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Clinical Trial Protocol CFTY720D2419 / NCT04667949

A 24-month, open-label, prospective, multicenter interventional, single-arm study assessing the efficacy and safety of fingolimod (Gilenya) 0.5 mg in relapsing multiple sclerosis (RMS) patients in China

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List of abbreviations

AE	Adverse Event
ACTH	Adrenocorticotropic Hormone
AKI	Acute Kidney Injury
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANA	Antinuclear Antibody
ARR	Annualized Relapse Rate
ASMA	Anti-Smooth Muscle Antibody
AST	Aspartate Aminotransferase
AV	Atrio-ventricular
BCVA	Best Corrected Visual Acuity
CBC	Complete Blood Count
CD-transferrin	Carbohydrate-deficient Transferrin
[redacted]	[redacted]
CDS	Core Data Sheet
CFR	Code of Federal Regulation
CKD	Chronic Kidney Disease
CMV	Cytomegalovirus
CO	Carbon Monoxide
COVID-19	Coronavirus disease 2019
CHF	Congestive hearts failure
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CT	Computed Tomography
CVD	Cardiovascular Disease
DILI	Drug Induced Liver Injury
DLCO	Carbon Monoxide Diffusing Capacity
DMT	Disease Modifying Therapies
DNA	DeoxyriboNucleic Acid
EBV	Epstein-Barr virus
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EDSS	Expanded Disability Status Scale
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
ERCP	Endoscopic Retrograde Cholangiopancreatography
EOS	End of Study
EOT	End of Treatment

FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume within 1 Second
FS	Functional System
FSH	Follicle-Stimulating Hormone
GBCA	Gadolinium-based Contrast Agent
GCP	Good Clinical Practice
GGT	Glutamyltransferase
GLDH	Glutamate Dehydrogenase
h	Hour
HA	Health Authority
HAV	Hepatitis type A virus
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B Surface Antigen
HBc	hepatitis B Core
HBV	Hepatitis Type B Virus
HCV	Hepatitis Type C Virus
HEV	Hepatitis Type E Virus
HIV	Human Immunodeficiency Virus
HSV	Herpes Simplex Virus
i.v.	intravenous
[redacted]	[redacted]
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
I/E	Inclusion/Exclusion
IFN	Interferon
IG	Immunoglobulin
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
JC virus	John Cunningham virus
LFT	Liver Function Test
MCV	Mean Corpuscular Volume
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
ml	milliliter(s)

MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NA	Not Applicable
[redacted]	[redacted]
NMPA	National Medical Products Administration
NFS	Nephrogenic Systemic Fibrosis
NYHA	New York Heart Association
OCT	Optical Coherence Tomography
PAC	Post Approval Commitment
PD	Proton Density
PFT	Pulmonary Function Test
PML	Progressive Multifocal Leukoencephalopathy
PRMS	Progressive Relapsing Multiple Sclerosis
PT	Preferred Term
QC	Quality Check
RBC	Red Blood Cell
RMS	Relapsing Multiple Sclerosis
RNA	Ribonucleic Acid
RRMS	Relapsing-remitting Multiple Sclerosis
s.c.	subcutaneous
SAE	serious adverse event
SD	standard deviation
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	serum glutamic pyruvic transaminase
SOC	System Organ Class
SPMS	Secondary Progressive Multiple Sclerosis
SSE	Skin Self Examination
SUSAR	Suspected Unexpected Serious Adverse Reactions
T1D	Type 1 Diabetes
T3	triiodothyronie
T4	tetraiodothyronine
TBIL	Total Bilirubin
TEAE	Treatment-emergent Adverse Event
TSH	Thyroid Stimulating Hormone
UK	United Kingdom
ULN	upper limit of normal
WBC	white blood cell(s)
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	A study drug used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug.
Dosage	Dose of the study treatment given to the participant in a time unit ((e.g. 100 milligram (mg) once a day, 75 mg twice a day))
Early withdrawal	Point/time when the participant 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.
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
End of Study (EOS)	EOS, used in the context of individual participants, refers to EOS visit
End of Treatment (EOT)	EOT refers to EOT visit. Any participants who discontinue from treatment should follow the assessments of the EOT visit.
Epoch	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, treatment, follow-up), which applies across all arms of a study.
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 Directive 2001/20/EC and is synonymous with “investigational new drug” or “test substance”
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Screen Failure	A participant who is screened but is not treated or randomized
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Study completion	Point/time at which the the last participant finishes his/her last visit.
Study drug discontinuation	Point/time when participant permanently stops taking study drug for any reason; may or may not also be the point/time of premature participant withdrawal.
Study drug/treatment	Any drug (or combination of drugs) administered to the participant as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy.
Study treatment discontinuation	When the participant permanently stops taking study treatment prior to the defined study treatment completion date

Participant	An individual who has consented to participate in this study. The term Participant may be used to describe either a healthy volunteer or a patient.
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Treatment number	A unique identifier assigned in non-randomized studies to each dosed participant, corresponding to a specific treatment arm
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and/or biological samples AND no longer wishes to receive study treatment AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. This request should be distinguished from a request to discontinue the study. Other study participant's privacy rights are described in the corresponding informed consent form.

Amendment 03 （13-Jun-2023)

The major purpose for the protocol amendment is: 1. To clarify and further detail the identification and situation when EOS visit is required in the study. 2. To describe more clearly about the analysis of T2 lesion-related MRI parameters that will be analyzed as secondary endpoints in Table 2-1 & section 8.3.2; T2 lesion volume is the parameter for disease burden and new/newly enlarged T2 lesion number is the parameter for inflammatory activity, which would be the appropriate endpoint to evaluate the efficacy of fingolimod on MRI lesion activity;

1. Change language in Table 2-1 and Section 8.3.2 from “T2 lesion- new/newly enhancing lesion number and volume” to “T2 lesion volume, new/newly enlarged T2 lesion number”.
2. In Table 8-1, add footnote “Any participants who discontinue from study should follow the assessments of the EOS visit if they agree. If EOT and EOS will be on the same day, only EOS visit is required.”
3. In Table 8-1, add footnote “EOS MRI only required when EOS occurred within 30 days after the last dose and there is no MRI at EOT.” to provide more clarification on EOS MRI assessment.
4. Change language under Section 8.4.2 from “Premature discontinuation visit (EOT)” to “Premature discontinuation from treatment (EOT), premature discontinuation from study (EOS)”, to add situation for EOS visit.
5. Remove “(EOT)” in the second paragraph under Section 8, and add “(see Table 8-1 for details)” to avoid discrepancy with table 8-1.

Other changes were made as below:

1. Use “participant” instead of “subject” to align with the Novartis protocol template Version 5.
2. In List of abbreviations, update “EOT” from “end of trial” to “end of treatment” to correct discrepancy.
3. In Glossary of terms, add “End of Study (EOS)” and “End of Treatment (EOT)” to provide definition of the EOS and EOT in context.
4. In Glossary of terms, update “Study completion” to correctly describe the term.
5. In Glossary of terms, update “Withdrawal of consent (WoC)” to align with the Novartis protocol template Version 5.
6. Under Section 1.1, update therapies available in China for patients with RRMS.
7. [redacted]
8. Language about Public Health Emergency mitigation procedures updated in Section 4.6 and Section 8 to align with the Novartis protocol template Version 5.
9. Under Section 6.2.1, change language from “MS treatment” to “MS disease modifying treatment”, in order to make description more accurate.

10. Under Section 6.2.2, change language from “IFN- ß, teriflunomide” to “other MS DMT (including but not limited to IFN- ß , teriflunomide)”, in order to make statement more accurate.
11. Update language under Section 7 to align with the Novartis protocol template Version 5.
12. Add “Data and samples collected from participants prior to screen failure may still be analyzed.” under section 8.1.1 to align with the Novartis protocol template Version 5.
13. Under Section 8.3.1, change “Annualized relapse rate (ARR)” to “MS relapse” to correctly reflect section content.
14. [redacted]
15. Update language under Section 9.1.3 to align with the Novartis protocol template Version 5.
16. Update language under Section 9.2 to align with the Novartis protocol template Version 5.
17. Update language under Section 9.3 to align with the Novartis protocol template Version 5.
18. Remove “Dose Reduced/increased” under Section 10.1.1 Adverse events, as this is not applicable in study.
19. Update language under Section 10.1.4 Pregnancy reporting to align with the Novartis protocol template Version 5.
20. Change language under Section 12.8.1 Primary endpoint(s) from "Considering 20% drop-out rate, the total sample size will be 100 subjects" to "Considering 20% drop-out rate, the total sample size will be **around** 100 participants." to make statement more accurate.
21. In Table 16.1, update Creatinine SI Units from “≥176umol/dL” to “≥176umol/L” to correct unit error.
22. In Table 16.1, remove item Eosinophils as this value will not be analyzed.

IRBs/IECs

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 02 （11-Oct-2021)

Amendment rationale

In response to the public health emergency (e.g. the COVID-19 pandemic), this protocol amendment introduces the possibility to collect safety information remotely, ship IMP directly to patients' home, collect PRO remotely and conduct consent remotely in the situation where it is not safe for the participants to attend on-site visit. The measures are temporary and should only be used in justified cases as assessed by the investigator (Section 4.6 Rationale for Public Health Emergency mitigation procedures; Section 6.7 Preparation and dispensation; Section 7 Informed consent procedures and Section 8 Visit schedule and assessments).

In addition, the ophthalmic guidance on diagnosis of macular edema is updated in this amendment. The OCT criteria in protocol 1.0 was referring to the optical coherence tomography (OCT) criteria made more than ten years ago. Since the OCT has shown major improvements in technology, old criteria (center point thickness>210 microns for OCT-3 or >200 microns for OCT-2) was outdated. Besides, the value may vary between different machines in local hospital, so it will be more reasonable to make a diagnosis based on ophthalmologist judgement with support of medical condition and OCT exam. To align with the advanced OCT technology and harmonize the diagnosis of macular edema with various OCT machines, the protocol is amended to include the confirmative diagnosis of macular edema based on the ophthalmologist judgement with the support of medical condition and OCT exam (Section 8.4.2 Ophthalmic examination and Section 16.6 Appendix 6 Guidance for Ophthalmic Monitoring).

Other updates or changes to provide more clarity were made as below:

1. Remove the maximum 5 days requirement for the use of corticosteroids under section 8.4.4.4 Infection based on local clinical practice in treating MS relapse

2. Remove the Proton Density (PD) under section 8.3.2 efficacy assessment 2 for editorial reasons; details of sequences collected are specified in vendor documents.

3. Change the language from "In case of new findings in the MRI images in comparison with the previous available MRI which are not compatible with MS lesions, the study drug will be discontinued" to "In case of new findings in the MRI images in comparison with the previous available MRI which are not compatible with MS lesions, the study drug will be interrupted", as the study drug may be restarted once the diagnosis clearly rules out e.g. progressive multifocal leukoencephalopathy (PML), this is specified under Appendix 7 Guidance on safety monitoring.

4.Clarify the detail definition of highly effective contraception which consistent with China label under section 5.2 Exclusion criteria to align with the Novartis newest protocol template.

In addition, editorial updates were made to align to the Novartis newest protocol template and to provide consistency throughout the protocol.

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

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Amendment 01 （28-Aug-2020)

Amendment rationale

The major purpose for the protocol amendment is to clarify the guidance and procedures related to exclusion criteria in the protocol per China clinical practice. Tests for excluding participants with severe active infections, active chronic infections (hepatitis, tuberculosis), Severe liver impairment (Child-Pugh class C) are listed in Table 8-1 Assessment Schedule. Hepatitis B test, Chest CT test and Prothrombin time were specified to be used for the patient screening.

Other major changes were made as below:

1. Detailed Pulmonary function monitoring guidance is added under Section 8.4.4.3. Pulmonary function test is required at the screening visit. Related changes are reflected in following sections in the protocol:
2. 5.2 Exclusion criteria #18 Updated the description of severe uncontrolled respiratory disease in pulmonary function test
3. Table 8-1 Assessment Schedule changed from as needed to S in screening visit
4. Section 8.4.5 Appropriateness of safety assessments
5. Changes due to the updated protocol template Version 3.0 language under Section 6.5.2.1 Follow up on potential drug-induced liver injury (DILI) cases
6. Changes were made to incorporate applicable changes in the Liver Safety Monitoring Guidance according to the China fingolimod label under Section 16.7- Appendix 16.7 Guidance on monitoring of participants with elevated liver function tests
7. Changes were made to clarify the electrocardiogram (ECG) requirement for baseline and first dose monitoring in Table 8-1 Footnote # 11 and 8.4.2 ECG
8. [redacted]
9. More clarification on the MRI acquisition process in Section 8.3.2 Efficacy assessment 2. and Table 8-1 Footnote # 9.
10. Section 4.5 Risks and Benefits: Added COVID-19 risk related to Gilenya
11. Section 4.5.1 Imaging Risk and Section 5.2 Exclusion criteria #19 – to incorporate Gd based contrast language and list MRI exclusions

Changes were incorporated to address the COVID-19 pandemic in the following sections:

- Section 6.7 Preparation and dispensation
- Section 7 Informed Consent Procedures
- Section 8 Visit Schedule and Assessments
- Section 8.4 Safety
- Section 8.4.1 Laboratory evaluations
- Section 12 Data analysis and statistical methods

Other change incorporated in this amendment:

1. Table 2-1 Objectives and related endpoints: [redacted]
2. Table 8-1 Assessment Schedule: Screening time was changed to -30 to -1 days; EDSS test X was added in the screening field to be consistent with Section 5.1 Inclusion criteria #6; Footnote 2 and 3 Provided detailed description on participants who complete the study to be consistent with section 9.1 Discontinuation. Addition of new column for 'EOT Visit' and marked applicable assessments at EOT visit; Correction of documentation type for Drug accountability (X to S); Removal of 'Visit numbers' row.
3. Modified Footnotes #1 and #10.
4. Section 8.2 Participant demographics/other baseline characteristics: Removed date of birth since it will not be collected in the study; Added race.
5. [redacted]
6. Section 10.1.3 SAE reporting: Removed the wordings "following the last administration of study treatment if there are post-treatment follow-up visits with no required procedures" since it's not applicable for the study.
7. Section 12.5 Analysis of secondary endpoints: Removed month 6 from analysis on MRI data to make it consistent with the study procedure. [redacted]
8. Section 16.6 Appendix 6 Provided more detailed guidance for Ophthalmic Monitoring. Section 8.4.4.2 Ophthalmic examination was been updated accordingly.
9. Section 15: Addition of Ledneva et al 2009 and deletion of Kurtzke 1983 references.
10. [redacted]
11. List of abbreviations and Protocol Summary were aligned according to the updates made in the protocol body, basis the amendment.
12. Section 16.7: Updated the Guidance on monitoring participants with A) notable lymphopenia and B) elevated BP.
13. Section 16.5: Updated the citations.
14. Section 16.4: Updated the EDSS steps 4.0, 4.5, 5.0, and 5.5.
15. Section 16.3 and Table 16-1: Clarifications made in the table.
16. Section 12.5.1: Deletion of sentence "For those participants who withdraw from the study, the analyses will include all data collected up to 2 months after treatment discontinuation unless explicitly stated otherwise".
17. Section 10.2.1: Added the example of CRF 'AE page, concomitant medical page' with respect to documentation of follow-up information.

