

Clinical Development

FTY720 (Fingolimod)

Protocol No. CFTY720D2399 / NCT01201356


**A single arm, open-label, multicenter study evaluating the long-term safety and tolerability of 0.5 mg fingolimod (FTY720) administered orally once daily in patients with relapsing forms of multiple sclerosis (LONGTERMS)**

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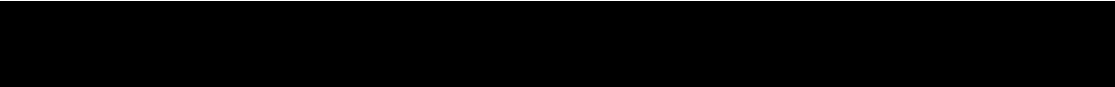
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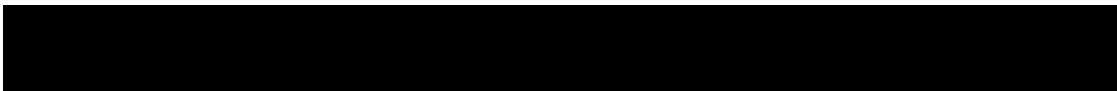
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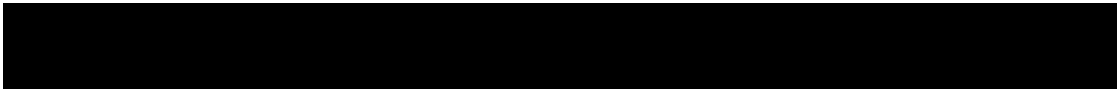
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## List of abbreviations

9-HPT	9-hole peg test
AE	adverse event
ACTH	adrenocorticotrophic hormone
Alb	albumin
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARR	annual relapse rate
AST	aspartate aminotransferase
AV	atrioventricular
BPM	beats per minute
eCRF	electronic case report/record form
CPO	Country Pharma Organization
CRO	Contract Research Organization
CSR	Clinical Study Report
D <sub>L</sub> CO	carbon monoxide diffusing capacity test
DS&E	Drug Safety & Epidemiology
ECG	electrocardiogram
EDC	electronic data capture
EDSS	expanded disability status scale
EOS	end of study
FDF	First dose of fingolimod
FEV1	forced expiratory volume over 1 second test
FSH	follicle-stimulating hormone
FVC	forced vital capacity test
GGT	gamma-glutamyl-transferase
HbA1c	glycated hemoglobin
HCG	human chorionic gonadotropin
HR	heart rate
IB	investigator's brochure

ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	identification
IEC	Independent Ethics Committee
IFN	interferon
IN	Investigator Notification
IRB	Institutional Review Board
IRT	Interactive Response Technology
LFT	liver function test
LN	lymph nodes
LUC	large unstained cells
MedDRA	medical dictionary for regulatory activities
MRI	magnetic resonance imaging
MS	multiple sclerosis
██████	██
NPDR	non-proliferative diabetic retinopathy
OCT	optical coherence tomography
p.o.	by mouth
PFT	pulmonary function test
PPMS	primary progressive multiple sclerosis
██████	██
██████	██
PT/INR	prothrombin time / international normalized ratio
RBC	red blood cell
RMP	risk management plan
RRMS	relapsing remitting multiple sclerosis
██████	████████████████████
SAE	serious adverse event
s.c.	subcutaneously
██████	██
SPMS	secondary progressive multiple sclerosis
SUSAR	suspected unexpected serious adverse reactions



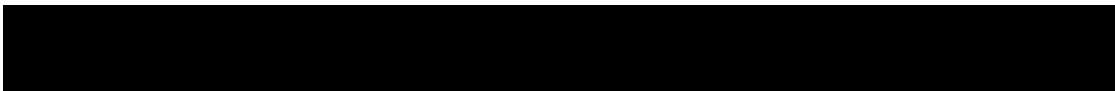
TBL

total bilirubin



ULN

upper limit of normal range





## Glossary of terms

Assessment	A procedure used to generate data required by the study
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to 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 prior to 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
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
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

## **Amendment 11 - present**

### **Amendment rationale**

The purpose of this amendment is to add information inadvertently deleted from Amendment 10 during the publishing process. This study is ongoing with approximately 4,150 enrolled patients. The amendment changes will provide further clarification on the conduct of the protocol.

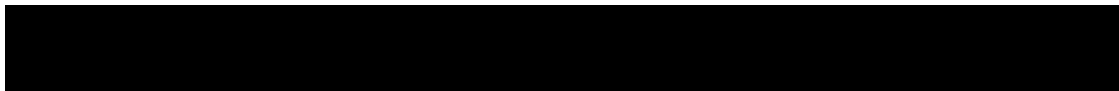
### **Changes to the protocol**

Footnotes for [Table 6-2](#) were inadvertently deleted from the previous amendment, and have been re-inserted in this version to provide further guidance for implementation of the protocol. Additionally, minor administrative errors have been updated throughout the document.

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 Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol are non-substantial and do not require IRB/IEC approval prior to implementation.



## Summary of previous amendments

### Amendment 10 – March 2016

#### Amendment Rationale

As the final label and reimbursement guidelines were unknown at the outset of the fingolimod clinical program, some patients enrolled in the core trials and subsequently transitioned into this protocol are currently ineligible for commercially reimbursed Gilenya. Based on the assumption that continued study participation means there is a positive benefit-risk paradigm for these patients, Novartis elected to extend this protocol for up to two additional years, to allow continued fingolimod use until countries and investigators can find alternate treatment solutions. Therefore, this protocol is being amended to update the study design, offering continued patient participation in a subset of patients (those unable to obtain access to/reimbursement for commercial Gilenya) for an additional (approximately) two years, through June 2018. In keeping with the original protocol objective, safety and tolerability data will continue to be collected during this time period.

This study is ongoing with approximately 4,150 enrolled patients. Endorsement of this amendment will allow patients whose disease is being managed by fingolimod to have continued access, while allowing for continued collection of long-term safety and tolerability data.

#### Changes to the protocol

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.

The major changes made to the protocol are summarized in this section. Other minor changes are incorporated directly into the protocol. The major changes include the following:

- Updates to Study objectives (Section 2), Study design (Section 3.1), Rationale of study design (Section 3.2), Rationale of dose/regimen, duration of treatment (Section 3.3), Population (Section 4), Study completion and post-study treatment (Section 5.5.11), Discontinuation of study treatment (Section 5.5.9), Laboratory evaluations (Section 6.5.4), Data analysis (Section 9), Guidance on Safety Monitoring (Section 13, Appendix 5), and the Schedule of assessments (Table 6-1).
- [REDACTED] Liver event and Laboratory trigger Definitions and Follow-up Requirements (Section 13, Appendix 6), and the Schedule of assessments for Part Two (Table 6-2).

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

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

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 protocol amendment.

## **Amendment 9 – September 2015**

### **Amendment rationale**

The protocol is 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. Second, this amendment provides details regarding the Study Completion visit scheduling for all patients, and re-introduces hematology testing at every visit.

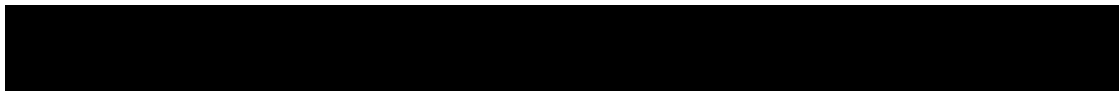
Notably, there have been reports of isolated cases of cryptococcal meningitis in patients with relapsing MS receiving fingolimod. As a result, the fingolimod local product labeling will be updated to guide prescribers for vigilance, early detection, and diagnosis of such cases, should they occur. Similarly, the infection safety monitoring guidance is being updated in this protocol.

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.

This study planned to end by 30-Jun-2016 in order to collect 60 months or more of long-term safety data for the majority of Phase II/III patients. Guidance regarding scheduling of the Study Completion visit is provided in order to streamline the study closure processes, specifically designating the Study Completion visit to occur at or shortly after sixty months of study participation for those patients who would reach 60 months by 30-Jun-2016. Patients not reaching 60 months by 30-Jun-2016 will have their study completion on or around 30-Jun-2016 (+/- 30 day visit window), and patient who have already reached 60 months should have their Study Completion visit at their next six monthly visit, or 30-Jun-2016, whichever comes first.

Hematology testing has been re-instituted at the six monthly visits (i.e., every study visit) to provide additional lymphocyte count information to study sites.

This study is an ongoing study with approximately 4,150 enrolled patients. These changes will ensure that study patients receive the same information and care that patients on commercial Gilenya will receive, provide additional lymphocyte monitoring, and clarify the upcoming study completion visit scheduling.



## Changes to the protocol

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.

The major changes made to the protocol are summarized in this section. Other minor changes are incorporated directly into the protocol. The major changes include the following:

- Updates to the Background ([Section 1.1](#)), Physical/neurological exam ([Section 6.5.1](#)), Skin assessments ([Section 6.5.2](#)), and Guidance on safety monitoring ([Appendix 5](#)) based on investigator brochure (Edition 18) updates.
- Updates to Study design ([Section 3.1](#)), Rationale of study design ([Section 3.2](#)), Population ([Section 4](#)), Study completion and post-study treatment ([Section 5.5.11](#)), and the Schedule of assessments ([Table 6-1](#)) related to Study Completion visit scheduling and/or re-introduction of hematology sampling at the 6-monthly visits.

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

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

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 protocol amendment.

## Amendment 8 – August 2014

### Amendment rationale

The primary objective of this study is to evaluate the continued safety and tolerability of fingolimod over longer periods of time. The Gilenya Risk Management Plan (RMP) provides guidance for the minimum safety monitoring required. During a review of the protocol, it was identified that the protocol has more stringent monitoring frequency than recommended in the RMP and standard of care. Thus, in an effort to reduce patient and site burden, in addition to managing internal resources, some clinical monitoring has been amended to reflect current RMP guidance. [REDACTED]

This is an ongoing study with approximately 4,000 enrolled patients. These changes will reduce patient and site burden while continuing to collect data supporting the study objectives, without negatively impacting standard of care or the final study results.

### Changes to the protocol

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.

[REDACTED]

The major changes made to the protocol are summarized in this section. Other minor changes are incorporated directly into the protocol. The major changes, outlined in Section 6, include the following:

- MRI frequency changed from annually to one at EOS
- Clinical laboratory collection changed from a biennial to annual collection, with urine pregnancy tests for females being substituted at the visits during which other clinical laboratory testing has been removed.

Additionally minor administrative changes have been made to either correct or clarify verbiage.

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

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

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 protocol amendment.

## **Amendment 7 – August 2013**

### **Amendment rationale**

Varicella zoster virus (VZV) antibody testing and surveillance in patients enrolled in this extension, including patients enrolled from core studies prior to implementation of mandatory pre-treatment anti-VZV antibody serology, has been clarified in accordance with the 2013 Core Data Sheet (CDS) update. The language is reinforced to ensure that previous history of varicella or varicella vaccination is adequately documented by a health care professional and wording has been strengthened regarding the need for patients to be tested for antibodies to determine prior VZV exposure and to vaccinate if negative.

The title of the study was changed back to the original version in response to feedback from the central ethics committee for France. This change indicates that only uncontrolled efficacy data are collected in this study, which may be subject to bias, as compared to the more rigorous efficacy data collected in a double-blind randomized study. Furthermore, the title clarifies that only patients with relapsing MS were included in the core studies from which the patients in trial D2399 are enrolled.

Several additional administrative changes were made to clarify the revised screening laboratory tests and schedule of assessments, which were implemented in Amendment 6.

Reversion of title back to original title will allow French cohort of patients to continue in the trial and ensure additional awareness of VZV guidance for all countries.

## Changes to the protocol

The major changes made to the protocol are summarized in this section. Other minor changes are incorporated directly into the protocol. The major changes include the following:

- Clarified VZV antibody guidance has been added.
- The protocol title has been modified.

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 Board (IRBs)/Independent Ethics Committee (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.

## Amendment 6 – July 2012

### Amendment rationale

A protocol amendment was released in February 2012 with preliminary recommendations for additional first-dose monitoring beyond 6 hours for patients meeting specific defined criteria, as well as country-specific guidelines for Germany which included continuous ECG monitoring during the 6-hour observation period.

This amendment implements final recommendations on first dose monitoring at treatment re-initiation (since recruitment is completed no treatment initiation per se will occur under this protocol). In addition, it removes the country-specific guidelines for Germany, as the monitoring procedures and safety assessments mandated in the protocol are deemed appropriate for adequately protecting the safety of patients with an increased risk of cardiovascular problems. However, this amendment clarifies that any additional procedures or assessments that may be required as per local prescribing information must be followed.

### Changes to the protocol

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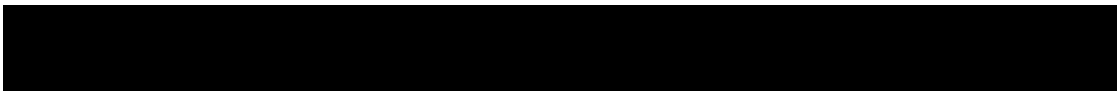
The major changes made to the protocol are summarized in this section. Other minor changes are incorporated directly into the protocol. The major changes include the following:

- Exclusion criteria related to the cardiovascular conditions are updated.
- Exclusion of patients taking medications that lower heart rate has been added.
- Germany country-specific recommendations removed; additional procedures and assessments required by local prescribing information should be followed accordingly.

- Appendix 4 Guidance for monitoring of patients taking their first dose of the study drug is updated to reflect final guidance.

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

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, as 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.





## Amendment 5-February 2012

### Amendment rationale

In November 2011, there was a sudden, unexplained death of a patient within 24 hours after the administration of the first dose of fingolimod 0.5 mg. While the cause of death was unknown and the role of fingolimod had not been confirmed or excluded, the event prompted a thorough review of cardiac safety data from clinical trials as well as spontaneous reports in the post-marketing setting.

Following this review, additional observation beyond 6 hours is recommended for individuals who may be at risk of later occurring events based on certain defined criteria. To that end, changes to the protocol are implemented in all countries to specify which ECG abnormalities and heart rate thresholds should lead to continued observation of patients beyond the mandatory 6-hour first dose observation period.

Continued observation beyond 6 hours is required for patients who, at the end of the first dose observation period, have a heart rate (HR) of <45 beats per minute (bpm), new onset second degree or higher AV block, or if the HR at 6 hours post-dose is the lowest value post-dose. Given that QT prolongation in the presence of marked bradycardia may be associated with increased risk of ventricular arrhythmias, it is specified that continued observation will also be required for patients whose QTc on the 6-hour ECG is 500 msec or greater. Continued observation should be maintained until the event leading to the continued observation has resolved. These criteria are in addition to those already in place, i.e. patients with symptomatic bradycardia and those in whom the 6-hour HR is the nadir of the observation period.

In addition to the guidance above, patients initiating or re-initiating treatment in Germany will also require continuous ECG monitoring during the 6-hour observation period. If this continuous ECG monitoring shows either persistent second degree AV block Mobitz type I at 6 hours, second degree AV Mobitz type II or higher, AV block at any time, or a HR at 6 hours post-dose that is 20 bpm or more lower than the pre-dose HR, extended monitoring will be necessary until the event leading to the extended monitoring has resolved. These guidelines will be specified where required throughout the protocol.

Patient enrollment started in September 2010. At the time of this amendment, approximately 3750 patients have enrolled into the study. It is not expected that the changes implemented in this amendment will affect the patient population.

### Changes to the protocol

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.

The major changes made to the protocol are summarized in this section. Other minor changes are incorporated directly into the protocol. The major changes include the following:

- Exclusion criteria related to the cardiovascular conditions are updated.

- Appendix 4 Guidance for monitoring of patients taking their first dose of the study drug is updated.
- Only for Germany: Patients requiring first dose monitoring will receive continuous 6-hour ECG monitoring after the first dose or upon re-initiation of fingolimod treatment after an interruption of greater than 14 consecutive days.

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

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, as 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.

## **Amendment 4-October 2011**

### **Amendment rationale**

This Amendment aims to further define the extended follow-up for patients who previously completed the phase II or III fingolimod clinical development studies in an interventional trial setting through 30-Jun-2016. It extends the enrollment to patients who have completed CFTY720D2309/E1 as well as the re-enrollment of CFTY720D2399 patients who have previously completed this study based on the original CFTY720D2399 study endpoint of local approval and reimbursement. Furthermore, this amendment will define additional assessments to evaluate the long-term efficacy of fingolimod in phase II and III trial patients. Lastly, this amendment aims to bring the study schedule of assessments as well as the safety monitoring guidelines in alignment with the fingolimod prescribing information of major countries where the medication has been registered.

As indicated in Amendment 3, patients who were participating in the fingolimod phase II/III development program have 2.5 to over 8 years of long-term exposure. The patient population included in these trials is particularly suitable for long-term evaluation for several reasons: patients have met specific inclusion/exclusion criteria, are well characterized at baseline, have a well-documented clinical course throughout their participation in the individual clinical trials and include patients who were randomized to placebo or active comparator during their core studies. Thus, these patients already have documented long-term data on the safety and efficacy of fingolimod treatment, coupled with careful baseline assessments. Maintaining these patients in the context of an interventional study will allow for the continued collection of rigorous long-term data. Therefore, in addition to following long-term safety, this amendment adds assessments to obtain additional long-term efficacy data, including confirmed relapse data and EDSS-based disability progression, as well as MRI assessments measuring lesion burden and brain atrophy.

Contrary to patients included in the phase II and pivotal MS studies, patients having participated in phase IIIb studies have limited fingolimod exposure in predominantly uncontrolled studies of short duration. Since these studies focused on specific safety assessments, MS baseline characteristics were not as well documented since patient selection

was not based on disease activity and history and the clinical course of MS during these short trials was not followed based on rigorous efficacy assessments, such as relapse confirmation, blinded EDSS rating, and MRI. Therefore, these patients will continue to follow the current study endpoint of local approval and reimbursement. The patients who are not eligible for reimbursement will be allowed to remain in this study for an additional 180 days.

