NOVARTIS

Clinical Development

FTY720/Fingolimod

Clinical Trial Protocol CFTY720D2312 / NCT01633112

A 12-month, randomized, rater- and dose-blinded study to compare the efficacy and safety of fingolimod 0.25 mg and 0.5 mg administered orally once daily with glatiramer acetate 20 mg administered subcutaneously once daily in patients with relapsing-remitting multiple sclerosis

Authors: [redacted]

Document type:	Amended Protocol Version
Version number:	v02 Clean
EUDRACT number:	Not applicable
Development phase:	IIIb
Release date:	20-Jul-2015

[redacted]

Table of contents

[redacted]

[redacted]

[redacted]

List of tables

List of figures

[redacted]

List of abbreviations

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AP	alkaline phosphatase
ARR	annualized relapse rate
AST	aspartate aminotransferase
AV	atrioventricular
CFR	United States Code of Federal Regulations
CNS	central nervous system
CO	carbon monoxide
CHMP	Committee for Medicinal Products for Human Use
CPO	Country Pharma Organization
CRF	case report forms
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
D_LCO	diffusion capacity of carbon monoxide
DMD	disease modifying drug
DS&E	Drug Safety and Epidemiology
DSMB	data safety monitoring board
DTPA	diethylenetriamine penta-acetic acid
eCRF	electronic case report/record form
ECG	electrocardiogram
EDSS	Expanded Disability Status Scale
EOT	end of treatment
FA	fluorescein angiography
FACS	fluorescein activated cell sorter
FAS	full analysis set
FEV_1	forced expiratory volume in 1 second
FS	functional system
FVC	forced vital capacity
Gd	gadolinium

[redacted]

GGT	gamma glutamyl-transferase
HbA1c	glycosylated hemoglobin/hemoglobin A1c
HRCT	high-resolution computed tomography
HSV	herpes simplex virus
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	independent ethics committee
IFN	interferon
Ig	immunoglobulin
IgG	immunoglobulin G
IM	intramuscular
IRB	institutional review board
IV	intravenous
IVRS	interactive voice response system
MedDRA	Medical Dictionary for Regulatory Activities
MS	multiple sclerosis
[redacted]	[redacted]
[redacted]	[redacted]
MRI	magnetic resonance imaging
OCT	optical coherence tomography
QoL	quality of life
[redacted]	[redacted]
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	pharmacodynamic
PFT	pulmonary function test
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PRO	patient reported outcome
RRMS	relapsing-remitting multiple sclerosis

[redacted]

SD	standard deviation
S1P	sphingosine 1-phosphate
SAE	serious adverse event
SC	subcutaneous
[redacted]	[redacted]
Treg	regulatory T cell
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	upper limit of normal
VZV	varicella zoster virus
WBC	white blood cells

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Baseline	The collection of pre-randomization information on subsequently randomized patients for future description and analysis. For any data analysis, the baseline for any data point will be clearly identified in the Statistical Analysis Plan.
Control drug	A study drug used as a comparator to reduce assessment bias, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e., before starting any of the procedures described in the protocol)
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug.”
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IVR system
Patient number	A number assigned to each patient who enrolls in the study. When combined with the center number, a unique identifier is created for each patient in the study.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study before the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomly assigned patient, corresponding to a specific treatment arm assignment
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study drug was discontinued whichever is later
Study drug	Any drug administered to the patient as part of the required study procedures; includes investigational drug and any control drugs
Study drug discontinuation	Point/time when patient permanently stops taking study drug for any reason; may or may not also be the point/time of premature patient withdrawal
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

[redacted]

Amendment 02

Amendment rationale

This amendment implements changes to the CFTY720D2312 protocol amendment 1 (dated 20-Nov-2012) to address recommendations and requests received from the United States (US) Food and Drug Administration (FDA).

The FDA has approved the Sponsor's proposal to reduce the sample size for this study. The FDA recommended to keep the number of patients in the fingolimod (FTY720) 0.25-mg treatment arm the same and agreed to reduce the other two treatment arms by up to 50% of the original sample size. This has led to a change in the randomization ratio between the three treatment groups and as a consequence an alteration of the calculated sample size. This sample size provides approximately 90% power for the primary objective. After the introduction of protocol amendment 2, the anticipated total number of patients to be screened is reduced to approximately 2610 from original 3190 patients. A screening failure rate of 25% is anticipated (supported by the current trend in this D2312 study [status Feb 2015]) and a total of 1960 randomized patients are targeted: fingolimod 0.25 mg (total 847 patients), fingolimod 0.5 mg (total 615 patients), and glatiramer acetate 20 mg (total 498 patients), respectively.

In addition, this amendment implements modifications to the inclusion/exclusion criteria. These modifications are prompted by:

- Feedback from study investigators and consultation with the study advisory group to help widening the pool of eligible subjects
- Alignment of the protocol with fingolimod's current US prescribing information and the prescribing information in other countries which are within the scope of this study as this is a Phase IIIb study with a marketed drug

The exclusion criterion 1 related to history of malignancy was rationalized to allow inclusion of patients who are now free of the past malignancy and have no trace of malignancy for the last 5 years.

The exclusion criterion 3 related to use of previous multiple sclerosis (MS) treatments was modified bearing in mind the likely duration of pharmacodynamic (PD) action of previous therapies and the assessments inherent in the screening assessments (e.g., complete blood counts) to rule out the persistence of such PD actions. Also, the criterion was modified to introduce guidance on the washout for newly approved disease-modifying therapies namely teriflunomide and dimethyl fumarate.

The requirement for serology testing of hepatitis A, B, C, and E, at Screening was omitted. This criterion (exclusion criterion 8 in protocol amendment version 1) has been modified to be in alignment with the current US prescribing information and the prescribing information in other countries which are within the scope of this study which does not require such screening before initiating treatment with fingolimod in clinical practice. The liver functions are being tested very closely at Screening, Baseline, and periodically during the study to capture any

[redacted]

instances of liver infections/impairment (if any) early and are considered as adequate safeguards.

The current exclusion criterion 8 regarding mandatory serologic screening for antibodies against varicella zoster virus (VZV) is a modification which also allows for alternative acceptable evidence of immunity (as per Center for Disease Control guidance). This brings the protocol in alignment with the guidance in the current US prescribing information in this context.

The current exclusion criteria 12, 13, and 14 have modified text to align with the US prescribing information and the prescribing information in other countries which are within the scope of this study. The exclusion clauses in protocol amendment version 1 were more restrictive than that recommended in the US prescribing information resulting in exclusion of those patients with certain pre-existing cardiac conditions or on concomitant drugs prolonging heart rate or atrioventricular (AV) conduction, who would have been otherwise eligible to initiate fingolimod with extended monitoring.

Certain clarifications and corrections were also done in the protocol as follows:

The exclusion criterion 16 provides clarification that patients with controlled asthma are allowed to participate in the study.

The prohibition period for the administration of a live or live-attenuated vaccine after fingolimod discontinuation was corrected from 12 to 8 weeks (as per US prescribing information).

Clarification was provided that the patients known to be allergic to gadolinium (Gd) may participate in the trial with magnetic resonance imaging (MRI) performance modified only to forgo contrasted MRI images.

The following erroneous paragraph was deleted: Patients experiencing bradycardia that has not resolved by the end of the 6-hour monitoring period must be hospitalized overnight. For these patients, the Day 2 dose of fingolimod should be given under the supervision of the treating physician, and the 6-hour monitoring period should be repeated per the procedures outlined for the first dose.

Throughout the protocol, clarifications of wording and correction of minor inconsistencies were provided for improved study conduct. This included allowance of use of topical and inhaled steroids for indications other than MS in Section 5.5.8, relaxation on the dosing adjustments of symptomatic therapies for optimal patient care in Section 5.5.8, details of the assessments to be performed for ophthalmologic examination in Table 6-1 and Table 6-2, [redacted].

In Appendix 3, investigators were guided to consider appropriate antihypertensive medication/dosage adjustment for newly diagnosed hypertension as well as an aggravation of a pre-existing condition. The earlier guidance to consider the discontinuation of study drug was deleted as it was an erroneous statement and not in line with the US prescribing information of fingolimod. Similarly, clarity was provided on the repeat testing in cases of

[redacted]

alanine aminotransferase/aspartate aminotransferase rise above 5 times the upper limit of normal (ULN).

Also, further clarity is being provided to investigators for interruption of glatiramer acetate when the lymphocyte count decreases below 50% of the baseline levels.

The protocol is also being amended to address safety updates in the investigator brochure (Edition 18) – in particular to provide additional guidance for safety monitoring for opportunistic infections and for basal cell carcinoma.

- Notably, there have been reports of isolated cases of cryptococcal meningitis in MS patients with relapsing MS receiving fingolimod. As a result, the fingolimod local product labeling will be updated to guide prescribers for vigilance, early detection, and diagnosis of such cases, should they occur. Similarly, the infection safety monitoring guidance is being updated in this protocol (Appendix 3).
- Basal cell carcinoma has been reported in patients receiving fingolimod. The physical examination section has been amended to ask patients about any new or worsening skin lesions and to instruct investigators to refer patients to the dermatologist in cases where suspected precancerous or cancerous skin lesions are identified.

The requirement for chest x-ray at Screening was removed as it was considered unnecessary by investigators, in line with the current safety profile of fingolimod. The pulmonary function testing and clinical examination of the respiratory system are considered to be adequate screening measures to evaluate pulmonary status.

[redacted]

Changes to the protocol

- The planned number of enrolled patients was reduced from 2250 to 1959 to provide a power of approximately 90% for the comparison of the annualized relapse rate (ARR) between fingolimod 0.5 mg to glatiramer acetate at a 2-sided significance level of 0.05. The power of the statistical test for the comparison of fingolimod 0.25 mg with glatiramer acetate will depend on whether the efficacy seen with fingolimod 0.5 mg is maintained in the lower dose (the 0.25-mg dose of fingolimod that has never been studied before). (Section 3.1, Section 4, and Section 9.6)
- The randomization ratio to the three treatment arms (fingolimod 0.25 mg, fingolimod 0.5 mg, and glatiramer acetate 20 mg) was changed from 1:1:1 to 5:3:2 to comply with the FDA recommendations on revision of the sample size in the three arms. The revised sample size calculation assumes that this switch will occur when a total of approximately 700 patients have been randomized to treatment under the original randomization ratio. (Section 3.1 and Section 4)
- The alpha-propagation procedure was replaced in protocol amendment 2 by a step-down hierarchical testing procedure in which the approved dose of fingolimod is initially tested against glatiramer acetate (at a 2-sided significance level of 0.05), and only if this initial test is significant will the low dose of fingolimod be tested against glatiramer acetate (also

[redacted]

at 2-sided significance level of 0.05). This change was introduced because of the alteration in the planned number of patients. (Section 9.4.2 and Section 9.6)

- Consequently, the original primary objective of the study "The primary objective is to demonstrate that at least 1 dose (0.5 mg or 0.25 mg) of fingolimod is superior to glatiramer acetate 20 mg subcutaneous (SC) in reducing the annualized relapse rate (ARR) up to 12 months in patients with relapsing-remitting MS" was reworded to: "The primary objective is to demonstrate that at least 1 dose (tested hierarchically 0.5 mg followed by 0.25 mg) of fingolimod is superior to glatiramer acetate 20 mg SC in reducing the ARR up to 12 months in patients with relapsing-remitting MS." (Section 2.1)
- [redacted]
- [redacted]
- Inclusion criterion 7 was removed and appropriate text was added to exclusion criterion 3 (see the following bullet point) with addition of instruction for dimethyl fumarate. (Section 4.1 and Section 5.5.8)
- Exclusion criterion 1 was changed as follows: Patients with a history of malignancy of any organ system (other than cutaneous basal cell carcinoma) in the last 5 years that do not have confirmation of absence of a malignancy prior to randomization. (Section 4.2)
- Exclusion criterion 3 was amended. The modified exclusion criterion is as follows: (Section 4.2)
  - Intravenous (IV) immunoglobulin (Ig) within 4 weeks before randomization
  - Immunosuppressive/chemotherapeutic medications (e.g., azathioprine, cyclophosphamide, methotrexate) within 6 months before randomization
  - Natalizumab within 2 months before randomization
  - Previous treatment with lymphocyte-depleting therapies (e.g., rituximab, alemtuzumab, ofatumumab, ocrelizumab, or cladribine) within 1 year before randomization
  - Previous treatment with mitoxantrone 6 months before randomization
  - Use of teriflunomide within 3.5 months prior to randomization, except if active washout (with either cholestyramine or activated charcoal) was done. In that case, plasma levels are required to be measured and to be below 0.02 mg/L before randomization.

    No washout period is necessary for patients treated with dimethyl fumarate, interferon (IFN) beta, or glatiramer acetate. Patients being treated with dimethyl fumarate, glatiramer acetate, or IFN beta at the screening visit can continue drug intake up to the day before Day 1 of this study (i.e., there is no need for a washout period).
- The earlier (in protocol amendment version 1) exclusion criteria 8 (screening for hepatitis A, B, C, and E) was removed. (Section 6.5.3.2 and Table 6-1)

[redacted]

- Current exclusion criterion 8 has the following modified text regarding VZV: Patients without acceptable evidence of immunity to VZV at randomization (See Appendix 3 for guidance on acceptable evidence of immunity and requirement for serologic testing). (Section 4.2, Section 6.5.3.2, and Table 6-1)
- Exclusion criterion 13 in protocol amendment version 1 has been modified and divided in exclusion criteria 12, 13, 14, and 15 (Section 4.2) as listed in the following 4 bullet points:
  - Exclusion criterion 12: Patients who in the last 6 months experienced any of the following cardiovascular conditions or findings in the screening electrocardiogram (ECG):
    - myocardial infarction
    - unstable angina
    - stroke
    - transient ischemic attack
    - decompensated heart failure requiring hospitalization or Class III/IV heart failure
  - Exclusion criterion 13: Patients with history or presence of a Mobitz Type II AV block, or a third-degree AV block or sick sinus syndrome, unless patient has a functioning pacemaker
  - Exclusion criterion 14: Patients with baseline QTc interval >500 msec
  - Exclusion criterion 15: Patients receiving Class Ia (e.g., ajmaline, disopyramide, procainamide, quinidine) or Class III antiarrhythmic drugs (e.g., amiodarone, bretylium, sotalol, ibutilide, azimilide, dofetilide)
- Exclusion criterion 15 in protocol amendment version 1 has become exclusion criterion 16 and is modified as follows: Patients with severe respiratory disease, pulmonary fibrosis, or Class III or IV chronic obstructive pulmonary disease, or with clinically significant lung pathology on chest x-ray. Patients with controlled asthma are allowed to enter the study. (Section 4.2)
- Exclusion criterion 14 in protocol amendment version 1 was deleted: Patients receiving current treatment with (at treatment initiation) beta blockers, heart-rate slowing calcium-channel blockers (e.g., ivadrabine, verapamil, or diltiazem), or other substances which may decrease heart rate such as digoxin, anticholinesterase agents, or pilocarpine. Advice from a cardiologist should be sought regarding the switch to nonheart rate lowering medicinal products. (Section 4.2)

  Similarly, text was deleted from Section 5.5.4 (Instructions for prescribing and taking study treatment): Due to a possible additive effect on heart rate reduction it is recommended not to initiate treatment with beta blockers, calcium-channel blockers, or digoxin within 1 week before randomization. In patients randomized to treatment with fingolimod, treatment with beta blockers, calcium-channel blockers, or digoxin should also not be initiated within one week after the start of study drug administration.
- Exclusion criterion 25 in protocol amendment version 1 has become exclusion criterion 26 and revised as follows: Patients with a score of 4 or 5 on the Suicidal Ideation item of the Columbia-Suicide Severity Rating Scale (C-SSRS) within 2 years of Screening, or any “yes” on the Suicidal Behavior item of the C-SSRS at Screening. (Section 4.2)

[redacted]

- Guidance was provided for re-screening of patients. (Section 4)
- Additional monitoring guidelines were added for patients with any pre-existing cardiovascular conditions and those receiving concurrent therapy with drugs that slow heart rate or AV conduction (e.g., beta blockers, heart rate lowering calcium-channel blockers such as diltiazem, verapamil, or digoxin). (Section 5.5.5)
- The following paragraph was deleted: "Patients experiencing bradycardia that has not resolved by the end of the 6-hour monitoring period must be hospitalized overnight." For these patients, the Day 2 dose of fingolimod should be given under the supervision of the treating physician, and the 6-hour monitoring period should be repeated per the procedures outlined for the first dose. (Section 5.5.5)
- Topical and inhaled steroids were allowed at the discretion of the treating neurologist for indications other than MS. (Section 5.5.8)
- There was modification to the statement regarding permitted medications for symptomatic treatment of MS. The current text reads as follows: Medications for the symptomatic treatment of MS such as baclofen, fampridine, methylphenidate, or modafinil are acceptable. As far as possible, every effort should be made to keep the dosages stable from Screening through end of treatment (EOT). (Section 5.5.8)
- The prohibition period for the administration of a live or live-attenuated vaccine after fingolimod discontinuation was corrected from 12 to 8 weeks. The statement that the vaccines may be administered once the lymphocyte counts are in laboratory normal range was deleted. (Section 5.5.9 and Appendix 3)
- Clarification is provided on what assessments are to be performed for ophthalmologic examination. The current text reads: The ophthalmology examination will include eye history, visual acuity, dilated ophthalmoscopy, and any procedures necessary to assess macular edema. Optical coherence tomography and fluorescein angiography will be done only if needed to confirm macular edema. (Table 6-1 and Table 6-2)
- Guidance was provided about the patients known to be allergic to Gd: The patients known to be allergic to Gd may participate in the trial with MRI assessment modified to forgo the contrasted MRI images. (Section 6.4.3)
- [redacted]
- [redacted]
- Guidance was provided when an MS relapse should be reported as a serious adverse event (SAE). The text reads: Any MS relapse, as a general rule, should be reported on the relapse CRF instead of the adverse event (AE)/SAE forms. However, if, in the judgment of the investigator, an MS relapse is unusually severe or unexpected and warrants specific notification, then an SAE form must be completed and submitted according to SAE reporting procedures outlined above. (Section 7.2.1)

[redacted]

- Guidance on safety monitoring was revised with respect to the actions to be taken with newly diagnosed hypertension. The current text is: Newly diagnosed hypertension as well as an aggravation of a pre-existing condition must be reported as an AE and appropriate antihypertensive medication/dosage adjustment must be considered by the investigator. (Appendix 3)
- Clarification was provided under guidance on monitoring of patients with elevated liver function tests (Appendix 3). The current text is: If alanine aminotransferase/aspartate aminotransferase values reach 5 times the ULN, confirmed upon repeat testing within 2 weeks of the initial result or sooner at the discretion of the investigator, the study drug must be permanently discontinued. Patients who develop symptoms suggestive of hepatic dysfunction such as unexplained vomiting or jaundice, should have liver enzymes checked and fingolimod should be discontinued if significant liver injury is confirmed.
- Investigators were advised to be vigilant for early diagnosis and treatment of cryptococcal meningitis and basal cell carcinoma (Appendix 3: Guidance for monitoring of infections; Section 6.5.1)
- The guidance to investigators for interruption of glatiramer acetate when the lymphocyte values decrease below 50% of baseline values was revised. (Appendix 3)
- Clarity was provided on the blinded and unblinded reporting of results for fingolimod. (Appendix 3)

Changes to specific sections of the protocol are shown in the track changes version of the protocol using ~~strike through red font for deletions~~ and red underlined for insertions.

A copy of this amended protocol will be sent to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and health authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the informed consent, sites are required to update and submit for approval a revised informed consent that takes into account the changes described in this amended protocol.

[redacted]

Amendment 01

Amendment rationale

This amendment implements changes to the CFTY720D2312 protocol (dated 23-Sep-2011) to address recommendations and requests received from the United States Food and Drug Administration (FDA) following their review of the protocol and to align aspects of the protocol with the current revised fingolimod (Gilenya™) label. [redacted]

The main changes involve inclusion of additional safety assessments, to allow comprehensive risk/benefit assessment of the 0.5 mg per day fingolimod dose [currently in the market], the lower 0.25 mg per day dose [under investigation in this study] and glatiramer acetate [control]. The safety assessments that are now being included for all participating patients are regular pulmonary function tests, dermatological examinations, ophthalmic examinations and assessment of suicidality. Specific guidance is provided for full workup in patients developing cardiac symptoms; pulmonary hypertension; ischemic or thrombotic events proteinuria. Suicidality assessment is also included in compliance with FDA guidance applicable to all drugs that have an effect on the central nervous system.

Safety sections of this protocol are revised with regard to cardiac safety. In December 2011, the company reported a sudden, unexplained death of a patient within 24 hours after the administration of the first dose of commercial fingolimod 0.5 mg. While the cause of death is unknown, the role of fingolimod cannot be confirmed or excluded. The reporting of this event prompted a thorough review the cardiac safety data from clinical trials as well as spontaneous reports in the post-marketing setting.

In order to align the protocol with the current revised fingolimod label, this amendment additionally updates and modifies (1) specific exclusion criteria, (2) selected safety monitoring guidance and (3) revision of the requirements for first dose monitoring following fingolimod interruption.

In addition, the amendment includes changes to facilitate the conduct of the study and includes clarifications of wording and other minor corrections.

The study is currently enrolling patients, and approximately 22 patients have been enrolled at the time of release of this amendment.

In summary the changes in the amendment refer to the following:

- pulmonary function testing
- dermatological examinations
- additional ophthalmological examination at 6 months
- body weight monitoring
- addition of certain laboratory analyses
- collection of laboratory analysis data that are not associated with a regular study visit
- provision for referral of patient to a specialist in the event of new significant cardiac or pulmonary hypertension symptoms

[redacted]

- inclusion of patients with higher glycosylated hemoglobin (HbA1c) levels but without diabetic neuropathy
- collection of additional baseline characteristics for diabetic patients
- provision for full diagnostic workup in patients with an ischemic or thrombotic adverse event
- a suicide severity rating assessment

Other changes to the protocol either for clarification, to improve conduct of the study, or to increase patient safety include:

- deletion of exclusion criterion regarding patients with history of vitamin B12 deficiency
- clarification of effective contraception methods
- deletion of redundant exclusion criterion pertaining to treatment with high dose steroids
- additional instructions to minimize risk of unblinding of blinded site personnel
- change of day of screening to be as early as 45 days prior to randomization
- further specification of study drug storage conditions
- [redacted]
- specification of assay for detecting hepatitis C virus
- [redacted]
- direction for central laboratory reporting of hematology results to maintain site blinding
- [redacted]
- minor wording corrections and administrative changes

The protocol has been amended to expand the population to be evaluated to include diabetic patients whose glycosylated hemoglobin levels are moderately elevated. The changes included in this amendment will provide additional data for the safety profiles of the study treatments.