18. Section 10.1.4: Added the sentence “If a female trial participant becomes pregnant, the study treatment should be stopped, and the trial participant must be asked to read and sign pregnancy consent form to allow the Study Doctor ask about her pregnancy”.
19. Section 9: Corrected the section heading.
20. Section 8.3.2: Section heading corrected.
21. Section 5.2 #4: Updated for ‘Screening’ QTc interval
22. Section 5.1 # 4 and #5: Clarification added regarding the number of documented relapses
23. [redacted]

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Protocol summary

Protocol number	CFTY720D2419
Full Title	A 24-month, open-label, prospective, multicenter interventional, single-arm study assessing the efficacy and safety of Fingolimod (Gilenya) 0.5 mg in relapsing multiple sclerosis(RMS) patients in China.
Brief title	Study of efficacy and safety of Fingolimod (Gilenya) in relapsing multiple sclerosis participants in China.
Sponsor and Clinical Phase	Novartis Phase IV
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this open-label, prospective, multi-center interventional, single-arm study in patients with relapsing form of MS, is to further explore the efficacy and safety profile of fingolimod in Chinese population. Based on that MS is a rare disease worldwide and a placebo controlled arm is deemed as unethical to participant because of other available DMTs in China, an open-label, single arm design is considered to be adequate for this study, as fingolimod is an approved therapy and continues to be effective and safe for RMS participants across various countries in the world.
Primary Objective(s)	To evaluate the efficacy of fingolimod 0.5mg on annualized relapse rate (ARR) in participants with RMS treated for up to 24 months.
Secondary Objectives	1. To evaluate the safety and tolerability of fingolimod 0.5mg in participants with RMS treated for up to 24 months. 2. To evaluate the efficacy of fingolimod 0.5mg on MRI lesions.
Study design	This is a 24-month, open-label, multicenter, interventional, single-arm study to collect efficacy, safety and health outcome data of fingolimod (Gilenya) 0.5 mg/day in China.
Population	The study population will consist of relapsing multiple sclerosis participants, aged 10-65 years (inclusive) with weight > 40 kg.
Inclusion criteria	1. Written informed consent must be obtained before any assessment is performed. 2. Male or Female with age: • 18 to 65 years old inclusive; • 10 to 17 years old inclusive with weight > 40kg. 3. Clinical definite diagnosis of Multiple Sclerosis according to the 2010 Revised McDonald criteria. 4. Participants with a diagnosis of relapsing multiple sclerosis prior to their enrollment to the study (signing the study consent form): • At least two documented relapses during the past 2 years, or • At least one documented relapse during the last year 5. With RMS that never used fingolimod before enrollment (including naive participants and participants who switched from previous DMTs). 6. Participants with EDSS score of 0 - 6.0 (inclusive) at Screening.
Key Exclusion criteria	1. Conditions include in contraindication section and special warning section as latest approval label in China.

	2. Patients treated with any other investigational drug for MS in the period. 3. Pregnant or nursing woman or woman of child-bearing potential not using effective contraception. 4. Patient intolerant to undergo MRI or presents contraindications to MRI (e.g., metallic implants, metallic foreign bodies, pacemaker, defibrillator) and the use of gadolinium-based agents (e.g. people with severe kidney failure, patients with previous severe allergic/anaphylactoid reaction to a gadolinium-based contrast agent; patients with severe renal disease ((Estimated Glomerular Filtration Rate (eGFR) <30 mL/min/1.73 m2),) or acutely deteriorating renal function, who would be at risk of nephrogenic systemic fibrosis). 5. Pediatric participant without confirmed history of chickenpox or confirmed documentation of a full vaccination course against varicella zoster virus (VZV). 6. Any disability that may prevent the participants from completing all study requirements, as assessed by the treating physician (e.g., mental disorder, blindness or deafness that is not appropriate for age, severe language difficulty). 7. Current medical or neurological condition that might impact efficacy assessments e.g. dementia, schizophrenia, bipolar disorder, major depression, history of multiple traumatic brain injuries, alcohol/drug abuse or dependence currently, or dependence within the last two years.
Study treatment	Fingolimod 0.5mg will be administered daily treated for up to 24 months.
Efficacy assessments	• MS relapse • [redacted] • Magnetic Resonance Imaging (MRI)
Key safety assessments	• Physical/neurological examination • Vital signs • Skin assessments • Laboratory evaluations • ECG • First dose monitoring • Ophthalmologic exams / Optical coherence tomography (OCT) • Pulmonary function test
Other assessments	[redacted]
Data analysis	All data will be analyzed using with summaries and/or statistical models appropriately. Annualized relapse rate (ARR) will be analyzed using a negative binomial model. Number and proportion of patients with new and newly enlarged T2 lesions will be statistically summarized as well as the number and proportion for patients with Gd-enhanced T1 lesions and the change of volume of T1 hypo-intense lesions from baseline. All safety [redacted] will also be statistically summarized appropriately.
Key words	Multiple sclerosis, relapse, efficacy, safety

1 Introduction

1.1 Background

Multiple Sclerosis (MS) is a chronic, immune-mediated disease of the central nervous system characterized by inflammation, demyelination and axonal/neuronal destruction, ultimately leading to severe disability (Trapp et al 1998, Sospedra and Martin 2005). Globally, the median estimated incidence of MS is 2.5 per 100,000 (ranging from 1.1 to 4.0 per 100,000) and the median estimated prevalence is 30.0 per 100,000 (ranging from 5.0 to 80.0 per 100,000) WHO and Multiple Sclerosis International Federation. 2008. At diagnosis, approximately 85% of patients have relapsing-remitting MS (RRMS), characterized by recurrent, acute episodes (relapses) of neurological symptoms. Approximately 50% of these patients progress to secondary progressive MS (SPMS) within 10 years, 90% within 25 years, when a less inflammatory, and more neurodegenerative. SPMS can also be segregated based on whether patients continue to experience relapses (relapsing form of SPMS) or not (purely progressive SPMS). About 10-15% of MS patients present with a primary progressive course (PPMS) defined by a continuous accumulation of neurological disability from symptom onset without superimposed exacerbations or remissions. Progressive relapsing MS (PRMS; chronic progressive from onset with infrequent relapses) is the least frequent form of MS (Keegan and Noseworthy 2002). So typically recurrent acute episodes (relapses) of neurological symptoms, which are followed by a complete or partial recovery is the basic feature of MS.

In China, several therapies are approved for patients with RRMS and fall within 4 classes of products: anti-CD20 monoclonal antibody (ofatumumab), dimethyl fumarate, DHODH inhibitor (teriflunomide), and S1P receptor modulator (siponimod, fingolimod and ozanimod). All are considered as immunomodulatory or immunosuppressive medications. Beta interferons have multiple immune actions but the means by which the drugs are effective in MS remains unknown. They have shown modest (~30%) effect on relapses and in the case of IFN β -1a, on disability (Goodin et al 2002). Teriflunomide, an orally active drug that inhibits lymphocyte proliferation. It selectively and reversibly inhibits dihydro-orotate dehydrogenase, an enzyme in the de novo synthesis pathway of pyrimidines, resulting in reduced proliferation of peripheral T- and B- lymphocytes, and hence reduce numbers of lymphocytes crossing the blood-brain barrier and causing CNS damage (Bar Or et al 2014) . Fingolimod (Gilenya) is a chemical entity for once daily oral administration which has been submitted to health authorities in the USA and in Europe late 2009 and subsequently in other countries worldwide to obtain market authorization. Since August 2010, fingolimod has been approved more than 70 countries for treatment of patients with relapsing of MS. Fingolimod is rapidly phosphorylated in vivo, and fingolimod-phosphate (fingolimod-P) acts as an agonist of G protein-coupled receptors for sphingosine-1 phosphate (S1P). More particularly, fingolimod-P acts as “super agonist” of the $S1P_1$ receptor on thymocytes and lymphocytes, inducing internalization and degradation of that receptor. This renders these cells unresponsive to $S1P_1$ signaling, thus depriving them of a signal necessary for egress from lymph nodes and secondary lymphoid tissues. The downstream result of this fingolimod induced interdiction of $S1P_1$ signaling is a marked reduction in the number of both B and T lymphocytes in the intravascular compartment and a decrease in recirculation of these cells to extravascular compartments, including the CNS.

Prior to submission, the efficacy profile of fingolimod was evaluated in five main studies. In two of the phase III clinical trials, Study CFTY720D2301 (acronym FREEDOMS I) and CFTY720D2309 (acronym FREEDOMS II), each 24-month placebo-controlled study, fingolimod demonstrated reduction of relapse rate, disability progression, MRI lesion counts and rate of brain atrophy (Kappos et al 2010) . In another Phase III trial, study CFTY720D2302 (acronym TRANSFORMS), a large active controlled study vs. intramuscular interferon beta-1a, fingolimod showed a significant reduction in relapse rate over the 12-month treatment period and reduced magnetic resonance imaging (MRI) lesion counts and rate of brain atrophy Kappos et al 2010. Study CFTY720D2399 (acronym LONGTERMS), an open-label, phase IIIb extension study, indicated that fingolimod treatment for up to 14 years had a sustained benefits for control of disease activity and disability progression without emerging safety concerns Cohen et al 2019.In the controlled pediatric study CFTY720D2311 (acronym PARADIGMS), it compared the efficacy of fingolimod to intramuscular interferon beta-1a in pediatric patients. It showed the annualized relapse rate (ARR), was significantly lower in patients treated with fingolimod than in patients who received interferon beta-1a.

The safety profile of fingolimod has been well characterized with approximately 296,714 patients in both clinical trials and the post –marketing setting, with the total patient exposure now at approximately 746,745 patient year by 30 Nov 2019. The safety profile in pediatric patients was overall similar to that seen in adult patients Chitnis et al 2018.

During the course of the fingolimod clinical development, several areas were identified as safety areas of note: bradyarrhythmias upon treatment initiation or on restarting after an interruption of fingolimod therapy of more than 14 days, liver transaminase elevations, hypertension, macular edema and infection.

Initiation of fingolimod treatment results in a transient decrease in heart rate and infrequently induces atrio-ventricular (AV) block. In MS clinical trials, the mean maximal decrease in heart rate after the first dose intake was 12~ 13 bpm and was seen at ~6 hours post-dose. Heart rates below 40 beats per minute were rarely observed in patients on fingolimod 0.5 mg/day. Heart rate progressively returned to baseline within 1 month of dose initiation despite continued dosing. In addition, a mild increase in blood pressure of approximately 2 mmHg diastolic and 3 mmHg systolic on average. This onset after approximately 1 months of treatment initiation persisted with continued treatment but reversed upon cessation of therapy. Hypertension was reported as an adverse event in 6.5% of patients on fingolimod 0.5 mg/day and in 3.3 % of patients on placebo in the 2-years placebo controlled study.

Liver enzyme elevations were seen in clinical trials. Asymptomatic elevations in serum levels of hepatic transaminases ≥3x upper limit of normal (ULN) and ≥5x ULN, were observed in 8.0% and 1.8% of patients treated with fingolimod 0.5 mg/day respectively compared to 1.9% and 0.9% for patients receiving placebo. The majority of elevations occurred within 12 months of therapy and returned to normal, generally within 2 months of discontinuation of therapy.

Macular edema occurred in 0.5% 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. The risk of developing macular edema appears to be increased in MS patients with a history of uveitis. There is limited data on fingolimod in MS patients with diabetes mellitus. In earlier renal

transplant clinical studies where patients with diabetes mellitus were included, therapy with fingolimod 2.5 mg/day and 5 mg/day resulted in a 2-fold increase in the incidence of macular edema. MS patients with diabetes mellitus are therefore expected to be at a higher risk for macular edema.

A key pharmacodynamic effect of fingolimod is a dose-dependent reduction of peripheral lymphocyte count to 20 - 30% of baseline values. This is due to the reversible sequestration of lymphocytes in lymphoid tissues. In multiple sclerosis clinical trials, the overall rate of infections (65.1%) at the 0.5 mg dose was similar to placebo Novartis 2019. However, bronchitis, herpes zoster and pneumonia, were more common in Gilenya treated patients Karlsson G,Francis and Schmouder R,et 2009. Serious infections occurred at a rate of 1.6% in the fingolimod 0.5 mg group versus 1.4% in the placebo group (2013) 2.5 Clinical Overview Rationale for changes to Core Data Sheet (CDS) / A full review and up date of sections, A full review and update of sections, "Warnings and Precautions", "Adverse Drug Reactions" and "Interactions" . In a second 2-year placebo controlled study, CFTYD2309, which was reported after approval of fingolimod, the safety profile seen in prior studies was largely confirmed, however in this study herpes zoster was reported more frequently in the fingolimod arms as compared to placebo (2.5% vs. 0.8% respectively) and basal cell carcinomas were more frequent in the fingolimod 0.5 mg group (2.8%) as compared to both, the fingolimod 1.25 mg and the placebo arms (1.6 and 0.6%) respectively. One fatal primary disseminated varicella zoster infection and one fatal herpes simplex encephalitis case have occurred in patients receiving the 1.25 mg/day dose; at the fingolimod 0.5 mg dose, one patient died in the post-marketing setting due to a disseminated varicella zoster infection in the context of high dose steroid treatment.