Phase II/III patients, who met the original study endpoint in CFTY720D2399 of approval and reimbursement for fingolimod in their respective countries will be invited to rejoin this study in order to continue participation through 30-Jun-2016 and add to the collection of long-term safety and efficacy data. In addition, patients from the CFTY720D2309/E1 study who may not have had the opportunity to enroll into this study based on the original study endpoint will also be invited to participate in this study through 30-Jun-2016.

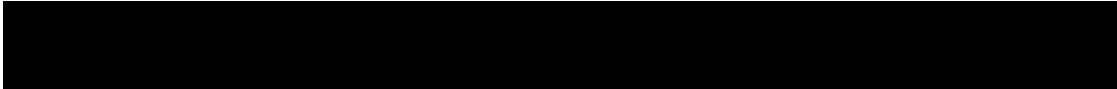
The schedule of assessments, frequency of visits, and the safety monitoring guidelines have been updated to reflect the fingolimod prescribing information of major countries where the medication has already been approved. Any additional assessments required by the local labels should be performed as required in the context of routine clinical care. In addition efficacy measurements, i.e. MRI assessments (including brain atrophy), relapse data, and disability progression, have been added for patients with a documented baseline in order to obtain additional long-term efficacy data.



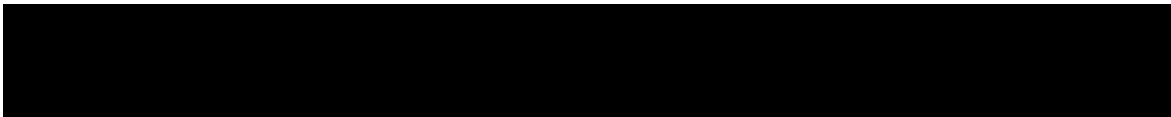
## Changes to the protocol

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.

The major changes made to the protocol are summarized in this section. Other minor changes are incorporated directly into the protocol. The major changes include the following:

- Phase IIIb study patients not eligible for reimbursement can remain in the study 180 days post fingolimod reimbursement.
  - Patients from CFTY720D2309/E1 can enter the trial and phase II/III patients who previously completed this trial can re-enter for long-term follow-up.
  - Inclusion/Exclusion criteria are updated.
  - First dose monitoring required following interruptions of study drug of greater than 14 consecutive days; previously, following interruption of 8 days or greater.
  - Optional pulmonary function testing (PFT) is added.
  - Skin exams are no longer required; remain as optional.
- 

- OCT and Ophthalmic exam frequency is adjusted.
- EDSS certification requirement added for investigators evaluating Phase II/III patients; collection of functional EDSS scores added for the Phase II/III patients.
- Visit frequency adjusted to every 6 months, starting with Visit 6.
- MRI testing added for Phase II/III patients.
- Definition of “confirmed relapses” is added; the confirmed relapse information is to be collected.
- Several laboratory tests are no longer being collected (HbA1c, HIV, hepatitis B and C, herpes simplex virus 1 and 2, and rubeola).

- 
- Changes to contraception requirements and to safety guidelines for pregnant patients.
  - Changes to safety guidelines for patients with elevated liver function tests, diagnosis of macular edema or basal cell carcinoma.

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

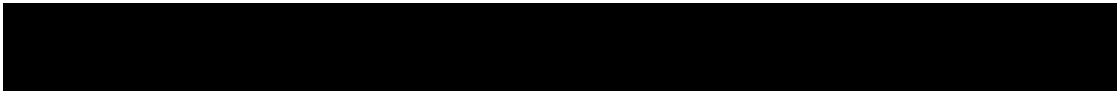
The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, as the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended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

## **Amendment 3-May 2011**

### **Amendment rationale**

Study CFTY720D2399 includes patients who previously participated in the fingolimod phase II (D2201) and phase III (D2301, D2302, D2309) studies and their associated extension trials (CFTY720D2201E1, CFTY720D2301E1, CFTY720D2302E1, CFTY720D2309E1). In addition, patients who have participated in and completed ongoing phase IIIb studies of fingolimod are also eligible. Patients who participated in the phase IIIb trials initiated treatment with fingolimod only recently. Patients who were participating in the phase II/III development program have 2-7 years of continuous exposure and met specific inclusion/exclusion criteria and have very well documented clinical course over those years. These latter patients provide valuable long-term data on safety and efficacy of fingolimod treatment, coupled with careful baseline assessments.

The rationale of this amendment is to allow further follow-up of those patients who previously completed the Phase II or III fingolimod clinical development trials in an interventional trial setting through 30-Jun-2016. In addition, this amendment will allow the re-enrollment of those phase II/III patients who have completed participation in one of the phase II/III extension studies, who remain on fingolimod therapy and wish to continue on fingolimod in a clinical trial setting.



Those patients originating from the phase IIIb program will be offered to transition into observational studies to collect long-term safety data in the setting of standard medical practice upon approval and reimbursement of fingolimod in the respective country, as foreseen in the original version of this protocol.

### **Changes to the protocol**

The changes made throughout the protocol update the study end for the Phase II/III patients to fingolimod registration, commercial availability and reimbursement OR through 30-June-2016, whichever is later.

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 Board (IRBs)/ Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, as 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.

## **Amendment 2-March 2011**

### **Amendment rationale**

The rationale for this amendment in Norway is to revise the study endpoint to 01-Aug-2012 is to allow patients who complete ongoing studies to receive continuous treatment with fingolimod and to collect long-term safety data for approximately 12 months following the completion of prior trial. As the study has not yet started in Norway, there is no impact on the patients or the study itself.

Additionally, the Exclusion criterion 10c is updated to be in accordance with the recommended wording in the Summary of Product Characteristics for fingolimod, as agreed upon by CHMP. The exclusion is expanded to arrhythmia requiring current treatment with Class Ia or III antiarrhythmic medications.

### **Changes to the protocol**

The changes made throughout the protocol are specific to Norway and update the study endpoint to reflect the time point approximately 12 months following the completion of the previous fingolimod trial or maximally through 01-Aug-2012.

The References section is updated to correct clerical errors.

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 Board (IRBs)/ Independent Ethics Committee (IECs) and Health Authorities.

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

## **Amendment 1-July 2010**

### **Amendment rationale**

- The rationale for this amendment in the UK is to revise the study endpoint to 31-Dec-2012 to be in line with the Commission Directive 2005/28/EC and the requirements of the UK Health Authority. As the study has not yet started, there is no impact on the patients or the study itself.
- The rationale for this amendment in Poland is to revise the study endpoint to 31-Dec-2012 in order to continue to provide patients treatment through what is considered a reasonable period of time for reimbursement to be achieved in Poland where thereafter patients can, if within their treatment plan, receive commercial supply as prescribed by their physician. As the study has not yet started, there is no impact on the patients or the study itself.

### **Changes to the protocol**

The changes made throughout the protocol are specific to Poland and the UK and update the study endpoint to reflect until fingolimod is registered and through approximately one-year post approval or maximally through 31-Dec-2012.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using red underlined for insertions.

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

The changes described in this amended protocol require IRB/IEC approval prior to implementation.



## Protocol synopsis

### Title of study:

A single arm, open-label, multicenter study evaluating the long-term, safety and tolerability of 0.5 mg fingolimod (FTY720) administered orally once daily in patients with relapsing forms of multiple sclerosis.

### Purpose and rationale:

The purpose of this study is to collect long-term safety, tolerability, efficacy, and health outcomes data in patients who participated in the fingolimod multiple sclerosis clinical development program.

### Objectives:

#### Primary Objectives:

This study is designed to evaluate the long-term safety and tolerability of fingolimod 0.5 mg/day in patients with MS for the duration of the study.

#### Secondary Objectives:

This study will also evaluate long-term efficacy of fingolimod 0.5 mg/day in patients with MS, as measured by disability progression, brain volume (atrophy), T1- (non-enhanced) and T2-weighted lesion volume and MS relapse occurrence in Study Part One.

### Population:

Approximately 5000 patients who have completed ongoing or planned clinical trials in the MS development program with fingolimod are expected to be enrolled in >500 centers worldwide.

### Inclusion/Exclusion criteria:

#### 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.
2. Patients who have completed designated ongoing or planned Novartis global clinical trials with fingolimod and are unable to obtain fingolimod outside a clinical trial.

#### Exclusion Criteria:

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

1. Premature permanent discontinuation from any fingolimod study due to:
  - a. An adverse event or serious adverse event or laboratory abnormality.
  - b. Conditions leading to permanent study drug discontinuation.
2. 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 hCG laboratory test (> 5 mIU/ml). Patients who temporarily or permanently discontinued from any fingolimod study because of pregnancy can be re-enrolled.
3. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, UNLESS they are using highly effective contraception during the study and for 2 months after stopping treatment. 'Highly effective contraception' defined as contraception which results in less than 1% unwanted pregnancies when used properly according to the label.

4. Chronic disease of the immune system other than MS which may require immunosuppressive treatment.
5. Severe active infection or active chronic infection.
6. Previous treatment with cladribine, cyclophosphamide or mitoxantrone.
7. Treatment with monoclonal antibodies (including Natalizumab) in the past 3 months.
8. Uncontrolled diabetes (HbA1c>9%).
9. Macular edema at Baseline.
10. Any medically unstable condition that may interfere with the patient's ability to cooperate and comply with the study procedures, as assessed by the treating physician.
11. Any of the following cardiovascular conditions:
  - a. myocardial infarction within the past 6 months prior to enrollment or current unstable ischemic heart disease;
  - b. cardiac failure at time of Screening (Class III & IV, according to New York Heart Association Classification) or any severe cardiac disease as determined by the investigator;
  - c. patients receiving current treatment with Class Ia or III antiarrhythmic drugs (e.g., quinidine, disopyramide, amiodarone, bretylium, sotalol, ibutilide, azimilide, dofetilide, ajmaline, procainamide);
  - d. second-degree AV block Type II or third-degree AV block or corrected QTc interval >450 msec in males or >470 msec in females;
  - e. sick sinus syndrome or sino-atrial heart block;
  - f. uncontrolled hypertension despite prescribed medications.
12. Any of the following pulmonary conditions during the previous fingolimod study or observed at the enrollment visit:
  - a. severe respiratory disease or pulmonary fibrosis;
  - b. active tuberculosis;
  - c. in patients enrolling from studies with regular spirometry: reduction of FEV1, FVC and/or DLCO below 60% of core study baseline values or if FEV1, FVC and/or DLCO at extension study baseline is the second of two consecutive pulmonary function tests with values <80% of core study baseline.
13. Severe liver impairment or chronic liver disease.
14. Positive screening for serological markers for hepatitis A, B, C and E indicating acute or chronic infection:
  - anti-hepatitis A virus IgM,
  - hepatitis B surface antigen and/or anti-hepatitis B core antigen IgM,
  - anti-hepatitis C virus IgG or IgM,
  - anti-hepatitis E virus IgM (if positive IgG: do hepatitis E virus-RNA polymerase chain reaction: if negative, patient can be included).

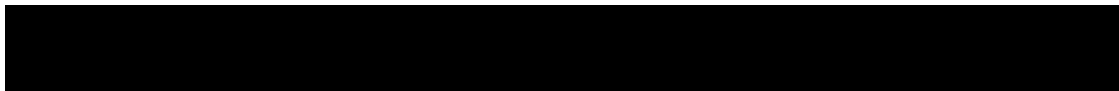
Note: The following patients, assuming they have normal aminotransferase activities, can be included in the trial:

- those testing positive for hepatitis B surface antibody, indicating hepatitis B immunization - OR-
- those testing positive for anti-hepatitis B core antigen IgG, indicating a cured hepatitis B - OR-
- those testing positive for anti-hepatitis A virus IgG, indicating a cured hepatitis A.

#### **Investigational therapy:**

All patients will receive open-label fingolimod 0.5 mg, taken p.o. once daily.

#### **Study design:**





This study uses an open-label, multi-center, single treatment arm design allowing patients participating in the fingolimod multiple sclerosis clinical development program to enroll to collect additional long-term safety, tolerability, efficacy, and health outcomes data.

This study has two parts:

- Part One, collecting long-term safety, tolerability, efficacy, and health outcomes data through approximately 30-Jun-2016, and
- Part Two\*, collecting limited safety data until approximately 30-Jun-2018, in a subset of patients participating in Part One, and other eligible patients from ongoing fingolimod trials (e.g., CFTY720D2312).

\*Eligibility for Part Two is defined as prior fingolimod study patients who are unable to obtain fingolimod outside a clinical trial.

By June 2016, investigators must determine commercial Gilenya eligibility for all active study patients (i.e., reimbursed for commercial Gilenya). Patients able to obtain commercial Gilenya will then have their End of Study (Part One) visit and exit the study, regardless of their post-study treatment decision (i.e., continuing on Gilenya commercially or transitioning to another treatment option). Patients discontinuing or completing the study at Part One who do not continue on commercial Gilenya must return for two follow-up study visits, 3-months and 6-months post-last dose of fingolimod. Patients who choose to continue on commercial Gilenya outside the study are exempted from the follow-up visits.

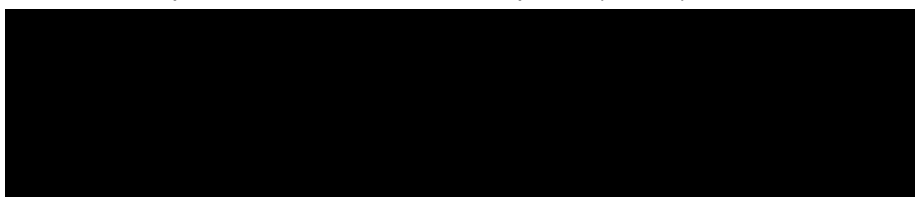
Patients not eligible for reimbursed, commercial Gilenya will be offered continued study participation in Part Two until their scheduled study visit closest to 30-Jun-2018 (+/- 30 day visit window), with a reduced assessment schedule (see Table 6-2), for the purpose of collecting additional long-term safety and tolerability data in support of the primary study objective. Patients discontinuing or completing the study after entering Part Two who do not continue on commercial Gilenya must return for one follow-up study visit, 3-months post-last dose of fingolimod. Patients who choose to continue on commercial Gilenya outside the study are exempted from the follow-up visit.

**Safety assessments:**

- Physical/neurological examination
- Vital signs
- Laboratory blood evaluations
- Eye exam by treating physician
- ECG
- Ophthalmologic Exam/Optical coherence tomography (OCT) by ophthalmologist, if clinically indicated
- Skin assessments, if clinically indicated
- Pulmonary function testing, if clinically indicated

**Efficacy assessments:**

- MS Relapse
- Expanded Disability Status Scale (EDSS)
- Magnetic Resonance Imaging (MRI)
- Multiple Sclerosis Functional Composite (MSFC)



**Data analysis:**

Unless otherwise specified, the following pertains to the entire study (Study Parts One and Two).

Long-term safety will be assessed based on adverse events (AEs), laboratory and vital signs as well as other investigations performed when clinically indicated. Analysis of the safety variables will be conducted on the safety set.

Incident rates (IRs) of adverse events per 100 patient-years will be summarized by highest assigned fingolimod dose (fingolimod 0.5 mg/day and any dose of fingolimod).

To further evaluate the risk with longer fingolimod exposure duration, IR if adverse events reported with different fingolimod exposure durations will be compared.

In addition, the incidence of adverse events (new or worsened from the long-term extension baseline) reported during the long-term extension will be summarized by primary system organ class and preferred term as frequency count and percentage of patients with adverse events.

The incidence of death, serious adverse events (SAEs), AEs leading to discontinuation, and other significant AEs will be summarized separately by primary system organ class and preferred term.

Laboratory data will be summarized using summary statistics of raw data and change from baseline values. For liver function tests, the frequencies and percentages of patients with elevations of 1, 2, 3, 5, and 10 times upper limit of normal will be summarized by visit (Study Part One only).

Vital sign data will be summarized as descriptive statistics for change from baseline value. The incidence rates of notable vital sign abnormalities will be summarized.

Summary statistics for ECG parameters (including pre-dose ECG for patients who have this evaluation done) will be summarized by visit. Incidence of abnormal ECGs by type of abnormality will be presented.

The incidence of macular edema events will be summarized as frequency distributions. The patient data listing will also be provided.

Pulmonary function test data (FEV<sub>1</sub>, FVC, and D<sub>L</sub>CO, percentage of predicted value for these three variables, and smoking status) will be summarized.

The skin assessment will be summarized based on abnormal findings.

The safety data will also be summarized by subgroups for the supportive safety analysis purpose.

The safety data obtained after discontinuation of the study drug will be summarized.

Descriptive statistics (along with change from baseline to post-baseline visit, where appropriate) will be presented for the following variables: Annual Relapse Rate (ARR), time to relapse (including HR), absolute EDSS scores, time to EDSS scores of 4, 6, 7, time to 6-month confirmed disability progression, absolute MSFC scores

[REDACTED]

[REDACTED]

## 1 Introduction

### 1.1 Background

Multiple Sclerosis (MS) is a chronic, demyelinating, immune-mediated disease of the central nervous system characterized by inflammation and destruction of myelin and axons (Trapp et al 1998, Sospedra et al 2005). 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, 90% within 25 years. Apart from these initially relapsing forms of MS, 10-15% 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) is a new chemical entity for once daily oral administration which completed phase III development and has obtained marketing authorization in the US, Europe and a number of other countries and regions since 2010.

Pharmacologically, fingolimod targets a novel class of G protein-coupled receptors (GPCRs) 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 (LNs) 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. FTY720-P (FTY720-phosphate) acts as a super agonist of the S1P1 receptor on lymphocytes, inducing its uncoupling/internalization. The internalization 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 LNs in experimental autoimmune encephalomyelitis (EAE)/MS, and this reduces their recirculation to the CNS and abrogates central inflammation.