Changes to the protocol

- The authors of the protocol were changed. (Title cover page)
- Background (Section 1.1) was revised to include updated patient exposure, updated summary of adverse events, addition of atrioventricular (AV) conduction safety information, and statement regarding patients with cardiovascular or cerebrovascular disease for which fingolimod is not recommended.
- [redacted]
- [redacted]

[redacted]

[redacted]

- The screening visit has been changed to occur up to 45 days prior to randomization (Section 3.1, Figure 3-1, Table 6-1)
- Inclusion criterion #4 was changed to remove reference to systemic steroid use because this was covered within exclusion criterion #4. (Section 4.1)
- The exclusion criterion regarding the use of intravenous immunoglobulin was changed for clarity to exclude any patients receiving intravenous immunoglobulin within 2 months prior to randomization. (Section 4.2)
- The exclusion criterion regarding uncontrolled diabetes was changed to allow participation by diabetics if their HbA1c level is 9% or less and they are without diabetic neuropathy. (Section 4.2)
- The exclusion criterion regarding history of vitamin B12 deficiency was removed. (Section 4.2)
- The exclusion criterion regarding serological markers to detect hepatitis C was changed to remove anti-hepatitis C virus IgM and to add hepatitis C virus RNA polymerase chain reaction (PCR) as an assay. (Section 4.2, Section 6.5.3.2, Table 6-1)
- Exclusion criteria were expanded to exclude patients with additional cardiovascular conditions and patients receiving treatments which may decrease heart rate. (Section 4.2)
- Exclusion criterion #15 was expanded to exclude patients who have clinically significant lung pathology by chest x-ray at Screening. A chest x-ray was added to assessments at the screening visit if an x-ray within the previous 3 months is not available. (Section 4.2, Table 6-1, Section 6.5.8)
- Exclusion criterion #22 pertaining to effective contraception was expanded to define highly effective methods of contraception. (Section 4.2)
- An exclusion criterion was added to exclude patients with a score of "yes" on item 4 or item 5 of the Suicidal Ideation section of the Columbia-Suicide Severity Rating Scale (C-SSRS), if this ideation occurred in the past 6 months prior to Screening, or "yes" on any item of the Suicidal Behavior section, except for the "Non-Suicidal Self-Injurious Behavior" in the past 2 years. (Section 4.2)
- [redacted]
- Because different sourcing strategies may be applied for glatiramer acetate depending on the country and because this control treatment is unblinded to the dispensing pharmacist and treating physician, medication numbering was removed as a requirement for the label for glatiramer acetate. (Section 5.1)
- The description of study drug storage specifies that all study drug is to be stored refrigerated. (Section 5.5.3)
- Management of patients with bradycardia following the first dose of fingolimod was changed to require overnight monitoring and second dose monitoring only if the patient was treated for the bradycardia. Patients experiencing prolonged QTc at 6 hours after first

[redacted]

dose of fingolimod are required to be monitored overnight and second dose monitoring is required. (Section 5.5.5)

- A statement was added in Section 5.5.9 to clarify that fingolimod may be restarted after a patient receives a live or live attenuated vaccine.
- Additional diabetes-specific baseline characteristics will be collected in patients with diabetes. (Section 6.2)
- The qualifications of the rater of the Expanded Disability Status Scale were clarified. (Section 6.4.2)
- A dermatological examination will be performed at Screening, 12 months, end of treatment, and end of study to identify new skin lesions. (Table 6-1, Table 6-2, Section 6.5, Section 6.5.10, and Section 9.5.2)
- Systolic and diastolic blood pressure will be measured in the supine position followed by measurements with the patient standing, with documentation of orthostatic hypotension if it occurs. (Section 5.5.5 and Section 6.5.2)
- Discharge criteria following first dose have been expanded to include review of ECG for AV block, prolonged QTc, and decreasing heart rate. They also include requirement for overnight hospitalization in the event that pharmacologic intervention is required during first dose observation period or for prolonged QTc. (Section 5.5.5)
- The requirement for restarting study drug and on-site monitoring after fingolimod interruption and restarting was changed. (Section 5.5.6)
- [redacted]
- Direction was added that the central laboratory will only report hematology absolute counts of eosinophils, basophils, and monocytes to maintain site blinding. The central laboratory will only report absolute total white blood cell, neutrophil, and lymphocyte counts to the site in case of a clinically notable abnormality. (Section 6.5.3.1)
- Body weight will be assessed at each visit to identify weight gain that may be indicative of edema. (Table 6-1, Section 6.5.2, Appendix 1)
- A footnote was added to Table 6-1 and Table 6-2 and text was added in Section 6.5.2 clarifying at which visits body temperature is to be measured.
- An additional ophthalmological examination will be performed at 6 months of treatment. (Table 6-1)
- Wording was added to clarify that blood samples are to be in the fasted state at the screening visit and to clarify that blood samples at subsequent visits are recommended to be in the fasted state. (Section 6.5.3)
- HbA1c will be included in all chemistry assessments. (Section 6.5.3.2)
- Uric acid and bicarbonate will be included in the serum chemistry assessments. (Section 6.5.3.2)
- Urinalysis will be performed at all visits. Procedures have been added to follow-up edema, weight gain, or proteinuria with additional urinalysis and follow-up by nephrologist if protein/creatinine ratio is abnormal. (Table 6-1, Table 6-2, and Section 6.5.3.3)

[redacted]

- Patients who experience new significant cardiac symptoms or symptoms of pulmonary hypertension are to be referred to a specialist for further diagnostic workup. (Section 6.5.1)
- [redacted]
- Pulmonary function tests (PFTs), including forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and diffusion capacity of carbon monoxide (D_LCO), will be performed at Screening, Month 6, Month 12, end of study, and 3 months after study drug discontinuation. (Table 6-1, Table 6-2, Section 6.5.9, Section 9.5.2, and References) Guidance for monitoring pulmonary function is provided in Appendix 3.
- Patients who are withdrawn from the study because of a respiratory adverse event(s) should be evaluated by a pulmonary specialist and further investigations (PFTs, chest x-ray or high-resolution computed tomography [HRCT], biopsy) as needed. (Section 6.5.9 and Section 7.1)
- The C-SSRS will be administered using an interactive voice response system (IVRS) at Screening and at every study visit after randomization. (Table 6-1, Table 6-2, Section 6.5.11, and Section 9.5.2)
- [redacted]
- Patients experiencing an ischemic or thrombotic adverse event are to be referred to a specialist for a diagnostic workup and management. (Section 7.1)
- Laboratory specimens that are not in association with a regular study visit are to be sent to the central laboratory for analysis and inclusion of the data in the study data sets. (Section 7.1)
- [redacted]
- Notable values for additional laboratory assessments have been added to Appendix 1 (Clinically notable laboratory values and vital signs), and some notable values were changed.
- Previous Appendix 3 was deleted because exclusion criterion referring to this appendix was deleted.
- Appendix 3 was revised to require discontinuation of study drug if clinical symptoms of infection accompany lymphopenia. Discontinuation of study drug for lymphopenia in the absence of clinical signs of infection is at the discretion of the investigator.
- Appendix 3 was revised to require discontinuation of study drug in patients receiving glatiramer acetate who develop significant lymphopenia.
- Appendix 4 was revised to include guidance on ophthalmic monitoring of patients with any visual disturbances while on therapy and in patients with diabetes mellitus or uveitis.

A copy of this amended protocol will be sent to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and Health Authorities.

[redacted]

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

[redacted]

Protocol synopsis

Title of study: A 12-month, randomized, rater- and dose-blinded study to compare the efficacy and safety of fingolimod 0.25 mg and 0.5 mg administered orally once daily with glatiramer acetate 20 mg administered subcutaneously once daily in patients with relapsing-remitting multiple sclerosis

Purpose and rationale: The purpose of this study is to compare the efficacy and safety of fingolimod 0.50 mg and fingolimod 0.25 mg to glatiramer acetate (20 mg) for the treatment of patients with relapsing-remitting multiple sclerosis (RRMS) as part of a postapproval commitment for the FDA.

[redacted]

Objectives:

Primary Objective:

The primary objective is to demonstrate that at least 1 dose (tested hierarchically 0.5 mg followed by 0.25 mg) of fingolimod is superior to glatiramer acetate 20 mg subcutaneous (SC) in reducing the annualized relapse rate (ARR) up to 12 months in patients with relapsing-remitting MS.

Secondary Objectives:

To evaluate in fingolimod 0.5 mg, fingolimod 0.25 mg, and glatiramer acetate 20 mg groups:

- the change from Baseline in brain volume at Month 12 or end of study
- the number of active T2 lesions (new or newly enlarging lesions compared with Baseline) at Month 12 or end of study.
- the proportion of patients free of new or newly enlarging T2 lesions compared to Baseline at Month 12 or end of study
- the change from Baseline in T2 lesion volume at Month 12 or end of study
- the change from Baseline in the number and volume of T1 hypointense lesions at Month 12 or end of study
- the number and volume of gadolinium (Gd)-enhancing T1 lesions at Month 12 or end of study
- the safety and tolerability up to Month 12
- the change from baseline in treatment satisfaction as measured by the Treatment Satisfaction Questionnaire for Medication (TSQM) at Month 12 or end of study

[redacted]

[redacted]

[redacted]

Population:

The study population will consist of adult male and female patients with RRMS. Treatment-naïve patients and patients previously treated with disease-modifying therapies for MS, with the exception of S1P modulator therapy, are eligible to participate in the study. The anticipated total number of patients to be screened is approximately 2610, with approximately 1960 patients randomly assigned to study treatment.

Key Inclusion/Exclusion criteria:

Inclusion criteria:

1. Written informed consent must be obtained before any assessment is performed
2. Male and female patients 18 to 65 years of age, inclusive.
3. Patients with RRMS, as defined by 2010 revised McDonald criteria.
4. Patients must be neurologically stable with no onset of relapse within 30 days of randomization.
5. Patients with at least 1 documented relapse during the previous year or 2 documented relapses during the previous 2 years before randomization.
6. Patients with an Expanded Disability Status Scale (EDSS) score of 0 to 6.0, inclusive, at Screening. A score of 6.0 indicates unilateral assistance (cane or crutch) required to walk at least 100 meters with or without resting.

Exclusion criteria:

1. Patients with a history of malignancy of any organ system (other than cutaneous basal cell carcinoma) in the last 5 years that do not have confirmation of absence of a malignancy prior to randomization.
2. Patients with an active chronic disease (or stable but treated with immune therapy) of the immune system other than MS (e.g., rheumatoid arthritis, scleroderma, Sjogren's syndrome, Crohn's disease, ulcerative colitis) or with a known immunodeficiency syndrome (HIV-antibody positive, AIDS, hereditary immune deficiency, drug-induced immune deficiency).
3. Patients who have been treated with:
    - Intravenous (IV) immunoglobulin (Ig) within 4 weeks before randomization
    - Immunosuppressive/chemotherapeutic medications (e.g., azathioprine, cyclophosphamide, methotrexate) within 6 months before randomization
    - Natalizumab within 2 months before randomization
    - Previous treatment with lymphocyte-depleting therapies (e.g., rituximab, alemtuzumab, ofatumumab, ocrelizumab, or cladribine) within 1 year before randomization
    - Previous treatment with mitoxantrone within 6 months before randomization
    - Use of teriflunomide within 3.5 months prior to randomization, except if active washout (with either cholestyramine or activated charcoal) was done. In that case, plasma levels are required to be measured and be below 0.02 mg/L before randomization

[redacted]

No washout period is necessary for patients treated with dimethyl fumarate, interferon (IFN) beta, or glatiramer acetate.

Patients being treated with dimethyl fumarate, glatiramer acetate, or IFN beta at the Screening visit can continue drug intake up to the day before Day 1 of this study (i.e., there is no need for a washout period).

4. Patients who have been treated with systemic corticosteroids or adrenocorticotropic hormones in the past 30 days prior to the screening magnetic resonance imaging (MRI) procedure.
5. Patients with uncontrolled diabetes mellitus (glycosylated hemoglobin >9%) or with diabetic neuropathy.
6. Patients with a diagnosis of macular edema during Screening (patients with a history of macular edema will be allowed to enter the study provided that they do not have macular edema at Screening).
7. Patients with severe active bacterial, viral, or fungal infections.
8. Patients without acceptable evidence of immunity to varicella zoster virus (VZV) at randomization (See Appendix 3 for guidance on acceptable evidence of immunity and requirement for serologic testing).
9. Patients who have received any live or live-attenuated vaccines (including VZV, herpes simplex, or measles) within 1 month before randomization.
10. Patients who have received total lymphoid irradiation or bone marrow transplantation.
11. Patients with any unstable medical/psychiatric condition, as assessed by the primary treating physician at each site.
12. Patients who in the last 6 months experienced any of the following cardiovascular conditions or findings in the screening electrocardiogram (ECG): myocardial infarction, unstable angina, stroke, transient ischemic attack or decompensated heart failure requiring hospitalization or Class III/IV heart failure.

Investigational drug:

- Fingolimod (FTY720) 0.5-mg capsules for oral administration once daily
- Fingolimod (FTY720) 0.25-mg capsules for oral administration once daily

Both strengths of fingolimod capsule will be identical in appearance and will be packaged in identical bottles.

Control drug:

Glatiramer acetate 20-mg SC injection once daily.

Study design:

This is a multicenter, randomized, rater- and dose-blinded study to compare the efficacy and safety of 0.25 mg and 0.5 mg of fingolimod with glatiramer acetate 20 mg SC in patients with RRMS.

This study will consist of 3 periods:

- Screening Period: up to 45 days for all patients
- Treatment Period: 12 months of glatiramer acetate 20 mg, fingolimod 0.25 mg, or fingolimod 0.5 mg
- Follow-up Period will occur 3 months (12 weeks) after the last dose of study drug for all patients

After signing the informed consent, patients will enter the Screening Period to determine eligibility for the study. After inclusion/exclusion criteria are reviewed again and after safety assessments are conducted, patients will enter the Treatment Period and will be randomly assigned into one of three groups (for details about the randomization see Section 9.6 - Sample size calculation):

- Group 1 will receive fingolimod 0.5 mg orally once a day for up to 12 months
- Group 2 will receive fingolimod 0.25 mg orally once a day for up to 12 months

[redacted]

- Group 3 will receive glatiramer acetate 20 mg subcutaneously once a day for up to 12 months

Patients will take their first dose of study drug at Visit 2. Thereafter, patients in each fingolimod treatment arm will take 1 capsule orally once a day for 12 months. Patients in the glatiramer acetate treatment arm will self-administer an SC injection of 20 mg of glatiramer acetate once a day for 12 months. In order to ensure patient safety 6-hour first dose monitoring procedures are to be followed for patients receiving fingolimod. First-dose monitoring is to be conducted by the primary treating physician.

Starting at Visit 3/Month 1, all visits in the Treatment Period have a visit window of ±5 days. At Visit 7/end of treatment (EOT)/Month 12, the study staff should complete the study completion electronic case report form (eCRF).

The end-of-study follow-up visit will occur 3 months (12 weeks) after the last dose of study drug administration (for patients who complete the study and for patients who prematurely discontinue the study).

Efficacy assessments:

- MS ARR
- Magnetic resonance imaging (MRI)
- [redacted]
- [redacted]

Safety assessments:

- Physical and neurological examination
- Vital sign measurements
- Laboratory evaluations
- ECG results
- Ophthalmologic examinations
- Pulmonary function tests
- Dermatological examination
- Columbia-Suicide Severity Rating Scale

[redacted]

Quality of life assessments:

- Patient-reported outcomes for multiple sclerosis (TSQM, [redacted])

Data analysis:

The primary outcome is the ARR which is defined as the average number of confirmed relapses per year (i.e., the total number of confirmed relapses divided by the total days in the study multiplied by 365.25). For the primary analysis, the number of relapses will include all the confirmed relapses experienced during the study. The time spent in the study will correspond to the observation period for all the relapses from first dose on study drug to end of study.

The 2 doses of fingolimod will be tested hierarchically versus glatiramer acetate in a step-down procedure. For each of the 2 fingolimod doses, the null hypothesis is that there is no difference in the ARRs between patients treated with fingolimod and patients treated with glatiramer acetate versus the alternative hypothesis that there is a difference between the 2 treatment groups. The null hypothesis will be rejected if the observed P value for the between-treatment comparison is less than the significance level as specified in multiplicity adjustment procedure.

[redacted]

H_{01}: $\mu_{FTY\ 0.5\ mg} = \mu_{glatiramer\ acetate}$ versus H_{A1}: $\mu_{FTY\ 0.5\ mg} \neq \mu_{glatiramer\ acetate}$

H_{02}: $\mu_{FTY0.25\ mg} = \mu_{glatiramer\ acetate}$ versus H_{A2}: $\mu_{FTY0.25\ mg} \neq \mu_{glatiramer\ acetate}$

No formal hypothesis will be tested between the 2 fingolimod doses because the study is not powered to detect a difference in treatment effect between these doses.

The hypotheses will be tested using a negative binomial regression model with log link, using treatment, number of relapses in the previous year before study enrollment, baseline EDSS, and baseline number of Gd-enhancing T1 lesions and country (or region) as covariates. In the analysis, the response variable is the number of confirmed relapses for each patient. The patient's time in the study (natural log of time in years) is used as an offset variable to obtain the ARR, adjusted for the varying lengths of patient's time in the study (time in years). The treatment effect of fingolimod doses versus glatiramer acetate will be presented as an ARR ratio with corresponding 95% confidence intervals and p values.

To adjust for multiple testing in this study, a step-down hierarchical testing procedure will be used. There are 2 hypotheses being tested (H01, H02). Because it is highly likely that the approved dose of fingolimod (0.5 mg) is more efficacious than the lower dose (0.25 mg), the approved dose of fingolimod is initially tested against glatiramer acetate at a 2-sided significance level of 0.05. Only if this initial test H01 is rejected will H02, the low dose of fingolimod, be tested against glatiramer acetate also at a 2-sided significance level of 0.05.

The sample size calculations and power considerations follow the method outlined in Keene et al., 2007 with a constant dispersion parameter k (k=0.2231). The power of the study was evaluated under various ARR assumptions and various dropout patterns based on the cumulative literature on glatiramer acetate and the Novartis data on fingolimod. The anticipated ARR for patients treated with 0.5 mg fingolimod is $\mu_{FTY\ 0.5\ mg}$=0.195, the ARR for those treated with glatiramer acetate is $\mu_{glatiramer\ acetate}$=0.30. Therefore, the estimated ARR reduction for fingolimod 0.5 mg versus glatiramer acetate is 35%. Assuming a dropout rate of 15% based on data from this D2312 study (status Feb-2015), the total 1960 randomized patients with approximately 847 patients in the fingolimod 0.25-mg group, 615 patients in the fingolimod 0.5-mg group, and 498 patients in the glatiramer acetate 20-mg group will achieve approximately 90% statistical power for the comparison of fingolimod 0.5 mg versus glatiramer acetate at a 2-sided significance level of 0.05. This calculation takes into account that patients who discontinue prematurely from the study can participate with partial data to the primary endpoint.

Fingolimod 0.25 mg has never been studied in a clinical trial in MS. Based on PK/PD modeling results, it is anticipated that the ARR in patients treated with fingolimod 0.25 mg is approximately 15% higher than in those treated with fingolimod 0.5 mg. In line with the PK/PD modeling, the anticipated ARR in patients treated with fingolimod 0.25 mg is $\mu_{FTY\ 0.25\ mg}$=0.225, which corresponds to a 25% reduction in ARR in patients treated with fingolimod 0.25 mg compared to those treated with glatiramer acetate. Following the multiplicity adjustment procedure, the power to detect a 25% reduction in ARR for patients treated with fingolimod 0.25 mg compared with patients treated with glatiramer acetate is approximately 68% at a 2-sided significance level of 0.05, if the primary objective for the fingolimod 0.5-mg dose can be rejected first. A formal comparison between the two fingolimod doses is not intended, as the study is not powered for such a comparison.

The statistical software R (Version 2.13.1, open source) and the R library packages "MASS" and "PSCL" were used for sample size calculations and power analysis.

[redacted]

1 Introduction

1.1 Background

Multiple sclerosis (MS) is a chronic inflammatory autoimmune disease of the central nervous system (CNS) causing pronounced neurological disability in young adults, primarily women, with disease onset typically occurring between the ages of 20 and 40 years. The approximate prevalence rate of MS in the United States is 400,000 (0.1%).

Typically recurrent acute episodes (relapses) of neurological symptoms, which are followed by a complete or partial recovery, can be observed during the relapsing-remitting multiple sclerosis (RRMS) disease course. Approximately 50% of these patients progress to secondary progressive MS (SPMS) within 10 years and 90% within 25 years. Apart from these initially relapsing forms of MS, 10% to 15% of patients present with primary progressive MS (PPMS), which is characterized by steady deterioration of impairment without prior experience of relapses (Keegan et al, 2002).

Fingolimod (FTY720) Gilenya® is an oral, once-daily immunomodulatory drug that has been approved for the treatment of relapsing MS in the United States, Europe, and other countries. Pharmacologically, fingolimod, after phosphorylation to fingolimod-phosphate (fingolimod-P) targets a class of G protein-coupled receptors, which bind the pleiotropic sphingolipid mediator sphingosine 1-phosphate (S1P) and acts in large part by down-modulating S1P/S1P receptor responses in the immune and the central nervous systems. It causes a reversible sequestration of a proportion of CD4+ and CD8+ positive T cells and B cells from blood and spleen into lymph nodes and Peyer's patches, apparently without affecting many of the functional properties of these cells. Under normal circumstances, T cells selectively require S1P1 activation for emigration from the thymus, and both T and B cells require this receptor for egress from peripheral lymphoid organs. Fingolimod-P acts as a super-agonist of the S1P1 receptor on lymphocytes, inducing its uncoupling/internalization and intracellular lysosomal degradation. The internalization and degradation of S1P1 renders these cells unresponsive to S1P, depriving them of the obligatory signal to egress from lymphoid organs and recirculate to peripheral inflammatory tissues. As a consequence, autoaggressive T cells remain trapped in the lymphoid system, i.e., in the autoantigen-draining cervical lymph nodes in experimental autoimmune encephalomyelitis MS, which reduces their recirculation to the CNS and abrogates central inflammation.