As part of a post-approval commitment to China's health authorities, Novartis is conducting this post-approval commitment study (PAC) in order to evaluate the efficacy and safety profile of fingolimod in Chinese multiple sclerosis patients. The study will collect safety profile information related to clinical practice setting and long-term follow-up including, but not limited to infections, cardiac and vascular events (e.g. stroke, myocardial infarction, angina pectoris and peripheral vascular disease, second and third degree AV conduction block, hypertension), malignancies, pulmonary events, seizures, MS relapses, atypical severe neurological events and sudden/unexplained death.

1.2 Purpose

The purpose of this study is to collect 24-month efficacy, safety, tolerability, and health outcome data of fingolimod (0.5 mg per Day) in participants with relapsing multiple sclerosis (RMS) in China. This is a post approval commitment study for fingolimod.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To evaluate the efficacy of fingolimod 0.5mg on annualized relapse rate (ARR) in	• Annualized relapse rate(ARR)

Objective(s)	Endpoint(s)
participants with RMS treated for up to 24 months.	
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the safety and tolerability of fingolimod 0.5 mg in participants with RMS treated for up to 24 months.	• Adverse events (AE) and serious adverse events (SAE) Laboratory tests(hematology, biochemistry) • Vital signs • Electrocardiogram (ECG) • Ophthalmology
• To evaluate the efficacy of fingolimod 0.5 mg on MRI lesions.	• T1 hypo-intense lesion number and volume; T2 lesion volume, new/newly enlarged T2 lesion number; Gd-enhancing T1 lesion number and volume.
[redacted]	

3 Study design

This is a 24-month, open-label, multicenter, interventional, single-arm study to collect efficacy, safety and health outcome data of fingolimod (Gilenya) 0.5 mg/day in approximately 100 relapsing multiple sclerosis (RMS) participants in China.

The study will consist of three Phases (see Figure 3-1):

Screening (up to 1 month): After signing informed consent, participants will enter a Screening Phase to determine eligibility according to inclusion and exclusion criteria.

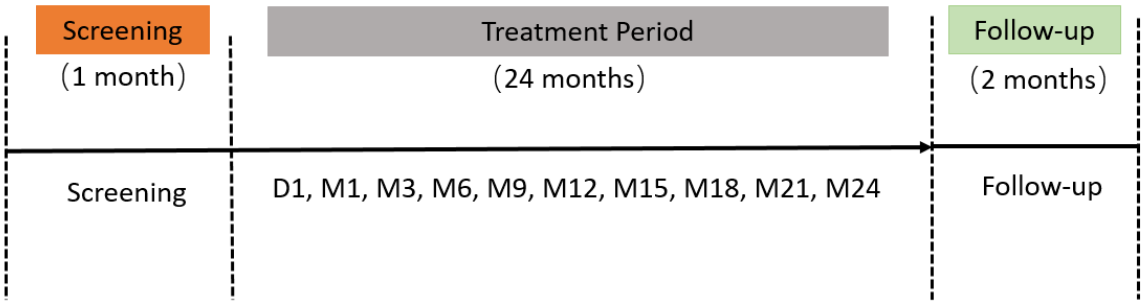
The investigator must ensure that all patients meet the inclusion and exclusion criteria to be eligible to enter the study.

Treatment Period (24 months): On visit Day 1, all eligibility criteria will be confirmed, including a pre-dose ECG and vital signs. The first dose of study drug will be taken in the clinic on Day 1 and the participant will be monitored for at least 6 hours after the first dose administration before discharge. Refer to Section 16.5 for Guidance for monitoring of patients taking their first dose of the study drug.

Then the participants should come to site and be evaluated month 1 and then every three months till the end of treatment up to 24 months.

Follow Up (2 months): Participants who completed Treatment Period will return for the Follow-up visit 2 months after the last dose of study drug.

Figure 3-1 Study design



4 Rationale

4.1 Rationale for study design

The clinical development program of fingolimod has demonstrated the efficacy and safety of fingolimod 0.5 mg/day dose for the treatment of participants with relapsing-remitting multiple sclerosis globally in clinical studies (CFTY720D2301, CFTY720D2309). Nonetheless there was no data from Chinese participants. Along with the local approval of fingolimod to treat RMS in China on 12-Jul-2019, National Medical Products Administration (NMPA) in China requested, as a post-approval requirement, to collect the efficacy and safety data of fingolimod 0.5mg/day in Chinese participants, including number of pediatric participants recruited will be based on natural occurrence.

This study is designed with the aim to obtain the efficacy, safety and health outcome data in Chinese RMS participants treated with fingolimod for 24 months. Given the limited population size of RMS patients in China because of the rare disease feature, and the concern that a placebo controlled arm is deemed as unethical to participant because of other available DMTs in China, an open-label, single arm design is considered to be adequate for this study, as fingolimod is an approved therapy and continues to be effective and safe for RMS participants across various countries in the world.

[redacted]

4.2 Rationale for dose/regimen and duration of treatment

The dose of Gilenya for participants enrolled in this study is set at 0.5 mg orally administered once daily. The dosage of 0.5 mg has been approved in China for the treatment of relapsing multiple sclerosis in adults and pediatric participants with age ≥ 10 years old and weight > 40 kg.

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Not applicable

[redacted]

4.5 Risks and benefits

The risk to participants in this study will be minimized by compliance with inclusion/exclusion criteria, close clinical monitoring, avoidance of prohibited treatments and adherence to investigator guidance regarding specific safety areas.

The risk profile of fingolimod includes bradyarrhythmia (including conduction effects) occurring post first dose, liver transaminase elevation, infection, macular edema, hypertension, clinically relevant bronchoconstriction and posterior reversible encephalopathy syndrome.

Women of child bearing potential must be informed that taking the study treatment 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 requirements outlined in the protocol. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study.

There is currently no data to inform incidence or severity of COVID-19 in patients receiving fingolimod. The immune system effects of fingolimod, integral to their mechanism of action in multiple sclerosis, may increase the risk of infections (including viral infections), as disclosed in the product label of drug.

Patients receiving fingolimod, who may have been exposed to individuals with COVID-19, who are experiencing protracted flu-like symptoms (particularly shortness of breath) consistent with COVID-19, or are confirmed to have COVID-19, should inform treatment physician as soon as possible. Whether there will be interruption of the use of fingolimod will be based on investigator's judgement.

4.5.1 Imaging Risk

A gadolinium-based contrast agent (GBCA) will be administered as an i.v. bolus during each MRI session. There is recent evidence of gadolinium deposition in brain tissues following use of GBCAs. Although no symptoms or diseases linked to gadolinium accumulation in the brain have been identified, health authorities took a precautionary approach (e.g., GBCA EMA restriction re brain deposit), noting that data on the long-term effects in the brain are limited. This led to the suspension of several linear GBCAs and the recommendation that another class of GBCAs known as macrocyclic agents be used as an alternative solution, as they are deemed more stable and have a lower propensity to release gadolinium than linear agents. Although this is highly debated, the current belief is that such agents, especially the linear gadolinium agents, may also increase the risk of a rare but serious disease called nephrogenic systemic fibrosis

(NFS). Few studies showed that use of linear agents in patients with normal kidney function or mild-to-moderate CKD (stage 3; eGFR 30-59 ml/min per 1.73 m^2) is without clinically significant risk of nephrogenic systemic fibrosis (NFS) (Ledneva et al 2009), however they should remain contraindicated in patients with acute kidney injury (AKI) or severe renal disease (stage 4 or 5 chronic kidney disease, CKD) (eGFR <30 ml/ min per 1.73 m^2). To prevent this risk and in accordance with health authority guidance (e.g., GBCA FDA guidance re NFS, GBCA UK HA (Health Authority) guidance re NFS), people with severe kidney failure, patients with previous severe allergic/anaphylactoid reaction to a gadolinium-based contrast agent; patients with severe renal disease (eGFR <30 mL/min/1.73 m^2), or acutely deteriorating renal function, who would be at risk of nephrogenic systemic fibrosis should be excluded from participating in this study as stipulated in the exclusion criterion.

4.6 Rationale for Public Health Emergency mitigation procedures

During a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, mitigation procedures to ensure participant safety and trial integrity may be implemented. Notification of the Public health emergency as declared by local or regional authorities should be discussed among investigators and Novartis All procedures adapted to the situation must be submitted, if required as per local regulations, through a protocol amendment for approval by local or regional Health Authorities and Ethics Committees prior to implementation of mitigation procedures. The measures (refer to Section 4.6 Rationale for Public Health Emergency mitigation procedures; Section 6.7 Preparation and dispensation; Section 7 Informed consent procedures and Section 8 Visit schedule and assessments for details) provide the possibility to collect safety information remotely, ship IMP directly to patients' home, collect PRO remotely and conduct consent remotely in situation it is not safe for the participants to attend on-site visit. The measures are temporary and should only be used in justified cases as assessed by the investigator.

5 Population

The study population will consist of adult relapsing multiple sclerosis participants aged 18-65 years (inclusive) and in pediatric relapsing multiple sclerosis participants of 10 years of age and older weighing more than 40kg.

Approximately 100 patients will be enrolled from around 10 to 15 centers in China.

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria at screening:

1. Written informed consent must be obtained before any assessment is performed.
2. Male or Female with age:

   18 to 65 years old inclusive;

   10 to 17 years old inclusive with weight > 40kg.
3. Clinical definite diagnosis of Multiple Sclerosis according to the 2010 Revised McDonald criteria Polman et al 2011 (refer to Section 16.3).

4. Participants with a diagnosis of relapsing multiple sclerosis prior to their enrollment to the study (signing the study consent form):
   - At least two documented relapses during the past 2 years, or
   - At least one documented relapse during the last year
5. With RMS that never used fingolimod before enrollment (including naive participants and participants who switched from previous DMTs).
6. Participants with EDSS score of 0 - 6.0 (inclusive) at Screening.

5.2 Exclusion criteria

Participants meeting any of the following criteria at screening will not be eligible for this study.

1. History of myocardial infarction, unstable angina pectoris, stroke/transient ischemic attack, decompensated heart failure with hospitalization or New York Heart Association (NYHA) Class III/IV heart failure (refer to Section 16.2) in the previous 6 months.
2. Treatment with Class Ia or Class III anti-arrhythmic drugs.
3. History or presence of Mobitz Type II 2nd degree or 3rd degree AV block or sick sinus syndrome, unless the participant has a pacemaker.
4. Screening and Baseline QTc interval ≥ 500 msec.
5. History of symptomatic bradycardia or recurrent syncope.
6. History of cardiac arrest, uncontrolled hypertension or severe sleep apnea.
7. Macular edema during screening visit.
8. Increased risk for opportunistic infections, including immunocompromised participants :
   - currently receiving immunosuppressive therapies
   - immunocompromised by prior therapies where in the respective approved medication labels suggested wash out of the previous ongoing MS Disease Modifying Therapies (DMT) is not being conducted prior to ICF
   - absolute lymphocyte count is below 0.2 x 10^9/L
9. Known active malignancies.
10. Use of teriflunomide within 3.5 months prior to baseline, except if active washout (with either cholestyramine or activated charcoal) was done prior to fingolimod first dose in study.
11. Under MS investigational drug clinical study.
12. Severe active infections, active chronic infections (hepatitis, tuberculosis), as assessed by the treating physician.
13. Severe liver impairment （Child-Pugh class C).
14. Pregnant or nursing woman or woman of child-bearing potential not using highly effective contraception.

    Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant. Highly effective contraception methods include:

    - Total abstinence (when this is in line with the preferred and usual lifestyle of the

participant. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or bilateral tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Use of oral, (estrogen and progesterone), injected, or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception.
In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate history of vasomotor symptoms)). Women are considered not of child bearing potential if they are post-menopausal or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks ago. 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.

15. Pediatric participant without confirmed history of chickenpox or confirmed documentation of a full vaccination course against varicella zoster virus.
16. Any disability that may prevent the participants from completing all study requirements, as assessed by the treating physician (e.g., mental disorder, blindness or deafness that is not appropriate for age, severe language difficulty).
17. Current medical or neurological condition that might impact efficacy assessments e.g. dementia, schizophrenia, bipolar disorder, major depression, history of multiple traumatic brain injuries, alcohol/drug abuse or dependence currently, or dependence within the last two years.
18. Advanced, severe progressive or unstable disease that may interfere with the safety, tolerability and study assessments, or put the participant at special risk, e.g. uncontrolled diabetes ((hemoglobin A1c (HbA1c)>9%)), severe uncontrolled respiratory disease (including but not limited to pulmonary fibrosis, abnormal pulmonary function tests values lower than 70% of predicted at screening), human immunodeficiency virus (HIV) infection, severe renal impairment.
19. Patient intolerant to undergo MRI or presents contraindications to MRI (e.g., metallic implants, metallic foreign bodies, pacemaker, defibrillator) and the use of gadolinium-based agents (e.g. people with severe kidney failure, patients with previous severe allergic/anaphylactoid reaction to a gadolinium-based contrast agent; patients with

severe renal disease (eGFR<30 mL/min/1.73 m^2), or acutely deteriorating renal function, who would be at risk of nephrogenic systemic fibrosis).

20. History of hypersensitivity to any of the Gilenya ingredients.
21. Participant will be excluded from participation, if they have participated in any other unapproved therapy clinical study within last 6 months of the ICF signature date.

6 Treatment

6.1 Study treatment

It is a single-arm, open-label study. The participants will take capsules of 0.5 mg fingolimod for oral administration.

6.1.1 Investigational and control drugs

Table 6-1 Investigational drug

Investigational Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
Fingolimod (Gilenya) 0.5mg	Capsule	Oral use	Open label	Sponsor (global)

6.1.2 Additional study treatments

No other treatment beyond investigational drug is included in this trial.

6.1.3 Treatment arms/group

All participants will receive open-label fingolimod 0.5 mg, orally, once daily.

