NOVARTIS

Clinical Development

[FTY720D/fingolimod]

Protocol No. CFTY720D2311 / NCT01892722

A two-year, double-blind, randomized, multicenter, active-controlled Core Phase study to evaluate the safety and efficacy of fingolimod administered orally once daily versus interferon β-1a i.m. once weekly in pediatric patients with multiple sclerosis with five-year fingolimod Extension Phase

Authors: [redacted]

Document type: Amended Protocol Version

EUDRACT number: 2011-005677-23

Version number: v07 Clean

Document Status Final

Development phase: IIIb

Release date: 16-Nov-2016

Table of contents

List of tables

List of figures

List of abbreviations

ADEM	Acute Disseminated Encephalomyelitis
AE	Adverse Event
Ag	Antigen
Alb	Albumin
AP	Alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AV block	Atrio-Ventricular block
CDC	Centers for Disease Control and Prevention
CNS	Central Nervous System
CUA lesion	Combined Unique Active lesion
eCRF	electronic Case Report/Record Form
BSSR	blinded sample size re-estimation
CPO	Country Pharma Organization
C-SSRS	Columbia Suicide Severity Rating Scale
CRO	Contract Research Organization
DLCO	Diffusion Lung capacity for Carbon Monoxide
DKEFS	Delis-Kaplan Executive Function System
DMTs	Disease Modifying Therapies
DS&E	Drug Safety & Epidemiology
DSS	Disability Status Scale
ECG	Electrocardiogram
EDC	Electronic Data Capture
EDSS	Expanded Disability Status Scale
EOS	End of Study
FAS	Full Analysis Set
FACS	Fluorescence Activated Cell Sorting
Fingolimod-P	Fingolimod-phosphate
FEV1	Forced Expiratory Volume at 1 second
Gd	Gadolinium
GGT	Gamma-Glutamyl Transferase
HCG	Human Chorionic Gonadotropin
HAV	Hepatitis A Virus
HB	Hepatitis B
HCV	Hepatitis C Virus
HEV	Hepatitis E Virus
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFN β	Interferon beta
Ig	Immunoglobulin
i.m.	intramuscular
i.v.	intravenous
IRB	Institutional Review Board

IVR	Interactive Voice Response system
kg	kilogram
LFT	Liver Function Test
n/neT2	New/Newly Enlarging T2 lesions
mg	milligram
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
o.d.	once a day
[redacted]	[redacted]
PPW	Premature Patient Withdrawal
PT/INR	Prothrombin Time/International Normalized Ratio
RRMS	Relapsing-Remitting Multiple Sclerosis
S1P	sphingosine-1 phosphate
SAE	serious adverse event
SDD	Study Drug Discontinuation
[redacted]	[redacted]
SPMS	Secondary Progressive Multiple Sclerosis
[redacted]	[redacted]
TBL	Total bilirubin
[redacted]	[redacted]
ULN	Upper Limit of Normal
VZV	Varicella-Zoster Virus

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
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug.”
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IVR system
Patient number	A number assigned to each patient who enrolls in the study. When combined with the center number, a unique identifier is created for each patient in the study.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study drug was discontinued whichever is later
Study drug	Any drug administered to the patient as part of the required study procedures; includes investigational drug and any control drugs
Study drug discontinuation	Point/time when patient permanently stops taking study drug for any reason; may or may not also be the point/time of premature patient withdrawal
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

Amendment 7: released 16-Nov-2016

Amendment rationale

Amendment 7 modifies the study duration from fixed 2 year duration to a flexible duration of up to 2 years. The change is being conducted because the study is currently overpowered due to the higher than anticipated observed relapse rate. The study shall maintain the required power of 80% to detect a 50% relative treatment effect on the annualized relapse rate (two-sided 5% alpha-level). Accordingly, Novartis proposes to change the trial design from a fixed 2-year study to an information-based flexible duration design study up to 2 years:

[redacted]

Higher relapse rates in pediatric versus adult MS are supported by recent literature (Benson et al 2014). Also, similar higher ARR rates were consistently seen in young versus older adults in the fingolimod Phase 3 RRMS program. Based on the first BSSR of the current study (n > 100 randomized subjects, data cut off 28-Sep-2015), relapse rates in the enrolled pediatric patient population are higher than those seen in adult patients from the fingolimod Phase 3 RRMS program which were originally used as the basis for the sample size calculation for this study. Based on the BSSR the power to detect a 50% relative treatment effect on the annualized relapse rate (ARR) is currently at 96%, instead of the protocol-assumed 80%, if the study was to be conducted as planned with a 2-year fixed duration in 190 patients.

It is quite apparent from these lines of direct (current blinded study data) and indirect evidence (publications) that the central statistical assumptions made for Study D2311 are overly conservative and are no longer valid. Based on these observations, the study design will be modified with this amendment (if sufficient information will be achieved by June 2017) to allow for a flexible study duration in order to retain the power of at least 80% for the detection of a 50% relative treatment effect. In line with the ICH harmonized Tripartite guideline on “Clinical Investigation of Medicinal Products in the Pediatric Population” [(ICH Guideline E11] this will make the study more efficient (shorten exposure time of vulnerable pediatric patients to an investigational drug with double dummy design) without loss of information or statistical power. [redacted]

Other changes to the protocol include the following.

Assessment of Gd enhancement is no longer required at the Month 18 scan and for all MRI Extension Phase scans due to concerns of possible accumulation of Gd in the brain for patients with repeated MRI scans with Gd enhancement. This assessment will be optional and may be conducted if the sites would normally conduct MRI scans with Gd enhancement in their normal practice.

Efficacy endpoints such as cumulative number of n/ne T2 lesions and number of Gd T1 lesions are modified to adjust for the variant study durations among patients. The sensitivity analysis with missing data imputation method for the primary endpoint and the key second endpoint is removed since it is no longer applicable for the new study design with flexible study duration.

Changes to the protocol

The main changes and Sections affected are listed as follows:

Protocol Synopsis and Protocol were updated throughout to incorporate the revised study design with respect to treatment duration in the Core Phase.

Section 3.1, 3.3, 3.5 and 4 were updated to describe [redacted] All patients that are enrolled in the Core Phase at the time of stopping the study will be considered to have completed the study if they return for their final visit. These patients would then be eligible to participate in the Extension Phase if they meet the in/ex criteria for the Extension Phase. In accordance with feedback received from health authorities and the acknowledgement of the scarcity of pre-pubertal patients in this indication the requirement for 20% pre-pubertal patients was removed in order to render recruitment for this study feasible.

Section 5.1 and 5.4 were updated to clarify the blinding rules for patients with a body weight of <40 kg at the start of the Core Phase. These patients will receive blinded medication in the Extension Phase if they did not have a dose increase in the Core Phase due to sustained body weight to >40 kg at two consecutive visits.

Section 6 Assessment Schedule Table 6-1 was updated to clarify which patients were required to have additional ophthalmology assessments and Assessment Schedule Table 6-3 was updated to change the months to be counted from the start of the Extension Phase and to provide clarity when PK sample is collected.

Section 6.4.1 was updated to make Gd administration for the Month 18 MRI and during the Extension Phase optional due to concerns for the possible accumulation of Gd in the brain. The notification criteria for MRI activity were also updated.

Section 6.7.1.1 provides clarification that the pediatric Qol assessment is done in patients up to <19 years of age.

Section 9.1 was revised to include an additional analysis population, fingolimod treated full analysis (Fingolimod treated FAS) to be used for long-term efficacy evaluations during fingolimod treatment.

Section 9.4 was modified to remove the language regarding 20% pre-pubertal patients to be enrolled, an additional cofactor was added to the binomial regression model and the supportive analysis section was updated to remove the sensitivity analysis using imputation for missing data.

Section 9.5.1 was updated to have the key secondary endpoint adjusted for the flexible study duration, and the supportive/sensitivity analysis section was updated to be consistent with flexible study duration.