In a large active controlled study (CFTY720D2302, TRANSFORMS) vs. intramuscular interferon beta-1a (IFN  $\beta$ -1a i.m.), fingolimod showed a significant reduction in relapse rate over the 12-month treatment period and also significantly improved MRI findings e.g. reduction in markers of inflammatory activity in the brain. A significant reduction in the loss of brain volume was detected, as compared to IFN $\beta$ -1a i.m. (Cohen et al. 2010). In a 2-year placebo-controlled study (CFTY720D2301, FREEDOMS), fingolimod demonstrated sustained reduction of relapse rate, delayed disability progression and demonstrated reduction in markers of inflammatory activity in the brain. As in TRANSFORMS, in FREEDOMS a significant reduction in the rate of brain atrophy was observed as compared to placebo as early as 6 months after the initiation of treatment, and consistently so at 12 and 24 months (Kappos et al. 2010).

The safety profile of fingolimod has been well characterized in the MS clinical development program. As of 29-Feb-2012, the MS clinical trials exposure in global and local studies is estimated to be approximately 16,500 patient-years, reached in more than 10,000 MS patients treated with fingolimod in Phase II, III, IIIb, and IV studies and their extensions. 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 AEs leading to discontinuation of study drug was slightly higher for the fingolimod 0.5 mg/day (10.5%) than the placebo group (8.7%), and higher again in the fingolimod 1.25 mg/day group (14.1%). The overall incidence of SAEs was comparable between fingolimod groups (11.6% and 10.5% for 1.25 mg/day and 0.5 mg/day, respectively) and placebo (12.2%).
- Specific AEs that were reported more commonly in MS patients treated with fingolimod than placebo included elevation of liver enzymes, in particular increases in ALT and GGT, reduction in white blood cell counts (lymphocytes and total WBC), transient bradycardia following the post first dose of fingolimod, macular edema, hypertension, dyspnea, bronchitis, and diarrhea. The AEs most prominently associated with fingolimod treatment, e.g. liver enzyme elevations, bradycardia, and macular edema appeared to show a dose related 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 (interferon 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 apparent dose effect. Two fatal infections occurred in the fingolimod 1.25 mg/day group: one case of disseminated varicella-zoster virus in a sero-negative patient receiving concomitant high dose steroid therapy for an MS relapse, and one case of herpes simplex encephalitis in a patient in whom initiation of acyclovir therapy was delayed by one week. 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. Cases of lymphoma (cutaneous T-cell lymphoproliferative disorders or diffuse B-cell lymphoma) were reported in premarketing clinical trials in MS patients receiving fingolimod at, or above, the recommended dose of 0.5 mg. Based on the small number of reported cases and short duration of exposure, the relationship to fingolimod remains uncertain.
- Initiation of fingolimod treatment has been associated with atrio-ventricular conduction delays usually as first-degree atrio-ventricular blocks (prolonged PR interval on ECG). Second-degree atrio-ventricular 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.

- The use of fingolimod in women who are or may become pregnant should only be considered if the potential benefit justifies the potential risk to fetus. Animal studies have shown reproductive toxicity including fetal loss and organ defects, notably persistent truncus arteriosus and ventricular septal defect. Furthermore, the receptor affected by fingolimod (sphingosine-1-phosphate receptor) is known to be involved in vascular formation during embryogenesis. The data available from the use of fingolimod in pregnant women are too limited to draw conclusions on safety of fingolimod in pregnancy. Since it will take approximately 2 months to eliminate the compound from the body upon stopping treatment, risk potential to the fetus may persist and contraception should be pursued during that period. The risk of teratogenic effects of fingolimod is being further addressed in a specific pregnancy registry. Fingolimod is excreted in milk of treated animals during lactation. Because of the potential for serious adverse drug reactions in nursing infants from fingolimod, women receiving fingolimod should not breast feed.
- The safety and tolerability profile did not change over time, as determined in the pooled data of the phase II and III studies and their respective open-label extension studies. In particular, the incidence of malignancies and serious infections did not increase over time. Further long-term data are however needed to better estimate the incidence of rare or time-dependent adverse events.

The current data showed no significant difference on efficacy between the fingolimod 1.25 mg/day and the 0.5 mg/day doses in phase III studies. Fingolimod 0.5 mg/day was associated with an overall more favorable risk/benefit profile than fingolimod 1.25 mg/day. Based on these data, the dose of fingolimod chosen for registration and for further clinical development is 0.5 mg/day.

In the post-marketing setting, isolated delayed onset events, including transient asystole and the one unexplained death, have occurred within 24 hours of the first dose. These cases have been confounded by concomitant medication and/or pre-existing diseases and the relationship to fingolimod is uncertain. Therefore, it is recommended that fingolimod not be initiated in patients with a history of cardiovascular or cerebrovascular disease or in those patients taking heart-rate lowering medications. Safety assessments in this study specifically address these areas of interest in the safety and tolerability profile of fingolimod over the long-term.

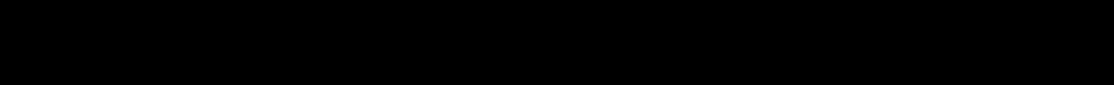
## **1.2 Purpose**

The purpose of this study is to collect long-term safety, tolerability, efficacy, and health outcomes data in patients who participated in the fingolimod multiple sclerosis clinical development program.

## **2 Study objectives**


### **2.1 Primary objectives**

This study is designed to evaluate the long-term safety and tolerability of fingolimod 0.5 mg/day in patients with MS for the duration of the study.



## 2.2 Secondary objectives

This study will also evaluate long-term efficacy of fingolimod 0.5 mg/day in patients with MS, as measured by disability progression, brain volume (atrophy), T1- (non-enhanced) and T2-weighted lesion volume and MS relapse occurrence in Study Part One.



## 3 Investigational plan

### 3.1 Study design

This study uses an open-label, multi-center, single treatment arm design allowing patients participating in the fingolimod multiple sclerosis clinical development program to enroll in order to collect additional long-term safety, tolerability, efficacy, and health outcomes data.

This study has two parts:

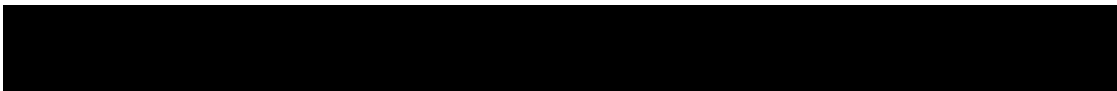
- Part One, collecting long-term safety, tolerability, efficacy, and health outcomes data through approximately 30-Jun-2016, and
- Part Two\*, collecting limited safety data until approximately 30-Jun-2018, in a subset of patients participating in Part One, and other eligible patients from ongoing fingolimod trials (e.g., CFTY720D2312).

\*Eligibility for Part Two is defined as prior fingolimod study patients who are unable to obtain fingolimod outside a clinical trial.

By June 2016, investigators must determine commercial Gilenya eligibility for all active study patients (i.e., reimbursed for commercial Gilenya). Patients able to obtain commercial Gilenya will then have their End of Study (Part One) visit and exit the study, regardless of their post-study treatment decision (i.e., continuing on Gilenya commercially or transitioning to another treatment option). Patients discontinuing or completing the study at Part One who do not continue on commercial Gilenya must return for two follow-up study visits, 3-months and 6-months post-last dose of fingolimod. Patients who choose to continue on commercial Gilenya outside the study are exempted from the follow-up visits.

Patients not eligible for reimbursed, commercial Gilenya will be offered continued study participation in Part Two until their scheduled study visit closest to 30-Jun-2018 (+/- 30 day visit window), with a reduced assessment schedule (see Table 6-2), for the purpose of collecting additional long-term safety and tolerability data in support of the primary study objective. Patients discontinuing or completing the study after entering Part Two who do not continue on commercial Gilenya must return for one follow-up study visit, 3-months post-last dose of fingolimod. Patients who choose to continue on commercial Gilenya outside the study are exempted from the follow-up visit.

Patients enrolling in either part of the study from blinded studies will remain blinded to the identity of the treatment in the previous study. In order to maintain the blind, the monitoring



immediately after the first dose of study drug will be performed by a blinded first-dose administrator.

### **3.2 Rationale of study design**

The clinical development program of fingolimod has demonstrated efficacy and a favorable benefit/risk ratio of the fingolimod 0.5 mg/day dose in patients with relapsing-remitting multiple sclerosis (RRMS), based on reduction in the annualized relapse rate, the reduction in risk for disability progression, and reduction of inflammatory activity and brain atrophy in the brain as evidenced by MRI. The safety profile of fingolimod has been well characterized in comparison to both placebo and a first-line treatment active comparator. The specific areas of concern in the safety profile of fingolimod have been identified and are addressed as appropriate in this protocol.

This study is designed to collect long-term safety, tolerability, efficacy and health outcomes data in eligible patients who participated in the fingolimod multiple sclerosis clinical development program.

An open-label, non-comparative single arm design is considered adequate for this type of long-term extension. Neither a placebo-control can be justified over the long-term nor does the logistical burden for patients and study sites justify the use of an active comparator arm.

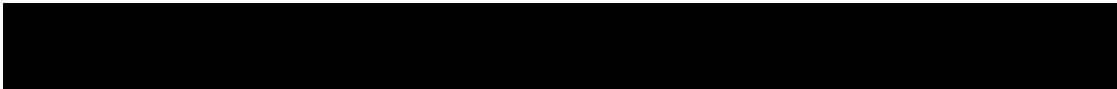
The visit and assessment schedule has been aligned with common medical practice in the care for patients with MS and with fingolimod treatment. Based on the assumption that continued study participation means there is a positive benefit-risk paradigm for these patients, Part Two of the protocol has been added, offering continued patient participation in a subset of patients (those unable to obtain access to/reimbursement for commercial Gilenya) for an additional (approximately) two years, through June 2018. This will allow continued fingolimod use until countries and investigators can find alternate treatment solutions.

In Study Part One, safety and tolerability data will be collected at regular intervals, in addition to EDSS assessments and periodic MRI scans, which will document chronic disease progression in terms of physical disability and brain tissue loss without undue burden on the patient. Study Part Two will collect safety and tolerability data only.

### **3.3 Rationale of dose/regimen, duration of treatment**

The dose and dosing regimen of fingolimod 0.5 mg once a day has been identified in the phase III development program of fingolimod in RRMS as providing the best benefit/risk ratio and is therefore the proposed dose and regimen in the registration files to the health authorities and is the approved dose where fingolimod has been registered.

The duration of treatment of a patient in this trial is dependent on which study the patient participated in previously as well as the availability of reimbursement for commercially available fingolimod in the respective country. The end of the study is planned for 30 June 2018 (+/- 3 months). Individual patient's end of treatment visits should occur at their routine 6 monthly scheduled visit closest to 30 June 2018 to ensure all patients complete within the window for the end of the study.



Patients participating in this study will provide clinical data of 7-15 years of exposure, which will provide information on the long-term safety, tolerability and efficacy profile to help in therapeutic decision making.

[Only in the UK and Poland: The duration of treatment of a patient in this trial is dependent on what study the patient participated in previously (phase II/III vs. other). Phase II/III patients will remain in the study maximally through 30-Jun-2016. Patients, who participated in any designated global fingolimod MS trial other than phase II/III (e.g. CFTY720D2316, CFTY720D2320, etc.), were allowed to remain in the study until the drug was registered and through approximately one-year post approval or maximally through 31-Dec-12.]

[Only for Norway: The duration of treatment of a patient in this trial ran for approximately 12 months following the completion of the previous fingolimod trial or maximally through 01-Aug-2012.]

### **3.4 Rationale for choice of comparator**

Not applicable.

### **3.5 Purpose and timing of interim analyses/design adaptations**

Periodic interim safety analyses to support regulatory updates may be warranted.

## **4 Population**

Approximately 5000 patients who have completed ongoing or planned clinical trials in the MS development program with fingolimod are expected to be enrolled in >500 centers worldwide.

This study will pool eligible patients participating in the fingolimod multiple sclerosis clinical development program to allow patients to receive continuous treatment with fingolimod and to collect long-term safety, tolerability, efficacy, and health outcomes data during Study Part One. In Study Part Two, only safety and tolerability data will be collected.

### **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.
2. Patients who have completed designated ongoing or planned Novartis global clinical trials with fingolimod and are unable to obtain fingolimod outside a clinical trial.

### **4.2 Exclusion criteria**

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

1. Premature permanent discontinuation from any fingolimod study due to:
  - a. An adverse event or serious adverse event or laboratory abnormality.
  - b. Conditions leading to permanent study drug discontinuation.
2. 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



hCG laboratory test (> 5 mIU/ml). Patients who temporarily or permanently discontinued from any fingolimod study because of pregnancy or nursing (lactating) can be re-enrolled.

3. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, UNLESS they are using highly effective contraception during the study and for 2 months after stopping treatment. ‘Highly effective contraception’ defined as contraception which results in less than 1% unwanted pregnancies when used properly according to the label.  
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.
4. Chronic disease of the immune system other than MS which may require immunosuppressive treatment.
5. Severe active infection or active chronic infection.
6. Previous treatment with cladribine, cyclophosphamide or mitoxantrone.
7. Treatment with monoclonal antibodies (including Natalizumab) in the past 3 months.
8. Uncontrolled diabetes (HbA1c>9%).
9. Macular edema at Baseline.
10. Any medically unstable condition that may interfere with the patient’s ability to cooperate and comply with the study procedures, as assessed by the treating physician.
11. Any of the following cardiovascular conditions:
  - a. myocardial infarction within the past 6 months prior to enrollment or current unstable ischemic heart disease;
  - b. cardiac failure at time of Screening (Class III & IV, according to New York Heart Association Classification) or any severe cardiac disease as determined by the investigator;
  - c. patients receiving current treatment with Class Ia and III antiarrhythmic drugs (e.g., quinidine, disopyramide, amiodarone, bretylium, sotalol, ibutilide, azimilide, dofetilide, ajmaline, procainamide);
  - d. second-degree AV block Type II or third-degree AV block or corrected QTc interval >450 msec in males or >470 msec in females;
  - e. sick sinus syndrome or sino-atrial heart block;
  - f. uncontrolled hypertension despite prescribed medications.
12. Any of the following pulmonary conditions during the previous fingolimod study or observed at enrollment visit:
  - a. severe respiratory disease or pulmonary fibrosis;
  - b. active tuberculosis;
  - c. in patients enrolling from studies with regular spirometry: reduction of FEV<sub>1</sub>, FVC and/or D<sub>L</sub>CO below 60% of core study baseline values or if FEV<sub>1</sub>, FVC and/or

D<sub>L</sub>CO at extension study baseline is the second of two consecutive pulmonary function tests with values <80% of core study baseline.

13. Severe liver impairment or chronic liver disease.
14. Positive screening for serological markers for hepatitis A, B, C, and E indicating acute or chronic infection:
  - anti-hepatitis A virus IgM,
  - hepatitis B surface antigen and/or anti-hepatitis B core antigen IgM,
  - anti-hepatitis C virus IgG or IgM,
  - anti-hepatitis E virus IgM (if positive IgG: do hepatitis E virus-RNA polymerase chain reaction; if negative, patient can be included).

Note: The following patients, assuming they have normal aminotransferase activities, can be included in the trial:

- those testing positive for hepatitis B surface antibody, indicating hepatitis B immunization -OR-
- those testing positive for anti-hepatitis B core antigen IgG, indicating a cured hepatitis B -OR-
- those testing positive for anti-hepatitis A virus IgG, indicating a cured hepatitis A.

## **5 Treatment**

### **5.1 Investigational and control treatment**

Open-label fingolimod 0.5 mg, taken p.o once daily.

Medication labels will comply with the legal requirements of each country and will be printed in the local language.

### **5.2 Treatment arms**

All patients will receive open-label fingolimod 0.5 mg, taken p.o. once daily.

### **5.3 Treatment assignment**

There is only one treatment arm in this trial which is open-label fingolimod 0.5 mg, taken p.o. once daily.

### **5.4 Treatment blinding**

As this trial is open-label single arm trial, treatment will not be blinded during the course of the study.

### **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 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 IRT system and provide the requested identifying information for the patient to register them into the IRT system. The assigned patient number should be entered in the field labeled “Patient ID” on the EDC data entry screen (e.g. enter ‘1’, ‘2’, etc.) Once assigned to a patient, the patient number will not be reused. If the patient fails to participate for any reason, the IRT system must be notified within 2 days that the patient was not enrolled. The reason for not being enrolled will be entered in the source documents.

### **5.5.2 Dispensing the study treatment**

Each study site will be supplied by Novartis with study drug in packaging of identical appearance.

The study drug packaging has a 2-part label. A unique medication number is printed on each part of this label. Investigator staff will identify the study drug package(s) to dispense to the patient by contacting the IRT system and obtaining the medication number(s). Immediately before dispensing the package to the patient, investigator staff will detach the tear-off portion of the label from the packaging and affix it to the source document (Drug Label Form) for that patient’s unique patient number and if applicable, logged in the IRT system drug accountability web-based portal.

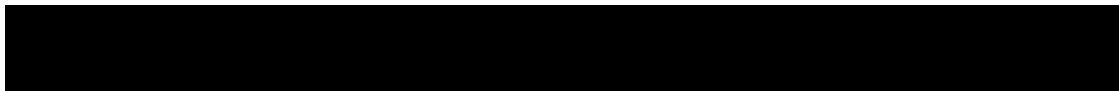
### **5.5.3 Supply, storage and tracking of study treatment**

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 according to the storage instructions specified on the drug labels. Should a storage excursion occur, the site must contact Novartis to determine if the study medication can continue to be used. Clinical supplies are to be dispensed only in accordance with the protocol.

Medication labels will be in the local language and 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 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 each visit, and 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 Novartis monitor or to the Novartis address provided in the investigator folder at each site.



#### **5.5.4 Instructions for prescribing and taking study treatment**

Study medication will be dispensed at the Baseline visit and each subsequent treatment visit thereafter as per the schedule of assessments. The patients will receive up to 6 bottles of oral medication containing 35 capsules per bottle at each visit, which will provide enough medication through their next regularly scheduled visit.

The investigator 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 the validity of the study. The patient should be instructed to contact the investigator if he/she is unable for any reason to take the study drug as prescribed. Instruction should also be given to the patient to open and use one bottle at a time. All unused medication as well as empty bottles should be returned to the investigator at the next regularly scheduled visit.