6.1.4 Treatment duration

The planned duration of treatment is 24 months. Participants may be discontinued from treatment earlier due to unacceptable toxicity whether it is related to study drug or not, disease progression and/or treatment is discontinued at the discretion of the investigator or the decision of participant or serious non-compliance to study protocol. For participants who in the opinion of the investigator are still deriving clinical benefit from fingolimod, every effort will be made to continue provision of study treatment.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

All drug used in previous MS disease modifying treatment should be captured on the "Previous MS disease modifying Treatment" eCRF.

All other concomitant medications taken within 30 days prior to Screening and during the study the respective information needs to be recorded in the eCRF. The investigator should instruct

the participant to notify the study site about any new medications he/she takes after the start of the study drug. Both the start date and the end date, for each medication should be captured on the Concomitant Medication CRF.

Use of the following treatments are recommended 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 5-20 µg/kg/min or epinephrine drip 2-10 µg/min) for treatment of non-responsive bradycardia.

For more recommendations for management of bradycardia, refer to Section 16.5.

A short course of intravascular corticosteroids (methylprednisolone) is allowed for the treatment of MS relapses.

The medications allowed for treatment of adverse reactions and MS relapses are not considered study supplies, and therefore, need to be supplied by the study site or only 0.5mg fingolimod will be supplied by sponsor.

6.2.2 Prohibited medication

Use of the following treatments are NOT allowed during the whole course of the study (use can be considered if the study drug has been permanently discontinued):

- anti-neoplastic;
- immunomodulatory or immunosuppressive therapies should be prohibited due to the risk of additive immune system effects (e.g. cyclosporine, azathioprine, methotrexate, cyclophosphamide);
- other concomitant treatment: immunoglobulins (IGs), monoclonal antibodies (including rituximab), other MS DMTs (including but not limited to IFN- ß, teriflunomide), adrenocorticotropic hormone (ACTH);
- during and for up to two months after treatment with fingolimod, vaccination may be less effective. The use of live attenuated vaccines may carry a risk of infections and should therefore be avoided.

6.2.3 Rescue medication

Not applicable.

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is first enrolled for screening and is retained as the primary identifier for the participant throughout his/her entire participation in the study. The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it (assigned by the investigator), so that

each participant is numbered uniquely across the entire database. Upon signing the informed consent form (ICF), the participant is assigned to the next sequential Participant No. available.

6.3.2 Treatment assignment, randomization

No randomization will be performed in this study. There is only one treatment arm in this study, which is fingolimod 0.5 mg, orally, once daily.

6.4 Treatment blinding

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

6.5 Dose escalation and dose modification

6.5.1 Dose modifications

Not applicable.

6.5.2 Follow-up for toxicities

6.5.2.1 Follow up on potential drug-induced liver injury (DILI) cases

Participants with transaminase increase combined with TBIL increase may be indicative of potential DILI and should be considered as clinically important events.

The threshold for potential DILI may depend on the participant's baseline aspartate aminotransferase (AST)/ALT and TBIL value; participants meeting any of the following criteria will require close follow-up as outlined below:

- For participants with normal alanine aminotransferase (ALT) and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN
- For participants with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline] OR [AST or ALT > 300 U/L] whichever occurs first combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

As DILI is essentially a diagnosis of exclusion, other clinical causes of abnormal liver tests should be considered and their role clarified before DILI is assumed as the cause of liver injury.

A detailed history, including relevant information such as review of ethanol consumption, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.

Laboratory tests should include ALT, AST, total bilirubin（TBIL）, direct and indirect bilirubin, glutamyltransferase (GGT), prothrombin time/ international normalized ratio (INR), alkaline phosphatase, albumin, and creatine kinase. If available, testing of Glutamate Dehydrogenase (GLDH) is additionally recommended.

Perform relevant examinations ((Ultrasound or MRI, Endoscopic Retrograde Cholangiopancreatography (ERCP)) as appropriate, to rule out an extrahepatic cause of cholestasis. Cholestasis is defined as an alkaline phosphatase (ALP) elevation > 2.0 x ULN with

R value < 2 in participants without bone metastasis, or elevation of the liver-specific ALP isoenzyme in participants with bone metastasis.

- Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤ 2), hepatocellular (R ≥ 5), or mixed (R >2 and < 5) liver injury. For children, there are caveats to calculating the R-ratio as normal levels of ALP are higher than in adults with standard ranges varying by developmental age. In clinical situations where it is suspected that ALP elevations are from an extrahepatic source, the GGT can be used if available. GGT may be less specific than ALP as a marker of cholestatic injury, since GGT can also be elevated by enzyme induction or by ethanol consumption. It is more sensitive than ALP for detecting bile duct injury.

Table 6-2 Guidance on specific clinical and diagnostic assessments which can be performed to rule out possible alternative causes of observed LFT abnormalities.

Disease	Assessment
Hepatitis A, B, C, E	• IgM anti- hepatitis type A virus (HAV); Hepatitis B surface antigen (HBsAg), IgM & IgG anti - hepatitis B core (HBc),HBV deoxyriboNucleic acid (DNA); anti-hepatitis type C virus (HCV), HCV ribonucleic acid (RNA), IgM & Ig Ganti- hepatitis type E virus (HEV), HEV RNA
CMV, HSV, EBV infection	• IgM & IgG anti-CMV (Cytomegalovirus), IgM & IgG anti- herpes simplex virus (HSV); IgM & IgG anti- epstein-barr virus (EBV)
Autoimmune hepatitis	• antinuclear antibody (ANA) & anti-smooth muscle antibody (ASMA) titers, total Immunoglobulin M (IgM), Immunoglobulin G (IgG), Immunoglobulin E (IgE), Immunoglobulin A (IgA)
Alcoholic hepatitis	• Ethanol history, GGT, mean corpuscular volume (MCV), carbohydrate-deficient transferrin (CD-transferrin)
Nonalcoholic steatohepatitis	• Ultrasound or MRI
Hypoxic/ischemic hepatopathy	• Medical history: acute or chronic congestive hearts failure (CHF), hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI
Biliary tract disease	• Ultrasound or MRI, ERCP as appropriate
Wilson disease (if <40 yrs old)	• Caeruloplasmin
Hemochromatosis	• Ferritin, transferrin
Alpha-1-antitrypsin deficiency	• Alpha-1-antitrypsin

Other causes should also be considered based upon participants' medical history ((hyperthyroidism / thyrotoxic hepatitis – triiodothyronine (T3), tetraiodothyronine (T4), Thyroid Stimulating Hormone (TSH); Cardiovascular Disease (CVD) / ischemic hepatitis – ECG, prior hypotensive episodes; type 1 diabetes (T1D) / glycogenic hepatitis)).

Following appropriate causality assessments, as outlined above, the causality of the treatment is estimated as "probable" i.e. >50% likely, if it appears greater than all other possible causes of liver injury combined. The term "treatment-induced" indicates probably caused by the

treatment, not by something else, and only such a case can be considered a DILI case and should be reported as an SAE.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified, should be considered as "medically significant," and thus, meet the definition of SAE and should reported as SAE using the term "potential drug-induced liver injury." All events should be followed up with the outcome clearly documented.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

The investigator must promote compliance by instructing the participant to take the study treatment exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study. The participant must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed. Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the participant. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

6.6.2 Emergency breaking of assigned treatment code

Not applicable.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section.

A unique medication number is printed on the study drug label. As per the treatment assigned to the participant, investigator staff will select the study treatment to dispense to the participant. The study drug has a 2-part label (base plus tear-off label), immediately before dispensing the package to the participant, site personnel will detach the outer part of the label from the package and affix it to the participant's source document.

Per Section 4.6, during a Public Health emergency delivery of IMP directly to a participant's home may be permitted (if allowed by Local or Regional Health Authorities and Ethics Committees as appropriate) in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. The dispatch of IMP from the site to the participant's home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 13 weeks supply. Sufficient supply will be provided for the participants in situations when the participants cannot visit sites for a longer period of time. In this case, regular phone calls or virtual contacts (every 3 months or more frequently if needed) will occur between the site and the participant for instructional purposes, safety monitoring, investigation of any adverse events, ensuring participants continue

to benefit from treatment, and discussion of the participant's health status until the participants can resume visits at the study site.

6.7.1 Handling of study treatment and other treatment

6.7.1.1 Handling 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 site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the Investigator's Brochure. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization Quality Assurance.

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

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Participants will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis/*sponsor* monitor or to the Novartis address provided in the investigator folder at each site.

6.7.1.2 Handling of additional treatment

Not Applicable.

6.7.2 Instruction for prescribing and taking study treatment

- Fingolimod (Gilenya) 0.5 mg, 1 capsule, orally.
- Once daily, preferably always at the same time of the day, with or without food.
- The first dose of the study drug administered at the Day 1 visit, should be taken in the clinic preferably on or before 12:00 PM (noon). The participant will be monitored by the site staff for at least 6 hours until discharge criteria are met (refer to Section 16.5 for Guidance for monitoring of patients taking their first dose of the study drug). Monitoring of re-initiation of first dose will be performed when: interruption of 1 day or more within the first 2 weeks of treatment, interruption of more than 7 days during the 3rd week and the 4th week of treatment and interruption of more than 14 days after the first month of treatment in a similar manner as the first intake of the study drug (refer to Section 16.5 for Guidance for monitoring of patients taking their first dose of the study drug).
- The treatment will last up to 24 months.

- It is recommended not to initiate treatment with beta-blockers, calcium-channel blockers or digoxin within one week before or after the first dose of the study drug due to a possible additive effect on heart rate reduction.
- Site staff will make sure to dispense sufficient amount of study drug to participants. The amount should cover the period until participants come back to the clinic at the latest visit window allowed in the protocol. When the participants return for the following study visit, the site staff will count the capsules left, log the amount left into a drug accountability log and re-distribute the drug to the participants following the same procedure described above.
- It is a single-arm open label study. Participant eligible for the study will be treated with fingolimod (Gilenya).
- Participants should be instructed to swallow whole capsule and not to chew or open it.
- If vomiting occurs during the course of treatment, participants should not take fingolimod (Gilenya) again before the next scheduled dose.
- Participants should be instructed not to make up missed doses. A missed dose is defined as a case when the full dose is not taken within 8 hours after the approximate time of the usually daily dosing. That day's dose should be omitted and the participant should continue treatment with the next scheduled dose.

7 Informed consent procedures

The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or their legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of FDA 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

A copy of the ICF(s) must be provided to the participant or their legally authorized representative.

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given his/her level of understanding. If the participant is capable of doing so, he/she

must indicate agreement by personally signing and dating the written informed consent document.

Information about common side effects already known about the investigational treatment can be found in the Investigator's Brochure (IB) (and/or Core Data Sheet for marketed drugs). This information will be included in the participant informed consent and should be discussed with the participant upon obtaining consent and also during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an Investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

Women of child bearing potential must be informed that taking the study treatment 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 requirements.

The following informed consents are included in this study:

- Main study consent for adults, which also included:
    - A subsection that requires a separate signature for the ‘Optional Consent for Additional Research’ to allow future research on data/samples collected during this study
    - Optional consent for activities that may be done outside of the study site
- Child Assent for 7-11 years old participants
- Adolescent Assent for 12-17 years old participants
- As applicable, Parent Legal Guardian consent
- As applicable, Pregnancy Follow-up consent for the pregnant participants
- As applicable, Pregnancy Follow-up consent for parent legal guardian of pregnant participants

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

As per Section 4.6, during a Public Health emergency that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local Health Authority. Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

8 Visit schedule and assessments

There are mandatory scheduled visits in the context of this interventional study. Table 8-1 lists all assessments scheduled at each visit. It is planned that participants should come to site and

be evaluated every three months till the end of treatment, following by two months' follow-up visit after the last treatment of fingolimod.

Participants who discontinue from study should be scheduled for a final evaluation visit (see Table 8-1 for details) if they agree, as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications not previously reported must be recorded on the CRF.

At the onset of any symptom indicative of a relapse during the study, participants may have unscheduled visits to confirm relapse and collect information. In addition, participants may have unscheduled visits for other reasons, including but not limited to infection, blurred vision. In case of MS relapse, these visits are essential for relapse evaluation and confirmation and have to be carefully documented on the Unscheduled Visit eCRFs. Exams to confirm relapse is based on investigator's discretion. During unscheduled visits for other reasons, information should be collected per Unscheduled Visit eCRFs.

Participants should follow as much as possible the visit schedule with an allowed “visit window” of ± 3 days for Month 1 and Month 3 visit and ± 5 days for Month 6, Month 9, Month 12, Month 15, Month 18, Month 21, Month 24 and 2-month follow up visit. In case a visit was performed outside the visit window, subsequent visits should be performed according to the original visit schedule and as applicable per study label guidelines necessary first dose monitoring should be performed at site. In the study, one month is defined as 30 calendar days.

As per Section 4.6, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowable by a local health authority, national and local regulations and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consultation) or visits by site staff/off-site healthcare professional(s) staff to the participant´s home, can replace certain protocol assessments, for the duration of the disruption until it is safe for the participant to visit the site again. If the Investigator delegates tasks to an off-site healthcare professional, the Investigator must ensure the individual(s) is/are qualified and appropriately trained to perform assigned duties. The Investigator must oversee their conduct and remain responsible for the evaluation of the data collected.

