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US Clinical Development and Medical Affairs - General Medicine

FTY720/Fingolimod

Clinical Trial Protocol CFTY720DUS40 / NCT03257358

A 12-Month, prospective, multicenter, two-cohort, nonrandomized, open-label study in adult patients with Relapsing Multiple Sclerosis (RMS), to investigate changes in immune phenotype biomarkers after treatment with 0.5 mg fingolimod (FTY720) [FLUENT]

Document type:	Clinical Trial Protocol
Version number:	00 (Original Protocol)
Clinical trial phase:	IV
Release date:	16-Jun-2017

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List of abbreviations

AE	Adverse Event
ALC	Absolute Lymphocyte Count
AV	Atrioventricular
B cell	A Sub-type of White Blood Cells
CD	Cluster Differentiation
CCR	C-C Chemokine Receptor
CFR	US Code of Federal Regulations
CNS	Central Nervous System
CRF	Case Report/Record Form (paper or electronic)
CXCR	C-X-C Chemokine Receptor
DS	Disease Steps
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDDS	Expanded Disability Status Scale
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDO	First Dose Observation
GCP	Good Clinical Practice
Gd	Gadolinium
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IN	Investigator Notification
IRB	Institutional Review Board
JCV	John Cunningham Virus
MedDRA	Medical dictionary for regulatory activities
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NARCOMS	North American Research Committee on Multiple Sclerosis
[redacted]	[redacted]
NK	Natural Killer Cells
PDDS	Patient Determined Disease Steps
PML	Progressive Multifocal Leukoencephalopathy
PRO	Patient Related Outcome
QM	Quality Management
QTc	Measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle.
RBC	Red Blood Cell
RMS	Relapsing Multiple Sclerosis
SAE	Serious Adverse Event
SDC	Study Discontinuation Completion
S1PR1	Sphingosine 1-phosphate receptor

SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
T cell	A Sub-type of White Blood Cells
TCM	T Central Memory Cells
TEM	T Effector Memory Cells
TIA	Transient Ischemic Stroke
Tn	Naïve T Cells
UNS	Unscheduled Visit
USPI	United States Package Insert
WBC	White Blood Cell
WHO	World Health Organization
WoC	Withdrawal of Consent

Glossary of terms

Cohort	A specific group of patients/subjects fulfilling certain criteria
Dosage	Dose of the Fingolimod treatment given to the patient in a time unit (e.g., 0.5mg once a day)
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 (eCRF's) which are used to capture data transcribed from paper source forms used at the point of care.
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (e.g., prior to starting any of the procedures described in the protocol)
Period	A portion of the study which serves a specific purpose. Typical epochs are: screening/recruitment, treatment, and follow-up
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug" or "investigational medicinal product."
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/subjects with established disease and in those with newly-diagnosed disease.
Patient/subject ID	A unique number assigned to each patient upon signing the informed consent
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), placebo/comparator active drug run-ins or background therapy
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 is defined as when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

Protocol summary

Protocol number	CFTY720DUS40
Full Title	A 12-Month, prospective, multicenter, two-cohort, nonrandomized, open-label study in adult patients with Relapsing Multiple Sclerosis (RMS), to investigate changes in immune phenotype biomarkers after treatment with 0.5mg fingolimod. [FLUENT]
Brief title	A Study of immune phenotype biomarkers in patients with Relapsing Multiple Sclerosis (RMS) after treatment with 0.5mg fingolimod
Sponsor and Clinical Phase	Novartis Pharmaceutical Corporation Phase IV
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to characterize phenotypic changes in the cellular components (biomarkers) of the innate (monocytes, neutrophils and NK cells) and adaptive (peripheral blood T cells and B cells) immune system, in patients with relapsing Multiple Sclerosis (RMS), initiating fingolimod therapy of 0.5mg/per day up to 12 Months of treatment in two treatment cohorts (Cohort 1 includes, fingolimod naïve patients, and Cohort 2 includes those who have been on fingolimod 0.5mg/day continuously for ≥ 2 years.). The study design is nonrandomized, open labeled and relies on the approved USPI (United States package insert) based enrollment criteria and thereby reflects real world conditions of routine clinical practice.
Primary Objective(s)	The primary objective of this study aims at characterizing phenotypic changes in the cellular components (biomarkers) of the innate (monocytes, neutrophils and NK cells) and adaptive (peripheral blood T cells, B cells) immune system including their subtypes, in patients with RMS, initiating fingolimod therapy of 0.5mg/day up to 12 Months of treatment (Cohort 1) and those patients who have been on fingolimod 0.5mg/day continuously for ≥ 2 years (Cohort 2). Both cohorts will continue treatment for the next 12 Months.
Secondary Objectives	Secondary objectives are to investigate the association between anti-John Cunningham virus (JCV) antibody status/index and phenotypic changes in innate and T and B cell subsets in patients on fingolimod therapy.

Study design	This study uses a two-cohort, nonrandomized, open-label multicenter design. Patients will be enrolled from up to 125 sites in the United States The study consists of two periods: screening (up to 4 Weeks) and fingolimod treatment period (Baseline to 12 Months). The total study duration is up to 13 Months. Follow-up Visits will be conducted at 3, 6 and 12 Months. Fingolimod treatment includes two cohorts. In the first cohort approximately 200 patients with RMS, who are newly prescribed commercially available fingolimod 0.5mg/day will participate in the study. In the second cohort approximately 200 RMS patients who have been on commercially available fingolimod 0.5mg/day continuously for at least ≥ 2 years will participate in the study. Cohort 2 will only serve as a referent cohort for Cohort 1 and is not intended to be a direct Cohort 1 comparator as no *a priori hypotheses* are to be examined.
Population	The study population will consist of 400 male and female patients (≥ 18 years of age) with a diagnosis of RMS. Cohort 1 will include 200 patients and Cohort 2 will include 200 patients.
Key Inclusion criteria	• Written informed consent must be obtained before any assessment is performed. • Males and females ≥ 18 years of age at the time of screening. • Patients diagnosed with relapsing forms of MS defined by the revised McDonald criteria (2010), Appendix 1. • Patients who will start commercially prescribed fingolimod therapy 0.5 mg/day or patients already on commercially prescribed fingolimod 0.5 mg/day continuously for at least 2 years.
Key Exclusion criteria	Since commercially prescribed fingolimod is being used in the study, contraindications as per the USPI will be adhered to which include • Patients who in the last 6 Months experienced myocardial infarction, unstable angina, stroke, Transient ischemic stroke (TIA), decompensated heart failure requiring hospitalization or Class III/IV heart failure

	• History or presence of Mobitz Type II second-degree or third-degree atrioventricular (AV) block or sick sinus syndrome, unless patient has a functioning pacemaker • Baseline QTc interval ≥ 500 msec • Treatment with Class I a or Class III anti-arrhythmic drugs • Patients who are participating in any other clinical trial with fingolimod (Cohort 2) • Patients who have had a hypersensitivity reaction to fingolimod or any of the excipients. Observed reactions include rash, urticaria and angioedema upon treatment initiation. *Note: Hypersensitivity reactions, including rash, urticaria, and angioedema have been reported with fingolimod in the post-marketing setting.*
Treatment	Fingolimod (FTY720D)
Efficacy assessments	• Patient Determined Disease Steps (PDDS) • Magnetic Resonance Imaging (MRI based variables)
Key safety assessments	• Adverse (AE) and Serious Adverse Events (SAE)
Other assessments	N/A
Data analysis	Novartis or a designated vendor will perform the statistical analysis. It is planned that data from all centers that participate in this protocol will be combined, so that an adequate number of patients will be available for the analysis. There will be three analyses in this study. 1. An interim analysis which is an early assessment to evaluate safety of Cohort 2 patients will be conducted when 50% of patients in Cohort 2 have completed the Month 6 follow-up visit. 2. A primary analysis based on all data collected on both Cohorts 1 and 2 patients will be conducted when all patients in Cohorts 1 and 2 complete the Month 6 follow up Visit which is the primary time point of interest of the study. 3. A final follow-up analysis will be conducted when all patients in Cohorts 1 and 2 complete the Month 12 follow up Visit of the study.