Study medication should be taken once a day, preferably at the same time every day, with or without food.

Once the eligibility of a patient for entry into the study has been confirmed based on the study inclusion/exclusion criteria, study medication will be dispensed via the IRT system (see [Section 5.5.2](#)).

Patients enrolling directly from a blinded study in which a blinded comparator arm exists (placebo or active comparator) may require blinded first dose observation, performed by a blinded first-dose administrator who cannot discuss the findings with the patients or anyone else associated with the clinical trial unless this is required for a medical reason.

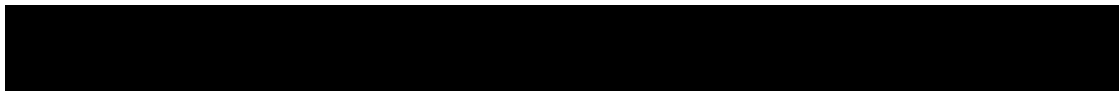
If patients transition into this extension study from the comparator arm of an open-label controlled study, the first dose of the study drug (capsules) administered at the Baseline visit in this study must be administered in the clinic under the supervision of the investigator or designee, or in accordance with the local label.

Similarly, any patient who re-initiates fingolimod treatment after an interruption, the first dose of the study drug (capsules) administered at treatment re-initiation must be administered in the clinic under the supervision of the investigator or designee, or in accordance with the local label if the following circumstances apply:

- 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.

Advice from a cardiologist should be sought and overnight monitoring with continuous ECG is required under the following circumstances:

- The pre-dose ECG shows a QTc interval >470 msec (females) or >450 msec (males) or a second degree or higher AV block
- The patient has relevant risk factors for QT prolongation, for example, hypokalaemia or hypomagnesemia, sick-sinus syndrome, or sino-atrial heart block



- The patient has known ischemic heart disease, history of myocardial infarction, congestive heart failure, history of cardiac arrest, cerebrovascular disease, uncontrolled hypertension or severe untreated sleep apnea period
- The patient has a history of recurrent syncope or symptomatic bradycardia
- The resting heart rate pre-dose is <45

For patients receiving (at treatment re-initiation) beta blockers, heart-rate slowing calcium channel blockers (e.g. ivadabine, verapamil, or diltiazem), or other substances which may decrease heart rate such as digoxin, anticholinesteratic agents or pilocarpine, advice from a cardiologist should be sought regarding the switch to non-heart-rate lowering medicinal products prior to re-initiating treatment. If a switch to non-heart rate lowering drugs is not possible, patients have to be observed overnight.

Patients transferring from blinded placebo-controlled or active comparator trials, or patients enrolling into the study who have been off fingolimod treatment for 90 days or more will need additional visits at 1 and 3 months post-first dose (see [Table 6-1](#) and [6-2](#)).

Patients requiring first dose monitoring should receive the first dose of study drug at the study center at a time which will allow for the required 6-hour post-dose monitoring to occur as well as to allow for additional time for extended monitoring, if necessary. The patient will stay at the study center for a minimum of 6 hours to monitor for signs and symptoms of bradycardia. All patients will have an ECG performed prior to dosing and at the end of the 6-hour monitoring period. Sitting heart rate and blood pressure will also be monitored before the first dose of fingolimod and every hour for at least six-hours thereafter. The patient may be discharged if specific discharge criteria (outlined in [Appendix 4](#)) are met. Hourly monitoring will be extended until findings have resolved if the discharge criteria are not met and should pharmacologic intervention be required during first-dose observation, overnight monitoring in a medical facility should be instituted and the first-dose monitoring procedures should be repeated upon the 2<sup>nd</sup> dose (see [Appendix 4](#) for Guidance for monitoring of patients taking their first dose of the study drug).

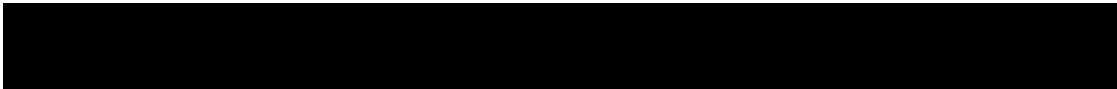
All medication prescribed and dispensed to the patient and all dose interruptions during the study must be recorded on the Dosage Administration Record eCRF.

All drug kits assigned by the IRT system will be recorded in the IRT system.

### **5.5.5 Permitted dose adjustments and interruptions of study treatment**

Study drug dose adjustments are not permitted, although interruptions may be warranted based on safety monitoring guidelines and should be recorded on the Dosage Administration Record eCRF.

Absolute lymphocyte count  $<0.2 \times 10^9/l$ , if confirmed, should lead to treatment interruption until recovery. (See [Appendix 5](#) for safety monitoring guidelines). Should the patient interrupt study drug, and the Investigator decide to re-initiate treatment with study drug, the first-dose monitoring procedure may be required for the restart of study drug (see [Appendix 4](#) for details).



### 5.5.6 Rescue medication

Not applicable.

### 5.5.7 Concomitant treatment

All on-going concomitant medications taken at the time of the Baseline visit and during the study must be recorded. In addition, any medications that may have been taken during any gap between the completion of the prior study and enrollment into this extension study should also be recorded, even if the medication is not ongoing at the time of enrollment. Medications that were recorded during the previous study and had a recorded end prior to completion of the previous study do not need to be re-recorded in this study. Both the start date and the end date for each medication should be captured on the “the “Concomitant Medications/Significant Non-Drug Therapies eCRF or Steroid treatment of MS relapses eCRF, as applicable. Use of the following treatments is allowed to manage potential adverse reactions associated with the study drug:

- anticholinergics (atropine s.c. or i.v.) for treatment of symptomatic bradycardia as the first line treatment, up to 3 mg/day;
- beta-agonists/sympathomimetics (dopamine drip 5-20µg/kg/min or epinephrine drip 2-10 µg/min) for treatment of non-responsive bradycardia.

For more recommendations for management of bradycardia, refer to [Appendix 4](#).

A standard short course of intravenous corticosteroids (3-5 days of up to 1,000 mg methylprednisolone/day) on an inpatient or outpatient basis is recommended for the treatment of relapses if clinically warranted (standard of care procedures should be followed during treatment) and should be recorded on the Steroid treatment of MS relapses eCRF. Tapering with oral corticosteroids is not recommended.

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of the study drug. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug must be recorded on the Concomitant medications/Significant Non-Drug Therapies eCRF or Steroid treatment of MS relapses eCRF.

Vaccination may be less effective during and for up to two months after treatment with fingolimod.

### 5.5.8 Prohibited treatment

Use of the following treatments is NOT allowed concomitantly with the study drug during the course of the study:

- Immunosuppressive medication (e.g. cyclosporine, azathioprine, methotrexate, cyclophosphamide, mitoxantrone, cladribine);
- Other concomitant medications: immunoglobulins, monoclonal antibodies, adrenocorticotrophic hormone (ACTH-other than if used as a short course (e.g. less than 1 week) for the treatment of MS relapse);
- Medications used to treat MS, which may include glatiramer acetate (Copaxone®), interferon β-1a i.m. (Avonex®), interferon β-1a s.c. (Rebif®), interferon β-1b

(Betaseron®/Betaferon®), natalizumab (Tysabri®), azathioprine, methotrexate or any other medications used as MS-disease-modifying agents;

- Class Ia (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol) antiarrhythmics.

The administration of any live or live attenuated vaccine (including for measles) should be avoided while patients are receiving study drug and for 2 months after study drug discontinuation. Following Varicella zoster virus (VZV) vaccination, the initiation of study drug should be postponed by 1 month to allow full effect of vaccination to occur.

### **5.5.9 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.

When a patient withdraws from Study Part One and does not continue on fingolimod, either in a study or non-study setting, they must return for two Follow-up visits, 3 months and 6 months after stopping study drug.

When a patient withdraws from Study Part Two, and does not continue on fingolimod, either in a study or non-study setting, they must return for one Follow-up visit, 3 months after stopping study drug.

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 appropriate eCRF.

Study drug must be discontinued for a given patient if the investigator determines that continuing it would result in a significant risk for that patient. In addition, study drug must be discontinued based on results of safety monitoring as outlined in [Appendix 5: Guidance on safety monitoring](#) and [Appendix 7: Guidance for Ophthalmic Monitoring](#). The following conditions/events may be considered sufficient to support a decision about the study drug discontinuation in individual cases:

- serious adverse event (e.g. cardiac failure, diagnosed malignancy, new neurological symptoms accompanied by MRI findings unexpected for MS) abnormal laboratory value(s) or abnormal test result(s) (e.g. ophthalmic findings).
- withdrawal of consent
- pregnancy (please see [Section 6.5.8](#) and [Section 7.3](#))
- use of prohibited medications, listed in [Section 4.2](#) and [Section 5.5.8](#).
- adverse events
- protocol deviation
- unsatisfactory therapeutic effect
- patient's condition no longer requires study treatment
- administrative problems (e.g. patient's non-compliance)
- discontinuation warranted as per local label requirements

In addition to scheduled visits, patients who discontinue study drug due to adverse events or abnormalities on safety monitoring tests must be followed up with additional visits as needed in order to confirm the resolution of abnormalities.

Document the date and primary reason for stopping the study drug on the appropriate page of the eCRF. If study medication is restarted as per protocol, the reason for the interruption of treatment and date of interruption should be appropriately documented in the source documents as well as in the Dosage Administration eCRF.

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, etc.

If a patient permanently discontinues from study drug, the investigator must also contact the IRT system to register the patient's discontinuation from study drug.

Patients who are prematurely withdrawn from the study will not be replaced by an equal number of newly enrolled patients.

#### **5.5.10 Emergency unblinding of treatment assignment**

Not applicable as this is an open-label study.

#### **5.5.11 Study completion and post-study treatment**

Study Part One completion is planned for 30 Jun 2016. Individual patient's end of treatment visits should occur at their routine 6 monthly scheduled visit closest to 30 June 2016 to ensure all patients complete within the window for the end of Study Part One.

The end of the study (completion of Study Part Two) is planned for 30 June 2018. Individual patient's end of treatment visits should occur at their routine 6 monthly scheduled visit closest to 30 June 2018 to ensure all patients complete within the window for the end of the study.

The investigator must provide follow-up medical care for all patients who are prematurely discontinued from the study, or must refer them back to their referring physician for appropriate care.

#### **5.5.12 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 [Section 5.5.9](#) 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 IRBs and/or ECs of the early termination of the trial.

## **6 Visit schedule and assessments**

[Table 6-1](#) and [6-2](#) list all assessments, and indicates with an "X" the visits when they are performed and recorded in the clinical database, with an "S" indicates when a performed



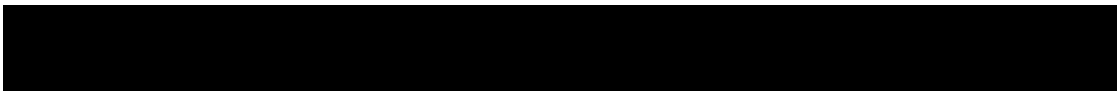
assessment is to be recorded on source documentation, and an “S1” indicates that source documentation should be present to confirm the procedure was performed as part of the previous fingolimod trial (Specific to the Baseline visit only). If an “S1” procedure was not performed in the previous trial, it has to be performed at Baseline. Assessments performed at the final visit of the previous fingolimod trial can fulfill the requirements of the Baseline only if they are completed within 14 days of enrollment in CFTY720D2399.

Patients should follow as much as possible the visit schedule with an allowed “visit window” of  $\pm 5$  days for bi-weekly visits, of  $\pm 10$  days for monthly visits, of  $\pm 14$  days for quarterly visits and of  $\pm 30$  days for bi-annual visits. If a visit was performed outside the visit window, any subsequent visits should be performed according to the original visit schedule. In the study, one month is defined as 30 calendar days.

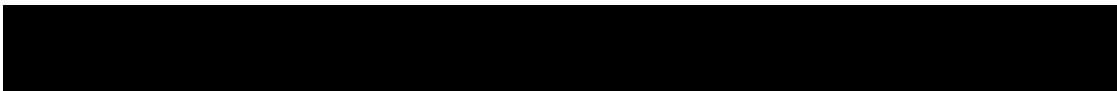
Upon availability of the locally approved prescribing information, completion of any additional assessments required by the local label becomes the responsibility of the investigator. The assessments should be completed for all patients, unless prohibited by local regulations. Any findings qualifying as AEs/SAEs should be reported as such.

**Table 6-1 Assessment schedule (Study Part One)**

Visit No.*	Base line V1	V112 <sup>1</sup>	V2	V3	V4	V5	V6	V7...	Study Completion or Premature Dis-continuation*	FU 1 <sup>14</sup>	FU 2 <sup>14</sup>
Study month	Day 1	Month 1	Month 3	Month 6	Month 9	Month 12	Month 18	Every 6 Months until SC			
Informed consent	XS										
Demography	S1										
Inclusion/exclusion criteria	XS										
Previous Study Details	XS										
Amendment 4 Details	Record when Amendment 4 is approved or at Baseline if newly enrolled under Amendment 4										
Amendment 8 Details	Record the signature date of the Amendment 8 patients informed consent										
Medical history	S1										
Concomitant meds	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS
Pregnancy test <sup>15</sup>	S1	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS
Physical/neuro logical exam	S1		S	S	S	S	S	S	S	S	S
MRI <sup>2</sup>	XS <sup>2a</sup>								XS		



Visit No.*	Base line V1	V112 <sup>1</sup>	V2	V3	V4	V5	V6	V7...	Study Completion or Premature Dis-continuation*	FU 1 <sup>14</sup>	FU 2 <sup>14</sup>	
Study month	Day 1	Month 1	Month 3	Month 6	Month 9	Month 12	Month 18	Every 6 Months until SC				
Skin exam by a qualified physician <sup>4</sup>	Record as needed											
Eye Exam <sup>5</sup>	S1		XS	XS					XS			
OCT/Ophthalmic Exam			XS <sup>5a</sup>	XS <sup>5a</sup>	Record as needed							
PFTs <sup>3</sup>	Record as needed											
Vital signs	S1	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	
Screening for hepatitis A, B, C & E and uncontrolled diabetes	XS											
Hematology/	S1	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	
Blood Chemistry	S1	XS	XS	XS	XS	XS		1/year	XS	XS	XS	
Serology <sup>6</sup>	XS											
Dispense study drug	S		S	S	S	S	S	S				
Collect unused study drug			S	S	S	S	S	S	S			
First dose monitoring <sup>7</sup>	XS	Record as needed										
First Dose ECG <sup>8</sup>	S1	Record as needed										
Dosage Administration Record	XS		XS	XS	XS	XS	XS	XS	XS			
EDSS <sup>12</sup>	S1			XS		XS	XS	XS	XS	XS	XS	
MSFC <sup>9</sup>	S1			XS		XS	XS	XS	XS	XS	XS	



Visit No.*	Base line V1	V112 <sup>1</sup>	V2	V3	V4	V5	V6	V7...	Study Completion or Premature Dis-continuation*	FU 1 <sup>14</sup>	FU 2 <sup>14</sup>
Study month	Day 1	Month 1	Month 3	Month 6	Month 9	Month 12	Month 18	Every 6 Months until SC			
MS relapse	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS
Steroid Use	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS
Adverse events/ SAEs	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS
Study Completion									XS		
<p>1. Visit 112 is only applicable for those patients rolling into this trial from any blinded study which has comparator treatment arms (placebo, or active comparator, e.g. study CFTY720D2309) or for any patient who has been off fingolimod treatment for 90 days or greater. All other patients will enroll at Baseline-V1 and come in 3 months later for V2.</p> <p>2. MRIs are required only for patients from phase II/III trials who had MRI assessments in prior FTY trials. Such patients will have the first MRI at V5. If a patient has already had V5 by the time Amendment 4 is approved, the patient should have an unscheduled MRI upon the approval of Amendment 4. Post-Amendment 8 approvals, only the Study Completion MRI is required.</p> <p>2a. Phase II/III patients that enroll /re-enroll into this study under Amendment 8 must have an MRI at the Baseline-V1 visit for new patients or at the re-enrollment visit for re-enrolled patients.</p> <p>3. Pulmonary function testing (FEV1, FVC, DLCO) will be performed if clinically indicated.</p> <p>4. A qualified physician includes either a dermatologist or a physician who has participated in a licensed training program. Record if performed.</p> <p>5. An eye exam will be performed by the treating physician.</p> <p>5a. A 3-month and 6-month OCT scan and ophthalmic exam will be done by an ophthalmologist on any patient who is rolling into this trial from any blinded study which has comparator treatment arms (placebo or active comparator, e.g. study CFTY720D2309) or for any patient who has been off fingolimod treatment for 90 days or greater. Then, to be recorded if performed.</p> <p>6. Serology testing (if not already performed in the previous fingolimod study) will be performed at the Baseline-V1 visit to measure Varicella-zoster virus IgG antibodies.</p> <p>7. Patients enrolling directly from a blinded study may require blinded first-dose observation. First-dose monitoring to be done on any patient who is rolling into this trial from any blinded study which has comparator treatment arms (placebo or active comparator, e.g. study CFTY720D2309) or enrolling from the comparator arm of an open-label controlled study or for any patient who has been off fingolimod treatment for the durations outlined in Appendix 4.</p> <p>8. First dose 12 lead ECGs (pre- and 6 hours post-dose) to be obtained only for those patients rolling into this trial from any blinded study which has comparator treatment arms (placebo) or for any patient who re-initiates fingolimod after having been off fingolimod treatment for the durations outlined in Appendix 4..</p> <p>9. The MSFC will only be done in patients who had previous MSFC assessments in their previous fingolimod study.</p>											