The lymphocytes trapped by fingolimod in the LNs contain the pro-inflammatory T-helper (CD4+) IL-17 producing lymphocyte subset (Th17): A T-helper subset which is derived from naïve T cells when these cells are stimulated in the presence TGF-β, IL-1β and IL-23. Th17 cells manifest a phenotype of increased IL-17 production. Th17 cells have been shown to play an important role in the induction of autoimmune disease, but are crucial for the immune response against fungi and extracellular bacteria. Regulatory T-cells (Treg) are a subset of predominantly CD4+ T-cells differentiated from naïve T-cells in the periphery after stimulation with TGFβ and antigen (iTreg) or generated in the thymus (nTreg); other regulatory T-cell subtypes exist, including CD8+ Tregs. Tregs play an important role in the regulation of immune function and prevention of autoimmune disease. A balance between Th17 and Tregs appears crucial for the maintenance of immune homeostasis.

[redacted]

In EAE, among other T-cells, Th17 cells transmigrate efficiently across the blood-brain-barrier (BBB), disrupt BBB tight junctions, highly express granzyme B and kill human neurons, and promote CNS inflammation through additional CD4+ T-cell recruitment (Kebir 2007). Accordingly, large numbers of Th17 cells are found in brain tissues from MS patients, particularly in acute and chronic active lesions (Tzartos 2008). Analysis of blood T-cells from fingolimod-treated MS patients now revealed strikingly reduced numbers of IL-17-producing Th17 cells in circulation (Mehling 2010), suggesting that fingolimod directly abrogates the inflammatory Th17 axis in MS.

Since fingolimod has a preferential impact on the levels of Th17 T-helper cells, the investigation of the counts and relative proportions of Th17 cells as compared to T-regulator (Treg) cells is of relevance for the determination of the effects of the drug on immune homeostasis, both in terms of immune defense as well as suppression of the auto-immunity.

In two Phase III studies in patients with RRMS fingolimod has demonstrated a significantly superior efficacy over current standard therapy with interferon (IFN) beta-1a intramuscular (IM) (standard of care) and over placebo, respectively:

In the one-year D2302 (TRANSFORMS) study in 1292 patients with RRMS, an active comparator trial against an established standard of care, fingolimod significantly reduced annualized relapse rates (ARR) by 52% (0.5 mg dose, ARR 0.21) and 38% (1.25 mg dose, ARR 0.26) vs. IFN beta-1a IM (ARR 0.43). These findings were supported by effects on disease activity as measured in brain magnetic resonance imaging (MRI) (Cohen et al, 2010).

- Results from the 2-year placebo-controlled D2301 (FREEDOMS) study in 1272 patients with RRMS show that fingolimod reduced the relapse rate by 54% for the 0.5 mg dose (ARR 0.18) and 60% for the 1.25 mg dose (ARR 0.16) compared to placebo (ARR 0.40; both comparisons $p<0.001$). In addition, fingolimod reduced the risk of progression of disability by 30 - 37% for patients on 0.5 mg ($p=0.024$) and 32 - 40% for those on 1.25 mg ($p=0.017$) compared to placebo over two years. These findings were supported by positive effects on brain lesions as measured by MRI scan (Kappos et al, 2010).

The safety profile of fingolimod has been well characterized in the MS clinical development program. As of 29 February 2012, the MS clinical trials exposure in global and local studies is estimated to be approximately 16,500 patient-years in more than 10,000 MS patients. For updated exposure and safety information, please refer to current investigator brochure.

The safety profile observed in the fingolimod MS clinical development program can be summarized as follows:

- The overall incidence of adverse events (AEs) leading to discontinuation of study drug in [Study CFTY720D2301] was comparable for the fingolimod 0.5 mg/day (7.5%) and placebo group (7.7%) but higher in the fingolimod 1.25 mg/day group (14.2%). The overall incidence of serious adverse events (SAEs) was comparable between fingolimod groups (11.9% and 10.1% for fingolimod 1.25 mg/day and fingolimod 0.5 mg/day, respectively) and placebo (13.4%).
- Specific AEs that were reported more commonly in MS patients treated with fingolimod than placebo included elevations of liver enzymes, in particular increases in alanine aminotransferase (ALT) and γ-glutamyltransferase (GGT), reductions in white blood cell (WBC) counts (lymphocytes and total WBC count), transient bradycardia after the first

[redacted]

dose of fingolimod, macular edema, hypertension, dyspnea, bronchitis, and diarrhea. The AEs most prominently associated with fingolimod treatment (eg, liver enzyme elevations, bradycardia, and macular edema) appeared to show a dose response. There were no AEs that appeared to be specifically related to long-term treatment with fingolimod.

- In general, the AE profile of fingolimod in MS patients did not depend on gender, age, or previous treatment with disease-modifying drugs. The only exception was liver enzyme elevations, which were more frequent in male patients than in female patients treated with fingolimod.
- The overall incidence of infections, including serious infections, was similar in the fingolimod treatment groups and the comparator arms (IFN or placebo) in both completed Phase III studies. A slightly higher frequency of lower respiratory tract infections (primarily bronchitis) was observed in fingolimod-treated patients, with an apparent dose effect. The current data showed no clear relationship between lymphocyte count and the incidence of infections on fingolimod treatment.
- The accumulated data from the MS program do not show an association of fingolimod therapy with the development of malignancies. In the FREEDOMS study, more cancers were seen in the placebo group than in the treated groups. Incidence estimates for various forms of skin cancer (and other malignancies) from pooled safety data are comparable between treatment groups and placebo. There appears to be no increased risk with greater duration of exposure (Kappos et al, 2010).
- Initiation of fingolimod treatment has been associated with atrioventricular (AV) conduction delays usually as first-degree AV blocks (prolonged PR interval on electrocardiogram [ECG]). Second-degree AV blocks, usually Mobitz Type I (Wenckebach), have been observed in less than 0.5% of patients receiving fingolimod 0.5 mg in clinical trials. The conduction abnormalities typically were transient, asymptomatic, usually did not require treatment, and resolved within the first 24 hours on treatment.
- Data on the safe use of fingolimod in pregnancy or with breast-feeding are limited, although preclinical data suggest risk to the fetus and newborn is possible.

In the post-marketing setting, isolated delayed onset events, including transient asystole and the 1 unexplained death, within 24 hours of the first dose, have occurred. These events have been confounded by concomitant medication and/or pre-existing diseases and the relationship to fingolimod is uncertain. It is recommended that fingolimod not be administered to patients with a history of cardiovascular or cerebrovascular disease or to those patients taking heart-rate lowering medication.

Glatiramer acetate consists of the acetate salts of synthetic polypeptides, containing 4 naturally occurring amino acids: L-glutamic acid, L-alanine, L-tyrosine, and L-lysine. The mechanisms by which glatiramer acetate acts in patients with MS are not fully understood. However, it is thought to act by modifying immune processes believed to be responsible for the pathogenesis of MS. This hypothesis is supported by findings of studies that have been carried out to explore the pathogenesis of experimental allergic encephalomyelitis.

Evidence supporting the effectiveness of glatiramer acetate (20 mg/day) in decreasing the frequency of relapses in patients with RRMS comes from 2 placebo-controlled studies. In a single centre study in 50 patients randomized equally to glatiramer acetate or placebo, the

[redacted]

average number of relapses per patient over 24 months was reduced from 2.7 on placebo to 0.6 in the glatiramer acetate arm (Bornstein et al, 1987). In a larger placebo-controlled multicentre study in 251 patients a reduction of the 2-year relapse rate from 1.68 on placebo to 1.19 on glatiramer acetate was observed (Johnson et al, 2001). Results in both studies were supported by beneficial effects of glatiramer acetate on MRI markers of inflammatory disease activity and on other relapse-related endpoints, as compared to placebo.

In addition, 3 trials comparing high-dose IFN with glatiramer acetate were conducted. In the REGARD (Rebif® versus glatiramer acetate in patients with RRMS) open-label study in 764 patients equally randomized to the two treatment arms, there were no significant differences between groups treated with 44 µg of subcutaneous (SC) IFN β-1a 3 times a week and 20 mg of SC glatiramer acetate daily after 96 weeks of treatment in the time of the first relapse, the annualized relapse rate (IFN β-1a 0.30; glatiramer acetate 0.29), or magnetic resonance imaging (MRI) outcomes (number and change in volume of T2 active lesions) (Mikol et al, 2008).

The dose-blinded BEYOND study (N = 2244 in a 1:2:2 ratio) compared 20 mg SC glatiramer acetate with 250 µg and 500 µg of SC IFN beta-1b every other day. Results showed that the ARR was similar between groups (IFN beta-1b SC 500 µg 0.33; IFN beta-1b SC 250 µg 0.36; glatiramer acetate 0.34), with no significant difference in the time of the first relapse or the proportion of patients remaining relapse free. For MRI data, there were no significant differences in gadolinium (Gd)-enhancing lesions, T1 lesions, or normalized brain volume between groups. There were significant differences in the cumulative number of new T2 lesions between the patients treated with IFN and glatiramer acetate, favouring IFN (O'Connor et al, 2009).

In the BECOME study in 75 patients with RRMS, efficacy of treatment with IFN beta-1b and glatiramer acetate was assessed by monthly MRI and relapse rate for up to 2 years. There were no significant differences in the number of combined active lesions on MRI between the 2 groups. Correspondingly, the ARR between the 2 treatment groups did not show significant differences (IFN beta-1b 0.37; GA 0.33) (Cadavid et al, 2009).

1.2 Purpose

The purpose of this study is to compare the efficacy and safety of fingolimod 0.50 mg and fingolimod 0.25 mg to glatiramer acetate (20 mg) for the treatment of patients with RRMS as part of a postapproval commitment for the FDA.

[redacted]

[redacted]

2 Study objectives

2.1 Primary objective

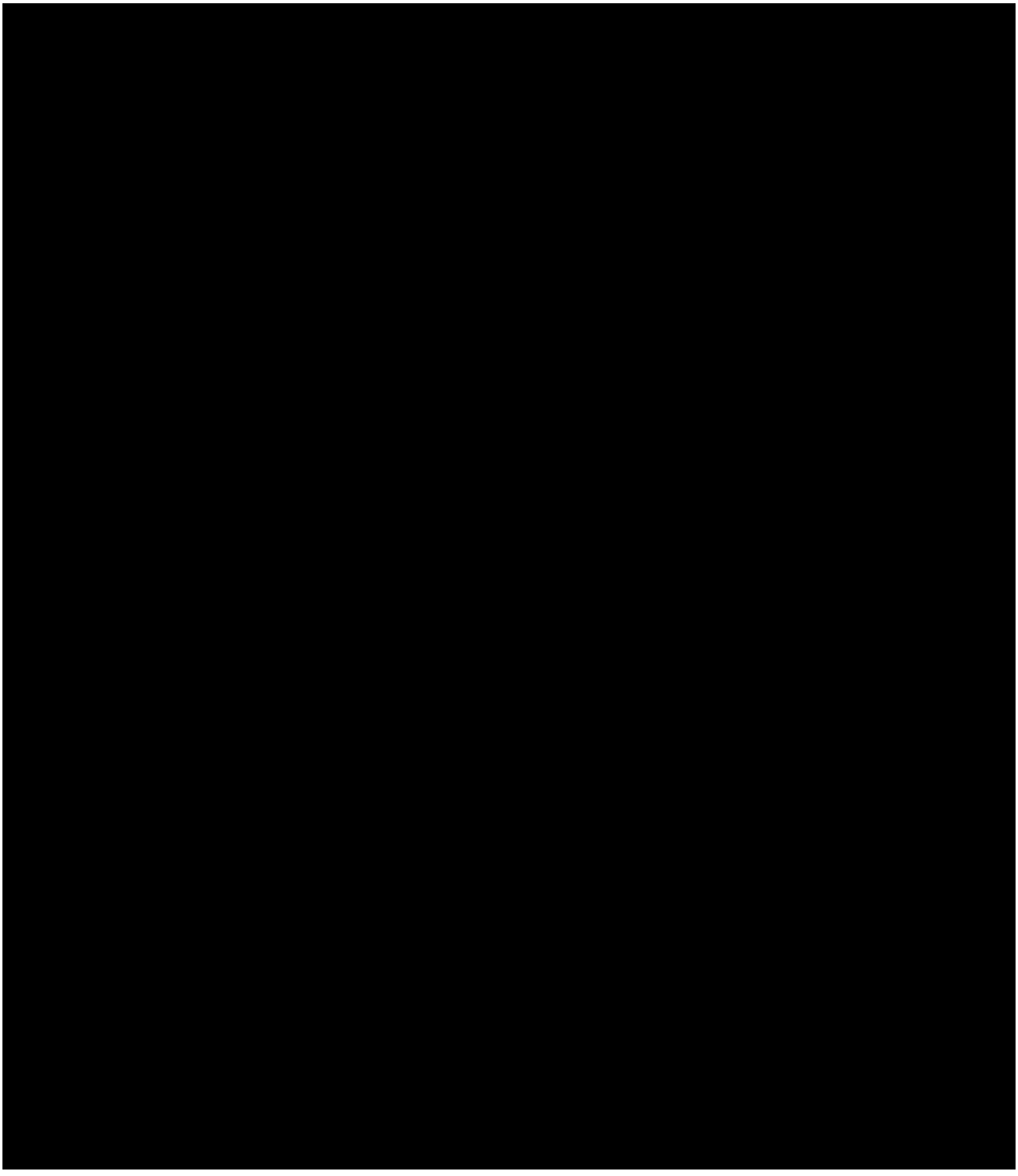
The primary objective is to demonstrate that at least one dose (tested hierarchically 0.5 mg followed by 0.25 mg) of fingolimod is superior to glatiramer acetate 20 mg SC in reducing the ARR up to 12 months in patients with relapsing-remitting MS.

2.2 Secondary objectives

To evaluate in fingolimod 0.5 mg, fingolimod 0.25 mg, and glatiramer acetate 20 mg groups:

- the change from Baseline in brain volume at Month 12 or end of study
- the number of active T2 lesions (new or newly enlarging lesions compared with Baseline) at Month 12 or end of study.
- the proportion of patients free of new or newly enlarging T2 lesions compared to Baseline at Month 12 or end of study
- the change from Baseline in T2 lesion volume at Month 12 or end of study
- the change from Baseline in the number and volume of T1 hypointense lesions at Month 12 or end of study
- the number and volume of Gd-enhancing T1 lesions at Month 12 or end of study
- the safety and tolerability up to Month 12
- the change from baseline in treatment satisfaction as measured by the Treatment Satisfaction Questionnaire for Medication (TSQM) at Month 12 or end of study

[redacted]



3 Investigational plan

3.1 Study design

This is a multicenter, randomized, rater- and dose-blinded study to compare the efficacy and safety of 0.25 mg and 0.5 mg of fingolimod with glatiramer acetate 20 mg SC in patients with

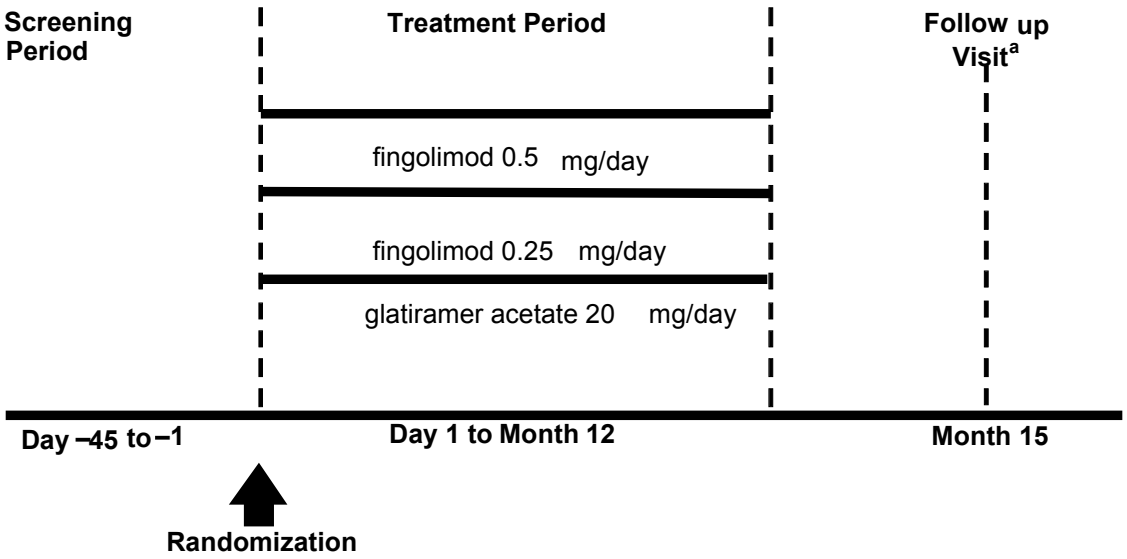
RRMS. Originally, approximately 2550 patients with RRMS were to be randomized, which has been reduced to a total of 1960 patients as per protocol amendment 2.

This study will consist of 3 periods:

- Screening Period: up to 45 days for all patients
- Treatment Period: 12 months of glatiramer acetate 20 mg, fingolimod 0.25 mg, or fingolimod 0.5 mg
- Follow-up Period will occur 3 months (12 weeks) after the last dose of study drug for all patients

The study design is presented in Figure 3-1.

Figure 3-1 Study design



a. Follow-up will occur 3 months (12 weeks) after the last dose of study drug for all patients.

The assessment schedule is presented in Table 6-1. After signing the informed consent, patients will enter the Screening Period to determine eligibility for the study. After inclusion/exclusion criteria are reviewed again and after study assessments are conducted, patients will enter the Treatment Period and will be randomly assigned into one of the three groups (for details about the randomization, see Section 9.6 - Sample size calculation):

- Group 1 will receive fingolimod 0.5 mg orally once a day for up to 12 months
- Group 2 will receive fingolimod 0.25 mg orally once a day for up to 12 months
- Group 3 will receive glatiramer acetate 20 mg subcutaneously once a day for up to 12 months

Patients will take their first dose of study drug at Visit 2. Thereafter, patients in each fingolimod treatment arm will take 1 capsule orally once a day for 12 months. Patients in the

[redacted]

glatiramer acetate treatment arm will self administer an SC injection of 20 mg of glatiramer acetate once a day for 12 months. In order to ensure patient safety during the first dose administration, patients will take the first dose at the study sites and procedures in the protocol must be followed for all patients receiving oral capsules as outlined in the first-dose monitoring instructions (Section 5.5.5). First-dose monitoring is to be conducted by the treating physician.

Starting at Visit 3/Month 1, all visits in the Treatment Period have a visit window of ±5 days. Sites are encouraged to comply with this visit window as much as possible.

The end-of-study follow-up visit will occur 3 months (12 weeks) after the last dose of study drug administration (for patients who complete the study and for patients who prematurely discontinue study).

[redacted]

3.2 Rationale of study design

A randomized parallel-group design has been chosen as it provides an unbiased assignment to treatment and allows the direct comparison of efficacy, tolerability, and safety of the 3 treatment arms. A double-blind design was considered not suitable for this study as it would require double-dummy treatment and thus daily sham injections for the two fingolimod arms. Daily sham injections for the majority of study patients in a study of 12-month duration are not considered to be ethical.

The confirmation of relapses as the primary outcome measure by a blinded rater, and the dose blinding between the two doses of fingolimod, will provide sufficient protection against bias, as will the full blinding of all MRI endpoints. ARR has been selected as primary endpoint as it represents a clinically relevant measure of disease activity and allows determination of treatment effect within 12 months.

[redacted]

[redacted]

3.3 Rationale of dose/regimen, duration of treatment

In previous Phase III studies in patients with RRMS, the doses of fingolimod 0.5 mg and fingolimod 1.25 mg were tested. Both doses showed similar efficacy in terms of relapse rate reduction, imaging parameters, and disability progression. The fingolimod 0.5-mg dose demonstrated a favorable safety profile compared with the fingolimod 1.25-mg dose based on the incidence of specific AEs of interest and the overall study drug discontinuation rate.

The minimal effective dose may not have been identified in the clinical development program, although the exposure-response model based on the ARR and T2 lesion count suggests that fingolimod 0.5 mg lies at the inflection point of the dose-response curve and that further reduction of the dose would lead to a reduction in treatment effect. Based on discussions with the FDA, the sponsor agreed to conduct further efficacy and safety assessments using a lower dose of fingolimod, with the 0.25 mg dose being the agreed-upon dose to study.

A 1-year treatment duration is suitable to detect the anticipated differences in treatment effect on relapse rate between drugs in this study.

3.4 Rationale for choice of comparator

In this study, the efficacy and safety of fingolimod 0.25 mg and fingolimod 0.5 mg will each be compared to glatiramer acetate 20 mg SC. An active comparator with established efficacy has been chosen as control for this study since placebo treatment for a duration of 1 year is not considered ethically acceptable, given the availability of several disease-modifying drugs, including fingolimod, for treatment of the target population of this study.

Glatiramer acetate is the most commonly prescribed disease modifying drug (DMD) in the United States and several other countries. Therefore it represents an acceptable alternative to treatment with fingolimod and an appropriate comparator in this study.

[redacted]

3.5 Purpose and timing of interim analyses/design adaptations

Not applicable.

4 Population

The study population will consist of adult male and female patients with RRMS who meet all of the inclusion criteria and none of the exclusion criteria defined in Section 4.1 and Section 4.2, respectively. Treatment-naïve patients and patients previously treated with disease-modifying therapies for MS, with the exception of S1P modulator therapy, are eligible

[redacted]

to participate in the study. Patients being treated with first-line DMDs at the screening visit can continue drug intake up to the day before Day 1 of this study (i.e., there is no need for a washout period).

