Depression

There was an imbalance between the number of patients in the fingolimod treatment group and the interferon β-1a treatment group with respect to reported depressed mood and anxiety.

Evidence Supporting an Association

The evidence supporting an association between fingolimod and increased risk of anxiety or depression is the quantitative difference in risk observed during this randomized controlled trial.

Evidence against an Association

Anxiety and depression are common comorbid conditions in all patients with MS, and so observing high rates of these diagnoses in this specific study population is not unexpected. The difference in rates observed between the groups is not statistically significant. There was no difference in anxiety or depression rates observed in studies of adults with MS that have many more patient-years of exposure comparing fingolimod to interferon β-1a treatment. There is no plausible mechanism to support an increased risk of anxiety and mood disorders in patients treated with fingolimod. The suicidality assessment of patients in this trial did not show a difference in severe depressed mood thoughts or behaviors.

The evidence does not provide more than a correlation between fingolimod treatment and anxiety/depression in pediatric patients with RMS at present. Safety reports and post-marketing experience should be monitored for any increased risk of affective disorders in pediatric patients with RMS.

3. Infections

Infections are a well-established adverse effect of fingolimod treatment based on findings in adults. Based on the safety data from this controlled trial, fingolimod increases the risk of bacterial, viral, and fungal infections in pediatric patients to the same degree as it does in adults and presumably by the same mechanisms.

4. Cardiovascular Effects

Bradyarrhythmia and hypertension are known identified risks with fingolimod treatment in adults. This controlled trial confirmed that pediatric patients have the same first dose risks of conduction and rhythm disturbances. Pediatric patients should have the same rigor in first dose monitoring as adults. Though based on small number of observations, the safety data demonstrate that patients treated with the 0.25 mg dose fingolimod require first dose monitoring when switching to the 0.5 mg dose. The chronic effects of fingolimod on heart rate and blood pressure attenuate, but the QTc prolongation may increase slightly in some pediatric patients with uncertain clinical significance. Post marketing reports should be monitored for evidence of any risks of long-term administration on cardiovascular health or cardiac adverse events.

5. Leukopenia/Lymphopenia

As in adult patients, fingolimod treatment reduces serum absolute lymphocyte and absolute neutrophil counts. The existing language regarding opportunistic infections in the adverse drug reactions is adequate.

6. Liver Transaminase Elevation

Pediatric patients experience elevations in ALT, AST, and GGT in response to chronic fingolimod treatment. The current label warnings regarding liver toxicity potential and suggested monitoring are adequate.

7. Hypersensitivity Reactions

Drug-related hypersensitivity reactions were noted in pediatric patients treated with fingolimod. The existing warnings and precautions are adequate to mitigate this risk.

8. Macular Edema

A pediatric patient in the fingolimod treatment group was diagnosed with macular edema. The existing warnings and recommendations regarding ophthalmological examination should be extended to include pediatric patients with RMS treated with fingolimod.

9. Basal Cell Carcinoma

There were no pediatric patients in the fingolimod treatment group who had skin lesions consistent with a pre-cancerous or cancerous diagnosis. Longer exposure durations in the post market setting may confirm this risk in pediatric patients and existing labeling should be retained and assumed as relevant to the pediatric population pending future findings.

9. Advisory Committee Meeting and Other External Consultations

Not applicable.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The label has not been finalized at the time of this review.

All safety-related sections will be reviewed and edited to comply with Agency labeling formatting requirements.

I concur with Novartis's proposed inclusion of Seizure and discussion of the pediatric seizure data (b) (4).

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not required for the safe use of fingolimod in patients aged 10-18 years old. Labeling can adequately explain the risk of fingolimod in pediatric patients. There are no new identified safety issues where a REMS would be expected to mitigate identified risks. The previous REMS for fingolimod, the goal of which was to inform healthcare professionals about the serious risks of fingolimod (bradyarrhythmia and atrioventricular block at treatment initiation, infections, macular edema, posterior reversible encephalopathy syndrome, respiratory effects, liver injury, and fetal risk) was satisfied on April 14, 2016.

12. Postmarketing Requirements and Commitments

A formal REMS does not appear necessary for any identified issues. We will request increased pharmacovigilance of new onset seizures and request summary reports to be filed on a regular basis for monitoring purposes. We will monitor reports related to anxiety, depression, skin malignancies, traumatic injuries, cardiac events, growth and development filed as adverse event reports. Novartis plans to continue to collect efficacy and safety data in the ongoing OLE trial of fingolimod in pediatric RMS, and we will review these data as well.

13. Appendices

13.1. References

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13.2. Financial Disclosure

There was one relevant financial disclosure on Form FDA 3455 for Study D2311. Dr. (b) (6), an investigator at (b) (6) (Study Center (b) (6)), disclosed approximately $938,000 in research grant funding from (b) (6) during the period 2012-2014 and approximately $20,000 in consulting fees for (b) (6). The site where Dr. (b) (6) served as an investigator enrolled (b) (6) patients during this trial. Review of these patients' histories revealed no significant protocol deviations. Novartis proposes that independent data monitoring, the contributions of multiple investigators, and blinded trial design minimized potential bias. Please refer to Section 6.1.2 "Financial Disclosure" for more discussion.

Covered Clinical Study (Name and/or Number): CFTY720D2311

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1027		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 995		

Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

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/s/

PAUL R LEE
05/11/2018

JOHN R MARLER
05/11/2018