Visit No.*	Base line V1	V112 <sup>1</sup>	V2	V3	V4	V5	V6	V7...	Study Completion or Premature Dis-continuation*	FU <sub>1</sub> <sup>14</sup>	FU <sub>2</sub> <sup>14</sup>
Study month	Day 1	Month 1	Month 3	Month 6	Month 9	Month 12	Month 18	Every 6 Months until SC			
<p>12. For patients who previously participated in phase II/III trials only (CFTY720D2201/E1, CFTY720D2301/E1, CFTY720D2302/E1, CFTY720D2309/E1, etc), EDSS will be assessed by a certified treating Physician (all phase II/III investigators and any new raters who join during the study will be required to provide one-time proof of Neurostatus EDSS certification). Physicians assessing EDSS for patients from phase IIIb trials do not have to be certified, and individual functional scores are not required.</p> <p>14. Follow up visits (FU) should be scheduled 3 months and 6 months (+/- 14 days) after the last dose of study medication. The follow-up visits should be done only on patients who have stopped the study but do not continue onto fingolimod, either in a study or non-study setting.</p> <p>15. Serum pregnancy tests are collected at visits where chemistry is collected. At other visits, urine pregnancy tests will be performed on-site with kits provided by the central lab.</p> <p>* At each visit the patient must be reminded of the importance of remaining vigilant for infections and, in women of child-bearing age, practicing contraception per protocol.</p> <p>** The Study Completion (SC) assessments to be performed if a patient has prematurely discontinued or if completed the study per protocol. For active patients, Study Completion assessments will be performed when the patient reaches 60 months participation in this study. For patients who have passed the 60 month milestone at the time of Amendment 10 approval at their study site must conduct their Study Completion visit at the next 6-monthly timepoint, or 30-Jun-2016, whichever comes first.</p>											

**Table 6-2 Assessment schedule (Study Part Two)**

Visit No.*	Visit 201A <sup>1</sup>	Visit 201B <sup>2</sup>	Visit 211 <sup>2</sup>	Visit 212 <sup>2</sup>	Visit 202	Visit 203	Visit 204...	Study Completion or Premature DC <sup>9</sup>	FU <sub>3</sub> <sup>10</sup>
Study month	Day1 <sup>1</sup>	Day1 <sup>2</sup> (First Dose Monitor)	Month 1 <sup>2</sup>	Month 3 <sup>2</sup>	Month +6/6	Month +12/12	Every 6 Months until SC		
Informed consent <sup>3</sup>	XS	XS							
Demography <sup>3</sup>	S1	S1							
Inclusion/exclusion criteria	XS	XS							
Previous Study	XS	XS							

Details <sup>3</sup>									
Medical History <sup>3</sup>	S1	S1							
Concomitant meds	XS	XS	XS	XS	XS	XS	XS	XS	XS
Physical/ neurological exam	S1	S1	S	S	S	S	S	S	S
Skin exam by a qualified physician <sup>4</sup>		Record in source as needed							
Eye Exam <sup>5</sup>	S1	S1		S	S				
OCT/Ophthalmic Exam				S <sup>6</sup>	S <sup>6</sup>				
PFTs		Record in source as needed							
Vital signs	S1	S1	XS	XS	XS	XS	XS	XS	XS
Hematology/ Chemistry/ Pregnancy <sup>7</sup>			S	S	S	S	S	S	S
Dispense study drug	S	S		S	S	S	S		
Collect unused study drug			S	S	S	S	S	S	
First dose monitoring <sup>8</sup>		XS	Record as needed						
First Dose ECG <sup>8</sup>		XS							
Dosage Administration Record	XS	XS		XS	XS	XS	XS	XS	
MS relapse	XS	XS	XS	XS	XS	XS	XS	XS	XS
Steroid Use	XS	XS	XS	XS	XS	XS	XS	XS	XS
Adverse events/ SAEs	XS	XS	XS	XS	XS	XS	XS	XS	XS
Study Completion								XS	

1. Visit 201A is applicable for current patients or those transitioning from another open-label fingolimod study
2. Visits 201B, 211 and 212 are applicable only for those patients transitioning from a blinded fingolimod study which has comparator treatment arms (placebo, or active comparator, e.g. study CFTY720D2312), from the comparator arm of an unblinded fingolimod study, or for patients who have interrupted treatment for durations as outlined in Appendix 4.
3. Informed consent, demography, previous study details, and medical history are only applicable if the patient enters Study Part Two from another study (i.e., not applicable for patients transitioning from Study Part One).
4. A qualified physician includes a dermatologist OR a physician who has participated in a licensed training program.
5. To be performed by the treating physician.
6. A 3-month and 6-month OCT scan will be done by an ophthalmologist for patients who enroll into this trial from any blinded study which has comparator treatment arms (placebo or active comparator, e.g. study

CFTY720D2312) OR for any patient who has been off fingolimod treatment for 90 days or greater. Then, to be recorded if performed.
7. Tests will be analyzed locally; results will not be recorded in the eCRF, but will remain as source documentation for ongoing safety assessment (clinically significant lab abnormalities should be reported as AEs).
8. First dose 12 lead ECGs (pre- and 6 hours post-dose) to be obtained only for those patients transitioning from a blinded fingolimod study which has comparator treatment arms (placebo, or active comparator, e.g. study CFTY720D2312), from the comparator arm of an unblinded fingolimod study, or for patients who have interrupted treatment for durations as outlined in Appendix 4.
9. The Study Completion (SC) assessments to be performed if a patient has prematurely discontinued or if completed the study per protocol.
10. Extension follow-up visit (EFU) should be scheduled 3 months (+/- 14 days) after the last dose of study medication. The follow-up visit should be done only for patients who have stopped the study but do not continue onto fingolimod, either in a study or non-study setting.
* At each visit the patient must be reminded of the importance of remaining vigilant for infections and, in women of child-bearing age, practicing contraception per protocol.

In addition to the above scheduled visits, patients may have unscheduled visits following an onset of MS relapse or for other reasons as necessary. All information should be collected per Unscheduled Visit eCRFs.

## 6.1 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data were collected from the patient during the previous fingolimod study which included: date of birth, age, sex, race, ethnicity, pre-treatments and source of patient referral. Relevant medical history/current medical condition data includes data until the start of study drug. Where possible, diagnosis and not symptoms were recorded. These data will be mapped to this dataset from the patient's previous fingolimod study.

The demography data collected in this study (date of birth and gender) will ensure the patients are linked to their previous study history.

Previous MS history (including history of relapses) was documented in the patient's medical chart and/or in documented dialog with the patient's referring physician. Information relating to a patient's MS history was collected during the previous fingolimod study which included: date of MS diagnosis, date of first MS symptoms, eye history (e.g. optic neuritis, uveitis), MS relapse history and history of medications used to treat MS and will be transferred directly into the database from the patient's previous fingolimod study.

The same information will be collected for any gap between the previous study (core or extension study, e.g. CFTY720D2309 or CFTY720D2309E) and this study.

## 6.2 Previous Study Details

In order to collect accurate information about the patient's previous fingolimod study details, the following records will be collected at the enrollment visit for each patient: the patient's previous fingolimod study number, center number, and patient number.



Upon the implementation of Amendment 4, the following information will be collected: the date of full approval for Amendment 4, whether or not the patient is re-enrolling into this study (defined as a patient who previously completed CFTY720D2399 based on the original study endpoint who is now re-entering the study using the originally assigned patient ID number) and the date of re-enrollment. In addition, data will be collected on any potential treatment gap during the time a patient may have temporarily been out of a fingolimod study and whether or not the patient went onto commercially available medication during the gap, if applicable.

### **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 patient receiving study medication: records of study medication dispensed and returned, dosages administered and intervals between visits. Appropriate data should be transcribed on the Dosage Administration Record (DAR) eCRF. To allow for accurate study reporting, the DAR will be closed at the completion of Study Part One and a new DAR eCRF will be opened in the Study Part Two.

Compliance will be assessed by the investigator and/or study personnel at each visit using capsule 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**

MS relapse activity and neurological impairment of MS as measured by the Expanded Disability Status Scale (EDSS), Magnetic Resonance Imaging (MRI) and by the Multiple Sclerosis Functional Composite (MSFC) will be obtained in Study Part One only in order to characterize the disease activity over the long term.

#### **6.4.1 MS relapse**

General definition of relapse: Appearance of a new neurological abnormality or worsening of previously stable or improving pre-existing neurological abnormality, separated by at least 30 days from onset of a preceding clinical demyelinating event. The abnormality must be present for at least 24 hours and occur in the absence of fever (<37.5°C) or infection.

Definition of confirmed relapse (For Study Part One only): A relapse must be confirmed by an EDSS certified Physician (see [Section 6.4.2](#)). It is recommended that this occur within 7 days of 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 two different Functional Systems (FS) of the EDSS or 2 points on one of the FS (excluding Bowel/Bladder or Cerebral FS).

A patient should report symptoms indicative of a MS relapse at a scheduled visit or at any other time during the study. Patients must be instructed to immediately contact the study site if he/she develops new, reoccurring or worsening neurological symptoms. Standard therapy with corticosteroids can be used.

For suspected MS relapses reported by the patients between the scheduled visits, the investigator will determine whether to bring the patient in for an unscheduled visit based on

the patient's condition and standard of care. For patients who come in for an unscheduled visit at the time of the suspected MS relapse, an EDSS evaluation must be performed to verify the relapse. Relapse severity will be determined based on relapse EDSS scores.

Upon receiving a report of symptoms indicative of a relapse, the investigator will assess whether the symptoms occur in the presence of fever or infection. If fever or infection can be excluded, the investigator will determine whether the patient will come in for an unscheduled visit and EDSS evaluation. 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 present at that time.

All relapses, confirmed (Study Part One only) and unconfirmed, will be recorded on the Summary of MS Relapses eCRF. Atypical relapses should be documented as adverse events or serious adverse events, depending on severity of relapse.

#### **6.4.2 Expanded Disability Status Scale (EDSS)**

EDSS will be determined only during Study Part One, based on neurological examination at scheduled visits according to [Table 6-1](#) and in the setting of a suspected MS relapse.

EDSS is a scale for assessing neurologic impairment in MS. It is a two-part system including: (1) a series of scores in each of eight functional systems, and (2) the EDSS steps (ranging from 0 (normal) to 10 (death due to MS)). The functional systems are Visual, Brain Stem, Pyramidal, Cerebellar, Sensory, Bowel and Bladder, Cerebral and other functions. It is recommended that fatigue will not be included into the Cerebral score of the EDSS.

For patients coming from phase II/III studies, EDSS will be assessed by a treating physician who has been EDSS trained. A one-time Neurostatus certification is required for all evaluating physicians who have patients enrolled from phase II/III studies. If a new rater is brought on board at any time throughout the study, proof of certification of that rater will be required at that time before any EDSS assessments can be done by the new rater. A certified backup evaluating physician should be appointed to conduct neurological examination ONLY when the primary evaluating physician is unavailable due to illness, vacation, or travel. Blinding of the evaluators is not required in this protocol and the PI can serve as the rater provided training requirements have been met.

For patients who transferred from trials other than the phase II/III trials, the individual functional scores do not need to be collected, and the evaluating physician performing EDSS assessments does not have to carry a certification.

EDSS assessments are detailed in [Table 6-1](#). Refer to [Appendix 8](#) for information on Expanded Disability Status Scale (EDSS).

#### **6.4.3 Magnetic resonance imaging (MRI)**

MRIs were added in Amendment 4, and are required only during Study Part One for the phase II/III patients who had MRI assessments in their prior fingolimod trial. Until Amendment 8 approval, annual MRIs are performed starting at Visit 5. Patients who have already completed V5 at the time of Amendment 4 approval should have an MRI recorded at the



nearest MRI visit (e.g., V7, V9). Upon Amendment 8 approval, the MRI schedule is revised to one MRI at Study Completion as outlined in [Table 6-1](#).

Any phase II/III patients who newly enroll or re-enroll into this study under Amendment 8 should have an MRI at the Baseline-V1 visit for newly enrolled patients, or at the re-enrollment visit (re-enrolled patients will enter back into the study based on where they previously left off when they completed the study based on the original endpoint; for example, if V3 was the last completed visit, V4 would be where the patient will begin again).

Assessment of disease activity by MRI will include evaluation of:

- T1-weighted hypointense lesion volume.
- T2-weighted new/enlarging hyperintense lesion count and total T2 volume.
- Brain volume.

The Investigator will be able to review all MRIs during the study. For analysis purposes, the MRIs will be reviewed and reported by a central MRI reader.

## Scanning

All sequences/scans will be performed according to the MRI manual.

The 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 if not done previously with the same MRI Central Reader, perform and submit a dummy scan, so-called “dummy or dry run” to assess the image quality and to evaluate the compatibility of the electronic data carrier. Once the dummy run has been accepted, all the parameter settings for the study specific MRI sequences must remain unchanged for the duration of the study.

## Data handling and evaluation

During the study, the quality of each scan performed will be assessed by the 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 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.

### 6.4.4 Multiple Sclerosis Functional Composite (MSFC)

The MSFC, performed only during Study Part One, is a composite measure encompassing the major clinical dimensions of arm, leg and cognitive function. The MSFC consists of three objective quantitative tests of neurological function:

- Nine hole peg test (arm dimension) measurement: right and left arm scores; metric: time in seconds to insert and remove 9 pegs.
- Timed 25 foot walk (leg dimension); measurement: a walk of 25 feet; metric: time taken in seconds.

- PASAT-3 min (cognitive function); measurement: paced auditory serial addition test, 3 minute version; metric: number of correct answers.

The PASAT-3 min auditory test tapes will be provided to the sites in the local language. Refer to [Appendix 2](#) for information on Multiple Sclerosis Functional Composite (MSFC).

MSFC will be assessed by a physician or qualified individual at each site on patients who have conducted the MSFC in their previous fingolimod studies. MSFC assessments are detailed in [Table 6-1](#). Refer to [Appendix 2](#) for information on Multiple Sclerosis Functional Composite (MSFC).

#### **6.4.5 Appropriateness of efficacy assessments**

MS relapse, MRI, as well as EDSS assessments in this patient population are standard outcome efficacy assessments in MS and serve to characterize the patient population included in this study as well as their disease activity and neurological status over the long-term in this study.

MSFC assessments will be continued in patients who had assessments done in their previous fingolimod studies to describe their functional status over the long-term in this study.

### **6.5 Safety**

- Physical/neurological examination
- Vital signs
- Laboratory blood evaluations
- Eye exam by treating physician
- ECG
- Ophthalmologic exams / Optical coherence tomography (OCT) by ophthalmologist, if clinically indicated
- Skin assessments, if clinically indicated
- Pulmonary function testing, if clinically indicated

#### **6.5.1 Physical/neurological examination**

A complete physical examination will be performed as described in [Table 6-1](#) and [6-2](#), and will include an assessment of skin, head and neck, lymph nodes, breast, heart, lungs, abdomen, back, and comments on general appearance. Initial neurological examination will be a part of the physical examination. 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, refer to [Section 6.5.2](#). All significant findings present prior to start of the study drug have been reported on the Relevant Medical History/Current Medical Conditions eCRF from the patient's previous fingolimod trial. Significant findings made after the start of study drug in this study which meet the definition of an AE must be recorded on the Adverse Event eCRF.

## 6.5.2 Skin assessments

If, during the course of the study, a patient has any dermatologic findings suspicious for being precancerous or cancerous, or if a skin disorder is diagnosed, this information should be documented on the Dermatologic Examination and/or Adverse Events eCRFs.

## 6.5.3 Vital signs

Vital signs will be recorded as described in [Table 6-1](#) and [6-2](#). Vital signs will include sitting pulse rate, sitting systolic and diastolic blood pressure, oral temperature (degrees Celsius). Height and body weight were collected at the screening visit of the patient's previous fingolimod trial.

Refer to Complete Guidelines for the monitoring of patients taking their first dose of the study drug as described in [Appendix 4](#).

## 6.5.4 Laboratory evaluations

Screening laboratory tests and routine blood samples as described in [Table 6-1](#) will be collected and analyzed by the central lab during Study Part One. During Study Part Two, laboratory tests will be collected and analyzed by the study site (i.e., locally, not using a central lab).

For Study Part One, details regarding collection of samples, shipment of samples, reporting of results, lab normal 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 lab at the earliest 48 hours after receipt of the samples by the central lab. Extreme values, specified in the "Criteria for clinically notable laboratory values and vital signs" are further specified in [Appendix 1](#), which will generate a "phone alert" to the investigator.

For Study Part Two, samples will be collected and reported in accordance with local laboratory policies. Lab results will not be recorded in the eCRF, but will remain as source documentation for ongoing safety assessment.

Investigators will be asked to comment on any abnormalities on the respective lab 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 source documents.

Abnormal laboratory values or test results should be recorded as adverse events only if they induce clinical signs or symptoms, are considered clinically significant or require therapy. Abnormal laboratory values alone should not be recorded on the adverse event eCRF; however, any diagnoses (or signs or symptoms, if a diagnosis is not possible) associated with the abnormal findings should be recorded on the adverse event eCRF.

### 6.5.4.1 Hematology

Hematology parameters will be collected as described in [Table 6-1](#) and [6-2](#), and will include: RBC count, total and differential WBC count (basophils, eosinophils, lymphocytes, monocytes, neutrophils, WBC segments), platelet count, hemoglobin, hematocrit, MCV,

MCH, MCHC, LUC, RBC morphology. Notable abnormalities are defined in the Criteria for clinically notable laboratory values and vital signs further specified in [Appendix 1](#).

#### 6.5.4.2 Clinical Chemistry

Blood samples will be collected as described in [Table 6-1](#) and [6-2](#), and will include the following parameters: sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen (BUN), random glucose, albumin, alkaline phosphatase, creatinine, ALT, AST, GGT, amylase, total bilirubin, conjugated bilirubin, total cholesterol, triglycerides, HDL and LDL. 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 ( $\geq 300$  U/L) is observed at any subsequent visits, a lipase should be tested to determine the origin of elevated amylase (pancreatic versus extra pancreatic). Refer to the Guidance on monitoring patients with elevated liver function tests in [Appendix 5](#).

It is recommended that patients without a health care professional confirmed history of chickenpox or documentation of a full course of vaccination with varicella vaccine undergo antibody testing to varicella zoster virus (VZV) before initiating fingolimod. Serology testing will therefore be performed at Baseline for any patient that has not undergone this testing during participation in their previous fingolimod trial to determine the patient's immune status (IgG antibodies will be measured) for varicella zoster virus. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with fingolimod.