	Analysis sets: Enrolled Set: All patients enrolled in one of the two cohorts will be included in the Enrolled Set. Safety Set: The Safety Set will include all patients who enrolled in one of the two cohorts and received at least one dose of fingolimod. Patients will be analyzed according to the cohort enrolled. Full Analysis Set (FAS): For this study, the Full Analysis Set is the same as the Safety Set. Patient demographics and other baseline characteristics: Data will be summarized with respect to demographics and baseline characteristics by cohort in the Safety Set. Primary variables: All analyses will be conducted by cohort for the Safety set. The primary variables are 1. Change from Baseline to Month 6 in CD4+ naïve T cells (CCR7+CD45RA+) 2. Change from Baseline to Month 6 in CD4+ central memory T cells (CCR7+CD45RA-CD45RO+) 3. Change from Baseline to Month 6 in CD4+ effector memory T cells (CCR7-CD45RA-CD45RO+) 4. Change from Baseline to Month 6 in CD4+ Th1 cells (CXCR3+) 5. Change from Baseline to Month 6 in CD4+ Th2 cells (CCR4+) 6. Change from Baseline to Month 6 in CD4+ Th17 cells (CCR6+) 7. Change from Baseline to Month 6 in CD8+ naïve T cells (CCR7+CD45RA+) 8. Change from Baseline to Month 6 in CD8+ central memory T cells (CCR7+CD45RA-CD45RO+) 9. Change from Baseline to Month 6 in CD8+ effector memory T cells (CCR7-CD45RA-CD45RO+) 10. Change from Baseline to Month 6 in naïve B cells (CD19+CD27-) 11. Change from Baseline to Month 6 in memory B cells (CD19+CD27+) 12. Change from Baseline to Month 6 in regulatory B cells (CD19+CD24+CD38+) 13. Change from Baseline to Month 6 in monocytes (CD14+) 14. Change from Baseline to Month 6 in neutrophils (CD16+)

	15. Change from Baseline to Month 6 in NK cells (CD56+) Descriptive statistics (sample size, mean, standard deviation, standard error of mean, minimum, first quartile, median, third quartile, interquartile range, and maximum) will be provided. The 95% confidence interval for the mean will be calculated. Analyses will be performed with respect to the actual value of primary variables by employing an analysis of covariance (ANCOVA) model with gender as a factor and duration of disease and corresponding baseline as covariates. The unadjusted as well as the adjusted least squares means will be provided together with a p-value. Percent change from baseline mean will also be reported. Majority of analyses will be descriptive in nature. The 95% confidence intervals will be provided for the estimate of parameters of interest. No imputation will be performed for missing data related to safety or efficacy. <u>Efficacy variables</u>: The following efficacy variables will be analyzed by cohort using data from patients in FAS. • Change from Baseline in Patient Determined Disease Steps (PDDS) • Change from Baseline in T2 lesion burden • New Gadolinium (Gd)-enhancing T1 lesion count Descriptive statistics (sample size, mean, standard deviation, standard error of mean, minimum, first quartile, median, third quartile, interquartile range, and maximum) will be provided. The 95% confidence interval for the mean will be calculated. <u>Safety variables:</u> The assessment of safety will be based mainly on the frequency of adverse events. Adverse events will be summarized by presenting the number and percentage of patients having any adverse event, having an adverse event in each system organ class and having each individual adverse event by cohort and overall. Any other information collected (e.g., severity or relationship to fingolimod) will be summarized, as appropriate. Safety Set will be used for the following analyses.

	In addition to the primary variables, the following secondary variables will be analyzed: 1. Change from Baseline to Months 3, and 12 in CD4+ naïve T cells (CCR7+CD45RA+); 2. Change from Baseline to Months 3, and 12 in CD4+ central memory T cells (CCR7+CD45RA-CD45RO+); 3. Change from Baseline to Months 3, and 12 in CD4+ effector memory T cells (CCR7-CD45RA-CD45RO+); 4. Change from Baseline to Months 3, and 12 in CD4+ Th1 cells (CXCR3+); 5. Change from Baseline to Months 3, and 12 in CD4+ Th2 cells (CCR4+); 6. Change from Baseline to Months 3, and 12 in CD4+ Th17 cells (CCR6+); 7. Change from Baseline to Months 3, and 12 in CD8+ naïve T cells (CCR7+CD45RA+); 8. Change from Baseline to Months 3, and 12 in CD8+ central memory T cells (CCR7+CD45RA-CD45RO+); 9. Change from Baseline to Months 3, and 12 in CD8+ effector memory T cells (CCR7-CD45RA-CD45RO+); 10. Change from Baseline to Months 3, and 12 in naïve B cells (CD19+CD27-); 11. Change from Baseline to Months 3, and 12 in memory B cells (CD19+CD27+); 12. Change from Baseline to Months 3, and 12 in regulatory B cells (CD19+CD24+CD38+); 13. Change from Baseline to Months 3, and 12 in monocytes (CD14+); 14. Change from Baseline to Months 3, and 12 in neutrophils (CD16+); 15. Change from Baseline to Months 3, and 12 in NK cells (CD56+); 16. Change from Baseline to Months 3, 6, and 12 in the anti-JCV antibody index; 17. Change from Baseline to Months 3, 6, and 12 in Hematology measurements; 18. Anti-JCV antibody status (+ or -) at Months 3, 6, and 12. For Variable 18, frequency count and percentage together with the 95% confidence interval for the proportion of anti-JCV antibody positive patients will be presented.

	For Variable 1-17, Descriptive statistics (sample size, mean, standard deviation, standard error of mean, minimum, first quartile, median, third quartile, interquartile range, and maximum) will be provided. The 95% confidence interval for the mean will be calculated. Correlation coefficients between changes in cellular (T, B and monocyte, neutrophil, NK) subsets, efficacy (MRI based variables and PDDS) and safety outcomes (anti-JCV antibody status and index) will be computed. Analyses of safety data will be by cohort based on the Safety Set. [redacted] Descriptive statistics (sample size, mean, standard deviation, standard error of mean, minimum, first quartile, median, third quartile, interquartile range, and maximum) will be provided. The 95% confidence interval for the mean will be calculated. [redacted] <u>Sample size estimation:</u> Cohort 1: A sample size of 200 patients will be able to detect an effect size of 0.30 with 89% power after adjusting for multiplicity of testing changes in 15 primary variables, at an overall significance level of 0.05. In addition, for both cohorts the primary interest is to estimate mean change from Baseline at various time points (Months 3, 6, and 12) of the primary and secondary variables. A sample size of 200 patients in each cohort will provide us the precision of estimates within 0.14 of the corresponding standard deviation of the variables of interest.
Key words	Multiple Sclerosis (MS), Relapsing Multiple Sclerosis (RMS), Fingolimod, FLUENT, Immune Phenotype

1 Introduction

1.1 Background

Fingolimod is a sphingosine 1-phosphate receptor (S1PR1) modulator approved for relapsing multiple sclerosis (RMS). This mechanism of action has a differential impact on multiple phenotypic subtypes of the immune system. Modulation of S1PRs favors CC-chemokine receptor 7 (CCR7)-mediated retention of naïve T (Tn) cells and central memory T (TCM) cells, including Th17 cells in lymph nodes, thereby reducing the trafficking of potentially autoreactive lymphocytes and preventing their infiltration into the central nervous system (CNS), Mehling et al 2008, 2010. Fingolimod reduces the numbers of CD4+ and CD8+ T cells, the effect being more pronounced for the CD4+ T cell subset, Song et al 2015. In contrast, effector memory T (TEM) cells, which lack CCR7, Sallusto et al 1999 do not regularly circulate through lymph nodes and are largely unaffected by fingolimod, Mehling et al 2008 and Brinkmann et al 2009. The relative sparing of TEM cells, which are important in immune surveillance, together with the preservation of function of sequestered lymphocytes, Kappos et al 2015, Brinkmann et al 2000, 2001 and 2002, suggests that key features of the immune system are maintained during fingolimod therapy. Chronic fingolimod therapy with 0.5mg/day results in lymphocyte counts of approximately 30% of the baseline lymphocyte count, Chun, J. and Hartung, H 2010; Francis et al 2014. However, Absolute Lymphocyte Counts (ALC) during fingolimod therapy is not a marker of immune competence and not related to risk of infections, Francis et al 2014, Fox et al 2014.