Table 8-1 Assessment Schedule

Period	Screening	Treatment Period												Follow-up Visit[2]
Visit Name	Screening	Day 1	Month 1	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24	EOT[3]	EOS[4]	Follow-up Visit
Days	-30	1 to 1	27 to 33	87 to 93	175 to 185	265 to 275	355 to 365	445 to 455	535 to 545	625 to 635	715 to 725	NA	NA	775 to 785
Informed consent	X													
Demography	X													
Inclusion / Exclusion criteria[6]	X	X												
MS history/current medical conditions[7]	X													
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Drug dispensation[1]		X	X	X	X	X	X	X	X	X				
Drug accountability[1]			S	S	S	S	S	S	S	S	S	S	S	
1st dose observation[8]		X												
Pregnancy and assessments of fertility[9]	S		S	S	S	S	S	S	S	S	S	S	S	S
Body Height	X													
Body Weight	X			X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	S	S			S		S		S		S	S	S	S
MS relapse[10]			X	X	X	X	X	X	X	X	X	X	X	X
EDSS	X	[redacted]												
MRI[11]	X						X				X	X	X[5]	
[redacted]														
Ophthalmic examination[12]	X			X	X		X				X	X	X	X
Dermatological examination	S				S		S		S		S	S	S	S
Electrocardiogram (ECG)[13]	X	X	X	X	X		X		X		X	X	X	X
Hematology	X		X	X	X	X	X		X		X	X	X	X

Period	Screening	Treatment Period												Follow-up Visit[2]
Visit Name	Screening	Day 1	Month 1	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24	EOT[3]	EOS[4]	Follow-up Visit
Days	-30	1 to 1	27 to 33	87 to 93	175 to 185	265 to 275	355 to 365	445 to 455	535 to 545	625 to 635	715 to 725	NA	NA	775 to 785
HIV screen	S													
Chemistry	X		X	X	X	X	X		X		X	X	X	X
Hepatitis B test[14]	S													
Chest CT (Computed Tomography)	S													
Prothrombin time	S													
Urinalysis	S		S	S	S	S	S	S	S	S	S	S	S	S
Reported AE/SAE		X	X	X	X	X	X	X	X	X	X	X	X	X
Pulmonary function tests	S	as needed	as needed	as needed	as needed	as needed	as needed	as needed	as needed	as needed	as needed	As needed	As needed	as needed

X Assessment to be recorded in the clinical database or received electronically from a vendor
S Assessment to be recorded in the source documentation only

[1] Drug accountability and dispensation will not be performed after participants discontinued the study or the study treatment.

[2]Participants that complete 24 months treatment period will complete the 2 months follow up visit; Participants that prematurely discontinue therapy and stay in the study for the whole 24 months will complete the 2-month follow up visit.

[3] Any participants who discontinue from treatment should follow the assessments of the EOT visit.

[4] Any participants who discontinue from study should follow the assessments of the EOS visit. If EOT and EOS will be on the same day, only EOS visit is required.

[5] EOS MRI only required when EOS occurred within 30 days after the last dose and there is no MRI at EOT.

[6] Inclusion/exclusion criteria need to be checked again before first dose of study drug.

[7] Previous medical history will be collected for each participant in order to capture pre-existing medical conditions. The number of documented relapse in previous 1 year and 2 years will be collected.

Period	Screening	Treatment Period												Follow-up Visit[2]
Visit Name	Screening	Day 1	Month 1	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24	EOT[3]	EOS[4]	Follow-up Visit
Days	-30	1 to 1	27 to 33	87 to 93	175 to 185	265 to 275	355 to 365	445 to 455	535 to 545	625 to 635	715 to 725	NA	NA	775 to 785

[8] Participants who newly initiate fingolimod therapy or restart fingolimod after dose interruption should be observed for 6 hours after treatment initiation per the local label. Monitoring of reinitiating of first dose will be performed when: interruption of 1 day or more within the first 2 weeks of treatment, interruption of more than 7 days during weeks 3 and 4 of treatment and interruption of more than 14 days after the first month of treatment.
[9] Blood pregnancy test will be performed at screening visit. Urine or Serum pregnancy test will be performed at following visits.
[10] Unscheduled visits are required to confirm MS relapse and additional EDSS assessments may be conducted.
[11] All participants will undergo MRI scanning of the brain at Screening, provided the participant meets all other Inclusion/Exclusion (I/E) criteria, Month 12 and Month 24 in accordance with the study Imaging Acquisition Guidelines. If required, unscheduled MRI scans will be conducted based on investigator's judgement.
[12] Screening visit and Month 3 visit will include ophthalmic symptoms, best corrected visual acuity and optical coherence tomography(OCT) for the measurement of central foveal thickness. All the other scheduled visits, the content will include any new ophthalmic symptoms and best corrected visual acuity.
[13] ECG to be obtained on Day 1 before Fingolimod dose administration and 6 hours post-first dose The first ECG will be performed on Day 1 to check the I/E criteria again. If the participant is eligible to be enrolled, the ECG result will be recorded as pre-dose ECG. The second ECG will be performed at 6 hours post dose. If extended monitoring is required, ECG will be performed by the end of extended monitoring. If study drug treatment is interrupted and treatment re-initiation meets the requirement for observation, the above procedures will be performed, identical to procedures conducted at Day 1.

[14] Hepatitis B test include: HBV surface antigen, surface antibody, E antigen, E antibody, core antibody; if abnormal finding on HBV surface antigen, HBV DNA copies test will be performed.

8.1 Screening

It is permissible to re-screen a participant if s/he fails the initial screening; re-screening should only occur after a participant has failed screening and re-screening window time is at the discretion of the investigator. A new participant ID should be assigned to the re-screened participant.

As per Section 4.6, during a Public Health emergency, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowable by a local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) or visits by site staff/ home nursing staff to the participant´s home, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again. In exceptional cases and after discussing with the study team, participant go to another hospital for safety test will be permitted.

8.1.1 Information to be collected on screening failures

Participants who sign an informed consent form and is subsequently found to be ineligible prior to starting treatment will be considered as a screen failure. The reason for screen failure should be recorded on the appropriate Case Report Form. The demographic information, informed consent, and inclusion/exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening period. Data and samples collected from participants prior to screen failure may still be analyzed.

Participants who have passed screening and fail to start treatment will be considered as an early terminator. The reason for early termination will be recorded on the appropriate Case Report Form.

8.2 Participant demographics/other baseline characteristics

Participant demographic and baseline characteristic data will be collected from the participant which included: age, race, sex, ethnicity, height and weight.

Previous MS history (including diagnosis and history of relapses), and current medical condition will be collected and recorded on CRF.

8.3 Efficacy

MS relapse activity and neurological impairment of MS as measured by Expanded Disability Status Scale (EDSS) (refer to Section 16.4 for EDSS assessment criteria) will be obtained in order to characterize the disease activity.

8.3.1 Efficacy assessment 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: A relapse must be confirmed by the Treating Physician. 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).

Only confirmed relapses will be included in the primary efficacy analysis. However, the relapse-related analyses will be repeated using all relapses to assess the sensitivity of the results.

Reporting of relapse : A participant may report symptoms indicative of a relapse at a scheduled visit or at any other time. Participants will be instructed to immediately contact the treating physician if he/she develops new or re-occurring or worsening neurological symptoms. At each scheduled visit, the participant will also be asked whether any such symptoms have occurred.

Upon reporting of symptoms indicative of a relapse, the treating physician will assess in an appropriate manner whether the symptoms occur in the presence of fever or infection. If fever or infection can be excluded, a neurological examination by the treating physician must be arranged as soon as possible. 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). Treatment with steroids should not begin prior to the assessment by the investigator.

Based on results of the neurological examination (change in FS and EDSS scores), the treating physician will assess if the relapse meets the criteria for “confirmed relapse” as per protocol and record relapse on the Summary of MS Relapses eCRF.

8.3.2 Efficacy assessment 2

Expanded Disability Status Scale (EDSS).

The EDSS is an ordinal scale used for assessing neurologic impairment in MS based on a neurological examination. It consists of scores in each of seven functional systems (FSs) that are then combined to determine the EDSS steps [ranging from 0 (normal) to 10 (death due to MS)]. The FSs are Visual, Brain Stem, Pyramidal, Cerebellar, Sensory, Bowel & Bladder, and Cerebral functions. The FSs and EDSS steps will be assessed in a standardized manner. EDSS is a widely used and accepted instrument to evaluate disability status at a given time and, longitudinally, to assess disability progression in clinical studies in MS.

[redacted] EDSS assessments obtained on an unscheduled visit can only be used to mark the onset of a possible sustained progression.

Patient who dies due to MS will be counted as progression. A patient who misses one or more scheduled visits that are preceded [redacted]

MRI parameters: T1 hypo-intense lesion number and volume; T2 lesion volume, new/newly enlarged T2 lesion number; Gd- enhancing T1 lesion number and volume;

All participants will undergo MRI scanning of the brain in accordance with the study Imaging Acquisition Guidelines during the Screening visit (up to 30 days prior to day 1), provided the participant meets all other I/E criteria, and then for the Month 12 and Month 24 visits. Each MRI scan performed for the study needs to be centrally reviewed by a neuro-radiologist from the sponsor designated imaging vendor as part of the efficacy analysis. Each site investigator will be responsible to have a qualified neuro-radiologist review each MRI scan to determine if there may be any incidental findings unrelated to the planned observations within the study protocol detected on the images. Refer to Section 16.7 Appendix 7 for Guidance on Safety monitoring.

Participant suspected MS relapse could undergo additional MRI scan on his/her own account in alignment with the investigator. To avoid potential interference caused by steroids used for the treatment of MS relapses, the following restrictions will be applied for this study:

- In case of relapse, if an MRI would have been scheduled within 30 days of the initiation of steroid treatment, this MRI should be performed before steroid treatment is initiated.
- No MRI scan should be performed while a participant is on intravenous steroid therapy and within 30 days after termination of steroid therapy.

Scanning

The contrast medium may occasionally cause nausea and vomiting. Allergic reactions may also occur very rarely and, in extremely rare instances, can be potentially serious and require immediate anti-anaphylactic treatment (i.v. epinephrine, dopamine, steroids, etc.)
T1-weighted images before and after administration of Gadolinium contrast medium as well as T2-weighted images will be performed.

Prior to the start of the study, a radiologist and technician from each center will receive an Imaging Acquisition Guideline, outlining technical implementation, image quality check (QC) requirements and MRI administrative procedures. Each site will be asked to program the MRI scanner acquisition technical parameters that are designated for evaluation of the study participants, perform and submit a phantom test scan using a QC phantom or equivalent, to generate images that will be transferred to the sponsors designated CRO to assess the image quality and to evaluate the compatibility of the electronic data carrier. Following the acceptance of the phantom test scan, all the parameter settings for the study specific MRI sequences must remain unchanged for the duration of the study unless the site is directed to adjust the settings by the imaging CRO following consultation with the sponsor.

8.3.3 Appropriateness of efficacy assessments

MS relapse, EDSS assessments as well as MRI parameters in this patient population are standard 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 study.

8.4 Safety

Safety assessments are specified as below with the assessment schedule detailing when each assessment is to be performed. If the COVID-19 pandemic limits or prevents on-site study visits, phone calls or virtual contacts should be conducted for safety monitoring and discussion of the participant´s health status, until the participant can again visit the site. In exceptional cases and after discussing with Novartis, safety tests could be performed outside of the investigator sites.

For details on AE collection and reporting, refer to AE section.

- Physical/neurological examination
- Vital signs
- Skin assessments
- Laboratory evaluations
- ECG
- First dose monitoring
- Ophthalmologic exams / Optical coherence tomography (OCT)
- Pulmonary function test

As per Section 4.6, during a Public Health regular phone or virtual calls can occur (every 12 weeks or more frequently if needed) for safety monitoring and discussion of the participant's health status until it is safe for the participant to visit the site again.

Table 8-2 Assessments & Specifications

Assessment	Specification
Physical	A physical examination may be performed at a scheduled visit and may include an assessment of skin, head and neck, lymph nodes, breast, heart, lungs, abdomen, back and/or comments on general appearance. A neurological examination may also be a part of the physical examination. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.
Vital signs	Vital signs include temperature, blood pressure and pulse measurements. Sitting pulse rate and blood pressure will be recorded at each visit and should be obtained after the patient has 5 minutes of rest. The pulse should be measured just prior to obtaining the blood pressure measurement. After the participant has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using an automated validated device, e.g. OMRON, with an appropriately sized cuff. The

Assessment	Specification
	repeated sitting measurements will be made at 1 - 2 minute intervals and the mean of the three measurements will be used. Clinically notable vital signs are defined in Appendix 1.
Skin assessments	A complete skin examination will be performed by a dermatologist or qualified physician as described in Table 8-1. The purpose of a skin examination at baseline is to exclude participants with suspicious skin lesions (pre-cancerous, cancerous) from the study and to document a baseline assessment in order to monitor participants with non-suspicious lesions for the duration of the study. It is recommended that all participants perform a skin self examination (SSE) on a monthly basis. Participants should be instructed on how to properly conduct these examinations. If the participant reports new or changed lesion(s) during the study, a skin exam should be performed by a dermatologist. In case of findings at any visit, suspicious for being precancerous or cancerous skin disorders, the investigator will refer the participant to a qualified physician for further examination and a biopsy may be required to rule out or to confirm diagnosis. Upon completion of the examination any new findings during the study will be transcribed in the Adverse Event eCRF.

8.4.1 Laboratory evaluations

Laboratory samples will be collected as described in Table 8-3 and analyzed by the local lab. Investigators will be asked to comment on these abnormalities on the respective lab result page, including a notation of the clinical significance of each abnormal finding in the participant's source documents. The laboratory sheets will be filed with the source documents. Mandatory hematology and chemistry test results should be recorded on the eCRF.

Any diagnosis (or signs or symptoms if a diagnosis is not possible) associated with the abnormal findings should be recorded on the adverse event eCRF.

Clinically notable laboratory findings are defined in Appendix 1.

In case of increases in liver function test (LFT), refer to Appendix 7 Guidance on Safety Monitoring.

In case of decreases in lymphocytes, refer to Guidance on monitoring of participants with notable lymphopenia in Appendix 7 Guidance on Safety Monitoring.

If the COVID-19 pandemic limits or prevents on-site study visits, the method of collection of samples may be modified by Novartis if applicable and if modified, will be communicated to the Investigator. In exceptional cases and after discussing with Novartis, safety tests could be performed outside of the investigator sites.

Table 8-3 Laboratory Evaluations

Test Category	Test Name
Hematology	Hemoglobin, Platelets, White blood cells (WBC), Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Other)

Test Category	Test Name
Hepatitis B test	HBV surface antigen, surface antibody, E antigen, E antibody, core antibody; if abnormal finding on HBV surface antigen, HBV DNA copies test will be performed.
Coagulation Function	Prothrombin time
Chemistry	ALT , AST , Creatinine, Direct Bilirubin, Total Bilirubin, Total Cholesterol
Urinalysis	Macroscopic Panel /Dipstick (Color, Blood, Glucose)
Additional tests	HIV antibodies
Pregnancy Test	Serum / Urine pregnancy test

8.4.2 Electrocardiogram (ECG)

ECGs will be collected at Screening visit, Day1, Month 1, Month 3, Month 6, Month 12, Month 18, Month 24, Premature discontinue from treatment (EOT), premature discontinue from study (EOS), Follow-up visit according to the assessment schedule and as needed if study drug is restarted after interruption.