Section 9.5.2 provides updates to secondary efficacy endpoints to be consistent with a flexible duration study. Statistical analysis methods were also revised.

Section 9.5.3 provides updates to safety variables to be consistent with a flexible duration study and [redacted] and pulmonary endpoints were revised/ further clarified.

Section 9.5.4 was revised to clarify that the Ped QoL test is only done in patients up to <19 years of age.

Section 9.6 was updated to include the revised sample size and to provide information for the planned BSSR. This section was also updated to include the stopping rules for the study based on the BSSR. If at the BSSR in H1 2017, the projection is that the estimated amount of information until the end of Q2 is sufficient to maintain an 80% power for the primary variable, then patients will be requested to come for their end of study visit by June 2017. If at the BSSR in H1 2017, the projection is that the estimated amount of information projected until the end of Q2 is unlikely to reach 80% power for the primary end point, the study will continue as originally planned until all patients complete the full two years of treatment.

Section 9.7 sample size for key secondary endpoint was updated.

Section 12 was updated with 2 new references.

Table 13-3 was updated to provide a vital sign notable range for patients >18 years of age.

Appendix 5 was added to provide details of the statistical plan to conduct the BSSR.

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

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

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

Amendment 6: released 22-Aug-16

Amendment rationale

Amendment 5 was released with a main goal to incorporate details of the 5-year Extension Phase into the overall study design. When updating the text to incorporate the Extension Phase the section on termination of the study (Section 5.5.11) was inadvertently not updated. This amendment is being implemented to provide clarification for the study termination text. The text has been revised to allow the study to be terminated as a whole and also to allow for termination of just the Core Phase or just the Extension Phase.

Changes to the protocol

Section 5.5.11 was updated to provide clarification that the study (overall study or just Core or Extension Phase) can be terminated at any time for any reason by Novartis.

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

Amendment 5: released 16-Jun- 2015

Amendment rationale

This study protocol is being amended to provide details for the 5-year Extension Phase of the study. The Extension Phase is being included (in the current protocol) as a phase of the overall study since this simplifies the approval process and creates less work for sites to implement. Patients that complete the 2-year Core Phase (on or off of study drug) will be eligible to enter a 5-year Extension Phase. [redacted]

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

- Notably, there have been reports of isolated cases of cryptococcal meningitis in adult MS patients with relapsing MS receiving fingolimod. As a result, the fingolimod local product labeling will be updated to guide prescribers for vigilance, early detection, and diagnosis of such cases, should they occur. Similarly, the infection safety monitoring guidance is being updated in this protocol.
- Basal cell carcinoma (BCC) has been reported in adult MS patients receiving fingolimod. The physical examination section has been amended to ask patients/caregivers about any new or worsening skin lesions and to instruct investigators to refer patients to the dermatologist in cases where suspected precancerous or cancerous skin lesions are identified. BCC is very rare in the pediatric population and has a very low metastatic potential. In the current protocol, physical exams (which include evaluation of skin) are done quarterly during the Core Phase with detailed dermatological examination done at

baseline and at the end of the Core Phase. The detailed dermatological examinations will be conducted every 2 years during the Extension Phase.

Changes to the protocol

The main changes and Sections affected are listed as follows:

Protocol Synopsis was updated to incorporate the Extension Phase into the overall study design.

Section 1 was updated to refer Investigators to the current IB for exposure and safety updates.

Section 2 was modified to add the Extension Phase objectives.

Section 3.1, 3.2 and 3.3 were updated to change terminology to align with the two phase study design and to provide a description of the Extension Phase and a brief rationale.

Section 4, 4.1 and 4.2 were modified to add the Extension Phase study population and to add the Extension Phase inclusion and Exclusion criteria.

Section 5.1, 5.2, 5.3 and 5.4 were modified to include the study treatment arms and to provide blinding information for the Extension Phase.

Section 5.5.1 was modified to include text to indicate that patients retain the same study number in the Extension Phase.

Section 5.5.4 was revised to update the first dose monitoring requirements for the Extension Phase and to include text to describe that careful planning of study visits is required to ensure that adequate study drug is available for the transition from Core Phase to the Extension Phase.

Section 5.5.7 was updated to indicate that there is no washout period required for IFN, dimethyl fumarate and glatiramer acetate for the Extension Phase for patients that stopped study drug treatment in the Core Phase and then started treatment with one of these agents.

Section 5.5.8 provides clarification that the excluded medications in Section 5.5.8 may be taken in the Core Phase once a patient permanently discontinued study drug. Patients starting treatment with these agents must meet the inclusion/exclusion criteria for washout requirements for entry into the Extension Phase.

Section 5.5.10 was updated to indicate that the Core Phase results of the Core Phase and the Extension Phase results will be reported separately. This will allow for required reporting of individual study phases to the Health Authorities.

Section 5.5.12 was added to provide the procedure for how to conduct an emergency breaking of the blinded treatment assignment in case of a medical emergency.

Section 5.5.12 was added to updated to indicate that the Independent EDSS rater is only required during the Core Phase in order to maintain blinding.

Section 6 was updated to provide Extension Phase visit windows, to provide details for when the 3M-FU visit is required and to provide a Table of Extension Phase visits and also to provide windows for the Extension Phase visits.

Section 6.4.1 was updated to indicate that the Investigator is allowed to view Extension Phase MRI's and that MRI notifications will not be sent during the Extension Phase.

Section 6.4.2 and 6.4.3 were modified to indicate that a blinded EDSS rater (independent evaluating physician) is not required for EDSS readings during the Extension Phase since all patients will be treated with fingolimod so blinding is not required.

Section 6.5.1 was revised to indicate that Investigators should ask the patient if they have any new or changed skin lesions as part of each physical examination and to refer patients to the dermatologist if suspicious lesions were identified.

Section 6.5.3 was updated to provide details of the first dose monitoring in the Extension Phase. First dose monitoring by the independent first dose monitoring team is required for the first dose of study medication taken in the clinic, but then subsequent restarts or drug dose increases may be conducted by the main study team if desired. Blinding is no longer required after the first dose administration blinded monitoring.

Section 6.7.2 was modified to include a single PK assessment in the Extension Phase to monitor blood concentrations after one month in the Extension Phase to allow for possible dose increase based on the blood concentrations of fingolimod for newly treated patients.

Section 9.1 was updated to update the Core Phase statistical analysis sets and to add the statistical analysis sets for the Extension Phase.

Section 9.5.1, 9.5.2, 9.5.3, 9.5.4 and 9.5.5 were updated to include the natural log as an offset for T2 lesion analysis, to add the Extension Phase efficacy and safety variables and to provide a PK assessment at Month 25.

Section 9.6 was updated to indicate the there was no sample size calculation for the Extension Phase. The Extension Phase sample size is dependent on the number of patients that complete the Core Phase and enroll into the Extension Phase.

Appendix 2 was updated to indicate that First dose monitoring is required by the independent first dose monitoring team in the Extension Phase only for the first dose of medication in the Extension Phase.

Appendix 3 Section 15.5 Guidance on monitoring of patients with infections was updated to provide additional guidance regarding infections.

Additional minor clarifications and editorial changes were made throughout the protocol for clarity and consistency across sections.

Summary of previous amendments

Amendment 4: released 23-Oct 2014

Amendment rationale

Amendment 4 implemented modifications based on feedback from 1) the study advisory group, 2) infectious disease experts 3) Investigators enrolling patients in the clinical trial and 4) health authority input.

Inflammatory disease activity in MS is expressed as clinical relapses and as inflammatory lesions on MRI, both of which have been shown to be predictive of future MS relapse activity. The current protocol inclusion criterion defines a population with active disease based on prior relapses. This inclusion criterion is now being expanded to additionally allow patients with evidence of active disease based on recent MRI activity alone (presence of Gd-enhancing lesions within 6 months prior to randomization) to be enrolled. This change reflects the current clinical practice in pediatric MS where decision making for switching treatments is commonly based on MRI activity and will appropriately increase the pool of patients that can be considered for the study (Banwell et al 2011, Yeh et al 2011).