In 2015, in the post marketing setting of longer term treated patients, two opportunistic infections Progressive Multifocal Leukoencephalopathy (PML) and Cryptococcal Meningitis manifested at a rare frequency, which led to label changes, United States package insert (USPI). Since these opportunistic infections had not been described until this point, these new findings triggered interest in yet unknown immune system changes in long term continuously treated patients. PML is caused by the John Cunningham virus (JCV) and its development is associated with the presence of anti-JCV antibodies in serum. PML risk can be stratified in seropositive MS patients based on serum anti-JCV antibody levels as measured by the index. The significance of anti-JCV antibody index changes during fingolimod treatment and its relationship to PML risk is unknown.

Although fingolimod induces lymphopenia, the relationship between phenotypic changes in the innate and adaptive components of the immune system during its long-term administration is unknown. Distinct immune subset changes with long term fingolimod treatment are incompletely understood and its pivotal trials did not investigate changes within immune cell subsets.

This study is being proposed to investigate the immune profile of patients over time to seek an improved understanding of immune effects with long term fingolimod therapy.

1.2 Purpose

The purpose of this study is to characterize changes in the types and sub-types of the innate (monocytes, neutrophils and NK cells) and adaptive (peripheral blood T cells and B cells)

immune system, in patients with relapsing Multiple Sclerosis (RMS), on fingolimod therapy of 0.5mg/per day up to 12 Months of treatment in two treatment cohorts (fingolimod naïve patients, or those previously treated continuously for at least ≥ 2 years.).

2 Study objectives and endpoints

2.1 Objectives and related endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s) • The primary objective of this study aims at characterizing phenotypic changes in the cellular components (biomarkers) of the innate (monocytes, neutrophils and NK cells) and adaptive (peripheral blood T cells, B cells) immune system including their subtypes, in patients with RMS, initiating fingolimod therapy of 0.5mg/ per day up to 12 Months of treatment (Cohort 1) and those patients who have been on fingolimod 0.5mg/day continuously for ≥ 2 years (Cohort 2). Both cohorts will continue treatment for the next 12 Months.	**Endpoint(s) for primary objective(s)** • Change from baseline to Month 6 of CD4+ and CD8+ naïve T cells (CCR7+CD45RA+), central memory T cells (CCR7+CD45RA-CD45RO+), and effector memory T cells (CCR7-CD45RA-CD45RO+) • Change from baseline to Month 6 of CD4+ Th1 (CXCR3+), Th2 (CCR4+) and Th17 (CCR6+) cells. • Change from baseline to Month 6 in naïve B cells (CD19+CD27-), memory B cells (CD19+CD27+) and regulatory B cells (CD19+CD24+CD38+) • Change from baseline to Month 6 in monocytes (CD14+), neutrophils (CD16+) and NK cells (CD56+).
Secondary Objective(s) Secondary objectives are to investigate the association between anti-JCV antibody status/index and phenotypic changes in innate and T and B cell subsets in patients on fingolimod therapy of 0.5mg/day.	**Endpoint(s) for secondary objective(s)** • Anti-JCV antibody status (+ or -) at Months 3, 6, and 12 • Change from baseline to Months 3, 6, and 12 in the anti-JCV antibody index • Change from baseline to Months 3 and 12 in CD4+ and CD8+ naïve T cells (CCR7+CD45RA+), central memory T cells(CCR7+CD45RA-), and effector memory T cells (CCR7-CD45RA-CD45RO+) • Change from baseline to Months 3 and 12, in CD4+ Th1 (CXCR3+), Th2 (CCR4+) and Th17 (CCR6+) cells

Objective(s)	Endpoint(s)
	• Change from baseline to Months 3 and 12 in naïve B cells (CD19+CD27-), memory B cells (CD19+CD27+) and regulatory B cells (CD19+CD24+CD38+) • Change from baseline to Months 3 and 12 in monocytes (CD14+), neutrophils (CD16+) and NK cells (CD56+)
[redacted]	

3 Investigational plan

3.1 Study design

This study uses a two-cohort, nonrandomized, open-label, multicenter design.

Cohort 1: In the first cohort approximately 200 patients with RMS, who are newly prescribed commercially available fingolimod 0.5mg/day will participate in the study.

Cohort 2: In the second cohort approximately 200 RMS patients who have been on commercially available fingolimod 0.5mg/day continuously without interruption of treatment for at least ≥ 2 years will participate in the study.

Patients from both cohorts will be recruited simultaneously from up to 125 MS centers in the United States. Both cohorts will run concurrently.

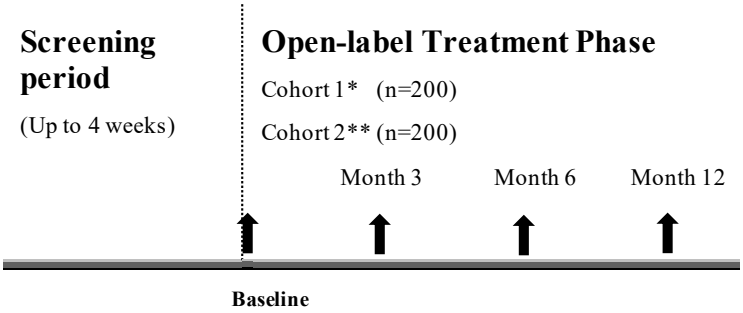
The study consists of two periods:

- Screening (up to 4 weeks)
- Treatment period from Baseline (end of screening period considered as Day 1) up to 12 Months

A schema of the study design is presented in Figure 3-1, while a detailed visit and assessment schedule can be found in Table 6-1.

1. An interim analysis will be conducted when 50% of patients in Cohort 2 have completed the Month 6 follow up Visit.
2. A primary analysis will be conducted when all patients complete the Month 6 follow up Visit, which is the primary time point of interest in the study.
3. A final analysis will be completed when all patients have completed the Month 12 follow up Visit of the study.

Figure 3-1 Study design



* Cohort 1: Patients will begin treatment of fingolimod 0.5mg/day for the next 12 Months

** Cohort 2: Patients who have been on fingolimod 0.5mg/day continuously for ≥ 2 years will continue treatment of fingolimod 0.5mg/day for the next 12 Months

3.1.1 Screening period (screening to treatment)

After signing the informed consent, patients will enter a screening phase. The duration of the screening period will be up to 4 weeks. Screening will be used to assess patient eligibility as per the USPI.

Additionally, during this period patients in Cohort 1 will be tapered from prohibited medications and treatments if required as per the USPI.

3.1.2 Treatment Period (Baseline to 12 Months)

Once patient eligibility is confirmed, patients from both treatment cohorts will enter the treatment period. At Baseline, which is the start of the treatment period, eligible patients in Cohort 1 will be prescribed commercially available fingolimod at 0.5mg/day. In Cohort 2 patients will continue with fingolimod treatment. Patients in both treatment cohorts will be on fingolimod (0.5mg/day) treatment from Baseline to 12 Months. Follow-up Visits will be conducted at 3, 6 and 12 Months.

3.2 Rationale for study design

The open label, multicenter study used in this study is aligned with the previous Biobank study and its extension (CFTY720DDE01 and CFTY720DDE01E1) performed for the indication of RMS and is in accordance with the health authority guidelines and feedback, including the United States Food and Drug Administration (FDA).