Patients who are negative for varicella-zoster virus IgG antibodies at baseline, and wish to be immunized, will need to interrupt study treatment for 2 months prior to vaccination. Following vaccination, the re-initiation of study drug should be postponed for 1 month to allow full effect of vaccination to occur. Patients who have been tested for VZV antibodies and have confirmed negative test results may continue participation, provided they are counseled on the importance of avoiding possible sources of exposure and the importance of informing their physician promptly, should any symptoms of infection develop. Patients who choose not to be vaccinated may enroll into this trial, per discretion of the investigator. 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. 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.

Patients will also be tested for uncontrolled diabetes and serological markers for hepatitis A, B, C and E indicating acute or chronic infection at baseline as part of the revised screening laboratory assessments as described in [Table 6-1](#).

Please refer to the Guidance on monitoring of patients with infections in [Appendix 5](#).

### **6.5.5 Ophthalmologic exams/ Optical coherence tomography (OCT)**

An eye examination will be performed by the treating physician as described in [Table 6-1](#). The treating physician should refer the patient to an ophthalmologist for an exam and/or OCT if clinically warranted. An OCT and ophthalmologic exam will be performed by an ophthalmologist at Month 3 for any patient rolling into this study from a blinded study which has comparator treatment arms (placebo or active comparator) and for any patient who has been off fingolimod treatment for 90 days or greater. The OCT will be done to evaluate the presence of any abnormalities consistent with macular edema.

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 7](#) for details on monitoring of patients with uveitis during the study.

Continuation of fingolimod in patients with macular edema has not been evaluated. A decision on whether or not study drug should be re-initiated after resolution of macular edema needs to take into consideration the potential benefits and risks to the individual patient.

Patients that are diagnosed with macular edema should be followed-up monthly after diagnosis of macular edema 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 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.

Please refer to the Guidance for Ophthalmic Monitoring [Appendix 7](#) for complete guidance for patients with diagnosis of macular edema.

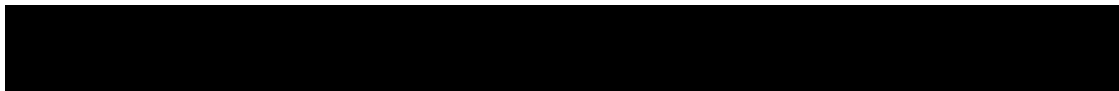
### **6.5.6 Electrocardiogram (ECG)**

First dose ECGs will be collected as described in [Table 6-1](#) and [6-2](#). Two ECGs are required for first-dose monitoring and will be performed for those patients rolling into this trial from a blinded trial, a trial which has a comparator treatment arm, as well as for any patient who has been off fingolimod treatment for the duration outlined in [Appendix 4](#).

The first ECG will be performed prior to the study drug administration; the second ECG will be performed approximately 6-hours post-first dose, prior to the patient being discharged. If study drug treatment is interrupted and treatment re-initiation meets the requirement for observation (See [Appendix 4](#)), the above procedures will be repeated.

### **6.5.7 Pulmonary function tests**

Pulmonary function tests (PFTs) evaluating forced expiration volume within 1 second (FEV1), forced vital capacity (FVC) and carbon monoxide diffusing capacity (DLCO) will be performed, when clinically indicated in the opinion of the treating physician.



### **6.5.8 Pregnancy and assessments of fertility**

Pregnancy tests will be performed for all women as detailed in [Table 6-1](#) and [6-2](#). During Study Part One, visits requiring serum pregnancy tests will be performed by the central lab; those visits requiring urine pregnancy tests will be performed locally using a urine dipstick kit provided by the central lab. During Study Part Two, pregnancy tests will be performed locally, serum at visits where blood chemistry samples are collected, and urine at any other time points.

Patients becoming pregnant must interrupt the study drug. If patients interrupt treatment because of a pregnancy, they can remain in the study and re-start fingolimod treatment after delivery and discontinuation of nursing. Pregnant patients continuing in the study during dose interruption will need to have regular visits and complete assessments deemed safe for her by the Principal Investigator. Prior to resuming fingolimod therapy and the mandatory on-site first-dose monitoring, patients must have a negative serum pregnancy test and must no longer be nursing.

### **6.5.9 Appropriateness of safety measurements**

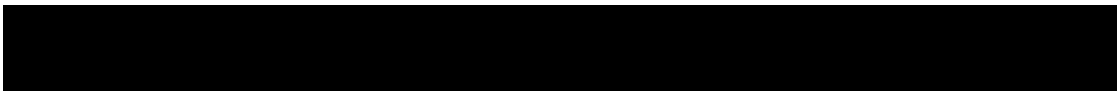
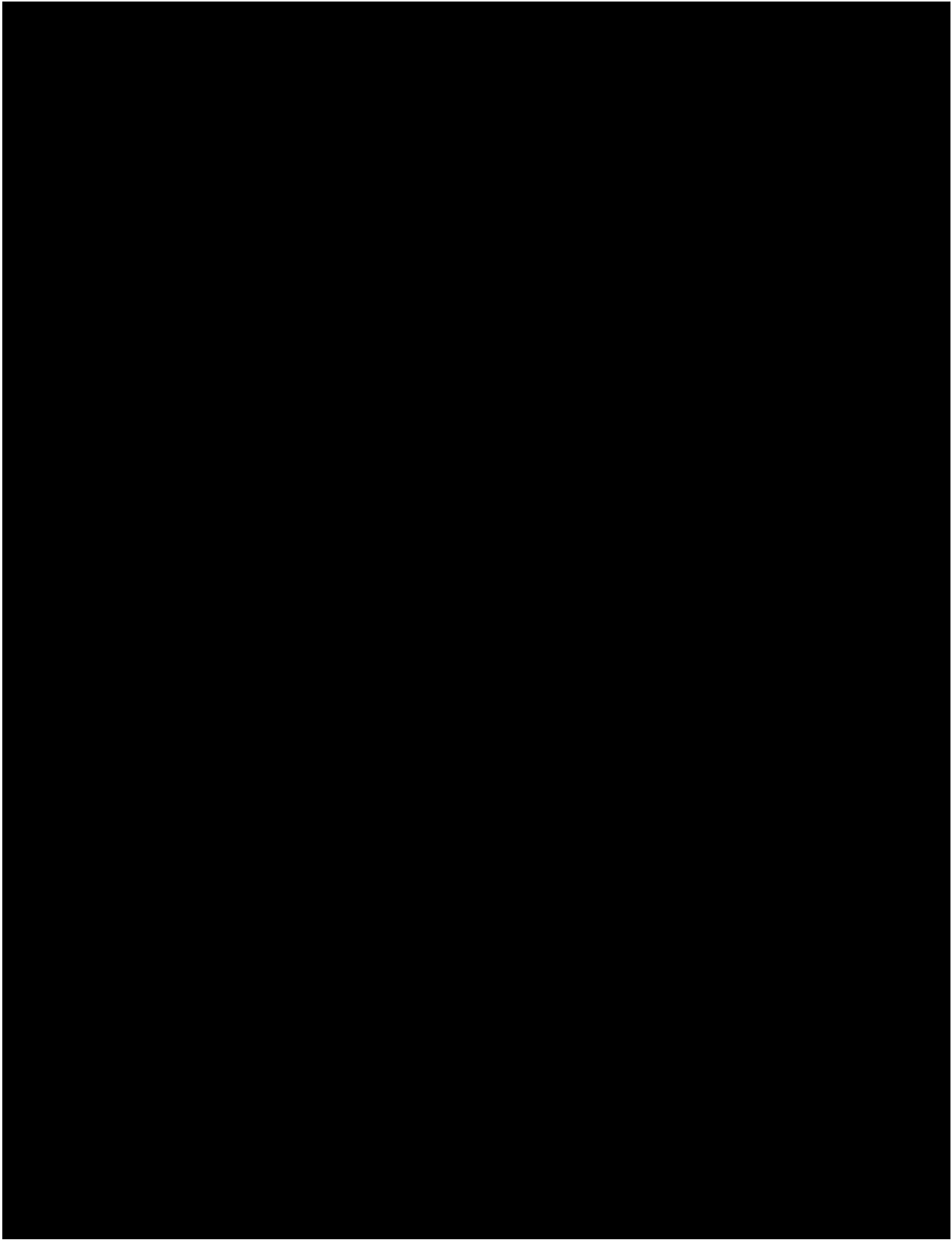
Beside routine safety assessments like physical and neurological examination, vital signs and laboratory assessments, few specific additional safety assessments are recommended in this extension study, based on the mechanism of action of fingolimod and previous clinical data.

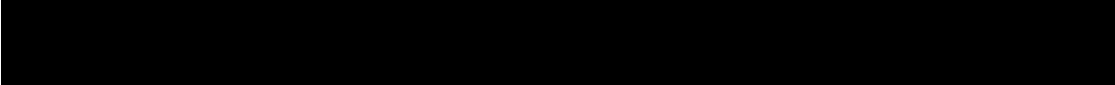
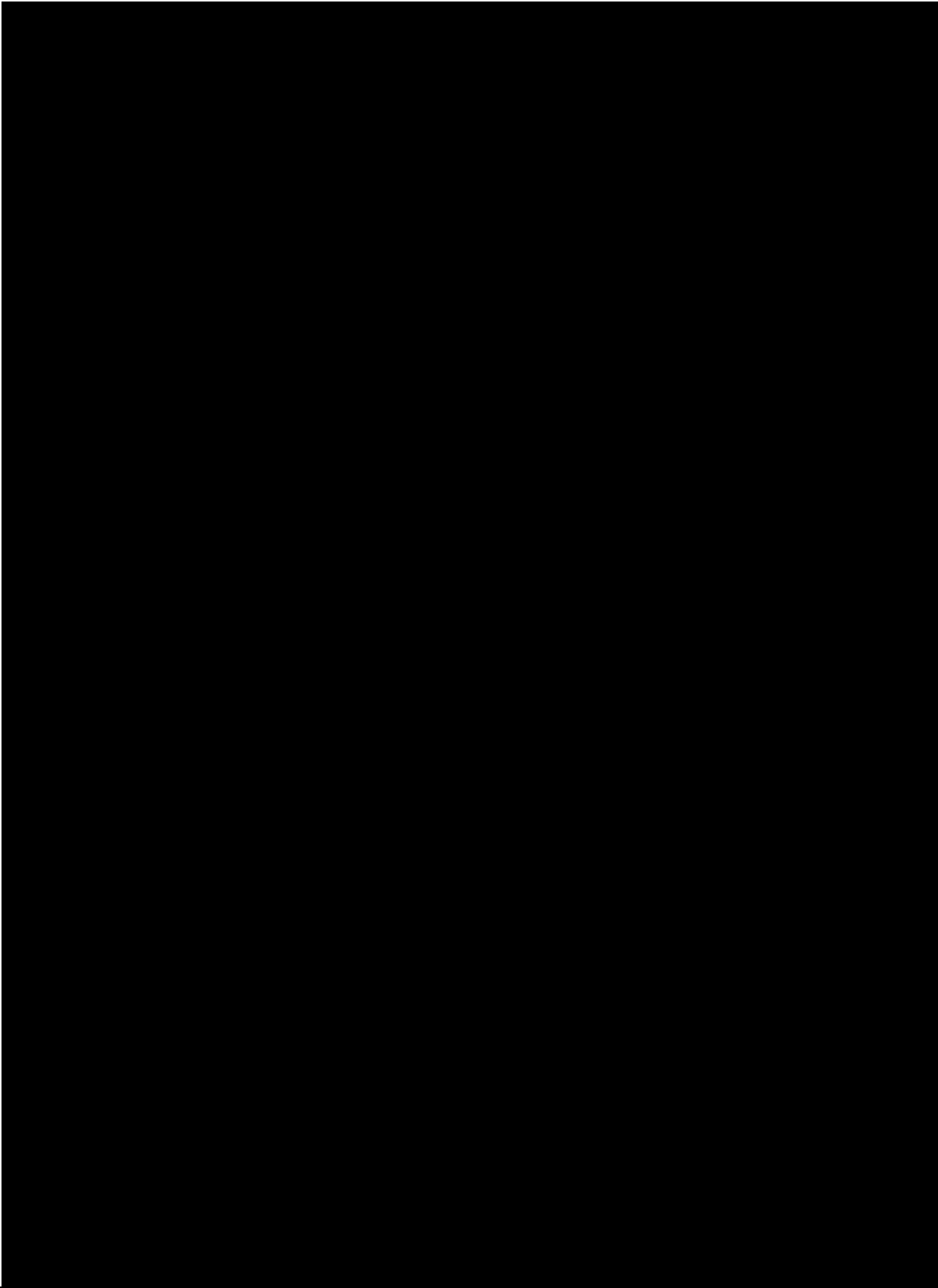
Effects of fingolimod on heart rate and conduction are expected and known based on the mechanism of action and previous clinical data. Clinically symptomatic cardiac events or clinically relevant ECG abnormalities have been reported at very low frequencies in the clinical development program, especially with the fingolimod 0.5 mg/day dose treatment. Therefore, upon initiation of the first dose of fingolimod, there must be a mandatory on site monitoring for a minimum of 6 hours, with additional monitoring as appropriate; refer to [Appendix 4](#) for detailed recommendations.

In addition to routine ophthalmologic examinations, OCT may be continued in this extension study for the evaluation of retinal thickness and the detection of macular edema. Macular edema is an adverse event of special interest in patients treated with fingolimod because of the higher incidence seen in treated patients compared to active and placebo control groups, particularly when higher doses were evaluated in the clinical development program. The majority of cases of macular edema observed in patients treated with fingolimod occurred within the first four months after initiation of treatment. Therefore, an OCT scan is foreseen to be completed at three and six months after treatment initiation/re-initiation for patients meeting this requirement as outlined in [Section 5.5.4](#).

In the fingolimod clinical development program, there is limited experience in multiple sclerosis patients with diabetes mellitus. Patients with diabetes mellitus are at increased risk of macular edema and may require additional ophthalmologic observation, as determined by the investigator.

As dose-dependent reversible reduction was observed in forced expiratory volume of patients treated with fingolimod, pulmonary function testing will be performed, if clinically indicated.







## 7 Safety monitoring

### 7.1 Adverse events

An adverse event 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 refers to the investigational drug, fingolimod given during this study. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of adverse events should be sought by non-directive 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 adverse events must be recorded on the Adverse Event eCRF pages with the following information:

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

An SAE is defined as an event which fulfills one or several of the following criteria:

- 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 (e.g. hospitalization for relapse treatment)
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

**Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see [Section 7.2](#).**

All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e., further observation only); study drug temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication given; non-drug therapy given; patient hospitalized/patient's hospitalization prolonged. Refer to the

Guidance on Safety Monitoring ([Appendix 5](#)). The action taken to treat the adverse event should be recorded on the Adverse Event eCRF.

Once an adverse event 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.

Information about side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications (Dear Doctor's letter). 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 6 weeks 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 6 week 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 SAE 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 department of Clinical Safety and Epidemiology, 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 case report form documentation at the study site.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE 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 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 (IN) to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) 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.

### **7.3 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. Pregnant women should be encouraged to participate in the pregnancy registry to collect additional safety data on this population.

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.

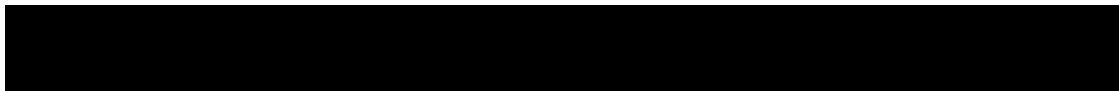
## **8 Data review and database management**

### **8.1 Site monitoring**

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and eCRFs 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 eCRFs, 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, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs 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 monitor access to all relevant source documents to confirm their consistency with the eCRF 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 eCRFs 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 Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC 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 Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

## **8.3 Database management and quality control**

Designated CRO personnel working on behalf of Novartis review the data entered into the eCRFs by investigational staff for completeness and accuracy and instruct 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 medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to the designated CRO (Part One only).

MRI readings will be processed centrally and the results will be sent electronically to the designated CRO.

ECGs will be done locally and the outcomes will be entered into the database.

Data about all study drug dispensed to the patient and all IRT recorded information will be tracked using an Interactive Response Technology system (IRT). The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to a designated CRO.

## **9 Data analysis**

Unless otherwise mentioned, all data collected from the first dose of fingolimod in the original core/extension studies, if available, and in this long-term follow-up study will be analyzed to evaluate the long-term safety, tolerability, and effectiveness of fingolimod 0.5 mg/day in patients with MS. The baseline relative to the first dose of fingolimod (FDF baseline) will be used where change from baseline is analyzed. All the summaries will be provided by the highest assigned fingolimod dose, (i.e., fingolimod 0.5 mg/day) and any dose of fingolimod.

During Study Part Two, only adverse events, first dose monitoring, vital signs, Ophthalmological exam/OCT, and relapse are collected. The analysis including data from Study Part Two will be specified in the relevant sections.

The follow-up data after discontinuation of the study treatment in Study Part One or Study Part Two will also be summarized where appropriate.

Summary statistics for continuous variables will include N, mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum.

Summary statistics for discrete variables will be presented in terms of absolute and relative frequencies. AE incidence adjusted by exposure is also used to evaluate the risk over time and presented as number of patients experiencing at least one event per 100 patient years of the at-risk population.

## **9.1 Analysis sets**

Assignment of patients into the different analysis sets will be performed prior to locking the database and beginning the data analysis.

Summary statistics will be provided for patient disposition (completers and premature study discontinuations) in this long-term follow-up study.

A table on number and percentage of patients with each protocol deviation in this long-term follow-up study will be provided.

In addition, the number of patients per analysis set will be tabulated.

### **Enrolled set**

The Enrolled set will consist of all patients who were assigned a subject ID in this long-term follow-up study.

### **Safety set**

The Safety set will consist of all patients that received at least one dose of study drug in this long-term follow-up study.

### **Fingolimod safety set**

The fingolimod safety set will include all patients who entered the long-term follow up study and received at least one dose of fingolimod in any study, i.e., in the original core/extension MS studies or this long-term follow up study.