Experience in the trial thus far has shown that serological testing and interpretation of vaccine generated immunity is complex and can be prone to errors. This is also reflected in the Centers for Disease Control and Prevention (CDC) guidelines. According to the CDC, "results of serum antibody tests in vaccinated persons are difficult to interpret. In vaccinated persons, antibody levels are often lower than following natural infection, and commercially available tests may not detect such low levels of antibody" (VPD Surveillance Manual 2012). "Serologic screening for measles, rubella, or mumps immunity before vaccination is not necessary and not recommended if a person has other acceptable evidence of immunity to these diseases. Similarly, post vaccination serologic testing to verify an immune response is not recommended." (CDC - Prevention of Measles, Rubella, Congenital Rubella Syndrome, and Mumps, 2013).Thus, in the current trial, serological testing for antibodies can lead to unnecessary exclusion of otherwise eligible patients and may lead to unwarranted vaccination in some patients. On the advice of infectious disease experts two of the serology screening exclusion criterion were combined to provide better clarification of the screening requirements. The exclusion criterion for positive antibodies to varicella zoster virus (VZV), measles, mumps, rubella, diphtheria, pertussis and tetanus was modified to align with the CDC criterion for acceptable evidence of immunity to determine a patient's immune status. The modifications made to the serology testing are also now aligned with the current prescribing information for fingolimod. Further, it should be noted that there is no safety signal for fingolimod in the adult population as far as diseases like measles, mumps, rubella, diphtheria, pertussis and tetanus are concerned and there is no requirement of serology testing for these antigens in the current prescribing information. Thus, the amended exclusion criterion is pragmatic, follows CDC guidance and the current fingolimod prescribing information and continues to appropriately filter a safe population to be enrolled in the study.

The exclusion criterion for patients testing positive for interferon-beta antibodies was removed. The clinical significance of presence of antibodies (binding or neutralizing) to interferon (especially at a single time point) is not certain (Polman et al 2010). Neutralizing antibodies (NAbs) can disappear over time. To be of significance in decision making for individual patients, the NAb should be seen to be persistent over time (high titre) and need to be correlated to the disease activity in a patient. In patients with low level of NAbs which are persistent over 3-6 months, additional testing with myxovirus resistance protein A needs to be conducted to determine the significance of NAbs. Hence, excluding otherwise eligible patients based on this single point testing is not justified. The neutralizing antibody testing at the end of study is retained in the protocol and will be used for sensitivity analysis.

Based on feedback from investigators and the study advisory group the exclusion criterion for prior immunosuppressive/immunomodulatory treatments was revised to reduce the number of excluded prior treatments and to specify appropriate washout periods as needed. The protocol exclusion of prior use of dimethyl fumarate was removed to allow dimethyl fumarate to be taken up to the start of study drug with no washout period required. This change was made given the very short half- life (~1h) for dimethyl fumarate (and the active metabolite mono-methyl fumarate) together with the protocol requirement for patients to have acceptable complete blood count prior to start of study drug. The protocol exclusion of prior use of teriflunomide was removed to allow teriflunomide to be taken up to 3.5 months of the start of study drug.

The Exclusion criterion for liver enzymes was revised to more closely align with the clinical experience with fingolimod. Fingolimod has shown a rather benign liver safety profile without any un-confounded cases of severe liver injury. Also, liver safety is being monitored closely throughout the study. The exclusion criteria for LFT's has been altered in adolescents in a manner consistent with adult fingolimod trials, but the criteria for pre-pubertal subjects have remained unchanged.

Levels of total alkaline phosphatase have also been allowed to be increased to up to 2 X ULN as in adolescents the elevation may be secondary to bone isoforms of the enzyme (growing bones; Turan et al 2011). Accordingly, the guidance on isolated elevations of alkaline phosphatase has been modified and will not necessarily require study drug discontinuation, and would be based on the PI's discretion if the elevations were thought to be more serious in nature. Guidelines for safety monitoring for alkaline phosphatase in Appendix 3 have also been updated.

To assist patients with travel restrictions, blood samples for liver panel assessments for Visit 51, 71 and 72 may be drawn by a local lab and the results reported to the Investigator within 48 hrs of obtaining the results. All safety guidelines will be followed and the results of the local laboratory values will be included in the eCRFs to document the values.

[redacted] all 'must' criteria for permanent study drug discontinuation are now provided in a single location in the protocol for clarity.

Appendix 3 safety monitoring guidelines were updated to provide clarification that lymphocyte values obtained from a local lab should also be included in the clinical database to ensure that the recovery from low lymphocyte values would be collected. This change was made because close monitoring of the recovery of lymphocyte values with fingolimod has not been studied in this patient population. Serology guidelines were updated to provide all related guidelines in a single location, and in [redacted]

The requirement for chest x-ray at screening and end of study visit was removed because of concerns from Investigators that this was an unnecessary radiation exposure to subjects. The pulmonary function testing and clinical examination of the respiratory system are considered to be adequate screening measures to evaluate pulmonary status.

Based on discussion with Investigators the central blinded MRI reading center will now provide MRI notifications during the course of the study if certain MRI activity criteria are

met for a given patient. The study advisory committee agreed to notifications based on " a combined unique active (CUA) lesion count (Gd-enhancing lesions + new/enlarging T2 lesions not associated with Gd-enhancement. This change was made to allow Investigators to be notified if patients have significant MRI lesion activity during the course of the study. The CUA lesion count was also added as an exploratory objective.

Changes to the protocol

The main changes and Sections affected are listed as follows:

Section 2.3 (Exploratory objectives) [redacted]

Section 4.1 (Inclusion criteria) was updated to allow for patients with Gd enhancing lesions within 6 months of randomization to enroll in the study.

Section 4.2 (Exclusion criteria) were updated to remove the criteria for exclusion based on IFN antibodies, to update the list of excluded medications and time requirements for washout periods, to revise the exclusion criteria for liver enzymes, to combine serology screening criteria and revise the requirements for serology for VZV, measles, mumps, rubella, diphtheria, tetanus and pertussis.

Section 5.5.7 (Concomitant treatment) was changed to require no washout period for patients treated with dimethyl fumarate.

Section 5.5.9 (Discontinuation of study treatment and premature patient withdrawal) was updated to include a list of conditions/findings that require permanent study drug discontinuation in a single location.

Section 5.2.12 (Role of site personnel) was updated to provide clarification for the pediatrician and first dose administrator's duties.

Section 6 (Visit schedule and assessments) was updated to allow extended time for screening assessments if required, chest x-ray was removed from Table 6-1 and IFN antibody testing was updated and moved to serology testing (Table 6-1).

Section 6.4.1 (Magnetic resonance imagining (MRI)) was revised to include criteria for central review monitoring for MS related MRI activity.

Section 6.5.4 (Laboratory evaluations) was updated to include the option for patients with travel restrictions to have local labs drawn for liver panel visits 51, 71 and 72. The serology section was simplified to align with other laboratory sections (serology guidelines were moved to Appendix 3).

[redacted]

Section 6.5.7 (Chest x-ray) was updated to remove the requirement for conducting chest x-rays during the study.

Section 9 (Data analysis) was updated to add pubertal status to supportive analysis for primary efficacy endpoint, to move key efficacy text to the correct section, to add exploratory variables to be summarized by visit with descriptive statistics, to add number of CUA lesions

at month 24 and remove SDMT for variables analyzed by rank ANCOVA, to remove chest x-ray from safety variables, to remove cognitive testing section as cognitive tests are efficacy variables.

Section 12 (References (available upon request)) was updated to add new references.

Appendix 2 (Guidelines for first dose monitoring) were updated to include only events related to first dose monitoring. Additional ECG criteria that apply to the entire study were moved to Section 5.5.9 for clarity.

Appendix 3 Section 15.2 (Guidance on monitoring of patients with elevated liver function tests) was updated to revise the guidance for alkaline phosphatase.