The studies mentioned above evaluated the immune profile of fingolimod treated patients up to 48 months (i.e., Baseline, 1 month, 4 months, 6 months and 48 months). An expected reduction in CD4+ and CD8+ naïve (Tn) and central memory T cells (TCM), as well as CD19+ B cells, persisted up to 48 months. Although CD4+ TEM were spared, a decrease in CD8+ effector memory T cells (TEM) was observed at 48 months. In contrast, CD14+ monocytes and CD56+ NK cells expanded over the course of treatment. These findings have important implications for immune surveillance (i.e., CD8+ TEM reduction) and development of opportunistic infection. While these studies assessed temporal changes in cell subsets during long term

therapy, their limitation indicated no correlation of changes in distinct cell types with clinical efficacy and/or therapeutic risk measures, lack of time points from 6 months to 48 months to understand when cellular changes occur, and lack of understanding for phenotype and function of T cell and B cell subsets, as well as the innate cell populations examined (e.g., Th1, Th2, Th17, CD56+ bright immunoregulatory vs. CD56 dim cytotoxic NK cells, CD14+ pro-inflammatory M1 vs anti-inflammatory M2 monocytes, etc.). Thus, the proposed FLUENT study adds new dimension with T cell and B cell subsets and includes additional time points to capture the dynamics and fully appreciate temporal changes in innate and adaptive immune cell populations over the course of fingolimod therapy in patients new to fingolimod and those who have been on continuous treatment for at least 2 years. Further, FLUENT will collect clinical efficacy outcomes (i.e., MRI based variables, PDDS, [redacted] etc) and therapeutic risk measures (i.e., PML risk as determined by anti-JCV antibody status and index) to be correlated with observed changes in distinct T cell (i.e., Tn, TCM, TEM, Th1, Th2 and Th17) and B cell (i.e., naïve, memory and regulatory) subsets over short and long term therapy. The addition of multiple time points is particularly relevant to cohort 2. A single time point would not only significantly limit the insights to be gleaned regarding the relationship between immunophenotype and clinical information (i.e., clinical efficacy and therapeutic risk) over time, the ability to appreciate changes would also be severely diminished and thereby introduce increased noise that would impact the interpretation of the data. Thus, FLUENT fills in the gaps of Biobank and adds new dimension to these previous studies.

The study population consists of adult patients with RMS who are either undergoing or are candidates for fingolimod therapy (note that a decision to initiate fingolimod has already been made). The study is designed to acquire information on immunological markers and clinical information in a manner that does not over-burden patients, caregivers or clinical sites but provides sufficient information to assess immune status. Its design relies on the approved USPI label based enrollment criteria and thereby reflects real world conditions of routine clinical practice.

Cohort 2 will provide data on patients who have been on fingolimod therapy continuously for at least 2 years and thereby reflects long term immunophenotypic changes consequent to this therapy. Cohort 1 will provide data on patients new to fingolimod therapy and therefore reveals acute changes in patients' immune profile. Data from Cohort 2 will provide a foundation to appreciate changes and detect patterns in immune phenotypes in patients newly initiated on fingolimod over the long term. Furthermore, Cohort 2 will provide [redacted] PML risk data on patients who have been on fingolimod therapy for an extended period. Cohort 2 will only serve as a referent cohort for cohort 1 and is not intended to be a direct Cohort 1 comparator as no *a priori hypotheses* are to be examined.

The study population will be described in more detail in Section 4 below.

3.3 Rationale for dose/regimen, route of administration and duration of treatment

Fingolimod treatment is prescribed to patients at a dose of 0.5mg/day in accordance with the product labelling. Please refer to the USPI.

3.4 Rationale for choice of comparator

No comparator is used in this study. The current study is designed to close the data gap as indicated in section 3.2. Once the immune phenotype profiling has been established we may plan for comparator studies.

3.5 Purpose and timing of primary analyses/design adaptations

The intention of the primary analyses is to provide results to be reported at medical congresses and published to enable data transparency and to provide clinical utility. Safety and efficacy variables, which include cellular changes, PML risk (anti-JCV antibody status and index), [redacted], will be analyzed together with demographics and baseline characteristics, as well as adverse events and serious adverse events.

A primary analysis will be conducted when all patients complete the Month 6 follow up which is the primary time point of interest in the study.

3.6 Risks and benefits

The study involves a FDA approved dose (0.5mg/day) and indication (RMS) of fingolimod. Therefore the study population will be examined within a known benefit/risk profile of fingolimod. Any procedural risks will be minimized using compliance with the eligibility criteria as well as optimal study procedures.

Patients will receive the benefit of being systematically monitored over a 12 Month period at regular follow-ups for immune phenotype profiling, which would not have taken place during normal routine follow up Visits.

4 Population

The study population will consist of male and female patients (≥ 18 years of age) with a diagnosis of MS. In the first cohort approximately 200 patients with RMS, who are newly prescribed commercially available fingolimod 0.5mg/day will participate in the study. In the second cohort approximately 200 RMS patients who have been on commercially available fingolimod 0.5mg/day continuously for at least ≥ 2 years will participate in the study.

The goal is to include 400 patients (Cohort 1, n=200 and Cohort 2 n=200) from up to 125 centers in the United States. Since a 25% screen failure rate is expected, approximately 533 patients will be screened.

Patients who discontinue after they have been enrolled will not be replaced.

4.1 Inclusion criteria

1. Written informed consent must be obtained before any study related assessment is performed.
2. Males and females ≥ 18 years of age at the time of screening.

3. Patients diagnosed with relapsing forms of MS defined by the revised McDonald criteria (2010), Appendix 1.
4. Patients who will start commercially prescribed fingolimod therapy 0.5mg/day or patients already on commercially prescribed fingolimod 0.5mg/day continuously for ≥ at least ≥ 2 years.

4.2 Exclusion criteria

Since commercially prescribed fingolimod is being used in the study, contraindications as per the USPI will be adhered to which include

1. Patients who in the last 6 months experienced myocardial infarction, unstable angina, stroke, Transient ischemic stroke (TIA), decompensated heart failure requiring hospitalization or Class III/IV heart failure
2. History or presence of Mobitz Type II second-degree or third-degree atrioventricular (AV) block or sick sinus syndrome, unless patient has a functioning pacemaker
3. Baseline QTc interval ≥500 msec
4. Treatment with Class I a or Class III anti-arrhythmic drugs
5. Patients who are participating in any other clinical trial with fingolimod (Cohort 2)
6. Patients who have had a hypersensitivity reaction to fingolimod or any of the excipients. Observed reactions include rash, urticarial and angioedema upon treatment initiation.

Note: Hypersensitivity reactions, including rash, urticaria, and angioedema have been reported with fingolimod in the post-marketing setting.

5 Fingolimod Treatment

5.1 Fingolimod treatment

Treatment involves routine standard of care with prescribed commercially available fingolimod. The drug will not be supplied by Novartis. Physicians will prescribe commercially available fingolimod which will be covered by the patient's insurance or by the patients themselves.

In Cohort 1 at the start of fingolimod treatment (Baseline), patients will undergo routine first dose observation (FDO) as per the USPI at the treating site. Once FDO has been completed in Cohort 1, thereafter all doses of fingolimod will be self-administered. In Cohort 2 fingolimod is self-administered.

Self-administration refers to patient self-treatment of the drug or by a trained caregiver regardless of whether dosing occurs at study site or at home. Instruction and training will be provided by site staff to patients/caregivers prior to treatment.

5.1.1 Fingolimod and control drugs

Fingolimod is commercially available and marketed in the United States.

There are no control drugs in this study.

5.1.2 Additional treatment

No additional treatments beyond commercially prescribed drug (fingolimod) are included in this trial.

5.2 Fingolimod Treatment cohorts

There are two cohorts in this study.

Cohort 1: Includes commercially prescribed fingolimod naïve patients.

Cohort 2: Includes patients who have continuously been on commercially prescribed fingolimod for ≥ 2 years.

Both treatment cohorts will remain on the treatment regimen of fingolimod of 0.5mg/day from Baseline (Visit 1) to a period of 12 Months.

5.3 Fingolimod Treatment assignment and randomization

There is only one treatment assignment in this study: commercially available 0.5mg/day of fingolimod. No randomization will be performed in this study.