The original anticipated total number of patients to be screened was approximately 3190, with approximately 2550 patients randomly assigned to the study treatment arms in a ratio of 1:1:1 under the assumption of a 20% screening failure rate. In protocol amendment 2, the anticipated total number of patients to be screened is reduced to approximately 2610. The screening failure rate is estimated to be 25% and a total of 1960 randomized patients are targeted. After the introduction of protocol amendment 2, and IRB approval at all sites in all countries, a new randomization ratio of 5:3:2 will be used for the 3 treatment arms of fingolimod 0.25 mg, fingolimod 0.5 mg, and glatiramer acetate 20 mg.

Refer to Section 9.6 (Sample Size Calculations) for details.

The inclusion and exclusion criteria will be assessed at Screening and Randomization Visit (before patient is randomly assigned to treatment using an interactive voice response system [IVRS]). The results of all screening assessments must be available before randomization. A subject who is under screening but has not been enrolled due to failure to meet the inclusion criteria or failure to be randomized within the specified time per protocol, may be considered for re-screening if a change in the patient's medical status or a modification of the study's eligibility criteria makes the patient potentially eligible. Re-screening will be allowed on a case-by-case basis upon approval by the study Medical Monitor. A new informed consent form should be signed in case of re-screening and a new number will be assigned to the subject. The required re-screening procedures should be discussed with the Medical Monitor.

4.1 Inclusion criteria

Patients eligible for inclusion in this study have to fulfill all of the following criteria:

1. Written informed consent must be obtained before any assessment is performed [redacted]
2. Male and female patients 18 to 65 years of age, inclusive
3. Patients with RRMS, as defined by 2010 revised McDonald criteria (Appendix 2)
4. Patients must be neurologically stable with no onset of relapse within 30 days of randomization
5. Patients with at least 1 documented relapse during the previous year or 2 documented relapses during the previous 2 years before randomization
6. Patients with an Expanded Disability Status Scale (EDSS) score of 0 to 6.0, inclusive, at Screening. A score of 6.0 indicates unilateral assistance (cane or crutch) required to walk at least 100 meters with or without resting.

4.2 Exclusion criteria

Patients fulfilling **any** of the following criteria are not eligible for inclusion in this study:

1. Patients with a history of malignancy of any organ system (other than cutaneous basal cell carcinoma) in the last 5 years that do not have confirmation of absence of a malignancy prior to randomization.

[redacted]

2. Patients with an active chronic disease (or stable but treated with immune therapy) of the immune system other than MS (e.g., rheumatoid arthritis, scleroderma, Sjogren's syndrome, Crohn's disease, ulcerative colitis) or with a known immunodeficiency syndrome (HIV-antibody positive, AIDS, hereditary immune deficiency, drug-induced immune deficiency).
3. Patients who have been treated with:
   - Intravenous (IV) immunoglobulin (Ig) within 4 weeks before randomization.
   - Immunosuppressive/chemotherapeutic medications (e.g., azathioprine, cyclophosphamide, methotrexate) within 6 months before randomization.
   - Natalizumab within 2 months before randomization.
   - Previous treatment with lymphocyte-depleting therapies (e.g. rituximab, alemtuzumab, ofatumumab, ocrelizumab, or cladribine) within 1 year before randomization.
   - Previous treatment with mitoxantrone within 6 months before randomization.
   - Use of teriflunomide within 3.5 months prior to randomization, except if active washout (with either cholestyramine or activated charcoal) was done. In that case plasma levels are required to be measured and be below 0.02 mg/L before randomization.

   No washout period is necessary for patients treated with dimethyl fumarate, IFN beta, or glatiramer acetate. Patients being treated with dimethyl fumarate, glatiramer acetate, or IFN beta at the screening visit can continue drug intake up to the day before Day 1 of this study (i.e., there is no need for a washout period).
4. Patients who have been treated with systemic corticosteroids or adrenocorticotropic hormones in the past 30 days prior to the screening MRI procedure.
5. Patients with uncontrolled diabetes mellitus (glycosylated hemoglobin [HbA1c] >9%) or with diabetic neuropathy.
6. Patients with a diagnosis of macular edema during Screening (patients with a history of macular edema will be allowed to enter the study provided that they do not have macular edema at Screening).
7. Patients with severe active bacterial, viral, or fungal infections.
8. Patients without acceptable evidence of immunity to varicella zoster virus (VZV) at randomization (See Appendix 3 for guidance on acceptable evidence of immunity and requirement for serologic testing).
9. Patients who have received any live or live-attenuated vaccines (including for VZV, herpes simplex, or measles) within 1 month before randomization.
10. Patients who have received total lymphoid irradiation or bone marrow transplantation.
11. Patients with any unstable medical/psychiatric condition, as assessed by the primary treating physician at each site.

[redacted]

12. Patients who in the last 6 months experienced any of the following cardiovascular conditions or findings in the screening ECG:
    - Myocardial infarction
    - Unstable angina
    - Stroke
    - Transient ischemic attack
    - Decompensated heart failure requiring hospitalization or Class III/IV heart failure

(Additional monitoring guidelines for patients with any pre-existing cardiovascular conditions are provided in Section 5.5.5.)

13. Patients with history or presence of a Mobitz Type II AV block, or a third-degree AV block or sick sinus syndrome, unless patient has a functioning pacemaker.
14. Patients with baseline QTc interval >500 msec.
15. Patients receiving Class Ia (e.g., ajmaline, disopyramide, procainamide, quinidine) or Class III antiarrhythmic drugs (e.g., amiodarone, bretylium, sotalol, ibutilide, azimilide, dofetilide).
16. Patients with severe respiratory disease, pulmonary fibrosis, or Class III or IV chronic obstructive pulmonary disease, or with clinically significant lung pathology on chest x-ray. Patients with controlled asthma are allowed to enter the study.
17. Patients with any of the following hepatic conditions:
    - severe hepatic injury (Child-Pugh Class C)
    - total bilirubin greater than 2 times the upper limit of the reference range, unless in context of Gilbert's syndrome
    - conjugated bilirubin greater than 2 times the upper limit of the reference range
    - aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 2 times the upper limit of the reference range
    - alkaline phosphatase (AP) greater than 2 times the upper limit of the reference range
    - gamma glutamyl-transferase (GGT) greater than 2 times the upper limit of the reference range
18. Patients with a screening WBC count $<3500/mm^3$ or lymphocyte count $<800/mm^3$.
19. Patients with any of the following neurologic/psychiatric disorders:
    - history of substance abuse (drug or alcohol) in the past 5 years or any other factor (i.e., serious psychiatric condition) that may interfere with the patient's ability to cooperate and comply with the study procedures
    - progressive psychiatric/neurological condition that may affect participation in the study
20. Patients who have received an investigational drug or therapy within 180 days or 5 half-lives of randomization, whichever is longer.
21. Patients with a history of hypersensitivity to any of the study drugs, to drugs of similar chemical classes, or to mannitol.

[redacted]

22. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin laboratory test.
23. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, UNLESS they are using highly effective contraception during dosing with study treatment. Highly effective contraception includes:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    - Male partner sterilization (at least 6 months prior to Screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient.
    - Use of oral, injected, or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example, hormone vaginal ring or transdermal hormone contraception, placement of an intrauterine device or intrauterine system.

    Women are considered post-menopausal and not of child-bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to Baseline. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.
24. Patients who have previously been treated with glatiramer acetate discontinued treatment due to lack of efficacy or tolerability.
25. Patients with a history of treatment with fingolimod.
26. Patients with a score of 4 or 5 on the Suicidal Ideation item of the Columbia-Suicide Severity Rating Scale (C-SSRS) within 2 years of Screening, or any “yes” on the Suicidal Behavior item of the C-SSRS at Screening.

[redacted]

5 Treatment

5.1 Investigational and control treatment

Investigational drug

- Fingolimod (FTY720) 0.5 mg capsules for oral administration once daily
- Fingolimod (FTY720) 0.25 mg capsules for oral administration once daily

Both strengths of fingolimod capsule will be identical in appearance and will be packaged in identical bottles. Medication labels will comply with the legal requirements of each country and be printed in the local language. The medication labels will supply the medication number and information on storage conditions.

Control drug

- Glatiramer acetate 20 mg SC injection once daily.

The medication labels will supply information on storage conditions.

5.2 Treatment arms

There are 3 treatment arms. In the study, patients will be randomized to fingolimod 0.5 mg, fingolimod 0.25 mg, or glatiramer acetate 20 mg (for details about the randomization, see Section 9.6 – Sample size calculation).

5.3 Treatment assignment

At the Randomization Visit, all eligible patients will be randomized via interactive voice response system (IVRS) to 1 of the three treatment arms. The investigator, who is usually the treating physician or his /her delegate, will contact the IVRS after confirming that the patient fulfills all the inclusion/exclusion criteria. The IVRS will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study drug to be dispensed to the patient. The randomization number will not be communicated to the caller.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IVRS provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of [redacted] using a validated system that automates the random assignment of medication numbers to study drug packs containing each of the study drugs.

The randomization scheme for patients will be reviewed and approved by [redacted] Biostatistics randomization team.

[redacted]

5.4 Treatment blinding

In order to maintain rater-blinding, all efficacy assessments will be obtained by an Independent Evaluating Physician who must not otherwise be involved with any aspects of patient care and management. Patient care and management and other aspects of the conduct of the study at the study site will be under the responsibility of the Treating Physician.

The independent evaluating physician will remain blinded until the database lock and data analysis has been completed. In order to maintain rater-blinding, all patients will be instructed to wear appropriate clothing to completely cover typical or actual injection sites before all scheduled visits and relapse-related neurologic examinations, and not to discuss their treatment or AEs (e.g., injection site reactions) with the independent evaluating physician. These instructions will also be included on the appointment reminder cards. This procedure is essential to maintain the blinding of the efficacy assessments during the study. The treating physician and all other study staff should not discuss study treatment or AEs with the independent evaluating physician in order to maintain the "rater blind."

All patients receiving injections will be known to the treating physician to be in the glatiramer acetate treatment arm, therefore, only patients receiving oral study drug will require first dose safety monitoring visit to be performed by the treating physician.

To maintain blinding of treatment assignment, all patients will receive the same cooling bag to carry study drug.

Because of the extended duration of first-dose monitoring of patients receiving fingolimod, it is recommended that first-dose monitoring is performed, as far as possible, in a manner that prevents blinded site personnel from becoming aware of the duration of the monitoring period.

In order to maintain the blind for Novartis [redacted] staff, manual review of data listings that could potentially unblind personnel will be performed by reviewers who are independent of the study team.

5.5 Treating the patient

5.5.1 Patient numbering

Each patient is uniquely identified in the study by a combination of his/her center number and patient number. The center number is assigned by Novartis [redacted] to the investigative site. Upon signing the informed consent form, the patient is assigned a patient number by the investigator. At each site, the first patient is assigned patient number 1, and subsequent patients are assigned consecutive numbers (e.g., the second patient is assigned patient number 2, the third patient is assigned patient number 3). The investigator or his/her staff will contact the IVRS and provide the requested identifying information for the patient to register them into the IVRS. Only the assigned patient ID will be uploaded automatically in the database. Once assigned to a patient, the patient number will not be reused. If the patient fails to be randomized for any reason, the IVRS must be notified as far as possible within 2 days that the patient was not randomly assigned. The reason for not being randomized will be entered on the screening log, and the demography eCRF should also be completed.

[redacted]

5.5.2 Dispensing the study treatment

Each study site will be supplied with study drug for each treatment arm. One component of the packaging has a 2-part label.

For fingolimod, each part of the label contains a medication number. At all drug dispensation visits, investigator staff will identify the fingolimod study drug package to dispense to the patient by calling the IVRS and obtaining the medication number.

In countries where the label contains a medication number, site staff will identify the glatiramer acetate study drug package to dispense to the patient by calling the IVRS and obtaining the medication number. In countries where the glatiramer acetate label does not contain a medication number, glatiramer acetate will be dispensed from bulk stock at the site. The IVRS will still be involved in tracking dispensation of glatiramer acetate study drug.

Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (drug label form) containing that patient's unique patient number.

5.5.3 Supply, storage, and tracking of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Upon receipt, all study drugs should be stored refrigerated according to the instructions specified on the drug labels. Clinical supplies are to be dispensed only in accordance with the protocol.

Medication labels will be in the local language and will comply with the legal requirements of each country. They will include storage conditions for the drug but no information about the patient except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study drug in a drug accountability ledger. Monitoring of drug accountability will be performed by the [redacted] field monitor during site visits and at the completion of the trial. Patients will be asked to return all unused study drug and packaging at the end of the study or at the time of study drug discontinuation.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all used and unused study drug, packaging, drug labels, and a copy of the completed drug accountability ledger to the [redacted] monitor or to the address provided in the investigator folder at each site.

Blinded study drug (fingolimod) and glatiramer acetate will be provided to the study centers; no study drug will need to be purchased locally. Fingolimod and glatiramer acetate should be stored in a limited-access area, according to the instructions on the study drug label.

5.5.4 Instructions for prescribing and taking study treatment

The study drugs (fingolimod 0.5-mg and 0.25-mg capsules and glatiramer acetate 20 mg) will be dispensed at the randomization visit (Visit 2). Drug will then be dispensed at scheduled Visits 3, 4, 5, and 6.

[redacted]

At Visits 2, 3, 4, 5, and 6, patients randomly assigned to fingolimod 0.25 mg or 0.5 mg will receive a bottled supply of oral medication containing a sufficient number of capsules until their next scheduled visit. At Visits 2, 3, 4, 5, and 6, patients randomly assigned to glatiramer acetate will receive a package containing a sufficient number of prefilled syringes to last until their next scheduled visit.

The fingolimod study drug needs to be taken once a day with or without food. Glatiramer acetate needs to be injected subcutaneously once a day. All study drugs should be administered preferably at the same time each day.

Site personnel will need to provide training to the patients or caregivers on the correct procedure for administration of SC injections. A patient leaflet will be provided with each supply of study drug. The patient leaflet describes information related to the study drug including: storage information, precautions, and instructions for administering SC injections. This information should be reviewed with the patients to ensure that they understand the correct procedure.

Once the eligibility of a patient for entry into the Treatment Period has been confirmed based on the study inclusion/exclusion criteria, the site will contact the IVRS to obtain a randomization number to identify study drug. Before administration of the first dose of the study drug, the investigator should reconfirm a list of concomitant medications taken by the patient.

The first dose of study drug is administered at the randomization visit (Visit 2). The treating physician will monitor the first dose intake in the clinic for at least 6 hours or longer if discharge criteria are not met in those patients receiving oral study drug (fingolimod) (see Section 5.5.5 for guidance for monitoring of patients taking their first dose of the study drug). Patients receiving injectable study drug do not require prolonged monitoring in the clinic after the first dose.

Throughout the study, careful planning of patient visits is required to make sure that the patients will have enough study drug to last until the next scheduled visit.

The investigator and study personnel should promote compliance by instructing the patient to take the study drug exactly as prescribed and by stating that compliance is necessary for the patient's safety and for the validity of the study. The patient should be instructed to contact the site if he or she is unable for any reason to take the study drug as prescribed.

All doses prescribed and dispensed to the patient and all dose interruptions during the study will be recorded in the IVRS and drug administration record in the eCRF.

5.5.5 Guidelines for monitoring patients taking their first dose of fingolimod

The patient will stay at the site for a minimum of 6 hours after the first dose of fingolimod to be monitored for signs and symptoms of bradycardia. All fingolimod patients will have an ECG performed prior to dosing and at the end of the 6-hour monitoring period. (Glatiramer acetate patients will have a single ECG during the randomization visit.) The treating physician is responsible for monitoring the patient following the first intake of fingolimod, as well as managing bradycardia symptoms should they occur. He or she must review vital signs during the 6-hour monitoring, post-dose ECG and assess discharge criteria at 6 hours after dosing.

[redacted]

Baseline or predose ECG should be provided by the site and be available for comparison to the postdose ECG in order to determine if discharge criteria are met.

Heart rate and blood pressure should be measured before the first dose of fingolimod, then every hour for at least 6 hours thereafter (by the treating physician or an assisting nurse). Blood pressure will be measured in the supine position and then the standing position at each time point. When obtaining the predose heart rate before the first dose, the patient should be allowed to rest in the supine position for 5 minutes before taking the heart rate. The heart rate and blood pressure measurements should be repeated twice to produce 3 baseline readings in the supine position for both heart rate and blood pressure (before the first dose of fingolimod only). Heart rate and blood pressure will then be measured in the same manner (i.e., 3 baseline readings) with the patient in the standing position before the first dose of fingolimod. For comparison to the postdose heart rate values, the lowest predose supine value and lowest predose standing value of heart rate should be used. Patients should receive the first dose of fingolimod before 12:00 PM (noon) in the outpatient setting.

Patients may be discharged after 6 hours ONLY if ALL of the following criteria are met:

- supine heart rate must be at least 45 beats per minute
- heart rate must not be the lowest hourly value measured during the observation period (which would suggest that nadir may not have been reached)
- patients must have no symptoms associated with decreased heart rate or must not have received treatment for bradycardia
- ECG at 6 hours after dosing should not show any new significant abnormalities (e.g., onset second-degree or third-degree AV block, QTc ≥500 msec) other than sinus bradycardia, that were not also observed at the patient's predose ECG

If the discharge criteria listed above are not met after 6 hours, observation must be continued until symptoms resolve.

If a patient requires treatment for bradycardia/bradyarrhythmia during the first dose observation, the patient should be monitored overnight, and the 6-hour monitoring procedure should be repeated for the second dose of study drug.

If a patient experiences a QTc interval greater than or equal to 500 msec at 6 hours after the first dose, the patient should be monitored overnight, and the 6-hour monitoring procedure should be repeated for the second dose of study drug.

Patients with some pre-existing conditions (e.g., ischemic heart disease, history of myocardial infarction, congestive heart failure, history of cardiac arrest, cerebrovascular disease, uncontrolled hypertension, history of symptomatic bradycardia, history of recurrent syncope, severe untreated sleep apnea, AV block, sinoatrial heart block) may poorly tolerate the fingolimod-induced bradycardia, or experience serious rhythm disturbances after the first dose of fingolimod. Prior to treatment with fingolimod, these patients should have a cardiac evaluation by a physician appropriately trained to conduct such evaluation, and, if treated with fingolimod, should be monitored overnight with continuous ECG in a medical facility after the first dose.

Since initiation of fingolimod treatment results in decreased heart rate and may prolong the QT interval, patients with a prolonged QTc interval (>450 msec males, >470 msec females)

[redacted]

before dosing or during a 6-hour observation period, or at additional risk for QT prolongation (e.g., hypokalemia, hypomagnesemia, congenital long-QT syndrome), or on concurrent therapy with QT-prolonging drugs with a known risk of torsades de pointes (e.g., citalopram, chlorpromazine, haloperidol, methadone, erythromycin) should be monitored overnight with continuous ECG in a medical facility.

Experience with fingolimod is limited in patients receiving concurrent therapy with drugs that slow heart rate or AV conduction (e.g., beta blockers, heart rate lowering calcium-channel blockers such as diltiazem or verapamil, or digoxin). Because the initiation of fingolimod treatment is also associated with slowing of the heart rate, concomitant use of these drugs during fingolimod initiation may be associated with severe bradycardia or heart block. The possibility of switching to drugs that do not slow the heart rate or AV conduction should be evaluated by the physician prescribing these drugs before initiating fingolimod. Patients who cannot switch should have overnight continuous ECG monitoring after the first dose.

In addition to protocol mandated safety assessments and monitoring procedures, additional assessments may be required as per local prescribing information and should be followed accordingly.

Patients should have written instruction on when to return to clinic and a 24-hour contact phone number to call in the event of any new or warranted symptoms (e.g., chest pain, dizziness, palpitations, syncope, nausea, vomiting). Patients should be instructed not to drive on the same day after the first dose of fingolimod administration.

Recommendations for management of bradycardia

Prior to the administration of study drug, if, in the opinion of the investigator, the patient's cardiovascular condition or medical history carry a significant risk for study participation, the patient should not be enrolled in the study, and the advice of a cardiologist should be sought.

Atropine (SC or IV) is recommended as the first line treatment of bradycardia, up to a maximum daily dose of 3 mg.

Furthermore, the common guidelines for treatment of bradycardia (e.g., ACLS guidelines) should be followed as appropriate:

- In case of clinical symptoms or hypotension, administration of atropine 1 mg, repeated administration in 3-5 minutes
- If heart rate and/or blood pressure remains unresponsive, consider administration of dopamine drip 5-20 ug/kg/min or epinephrine drip 2-10 ug/min
- Performance of transcutaneous pacing may also be considered

In the setting of decreased blood pressure, isoproterenol should be avoided/used with caution.

5.5.6 Permitted dose adjustments and interruptions of study treatment

Dose adjustments will not be allowed; however, drug interruptions will be allowed based on the judgment of the investigator. If an investigator determines that study drug should be stopped, then the SC injections or oral capsules, respectively, need to be stopped. Conditions or events that may lead to study drug interruptions based on investigator judgment and overall clinical assessment are:

[redacted]

- SAE
- emergency medical condition or unplanned hospitalization involving the use of prohibited medications (Section 5.5.9)
- abnormal laboratory value(s) or abnormal test or examination result(s) (e.g., ECG values, ophthalmic findings). See Appendix 3 and Appendix 4 for guidance on monitoring of patients with specific test abnormalities
- hypersensitivity to the study drug
- patient noncompliance
- vaccination

The 6-hour monitoring procedure when restarting study drug is mandatory in the following cases:

- 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 lasted for 4 weeks or more and was interrupted for more than 14 consecutive days.

Should a patient randomized to one of the fingolimod treatment arms interrupt the study drug as described above and should the investigator decide to reinitiate treatment with the study drug, the first dose intake at restart must take place at the study site to ensure at least 6-hour monitoring by the treating physician in a similar manner as the first intake of the study drug (see for guidelines for monitoring of patients taking their first dose of the study drug in Section 5.5.5).

A reason for the interruption of treatment and dates of interruption should be documented in the source documents as well as in the dosage administration eCRF.

5.5.7 Recommendations on treatment of multiple sclerosis relapse

A standard course of intravenous corticosteroids (methylprednisolone) on an inpatient or outpatient basis is allowed for treatment of relapses as clinically warranted. Steroid treatment should consist of 3 to 5 days and up to 1000 mg methylprednisolone/day.