Appendix 3 Section 15.4 (Guidance on monitoring of patients with notable lymphopenia) was changed to add a requirement to provide local lab results for lymphocyte monitoring in the clinical database.

Appendix 3 Section 15.6 (Guidance on vaccinations) was updated to provide guidelines for screening serology and other guidelines in a single location for clarity and ease of implementation.

Appendix 3 Section 15.8 (Guidance on monitoring of patients with diagnosis of macular edema) was updated to remove text for initiating study drug after resolution of macular edema.

[redacted]

Amendment 3: released 14-Jul-2014

Amendment rationale

Amendment 3 was created [redacted] to clarify the eligible age range for patients enrolled in Russia. This request was based on the local product information for Avonex (interferon-β-1a IM, the comparator used in the study) which contraindicates use of Avonex in children below 12 years of age in Russia (i.e. this is included in the Contraindication section of the local product information). Per protocol, Inclusion Criterion 2, the eligible age range for patients enrolled in the study is 10-17 years, inclusive. This amendment clarifies that if the local product information for Avonex specifically contraindicates use below a certain age, inclusion of such patients is not permitted in that country.

Changes to the protocol

The main changes and Sections affected are listed as follows:

Section 4.1 (Inclusion criteria) criterion 2 was modified to allow for countries like Russia to participate if interferon-β-1a IM was specifically contraindicated for use below a certain age based on the local product information (Contraindication section) for that country.

Amendment 2: released 11-Jul-2013

Amendment rationale

Amendment 2 implemented modifications based on requests received from national health authorities (e.g. modifications of first dose monitoring guideline with reference to local or regional product information for Gilenya in adults; to specify need for follow up of adverse events of interest (cardiac, liver, lung, eye) until resolution or stabilization; assessment of compliance; inclusion of puberty status as covariate in the statistical analysis) and incorporates feedback from investigators to further optimize the protocol and study conduct.

This amendment also further enhances and clarifies protocol exclusion criteria and safety monitoring guidelines related to infections and first dose cardiac effects. These modifications are made based on recommendations from pediatric infectious disease and pediatric cardiology specialist review of the protocol in the context of the known safety profile of fingolimod in adults in this regard.

This amendment also implements changes to exclusion criteria, assessments, study drug discontinuation criteria and safety monitoring related to liver functioning to align these to relevant aspects of the Novartis Clinical Safety Standard Hepatotoxicity Guideline and to implement the more specific – and partly more conservative - recommendations of the Novartis Investigational Liver Expert Team (iLET); given that this study is in a new population. In addition, changes related to ECG/QTc findings, pregnancy and suicidality assessments are made to further align these with the recent Novartis Clinical Safety Standard Guidelines.

Additionally, an optional, comprehensive cognitive testing battery [redacted] is being implemented to allow evaluation of change over time and generation of important data to better understand the utility of these tests in clinical studies in pediatric MS.

Other updates, clarifications and edits throughout the protocol were also made.

The study enrollment is expected to commence around the time of Amendment 2.

Changes to the protocol

The main changes and Sections affected are listed as follows:

Section 1 (Background) has been updated to include new relevant clinical safety information on fingolimod and a summary of relevant information from toxicology studies in neonatal and juvenile rats.

Section 4.1 (Inclusion criteria) criterion 3 was modified to implement the revised diagnosis criteria for pediatric MS.

Section 4.2 (Exclusion criteria) has been modified to update and/or clarify Exclusion criteria related to: differential diagnosis; excluded prior immuno-suppressive and immuno-modulatory medications; additional infectious agents leading to exclusion based on sero-status; cardiac disease/findings on screening ECG or treatment with QT prolonging drugs; hepatic conditions; addition of history of seizures (to reflect the warning and precaution

statement in the IFN β-1a i.m. (Avonex) product information); suicidality/riks of suicide; use of prior investigational drug or therapy.

Section 5.1 (Investigational and Control treatment) has been modified to allow initial titration of injectable study drug (IFN β-1a i.m. or placebo) to full dose of over 4 weeks and the use of prophylaxis and treatment of flu-like symptoms in order to reduce initial tolerability issues associated with IFN β-1a i.m. treatment initiation. These measures are standard clinical practice at many sites.

Section 5.5.6 (Recommendations for treatment of MS relapses) has been updated to add a maximum dose for i.v. corticosteroids for treatment of MS relapse and to prohibit use of oral taper after the i.v. course of steroids.

Section 5.5.7 (Concomitant treatments) has been modified to clarify that washout is not required for patients treated with IFN β or glatiramer acetate and that vigilance is needed during concomitant chronic use of medications with hepatotoxic potential as patients may be at a higher risk of liver adverse events.

Section 5.5.9 (Discontinuation of study treatment and premature patient withdrawal) has been updated to list ECG abnormalities that should lead to study drug discontinuation per ECG/QTc Clinical Standard Guideline.

Table 6-1 (Schedule of assessments) have been updated to include additional lab visits for evaluation of liver enzymes, to add capsule and syringe count as measure of compliance and to reflect or clarify other modifications in protocol assessments.

Section 6.5.2 (Ophthalmic examination) has been modified to omit the optional measurement of retinal nerve fiber layer thickness (RNFL) by OCT from the protocol as obtaining a meaningful assessment of this parameter in this study is unlikely (small sample size, different OCT devices at sites, variability in measurement).

Section 6.5.4 (Laboratory evaluations) was modified to add phenotyping of T cells and B cells to the hematology evaluation and serology testing for antibodies to additional infectious agents (herpes simplex virus, EBV, CMV for information on serostatus prior to study entry). This section was also updated to provide the complete list of parameter and markers that will be evaluated by the central laboratory as part of the exclusion criteria (e.g. infectious agents including hepatitis and HIV) or during the study (blood chemistry and endocrinology parameters).

Section 6.5.9 (Columbia Suicide Severity Rating Scale, C-SSRS) was updated to align with the current Novartis Clinical Standard Suicidality Guideline and to clarify that for patients unable/unwilling to answer the C-SSRS questions in the IVR system themselves and for all patients below the age of 12 years, another individual will enter the C-SSRS questions in to the IVR system on behalf of the patient. The IVR version of the C-SSRS used in the study has not been validated for use in patients below the age of 12 years.

Section 6.6 (Pregnancy and assessment of fertility) has been modified to include that female patients of childbearing potential who are sexually active will perform a monthly urine pregnancy test in addition to the serum tests performed at the scheduled visits.

Section 14 (Guidance for first dose monitoring) has been updated as recommended by pediatric cardiology specialist, local health authority and to align with ECG/QTc Clinical Safety Standard Guideline.

Section 15.2 (Guidance on monitoring of patients with elevated liver function tests) has been revised and updated to align with the Novartis Clinical Standard Guideline and the recommendations by the iLET.

Sections 15.5 and 15.6 (Guidance on monitoring of patients with infections, Guidance on vaccinations) have been updated as recommended by pediatric infectious disease specialist.

[redacted]

Additional minor clarifications and editorial changes were made throughout the protocol for clarity and consistency across sections.

Amendment 1: released 13 June 2012

Amendment rationale

Amendment 1 implemented changes to the CFTY720D2311 protocol to address recommendations and requests received from the [redacted] following their review of the protocol and to align aspects of the protocol with the current revised fingolimod (Gilenya™) label.

The main changes were:

- The change in study design from open-label/rater-blinded to double-blind/double dummy which was implemented in order to reduce the potential for bias that may be introduced in an open-label design due to the lack of blinding of patients, caregivers and investigators.
- The on-line pharmacokinetic (PK) assessment of fingolimod concentration levels at Month 1 was expanded to include all patients with a bodyweight of 40 kg or below in order to determine the need for an individual dose increase (from 0.25 mg to 0.5 mg) based on their individual concentration level rather than on PK results obtained from an initial subset of patients in this weight group.
- In order to align the protocol with the revised fingolimod label, the amendment additionally updated and modified (1) specific exclusion criteria, (2) the list of prohibited concomitant treatments, (3) selected safety monitoring guidance and (4) clarified the potential for drug-drug interaction with concomitant use of systemic ketoconazole.