5.4 Fingolimod Treatment blinding

The trial is an open-label study, thus fingolimod treatment will not be blinded during the course of the study.

5.5 Treating the patient

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

5.5.1 Patient numbering

Each patient is uniquely identified by a 7 digit Subject Number which is composed of a

i) 4 digit site number assigned by Novartis and a

ii) 3 digit sequential number assigned by the investigator.

Once assigned to a patient, the Subject Number will not be reused.

Example:

At Site 1 and Subject 1, the Subject number assigned is 0001-001

At Site 1, Subject 2, the Subject number assigned is 0001-002

Upon signing the informed consent form, the patient is assigned the next sequential number as given by the investigator using the next blank case report form (CRF) book available from the electronic data capture (EDC) system.

If an enrolled patient fails to be treated for any reason, the reason will be entered on the Screening Study Disposition, Electronic case report form (eCRF).

5.5.2 Dispensing Fingolimod

Not applicable. No drug is provided by the sponsor company Novartis nor the PI.

5.5.3 Handling of Fingolimod and additional treatment

5.5.3.1 Handling of Fingolimod treatment

Not applicable. No drug is provided by the sponsor company Novartis nor the PI.

5.5.3.2 Handling of additional treatment

Not applicable.

5.5.4 Instructions for prescribing and taking Fingolimod

Patients will be prescribed commercially available fingolimod as per their standard of routine care (Refer to the USPI). Drug will be covered by the patient's medical insurance or by the patient themselves.

The investigator must promote compliance by instructing the patient to take the fingolimod treatment exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient must be instructed to contact the investigator if he/she is unable for any reason to take the Fingolimod treatment as prescribed.

5.5.5 Permitted dose adjustments and interruptions of Fingolimod treatment

Not applicable.

5.5.6 Rescue medication

There is no rescue medication being provided/prescribed as part of the study. However, based upon safety and other assessments, investigator discretion, or for any reason, patients will be free to discontinue participation in the study at any time.

5.5.7 Concomitant medication

Concomitant medication information will be reported as per routine standard of care and recorded on the source document. Although no solicited concomitant medication information is required for the sponsor, if during the course of the study an adverse reaction (i.e., an adverse event associated or suspected with the use of the drug) is noted and Adverse events (AEs) or Serious Adverse events (SAEs) are noted, then the physician must record the events and medications as per instructions given in Section 7.1 and Section 7.2 of the protocol.

5.5.8 Prohibited medication

As per USPI.

5.6 Study completion and discontinuation

5.6.1 Study completion

A patient will be considered to have completed the study when the patient has completed the last visit planned in the protocol.

5.6.2 Unscheduled visit

An unscheduled visit (UNS) is a spontaneous visit and may take place at any time during the course of the clinical trial if and when the Investigator deems it necessary. The UNS assessments are detailed in Table 6-1 and must be recorded in the eCRF.

5.6.2.1 Study Discontinuation visit

Patients who discontinue study participation for reasons cited either by the patient or Investigator should return to the study site for a study discontinuation completion (SDC) Visit. The SDC Visit should be scheduled to occur as soon as possible or at least within 14 Days of the last fingolimod treatment. In case this Visit does not occur within 14 Days then the date when the patient returns must be documented and reported in the SDC eCRF. At the SDC Visit, assessments will be performed as per the assessment schedule as outlined in Table 6-1.

After SDC, at a minimum, in abbreviated visits, the following data should to be collected at clinic visits or via telephone visits:

- Adverse events/Serious Adverse Events

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

5.6.3 Withdrawal of informed consent

Patients/subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent from the study is defined as when a patient:

- Does not want to participate in the study anymore

or

- Does not want any further visits or assessments

or

- Does not want any further study related contacts

or

- Does not allow analysis of already obtained biologic material

In this situation, the investigator must make every effort (e.g., telephone, e-mail, letter) to determine the primary reason for the patient's decision to withdraw his/her consent and record this information.

Study participation 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 patient are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in the assessment Table 6-1.

5.6.4 Loss to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g., dates of telephone calls, registered letters, etc. A patient cannot be considered as lost to follow-up until the time point of his/her scheduled end of study visit has passed.

5.6.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrolment). Should this be necessary, the patient must be seen as soon as possible and treated as a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

6 Visit schedule and assessments

Table 6-1 lists all of the assessments and indices with an "X" when the Visits are performed.

Patients/subjects must be seen for all visits on the designated day, or as close to it as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the study discontinuation completion visit (SDC) will be performed.

Table 6-1 Assessment schedule

Days/ Months	-Day up to 4 weeks Screening period	Baseline (Day 1)	Month 3	Month 6	Month 12/ SDC	**Unscheduled visit**
Visit No	1	2	3	4	5/ 99	
Visit Window (days)			±7	±14	±14/ < 14	
Obtain informed consent	X					
Inclusion/exclusion criteria	X	X				
Demographics	X					
MS medical history / previous therapies	X					
Drug Regimen	X*	X^	X	X	X	X
RMS (Yes/No)	X	X	X	X	X	
Magnetic Resonance Imaging (MRI) review (if available)**	X	X	X	X	X	
Patient Determined Disease Steps (PDDS)***		X	X	X	X	X
Collection of blood samples		X	X	X	X	X
Steroid use for MS	X	X	X	X	X	X
AE /SAE	X	X	X	X	X	X

SDC: Study discontinuation completion Visit will take place for those patients who discontinue study participation. This Visit is to be scheduled to occur as soon as possible or at least within 14 days of the last fingolimod treatment

* **Drug dosing information** at Screening will report first date of treatment, dosage and frequency for patients in Cohort 2

^ At the Baseline Visit for all patients in Cohort 1 collection of blood samples must be performed prior to administration of the first dose of fingolimod

** **MRI** If patient had/ has a MRI that is performed as part of routine standard of care

*** **PDDS** is a non-copyrighted patient self-assessment tool which estimates disability in MS patients, Learmonth et al 2013

6.1 Information to be collected on screen failures

All subjects who sign informed consent but discontinue prior to Visit 2 (Baseline) are considered screen failures.

The Screening Visit Date, Demography, Informed Consent, Inclusion/Exclusion Criteria, Subject Rescreening, and the Screening Phase Disposition eCRFs must be completed. The Adverse Event eCRF and a paper SAE form must be completed for any SAE that occurs during the screening period. Adverse events that are not SAEs will be followed by the Investigator and collected only in the source data. The Withdrawal of Informed Consent (WoC) eCRF must be completed if consent was withdrawn during the Screening period before the subject was enrolled.

6.2 Rescreening

Rescreening may be allowed under certain conditions. Requests from the Investigator/site staff to rescreen patients will be handled on a case-by-case basis with Medical Monitor approval required prior to proceeding with rescreening. Rescreening cannot be done if a patient was previously enrolled into the study.

If a patient rescreens for the study, the patient must sign a new Informed consent form (ICF) and must be issued a new patient number prior to any screening assessments conducted under the new patient number. The date of the new informed consent signature must be entered on the Informed consent eCRF to correspond to the new patient number.

6.3 Patient recruitment

Patient recruitment will end on June 30th 2018 i.e., the last patient first visit (LPFV). The last patient last visit (LPLV) will take place no later than June 30th 2019 (12 Month Visit date).

6.4 Assessments

6.4.1 Informed consent

Written informed consent must be obtained prior to any screening procedures at Visit 1/Screening and will be recorded in the eCRF.

6.4.2 Inclusion/ Exclusion criteria

As per the USPI label all patients must meet all the inclusion and none of the exclusion criteria at Visit 1/Screening. A reconfirmation is required at Visit 2/ Baseline prior to administration of the drug. This will be recorded in the eCRF.

6.4.3 Demographics

Patient demographic data will be recorded at Visit 1/Screening. Data to be collected on all patients include: date of birth, patient initials, age, sex, race and ethnicity. This will be recorded in the eCRF.