At Day1, two to three ECGs will be performed. The first ECG will be performed on Day 1 to check the I/E criteria again. If the participant is eligible to be enrolled, the ECG result will be recorded as pre-dose ECG. The second ECG will be performed approximately 6-hours post-first-dose. If extended monitoring is needed, then a third ECG will be performed by the end of extended monitoring.

If study drug treatment is interrupted and treatment re-initiation meets the requirement for observation, the above procedures will be repeated, identical to procedures conducted at Day 1.

For any ECGs with participant safety concerns, an additional ECG must be performed to confirm the safety finding. Clinically significant abnormalities must be recorded on the CRF as adverse events.

All the below ECG parameters will be captured in the eCRF: heart rate, PR interval, QRS duration, QT and QTc interval. 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.

8.4.3 Pregnancy and assessments of fertility

To confirm an eligibility of a woman of child bearing potential for the study, a blood pregnancy test should be performed at Screening visit. Participants, who are determined and documented to be surgically-sterile or post-menopausal for 12 months or longer prior to Screening, are not required to undergo pregnancy testing.

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner and women whose partners have been sterilized by vasectomy or other means, unless they meet the following definition of post-menopausal: 12 months of natural

(spontaneous) amenorrhea or 6 months of spontaneous amenorrhea with serum follicle-stimulating hormone (FSH) levels >40 mIU/m or 6 weeks post surgical bilateral oophorectomy with or without hysterectomy OR are using one or more of the following highly effective contraception: surgical sterilization, hormonal contraception, and double-barrier methods. Acceptable methods of contraception may include total abstinence at the discretion of the investigator in cases where the age, career, lifestyle, or sexual orientation of the participant ensures compliance. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Reliable contraception should be maintained throughout the study and for 2 months after study drug discontinuation.

Additional Urine or Serum Pregnancy tests may be performed at scheduled assessment visit. The positive urine test needs to be confirmed with serum test.

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child-bearing potential must also be available as source documentation in the following cases:

1. Surgical bilateral oophorectomy without a hysterectomy
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, FSH testing is required of any female participant regardless of reported reproductive/menopausal status at screening/baseline.

During a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, if participants cannot visit the site to have urine or serum pregnancy tests, urine pregnancy test kits for home use may be used if allowed by local regulations. Relevant participants can perform the urine pregnancy test at home and report the result to the site. It is important that participants are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A communication process should be established with the participant so that the Site is informed and can verify the pregnancy test results (e.g., following country specific measures).

8.4.4 Other safety evaluations

8.4.4.1 First dose monitoring

For safety concern, the first dose of fingolimod administered at Day 1 in this study must be administered in the clinic under the supervision of the investigator. It is recommended that the first dose be administered in the morning, before 12 noon to allow for adequate monitoring time. The patient will stay at the study center for a minimum of 6 hours. Heart rate and blood pressure will be monitored hourly during the six hour stay and discharged if specific discharge criteria (outlined in Section 16.5) are met. Hourly monitoring will be extended if the discharge criteria are not met. Some participants may be required to return to the study center for 6 hours following the 2nd dose if they meet the monitoring criteria as outlined in Section 16.5.

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 participant's safety and

the validity of the study. The participant should be instructed to contact the investigator if he/she is unable for any reason to take the study drug as prescribed.

Should the participant interrupt the study drug, and should the investigator decide in agreement with the sponsor to re-initiate treatment with the study drug, the first dose intake at re-start must take place at the study site to ensure 6-hour monitoring by the First Dose Administrator in a similar manner as the first intake of the study drug. It is recommended not to initiate beta-blockers and calcium-channel blockers treatment in 24-hours prior or concomitant to re-initiation of the study drug administration due to a possible additive effect on heart rate reduction.

Monitoring of reinitiating of first dose will be performed when: interruption of 1 day or more within the first 2 weeks of treatment, interruption of more than 7 days during weeks 3 and 4 of treatment and interruption of more than 14 days after the first month of treatment.

8.4.4.2 Ophthalmic examination

A complete ophthalmic examination will be performed by an ophthalmologist as described in Table 8-1.

At Screening and Month 3, Best Corrected Visual Acuity (BCVA) and Optical Coherence Tomography (OCT) for the measurement of central foveal thickness will be collected.

At all other scheduled visits, BCVA and new ophthalmic symptoms will be collected. In the case of confirmed of visual acuity decline, an optical coherence tomography will be conducted by the investigator's discretion.

Details on the ophthalmic examinations are provided in the Guidance for Ophthalmic Monitoring Section 16.6.

The ophthalmologist will describe examination findings on an examination worksheet provided by the investigative site. The worksheet will be transferred to the site where the data will be transcribed to the Ophthalmic Examination eCRF.

Participants with newly diagnosed uveitis after initiation of study drug will require more frequent ophthalmic evaluations. Refer to Section 16.6 for the Guidance for Ophthalmic Monitoring for details on monitoring of participants with uveitis during the study.

During the study, participants with a diagnosis of macular edema must interrupt the study drug. These patients must be followed-up 1 month and 3 month after diagnosis of macular edema and more frequently if needed based on the ophthalmologist’s judgement. Further ophthalmologic evaluations 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 participant does not show definite signs of improvement on examination by specialist testing (e.g. OCT, FA) 6-8 weeks after interruption of study drug, then therapy for macular edema in conjunction with an ophthalmologist experienced in the management of this condition should be initiated.

Re-initiation of the study drug can only be considered if the macular edema has resolved completely, the individual risk-benefit is favorable (as determined by the Investigator, in agreement with the Ophthalmologist) and after discussion with the Novartis Medical Advisor.

The patients must have follow up ophthalmic examinations at one month after study drug is re-initiated, three months later and then every 3 months up to one year, and every 6 months thereafter.

8.4.4.3 Pulmonary function test

Pulmonary Function tests evaluating forced expiratory volume within 1 second (FEV1) and carbon monoxide (CO) diffusing capacity (D_LCO) will be performed for all the patients at screening period and can be performed when participants with any reported AE related to respiratory disease during the treatment period, as per investigator discretion.

The FEV1 describes the volume (in Liters) that is expelled within one second of forced expiration after a maximal inspiration and reflects the large airway resistance. A decrease in FEV1 serves as a good parameter for detection of an obstructive ventilatory defect.

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

Based on the investigator's judgement, pulmonary function test (PFT) can be performed when participants with AE related to respiratory disease during the treatment period. In case of reduction of FEV1 and/or D_LCO below 80% of baseline values the patient's pulmonary status will require a follow-up as soon as possible. Should the repeat PFT values (FEV1 and/or D_LCO) remain below 80% of baseline values, the patient will be referred to pneumologist (pulmonologist) for further evaluation and treatment. In case of reduction of FEV1 and/or D_LCO below 60% of baseline value in any visit, the study drug is recommended to be interrupted and suggest to refer the patient a pneumologist (pulmonologist) immediately for further evaluation and treatment. In case of persistent reduction of FEV1, and/or D_LCO below 80% of baseline values over 3-month period despite of appropriate treatment, the Primary Treating Physician may consider an interruption of the study drug. This decision may be discussed with Novartis Medical Advisor. Investigators will be asked to comment on the result of pulmonary function test. The pulmonary function test report will be filed with the source documents. Abnormal results and 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.

8.4.4.4 Infection

The immune system effects of fingolimod may increase the risk of infections, including opportunistic infections. Before initiating study treatment, a complete blood count (CBC) will be collected and active infections are excluded. During the study treatment, a complete blood count will be collected regularly. Participants receiving fingolimod should report any signs or symptoms of infection to their investigator during therapy. Because elimination of fingolimod after discontinuation of fingolimod may take up to two months, vigilance for infection should be continued throughout this period. However, co-administration of a short course of corticosteroids treatment for relapse did not increase the overall rate of infection in participants treated with fingolimod in the Phase III clinical trials, compared to placebo.

8.4.5 Appropriateness of safety measurements

Beside routine safety assessments (physical and neurological examination, vital signs and laboratory assessments) few specific additional safety assessments are recommended in this study which are expected and known 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 mechanism of action and previous clinical data. Although clinically symptomatic cardiac events or clinically relevant ECG abnormalities have been reported at very low frequencies in the clinical development program especially with fingolimod 0.5mg/day dose treatment initiation of fingolimod will be monitored over 6 hours at the investigational site in this study.

Ophthalmologic examinations will be conducted in this study based on its previous use in the evaluation of retinal thickness and the detection of macular edema. Macular edema is an adverse event of special interest in participants treated with fingolimod because of the higher incidence seen in treated participants 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 participants treated with fingolimod occurred within the first three to four months after initiation of treatment. Therefore, an OCT scan is foreseen to be completed at Screening and Month 3.

Annual complete skin examinations have also been included to support regular monitoring of participants for the potential development of new skin cancers during the study.

Minor dose-dependent reductions in FEV1 and D_LCO values were observed with fingolimod treatment starting at month 1 and remaining stable thereafter. And the reduction of FEV1 and D_LCO from baseline value is resolved after treatment discontinuation. So pulmonary function tests will be conducted in all the participants at the screening and can be performed when participants with any reported AE related to respiratory disease, as per the investigator's discretion.

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

The impact of multiple sclerosis on neurologic impairment will be assessed by Expanded Disability Status Scale (EDSS).

The objectives of EDSS are to confirm relapse [redacted], it can be used in all the MS participants. The EDSS is an ordinal scale used for assessing neurologic impairment in MS based on a neurological examination. The scale consists of seven functional systems (FSs) and an ambulation score that are then combined to determine the EDSS steps. The FSs are Visual, Brain Stem, Pyramidal, Cerebellar, Sensory, Bowel & Bladder, and Cerebral functions. EDSS steps (ranging from 0(normal) to 10(death due to MS)), the higher score means the worsening of neurological status. The FSs and EDSS steps will be assessed in a standardized manner.

EDSS assessments are scheduled at screening visit, [redacted] In the case of MS relapse, EDSS assessment is required at every unscheduled visit to confirm relapse.

[redacted]

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation from study treatment and from study

Discontinuation of study treatment for a participant occurs when study treatment is permanently stopped for any reason (prior to the planned completion of the study drug administration, if any) and can be initiated by either the participant or the investigator.

The investigator must discontinue study treatment for a given participant if, he/she believes that continuation would negatively impact the participant's well-being.

Discontinuation from study treatment is required under the following circumstances:

- Participant/guardian decision
- Pregnancy

- Use of prohibited treatment as per recommendations in the prohibited treatment section
- Any situation in which continued study participation might result in a safety risk to the participant

Take into consideration the following to establish the list of circumstances under which study treatment must be discontinued:

- Adverse events, abnormal laboratory values or abnormal test result that indicate a safety risk to the participant. Refer to Section 16.7 for Guidance for safety monitoring
- Unsatisfactory therapeutic effect
- Participant's condition no longer requires study treatment

If discontinuation from study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the participant's discontinuation from study treatment and record this information.

Participants who discontinue from study treatment should be asked to agree to **return for the end of treatment (EOT) and follow up visits indicated** in the Assessment Schedule Table 8-1 (refer to section 8).

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule.

After discontinuation from study treatment, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments
- Adverse Events / Serious Adverse Events

9.1.2 Discontinuation from study

Discontinuation from study is when the participant permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason. If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table (refer to Section 8).

9.1.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits or fail to respond to any site attempts to contact them without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent/ exercise data privacy rights, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.2 Withdrawal of informed consent/opposition to use data/ biological samples

Participants may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent/ exercise the use of their data/privacy rights occurs in countries where the legal justification to collect and process the data is consent and only when a participant:

- Explicitly requests to stop use of their data

and

- No longer wishes to receive study treatment
- Does not want any further visits or assessments (including further study-related contacts)

This request should be per local regulations (e.g. in writing) and recorded in the source documentation.

Withdrawal of consent impacts ability to further contact the participant, collect follow-up data (e.g. to respond to data queries) and potentially other country-specific restrictions. It is therefore very important to ensure accurate recording of withdrawal vs. discontinuation based on the protocol definitions of these terms.

In this situation, the Investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw their consent/exercise data privacy rights and record this information. The Investigator shall clearly document if the participant has withdrawn his/her consent for the use of data in addition to a study discontinuation.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. If the participant agrees, a final evaluation at the time of the participant's study withdrawal of consent/ exercise data privacy rights should be made as detailed in the assessment table (refer to Section 8).

Further details on withdrawal of consent or the exercise of participants' data privacy rights are included in the corresponding informed consent form.

9.2.1 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason.

Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider the participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a participant who discontinued from study treatment and treated as a prematurely withdrawn participant. 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 participant's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.3 Study completion and post-study treatment

Study completion is defined as when the last participant finishes their 2-month follow up visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator (e.g. Each participant will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them in the scope of the trial).

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a participant or clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual participant and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on study related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The severity grade

mild: usually transient in nature and generally not interfering with normal activities

moderate: sufficiently discomforting to interfere with normal activities

severe: prevents normal activities

2. its relationship to fingolimod.

3. its duration (start and end dates) or if the event is ongoing and the outcome of not recovered/not resolved must be reported
4. whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding with study treatment

AEs associated with infections will be recorded on the AE eCRF pages. Refer to Section 16.7 Appendix 7 to see Guidance on monitoring patients with infections.

All adverse events will be treated appropriately per investigators clinical judgement. Treatment may include one or more of the following:

- Dose not changed
- Drug interrupted/permanently discontinued

Refer to Section 16.7 for Guidance on safety monitoring.