### **Fingolimod Full Analysis Set**

The fingolimod full analysis set (FAS) will include all patients who entered the long-term follow-up study and received at least one dose of fingolimod in any study, i.e., in the original core/extension MS studies or this long-term follow up-study.



### **9.1.1 Subgroup**

All analyses including data collected during Study Part two will be conducted based on the subgroup of patients who entered Study Part Two, which includes all patients with at least one dose of study medication after completing Study Part One.

## **9.2 Patient demographics and other baseline characteristics**

Demographic and background information collected from the clinical studies (core & extensions) from which the patients are transferred to this long-term extension study will be summarized. Background information includes prior MS treatment including previous exposure to fingolimod, relevant medical history / current medical conditions, duration of the disease, and baseline EDSS. Identification of clinical study participation prior to transfer into this long-term extension study will also be provided. Summaries will be provided based on the enrolled set.

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

Use of concomitant medications in this long-term follow-up study will be listed and summarized based on the Safety set to support the analysis including data from Study Part One or based on the subgroup of patients who entered Study Part Two of the Safety set to support the analyses including data from Study Part Two.

## **9.4 Analysis of the primary variable(s)**

### **9.4.1 Variable**

Long-term safety will be assessed based on adverse events (AEs), laboratory and vital signs as well as other investigations performed when clinically indicated.

Analysis of the safety variables will be conducted on

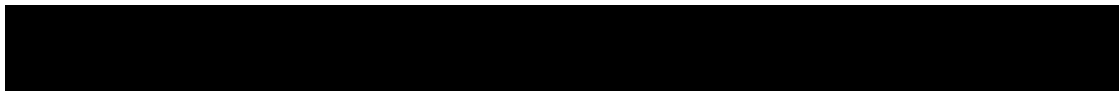
- Safety set: for any analyses including data collected during the long-term follow up study only
- Fingolimod safety set: for analyses including data from first dose of fingolimod in the original core/extension study, if there is any, and in the long-term follow up study.

Given the nature of the design, the data will be presented using descriptive statistics and no inferential analyses are planned.

#### **9.4.1.1 Adverse events (AEs)**

Incidence rates (IRs) of adverse events per 100 patient-years will be summarized by highest assigned fingolimod dose (fingolimod 0.5 mg/day and any dose of fingolimod) based on the fingolimod safety set.

To further evaluate the risk with longer fingolimod exposure duration, adverse events reported with different fingolimod exposure durations will be assessed based on the fingolimod safety set.



In addition, the incidence of adverse events (new or worsened from the long-term extension baseline) reported during the long-term follow up study will be summarized by primary system organ class and preferred term as frequency count and percentage of patients with adverse events based on the safety set.

- Any adverse events
- Serious adverse events (SAEs)
- Suspected study drug related adverse events
- Adverse events leading to discontinuation
- Deaths

All information pertaining to serious adverse events and deaths noted during this study will be listed by center and patient number.

The same analysis including data collected during the Study Part Two will be conducted for the subgroup of patients who entered Study Part Two.

#### **9.4.1.2 Laboratory**

Laboratory data collected up to the end of Study Part One will be summarized by presenting summary statistics of actual values and change from the first dose of fingolimod FDF baseline values and by presenting shift tables using clinically notable ranges (FDF baseline to most extreme post-baseline value). For liver function tests, the frequencies and percentages of patients with elevations of 1, 2, 3, 5, and 10 times upper limit of normal will be summarized by visit. [REDACTED]

A listing of laboratory data for patients with abnormal findings will be provided. In Study Part Two, only local laboratory test is performed for AE reporting purpose according to local policies and no laboratory data is reported in the clinical data base for analysis.

#### **9.4.1.3 Vital signs**

Vital sign data collected up to the end of Study Part One will be summarized as descriptive statistics for change from FDF baseline value. The incidence rates of notable vital sign abnormalities will be summarized.

A listing of vital sign data for patients with abnormal findings will be provided.

The same analysis including data collected during the Study Part Two will be conducted for the subgroup of patients who entered Study Part Two.

#### **9.4.1.4 Electrocardiograms**

Analysis will be performed for first dose ECGs during the long-term follow up study based on the safety set.

Summary statistics for ECG parameters (including pre-dose ECG for patients who have this evaluation done) will be summarized by time point and visit. Incidence of abnormal ECGs will be presented.

A listing of ECG data for patients with abnormal findings will be provided.

[REDACTED]

The same analysis including data collected during the Study Part Two will be conducted for the subgroup of patients who entered Study Part Two.

#### **9.4.1.5 Ophthalmic assessments**

The incidence of macular edema events during Study Part One will be summarized as frequency distributions based on the safety set. The patient data listing will also be provided.

During Study Part Two, ophthalmic assessments will be conducted for safety monitoring purposes at the Month 1 visit and Month 3 visit only for patients who transitioned from a blinded fingolimod study with comparator treatment arms. The patient is not reported in the clinical database for analysis.

#### **9.4.1.6 Pulmonary function tests**

Pulmonary function test data (FEV<sub>1</sub>, FVC, and DLCO, percentage of predicted value for these three variables, and smoking status) collected during Study Part One will be listed based on the safety set. During Study Part Two, PFT assessment will be conducted as need for safety monitoring purpose and the patient data is not reported in the clinical database for analysis.

#### **9.4.1.7 Skin assessment**

The skin assessments during Study Part One will be listed for those who had abnormal findings based on the safety set. During Study Part Two, skin assessment will be conducted as need for safety monitoring purpose and the patient data is not reported in the clinical database for analysis.

### **9.4.2 Handling of missing values/censoring/discontinuations**

Missing values will not be imputed.

### **9.4.3 Supportive analyses**

In addition, adverse events will be summarized by subgroup that will be defined in the statistical analysis plan, such as:

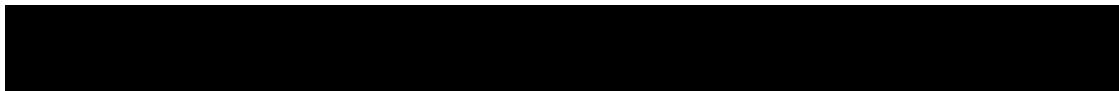
- Duration of fingolimod exposure.
- Previous core/extension trials: Phase II/III studies (i.e., D2201, D2301, D2302, and D2309).

The follow-up safety data after discontinuation of the study drug will be summarized.

## **9.5 Analysis of secondary variables**

### **9.5.1 Efficacy variables**

The following long-term efficacy data will be evaluated as secondary endpoints in the trial. Time-to-event variables will use FDF baseline visit as the start date. Estimates will be provided for patients who have taken at least one dose of fingolimod.





### 9.5.1.1 MS Relapse

Descriptive statistics on the Annual Relapse Rate (ARR) will be presented. ARR (for each patient) is calculated as the total number of relapses divided by total number of days on study, multiplied by 365.25. The ARR for the whole treatment group is the mean of ARR from all patients in the group. Data on time to relapse will also be summarized. In addition, model based estimates will be obtained by fitting a negative binomial regression model adjusted for the number of relapses in the last two years at core baseline and FDF baseline EDSS score, with the logarithm of the duration of the observation period as the offset variable. All the analyses will be done for all relapses (confirmed and unconfirmed) and for confirmed relapses.

All MS relapses are collected during Study Part Two for safety monitoring purposes. Analysis including any relapse data collected during Study Part Two will be conducted based on the fingolimod safety set for the subgroup of patients who entered Study Part Two.

### 9.5.1.2 MRI

Descriptive statistics on number of new / newly enlarging T2 lesions, T2 lesion total volume, T1 black hole volume and brain volume (atrophy) for change from previous scan and change from FDF baseline will be presented by time for appropriate subgroups of patients. Model based estimates will also be provided for the following endpoints:

**New / newly enlarging T2 lesions:** the annualized rate of new/newly enlarging T2 lesions will be estimated based on a negative binomial regression model with log-link. The number of new / newly enlarging T2 lesions relative to FDF baseline will be used as the response variable, and the natural log of the time (in years) of the MRI-assessment from the baseline/screening scan will serve as the offset variable to adjust for the various lengths of follow-up times between patients. The model will include treatment and baseline volume of T2 lesions as continuous covariates.

**Brain volume:** Percent brain volume change from baseline will be estimated based on a mixed effects model with repeated measures and auto-regressive within-subject covariance structure of first order will be used with visit, treatment, core baseline normalized brain volume, number of Gd-enhancing lesions at FDF baseline, and T2 lesion volume at FDF baseline as fixed effects, and individual patient as a random effect. Kenward and Rogers' adjustment for the degrees of freedom will be applied. Annualized rate of brain atrophy (ARBA) will also be estimated based on the same mixed effects model.

### 9.5.1.3 EDSS

Descriptive statistics on absolute EDSS scores (overall and by function), change from FDF baseline, and count (%) based on EDSS change categories will be presented. The proportion of patients with 6-month confirmed disability progression will be presented. Data on time to 6-month confirmed disability progression, and EDSS score of 4, 6, 7 will be summarized.

EDSS will be used for the confirmation of MS relapse and the confirmation of disability progression. Disability progression in this study is defined as an increase in the EDSS score by 1.5 point for patients with an FDF baseline EDSS of 0, 1 point for patients with an FDF baseline EDSS of  $\geq 1$  and  $\leq 5.5$ , and by 0.5 points for patients with an FDF baseline EDSS  $> 5.5$ , confirmed after 6 months and at all intermediate EDSS assessments.

#### **9.5.1.4 MSFC**

Descriptive statistics on absolute MSFC scores and change from FDF baseline will be presented for patients who have done this evaluation.

The MSFC is based on 3 components (dimensions): leg, arm, and cognitive function and the corresponding tests are 25-foot Timed Walk (T25FW), 9-Hole Peg Test (9HPT), and Paced Auditory Serial Addition Test (PASAT3). The scores for these 3 components are combined to create a single score that is used to detect changes over time. This is done by creating z-scores for each component and averaging them to create the overall z-score. In general, z-scores involve comparing each test result with that found in a reference population, a process called standardization. The z-score for each component is calculated by subtracting the mean of the reference population from the test result and then dividing by the standard deviation of the reference population. The mean and standard deviation from the test results at core baseline visit will be used as the reference population. The exact formulas will be given in the statistical analysis plan.



#### **9.6 Sample size calculation**

Given that this is a long-term extension study with primary descriptive purpose, no formal sample size calculation will be used to determine enrollment in this study. The sample size is defined by the number of patients coming from ongoing/new core/extension trials that meet the inclusion and exclusion criteria. It is estimated that about 5000 patients will be enrolled in this trial.



## **9.7 Power for analysis of key secondary variables**

Not applicable.

## **9.8 Interim analyses**

Periodic interim safety analyses to support regulatory updates and interim reports may be warranted.

As this is an open-label, multi-center, single treatment arm long-term safety and tolerability study without formal hypothesis tests, there is no relevance on blinding or alpha-adjustment.

## **10 Ethical considerations**

### **10.1 Regulatory and ethical compliance**

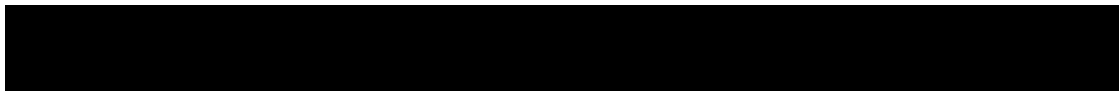
This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of 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/her understanding. If the patient is capable of doing so, he/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 source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP 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 Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Women of child bearing potential should be informed that taking the study drug may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.



### **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 Institutional Review Board/Independent Ethics Committee/Research Ethics Board (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 before study initiation. Prior to 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 monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis 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](http://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.

## **11 Protocol adherence**

Investigators ascertain 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 a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and 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 CSR.

### **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 prior to 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 at the study site should be informed within 10 working days.



## 12 References (available upon request)

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[REDACTED]

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Trapp BD, Peterson J, Ransohoff M, et al (1998). Axonal transection in the lesions of multiple sclerosis. *The New England Journal of Medicine*; 338:278-85.

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## 13 Appendices

### Appendix 1: Clinically notable laboratory values and vital signs

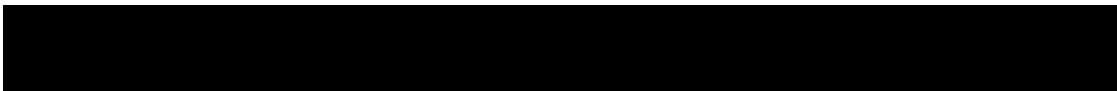
Only selected lab parameters identified as notable which have been shown to be sensitive to fingolimod exposure are included.

#### CRITERIA FOR NOTABLE LABORATORY ABNORMALITIES

<b>Notable Values</b>		
<b>Laboratory Variable</b>	<b>Standard Units</b>	<b>SI Units</b>
<b>LIVER FUNCTION AND RELATED VARIABLES</b>		
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
<b>RENAL FUNCTION / METABOLIC AND ELECTROLYTE VARIABLES</b>		
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
BUN	≤ 2 mg/dL	≤ 0.7 mmol/L
	≥ 30 mg/dL	≥ 10.7 mmol/L
Sodium	< 125 mEq/L	< 125 mmol/L
	>154 mEq/L	>154 mmol/L
Chloride	≤85 mEq/L	≤ 85 mmol/L
	≥119 mEq/L	≥119 mmol/L
Potassium	≤ 3.0 mEq/L	≤ 3.0 mmol/L
	≥ 6.0 mEq/L	≥ 6.0 mmol/L
Magnesium	≤ 1.0 mg/dL	≤ 0.40 mmol/L (in all other countries)
	≥ 3.0 mg/dL	≤ 0.41 mmol/L (in Canada)
Calcium	≤ 7.5 mg/dL	≤ 1.87 mmol/L
	≥ 11.6 mg/dL	≥ 2.89 mmol/L
Phosphate	≤ 2.0 mg/dL	≤ 0.65 mmol/L
	≥ 5.3 mg/dL	≥ 1.71 mmol/L

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

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



## **Appendix 2: Multiple Sclerosis Functional Composite Measure (MSFC)**

### **MSFC-INSTRUCTIONS**

(from the "Administration and Scoring Manual for the Multiple Sclerosis Functional Composite Measure (MSFC)" by [Fischer JS et al, 2001](#))

### **STANDARDIZING MSFC ADMINISTRATION**

The MSFC should be administered as close to the beginning of a study visit as possible, but definitely before the patient does a distance walk. MSFC components should be administered in the following order:

1. Trial 1, Timed 25-Foot Walk
2. Trial 2, Timed 25-Foot Walk
3. Trial 1, Dominant Hand, 9-HPT
4. Trial 2, Dominant Hand, 9-HPT
5. Trial 1, Non-Dominant Hand, 9-HPT
6. Trial 2, Non-Dominant Hand, 9-HPT
7. PASAT

### **INSTRUCTIONS FOR THE TIMED 25 FOOT WALK**

#### **DESCRIPTION**

The Timed 25-Foot Walk is a quantitative measure of lower extremity function. It is the first component of the MSFC administered at each visit. The patient is directed to one end of a clearly marked 25-foot (7.62 m) course and is instructed to walk 25 feet (7.62 meter) as quickly as possible, but safely. The task is immediately administered again by having the patient walk back the same distance. Patients may use assistive devices when doing this task. In clinical trials, it is recommended that the study physician selects the appropriate assistive device for each patient.

#### **MATERIALS NEEDED**

Stopwatch, clipboard, Timed 25-Foot Walk Record Form, marked 25-foot (7.62 m) distance in an unobstructed hallway, assistive device (if needed).

#### **TIME LIMIT PER TRIAL**

3 minutes (180 seconds) per trial.



## **INSTRUCTIONS FOR THE 9-HOLE PEG TEST**

### **DESCRIPTION**

The 9-HPT is a quantitative measure of upper extremity (arm and hand) function. The 9-HPT is the second component of the MSFC to be administered. Both the dominant and non-dominant hands are tested twice (two consecutive trials of the dominant hand, followed immediately by two consecutive trials of the non-dominant hand). It is important that the 9-HPT be administered on a solid table (not a rolling hospital bedside table) and that the small rubber feet are fixed under the 9-HPT apparatus (or the apparatus be anchored by other method).

### **MATERIALS NEEDED**

9-HPT apparatus, stopwatch, clipboard, 9-HPT Record Form

TIME LIMIT PER TRIAL

5 minutes (300 seconds)

## **INSTRUCTIONS FOR THE PACED AUDITORY SERIAL ADDITION TEST (PASAT)**

### **DESCRIPTION**

The PASAT is a measure of cognitive function that specifically assesses auditory information processing speed and flexibility, as well as calculation ability. The PASAT is the last measure administered at each visit. It is presented on audio CD to control the rate of stimulus presentation. Single digits are presented every 3 seconds and the patient must add each new digit to the one immediately prior to it. The test result is the number of correct sums given (out of 60 possible). To minimize familiarity with stimulus items in clinical trials and other serial studies, two alternate forms have been developed; the order of these should be counterbalanced across testing sessions.

### **MATERIALS NEEDED**

CD player, audio CD with PASAT stimuli, clipboard, PASAT Record Forms.

### Appendix 3: New York Heart Association Functional Classification

Class I	Patients have cardiac disease but <i>without</i> the resulting <i>limitations</i> of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Patients have cardiac disease resulting in <i>slight limitation</i> of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Patients have cardiac disease resulting in <i>marked limitation</i> of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Patients have cardiac disease resulting in <i>inability</i> to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.



## **Appendix 4: Guidance for Monitoring of patients taking their first dose of the study drug**

Initiation of fingolimod treatment results in a transient decrease in heart rate. After the first dose, the heart rate decrease starts within an hour and the Day 1 decline is maximal within 6 hours. With continued dosing, heart rate returns to baseline within one month of chronic treatment. In patients receiving fingolimod 0.5 mg this decrease in heart rate, as measured by pulse, averages approximately 8 beats per minute (bpm). Heart rates below 40 bpm were rarely observed. Patients who experienced bradycardia were generally asymptomatic but some patients experienced mild to moderate symptoms.