6.4.4 Multiple Sclerosis Medical History and Previous Therapies

Relevant medical MS history and previous therapies pertaining to MS will be recorded at Visit 1/Screening in the eCRF. Significant findings that are observed after the patient has signed the informed consent form and that meet the definition of an AE must be recorded in the AE eCRF.

6.4.5 Drug regimen

For patients in Cohort 2, date of first treatment, dose and frequency will be reported at Visit 1/Screening eCRF. At Visit 2/ Baseline date of treatment, dose and frequency will be reported for both Treatment Cohorts in the eCRF.

At the subsequent visits, patient compliance will be reported: if the patient is taking their medication regularly as prescribed, if the patient has missed any doses and how often the patients have missed their dose. All information will be recorded in the eCRF at the Visits as outlined in the Table 6-1

The investigator/qualified site staff should promote compliance by instructing patients to attend the study visits as scheduled, to take the fingolimod treatment exactly as prescribed, and reiterate that compliance is necessary for patient safety and the validity of the study.

Patients should be instructed to contact the investigator/qualified site staff if he/she is unable for any reason to attend a study visit as scheduled, or if he/she is unable for any reason to take their prescribed treatment.

6.4.6 Relapsing Multiple Sclerosis

The current condition i.e., if yes or no pertaining to Relapsing multiple sclerosis will be recorded in the eCRF at the Visits as outlined in Table 6-1.

6.4.7 Magnetic Resonance Imaging Review

Magnetic Resonance Imaging data, if available from standard of routine care will be reviewed and standard MRI measures as outlined below will be recorded in the eCRF at the Visits as outlined in Table 6-1.

- Change from Baseline in T2 lesion burden
- New Gadolinium (Gd)-enhancing T1 lesion count;

6.4.8 Patient Determined Disease Steps (PDDS)

The PDDS scale, Appendix 3, Learmonth et al 2013, North American Research Committee on Multiple Sclerosis (NARCOMS) Registry is a self-assessment scale of MS disease status, collected by the NARCOMS at enrollment and in follow-up surveys of adult patients of MS. Data from this scale will be recorded in the eCRF at the Visits as outlined in Table 6-1.

The impact of MS on disease status will be assessed by the following measure:

- The Patient Determined Disease Steps (PDDS) scale, Appendix 3, NARCOMS Registry

The PDDS self-assessment scale will be completed by the patient at the follow up Visits as outlined in the visit schedule Table 6-1.

The PDDS scale focusses mainly on disability of the patient and has nine ordinal levels ranging between 0 (normal) and 8 (Bedridden). Lower scores reflect better gait. It takes an estimated 10-15 minutes to complete the PDDS.

6.4.9 Biomarkers and Hematology Assessments

Blood samples (approximately 60-80 ml) will be collected as per the Visit schedule outlined in Table 6-1. For each Visit a total of up to 80 ml blood will be drawn (please refer to Laboratory manual) for biomarker and hematology assessments.

Note: In Cohort 1 patients it is critical that the blood sample, must be collected prior to administration of fingolimod, FDO.

A central laboratory will be used for analysis of all specimens collected. A laboratory manual with information on blood sample collection, handling, shipment of samples, processing and reporting of results will be provided.

6.4.9.1 Biomarkers

Table 6-2 Biomarkers

	Type of Biomarker
1	CD4+ naïve T cells (CD3+CD4+CCR7+CD45RA+)
2	CD8+ naïve T cells (CD3+CD8+CCR7+CD45RA+)
3	CD4+ central memory T cells (CD3+CD4+CCR7+CD45RA-CD45RO+)
4	CD8+ central memory T cells (CD3+CD8+CCR7+CD45RA-CD45RO+)
5	CD4+ effector memory T cells (CD3+CD4+CCR7- CD45RA-CD45RO+)
6	CD8+ effector memory T cells (CD3+CD8+CCR7- CD45RA-CD45RO+)
7	CD4+ Th1 cells (CD3+CD4+CXCR3+)
8	CD4+ Th2 cells (CD3+CD4+CCR4+)
9	CD4+ Th17 cells (CD3+CD4+CCR6+)
10	CD19+ naïve B cells (CD19+CD27-)
11	CD19+ memory B cells (CD19+CD27+)
12	CD19+ regulatory B cells (CD19+CD24+CD38+)
13	Monocytes (CD14+)
14	Neutrophils (CD16+)
15	NK cells (CD56+)
16	Anti-JCV antibody status
17	Anti-JCV antibody index
[redacted]	[redacted]

Any biomarker samples derived from the sample that remain after the analysis may be stored for up to 15 years (depending on the local regulations) to research scientific questions related to MS and evaluate additional biomarkers not yet identified in this protocol. The material can be destroyed on patient's request at any time point.

6.4.9.2 Hematology Assessments

Hematology assessments include: red blood cell (RBC) count, RBC morphology, white blood cell (WBC) count with absolute and differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils and segmented neutrophils), platelet count, hemoglobin and hematocrit

Clinically notable laboratory findings are defined in Appendix 2.

6.4.10 Steroid use for MS

The use of steroids i.e., if yes or no, steroid name, dose, start date, current use or stop date, will be recorded in the eCRF at the Visits as outlined in Table 6-1.

6.5 Efficacy

1. PDDS
2. MRI based variables if available

6.5.1 Appropriateness of efficacy assessments

The Patient Determined Disease Steps (PDDS) scale is a standard outcome efficacy assessment in MS to characterize the disease status in this patient population, Appendix 3, Learmonth et al 2013, NARCOMS Registry .

The PDDS is an alternative to other, more complex, self-reported versions of the Expanded Disability Status Scale (EDDS) that have correlated well with the classical EDSS, Lechner-Scott et al 2003. Researchers could adopt the PDDS in clinical research and practice involving patients with MS alongside the EDSS or when the EDSS is impractical, too costly, or inconvenient. The PDDS scale is simple, economical, and efficient in comparison to the EDSS and Disease Steps (DS) and offers a potentially useful Patient related outcome (PRO) of disability for clinical research and practice in MS, Learmonth et al 2013.

The MRI data that is readily available on file includes clinical information in a manner that does not over-burden patients, caregivers or clinical sites

6.6 Safety

Standard of routine care of patients will be followed at the investigator site. Information will be captured in the source document and retained in the patient files. The sponsor is not soliciting safety data capture for this study. However, if during the course of the study an adverse reaction (i.e., an AE associated or suspected with the use of the drug) is noted and the AEs or SAEs are noted, then the physician must record the events as per instructions given in Section 7.1 and Section 7.2 of the protocol.

6.6.1 Pregnancy and assessments of fertility

Standard of routine care of patients is to be followed. The sponsor is not soliciting pregnancy data. However, if a patient is being treated with fingolimod and becomes pregnant, the Investigator must report this pregnancy according to the protocol Section 7.3.

6.7 Other assessments

6.7.1 Clinical Outcome Assessments (COAs)

6.7.1.1 Patient Reported Outcomes (PRO)

All PDDS questionnaires will be kept with the patient's file as a source document. Completed questionnaires will be reviewed and examined by the investigator, for responses that may indicate AEs or SAEs. The investigator should review not only the responses to the questions in the questionnaires but also for any unsolicited comments written by the patient. If AEs or SAEs are confirmed, then the physician must record the events as per instructions given in Section 7.1 and Section 7.2 of the protocol.

7 Safety monitoring

7.1 Adverse events

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

In addition, all reports of intentional misuse and abuse of the product are also considered an adverse event irrespective if a clinical event has occurred.

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

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.

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for laboratory and other test abnormalities are included in Appendix 2.

Adverse events must be recorded in the Adverse Events eCRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information:

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

its relationship to the Fingolimod treatment

- Yes
- No

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- no action taken (e.g., further observation only)
- Fingolimod treatment dosage increased/reduced
- Fingolimod treatment interrupted/withdrawn
- concomitant medication or non-drug therapy given
- non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged (see Section 7.2 for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

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

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB). This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the medicinal product 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 has then to be discussed with the patient.