Standard-of-care procedures will be followed during treatment of relapses.

Use of any oral tapering is not permitted.

The use of steroid therapy should be recorded in the use of steroids for treatment of relapses eCRF. Refer to Section 6.4.3 for the instruction on conduct of the study MRI during relapse and steroid treatment.

Investigators should consider the added immunosuppressive effects of corticosteroid therapy and increase vigilance regarding infections during such treatment and in the weeks following administration.

Should a patient show evidence or suspicion of infection, please refer to the guidance on monitoring of patients with infections outlined in Appendix 3.

[redacted]

Should a patient develop any neurological symptoms or signs, unexpected for MS in the opinion of the investigator or accelerated neurological deterioration, the investigator should immediately schedule an MRI and follow the guidance on monitoring of patients with symptoms or signs of neurological deterioration inconsistent with MS outlined by Appendix 3. Steroids should not be taken before conducting the unscheduled MRI.

5.5.8 Concomitant treatment

All concomitant medications taken within 30 days before Screening (Visit 1) and during the study must be recorded. Both the start date and the end date for each medication should be captured on the prior medications/significant nondrug therapies eCRF, the previous MS treatment eCRF, the concomitant medications/significant nondrug therapies eCRF, and the steroid treatment of MS relapses eCRF.

Patients taking dimethyl fumarate, glatiramer acetate, or IFN beta before study entry may continue to take this medication up to the last day before randomization. These patients will be randomly assigned to and start study drug on the day of their next scheduled dose.

A standard short course of corticosteroids (methylprednisolone IV) is allowed for treatment of relapses (Section 5.5.7). Treatment with topical corticosteroids in the eyes, ears, or nose, on the skin or through inhalation, is also allowed, if the potential systemic absorption of the corticosteroid component due to that treatment can be regarded as negligible and the condition being treated does not warrant study discontinuation per protocol. If a course of systemic corticosteroid treatment is required for treatment of uveitis, this is also acceptable.

The medications allowed for the treatment of adverse reactions and relapses are not considered study supplies and, therefore, need to be supplied by the study site.

Medications for the symptomatic treatment of MS such as baclofen, fampridine, methylphenidate, or modafinil are acceptable. As far as possible, every effort should be made to keep the dosages stable from Screening through EOT.

The investigator should instruct the patient to notify the study site about any new medications that they take after the start of the study drug. All medications and significant nondrug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug must be recorded on the concomitant medications/significant nondrug therapies eCRF and steroid therapies eCRF.

5.5.9 Prohibited treatment

Use of the following treatments is NOT allowed after randomization:

- Immunosuppressive medication (e.g., cyclosporine, azathioprine, methotrexate, cyclophosphamide, mitoxantrone, cladribine)
- Other concomitant medications: immunoglobulins, monoclonal antibodies (including natalizumab), IFN beta, adrenocorticotropic hormone, other disease-modifying medications approved for MS including those approved subsequent to the start of this study

The administration of any live or live-attenuated vaccine (including for measles) is prohibited while patients are receiving fingolimod and for 8 weeks after fingolimod discontinuation.

[redacted]

5.5.10 Discontinuation of study treatment and premature patient withdrawal

Patients may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

If premature withdrawal occurs for any reason, the investigator must make every effort to determine the primary reason for a patient's premature withdrawal from the study and record this information on the study completion eCRF.

Patients may be withdrawn from the study for any of the following reasons:

- Withdrawal of the informed consent
- Lost to follow-up
- Withdrawal at the investigator's discretion

Patients who discontinue study drug should NOT be considered withdrawn from the study unless one of the previous reasons apply. These patients are required to follow the abbreviated schedule of assessment (see Table 6-2). Patients who discontinue the study drug should be treated according to the best standard of care. Protocol violations should not lead to patient withdrawal unless they indicate a significant risk to the patient's safety.

For patients who are lost to follow-up (i.e., those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should show due diligence by documenting in the source documents steps taken to contact the patient (e.g., dates of telephone calls, registered letters). In case of death, a patient will be considered withdrawn from the study.

The appropriate personnel from the site and Novartis [redacted] will assess whether study treatment should be discontinued for any patient whose treatment code has been broken inadvertently for any reason. Patients who discontinue study treatment should NOT be considered withdrawn from the study. A Study Drug Discontinuation Form should be completed, giving the date and primary reason for stopping study treatment. See Section 6 for the required assessments of these patients after discontinuation of study treatment. The investigator must also contact the IVRS to register the patient's discontinuation from study drug.

5.5.11 Emergency unblinding of treatment assignment for patients on fingolimod

Emergency unblinding should only be undertaken when it is essential to treat the patient safely and efficaciously. Most often, study drug discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency code breaks are performed using the IVRS. When the investigator contacts the system to unblind a patient, he or she must provide the requested patient identifying information and confirm the necessity to unblind the patient. The investigator will then receive details of the drug treatment for the specified patient and a fax or e-mail confirming this information. The system will automatically inform the [redacted] monitor for the site and the clinical leader at Novartis [redacted] that the code has been broken.

[redacted]

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IVRS in case of emergency. The investigator will inform the patient how to contact his/her backup in cases of emergency when he or she is unavailable. The investigator will provide protocol number, study drug name if available, patient number, and instructions for contacting the local Novartis CPO (or any entity to which it has delegated responsibility for emergency code breaks) to the patient in case emergency unblinding is required at a time when the investigator and backup are unavailable.

5.5.12 Study completion and post-study treatment

The study will be considered completed for an individual patient when he or she completes Visit 7/EOT.

Patients who are prematurely withdrawn from the study will not be replaced.

The investigator also must provide follow-up medical care for all patients who are prematurely withdrawn from the study or must refer them for appropriate ongoing care.

5.5.13 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated as described in Table 6-2 for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the institutional review boards (IRBs) or independent ethics committees (IECs) of the early termination of the trial.

6 Visit schedule and assessments

The assessment schedule listing all assessments and visits to be performed under this protocol is provided in Table 6-1.

Starting at Visit 3, the visit window for all study visits is ±5 days. Sites are encouraged to comply with this visit window as much as possible. Follow-up will occur within 3 months after the last dose of study drug for all patients (i.e., 3 months from the last study drug dose/EOT for patients who completed the study or 3 months from the last study drug dose for patients who were discontinued from the study). For any patients who permanently discontinue study drug early but decide to continue in the study, if the follow-up visit falls within the visit window for a scheduled visit, then assessments for both visits should be combined and completed. In addition to the scheduled visits, patients may have unscheduled visits following an onset of MS relapse or for other reasons as indicated in the protocol. All information should be collected per the unscheduled visit eCRF.

Table 6-1 Assessment schedule

Period	Screening	Treatment Period						FU[a]
Visit	1	2	3	4	5	6	7/EOT	
Month	Day –45 to –1	Day 1 Randomization	1	3	6	9	12	EOT +3
Visit window (days)			±5	±5	±5	±5	±5	±5
Obtain informed consent	X							
Background/demography	X							
Inclusion/exclusion criteria	X	X						
Medical history	X							
MS history/MS treatment	X							
Prior/concomitant medication	X	X	X	X	X	X	X	X
Pregnancy test (serum)	X							
Pregnancy test (urine dipstick)		X	X	X	X	X	X	X
Physical examination	X			X			X	X
Ophthalmologic examination[b]	X			X	X		X	
Dermatology examination	X						X	
Randomization		X						
Vital signs[c]/body weight	X	X	X	X	X	X	X	X
Pulmonary function tests	X				X		X	X
12-lead electrocardiogram	X	X[d]					X	
Blood chemistry and hematology	X		X	X	X	X	X	X
Retrospective analysis blood sample	X							
[redacted]								
Serology	X							
[redacted]								
First-dose monitoring		X						
Urinalysis	X	X	X	X	X	X	X	X
Study drug dispensation		X	X	X	X	X		
Study drug accountability			X	X	X	X	X	
Magnetic resonance imaging	X						X	
EDSS	X						X	X
[redacted]								
MS relapse[g]	X	X	X	X	X	X	X	X
[redacted]								
TSQM	X				X		X	
C-SSRS	X	X		X	X	X	X	X
Adverse events/SAEs	X	X	X	X	X	X	X	X
Study completion form							X	

Abbreviations: C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; EDSS=expanded disability status scale; EOT=end of treatment; FU=follow-up; HSV=herpes simplex virus; MS=multiple sclerosis; [redacted]; SAE=serious adverse event; [redacted]; TSQM=treatment satisfaction questionnaire for medication.

a. Follow-up will occur 3 months (12 weeks) after the last dose of study drug for all patients.

b. The ophthalmology examination will include eye history, visual acuity, dilated ophthalmoscopy, and any procedures necessary to assess macular edema. Optical coherence tomography and fluorescein angiography will be done only if needed to confirm macular edema.

c. Body temperature is collected only at Screening, Visit 7/EOT, and at the follow-up visit.

d. A 12-lead ECG will be performed before fingolimod and glatiramer acetate administration, and 6 hours after the fingolimod administration only.

[redacted]

e. Patients will be tested for human immunodeficiency virus, varicella zoster virus (as per guidance in Appendix 3), HSV-1, HSV-2, and rubeola virus.

[redacted]

g. Patients should report symptoms indicative of a relapse at a scheduled visit or at any other time and will be instructed to immediately contact the treating physician if they develop new or reoccurring or worsening neurological symptoms. A neurological examination by the independent evaluating physician must be arranged **as soon as possible, preferably** within 7 days of the onset of symptoms.

[redacted]

Table 6-2 Abbreviated schedule of assessments for patients who discontinue study drug

Period	**Off-Treatment**		
Visit	**5**	**6**	**7/EOS**
Month	**6**	**9**	**12**
Visit window (days)	**±5**	**±5**	**±5**
MS relapses[a]	X	X	X
MS treatment/steroids	X	X	X
Concomitant medications	X	X	X
Magnetic Resonance Imaging			
EDSS			X
[redacted]			
TSQM			X
C-SSRS	X	X	X
Physical exam	X		X
Ophthalmologic exam[c]			X
Dermatology examination			X
Vital signs[d]/body weight	X	X	X
Pulmonary function tests			X
Laboratory values	X[e]	X[e]	X
[redacted]			
Adverse events	X	X	X
SAE reporting	X	X	X

Abbreviations: C-SSRS=Columbia-Suicide Severity Rating Scale; EDSS=expanded disability status scale; EOS=end of study; MS=multiple sclerosis; [redacted]; SAE=serious adverse event; [redacted]; TSQM=treatment satisfaction questionnaire for medication.

a. Patients should report symptoms indicative of a relapse at a scheduled visit or at any other time and will be instructed to immediately contact the treating physician if they develop new or reoccurring or worsening neurological symptoms. A neurological examination by the independent evaluating physician must be arranged **as soon as possible, preferably** within 7 days of the onset of symptoms.

[redacted]

c. The ophthalmology examination will include eye history, visual acuity, dilated ophthalmoscopy, and any

[redacted]

procedures necessary to assess macular edema. Optical coherence tomography and fluorescein angiography will be done only if needed to confirm macular edema.

d. Body temperature is collected only at Visit 7/EOS.

e. Urinalysis only.

[redacted]

6.1 Information to be collected on screening failures

Those patients who have signed informed consent and fail to meet all inclusion/exclusion criteria will not be randomized and will be deemed screening failures. A reason will be documented on the screening log eCRF.

6.2 Patient demographics/other baseline characteristics

Demographic data will be collected and recorded in the demography eCRF including date of birth, sex, and race. Multiple sclerosis history and previous MS treatment will be recorded in the MS history and previous MS treatment eCRF pages, respectively. The majority of evaluations (Table 6-1) will be performed at Screening. Only review of inclusion/exclusion criteria, vital signs, ECG, and urine pregnancy test (if applicable) will be repeated at Day 1, (randomization). The baseline laboratory values should be available before randomization (part of assessment of inclusion/exclusion criteria).

The treating physician will ask about relevant diseases of the following organs and organ systems: skin; eyes, ears, nose, throat, head and neck (including the thyroid); lungs; heart; breasts; abdomen; lymph nodes; musculoskeletal (including extremities and spine); genitourinary, gynecological organs; and rectum. History of allergies, in particular with respect to Gd-diethylenetriamine penta-acetic acid (Gd-DTPA) will be queried. Patients will be asked if they have a history of alcohol or drug abuse or a history of psychiatric disorders. Any previous disease or surgeries will also be documented. Medical history should be supplemented by review of the patient's medical chart and/or by documented dialog with the patient's treating physician. The source of information will be recorded in the relevant medical history/current medical conditions eCRF.

Previous MS history (including history of relapses) needs to be documented in the patient's medical chart and/or in documented dialog with the patient's treating physician.

Information relating to MS history will be collected in the study including: date of MS diagnosis, date of MS symptoms, eye history (e.g., optic neuritis or uveitis), MS relapse history (i.e., number of relapses since first MS symptoms and number of relapses that required steroid treatment), and history of medications used to treat MS. These data will be collected and recorded in the MS medical history, ophthalmology screening, and MS treatment eCRFs. Medications used to treat MS may include glatiramer acetate, IM IFN beta-1a, SC IFN beta-1a, IFN beta-1b, natalizumab, azathioprine, methotrexate, or any other medications used as MS treatments.

During the study medications to treat MS-related symptoms should be recorded in the concomitant medication eCRF. Multiple sclerosis history should be supplemented by review of the patient's medical chart and/or by documented dialog with the patient's primary treating physician.

[redacted]

In patients with diabetes, diabetes-specific medical history to be collected and recorded in the eCRF will include type 1 vs. type 2, date of diabetes diagnosis, antidiabetic therapy, and presence of diabetes-related complications.

6.3 Treatment exposure and compliance

In order to collect accurate information about the study drug exposure, the following records should be maintained for each randomly assigned patient: records of study drug dispensed and returned, dosages administered (in blinded fashion) and intervals between visits. These data should be transcribed on the dosage administration record eCRF.

Compliance will be assessed by the investigator and/or study personnel at each visit using capsule and syringe counts and information provided by the patient. A monitor will perform and document drug accountability during site visits and at the end of the study.

6.4 Efficacy

6.4.1 Multiple sclerosis relapse

Patients should be instructed to report symptoms indicative of an MS relapse at any time, regardless of whether a visit is scheduled. A patient must be instructed to immediately contact the study site if a new, reoccurring, or worsening neurological symptom develops.

- **General definition of relapse**: appearance of a new neurological abnormality or worsening of previously stable or improving preexisting neurological abnormality, separated by at least 30 days from onset of a preceding clinical demyelinating event. The abnormality must be present for at least 24 hours and occur in the absence of fever (<37.5°C) or infection.
- **Definition of confirmed relapse**: a relapse must be confirmed by the independent evaluating physician (neurologist). It is recommended that this occur as soon as possible but no more than 7 days from the onset of symptoms. A relapse is confirmed when it is accompanied by an increase of at least half a step (0.5) on the EDSS or an increase of 1 point on 2 different functional systems (FSs) of the EDSS or 2 points on 1 of the FS (excluding bowel and bladder and cerebral FSs).

Reporting of relapse

In order to maintain rater-blinding, a special coordination between the treating physician and the independent evaluating physician (blinded rater) must be followed for relapse assessment. A patient may report symptoms indicative of a relapse at a scheduled visit or at any other time. Patients will be instructed to immediately contact the treating physician if they develop new or reoccurring or worsening neurological symptoms.

Upon reporting symptoms indicative of a relapse, the treating physician will assess whether the symptoms had onset in the presence of fever or infection. If fever or infection can be excluded, a neurological examination by the independent evaluating physician must be arranged **as soon as possible, preferably** within 7 days of the onset of symptoms. If fever or infection cannot be excluded, the neurological examination will be postponed until the fever or the infection has ceased (provided that the symptoms indicative of a relapse are still

[redacted]

present). Treatment with steroids should not begin before the assessment by the independent evaluating physician.

Based on results of the neurological examination (change in FS and EDSS scores) provided by the independent evaluating physician, the treating physician will record if the relapse meets the criteria for "confirmed relapse" as per protocol [redacted]. All relapses, whether confirmed or unconfirmed, [redacted] should be recorded on the summary of MS relapses eCRF.

[redacted]

6.4.2 Expanded Disability Status Scale

The EDSS is a scale for assessing neurologic impairment in MS and will be used to confirm an MS relapse. It is a 2-part system including: (1) a series of scores in each of the 8 FSs and (2) steps ranging from 0 (normal) to 10 (death due to MS). The FSs are Visual, Brain Stem, Pyramidal, Cerebellar, Sensory, Bowel and Bladder, Cerebral, and other functions. Fatigue is not to be considered in determining the Cerebral Functional score.

The EDSS will be derived based on the neurological examination performed by the independent evaluating physician, a neurologist with experience with MS patients. Other qualified individuals (e.g., registered nurse or nurse practitioner) with documented experience in MS clinical trials might be considered for the role of EDSS rater if approved by Novartis' Medical Advisor. At site initiation, the EDSS rater must have received level "C" Neurostatus certification within the previous year unless the EDSS rater regularly performs the assessment, in which case the certification can be up to 2 years old. All EDSS raters must be recertified every 2 years. It is recommended that a backup EDSS rater be available at each site. The EDSS assessments will be done as detailed in Table 6-1 or Table 6-2 for patients that discontinued study drug or as needed during relapse assessments.

6.4.3 Magnetic Resonance Imaging (MRI)

All MRIs will be performed at the visits as indicated in Table 6-1 or Table 6-2 for patients that discontinued study drug.

The treating physician will be able to review all MRIs during the study. For analysis purposes, the scheduled MRIs will be reviewed and measures recorded by a blinded central MRI reader.

[redacted]

Restrictions for magnetic resonance imaging schedule

To avoid potential interference caused by steroids used for the treatment of MS relapses, the following restrictions apply for this study:

- In case of relapse, if an MRI is scheduled within 30 days of the initiation of steroid treatment, this MRI should be performed before steroid treatment is initiated
- No MRI scan should be performed while a patient is on steroid therapy or within 30 days after termination of steroid therapy

Scanning T1-weighted image before and after administration of contrast medium (0.1 mmol/kg Gd-DTPA) as well as T2-weighted (T2 and proton density) images will be performed.

The contrast agent may occasionally cause nausea and vomiting. Allergic reactions may also occur very rarely and, in extremely rare instances, can be potentially serious and require immediate anti-anaphylactic treatment (IV epinephrine, dopamine, steroids, etc.). The patients known to be allergic to Gd may participate in the trial with MRI assessment modified to forgo contrasted MRI images.

Before the start of the study, a radiologist and technician from each center will receive an MRI manual outlining technical implementation, image quality requirements, and MRI administrative procedures. Each site will be asked to program the MRI scanner that is designated for evaluation of the study patients and perform and submit a “dummy scan” or “dry run” to assess the image quality and to evaluate the compatibility of the electronic data carrier. Once the dummy scan has been approved by the central MRI reader, all parameter settings for the study-specific MRI sequences must remain unchanged for the duration of the study.

Data handling and evaluation

The quality of each scan performed will be assessed by the blinded MRI reader. As soon as the scan is received by the central MRI reading center, it will be evaluated for quality, completeness, and adherence to the protocol. Confirmation of MRI quality or a description of the quality problems, if detected, will be communicated to the site. If the scan is incomplete or incorrectly performed, the study center will be asked to repeat it as soon as possible. After completion of the quality check, all scans will be analyzed according to the MRI protocol.

6.5 Safety Assessments

Safety assessments include the following:

- Physical and neurological examination
- Vital sign measurements
- Laboratory evaluations
- ECG results
- Ophthalmologic examinations
- Pulmonary function tests (PFTs)
- Dermatological examination
- C-SSRS

6.5.1 Physical examination

A complete physical examination will be performed at visits as described in Table 6-1 or Table 6-2 for patients that discontinued study drug and will include an assessment of skin, head and neck, lymph nodes, heart, lungs, abdomen, and back, and comments on general appearance. Initial neurological examination (with fundoscopic examination) will be a part of the physical examination at Screening and if warranted by an unscheduled visit. Investigators

should ask the patient if they have any new or changed skin lesions as part of each physical examination. If skin lesions (suspected to be precancerous or cancerous) are identified during the physical examination, the patients should be referred to a dermatologist. (Also refer to Section 6.5.10 for dermatological examination).

All significant findings that are present at Screening must be reported on the relevant medical history/current medical conditions eCRF. Significant findings made after randomization that meet the definition of an AE must be recorded on the AEs eCRF.

Patients who experience new significant cardiac symptoms (e.g., congestive heart failure, new murmur, ischemic heart disease) or symptoms consistent with pulmonary hypertension (e.g., exertional dyspnea, chest pain, and syncope), should be referred to a specialist (e.g., cardiologist) for further diagnostic workup (e.g., echocardiography) and appropriate management as close as possible to the time of the onset of symptoms.

6.5.2 Vital signs

Vital signs will be collected as described in Table 6-1. These will include supine and standing heart rate and systolic and diastolic blood pressures. After the patient has been supine for 5 minutes, systolic and diastolic blood pressure will be measured 3 times using an automated validated device (e.g., OMRON) with an appropriately sized cuff. The repeat measurements will be made at 1- to 2-minute intervals, and the mean of the 3 measurements will be used. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. Heart rate and blood pressure will then be measured in the same manner with the patient in the standing position. A sudden, significant fall in blood pressure (>20 mm Hg systolic or >10 mm Hg diastolic) between 2 and 5 minutes after standing from the supine position will be defined as orthostatic hypotension.

Body weight will be measured as described in Table 6-1. Body temperature will be measured only at Screening, Visit 7/EOT, and at follow-up.

Clinically notable vital signs are defined in Appendix 1.

6.5.3 Laboratory evaluations

Routine blood samples will be collected as described in Table 6-1 and Table 6-2 and analyzed by the central laboratory. Blood samples taken at the screening visit are to be in the fasting state. Blood samples taken at subsequent visits are recommended to be in the fasting state. Details regarding collection of samples, shipment of samples, reporting of results, laboratory reference ranges, and alerting abnormal values will be supplied to the site before site initiation in a study laboratory manual. The results of the analysis will be made available to each site by the central laboratory, at the earliest, 48 hours after receipt of the samples by the central laboratory.