In December 2011, the company reported a sudden, unexplained death of a patient within 24 hours after the administration of the first dose of commercial fingolimod 0.5 mg. While the cause of death is unknown, the role of fingolimod cannot be confirmed or excluded. The reporting of this event prompted a thorough review the cardiac safety data from clinical trials as well as spontaneous reports in the post-marketing setting. This resulted in recommendations for additional first dose monitoring observation beyond 6 hours across all fingolimod protocols in patients meeting specific defined criteria at the end of the 6 hour observation period. For this protocol: patients that have a heart rate (HR) of <55 beats per

minute (bpm) (in patients 12 years or older) or 60 bpm (in patients below 12 years), new onset second degree or higher AV block, HR at 6 hours post-dose is the lowest value post-dose, and/or QTc on the 6-hour ECG is 500 msec or greater.

Other updates, clarifications and edits throughout the protocol were also made.

The study had not recruited any patients at the time of Amendment 1.

Changes to the protocol

Section 1 has been updated to include the latest information on fingolimod.

Sections 3.1, 3.2, 3.3, 5.4 and 15.4 have been modified to reflect changes necessary due to the change in study design from open-label to double-blind, double-dummy.

Section 4.2 has been updated with changes to the following Exclusion criteria: Exclusion 6: modified to also exclude patients treated with antiarrhythmic drugs and heart rate-lowering drugs at study entry. Exclusion 14: updated to further clarify exclusions related to severe cardiac disease or significant findings on screening ECG. Exclusion18: modified to exclude patients with severe renal insufficiency only.

Section 5.5.5 has been updated to include more specific details on conditions/events that may lead to study drug interruptions.

Section 5.5.7 has been updated to include that concomitant use of systemic ketoconazole may lead to an increase in fingolimod plasma levels and thus patients may be at a higher risk for adverse events.

Section 5.5.8 has been updated to add antiarrhythmic drugs and heart rate-lowering drugs to list of treatments not allowed concomitantly with study drug due to the potential for additional effects of fingolimod on slowing the heart rate.

Section 5.5.12 has been updated to include a separate First Dose Administrator as part of site personnel to avoid potential unblinding of the treating physician that may occur due to the well characterized treatment-initiation effect of fingolimod on the heart rate.

Sections 5.4, 5.5.12 and 6.4.2 have been modified to omit the requirement for confirmation of MS relapse by an independent Adjudication Committee. With the change to a double-blinded design, this additional confirmation is no longer required.

Table 6-1 and Table 6-2 have been modified to include Columbia Suicide Severity Rating Scale (C-SSRS) at all visits including any unscheduled visits.

Section 6.6 has been modified to implement the same requirement for highly effective contraception in all female patients of childbearing potential as was defined for fingolimod.

Section 7.3 has been modified to delete reference to the voluntary fingolimod-specific pregnancy registry. The double-blinded design of the amended protocol prevents identifying potential pregnancies in fingolimod treated patients that may occur in the course of this study.

Sections 3.3 and 9.5.5 has been updated in regards to on-line PK analysis and individual dose-adjustment. Section 9.5.5 has additionally been updated to add concomitant medications as a covariate to be examined in the population PK analysis.

Section 9.1 (Analysis sets) has been updated to add the Per-protocol set to be used for the supportive analysis of the primary efficacy variable.

Appendix 1 has been updated to modify selected laboratory and vital signs notable values for the pediatric population.

Section 14 Guidance for first dose monitoring has been updated in regards to the discharge criteria.

Additional minor clarifications and editorial changes were made throughout the protocol to reflect study design change and consistency.

Protocol synopsis

Title of study: A two-year, double-blind, randomized, multicenter, active-controlled Core Phase study to evaluate the safety and efficacy of fingolimod administered orally once daily versus interferon β-1a i.m. once weekly in pediatric patients with multiple sclerosis with five-year fingolimod Extension Phase

Purpose: The purpose of this study is to seek regulatory approval for use of fingolimod in a pediatric population with MS aged 10 to less than 18 years old. This study is conducted in line with the Pediatric Investigational Plan agreed with the EMA (under EU pediatric regulation (EC) No 1901/2006) and the post-marketing requirements in the US.

Objectives:

Core Phase:

Primary objective

To evaluate the efficacy of fingolimod relative to intramuscular IFN β-1a in reducing the frequency of relapses as assessed by the annualized relapse rate in children/adolescent MS patients aged 10 to less than 18 years treated for up to 24 months.

Key secondary objective

To evaluate the efficacy of fingolimod relative to IFN β-1a in reducing the number of new/newly enlarging T2 (n/neT2) lesions in children/adolescent MS patients aged 10 to less than 18 years treated for up to 24 months.

Other secondary objectives

- To evaluate the safety of fingolimod relative to IFN β-1a in children/adolescent MS patients.
- To evaluate the effect of fingolimod relative to IFN β-1a in children/adolescent MS patients on other relapse-related parameters:
  - Time to first relapse
  - Proportion of patients relapse-free
- To evaluate the effect of fingolimod relative to IFN β-1a in children/adolescent MS patients on T1 Gd-enhancing lesions on brain MRI.
- To study the pharmacokinetics of fingolimod and fingolimod-P in children/adolescent MS patients treated for up to 24 months.
- To study the pharmacokinetic/pharmacodynamic relationship for key efficacy and safety outcomes in children/adolescent MS patients treated for up to 24 months.

Exploratory objectives

- To explore the effects of fingolimod relative to IFN β-1a on other MRI measures including change in total T2 hyperintense and [redacted] lesion volumes, [redacted] and brain volume change in children/adolescent MS patients.
  - [redacted]
  - [redacted]
  - [redacted]

Fingolimod Extension Phase:

- To examine long-term safety, tolerability and efficacy parameters in patients treated with fingolimod
- To examine the effects of fingolimod on safety, tolerability and efficacy parameters in patients who were treated with inferferon-β-1a in the Core Phase.

- [redacted]

Population: Male and female patients with multiple sclerosis (MS) aged 10 to less than 18 years will be included in this Core Phase study. Patients will be recruited into two cohorts based on their puberty status (pre-pubertal, pubertal). The study will be conducted in centers worldwide. Approximately 190 patients will be randomized to receive either fingolimod or IFN β-1a.

The population of the Extension Phase will consist of patients who complete participation in the Core Phase

- Patients who complete the Core Phase on study drug will be allowed to enter the Extension Phase without any further criteria.
- Patients who complete the Core Phase but prematurely discontinued study drug during the Core Phase for any reason will be assessed for eligibility in the Extension Phase based on the exclusion criteria.

Inclusion criteria:

Core Phase:

1. Written informed consent must be obtained before any assessment is performed.
2. Male and female patients aged 10-17 years old*, inclusive (i.e., have not yet had their 18th birthday) at randomization.
3. A diagnosis of MS as defined by the revised consensus definition for pediatric MS (Krupp et al 2013, Polman et al 2011)

   Central review of the diagnosis of pediatric MS will be required for all patients prior to randomization.
4. At least one MS relapse/attack during the previous year or two MS relapses in the previous two years prior to screening, or evidence of one or more Gd enhancing lesions on MRI within 6 months prior to randomization (including screening MRI).
5. Expanded Disability Status Scale (EDSS) score of 0 to 5.5, inclusive.

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

Fingolimod Extension Phase:

Criterion applies to all patients entering the Extension Phase.