6. Conditions that were already present at the time of informed consent should be recorded in medical history of the participant.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- 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 signing the informed consent
  - social reasons and respite care in the absence of any deterioration in the participant's general condition
  - 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
- is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as “medically significant”. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All malignant neoplasms will be assessed as serious under “medically significant” if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days after the last study visit must be reported to Novartis safety immediately, without undue delay, under no circumstances later than within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. Information about all SAEs is collected and recorded on the eSAE with paper backup Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode

within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a CMO & PS 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 study treatment 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 EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

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

10.1.4 Pregnancy reporting

Pregnancies

If a female trial participant becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the Investigator to collect and report information regarding the pregnancy. To ensure participant safety, woman of child-bearing potential should report immediately to the investigator any pregnancy during and up to two months following discontinuation of fingolimod treatment. Each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. Study drug will be discontinued but participants can still stay in the study for follow-up visit.

Pregnancy should be recorded and reported by the Investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported. After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (EMA (European Medicines Agency) definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure participant safety and enhance reliability in determining the hepatotoxic potential of fingolimod, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities / adverse events have to be considered during the course of the study (irrespective of whether classified/reported as AE/SAE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and contributing factors are recorded on the appropriate CRFs

Please refer to Section 16.7 for complete definitions of liver laboratory triggers and liver events.

Every liver event defined in Section 16.7 should be followed up by the investigator at the study site, as summarized below. Additional details on actions required in case of liver events are under investigator's discretion. Repeat liver chemistry tests to confirm elevation.

- These liver chemistry repeats should be performed using the local laboratory used by the site. Repeated laboratory test results must be reported as appropriate.
- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment section), if appropriate
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event

- The follow-up of the liver event based on investigator's discretion can includes: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

All follow-up information and procedures performed must be recorded as appropriate in the CRF (e.g. AE page, concomitant medical page).

11 Data Collection and Database management

11.1 Data collection

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the participant data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

11.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (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.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator’s meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eSource DDE or

eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each participant 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 CRFs must be traceable to these source documents in the participant's file. Data not requiring a separate written record will be defined before study start and will be recorded directly on the CRFs. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

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

12 Data analysis and statistical methods

The analysis will be conducted on all participant data at the time of end of study (i.e. including data from the Safety Follow-up epoch).

[redacted]

There will be no hypothesis testing performed in this study. Data will be mainly statistically described. In general, categorical data will be presented as frequency and percentage; continuous data will be summarized by mean, standard deviation (SD), median, minimum, and maximum. For primary efficacy endpoints, the point estimate and confidence interval will be model-based. Additional analysis populations may be defined and sensitivity analyses may be conducted to evaluate the impact of COVID-19 pandemic.

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

The Full Analysis Set (FAS) comprises all participants who have signed the Informed Consent and who have received at least one dose of study treatment. The FAS will be used for the summary of demography and baseline characteristics as well as for all efficacy analyses.

The Safety Set includes all participants who have signed the Informed Consent and who have received at least one dose of study treatment. The Safety Set will be used for all safety analyses.

12.2 Participant demographics and other baseline characteristics

Demographics, MS disease history, MRI baseline characteristics will be listed and summarized with descriptive statistics as appropriate. Relevant medical histories and current medical conditions at baseline will be coded by system organ class (SOC) and preferred term (PT).

12.3 Treatments

Exposure to investigational study drug is defined as the number of days spent on study treatment. Intermediate treatment interruptions will be subtracted from drug exposure. Exposure to investigational study drug will be summarized with number and percentage of participants by time category, and with summary statistics of the number of participant years of exposure.

Prior and concomitant medications will be coded according to the WHO Drug Reference List dictionary, with Anatomical Therapeutic Classification (ATC) class and preferred term. Concomitant medications prior to and after the start of the study treatment will be listed.

12.4 Analysis of the primary endpoint(s)

12.4.1 Definition of primary endpoint(s)

The primary endpoint is the annualized relapse rate (ARR), which is defined as the number confirmed MS relapses in a year.

Only confirmed relapses will be considered for the primary analyses. The definitions of relapses and confirmed relapses are given in Section 8.3.1.

12.4.2 Statistical model, hypothesis, and method of analysis

In the primary analysis, the ARR will be estimated by a negative binomial regression model with log-link function, the cumulative number of confirmed MS relapses per participant as the response variable, number of relapses in the previous year (or two years) before enrollment, baseline EDSS and baseline number of Gd-enhancing T1 lesions at baseline as covariates. Natural log of time on study in years will be used as the offset variable to account for the varying lengths of participants' time in the study. The adjusted ARR (i.e., model-based estimate adjusted for covariates) and the corresponding 95% confidence interval will be obtained.

The primary analysis will be performed for FAS.

12.4.3 Handling of missing values/censoring/discontinuations

For participants who early withdraw from the study, the number of relapses up to the study discontinuation will be used for the primary analysis. No imputation will be applied to the incomplete study duration.

The primary negative binomial regression model with an offset for the time in study adjusts for missing information (drop-out) under the assumption of non-informative drop-out, information is missing at random, and constant relapse rate over time.

12.4.4 Sensitivity and Supportive analyses

The primary analysis will be repeated based on all reported MS relapses (rather than on only the confirmed ones) for FAS population.

A summary of ARR time-based and ARR patient-based will also be given. Time-based ARRs are calculated by taking the total number of relapses observed for all participants in FAS divided by the total number of days in study of those participants and multiplied by 365.25 days. Also patient-based ARR is presented, where individual ARRs are computed and summarized over participants for FAS population. For above ARR calculations, the analysis will consider confirmed relapses only.

Additional sensitivity analyses may be defined in the analysis plan.

12.5 Analysis of secondary endpoints

The following MRI efficacy variables will be statistically summarized based on FAS:

- The number and proportion of patients with new and newly enlarged T2 lesions at 12 month and 24 months;
- The number and proportion of patients with Gd-enhanced T1 lesions at 12 month and 24 months;
- Change and % change from baseline in volume of T1 hypo-intense lesions at month 12 and month 24.

12.5.1 Safety endpoints

For all safety analyses, the safety set will be used.

Safety assessments will include: adverse events (AEs), laboratory tests, vital signs, ophthalmic examinations, dermatology assessment, and ECG data.

An AE will be considered as treatment-emergent adverse event (TEAE) if it starts on or after first treatment with fingolimod during the study. TEAE will be summarized by presenting the number and percentage of participants experiencing adverse events by system organ class (SOC), preferred term (PT) and severity of adverse events.

Severe AEs, serious AEs, drug related AEs and the AEs leading to premature discontinuation of study drug will be presented in a similar format as adverse events.

Laboratory and vital sign data will be presented by clinical notable ranges.

The clinical notable abnormality of ophthalmic and dermatology data will be summarized as AE.

The (uncorrected) QT interval of ECG will be corrected according to the Bazett's and Fridericia formulae and then summarized by visit. Abnormal findings from ECG will be summarized as AE as well.

For the first dose administration monitoring, the change from pre-dose of pulse rate and BP at each hour will be summarized and the individual plots over time will be provided. The incidence rate of abnormal ECG findings at pre-dose and 6 hours post-dose, as well as the corrected QT change in category from pre-dose to 6 hours post-dose will be presented.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

The assumption of true ARR is based on previous studies of fingolimod and literature review (see Table 12-1). ARR ranged from 0.16 to 0.21 in non-Chinese populations from three controlled studies for fingolimod 0.5 mg (FREEDOMS, FREEDOMS II, TRANSFORMS). The similar ARR was reported in Chinese population treated by teriflunomide 14 mg (ARR = 0.18, TOWER). Two observational studies reported ARR at 0.38 in Chinese population treated by interferon-β 250 µg , and ARR at 0.21 in non-Chinese population treated by teriflunomide 14 mg (Teri-RADAR). The ARR reported in Chinese population from placebo group was 0.63 (TOWER). The true ARR is assumed ranging from 0.20 to 0.38 for this Chinese interventional study.

Table 12-1 ARR data on RRMS from historical studies

Study/Reference	Study Population	ARR (FTY 0.5 mg)	ARR (placebo)	ARR (Interferon-β 250 µg)	ARR (Teriflunomide 14 mg)
Interventional studies					

Study/Reference	Study Population	ARR (FTY 0.5 mg)	ARR (placebo)	ARR (Interferon-β 250 µg)	ARR (Teriflunomide 14 mg)
FREEDOMS (non-Chinese)	RRMS	0.18 (0.15, 0.22)	0.40 (0.34, 0.47)	NA	NA
FREEDOMS II (non-Chinese)	RRMS	0.21 (0.17, 0.25)	0.40 (0.34, 0.48)	NA	NA
TRANSFORMS (non-Chinese)	RRMS	0.16 (0.12, 0.21)	NA	0.33 (0.26, 0.42)	NA
TOWER, NCT00751881 (Chinese)	RRMS	NA	0.63 (0.44, 0.92)	NA	0.18 (0.09, 0.36)
Observational studies					
NCT00370071, 2006 (Chinese)	RRMS	NA	NA	0.38 (-,-)	NA
Teri-RADAR, 2019 (non-Chinese)	RRMS	NA	NA	NA	0.21 (0.11, 0.39)

Assume ARR follows negative binomial distribution (~ NB(μ, k)). The dispersion parameter k is set as 1 based on the historical data. The 95% upper limit and lower limit of estimated ARR are calculated by normal approximation approach for sample size estimation. Assuming ARR at 0.25, sample size of 80 participants will serve the 95% probability for estimated ARR within [0.13 to 0.37], which will be lower than the ARR observed in Chinese population treated by interferon-β 250 µg. Assuming ARR at 0.38, sample size of 80 is expected to show a lower ARR than placebo, with 95% probability within [0.22, 0.54]. So the sample size of 80 participants is considered. Considering 20% drop-out rate, the total sample size will be around 100 participants.

Sample size calculation was performed in nQuery.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the International Council for Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol,

written informed consent form, consent form updates, participant recruitment procedures (e.g. advertisements) and any other written information to be provided to participants. 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 Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an 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 and Health Authorities, where required, it cannot be implemented.

14.1 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 prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any participant 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 according to local regulations.

15 References

References are available upon request

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16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

Table 16-1 Criteria For Notable Laboratory Abnormalities

Notable Values		
Laboratory Variable	**Standard Units**	**SI Units**
Serum glutamic oxaloacetic transaminase (SGOT) (AST)	>82 U/L	>82 U/L
Serum glutamic pyruvic transaminase (SGPT) (ALT)	>90 U/L	>90 U/L
Total bilirubin	≥ 2.0 mg/dL	≥ 34.2 µmol/L
RENAL FUNCTION / METABOLIC VARIABLES		
Creatinine	≥2.0 mg/dL	≥176umol/L
Cholesterol	≥ 240 mg/dL	≥ 6.21 mmol/L
Triglycerides	≥ 300 mg/dL	≥ 3.39 mmol/L
HEMATOLOGY VARIABLES		
Hemoglobin	≤ 10.0 g/dL	≤ 100g/L
Platelets (Thrombocytes)	≤ 100 k/mm^3	≤ 100 x 10^9/L
	≥ 600 k/mm^3	≥ 600 x 10^9/L
Leukocytes (WBCs)	≤ 2.0 k/mm^3	≤ 2.0 x 10^9/L
	≥ 15 k/mm^3	≥ 15x 10^9/L
HEMATOLOGY VARIABLES: DIFFERENTIAL		
Granulocytes (Poly, Neutrophils)	≤ 1,000/mm^3	≤ 1 x 10^9/L
	≥12000/mm^3	≥ 12 x 10^9/L
Lymphocytes	<200/mm^3	<0.2 x 10^9/L
	≥8000/mm^3	≥8 x 10^9/L
Red blood cells (RBCs)	<3,300,000/mm^3	<3.3 x 10^{12}/L
	>6,800,000/mm^3	>6.8 x 10^{12}/L

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

Body weight (kg)	± 7% from baseline weight

16.2 Appendix 2 New York Heart Association Functional Classification

Class I	Patients have cardiac disease but without the resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Patients have cardiac disease resulting in slight limitation 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 marked limitation 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 inability 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.

16.3 Appendix 3 McDonald criteria

Clinical Presentation	Additional Data Needed for MS Diagnosis
no less than 2 attack[a] ; objective clinical evidence of ≥2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack[b]	None[c]
no less than 2 attack[a]; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by: ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord) [d;] or Await a further clinical attack[a] implicating a different CNS site
1 attack[a]; objective clinical evidence of ≥2 lesions	Dissemination in space, demonstrated by: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time;or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack[a]
1 attack[a]; objective clinical evidence of 1 lesion (clinically isolated syndrome)	Dissemination in space, demonstrated by: For DIS: ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS(periventricular, juxtacortical, infratentorial, or spinal cord) [d]; or Await a second clinical attack[a] implicating a different CNS site; and Dissemination in time, demonstrated by: For DIT: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack[a]
Insidious neurological progression suggestive of MS(PPMS)	1 year of disease progression(retrospectively or prospectively determined) plus 2 of 3 of the following criteria [d]: 1.Evidence for DIS in the brain based on ≥1 T2 lesions in the MS-characteristic(periventricular, juxtacortical, or infratentorial) regions 2.Evidence for DIS in the spinal cord based on ≥2 T2 lesions in the cord 3.Positive CSF(isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)
If the Criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is “MS”; if suspicious, but the Criteria are not completely met, the diagnosis is “possible	

Clinical Presentation	Additional Data Needed for MS Diagnosis
MS"; if another diagnosis arises during the evaluation that better explains the clinical presentation, then the diagnosis is "not MS."	
[a]An attack(relapse; exacerbation) is defined as patient-reported or objectively observed events typical of an acute inflammatory demyelinating event in the CNS, current or historical, with duration of at least 24 hours, in the absence of fever or infection. It should be documented by contemporaneous neurological examination, but some historical events with symptoms and evolution characteristic for MS, but for which no objective neurological findings are documented, can provide reasonable evidence of a prior demyelinating event. Reports of paroxysmal symptoms (historical or current) should, however, consist of multiple episodes occurring over not less than 24 hours. Before a definite diagnosis of MS can be made, at least 1 attack must be corroborated by findings on neurological examination, visual evoked potential response in patients reporting prior visual disturbance, or MRI consistent with demyelination in the area of the CNS implicated in the historical report of neurological symptoms.	
[b]Clinical diagnosis based on objective clinical findings for 2 attacks is most secure. Reasonable historical evidence for 1 past attack, in the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristics for a prior inflammatory demyelinating event; at least 1 attack, however, must be supported by objective findings.	
[c]No additional tests are required. However, it is desirable that any diagnosis of MS be made with access to imaging based on these Criteria. If imaging or other tests(for instance, CSF) are undertaken and are negative, extreme caution needs to be taken before making a diagnosis of MS, and alternative diagnoses must be considered. There must be no better explanation for the clinical presentation, and objective evidence must be present to support a diagnosis of MS.	
[d]Gadolinium-enhancing lesions are not required; symptomatic lesions are excluded from consideration in participants with brainstem or spinal cord syndromes.	
MS=multiple sclerosis; CNS=central nervous system; MRI=magnetic resonance imaging; DIS=dissemination in space; DIT=dissemination in time; PPMS=primary progressive multiple sclerosis; CSF=cerebrospinal fluid; IgG=immunoglobulin G.	