Investigators will be asked to comment on those abnormalities on the respective laboratory result page, including a notation of the clinical significance of each abnormal finding in the patient’s source documents. The laboratory sheets will be filed with the patient’s source documents. Abnormal laboratory values should not be recorded on the AE eCRF; however,

[redacted]

any diagnoses (or signs or symptoms if a diagnosis is not possible) associated with the abnormal findings should be recorded on the AE eCRF.

Clinically notable laboratory findings are defined in Appendix 1.

6.5.3.1 Hematology

Hematology parameter blood samples will be collected as described in Table 6-1 and will include: red blood cell count, total and differential WBC count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), platelet count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and red blood cell morphology. In a subset of patients CD4+, CD8+, T_h17, T_{reg}, and other T-lymphocyte subsets will be determined.

For study blinding purposes (of fingolimod arms) only the absolute counts for eosinophils, basophils, and monocytes will be communicated to sites by the central laboratory. The absolute total WBC, neutrophil, and lymphocyte counts will be measured at each visit by the central laboratory and will be blinded from the sponsor and the Investigator and will only be communicated to the site in case of a notable abnormality as defined in Appendix 1 and as per guidance in Appendix 3.

6.5.3.2 Clinical chemistry and blood serology

Blood samples will be collected as described in Table 6-1 and will include the following parameters: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphate, blood urea nitrogen, uric acid, random glucose, albumin, AP, creatinine, ALT, AST, GGT, amylase, total bilirubin, conjugated bilirubin, HbA1c, total cholesterol, triglycerides, high-density lipoprotein, and low-density lipoprotein. Abnormal laboratory parameters inconsistent with clinical presentation of MS or suspicious of underlying medical condition should be repeated for accuracy.

If an increase of amylase above the clinically notable value (≥300 U/L) is observed at any postrandomization visit, lipase should be tested to determine the origin of elevated amylase (pancreatic versus extra-pancreatic).

Serology testing will also be performed in all patients at Screening to determine the patient's immune status with respect to the following viruses:

- Herpes simplex virus-1 (HSV-1)
- Herpes simplex virus-2 (HSV-2)
- Rubeola **(**Measles**)**
- Human immunodeficiency antibodies

Patients without acceptable evidence of immunity against VZV (per Appendix 3) at Screening will be excluded from the study. Patients testing positive for HIV are excluded from the study.

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

[redacted]

A positive IgG antibody result does not indicate active infection per se, but only evidence of prior exposure to viral antigens through past infection or vaccination. Patients with prior infection may be at risk of viral reactivation (e.g., cold sores, genital ulcers or shingles) and should be instructed to inform the investigator of any signs or symptoms suggestive of these conditions, so that prompt treatment may be initiated.

If a patient experiences symptoms of a new ischemic or thrombotic AE, the following additional laboratory assessments should be performed: prothrombin time/partial thromboplastin time, homocysteine, activated protein C, lupus anticoagulant, antiphospholipid antibody, protein C, protein S, fibrinogen, and antithrombin III.

A serum pregnancy test will be conducted at Screening on all females, regardless of child-bearing potential.

[redacted]

6.5.3.3 Urinalysis

Urinalysis will be performed as indicated in Table 6-1 and Table 6-2. The following parameters will be analyzed: leukocytes, specific gravity, bilirubin, blood, glucose, ketones, pH, protein, and urobilinogen.

If a patient experiences edema or significant weight gain (Appendix 1), urinalysis by dipstick for proteinuria will be performed. If dipstick urinalysis detects proteinuria, urinalysis should be repeated. If proteinuria is confirmed upon repeat testing, the protein/creatinine ratio should be determined in a spot urine sample. In case of abnormal spot urine protein/creatinine ratio, the patient should be referred to a nephrologist for further evaluation and assessments, including possible 24-hour urine collection.

6.5.4 Electrocardiogram

Standard 12-lead ECGs will be collected as described in Table 6-1. Digital ECG devices will be provided to each clinical site by the central ECG reader for the duration of the study. The screening ECG report from the central reader must be available to confirm patient eligibility before randomization. A 12-lead ECG will be performed at Visit 2 before study drug administration for patients receiving fingolimod and patients receiving glatiramer acetate and 6 hours after the study drug administration, for patients receiving fingolimod only.

See Section 5.5.5 for guidelines for monitoring patients taking their first dose of fingolimod who had a prolonged QTc interval (>450 msec males, >470 msec females) before dosing or during a 6-hour observation period, or at additional risk for QT prolongation (e.g., hypokalemia, hypomagnesemia, congenital long-QT syndrome), or on concurrent therapy with QT-prolonging drugs with a known risk of torsades de pointes.

Detailed instructions describing the process for recording and transmission of the ECGs will be outlined in the study-specific manual and provided to the site before the start of the study. Paper ECGs will be printed, photocopied to preserve the ink if necessary, and kept at the site as source documentation.

[redacted]

Interpretation of the tracing must be made by a qualified physician. Each ECG tracing should be labeled with the study number, patient initials, patient number, date, and kept in the source documents at the study site. Only clinically significant abnormalities should be reported as medical history/current medical conditions or AEs on the eCRF. Clinically significant findings must be discussed with the Medical Monitor before enrolling the patient in the study.

6.5.5 Ophthalmologic examinations and optical coherence tomography

An ophthalmic examination will be performed to screen for macular edema as described in Table 6-1 and Table 6-2 for patients that discontinued study drug. An optical coherence tomography (OCT) and fluorescein angiography (FA) will be done only if needed to confirm macular edema. If there is a suspicion of macular edema at Screening, an OCT and FA should be performed to confirm the diagnosis. If the diagnosis is confirmed, the patient should be deemed a screening failure and should not be randomly assigned.

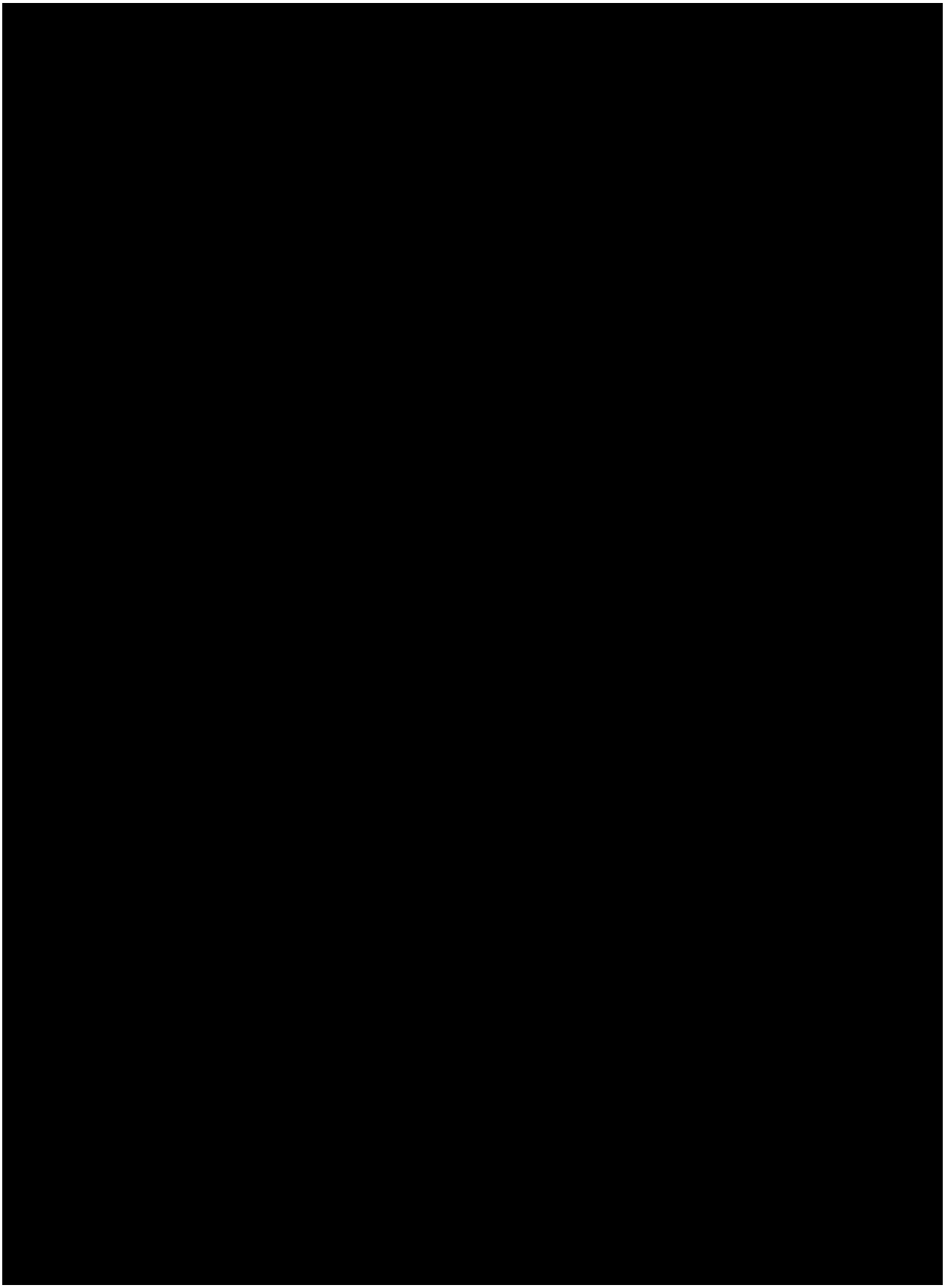
Patients with a history of or newly diagnosed uveitis after initiation of study drug may require more frequent ophthalmic evaluations. Refer to the Guidance for Ophthalmic Monitoring (Appendix 4) for details on monitoring of patients with uveitis during the study.

Study drug must be discontinued in any patient who has a diagnosis of macular edema confirmed by OCT and FA.

Patients with a diagnosis of macular edema must be followed up monthly and more frequently if needed based on the ophthalmologist's judgment. Further ophthalmologic evaluations will be conducted until such time as resolution is confirmed or no further improvement is expected by the ophthalmologist (based on a follow-up period of not less than 3 months). If the patient does not show definite signs of improvement on examination by specialized testing (e.g., OCT) 6 to 8 weeks after discontinuation of study drug, then therapy for macular edema in conjunction with an ophthalmologist experienced in the management of this condition should be initiated.

6.5.6 Pregnancy and assessments of fertility

Serum pregnancy test will be performed for all women by the central laboratory as detailed in Table 6-1. Patients becoming pregnant will be recommended to interrupt the study drug. Additional pregnancy testing may be performed at the investigator's discretion during the study.



6.5.8 Chest x-ray

This section is no longer applicable after the changes made at protocol amendment 2.

6.5.9 Pulmonary function tests

Pulmonary function tests evaluating FEV_1, FVC, and D_LCO will be performed at Screening, Month 6, Month 12, End of Study, and 3 months after study drug discontinuation as indicated in Table 6-1 and Table 6-2. This test will be conducted in all patients who are enrolled into the study and in the manner consistent with the standard pulmonary laboratory practice.

Any condition that might affect the outcome of PFTs including infection, respiratory symptoms, occupational exposures (including asbestos), and cigarette smoking, needs to be collected before every PFT testing and transcribed to the PFT eCRF page.

Patients who discontinue study drug due to respiratory AE(s) should be evaluated by a pulmonary specialist and further investigations (e.g., PFTs, chest x-ray or HRCT, biopsy) should be performed as needed.

Spirometry

The technician should demonstrate the appropriate technique to the patient and follow the standard procedure. The quality of the tests must be accounted for including the technicians' comments (especially when, despite proper coaching of the patient, full collaboration cannot be achieved). The FEV_1/FVC ratio will be calculated centrally by the trial statistician.

A minimum of 3 acceptable maneuvers will be performed at each visit. The acceptability criteria are a satisfactory start of test and a satisfactory end of test. In addition, the technician should observe that the patient understood the instructions and performed the maneuver with a maximum inspiration, a good start, a smooth continuous exhalation, and maximal effort. The largest FVC and the largest FEV_1 will be recorded, after examining the data from all of the acceptable curves, even if the 2 values do not come from the same curve. Please refer to the American Thoracic Society/European Respiratory Society guidelines for standardization of spirometry (Miller et al, 2005a; Miller et al, 2005b) and single breath determination of carbon monoxide uptake in the lung (MacIntyre et al, 2005).

If for any reason a patient is permanently discontinued from study medication the patient will have PFTs performed at his last visit or within 30 days of the study drug discontinuation. Refer to Appendix 3 for Guidance on monitoring patients with pulmonary function safety concern.

Forced expiratory volume in 1 second (FEV_1):

The FEV_1 describes the volume (in Liters) that is expelled within one second of forced expiration after a maximal inspiration and reflects the large airway resistance. A decrease in FEV_1 serves as a good parameter for detection of an obstructive ventilatory defect.

Forced vital capacity (FVC):

The FVC denotes the volume of gas (in Liters) which is exhaled during a forced expiration starting from a position of full inspiration and ending at complete expiration. This parameter

[redacted]

is normal or might be slightly decreased in obstructive disease but shows a mild to severe decrease in restrictive disease.

Diffusion capacity of carbon monoxide (D_LCO):

Gas exchange is assessed by the D_LCO evaluated by the single breath holding method. It is a measurement of carbon monoxide (CO) transfer from the lung to pulmonary capillary blood over a breath-holding period. Due to ability of CO to bind to hemoglobin, the diffusion capacity needs to be corrected for hemoglobin to reflect an altered lung gas transport rather than altered hemoglobin.

The average of at least 2 acceptable tests that meet the repeatability requirement of either being with 3 mL CO/min/mm Hg (or 1 mmol/min/kPa) of each other or being within 10% of the highest value should be reported.

A D_LCO test is acceptable if it fulfills all the following criteria:

- Use of proper quality-controlled equipment
- Inspired volume of greater than 85% of largest vital capacity in less than 4 seconds
- A stable calculated breath hold for 10 (±2) seconds. There should be no evidence of leaks or Valsalva or Mueller maneuvers
- Expiration in less than 4 seconds (and sample collection time less than 3 seconds), with appropriate clearance of dead space and proper sampling/analysis of alveolar gas

All values must be corrected for hemoglobin concentration in the study.

The D_LCO is usually expressed in European CI conventional units: mL CO/min/torr (or mL CO/min/mm Hg), whereas the US mainly uses SI units: mmol CO/min/kPa (Conversion factor: SI units × 2.986 = CI units).

6.5.10 Dermatological examination

A dermatologist will complete a dermatological examination as outlined in Table 6-1 and Table 6-2 to support monitoring of patients for the potential development of new skin cancers during the study. For patients who discontinue treatment early, a dermatological examination should be performed at end of study. Study drug should be discontinued in patients who develop a new skin cancer during the study.

6.5.11 Columbia-Suicide Severity Rating Scale

The C-SSRS, is a semi-structured interview designed to systematically assess and track suicidal AEs (behavior and ideation) throughout different settings including clinical studies.

The C-SSRS captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors. The C-SSRS will be administered by an IVRS with the patient entering responses directly into the IVRS. Caregivers will not be allowed to answer the C-SSRS questions on behalf of the patient. Sites must review reports received from the system for any answers indicative of suicidal ideation and AEs. Adverse events ascertained through the administration of the C-SSRS will be documented. This scale was developed by researchers at Columbia University and will be administered in this study as specified in the assessment schedules

[redacted]

(Table 6-1 and Table 6-2). In case the score is 4 or above, the patient must be referred to the health care professional for further assessment and/or treatment.

6.5.12 Appropriateness of safety measurements

The safety assessments selected are standard for this indication and patient population. Ophthalmic evaluation has been included for detection of macular edema. Macular edema is an AE of special interest in patients treated with fingolimod because of the higher incidence seen in treated patients compared with active and placebo control groups in previous studies.

6.6 Other assessments

6.6.1 Health-related quality of life

Patients must complete the TSQM, [redacted] questionnaires before other clinical assessments at any given visit. Completed questionnaires will be reviewed and examined by the investigator before the clinical examination for responses that may indicate potential AEs or SAEs. The investigator should review not only the responses to the questions in the questionnaires but also for any unsolicited comments written by the patient.

If the occurrence of AEs or SAEs is confirmed, the physician must record the events. Investigators should not encourage the patients to change the responses reported in the questionnaires.

6.6.1.1 Treatment Satisfaction Questionnaire for Medication v1.4 (TSQM v1.4)

Treatment Satisfaction Questionnaire for Medication (TSQM) was developed and validated as a general measure for treatment satisfaction (Atkinson 2004). The TSQM version 1.4 contains 14 items assessing the following 4 domains: Global Satisfaction, Effectiveness, Side Effects, and Convenience. This PRO must be completed prior to any other study visits assessments at the baseline, 6 and 12 month visits.

[redacted]

[redacted]

6.6.2 Resource utilization

Not applicable.

6.6.3 Pharmacogenetics/pharmacogenomics

Not applicable.

[redacted]

[redacted]

7 Safety monitoring

7.1 Adverse events

An AE is 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 that is given during any phase of the study. Medical conditions and diseases present before starting study drug are only considered AEs if they worsen after starting study drug. Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of AEs should be sought by nondirective questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. All AEs must be recorded in the AEs eCRF with the following information:

1. the severity grade (mild, moderate, or severe)
2. its relationship to the study drug(s) (suspected/not suspected)
3. its duration (start and end dates or if continuing at final examination)
4. whether it constitutes a serious AE (SAE)

An SAE is defined as an event which:

- is fatal or life threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- 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
  - elective or preplanned treatment for a preexisting 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
- 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 previously listed

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements (Section 7.2).

All AEs should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e., further observation only); study drug dose adjusted/temporarily

[redacted]

interrupted; study drug permanently discontinued due to this AE; concomitant medication given; nondrug therapy given; or patient hospitalized/patient's hospitalization prolonged. The action taken to treat the AE should be recorded on the AE CRF.

For patients who experience an ischemic or thrombotic AE, specialist advice should be sought to determine diagnostic and therapeutic procedures. If a laboratory screen for coagulation abnormalities is deemed appropriate, it should include the following additional assessments: prothrombin time/partial thromboplastin time, homocysteine, activated protein C, lupus anticoagulant, antiphospholipid antibody, protein C, protein S, fibrinogen, and antithrombin III.

Patients who discontinue due to respiratory AEs should be evaluated by a pulmonary specialist and additional investigations (e.g., PFTs, chest x-ray or HRCT, biopsy) should be performed as needed.

Once an AE is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome. Sites should send all unscheduled laboratory samples to the central laboratory to ensure that the laboratory data are included in the clinical database and reported.

Information about common side effects already known about the investigational drug can be found in the investigator brochure or will be communicated between investigator brochure updates in the form of investigator notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

7.2 Serious adverse event reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until 30 days after the patient has stopped study participation (defined as time of last dose of study drug taken or last visit whichever is later), must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30-day period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess the relationship of any SAE to study drug, complete the Serious Adverse Event Report Form in English, and send the completed, signed form by fax within 24 hours to the local Novartis Drug Safety and Epidemiology Department. The telephone and telecopy number of the contact persons in the local Clinical Safety and Epidemiology Department, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the CRF documentation at the study site.

[redacted]

Follow-up information is sent to the same person to whom the original Serious Adverse Event Report Form was sent, using a new Serious Adverse Event Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the investigator's brochure or package insert (new occurrence) and is thought to be related to the Novartis study drug, a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an investigator notification to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected unexpected serious adverse reactions will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

7.2.1 Serious adverse event notification: multiple sclerosis relapse

Any MS relapses, as a general rule, should be reported on the relapse CRF instead of the AE/SAE forms. However, if, in the judgment of the investigator, any MS relapse is unusually severe and warrants specific notification, then an SAE Report Form must be completed and submitted according to SAE reporting procedures outlined above.

7.3 Pregnancies

To ensure patient safety, each pregnancy in a patient on study drug must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

7.4 Data safety monitoring board

An FTY720 data safety monitoring board (DSMB) has been established with a primary goal to monitor the safety of patients participating in all FTY720 studies, including the present study. The DSMB is an external board comprising specialists with specific knowledge of MS and other areas related to the safety of FTY720. Specific AEs of interest from this study will be submitted for review and evaluation by the DSMB.

[redacted]

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative (i.e., CRO monitor or clinical team manager) will review the protocol and (e)CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the (e)CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, ECGs, MRI films, and the results of any other tests or assessments. All information on (e)CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the field monitor access to all relevant source documents to confirm their consistency with the (e)CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the (e)CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the eCRF using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the electronic data capture system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the CRO working on behalf of Novartis. The investigator must certify that the data entered into the eCRF are complete and accurate. After database lock, the investigator will receive a CD-ROM of the patient data for archiving at the investigational site.

8.3 Database management and quality control

Novartis or designated CRO working on behalf of Novartis review the data entered into the eCRFs by investigational staff for completeness and accuracy and instructs the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data.

Concomitant medication entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system.

[redacted]

Medical history/current medical conditions and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Laboratory samples, ECG readings, MRI readings, [redacted] will be processed centrally and the results will be sent electronically to a designated CRO.

Randomization codes and data about all study drug dispensed to the patient and all IVRS recorded dosage changes will be tracked using an IVRS. The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

Each occurrence of a code break via IVRS will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

9 Data analysis

9.1 Analysis sets

The following analysis sets will be used:

- Randomized set: consists of all patients who are assigned randomization numbers. The patients in this set are called randomized patients. This set will be used to summarize patient disposition, demographic and baseline characteristics, and protocol deviation information.
- Full-analysis set (FAS): Consists of all patients who are randomly assigned and take at least 1 dose of study drug. Following the intent-to-treat principle, patients will be grouped according to the assigned treatment at randomization. Efficacy analyses will be performed on the FAS unless otherwise notified.
- Per-protocol set: Consists of all patients in the FAS who do not have any major protocol deviations that could confound the interpretation of analyses conducted on the FAS. Major protocol deviations will be determined according to the predefined protocol deviation criteria before treatment unblinding. Any efficacy data after study drug discontinuation will be excluded. The per-protocol set will only be used for the supportive analyses of the primary efficacy variable.
- Safety set: Consists of all patients in the FAS who take at least 1 dose of study drug. Patients will be analyzed according to the treatment they have actually taken. Safety and tolerability analyses will be performed on the safety set unless otherwise notified.
- Follow-up set: The follow-up set consists of all patients in the safety set who have follow-up visit data or who have at least 1 safety assessment (AEs, laboratory test, vital sign measurement, or ophthalmology assessments) 46 days or more than 46 days after study drug discontinuation. Patients will be grouped in the same way as previously described for the analysis on the safety set. Only the safety follow-up data analysis will be performed on the follow-up set.