1. Patients that originally met Core Phase Inclusion criteria and completed the Core phase on or off of study drug.

Exclusion criteria:

Core Phase:

1. Patients with progressive MS.
2. Patients with an active, chronic disease (or stable but treated with immune therapy) of the immune system other than MS (e.g. Sjögren's disease, systemic lupus erythematosus) or with a known immunodeficiency syndrome (AIDS, hereditary immune deficiency, drug induced immune deficiency) or tested positive for HIV.
3. Patients with widespread and symmetric white matter alterations in the Screening MRI suggestive of other demyelinating disorders (e.g. metabolic disorders, mitochondrial disorders).
4. Patients meeting the definition of ADEM (Krupp et al 2013); patients meeting criteria for neuromyelitis optica (Wingerchuk et al 2006) or tested positive for aquaporin 4 (AQP4) at Screening.

5. Patients treated with:
    - Systemic corticosteroids or adrenocorticotropic hormone (ACTH) in the 30 days prior to Screening MRI scan
    - High dose intravenous immunoglobulin within 2 months prior to randomization
    - Natalizumab within 3 months or teriflunomide within 3 ½ months prior to randomization
    - Immunosuppressive/immunomodulatory medications such as azathioprine, methotrexate, laquinimod, ofatumumab, ocrelizumab within 6 months prior to randomization.
    - Alemtuzumab, cladribine, cyclophosphamide, mitoxantrone or rituximab at any time.
    - Fingolimod at any time.
    - The following antiarrhythmic drugs at Screening: Class Ia (e.g. quinidine, disopyramide) or Class III (e.g. amiodarone, sotalol) anti-arrhythmics
    - Concurrently treated with heart-rate-lowering drugs at Screening e.g.: Beta blockers, heart-rate lowering calcium channel blockers (e.g. verapamil, diltiazem or ivabradine), digoxin, anticholinesteratic agents, pilocarpine. Advice from a cardiologist should be sought regarding the switch to non-heart-rate lowering medicinal products.
6. Patients diagnosed with macular edema during the pre-randomization phase.
7. Patients with active systemic bacterial, viral or fungal infections, including tuberculosis.
8. Patients without acceptable evidence of immunity to varicella-zoster virus, mumps, measles, rubella, diphtheria, tetanus and pertussis at Randomization (See Appendix 3 Guidance on vaccinations for guidance on acceptable evidence of immunity and requirements for serologic testing).
9. Patients who have received any live or live attenuated vaccines (including for varicella-zoster virus or measles) within one month prior to randomization.
10. Patients with a history or presence of malignancy.
11. Patients with any medically unstable condition, as assessed by the primary treating physician at each site.
12. Patients with any severe cardiac disease or significant findings on the screening ECG, such as:
    - History of symptomatic bradycardia or recurrent syncope
    - Known ischemic heart disease
    - History of congenital heart disease (except conditions such as small patent ductus arteriosus, atrial septal defect, ventricular septal defect, or an ECG or rhythm abnormality, which have been assessed by a pediatric cardiologist and considered to be clinically insignificant).
    - Cerebrovascular disease
    - History of myocardial infarction
    - Congestive heart failure
    - History of cardiac arrest
    - Uncontrolled hypertension despite prescribed medications
    - Resting (sitting) heart rate <55 bpm (in patients 12 years or older) and <60 bpm (in patients below 12 years)
    - Severe untreated sleep apnea.
    - Sick sinus syndrome or sino-atrial heart block
    - QTcF interval >450 msec in males and >460 msec in females or relevant risk factors for QT prolongation (e.g. hypokalaemia, hypomagnesemia, congenital QT prolongation) or treatment with QT prolonging drugs with a known risk of Torsades de pointes (e.g., citalopram, chlorpromazine, haloperidol, methadone, erythromycin) or history of familial long QT syndrome or known family history of Torsades de Pointes.

- Second degree Mobitz type II or higher AV block

13. Patients with any pulmonary conditions, as determined by the investigator, including severe asthma defined as per the 2010 WHO uniform definition on severe asthma (Bousquet et al 2010).
14. Positive results of screening period testing for serological markers for hepatitis A, B, C, and E indicating acute or chronic infection:
    - anti-HAV IgM
    - HBs Ag and/or anti-HBc IgM
    - anti-HCV IgG or HCV-RNA PCR
    - anti- HEV IgM (if positive IgG: do HEV-RNA PCR: if negative, patient can be included)
15. Patients with any of the following hepatic conditions:
    - Chronic liver or biliary disease, acute or chronic pancreatitis, with the exception of Gilbert's syndrome
    - Liver enzymes
        - ALT, AST, alkaline phosphatase, GGT, >2 x upper limit of normal (ULN) range for age (for pre-pubertal patients > 1 X ULN or > 2X ULN if currently treated with IFN or glatiramer acetate). Elevations of alkaline phosphatase should not be used in isolation to exclude subjects, and would require Investigator discretion.
        - Bilirubin elevations not in the context of Gilberts Syndrome: Total and conjugated bilirubin >1.5 XULN (for pre-pubertal patients >1 X ULN or > 1.5 X ULN if currently treated with IFN or glatiramer acetate).
16. Patients with severe renal insufficiency (GFR <30 ml/min/1.73 m^2).
17. Patients with lymphocyte count < 800 cells/mm^3.
18. Patients with any of the following neurologic /psychiatric disorder:
    - History of any type of epileptic seizure(s) as well as psychogenic non-epileptic seizure(s) during the past 12 months before screening;
    - History of substance abuse (drug or alcohol) or any other factor (i.e., serious psychiatric condition) that may interfere with the subject's ability to cooperate and comply with the study procedures;
    - Progressive neurological disorder, other than MS, which may affect participation in the study or require the use of medications not allowed by the protocol
19. Patients unable to undergo MRI scans, including those with claustrophobia or a history of severe hypersensitivity to gadolinium-DTPA.
20. Pregnant or nursing females, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive HCG laboratory test.
21. Female patients of childbearing potential, defined as all females physiologically capable of becoming pregnant, unless they agree to abstinence or, if sexually active, the use of contraception as defined in Section 6.6.
22. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes.
23. Patients with a score of "yes" on item 4 or 5 of the Suicidal Ideation section of the C-SSRS, if this ideation occurred in the past 6 months, or with a score of "yes" on any item of the Suicidal Behavior section, except for "Non-Suicidal Self Injurious Behavior", if this behavior occurred in the past 2 years.
24. Patients who have received an investigational drug within 180 days or 5 half-lives of randomization, whichever is longer.

    No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

Fingolimod Extension Phase:

Criteria apply to patients who completed the Core Phase, but prematurely discontinued study drug.

1. Premature discontinuation of the study drug during the Core Phase due to an adverse event, serious adverse event, laboratory abnormality or conditions leading to permanent study drug discontinuation due to safety reasons as described in the protocol.

   Note: If a patient was discontinued due to lack of efficacy in the Core Phase, the patient may be offered the option to enter the extension trial if the investigator determines it is in the patient's best interest when considering all available treatment options.
2. Patients with known new events or concomitant medications that would exclude them from the Core Phase exclusion criteria. Serological or other additional tests will not be required.

Investigational therapy: Core Phase and Fingolimod Extension Phase

- Fingolimod 0.5 mg capsules, administration orally once daily in patients weighing more than 40 kg (at treatment initiation and/or during study)
- Fingolimod 0.25 mg capsules, administration orally once daily in patients weighing 40 kg or less. The dose may be increased to 0.5 mg based on the results of the on-line PK assessment or can be increased if the patient has an increase in body weight >40 kg at 2 consecutive visits at least 3 months apart.

Reference therapy: Core Phase

- Interferon β-1a 30 µg (Avonex®) pre-filled syringes, administration intramuscular (i.m.) injection once weekly

Matching placebo formulations for blinding of investigational and reference therapies: Core Phase

- Matching fingolimod placebo capsules
- Matching interferon β-1a placebo pre-filled syringe

Study design:

The study is divided into a Core Phase, which includes the Pre-Randomization Period and the Double-Blind Treatment Period, and an Extension Phase in which all patients will be treated with fingolimod.