The investigator must also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to fingolimod treatment. This information must be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

7.2 Serious adverse events

7.2.1 Definition of 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:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
  - 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
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, e.g., defined as an event that jeopardizes the patient or may require medical or surgical intervention.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the patient 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 Annex IV, ICH-E2D Guideline).

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 patient or might require intervention to prevent one of the other outcomes listed above. 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 Annex IV, ICH-E2D Guideline).

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

7.2.2 Serious Adverse Event reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days [after the last study visit/ following the last administration of fingolimod treatment if there are post-treatment follow-up visits with no required procedures] must be reported to Novartis safety within 24 hours of learning of its

occurrence. Any SAEs experienced after the 30 day period [after the last study visit/ following the last administration of fingolimod treatment if there are post-treatment follow-up visits with no required procedures] should only be reported to Novartis safety if the investigator suspects a causal relationship to fingolimod treatment.

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.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE to *each specific component of fingolimod treatment, (if fingolimod treatment consists of several components)* complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signature are to be found in the investigator folder provided to each site.

Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or USPI (new occurrence) and is thought to be related to the fingolimod treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same fingolimod 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.

7.3 Pregnancy reporting

7.3.1 Reporting to Novartis

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

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the fingolimod treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

7.3.2 Pregnancy Registry

A pregnancy registry has been established to collect information about the effect of fingolimod use during pregnancy. Physicians are encouraged to enroll pregnant patients, or pregnant women may register themselves in the fingolimod pregnancy registry by calling [redacted] at [redacted], sending an email to [redacted] or visiting www.gilenyapregnancyregistry.com. Clinicaltrials.gov Identifier: NCT01285479

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and Good clinical practice (GCP) compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of data capture / data entry, the adherence to the protocol, the progress of enrollment and to Good Clinical Practice. 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 designated vendor or a centralized Novartis CRA organization. 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 patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the 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 eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients/subjects will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to US CFR 21Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until

they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of data to Novartis or to a designated vendor working on behalf of Novartis. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

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

Previous or current steroid medications or therapies for MS entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis or a designated vendor.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis. Any changes to the database after that time can only be made after written agreement by a responsible party at Novartis.

8.4 Data Monitoring Committee

Not required.

8.5 Adjudication Committee

Not required.

9 Data analysis

Novartis or a designated vendor will perform the statistical analysis.

The analysis will be conducted on patient data at the designated time points as indicated below. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

There will be three analyses in this study.

1. An interim analysis which is an early assessment to evaluate safety of Cohort 2 patients will be conducted when 50% of patients in Cohort 2 have completed the Month 6 follow-up visit.

2. A primary analysis based on all data collected on both Cohorts 1 and 2 patients will be conducted when all patients in Cohorts 1 and 2 complete the Month 6 follow up Visit, which is the primary time point of interest of the study.
3. A final follow-up analysis will be conducted when all patients in Cohorts 1 and 2 complete the Month 12 follow up Visit of the study.

9.1 Analysis sets

Enrolled Set: All patients enrolled in one of the two cohorts will be included in the Enrolled Set.

Safety Set: The Safety Set will include all patients who enrolled in one of the two cohorts and received at least one dose of fingolimod during the study. Patients will be analyzed according to the cohort enrolled.

Full Analysis Set: For this study, the Full Analysis Set is the same as the safety set defined above.

9.2 Patient demographics and other baseline characteristics

Data will be summarized with respect to demographics and baseline characteristics by cohort for patients in the Safety Set.

9.3 Treatments

Exposure to fingolimod will be presented using summary statistics by cohort for patients in the Safety Set.

9.4 Analysis of the primary variable(s)

9.4.1 Primary Variable(s)

All analyses will be conducted by cohort for the Safety Set.

The primary variables are:

1. Change from Baseline to Month 6 in CD4+ naïve T cells (CCR7+CD45RA+)
2. Change from Baseline to Month 6 in CD4+ central memory T cells (CCR7+CD45RA-CD45RO+)
3. Change from Baseline to Month 6 in CD4+ effector memory T cells (CCR7-CD45RA-CD45RO+)
4. Change from Baseline to Month 6 in CD4+ Th1 cells (CXCR3+)
5. Change from Baseline to Month 6 in CD4+ Th2 cells (CCR4+)
6. Change from Baseline to Month 6 in CD4+ Th17 cells (CCR6+)
7. Change from Baseline to Month 6 in CD8+ naïve T cells (CCR7+CD45RA+)
8. Change from Baseline to Month 6 in CD8+ central memory T cells (CCR7+CD45RA-CD45RO+)
9. Change from Baseline to Month 6 in CD8+ effector memory T cells (CCR7-CD45RA-CD45RO+)
10. Change from Baseline to Month 6 in naïve B Lymphocytes (CD19+CD27-)

11. Change from Baseline to Month 6 in memory B Lymphocytes (CD19+CD27+)
12. Change from Baseline to Month 6 in regulatory B Lymphocytes (CD19+CD24+CD38+)
13. Change from Baseline to Month 6 in monocytes (CD14+)
14. Change from Baseline to Month 6 in neutrophils (CD16+)
15. Change from Baseline to Month 6 in NK cells (CD56+)

Descriptive statistics (sample size, mean, standard deviation, standard error of mean, minimum, first quartile, median, third quartile, interquartile range, and maximum) will be provided. The 95% confidence interval for the mean will be calculated.

Analyses will be performed with respect to the actual value of primary variables by employing an analysis of covariance (ANCOVA) model with gender as a factor and duration of disease and corresponding baseline as covariates. The unadjusted as well as the adjusted least squares means will be provided together with a p-value.

Percent change from baseline mean will also be reported.

9.4.2 Statistical model, hypothesis, and method of analysis

Majority of analyses will be descriptive in nature. The 95% confidence intervals will be provided for the parameters of interest.

9.4.3 Handling of missing values/censoring/discontinuations

No imputation will be performed for missing data related to safety or efficacy.

9.4.4 Sensitivity analyses

Not applicable.

9.5 Analysis of secondary variables

Secondary variables consist of both efficacy and safety variables.

9.5.1 Efficacy variables

The following efficacy variable will be analyzed by cohort using data from patients in FAS.

- Change from Baseline in Patient Determined Disease Steps (PDDS);
- Change from Baseline in T2 lesion burden;
- New Gd-enhancing T1 lesion count

Descriptive statistics (sample size, mean, standard deviation, standard error of mean, minimum, first quartile, median, third quartile, interquartile range, and maximum) will be provided. The 95% confidence interval for the mean will be calculated.

9.5.2 Safety variables

The assessment of safety will be based mainly on the frequency of adverse events.

Adverse events will be summarized by presenting the number and percentage of patients having any adverse event, having an adverse event in each system organ class and having each

individual adverse event by cohort and overall. Any other information collected (e.g., severity or relationship to fingolimod) will be summarized, as appropriate.

Serious adverse events and adverse events leading to discontinuation of study will be summarized by system organ class and preferred term for each cohort and overall.

Safety Set will be used for the following analyses.

In addition to variables presented in Section 9.4.1, the following secondary variables will be analyzed:

1. Change from Baseline to Months 3, and 12 in CD4+ naïve T cells (CCR7+CD45RA+);
2. Change from Baseline to Months 3, and 12 in CD4+ central memory T cells (CCR7+CD45RA-CD45RO+);
3. Change from Baseline to Months 3, and 12 in CD4+ effector memory T cells (CCR7-CD45RA-CD45RO+);
4. Change from Baseline to Months 3, and 12 in CD4+ Th1 cells (CXCR3+);
5. Change from Baseline to Months 3, and 12 in CD4+ Th2 cells (CCR4+);
6. Change from Baseline to Months 3, and 12 in CD4+ Th17 cells (CCR6+);
7. Change from Baseline to Months 3, and 12 in CD8+ naïve T cells (CCR7+CD45RA+);
8. Change from Baseline to Months 3, and 12 in CD8+ central memory T cells (CCR7+CD45RA-CD45RO+);
9. Change from Baseline to Months 3, and 12 in CD8+ effector memory T cells (CCR7-CD45RA-CD45RO+);
10. Change from Baseline to Months 3, and 12 in naïve B cells (CD19+CD27-);
11. Change from Baseline to Months 3, and 12 in memory B cells (CD19+CD27+);
12. Change from Baseline to Months 3, and 12 in regulatory B cells (CD19+CD24+CD38+);
13. Change from Baseline to Months 3, and 12 in monocytes (CD14+);
14. Change from Baseline to Months 3, and 12 in neutrophils (CD16+);
15. Change from Baseline to Months 3, and 12 in NK cells (CD56+);
16. Change from Baseline to Months 3, 6, and 12 in the anti-JCV antibody index;
17. Change from Baseline to Months 3, 6, and 12 in Hematology measurements;
18. Anti-JCV antibody status (+ or -) at Months 3, 6, and 12.