[redacted]

9.2 Patient demographics and other baseline characteristics

Demographics and background information will be summarized using frequency distributions for categorical variables and descriptive statistics of mean, SD, minimum, median, and maximum for continuous variables. Background information includes prior MS treatment, relevant medical history/current medical conditions, duration of the disease, the number of relapses experienced in the last 2 years before study enrollment, baseline MRI assessments, and baseline EDSS.

9.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

Duration (days) of exposure to study drug will be summarized by treatment group. Frequency distributions will be used to summarize patient disposition and reasons for discontinuation of study drug. Patients who prematurely discontinue the study drug will be listed along with the reason for discontinuation.

The cumulative corticosteroid dose used after the start of study drug for the treatment of MS relapses will be summarized by treatment group in dose equivalent to methylprednisolone (the conversion factors will be detailed in the statistical analysis plan). The cumulative duration of the corticosteroid use will be summarized similarly.

9.4 Analysis of the primary variable

The primary analysis will be based on the FAS.

9.4.1 Variable

The primary outcome is the ARR which is defined as the average number of confirmed relapses per year (i.e., the total number of confirmed relapses divided by the total days in the study multiplied by 365.25). For the primary analysis, the number of relapses will include all the confirmed relapses experienced during the study. The time spent in the study will correspond to the observation period for all the relapses from first dose on study drug to end of study.

9.4.2 Statistical model, hypothesis, and method of analysis

The two doses of fingolimod will be tested hierarchically versus glatiramer acetate in a step-down procedure. For each of the two fingolimod doses, the null hypothesis is that there is no difference in the ARRs between patients treated with fingolimod and those treated with glatiramer acetate versus the alternative hypothesis that there is a difference between the two treatment groups. In order to preserve the Type I experiment-wise error rate, the null hypothesis will be rejected if the observed p value for the between-treatment comparison is less than the significance level as specified in the multiplicity adjustment procedure described later in this section.

H_{01}: $\mu_{\text{FTY 0.5 mg}} = \mu_{\text{glatiramer acetate}}$ versus H_{A1}: $\mu_{\text{FTY 0.5 mg}} \neq \mu_{\text{glatiramer acetate}}$

H_{02}: $\mu_{\text{FTY 0.25 mg}} = \mu_{\text{glatiramer acetate}}$ versus H_{A2}: $\mu_{\text{FTY 0.25 mg}} \neq \mu_{\text{glatiramer acetate}}$

[redacted]

No formal hypothesis will be tested between the 2 fingolimod doses because the study is not powered to detect a difference in treatment effect between these doses.

The hypotheses will be tested using a negative binomial regression model with log link, using treatment, number of relapses in the previous year before study enrollment, baseline EDSS, and baseline number of Gd-enhancing T1 lesions and country (or region) as covariates. In the analysis, the response variable is the number of confirmed relapses for each patient. The patient's time in the study (natural log of time in years) is used as an offset variable to obtain the ARR, adjusted for the varying lengths of patient's time in the study (time in years). Study centers will be pooled to country or region (based on geographical proximity and/or known or expected regional differences in medical care) in order to minimize the impact of low-enrolling centers/countries on the analysis (such as nonconvergence of the analysis model). Details of pooling will be provided in the statistical analysis plan before database lock. The SAS procedure GENMOD (or other software with similar functionality) will be used to conduct the analysis.

The treatment effect of each dose of fingolimod versus glatiramer acetate will be presented as an ARR ratio with corresponding 95% confidence intervals and p values. The relative reduction in ARR will be presented as "percentage change," calculated as ($\hat{\mu}_{FTY} / \hat{\mu}_{GA}$ -1).

Multiplicity adjustment for statistical hypothesis testing

The primary hypotheses tests will be tested using a hierarchical step-down procedure to control the experiment-wise error rate.

This study is designed to compare each of 2 doses of fingolimod to glatiramer acetate based on ARR. There are 2 hypotheses being tested (H01, H02).

Because it is highly likely that the approved dose of fingolimod (0.5 mg) is more efficacious than the lower dose (0.25 mg), the approved dose of fingolimod is initially tested against glatiramer acetate at a 2-sided significance level of 0.05. Only if this initial test H01 is rejected will H02, the low dose of fingolimod, be tested against glatiramer acetate also at a 2-sided significance level of 0.05.

Different scenarios of the anticipated treatment effect between fingolimod 0.5mg or 0.25mg versus glatiramer acetate have been evaluated based on the available data on fingolimod and the cumulative literature on glatiramer acetate. A 30% treatment benefit of fingolimod 0.5mg over glatiramer acetate could be anticipated on the basis of double-blind, 24-months, placebo-controlled studies of glatiramer acetate (Johnson et al, 2001) and fingolimod [Study CFTY720D2301] alone. However, more recent studies on glatiramer acetate, in a less active population, in a total of over 3000 patients, suggest that the efficacy of glatiramer acetate on ARR and other endpoints is similar to that of IFN beta-1a SC (REGARDS) or IFN beta-1b SC (BEYOND). The observed relapse rates on glatiramer acetate were 0.29 in REGARDS and 0.34 in BEYOND, compared to 0.3 (INF beta-1a SC) and 0.33 (INF beta-1b SC), respectively. In Study FTY720D2302, a double-blind 1-year study, fingolimod 0.5 mg was directly compared to IFN beta-1a IM. The ARR (0.21) in patients treated with fingolimod 0.5 mg was reduced by 52% compared to the ARR (0.43) in patients treated with INF beta-1a IM. Overall, the reduction in ARR in patients treated with fingolimod 0.5 mg compared to those treated with glatiramer acetate can be expected in the range of 30% to 50%. For the

[redacted]

purpose of this study, a 35% lower ARR in patients treated with fingolimod 0.5 mg (ARR=0.195) compared to those treated with glatiramer acetate (ARR=0.30) is assumed.

Fingolimod 0.25 mg has never been tested in a clinical trial. Based on PK/PD modeling a 14% higher ARR in patients on fingolimod 0.25 mg compared to those on fingolimod 0.5 mg is anticipated. However, the uncertainty of this estimate is substantial. A 95% confidence interval from the PK/PD model for the ARR in patients on fingolimod 0.25 mg ranges from ARR=0.183 to ARR=0.303. For the purpose of this study, an ARR of 0.225 is assumed in patients treated with fingolimod 0.25 mg, which corresponds to an increase in ARR of approximately 15% compared to fingolimod 0.5 mg and a relative treatment effect of 25% compared to glatiramer acetate.

9.4.3 Handling of missing values, censoring, and discontinuations

All patients in the FAS will be included in the primary analysis, i.e., the number of confirmed relapses observed up to the end of patient's participation in the study. Patients who discontinue from study treatment will remain in the study and follow the assessment schedule. Relapses will be counted regardless of whether a patient is on or off study drug. Therefore, it is expected that all randomized patients can contribute to the primary analysis. The primary analysis model adjusts for missing information (early study discontinuations) under some statistical assumptions (noninformative dropouts and constant ARR).

Additionally the following supportive analyses will be conducted:

The primary analysis will be repeated using the per-protocol set to provide an analysis of on-treatment data from patients who have no major protocol violations. Relapses that occurred after permanent discontinuation of study drug will be excluded and log (time on study drug in years) rather than log (time on study in years) will be used as the offset variable in the negative binomial model with log link.

To assess the impact of missing data on the primary analysis, a sensitivity analysis will be performed on ARRs in the full-analysis set using a nonparametric method with imputations. The ARRs will be analyzed by means of a rank analysis of covariance (ANCOVA) with treatment, and number of relapses in the previous year before study enrollment, baseline EDSS, and baseline number of Gd-enhancing T1 lesions as covariates (Stokes 2000). An adjustment for country or region can be considered prior to database lock and will be defined in the analysis plan. A month-by-month imputation scheme will be used whereby missing data in any given month of the study will be imputed with the overall mean number of relapses (calculated from all patients across all treatment groups) in the corresponding month.

A supplementary analysis using the same negative binomial model as in the primary analysis to be performed on all relapses (i.e., confirmed and unconfirmed relapses) in the full-analysis set will be performed. Additional analyses to further assess the robustness of the results maybe prespecified in the statistical analysis plan.

[redacted]

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

All efficacy analyses of secondary variables specified in this section will be conducted on the full-analysis set unless otherwise specified.

Magnetic resonance imaging (MRI)

The analyses on MRI parameters will be performed on the full analysis set in the subset of patients who have MRI scans done during the study.

The MRI efficacy variables are listed as following:

- Percent change in brain volume from baseline at Month 12 or end of study
- Number of new and newly enlarging T2 lesions (compared with baseline MRI scan) at Month 12 or at end of study
- Proportion of patients free of new/newly enlarging T2 lesions compared to baseline at Month 12 or end of study
- Change (and % change) from Baseline in total volume of T2 lesions at Month 12 or end of study
- Number of new T1 hypointense (acute or chronic) lesions compared to baseline, at Month 12 or end of study
- Change and % change from baseline in total volume of T1 hypointense lesions (acute or chronic) at Month 12 or end of study
- Number of Gd-enhancing T1 lesions at Month 12 or end of study
- Total volume of Gd-enhancing T1 lesions at Month 12 or end of study

The number of new or newly enlarging T2 lesions at Month 12 or end of study and number of Gd-enhancing T1 lesions at Month 12 or the end of study will be analyzed using a negative binomial regression model with log link, using treatment, age, baseline T2 lesion number, baseline number of Gd-enhancing T1 lesions, and the number of relapses experienced in the previous year before study enrollment as covariates. An adjustment for country or region can be considered prior to database lock and will be defined in the analysis plan. For the analysis of T2 lesions, an offset variable will be used in the negative binomial analysis to adjust for the time in years (since start of study drug).

The proportion type variables will be analyzed using a logistic regression model with treatment, age, corresponding baseline value, baseline number of Gd-enhancing T1 lesions, and the number of relapses experienced in the previous year before study enrollment as covariates. An adjustment for country or region can be considered prior to database lock and will be defined in the analysis plan.

The continuous variables (change, percent change, and total volume) will be analyzed using a rank ANCOVA model adjusted for treatment, age, corresponding baseline value, and the number of relapses experienced in the previous year before study enrollment as covariates. An adjustment for country or region can be considered prior to database lock and will be defined in the analysis plan. A parametric analysis, especially for the change in brain volume, may be specified in the statistical analysis plan prior to database lock.

[redacted]

Relapses

All relapse-related analyses use confirmed relapses only, unless otherwise specified.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.5.2 Safety variables

All safety analyses will be conducted on the safety set.

Safety assessments will include: AEs, infections, bradycardia events, laboratory test results, vital sign measurements, dermatological examinations, PFTs, ophthalmic examinations, ECG data, and C-SSRS.

Adverse events will be summarized by presenting, for each treatment group, the number and percentage of patients having any AE by primary system organ class and preferred term. Infections will be considered AEs and summarized with the AEs. Severe AEs, SAEs, drug-related AEs, and the AEs leading to premature discontinuation of study drug will be presented in a similar format as AEs. Infections will also be summarized separately. Notable events will include death, nonfatal SAEs (including infections), and AEs (including infections) leading to study drug discontinuation. The frequencies and percentages of patients will be tabulated by treatment group.

Laboratory data will be summarized by presenting summary statistics of raw data and change from baseline values, by presenting shift tables using clinically notable ranges (Baseline to most extreme post-baseline value), and by flagging notable values in data listings. For liver function tests, the frequencies and percentages of patients with elevations of 1, 2, 3, 5, and 10 times the upper limit of normal will be summarized by visit and treatment group.

Estimated creatinine clearance will be summarized by presenting summary statistics by visit and treatment group. Change from baseline analyses will be presented by visit and treatment group.

Vital sign data will be summarized by presenting summary statistics for change from baseline values (both for the period 6 hours after the first dose and for further assessments by visit and by end of treatment). The incidence rates of notable vital sign abnormalities will be summarized. Further, the frequency distribution for pulse by visit and the frequency distribution for percent decline in pulse during first 6 hours will be presented.

Body weight and temperature data will be summarized by presenting summary statistics for change from baseline values by visit and at end of treatment. The incidence rates of notable weight and temperature abnormalities will be summarized.

Dermatological examination tables and patient listing will be summarized by visit and treatment group.

Pulmonary function test data will consist of the following parameters: FEV_1, FVC, FEV_1/FVC, and D_LCO. Summary tables and listings will be produced for both absolute values and percentage of predicted value when applicable. The data will be summarized by presenting

[redacted]

summary statistics of change from baseline. A FEV_1, FVC, FEV_1/FVC, D_LCO measurement below 80% of predicted will be considered to be abnormal.

The ophthalmic data will be summarized using distribution tables, summary statistics, and change from baseline by visit and treatment group. The patient listing will also be provided. The incidence (number and percentage) of macular edema in patients with and without diabetes will be reported by treatment group. Further analyses can be specified depending on the number of patients with diabetes in the trial.

The ECG intervals will be summarized by presenting summary statistics for change from baseline values by visit. The (uncorrected) QT interval will be corrected according to the Fridericia's formula. The maximum increase in corrected QT interval from baseline will be summarized and the frequencies of patients who fulfill the abnormality criteria based on the corrected QT interval will be calculated.

Frequency distribution of treatment-emergent suicidal ideation and behaviors from C-SSRS will be summarized.

Follow-up visit data will be summarized to assess patient's safety after discontinuation of the study drug.

9.5.3 Resource utilization

Not applicable.

9.5.4 Health related quality of life

Analysis of Treatment Satisfaction Questionnaire for Medication (TSQM v1.4)

The primary analysis for the TSQM will be between group change in Global Satisfaction from baseline to Month 12. Analyses of the Effectiveness, Side Effects, and Convenience domains will also be conducted.

For the TSQM, responses to items are summed and transformed so that higher scores indicate greater satisfaction. Specifically, TSQM scale scores are computed by adding the items loading on each domain. The lowest possible score is subtracted from the composite score and divided by the greatest possible score range. This provides a transformed score between 0 and 1 that is then multiplied by 100. If more than one item is missing from a subscale of the TSQM for a particular patient, this subscale should be considered invalid for that respondent.

[redacted]

9.6 Sample size calculation

The study will randomize a total of 1960 patients, and is planned to provide approximately 90% power for the comparison of fingolimod 0.5 mg to glatiramer acetate at a 2-sided significance level of 0.05.

The sample size calculation is based on simulations from a negative binomial distribution with a constant dispersion parameter k.

The power of the study was evaluated under various ARR assumptions and various dropout patterns based on the cumulative literature on glatiramer acetate and the Novartis data on fingolimod. The basis of the assumptions for this study and their level of uncertainty are presented in Section 9.4.2 under the sub-header "Multiplicity adjustment for statistical hypothesis testing". The anticipated overdispersion parameter (k=0.2231) was observed in the Month-12 analysis of Study CFTY720D2301. The anticipated ARR for patients treated with 0.5 mg fingolimod is $\mu_{FTY\ 0.5\ mg}$=0.195, the ARR for those treated with glatiramer acetate is $\mu_{glatiramer\ acetate}$=0.30. Therefore, the estimated ARR reduction for fingolimod 0.5 mg versus glatiramer acetate is 35%.

The total sample size of 1960 randomized is predetermined but the exact sample size of each arm will depend on when the randomization ratio switch occurs. For example, if the randomization ratio is switched when a total of 800 patients have been randomized from an original ratio of 1:1:1 for fingolimod 0.25 mg, fingolimod 0.5 mg, or glatiramer acetate, respectively to a ratio of 5:3:2, then 847 patients will be randomized to fingolimod 0.25 mg, 615 patients to fingolimod 0.5 mg and 498 patients glatiramer acetate, which will provide

[redacted]

more than 90% power to demonstrate superiority of fingolimod 0.5 mg dose versus glatiramer acetate in terms of ARR at a 2-sided significance level of 0.05 assuming a 15% drop-out rate. The calculations take into account that patients who discontinue prematurely from the study can participate with partial data to the primary endpoint.

Fingolimod 0.25 mg has never been studied in a clinical trial in MS. Based on PK/PD modeling results, it is anticipated that the ARR in patients treated with fingolimod 0.25mg is approximately 15% higher than in those treated with fingolimod 0.5mg. However, the uncertainty of this estimate is high; the 95% confidence interval of the estimated ARR in fingolimod 0.25 mg group ranges from 0.18 to 0.30. It is therefore anticipated that fingolimod 0.25mg is less efficacious than fingolimod 0.5mg, but more efficacious than glatiramer acetate. In line with the PK/PD modeling the anticipated ARR in patients treated with fingolimod 0.25 mg is $\mu_{FTY\ 0.25\ mg}$=0.225, which corresponds to a reduction in ARR of 25% in patients treated with fingolimod 0.25 mg compared to those treated with glatiramer acetate.

Following the multiplicity adjustment procedure in Section 9.4.2, the power to detect a 25% reduction in ARR for patients treated with fingolimod 0.25 mg compared with patients treated with glatiramer acetate is approximately 68% at a 2-sided significance level of 0.05, if the primary objective for the fingolimod 0.5-mg dose can be rejected first. If fingolimod 0.25 mg is similarly efficacious as fingolimod 0.5 mg (i.e., ARR reduction versus glatiramer acetate is 35% rather than 25%), the power to detect this treatment effect at a 2-sided significance level of 0.05 is approximately 88%. If fingolimod 0.25 mg is similarly efficacious as glatiramer acetate (i.e., estimated ARR in the fingolimod 0.25-mg group is at the high end of range proposed by the PK/PD model), there will be no significant difference at a 2-sided significance level of 0.05.

The statistical software R (Version 2.13.1, open source) and the R library packages “MASS” and “PSCL” were used for sample size calculations and power analysis.

9.7 Power for the key secondary hypotheses

Not applicable.

[redacted]

9.9 Interim analysis

Not applicable. No interim analysis is planned for this study.

[redacted]

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented 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.

10.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his or her understanding. If the patient is capable of doing so, he or she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e., all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient's source documents.

[redacted] will provide to investigators in a separate document a proposed informed consent form that complies with the ICH Good Clinical Practice guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by [redacted] before submission to the IRB/IEC, and a copy of the approved version must be provided to the [redacted] monitor after IRB/IEC approval.

10.3 Responsibilities of the investigator and IRB/IEC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted IRB/IEC before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to Novartis/[redacted] before study initiation. Before study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis/[redacted] monitors, auditors, Novartis/[redacted] Clinical Quality Assurance representatives, designated agents of Novartis/[redacted] IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis [redacted] immediately that this request has been made.

10.4 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

[redacted]

11 Protocol adherence

Investigators agree that they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the trial to request approval of a protocol deviation as no authorized deviations are permitted. If the investigator feels that a protocol deviation would improve the conduct of the study, this must be considered a protocol amendment. Unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC, it cannot be implemented. All significant protocol deviations will be recorded and reported in the clinical study report.

11.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC. Only amendments that are required for patient safety may be implemented before IRB/IEC approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC of the study site should be informed within 10 working days.

12 References (Available Upon Request)

Atkinson MJ, Sinha A, Hass SL, et al. (2004) Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. *Health Qual Life Outcomes*; 2:12.

Bar-Or A, Fawaz L, Fan B, et al. (2010) Abnormal B-cell cytokine responses a trigger of T-cell-mediated disease in MS? *Ann Neurol* 67(4):452-61.

Bornstein MB, Miller A, Slagle S, et al. (1987) A Pilot Trial of Cop 1 in Exacerbating-Remitting Multiple Sclerosis *N Engl J Med* Aug 13;317(7):408-14.

Cadavid D, Wolansky LJ, Skurnick J, et al. (2009) Efficacy of treatment of MS with IFNbeta-1b or glatiramer acetate by monthly brain MRI in the BECOME study , *Neurology*., 72(23):1976-1983.

Cohen JA, Barkhof F, Comi G, et al. (2010) Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis; *N. Engl. J. Med*. 362(5), 402-15. Fingolimod Phase III trial.

Darlington PJ, Touil T, Doucet J-S, et al. (2013) Diminished Th17 (not Th1) responses underlie multiple sclerosis disease abrogation after hematopoietic stem cell transplantation. *Ann Neurol* 73(3):341-354.

[redacted]

Johnson KP, Brooks BR, Cohen JA, et al.; The copolymer 1 MS study Group. (2001) Copolymer-1 reduces relapse rate and improves disability in relapsing remitting multiple

[redacted]

sclerosis: results of a phase III multicenter, double-blind, placebo-controlled trial. 1995. *Neurology*: 57 (12 Suppl 5):S16-24.

Kappos L, Radue EW, O'Connor P, et al. (2010) A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N. Engl. J. Med.* 362(5), 387–401. Fingolimod Phase III trial.

Kebir H, Kreymborg K, Ifergan I, et al. (2007) Human Th17 lymphocytes promote blood-brain barrier disruption and central nervous system inflammation *Nature Medicine* 13(10) 1173-5.

Keegan BM, Noseworthy JH. (2002) Multiple sclerosis. *Annu Rev Med*.;53:285-302.

Keene CD, Sonnen JA, Swanson PD, et al. (2007) Neural transplantation in Huntington disease: long-term grafts in two patients. *Neurology* 68(24):2093–8.

MacIntyre N, Crapo RO, Viegi G, et al. (2005). Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J* 26(4):720-35.

McDonald WI, Compston A, Edan G, et al. (2001) Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Ann Neurol* 50(1):121-7.

Mehling M, Lindberg R, Raulf F, et al. (2010) Th17 central memory T cells are reduced by FTY720 in patients with multiple sclerosis *Neurology* 75(5): 403-10.

Mikol DD, Barkhof F, Chang P, et al.; REGARD study group. (2008) Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the REbif vs Glatiramer Acetate in Relapsing MS Disease [REGARD] study): a multicentre, randomised, parallel, open-label trial. *Lancet Neurol* 7(10), 903-14.

Miller MR, Crapo R, Hankinson J, et al. (2005a) General considerations for lung function testing. *Eur Respir J* 26(1):153-61.