Core Phase:

The Core Phase is a 24-month, double-blind, randomized, active-controlled, parallel-group multicenter study phase to evaluate the safety and efficacy of fingolimod compared to IFN β-1a in children/adolescent patients aged 10-17 (not yet had their 18th birthday) with MS.

After obtaining informed consent, patients will complete the screening and baseline assessments of the pre-randomization period to confirm eligibility for the study. At Day 1, the first visit in the double-blind treatment period, eligible patients will be randomized to one of the two treatment arms (fingolimod or IFN β-1a).

All patients will be required to remain at the site for at least 6 hours after the first oral capsule intake (first dose monitoring on Day 1). All patients should also receive their first injection at the site.

Post-randomization visits (after Day 1) are scheduled at 2 weeks, 1 month, 2 months, 3 months and then every 3 months during the double-blind treatment period. Additionally, blood sampling for liver function tests will be performed at 6 weeks and at 4 and 5 months.

Blood samples for pharmacokinetic purposes will be collected on Day 1 before and approximately 5-6 hours after the first oral capsule, and at any time for all other visits. The only exception will be the Month 1 visit when two samples will be collected, one at pre-dose (i.e. before the oral dose administration) and one approximately 5-6 hours post-dose.

The end of the Core Phase of the study will be determined by a blinded sample size re-estimation (BSSR). The study shall maintain the required power of 80% to detect a 50% relative treatment effect on the annualized relapse rate (two-sided 5% alpha-level). Accordingly, Novartis proposes to change

the trial design from a fixed 2-year study to an information-based flexible duration design study with study duration of up to 2 years:

[redacted]

Patients who prematurely discontinue study drug and remain in the study will be followed in an abbreviated schedule of assessments for the duration of the double-blind treatment period. Upon discontinuation of the study drug, patients must complete the Visit 14 end of study phase (EOS-CP) visit as soon as possible, followed by a 3-month follow-up visit, before continuing in the abbreviated schedule of assessments.

Patients who complete the double-blind treatment phase (on or off study drug) may be eligible to enter a long-term Extension Phase to receive treatment with fingolimod. Patients who complete the double-blind treatment period on study drug, but do not enter the Extension Phase will return for a follow-up visit 3 months after the Visit 14- EOS-CP visit.

Fingolimod Extension Phase:

The Extension Phase is a 60-month (5 year) study phase for eligible patients who complete the Core Phase of the study and meet all inclusion/exclusion criteria. All patients will be treated with fingolimod (either 0.5 mg/d or 0.25 mg/d based on body weight). To comply with local requirements if, in a specific country/site the Extension Phase is not allowed by the Health Authority/IRB then that country/site will not be required to participate in the Extension Phase.

The Core Phase treatment will remain blinded until the Core Phase database is locked.

The first dose of study drug will be provided in the clinic at Visit 15 (the day after study completion of the Core Phase), following the first dose monitoring procedures. The first dose monitoring in the Extension Phase must be conducted by the independent first dose administration team and is required for all patients in order to maintain blinding of the Core Phase treatment.

Patients randomized in the Core Phase to receive fingolimod will continue to receive the same dose of fingolimod (A dose increase at Visit 15 is possible if the patient had a sustained increase in weight to >40 kg at two consecutive visits at least three months apart). Patients randomized to receive interferon-β-1a during the Core Phase of the study will be assigned to receive fingolimod (0.5 or 0.25 mg/d based on body weight; the body weight of a patient must be sustained at >40 kg at two consecutive visits at least three months apart for a patient to receive the 0.5 mg/d dose of fingolimod at the start of the Extension Phase).

Visits after Extension Day 1 are scheduled in 2 weeks, 1 month, 2 months, 3 months, 6 months, 9 months, 12 months and then every 6 months for the duration of the Extension Phase.

All patients who prematurely discontinue study drug must complete the end of treatment visit assessments as soon as possible, followed by a 3-month follow-up visit.

Efficacy assessments: MS relapses, MRI, EDSS, Cognitive Testing Battery

Other assessments: Adverse events, physical examination (including skin examination), [redacted] ophthalmologic examination, pulmonary function tests, vital signs, laboratory evaluations, ECG, [redacted]

Data analysis:

The Core Phase primary efficacy variable is the annualized relapse rate (ARR), which will be analyzed using a negative binomial regression model adjusted for treatment, number of relapses in the previous

two years before study enrollment, pubertal status, and region. For the primary analysis, the number of relapses will include all the confirmed relapses experienced during the study. The time spent in the study will correspond to the observation period for all the relapses from first dose on study drug to end of study.

The null hypothesis for the primary analysis states that: there is no reduction in the ARR of patients treated with fingolimod 0.5 mg compared to patients treated with IFN β-1a i.m., while the alternative hypothesis states there is a reduction of the annualized relapse rate (ARR) in the fingolimod treated patients.

The test of the hypotheses will be based on a negative binomial regression model with log link, using treatment, number of relapses in the previous two years before study enrollment, pubertal status, and region as covariates. Study centers are consolidated by country. In order to minimize the impact of low-enrolling countries on the analysis (such as non-convergence of the analysis model), countries will be pooled into regions based on geographical proximity. Details will be provided in the statistical analysis plan prior to database lock.

All patients in the Full Analysis Set (FAS) will be included in the primary analysis, i.e., the number of confirmed relapses observed up to the end of patient's participation in the study. Relapses will be counted regardless of whether a patient is on or off study drug. Therefore it is expected that all randomized patients can contribute to the primary analysis. The primary analysis model adjusts for missing information (early study discontinuations) under some statistical assumptions (non-informative dropouts and constant ARR).

The response variable for this analysis is the number of confirmed relapses for each patient, and the quadratic variance estimate will be used. The natural log of (time in study for each patient) will be used as the offset to account for the varying lengths of patients' time in the study. The null hypothesis will be rejected if the observed p-value is less than the significance level of 0.05.

The Extension Phase is designed to obtain long-term safety, tolerability and efficacy data in patients treated with fingolimod. The study will also examine the safety, tolerability and effectiveness of converting patients from interferon-β-1a treatment in the Core Phase to fingolimod treatment in the Extension Phase.

1 Introduction

1.1 Background

Multiple sclerosis (MS) is a chronic, immune-mediated and demyelinating and likely neurodegenerative disorder of the central nervous system (CNS), characterized by inflammation, demyelination, and axonal/neuronal destruction ultimately leading to severe disability. MS affects up to an estimated 2.5 million individuals worldwide, with females affected 2-3 times as frequently as males. At diagnosis approximately 85% of patients overall have relapsing-remitting MS (RRMS) characterized by recurrent, acute episodes (relapses) of neurological symptoms. Over time patients with RRMS progress to secondary progressive MS, when a less inflammatory, and more neurodegenerative, course takes precedence. 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 relapses or remissions. Progressive relapsing MS (PRMS; chronic progressive from onset with infrequent relapses) is the least frequent form of MS.

The average age of onset of MS is 29 years; with the disease being rare before 16 years of age. The true incidence of pediatric MS is not known, however, it is estimated that around 5% (different estimated range from 0.4 to 10.5%) of MS cases will manifest the disease in childhood and adolescence and that less than 2% will do so before the age of 10 years (Renoux et al. 2007; Pohl et al 2008; Chitnis et al. 2009). As a consequence of the rarity of onset and diagnosis of MS during childhood the population prevalence estimates for pediatric MS are low, ranging from 1.3-2.5/100,000 (Gadoth 2003). Although little prevalence data on pediatric MS exist from formal epidemiological studies, existing surveys support these estimates (De Sa et al 2006; Melcon et al 2008).

As in adults, diagnosis of MS in pediatric patients is made based on clinical and MRI features. There are distinct challenges in the diagnosis of MS in the pediatric population. The higher frequency of acute disseminated encephalomyelitis (ADEM), a disorder whose symptoms can overlap clinically and neuroradiologically with MS, and the increased chance of leukodystrophies and metabolic disorders, complicates the differential diagnosis of pediatric-onset MS relative to adult onset MS (Krupp et al 2007, Venkateswaran and Banwell 2010). According to the consensus definition proposed by the International Pediatric Study Group (Krupp et al 2007), a diagnosis of MS in pediatric patients requires multiple episodes of CNS demyelination separated in time and space, as specified for adults. In the pediatric population, these events must not meet ADEM criteria. In the absence of at least two clinical events, MRI can be used to meet the dissemination in space and time requirements.