Initiation of fingolimod treatment has been associated with AV conduction delays, usually as first-degree atrio-ventricular blocks. Second-degree AV blocks, usually Mobitz type I (Wenckebach) have been observed in less than 0.5% of patients receiving Gilenya 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. Isolated cases of transient, spontaneously resolving complete AV block have been reported during post-marketing use of fingolimod 0.5 mg.

Therefore, guidance on the monitoring of patients taking their first dose or re-initiating treatment after interruption of treatment is provided.

The on-site first-dose administration monitoring is mandatory for the following patients:

- At the Baseline visit, in all patients enrolling into this trial from blinded controlled trials and patients from open-label controlled trials coming off the comparator arm.
- Patients who are off fingolimod treatment for the following durations:
- 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.

If applicable, the independent first-dose monitoring physician is responsible for monitoring following the 1<sup>st</sup> intake of the study drug and management of bradycardia symptoms should these occur. He/she must review vital signs during 6-hour monitoring, post-dose ECG and assess discharge criteria at 6 hours post-dose.

Baseline or pre-dose ECG should be provided by the site and be available for comparison to the post-dose ECG in order to determine if discharge criteria are met. The pre-dose ECG will help detect potential risk factors, in particular atrio-ventricular (AV) conduction and rhythm disorders. The 6-hour ECG will help detect otherwise asymptomatic electrocardiographic events (specifically conduction delays) prior to discharging the patient from the clinic.

Sitting heart rate and blood pressure should be measured prior to the 1<sup>st</sup> dose of the study drug and every hour for at least 6 hours thereafter. If required, this would be performed by the independent first-dose monitoring physician. When obtaining the pre-dose heart rate prior to the 1<sup>st</sup> dose intake, the patient should be allowed to rest sitting for 5 minutes. Then the sitting

heart rate should be taken. The sitting heart rate and blood pressure measurements should be collected three times to produce three baseline readings for both heart rate and blood pressure (prior to the 1<sup>st</sup> dose of the study drug only). For comparison to the post-dose heart rate values, the lowest pre-dose value of heart rate should be used.

Patients should receive the first dose of the study drug in the outpatient setting and at a time which will allow for the required 6-hour post-dose monitoring as well as additional monitoring beyond that time point, if necessary.

After 6 hours monitoring, patients may be discharged if all of the following discharge criteria are met:

- Pulse rate at discharge must be at least 45 bpm
- Pulse rate at discharge must not be the lowest hourly value measured during the observation period (suggesting that the maximum pharmacodynamic effect on the heart is not yet manifest)
- Patients must have no symptoms associated with decreased pulse rate or rhythm abnormalities
- ECG at 6 hours should not show any significant abnormalities (e.g. second-degree or third-degree AV block, QTc  $\geq$  500 ms)

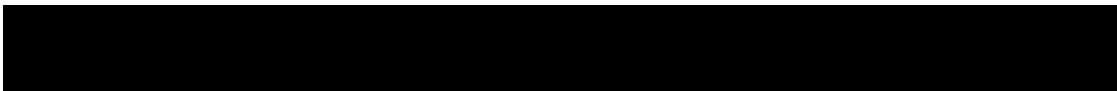
Should post-dose bradyarrhythmia-related symptoms occur, the patient should be monitored until the symptoms have resolved. Should a patient require pharmacologic intervention during the first dose observation, overnight monitoring with continuous ECG in a medical facility should be instituted and the first dose monitoring strategy should be repeated after the second dose of fingolimod.

Overnight monitoring with continuous ECG is required if the ECG at 6 hours shows a QTc interval  $\geq$ 500 msec

Advice from a cardiologist should be sought and overnight monitoring with continuous ECG is required under the following circumstances:

- The pre-dose ECG shows a QTc interval  $>$ 470 msec (females) or  $>$ 450 msec (males) or a second degree or higher AV block
- The patient has relevant risk factors for QT prolongation, for example, hypokalaemia or hypomagnesemia, sick-sinus syndrome, or sino-atrial heart block
- The patient has known ischemic heart disease, history of myocardial infarction, congestive heart failure, history of cardiac arrest, cerebrovascular disease, uncontrolled hypertension or severe untreated sleep apnea period
- The patient has a history of recurrent syncope or symptomatic bradycardia

For patients concurrently treated with beta-blockers or other heart-rate lowering drugs (such as verapamil, diltiazem, digoxin or ivabradine) advice from a cardiologist should be sought regarding switch to non heart-rate lowering drugs. If a switch to non-heart rate lowering drugs is not possible, overnight continuous ECG monitoring is required.



In addition to protocol mandated safety assessments and monitoring procedures, additional procedures and 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 (chest pain, dizziness, palpitations, syncope, nausea and vomiting, etc.). Patients should be instructed not to drive themselves after the first dose of study drug administration.

If a patient requires treatment for bradycardia/bradyarrhythmia during the first-dose observation period, the patient should be hospitalized for overnight monitoring and the first-dose monitoring procedures should be repeated for the second dose of study drug.

### **Recommendations for management of bradycardia**

Prior to the administration of study drug, clinicians should be particularly mindful of patients who have a low pulse at baseline or those patients switching to a non-heart rate lowering drug 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.

## **Appendix 5: Guidance on safety monitoring**

### **Guidance on monitoring of patients with elevated blood pressure**

Patients who have at least two out of the three sitting readings of blood pressure (systolic BP  $\geq 140$  and/or diastolic BP  $\geq 90$  mmHg) should be followed up in one month by an unscheduled visit if the scheduled visit is not due. If systolic BP  $\geq 140$  and/or diastolic BP  $\geq 90$  mmHg values are confirmed in two sitting readings out of three in 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  $>160/100$  mmHg on 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 discontinuation of the study drug may be considered by the investigator.

### **Guidance on monitoring of patients with elevated liver function tests**

For detailed guidance on handling specific laboratory or AE pattern, refer to [Appendix 6](#).

For any unscheduled laboratory assessments performed locally, an identical sample should also be sent to the central laboratory (Study Part One only) 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 eCRF. 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 lymphocyte counts are expected to be around  $0.5-0.6 \times 10^9/L$  or  $500-600$  cells/ $\text{mm}^3$ . As such, the absolute total WBC, neutrophil and lymphocyte counts will be measured at each visit  $y$ . If the absolute lymphocyte count drops below  $0.2 \times 10^9/L$  or  $200$  cells/ $\text{mm}^3$  lymphocyte counts should be repeated regularly, at least monthly, and the patient should be reminded of the risk of infections and instructed to promptly report any symptoms of infections to the investigator. If monthly site visits create a logistical burden for the patient, local lymphocyte testing can be performed, with an eCRF comment added that lymphocyte counts were obtained locally and reviewed by the investigator. Study drug should be temporarily interrupted at the discretion of the investigator. Recovery of lymphocyte counts is expected to take approximately 1-2 months after stopping study drug given the long half-life of fingolimod. The patient should be evaluated and monitored for infections on a regular basis during this period.

### **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 may 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.

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 (with bacterial (e.g. atypical mycobacteria), viral (e.g. HSV, VZV, JCV), or fungal (e.g. cryptococcus agents), should remind the patient of the risk of infections, and 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 investigational 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 antimicrobial therapy on the basis of clinical diagnosis or suspicion thereof (e.g. antiviral treatment for herpes simplex or zoster) in consultation with infectious disease experts, as appropriate.

Investigators should be aware that in the post marketing setting with Gilenya, 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 treatment should be initiated as soon as possible. The investigator should inform the Novartis medical expert of any such cases.

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.

#### Profiling of infection risk in study patients based on anti-viral IgG antibody test results

As a conservative measure before initiation of any immune-modulating drug, patients without a history of chickenpox or without vaccination against varicella zoster virus (VZV) should be tested for antibodies to VZV. 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 varicella zoster virus (VZV) is performed in the study 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 study drug.

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.

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

It is also important to ask the patient 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 should be avoided while patients are taking study drug and for 2 months after study drug discontinuation. Vigilance for infection should be continued throughout this time period. Following VZV vaccination, the initiation of study drug should be postponed for 1 month to allow full effect of vaccination to occur.

Vaccination may be less effective during and for up to two months after treatment with fingolimod.



## Appendix 6: Liver event and Laboratory trigger Definitions and Follow-up Requirements

### Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	<ul style="list-style-type: none"> <li>• 3 x ULN &lt; ALT / AST ≤ 5 x ULN</li> <li>• 1.5 x ULN &lt; TBL ≤ 2 x ULN</li> </ul>
LIVER EVENTS	<ul style="list-style-type: none"> <li>• ALT or AST &gt; 5 × ULN</li> <li>• ALP &gt; 2 × ULN (in the absence of known bone pathology)</li> <li>• TBL &gt; 2 × ULN (in the absence of known Gilbert syndrome)</li> <li>• ALT or AST &gt; 3 × ULN and INR &gt; 1.5</li> <li>• Potential Hy's Law cases (defined as ALT or AST &gt; 3 × ULN and TBL &gt; 2 × ULN [mainly conjugated fraction] without notable increase in ALP to &gt; 2 × ULN)</li> <li>• Any clinical event of jaundice (or equivalent term)</li> <li>• ALT or AST &gt; 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia</li> <li>• Any adverse event potentially indicative of a liver toxicity*</li> </ul>

\*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms  
TBL: total bilirubin; ULN: upper limit of normal

### Follow Up Requirements for Liver Events and Laboratory Triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case <sup>a</sup>	<ul style="list-style-type: none"> <li>• Discontinue the study treatment immediately</li> <li>• Hospitalize, if clinically appropriate</li> <li>• Establish causality</li> <li>• Complete liver CRF</li> </ul>	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution <sup>c</sup> (frequency at investigator discretion)
<b>ALT or AST</b>		
> 8 × ULN	<ul style="list-style-type: none"> <li>• Discontinue the study treatment immediately</li> <li>• Hospitalize if clinically appropriate</li> <li>• Establish causality</li> <li>• Complete liver CRF</li> </ul>	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution <sup>c</sup> (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	<ul style="list-style-type: none"> <li>• Discontinue the study treatment immediately</li> <li>• Hospitalize, if clinically appropriate</li> <li>• Establish causality</li> <li>• Complete liver CRF</li> </ul>	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution <sup>c</sup> (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	<ul style="list-style-type: none"> <li>• Repeat LFT within 48 hours</li> <li>• If elevation persists, continue follow-up monitoring</li> <li>• If elevation persists for more than 2 weeks, discontinue the study drug</li> <li>• Establish causality</li> </ul>	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution <sup>c</sup> (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
	<ul style="list-style-type: none"> <li>Complete liver CRF</li> </ul>	
> 3 × ULN accompanied by symptoms <sup>b</sup>	<ul style="list-style-type: none"> <li>Discontinue the study treatment immediately</li> <li>Hospitalize if clinically appropriate</li> <li>Establish causality</li> <li>Complete liver CRF</li> </ul>	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution <sup>c</sup> (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	<ul style="list-style-type: none"> <li>Repeat LFT within the next week</li> <li>If elevation is confirmed, initiate close observation of the patient</li> </ul>	Investigator discretion Monitor LFT within 1 to 4 weeks
<b>ALP (isolated)</b>		
> 2 × ULN (in the absence of known bone pathology)	<ul style="list-style-type: none"> <li>Repeat LFT within 48 hours</li> <li>If elevation persists, establish causality</li> <li>Complete liver CRF</li> </ul>	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
<b>TBL (isolated)</b>		
> 2 × ULN (in the absence of known Gilbert syndrome)	<ul style="list-style-type: none"> <li>Repeat LFT within 48 hours</li> <li>If elevation persists, discontinue the study drug immediately</li> <li>Hospitalize if clinically appropriate</li> <li>Establish causality</li> <li>Complete liver CRF</li> </ul>	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution <sup>c</sup> (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	<ul style="list-style-type: none"> <li>Repeat LFT within the next week</li> <li>If elevation is confirmed, initiate close observation of the patient</li> </ul>	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	<ul style="list-style-type: none"> <li>Discontinue the study treatment immediately</li> <li>Hospitalize the patient</li> <li>Establish causality</li> <li>Complete liver CRF</li> </ul>	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution <sup>c</sup> (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	<ul style="list-style-type: none"> <li>Consider study treatment interruption or discontinuation</li> <li>Hospitalization if clinically appropriate</li> <li>Establish causality</li> <li>Complete liver CRF</li> </ul>	Investigator discretion
<sup>a</sup> Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN <sup>b</sup> (General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia <sup>c</sup> Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.		

## Appendix 7: Guidance for Ophthalmic Monitoring

Fingolimod has previously been associated with a two-fold increase in the risk of macular edema in renal transplant patients receiving cyclosporine. Macular edema occurred in 0.4% of patients treated with fingolimod 0.5 mg/day. Approximately 75% of cases occurred within the first 3-4 months of therapy. The macular edema generally improved or resolved spontaneously after drug discontinuation.

An ophthalmic examination by an ophthalmologist or neurologist will be conducted in accordance with [Table 6-1](#) and [6-2](#). Similar assessments must be performed at an unscheduled ophthalmology visit for any patient who presents with new visual symptoms or decrease in visual acuity.

1. The ophthalmic examinations will consist of best corrected visual acuity using a visual acuity chart with equal spacing between letters and between lines. 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.
2. Optical Coherence Tomography (OCT) scan should be performed if considered clinically indicated. OCT is required for patients transferring into this trial from a blinded study with a comparator arm at the Month 3 and Month 6 visits and in patients transferring from the control arm of open-label controlled studies. The OCT will be done to evaluate the presence of any abnormalities consistent with macular edema.

### Guidance on monitoring patients for possible macular edema

When macular edema is suspected, a complete ophthalmic evaluation should be performed including, but not limited to, best-corrected visual acuity, dilated ophthalmoscopy, fundus examination and OCT. Patients with history of uveitis and patients with diabetes mellitus are at an increased risk of macular edema and may require more frequent ophthalmic evaluations, per investigator's discretion.

Based on ophthalmic monitoring during the study, study drug must be interrupted in any patient who meets one of the following criteria:

- Patient who is diagnosed to have macular edema.
- Patient who has a decrease in visual acuity (2 line or greater loss on low or normal contrast chart) and an abnormal OCT (> 20% increase in central foveal thickness compared to baseline OCT or cystic changes in the fovea).

A fluorescein angiogram is recommended to evaluate for the presence of vascular leakage in these patients and patients must be encouraged to stay in the study to track resolution of these changes during subsequent visits.

These patients should be followed-up 1 month and 3 months after diagnosis of macular edema and more frequently, if needed, based on the investigator'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). These evaluations will include repeat best-corrected visual acuity, fundus examination and OCT. Fluorescein angiography (FA) is repeated at the discretion of the

ophthalmologist. If the patient does not show definite signs of improvement on examination by specialist testing (e.g. OCT, FA) 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.

Continuation of fingolimod in patients with macular edema has not been evaluated. A decision on whether or not study drug should be re-initiated after resolution of macular edema needs to take into consideration the potential benefits and risks to the individual patient.

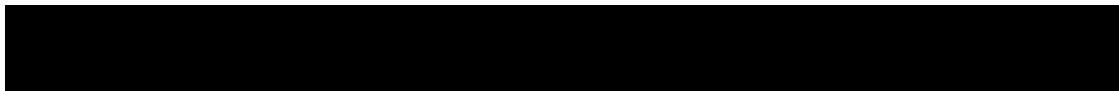
An interruption or discontinuation of the study drug should be clearly documented and reflected on Dosage Administration Record eCRF. AE/SAEs need to be filed as appropriate. For patients discontinuing study drug for any of the above ophthalmic reasons, copies of the colored OCT and fluorescein angiography (if performed) 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 baseline can enter the study given that there is no evidence of macular edema in the baseline 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 planitis, vasculitis, chorioretinitis) under the discretion of the investigator should undergo an ophthalmic examination. 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.

The diagnosis of macular edema will lead to study drug interruption (refer to Guidance for monitoring of patients with macular edema above).



## **Appendix 8: EDSS Assessment Criteria**

### **EXPANDED DISABILITY STATUS SCALE**

- 0** = normal neurological exam (all FS grade 0)
- 1.0** = no disability, minimal signs in one FS (one FS grade 1)
- 1.5** = no disability, minimal signs in more than one FS (more than one FS grade 1)
- 2.0** = minimal disability in one FS (one FS grade 2, others 0 or 1)
- 2.5** = minimal disability in two FS (two FS grade 2, others 0 or 1)
- 3.0** = moderate disability in one FS (one FS grade 3, others 0 or 1) though fully ambulatory; or mild disability in three or four FS (three/four FS grade 2, others 0 or 1) though fully ambulatory
- 3.5** = fully ambulatory but with moderate disability in one FS (one FS grade 3) and mild disability in one or two FS (one/two FS grade 2) and others 0 or 1;  
or fully ambulatory with two FS grade 3 (others 0 or 1);  
or fully ambulatory with five FS grade 2 (others 0 or 1)
- 4.0** = ambulatory without aid or rest for some 500 meters; up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps
- 4.5** = ambulatory without aid or rest for some 300 meters; up and about much of the day, characterized by relatively severe disability usually consisting of one FS grade 4 and combination of lesser grades exceeding limits of previous steps
- 5.0** = ambulatory without aid or rest for about 200 meters (usual FS equivalents include at least one FS grade 5, or combinations of lesser grades usually exceeding specifications for step 4.5)
- 5.5** = ambulatory without aid or rest about 100 meters
- 6.0** = unilateral assistance (cane or crutch) required to walk about 100 meters with or without resting
- 6.5** = constant bilateral assistance (canes or crutches) required to walk at least 20 meters without resting
- 7.0** = unable to walk 5 meters even with aid, essentially restricted to wheelchair; wheels self and transfers alone; up and about in wheelchair some 12 hours a day
- 7.5** = unable to take more than a few steps; restricted to wheelchair; may need some help in transferring and in wheeling self
- 8.0** = essentially restricted to bed or chair or perambulated in wheelchair, but out of bed most of day; retains many self-care functions; generally has effective use of arms
- 8.5** = essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions
- 9.0** = helpless bed patient; can communicate and eat

**9.5** = totally helpless bed patient; unable to communicate effectively or eat/swallow

**10.0** = death due to MS