Miller MR, Hankinson J, Brusasco V, et al. (2005b) Standardisation of spirometry. *Eur Respir J* 26(2):319-38.

O'Connor P, Filippi M, Arnason B, et al. (2009) 250 microg or 500 microg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study; *Lancet Neurol* Oct*:*8(10):889-97.

Panitch H, Goodin DS, Francis G, et al.; EVIDENCE Study Group; Evidence of Interferon Dose-response: European North American Compartative Efficacy; University of British Columbia MS/MRI Research Group. (2002) Randomized, comparative study of interferon beta-1a treatment regimens in MS: The EVIDENCE Trial. *Neurology* 59(10):1496-506.

Polman CH, Reingold SC, Edan G, et al. (2005) Diagnostic criteria for multiple sclerosis: 2005 revisions to the ‘‘McDonald Criteria.’’ *Ann Neurol* 58(6):840–6.

Polman CH, Reingold SC, Banwell B, et al. (2011) Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 69(2):292-302.

Stokes ME, Davis CS, Koch GG. (2000) *Categorical data analysis using the SAS system*. SAS Institute, Inc., Cary, N.C.

[redacted]

[redacted]

Tzartos JS, Friese MA, Craner MJ, et al. (2008) Interleukin-17 production in central nervous system-infiltrating T cells and glial cells is associated with active disease in multiple sclerosis. *Am J Pathol* 172(1):146-155.

[redacted]

13 Appendices

Appendix 1: Clinically notable laboratory values and vital signs

Only selected lab parameters identified as notable which have been shown to be sensitive to fingolimod exposure are included.

CRITERIA FOR NOTABLE LABORATORY ABNORMALITIES

Notable Values		
Laboratory Variable	**Standard Units**	**SI Units**
LIVER FUNCTION AND RELATED VARIABLES		
SGOT (AST)	>82 U/L	>82 U/L
SGPT (ALT)	>90 U/L	>90 U/L
Total bilirubin	≥2.0 mg/dL	≥34.2 μmol/L
Alkaline phosphatase	>280 U/L	>280 U/L
RENAL FUNCTION / METABOLIC AND ELECTROLYTE VARIABLES		
Glucose `	≥200 mg/dL	≥11.11 mmol/L
Creatinine	≥2.0 mg/dL	≥176 umol/L
Amylase	≥300 U/L	≥300 U/L
Cholesterol	≥240 mg/dL	≥6.21 mmol/L
Triglycerides	≥300 mg/dL	≥3.39 mmol/L
Blood urea nitrogen (BUN)	≤2 mg/dL ≥30 mg/dL	≤0.7 mmol/L ≥10.7 mmol/L
Sodium	<125 mEq/L >154 mEq/L	<125 mmol/L >154 mmol/L
Chloride	≤85 mEq/L ≥119mEq/L	≤85 mmol/L ≥119 mmol/L
Potassium	≤3.0 mEq/L ≥6.0 mEq/L	≤3.0 mmol/L ≥6.0 mmol/L
Magnesium	≤1.0 mg/dL ≥3.0 mg/dL	≤0.40 mmol/L ≥1.23 mmol/L
Calcium	≤7.5 mg/dL ≥11.6 mg/dL	≤1.87 mmol/L ≥2.89 mmol/L
Phosphate	≤2.0 mg/dL ≥5.3 mg/dL	≤0.65 mmol/L ≥1.71 mmol/L

Notable Values		
Laboratory Variable	**Standard Units**	**SI Units**
HEMATOLOGY VARIABLES		
Hemoglobin	≤10.0 g/dL (M/F)	≤100 g/L (M/F)
Platelets (Thrombocytes)	≤100 k/mm^3 ≥600 k/mm^3	≤100 x 10^9/L ≥600 x 10^9/L
Leukocytes (WBCs)	≤2.0 k/mm^3 ≥15 k/mm^3	≤2.0 x 10^9/L ≥15 x 10^9/L
HEMATOLOGY VARIABLES: DIFFERENTIAL		
Granulocytes (Poly, Neutrophils)	≤1,000 /mm^3 ≥12000/mm^3	≤1 x 10^9/L ≥12 x 10^9/L
Lymphocytes	<200/mm^3 ≥8000/mm^3	<0.2 x 10^9/L ≥8 x 10^9/L
Red blood cells	<3,300,000/mm^3 >6,800,000/mm^3	<3.3 x 10^{12}/L >6.8 x 10^{12}/L

NOTABLE VITAL SIGNS AND BODY WEIGHT	
Vital Sign Variable	**Notable Criteria**
Pulse (beats/min)	>120 bpm or Increase of ≥15 bpm from baseline Or <50 bpm or Decrease of ≥15 bpm from baseline
Systolic BP (mm Hg)	≥160 mm Hg or Increase of ≥20 mm Hg from baseline Or ≤90 mm Hg or Decrease of ≥20 mm Hg from baseline
Diastolic BP (mm Hg)	≥100 mm Hg or Increase of ≥15 mm Hg from baseline Or ≤50 mm Hg or Decrease of ≥15 mm Hg from baseline
Body Temperature (°C)	>38.3°C/101°F
Body Weight (kg)	± 7% from baseline weight

[redacted]

Appendix 2: 2010 Revisions to the McDonald diagnosis criteria for MS

Guidelines from International Panel on the diagnosis of MS

(McDonald et al, 2001; Polman et al, 2005; Polman et al, 2011)

Clinical Presentation	Additional Data Needed for MS Diagnosis
2 or more attacks[a]; objective clinical evidence of 2 or more lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack[b]	None[c]
Two or more attacks[a]; objective clinical evidence of 1 lesion	**Dissemination in space**, demonstrated by: ≥1 T2 lesion in at least two out of four MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)[d] OR Await a further clinical attack[a] implicating a different CNS site
One attack[a]; objective clinical evidence of 2 or more lesions	**Dissemination in time**, demonstrated by: Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time. OR A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan. OR Await a further clinical attack[a]

[redacted]

One attack[a]; objective clinical evidence of 1 lesion (clinically isolated syndrome)	**Dissemination in space and time, demonstrated by:** **For DIS** ≥1 T2 lesion in at least two out of four MS-typical regions of the CNS periventricular, juxtacortical, infratentorial, or spinal cord)[d] OR Await a second clinical attack[a] implicating a different CNS site **AND** **For DIT** Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time. OR A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan. **OR** Await a second clinical attack[a]

If the Criteria are fulfilled the diagnosis is MS.

[a.]An attack (relapse; exacerbation) is defined this as patient-reported or objectively observed events typical of an acute inflammatory demyelinating event in the CNS, current or historical, with duration of at least 24 hours, in the absence of fever or infection. It should be documented by contemporaneous neurological examination, but some historical events with symptoms and evolution characteristic for MS, but for which no objective neurological findings are documented, can provide reasonable evidence of a prior demyelinating event. Reports of paroxysmal symptoms (historical or current) should, however, consist of multiple episodes occurring over not less than 24 hours. Before a definite diagnosis of MS can be made, at least one attack must be corroborated by findings on neurological examination, visual evoked potential (VEP) response in patients reporting prior visual disturbance, or MRI consistent with demyelination in the area of the CNS implicated in the historical report of neurological symptoms.

[b]Clinical diagnosis based on objective clinical findings for two attacks is most secure. Reasonable historical evidence for one past attack, in the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristics for a prior inflammatory demyelinating event; at least one attack, however, must be supported by objective findings.

[c]No additional tests are required. However, it is desirable that any diagnosis of MS be made with access to imaging based on these Criteria. If imaging or other tests (for instance, CSF) are undertaken and are NEGATIVE, extreme caution needs to be taken before making a diagnosis of MS and alternative diagnoses must be considered. There must be no better explanation for the clinical presentation and objective evidence must be present to support a diagnosis of MS.

[d]Gadolinium-enhancing lesions are not required; symptomatic lesions are excluded from consideration in subjects with brainstem or spinal cord syndromes.

[redacted]

Appendix 3: Guidance on safety monitoring

Patients whose blood pressure reading is ≥140 (systolic) and/or ≥90 mm Hg (diastolic) should have their blood pressure retested after 15 minutes of rest. If the blood pressure is still elevated, they should be followed up in one month by an unscheduled visit if the scheduled visit is not due. Should systolic BP ≥140 and/or diastolic BP ≥90 mm Hg values be confirmed at the second visit, the patient should be referred to his primary care physician, an independent internist or to the specialty hypertension clinic for evaluation, diagnosis and treatment of hypertension.

Patients with BP values of >160/100 mm Hg (confirmed by repeat testing) at any visit during the study should be immediately referred as above for evaluation, diagnosis and treatment of hypertension.

Newly diagnosed hypertension as well as an aggravation of a preexisting condition must be reported as an AE and appropriate antihypertensive medication/dosage adjustment must be considered by the investigator.

Guidance on monitoring of patients with elevated liver function tests

In case of detection of elevated ALT/AST values >2 and <5 times the ULN range, additional blood chemistry panel including ALT, AST, AP, GGT, total and conjugated bilirubin, albumin may be performed at the investigator's discretion.

If ALT/AST values reach 5 times the ULN, confirmed upon repeat testing within two weeks of the initial result or sooner at the discretion of the investigator, the study drug must be permanently discontinued. Patients who develop symptoms suggestive of hepatic dysfunction such as unexplained vomiting or jaundice, should have liver enzymes checked and fingolimod should be discontinued if significant liver injury is confirmed.

In case of isolated elevation of bilirubin over 2.0 mg/dl (34.2 umol/L) unless in context of Gilbert's syndrome, confirmed upon repeat testing within two weeks of the initial result, the investigator must discontinue the study drug. Additional evaluations may be performed at the discretion of the investigator.

For any unscheduled laboratory assessments performed locally, an identical sample should also be sent to the central laboratory for analysis and capture in the central database.

An interruption or discontinuation of the study drug should be clearly documented and reflected on Dosage Administration Record CRF. AE/SAEs need to be filed as appropriate.

Guidance on monitoring of patients with notable lymphopenia

Fingolimod results in sequestration of a proportion of the circulating lymphocytes in lymph nodes with resultant reduction in circulating lymphocyte counts. Average circulating lymphocytes counts are expected to be around 0.5 -0.6 $x10^9$ /L or 500- 600 cells/mm^3. Please see Investigator Brochure for more details. As such, the absolute total WBC, neutrophil and lymphocyte counts will be measured at each visit by the central laboratory, but will be reported blinded for subjects randomized to fingolimod. Lymphocyte counts below $0.2x10^9$/L in patients randomized to fingolimod treatment are reported unblinded and require repeat

[redacted]

testing within 2 weeks. If the repeat test confirms lymphocyte counts below $0.2x10^9$/L, the investigator should perform at least monthly retests. Results will only be reported blinded again once they reach $0.6x10^9$/L.

If the repeat test confirms the lymphocyte count is below $0.2x10^9$/L or 200 cells/mm^3 and there are no signs or symptoms of infection, the patient can continue on study medication at the discretion of the investigator with regular monitoring for signs of infections.

If the patient presents with signs of infection and the lymphocyte count is below $0.2x10^9$/L, the study drug must be temporarily interrupted, and the investigator should consider treatment with a specific therapy on the basis of the clinical diagnosis in consultation with an infectious disease specialist. Reinitiation of the study drug can only be considered once the lymphocyte count reaches 600 cells/mm^3 as confirmed by the central laboratory and after discussion with the Medical Monitor.

If the patient is randomized to the glatiramer acetate treatment group and presents with significant lymphopenia (<50% baseline) confirmed on repeat test by central laboratory within two weeks, study drug must be interrupted and further diagnostic work-up needs to be initiated. The investigator should only consider re-initiation of the glatiramer acetate after a thorough diagnostic workup has been performed, diagnosis/cause for the lymphopenia has been established, treatment has been initiated as adequate, and only after discussion with Medical Monitor and if the patient shows no signs or symptoms of infection or malignancy.

Guidance on monitoring of patients with symptoms of neurological deterioration, inconsistent with MS course

Should a patient develop any manifestations that, in opinion of the investigator, are atypical for multiple sclerosis including unexpected neurological or psychiatric symptom/signs (e.g. rapid cognitive decline, behavioral changes, cortical visual disturbances or any other neurological cortical symptoms/sign), or any symptom/sign suggestive of an increase of intracranial pressure or accelerated neurological deterioration, the investigator should schedule a complete physical and neurological examination and an MRI as soon as possible and before beginning any steroid treatment. Conventional MRI as defined in the protocol as well as Fluid-attenuated Inversion Recovery (FLAIR) and Diffusion-weighted imaging (DWI) sequences are recommended for differential diagnosis of Posterior reversible encephalopathy syndrome. The MRI must be evaluated by the local neuroradiologist. The investigator will contact the Medical Advisor at Novartis to discuss findings and diagnostic possibilities as soon as possible. AE/SAEs need to be filed as appropriate.

In case of new findings in the MRI images in comparison with the previous available MRI which are not compatible with MS lesions, the study drug will be discontinued and other diagnostic evaluations need to be performed at the discretion of the investigator. In case of presence of new hyperintense T2-weighted lesions in the MRI which may be infectious in origin it is recommended to collect a cerebrospinal fluid sample if indicated. Analysis of the CSF sample including cellular, biochemical and, microbiological analysis (e.g. herpes virus, JC virus), to confirm/exclude an infection (e.g. PML) should be performed. In the event of suspected CNS infection, a CSF aliquot should be sent to a central laboratory (designated by the sponsor) for confirmatory testing.

[redacted]

Only when the differential diagnosis evaluations have excluded other possible diagnosis than MS and after discussion with the Medical Advisor at Novartis, the study drug may be restarted.

Guidance on monitoring of patients with infections

All infections that develop during the study will be reported as AEs. Investigators are requested to specifically ask about infections at each visit. Treatment and additional evaluations will be performed at discretion of the investigator.

The investigator should be vigilant for risk of infections including opportunistic infections due to bacterial infections (e.g., atypical mycobacteria), viral infections (e.g., HSV, VZV, JCV), or fungal infections (e.g., cryptococcus agents) and should remind the patient of the risk of infections and to instruct them to promptly report any symptoms of infections to the investigator. The patients must also be reminded to always carry their Patient Information Card (with site contact information and which identifies them as participants in a clinical study with an agent with potential immunosuppressive effects) and to show this to any local healthcare provider they may consult and ask that the investigator be contacted.

When evaluating a patient with a suspected infection, the most sensitive tests available should be used (i.e. that directly detect the pathogen, as with PCR).

The investigator should consider early treatment with specific therapy on the basis of clinical diagnosis or suspicion thereof (e.g., antiviral treatment for herpes simplex or VZV; treatment for cryptococcus) in consultation with infectious disease experts, as appropriate. Investigators should be aware that in the post-marketing setting with fingolimod, isolated cases of cryptococcal meningitis have been reported. Patients reporting symptoms and signs (such as, but not limited to, headache accompanied with stiff neck, sensitivity to light, fever, confusion, tiredness, body aches, chills, vomiting, and/or nausea) consistent with meningitis should undergo prompt diagnostic evaluation. If (cryptococcal) meningitis is diagnosed, appropriate antibiotic treatment should be initiated as soon as possible. The investigator should inform the Novartis medical expert and the CRO's medical expert of any such cases.

Suspension of treatment with fingolimod should be considered if a patient develops a serious infection, and consideration of benefit-risk should be undertaken prior to re-initiation of therapy.

Investigators should consider the added immunosuppressive effects of corticosteroid therapy for treatment of MS attack/relapse and increase vigilance regarding infections during such therapy and in the weeks following administration.

Patients should be evaluated for evidence of immunity to VZV based on any of the following:

- Laboratory evidence of immunity or laboratory confirmation of disease
- Diagnosis or verification of a history of VZV or herpes zoster by a health care provider

To verify a history of VZV, health care providers should inquire about:

[redacted]

- An epidemiologic link to another typical VZV case or to a laboratory confirmed case, or
- Evidence of laboratory confirmation, if testing was performed at the time of acute disease

The VZV vaccination of antibody-negative patients should be considered prior to commencing treatment with fingolimod, following which initiation of study drug should be postponed for at least 1 month to allow full effect of vaccination to occur.

Serology testing for antibody status of HSV-1 and HSV-2 and rubeola (measles) is performed at screening to profile infection risk in study patients. The investigator should inform the patients of their immune status based on these serology results and of the potential risks of primary infections or viral reactivation while taking fingolimod.

A positive IgG antibody test result does not indicate active infection per se, but only evidence of exposure to viral antigens via past infection or vaccination. These patients may however, be at risk for viral reactivation, which may manifest as:

- VZV virus IgG positive: Shingles
- HSV-1 IgG positive: Cold sores
- HSV-2 IgG positive: Herpes genitalis

The investigator should instruct the patient to be alert to and report any symptoms or signs suggestive of cold sores, genital ulcers or shingles, so that appropriate anti-viral treatment can be initiated in consultation with a local infectious disease expert (if needed).

A negative IgG antibody test result for HSV-1, HSV-2, and rubeola places patients at risk for more severe and atypical manifestations of primary infection in the event they are exposed to these viruses while they are immunosuppressed (taking study drug and/or corticosteroids).

Patients who are negative for HSV-1 IgG, HSV-2 IgG and rubeola antibodies should be instructed to promptly report any exposure to these viruses i.e. to a person with cold sores, herpes genitalis, respectively. In case of exposure, early treatment with appropriate antiviral drugs should be considered in consultation with a local infectious diseases expert.

It is also important to ask the patient receiving fingolimod to report if they are exposed to anyone who has recently received a live or live attenuated vaccine and manifested a skin rash after the vaccination so that it can be decided, in consultation with an infectious disease expert, if antiviral therapy is warranted.

It should be noted that live or live attenuated vaccines are prohibited while fingolimod patients are taking study drug and for 8 weeks after study drug discontinuation.

Guidance on monitoring pulmonary function

Patients reporting any respiratory symptoms such as dyspnea, shortness of breath, chest tightness, wheezing should be seen at an unscheduled visit for clinical assessment. A full pulmonary function test (FEV_1, FVC, and D_LCO_c [i.e., $D_LCO$corrected]) and a bronchodilator reversibility test need to be performed, preferably on the same day. If PFTs demonstrate reduction of FEV_1 or FVC values to 80% or below of baseline values, initiation of treatment with bronchodilators will be considered.

[redacted]

In case of reduction of FEV_1, FVC, and/or D_LCO_c below 80% of baseline values, the patient's pulmonary status will require a follow-up as soon as possible within no more than 1 month, including history of respiratory symptoms (eg, dyspnea, shortness of breath, chest tightness, wheezing), physical examination, FEV_1, FVC, D_LCO_c measurement, and a bronchodilator reversibility test.

Should repeat PFT values (FEV_1, FVC, and/or D_LCO_c) remain below 80% of baseline values or should a worsening of the previously reported respiratory symptoms be observed, the patient will be referred to pneumologist (pulmonologist) for further evaluation, including chest HRCT and treatment. A standard referral letter explaining a reason for referral should be accompanied by the sponsor's information letter about the investigational drug (FTY720).

In case of reduction of FEV_1, FVC, and/or D_LCO_c below 60% of baseline value in any visit, the study drug should be discontinued and the patient must be immediately referred to pneumologist (pulmonologist) for further evaluation, including chest HRCT and treatment.

In case of persistent reduction of FEV_1, FVC, and/or D_LCO_c below 80% over 3-month period despite appropriate treatment, the Primary Treating Physician should consider an interruption of the study drug. This decision may be discussed with Medical Monitor.

[redacted]

Appendix 4: Guidance for ophthalmic monitoring

In MS studies, macular edema was reported in 0.4% of patients receiving fingolimod 0.5 mg, and the majority occurred in the first 3-4 months. Some patients presented with blurred vision or decreased visual acuity, but others were asymptomatic and diagnosed during routine ophthalmological examinations. Macular edema generally improved or resolved spontaneously after discontinuation; continuation of fingolimod in patients with macular edema has not been evaluated. Patients with diabetes mellitus or with uveitis are at increased risk of macular edema. Fingolimod has not been studied in multiple sclerosis patients with concomitant diabetes mellitus.

Ophthalmic examinations, including optical coherence tomography (OCT) and fluorescein angiography (FA), for assessment of macular edema are scheduled as outlined in Table 6-1. Similar assessments must be performed as part of an unscheduled ophthalmology visit for any patient who presents with new visual symptoms. If patients report visual disturbances at any time while on therapy, evaluation of the fundus, including the macula, should be carried out by an ophthalmologist.

Guidance on monitoring patients for possible macular edema

If macular edema is suspected during the study, an OCT must be performed as a confirmatory test. If macular edema diagnosis is confirmed on OCT, study drug must be permanently discontinued.

These patients must be followed-up with monthly ophthalmologic evaluations, including OCT, until such time as resolution is confirmed or no further improvement is expected by the ophthalmologist (based on a follow-up period of not less than three months). If the patient does not show definite signs of improvement on examination by specialist testing (e.g., OCT) after 6-8 weeks after discontinuation of study drug, then therapy for macular edema in conjunction with an ophthalmologist experienced in the management of this condition should be initiated and further managed by the ophthalmologist until either resolution of the macular edema or there is absence of any evidence of further improvement.

The discontinuation of the study drug should be clearly documented and reflected on Dosage Administration Record CRF. AE/SAEs need to be filed as appropriate. For patients discontinuing study drug due to a diagnosis of macular edema, copies of the colored OCT as well as source documents of ophthalmic examination should be kept at the site as source documents. These documents may need to be submitted for review by an independent panel if needed.

Guidance on monitoring patients with uveitis

Patients with a history of uveitis or findings compatible with active uveitis at screening can enter the study given that there is no evidence of macular edema in the screening ophthalmic examination.

In order to specifically assess the risk of macular edema in the MS population with co-existing uveitis, each patient with findings in any ophthalmic examination compatible with active uveitis (e.g., significant anterior chamber cell or flare, vitreous cell or flare, pars

[redacted]

planitis, vasculitis, chorioretinitis) under the discretion of the investigator should undergo more frequent ophthalmic examinations. It is the discretion of the investigator to determine the frequency of these ophthalmic examinations. Adjustments to the schedule can be made to align these evaluations with other planned study visits.

A suspicion of macular edema will require an OCT to be performed (refer to Guidance for monitoring of patients with macular edema above).

[redacted]