16.4 Appendix 4 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 ≥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 ≥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 ≥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 for ≥100 meters

6.0 = unilateral assistance (cane or crutch) required to walk at least 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

16.5 Appendix 5 Guidance for Monitoring of patients taking their first dose of the study drug

At treatment initiation, fingolimod induces a dose dependent reduction in heart rate (by approximately 12-13 bpm at 0.5 mg) that is maximal within 6 hours after the first dose administration, and then attenuates over days to weeks with continued dosing. This effect is asymptomatic in the vast majority of patients. No medical intervention to treat that effect was needed in any of the patients in the Phase II and III MS trials. Concomitant changes on the ECG/Holter were restricted to transient second degree type I atrio-ventricular block (Wenckebach) of benign nature, on day 1 of treatment. One case of third degree atrio-ventricular block 3 hours after first dose administration of fingolimod 1.25 mg was reported. This incident was self-limiting without symptoms, no sequelae and lasted 30 seconds. Please see Investigator Brochure for more details. As such, the following guidelines have been put in place to support the safe initiation of therapy with fingolimod.

At the Day 1 visit, participant enroll into this study is naive participant who has never use fingolimod before recruitment, so first dose administration monitoring will be mandatory on-site monitoring as described below.

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. Sitting heart rate and blood pressure should be measured prior to the 1st dose of the study drug then every hour for at least 6 hours thereafter (by the First Dose Administrator). When obtaining the pre-dose heart rate prior to the 1st dose intake, the participant 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 collect three times to produce three baseline readings for both heart rate and blood pressure (prior to the 1st 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. Participants should receive the first dose of the study drug before 12:00 PM (noon) in the outpatient setting. Participants may be discharged after 6 hours ONLY if ALL of the following discharge criteria are met.

- Heart rate at discharge must be at least 51 bpm(in patient 18 years or older), 55 bpm(in patients 12 years or older) or 60 bpm (in children ≥10 years and below 12)
- Heart rate at discharge must be greater than 80% of baseline value (Table 16-2 below)
- Heart rate at discharge must not be the lowest hourly value measured during the observation period (which would be suggestive of a continuing progressive decline in heart rate)
- Participants must have no symptoms associated with decreased heart rate
- ECG at 6 hours should not show any new significant abnormalities other than sinus bradycardia not observed at the patient's pre-dose ECG

Participants 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.). Participants should be instructed not to drive themselves after the first dose of study drug administration.

Participants whose heart rate drops by more than 30% (as a result of strong sensitivity to the study drug) from pre-dose at any time during the 6-hour monitoring period may be discharged,

provided they meet the discharge criteria, but must return on Study Day 2 to take the second dose of the study drug and must be monitored as on Study Day 1.

If the above discharge criteria are not met, participants should continue to be observed until they are met. Participants experiencing any symptomatic event associated with reduction of the heart rate in the first 24 hours must take the Day 2 dose of study drug at the study center and must be monitored hourly for 6 hours before discharge. After the 6 hour monitoring participants may be discharged only if they meet the discharge criteria described above.

Table 16-2 Heart rate table for cardiac release criteria

Baseline Heart Rate	Minimum HR at 6hr post 1st dose of the study drug eligible for release	HR reduction within 6hr monitoring indicating need for monitoring after 2nd dose
45	40	31
46	40	32
47	40	33
48	40	33
49	40	34
50	40	35
51	40	35
52	41	36
53	42	37
54	43	38
55	44	39
56	45	39
57	45	40
58	46	41
59	47	41
60	48	43
61	49	43
62	50	43
63	50	44
64	51	45
65	52	46
66	53	46
67	54	47
68	54	48
69	55	48
70	56	49
71	57	50
72	58	50
73	58	51
74	59	52
75	60	53

Baseline Heart Rate	Minimum HR at 6hr post 1st dose of the study drug eligible for release	HR reduction within 6hr monitoring indicating need for monitoring after 2nd dose
76	61	53
77	62	54
78	62	55
79	63	55
80	64	56
81	65	57
82	66	57
83	66	58
84	67	59
85	68	60
86	69	60
87	70	61
88	70	62
89	71	62
90	72	63
91	73	64
92	74	64
93	74	65
94	75	66
95	76	67
96	77	67
97	78	68
98	78	69
99	79	69
100	80	70
101	81	71
102	82	71
103	82	72
104	83	73
105	84	74
106	85	74
107	86	75
108	86	76
109	87	76
110	88	77
111	89	78
112	90	78
113	90	79
114	91	80

Baseline Heart Rate	Minimum HR at 6hr post 1st dose of the study drug eligible for release	HR reduction within 6hr monitoring indicating need for monitoring after 2nd dose
115	**92**	**81**
116	**93**	**81**
117	**94**	**82**
118	**94**	**83**
119	**95**	**83**
120	**96**	**84**
121	**97**	**85**
122	**98**	**85**
123	**98**	**86**
124	**99**	**87**
125	**100**	**88**
126	**101**	**88**
127	**102**	**89**
128	**102**	**90**
129	**103**	**90**
130	**104**	**91**

Recommendations for management of bradycardia

Clinicians should be particularly mindful of participants who have a low heart rate at pre-dose (spontaneously or through drug induced β-receptor blockade), prior to administration of the study drug.

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.

16.6 Appendix 6 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. There have been macular edema cases in the treatment of fingolimod, therefore careful ophthalmic monitoring is being implemented to permit early detection of this event, should it occur.

A complete ophthalmic examination by an ophthalmologist will be conducted in accordance with Table 8-1. Similar assessments must be performed at an unscheduled ophthalmology visit for any participant who presents with new visual symptoms or decrease in visual acuity.

The following assessments will be performed at the ophthalmic examinations:

1. Best corrected visual acuity using a visual acuity chart with equal spacing between letters and between lines

2. Optical Coherence Tomography (OCT) is required for participants at Screening and Month 3 visit. OCT may be required at other visits to evaluate macular thickness under the investigator's discretion.

At baseline, if there is a suspicion of macular edema and increased central foveal thickness by OCT, then a fluorescein angiogram may be performed (at the discretion of the ophthalmologist). Participants with diagnosed macular edema at Screening should be deemed a screening failure and should not be enrolled. 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.

During the study, participants with a diagnosis of macular edema during the study must interrupt the study drug. These patients must be followed-up 1 month and 3 month after diagnosis of macular edema and more frequently if needed based on the ophthalmologist's judgement. Further ophthalmologic evaluations 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 performed at the discretion of the ophthalmologist. If the participant does not show definite signs of improvement on examination by specialist testing (e.g. OCT, FA) 6-8 weeks after interruption of study drug, then therapy for macular edema in conjunction with an ophthalmologist experienced in the management of this condition should be initiated.

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

Re-initiation of the study drug can only be considered if the macular edema has resolved completely, the individual risk-benefit is favorable (as determined by the Investigator, in agreement with the Ophthalmologist) and after discussion with the Novartis Medical Advisor. The patients must have follow up ophthalmic examinations at one month after study drug is re-initiated, three months later and then every 3 months up to one year, and every 6 months thereafter.

For participants discontinuing study drug for any of the above ophthalmic reasons, copies and source documents of the related 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

Participants 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 coexisting uveitis, each participant 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 may lead to study drug interruption. But the decision on whether or not fingolimod therapy should be interrupted needs to take into account the potential benefits and risks for the individual participant.

16.7 Appendix 7 Guidance on safety monitoring

Guidance on monitoring of patients with elevated blood pressure

Participants who have at least two out of the three sitting readings of blood pressure (systolic BP ≥140 and/or diastolic BP ≥90 mmHg) should be recommended referred to his primary care physician, an independent internist or to the specialty hypertension clinic for evaluation, diagnosis and treatment of hypertension. Participants 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 pre-existing condition must be reported as an AE and discontinuation of the study drug may be considered by the investigator.

Guidance on monitoring of participants with elevated liver function tests

Table 16-3 Liver event and laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers If ALT, AST and total bilirubin normal at baseline:	• ALT or AST > 5 × ULN • ALP> 2 × ULN (in the absence of known bone pathology) • Total bilirubin > 3 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and Total bilirubin > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*
If ALT or AST abnormal at baseline:	• ALT or AST > 2x baseline or > 300 U/L (whichever occurs first)
*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; non-infectious hepatitis; benign, malignant and unspecified liver neoplasms ULN: upper limit of normal	

During clinical trials, elevations 3 times the upper limit of normal (ULN) or greater in liver transaminases occurred in 8% of patients treated with fingolimod 0.5 mg compared to 2% of placebo patients. Elevations of 5 times the upper limit of normal occurred in 2% of patients on fingolimod and 1% of patients on placebo. Serum transaminase levels returned to normal within approximately 2 months after discontinuation of fingolimod.

If repeat ALT/AST values reach 5 times the ULN, the study drug will be interrupted until the results return within the normal range. More frequent monitoring should be instituted, including serum bilirubin, alkaline phosphatase (ALP) and other evaluations per discretion of the investigator. The study drug may be re-started once results return within normal range and per discretion of the investigator.

Patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained vomiting, abdominal pain, fatigue, anorexia, jaundice or dark urine, should have liver enzymes checked, and fingolimod should be discontinued if significant liver injury is confirmed. Re-initiation of study drug will be dependent on whether or not another cause of liver injury is determined, and on the benefits to the patient of resuming therapy versus the risks of recurrence of liver dysfunction and per the discretion of the investigator.

More frequent liver monitoring may be instituted based on the clinical judgement in the below condition:

- For participants with normal ALT and AST and TBIL value at baseline: detection of elevated ALT/AST values of >3.0 x ULN and total bilirubin > 2.0 x ULN
- For participants with elevated AST or ALT or TBIL value at baseline: detection of elevated [AST or ALT > 2 x baseline] OR [AST or ALT > 300U/L] (whichever occurs first) combined with [TBIL > 2 x baseline AND > 2.0 x ULN

Patients should be monitored for signs and symptoms of any hepatic injury. Measure liver transaminase and bilirubin levels promptly in patients who report symptoms that may indicate liver injury, including new or worsening fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. In this clinical context, if the patient is found to have ALT/AST values of >3.0 x ULN with total bilirubin > 2.0 x ULN, treatment with fingolimod may be interrupted based on the clinical judgement. Treatment should not be resumed if a plausible alternative etiology for the signs and symptoms cannot be established, because these patients are at risk for severe drug-induced liver injury.

Because fingolimod exposure is doubled in patients with severe hepatic impairment, these patients should be closely monitored, as the risk of adverse reactions is greater.

Re-initiation of the study drug shall be considered once the liver enzymes are within the normal reference range and/or patients have clinically recovered from liver injury signs based on your clinical judgement, and kindly reach out to Medical Advisor at Novartis for any further clarification. In case it is agreed to re-start the study drug, weekly liver function test may be performed for patient's safety. Advise patients that they should contact their physician if they have any unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine. The deterioration of new elevations above 2 times the ULN with worsening of liver injury clinical signs/symptoms based on investigator's clinical judgement may lead to permanent discontinuation of study drug in the best interest of patient's safety.

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 participants with notable lymphopenia

Fingolimod results in sequestration of a proportion of the circulating lymphocytes in lymph nodes with resultant reduction in circulating lymphocyte counts. Average circulating lymphocytes counts are expected to be around 0.5-0.6 $x10^9$/L or 500-600 cells/mm^3. Please see Investigator Brochure for more details. As such, the absolute total WBC, neutrophil and lymphocyte counts will be measured at each visit by the local laboratory. In case of lymphocyte alert, lymphocyte count should be repeated in two weeks by the local laboratory. If the repeat test confirms the lymphocyte count is below 0.2 $x10^9$/L or 200 cells/mm^3, the study drug must be interrupted and the lymphocytes count needs to be monitored every two weeks until levels reach around 0.5-0.6 $x10^9$/L or 500-600 cells/mm^3 values. Recovery of lymphocyte counts is expected to take several weeks given the long half life of fingolimod. The participant should be evaluated and monitored for infections on a regular basis during this period.

Re-initiation of the study drug can only be considered once the lymphocyte counts is around 0.5-0.6 $x10^9$/L or 500-600 cells/mm^3as confirmed by the local lab, for further detailed information please refer to the latest Investigator Brochure or label of fingolimod.

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

Should a participant 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 may 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 neuro-radiologist and investigator. The investigator will contact the Medical Representative at Novartis to discuss findings and diagnostic possibilities as soon as possible. AE/SAEs need to be filed as appropriate.

In case of new findings in the MRI images in comparison with the previous available MRI which are not compatible with MS lesions, the study drug will be interrupted and other diagnostic evaluations need to be performed at the discretion of the investigator. In case of presence of new hyper-intense 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, John Cunningham virus (JC virus)), to confirm/exclude an infection ((e.g. progressive multifocal leukoencephalopathy (PML)) should be performed.

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

Guidance on monitoring of participants with infections

Initiation of treatment with Fingolimod should be delayed in patients with severe active infection until resolution. If a patient develops a serious infection, suspension of Fingolimod should be considered and consideration of benefit-risk should be undertaken prior to re-initiation of therapy.

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 remind the participant of the risk of infections and to instruct them to promptly report any symptoms of infections to the investigator.

The investigator should consider early treatment with specific 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. 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.

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 are prohibited while patients are taking study drug and for 2 months after study drug discontinuation. They may be administered, thereafter, once there is confirmation that lymphocyte counts are in the normal range.