For Variable 18, frequency count and percentage together with the 95% confidence interval for the proportion of JCV antibody positive patients will be presented.

For Variables 1-17, Descriptive statistics (sample size, mean, standard deviation, standard error of mean, minimum, first quartile, median, third quartile, interquartile range, and maximum) will be provided. The 95% confidence interval for the mean will be calculated.

In addition, correlation coefficients between changes in cellular (T, B and monocyte, neutrophil, NK) subsets and efficacy (MRI based variables and PDDS) and safety outcomes (anti-JCV antibody status and index) will be computed. Analyses of safety data will be by cohort based on the Safety Set.

9.5.3 Biomarkers

See Sections 9.4.1, 9.5.1 and 9.5.2

9.7 Interim analyses

As previously mentioned, two interim analyses of data will be performed prior to the final analysis at Month 12.

1. The first interim analysis is an early assessment to evaluate safety of Cohort 2 patients. This will be conducted when 50% of patients in Cohort 2 have completed the Month 6 follow up. For this analysis, primary variables, demographics, baseline characteristics, adverse events, and serious adverse events will be summarized.
2. The second interim analysis is the primary analysis for this study. This analysis will be conducted when all patients in Cohorts 1 and 2 complete Month 6 (primary time point of interest) of study. All data collected on patients from both Cohorts 1 and 2 will be included in this analysis. These data will be analyzed as mentioned in Sections 9.4, 9.5, and 9.6.

This is an open-label, single arm study, and has no active control. The first interim analysis is a summarization of data from Cohort 2 only and no confirmatory hypothesis will be tested. Thus, the multiplicity adjustment of the level of significance for the primary analysis due to the first interim analysis is not relevant in this study. Results obtained from these interim analyses may be reported and published externally for communication to health care professions, as appropriate.

9.8 Sample size calculation

Cohort 1: A sample size of 200 patients will be able to detect an effect size of 0.30 with 89% power after adjusting for multiplicity of testing changes in 15 primary variables, at an overall significance level of 0.05.

In addition, for both cohorts the primary interest is to estimate mean change from Baseline at various time points (Months 3, 6, and 12) of the primary and secondary variables. A sample

size of 200 patients in each cohort will provide us the precision of estimates within 0.14 of the corresponding standard deviation of the variables of interest.

10 Ethical considerations

10.1 Regulatory and ethical compliance

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

10.2 Informed consent procedures

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

Novartis will provide to investigators in a separate document a proposed ICF23 that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Women of child bearing potential must be informed that taking the fingolimod 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 requirement for the duration of the study. If there is any question that the patient will not reliably comply, they must not be entered in the study.

10.3 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, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to patients/subjects. 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.

10.4 Publication of study protocol and results

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

10.5 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed by Novartis Pharma Auditing and Compliance Quality Assurance, a group 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.

11 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 patients/subjects should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

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.

11.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients/subjects 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 patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety Monitoring must be followed.

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13 Appendix 1: 2010 Revisions to the McDonald diagnosis criteria for MS

Revision to the McDonald diagnosis criteria for MS

Clinical Presentation	Additional Criteria to Make diagnosis
≥ 2 attacks, objective clinical evidence of ≥ 2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack	None
≥ 2 attacks; objective clinical evidence of 1 lesion	Dissemination in space (DIS) demonstrated by: ≥ 1 T2 lesion in at least 2 of 4 MS typical regions of the CNS (periventricular, juxtacortical, infratentorial, spinal cord); OR Await a further clinical attack implicating a different CNS site
1 attack, objective clinical evidence of ≥ 2 lesions	Dissemination in time (DIT) demonstrated by: Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time; OR A new T2 and / or gadolinium-enhancing lesion(s) on follow up MRI, irrespective of its timing with reference to a baseline scan; OR Await a second clinical attack
1 attack, objective clinical evidence of 1 lesion (clinically isolated syndrome)	Dissemination in space and time demonstrated by: For DIS: ≥ 1 T2 lesion in at least 2 of 4MS typical CNS regions (periventricular, juxtacortical, infratentorial, spinal cord); OR Await a second clinical attack implicating a different CNS site AND For DIT: Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time; OR A new T2 and / or gadolinium-enhancing lesion(s) on follow up MRI, irrespective of its timing with reference to a baseline scan; OR Await a second clinical attack
Insidious neurological progression suggestive of MS (PPMS)	One year of disease progression (retrospectively or prospectively) AND 2 out of 3 of the following criteria: 1. Evidence of DIS in the brain based on ≥ 1 T2 lesion in MS-characteristic regions (periventricular, juxtacortical or intratentorial); 2. Evidence of 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)

14 Appendix 2: Clinically notable laboratory values

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

Laboratory Variable	Standard Units	SI Units
Hematology variables		
Hemoglobin	≤10.0 g/dL	≤100 g/L
Platelets	≤100 k/mm3	≤100 x 109/L
	≥600 k/mm3	≥600 x 109/L
White Blood Cells	≤2.0 k/mm3	≤2.0 x 109/L
	≥15 k/mm3	≥15 x 109/L
Hematology variables - differential		
Neutrophils	≤ 1,000 /mm3	≤1 x 109/L
	≥12000/mm3	≥12 x 109/L
Lymphocytes	<200/mm3	<0.2 x 109/L
	≥8000/mm3	≥8 x 109/L

15 Appendix 3: Patient Determined Disease Steps (PDDS)

Please read the choices listed below and choose the one that best describes your own situation. This scale focuses mainly on how well you walk. You might not find a description that reflects your condition exactly, but please mark the one category that describes your situation the closest.

0	**Normal**	I may have some mild symptoms, mostly sensory due to MS but they do not limit my activity. If I do have an attack, I return to normal when the attack has passed.
1	**Mild Disability**	I have some noticeable symptoms from my MS but they are minor and have only a small effect on my lifestyle.
2	**Moderate Disability**	I don't have any limitations in my walking ability. However, I do have significant problems due to MS that limit daily activities in other ways.
3	**Gait Disability**	MS does interfere with my activities, especially my walking. I can work a full day, but athletic or physically demanding activities are more difficult than they used to be. I usually don't need a cane or other assistance to walk, but I might need some assistance during an attack
4	**Early Cane**	I use a cane or a single crutch or some other form of support (such as touching a wall or leaning on someone's arm) for walking all the time or part of the time, especially when walking outside. I think I can walk 25 feet in 20 seconds without a cane or crutch. I always need some assistance (cane or crutch) if I want to walk as far as 3 blocks
5	**Late Cane**	To be able to walk 25 feet, I have to have a cane, crutch or someone to hold onto. I can get around the house or other buildings by holding onto furniture or touching the walls for support. I may use a scooter or wheelchair if I want to go greater distances.
6	**Bilateral Support**	To be able to walk as far as 25 feet I must have 2 canes or crutches or a walker. I may use a scooter or wheelchair for longer distances.
7	**Wheelchair/Scooter**	My main form of mobility is a wheelchair. I may be able to stand and/or take one or two steps, but I can't walk 25 feet, even with crutches or a walker.
8	**Bedridden**	Unable to sit in a wheelchair for more than one hour.