There are few studies on the natural history of pediatric onset MS, and most of these studies describe (retrospectively) either single cases or small series. The largest pediatric MS cohort described to date is in 394 patients with disease onset at or before 16 years of age (Renoux et al 2007). The initial course of MS is more often relapsing-remitting in pediatric onset MS (up to 98%) than in adult onset (approximately 85%). The relapse rate in pediatric MS is reported to be higher than in adult onset MS (Trojano et al 2002; Weinshenker et al 1989a; Weinshenker et al 1989b, Yeh et al 2009). Although MRI features in pediatric MS are less

well described, available data show that there are clear similarities to adult onset MS. Children, however, tend to have a higher number of T2 lesions at the time of first event than adults (Waubant et al 2009) and a lower propensity for lesions to enhance with gadolinium (Banwell et al 2007). A consistent finding in most of the pediatric cohort studies is lower disability scores in pediatric MS compared to adult MS, even when disease duration is taken into account. In the cohort described by (Renoux et al 2007), the estimated median times from onset to the assignment of Disability Status Scale (DSS) scores of 4, 6 and 7 were 20 years, 29 years and 37 years, respectively. Compared to the adult-onset population, the time to DSS scores of 4, 6 and 7 were approximately 10 years longer for patients with childhood onset MS. As well, the estimated time to conversion to a secondary progressive course (SPMS) was approximately 10 years longer in childhood onset vs. adult onset MS. Despite this slower progression of disability, the age of conversion to SPMS was lower by approximately 10 years in childhood onset vs. adult-onset MS, such that the life-time impact of pediatric MS exceeds that of adult-onset MS.

As in adults, treatment strategies in pediatric MS are focused on treatment of acute relapses, treatment of MS symptoms, and disease-modification. The effectiveness of therapies used for these purposes have, however, not been demonstrated in pediatric MS populations.

Several disease modifying therapies are available for the treatment of adult patients with relapsing MS (beta interferon, glatiramer acetate, natalizumab, fingolimod) to reduce relapses and, except glatiramer acetate, to slow disability progression. Interferon beta and glatiramer acetate are frequently used to treat pediatric patients with relapsing MS, though none has been studied formally. Based on limited published data, suggesting that the safety profile in adolescents is similar to that seen in adults, three interferon beta agents (two IFN β-1a and one IFN β-1b) were approved in the EU for the use in adolescent patients with relapsing MS aged 12 years and above. There are some reports on the use of natalizumab in pediatric MS patients (Ghezzi et al 2010), but there are safety concerns regarding its use in this population (Yeh and Weinstock-Guttman 2010). There is no experience to date with the use of fingolimod in pediatric MS patients.

Fingolimod in MS

Fingolimod (Gilenya™) is an orally active sphingosine-1 phosphate (S1P) receptors modulator that is approved for use in adults with relapsing MS in more than 55 countries worldwide including the EU and the USA. The approved dose is 0.5 mg per day.

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.

The efficacy of fingolimod has been demonstrated in 3 studies (two 2-year placebo-controlled studies, Study FTY720D2301 and Study FTY720D2309) and 1 active controlled 1-year study (Study FTY720D2302) which evaluated once daily doses of fingolimod 0.5 mg and 1.25 mg in adult patients with relapsing-remitting MS (RRMS). In these studies, fingolimod 0.5 mg demonstrated a reduction of relapse rate by 48% to 54% relative to placebo while also reducing the risk of disability progression by 17% to 30% relative to placebo over 2 years. In addition, fingolimod was superior to one of the currently approved first-line MS therapies (interferon (IFN) β-1a; Avonex®) in reducing the frequency of relapses over 1 year by up to 52%. The clinical benefits of fingolimod were further supported by the efficacy seen on multiple magnetic resonance imaging (MRI) measures, including reducing the numbers of new T2 lesions and Gd-enhancing lesions, the total T2 and T1 lesion burden and increasing the proportions of patients free of new lesion activity. Additionally, treatment with fingolimod was consistently found to reduce brain atrophy, the first prospective demonstration for an approved MS therapy. In the long-term, open-label extension of a Phase II study (FTY720D2201E1), data up to 7 years of exposure showed sustained low levels of MS disease activity as manifest by low relapse rates, low lesion counts on brain MRI and low rate of disability progression.

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

The overall incidence of AEs leading to discontinuation of study drug was comparable for the fingolimod 0.5 mg/day (10.5%) and placebo group (8.7), but higher in fingolimod 1.25 mg/day group (14.1%). The overall incidence of SAEs was comparable between fingolimod groups (11.6% and 10.5% for 1.25 mg/day and 0.5 mg/day, respectively) and placebo (12.2%).

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 and macular edema.

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 ~ 8 bpm and was seen within the first 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 1-2 mmHg diastolic and 2-3 mmHg systolic on average was observed. This onset after approximately 2 months of treatment initiation and persisted with continued treatment but reversed upon cessation of therapy. Hypertension was reported as an adverse event in 6.1% of MS patients on fingolimod 0.5 mg/day and in 3.8 % of patients on placebo in the 2-years placebo controlled study.

Fingolimod treatment led to increases in liver enzymes, (particularly alanine aminotransferase (ALT) and gamma-glutamyl-transferase (GGT), of 3-fold the upper limit of normal range in approximately 9-10% of fingolimod 0.5 mg treated patients, predominantly during the first 6 months, and with a strong male predominance. No cases of liver failure have been reported in over 4000 patients treated in clinical trials with fingolimod. Liver enzymes returned to normal within 6 months after treatment discontinuation. Small increases from baseline in total cholesterol and triglycerides were seen for fingolimod treated patients.

Macular edema occurred in 0.4% of patients treated with fingolimod 0.5 mg/day. Approximately 75% of cases occurred within the first 3-4 months of therapy. The macular edema generally improved or resolved spontaneously after drug discontinuation. 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.

Dose-dependent reductions in forced expiratory volume over 1 second (FEV1) and diffusion lung capacity for carbon monoxide (DLCO) were observed in patients treated with fingolimod. In MS controlled trials, mean reduction from baseline in percentage of predicted FEV1 at Month 1 was 1.89% for fingolimod 0.5 mg and 0.16% for placebo. At Month 24, the reduction from baseline in the percent of predicted values for FEV1 was 2.65% for fingolimod 0.5 mg and 1.24% for placebo. For DLCO, the reductions from baseline in percent of predicted values at Month 24 were 3.29% for fingolimod 0.5 mg and 1.16% for placebo. The changes in FEV1 appear to be reversible after treatment discontinuation. There is insufficient information to determine the reversibility of the decrease of DLCO after drug discontinuation. Cough and dyspnea were the most frequently reported respiratory AEs in the fingolimod 1.25 mg and 0.5 mg groups, but without significant differences between fingolimod patients and placebo [cough 9.1% and 9.6% for fingolimod 1.25 mg and 0.5 mg respectively, placebo 10.4%; dyspnea 7.2% and 6.0% for fingolimod 1.25 mg and 0.5 mg respectively, placebo 6.2%]. Few patients with a history of asthma experienced changes in PFTs to less than 80% or 60% of baseline values at a single visit or 2 consecutive visits. Overall, there was no evidence that patients with a history of asthma were at increased risk of pulmonary function changes amongst the treatment groups.

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. The overall rate of infections (in study D2301 72% on fingolimod vs. 72% on placebo) and serious infections (in study D2301 1.6% on fingolimod vs. 1.9% on placebo) at the 0.5 mg/day dose, fingolimod was similar to placebo. However, lower respiratory tract infections, primarily bronchitis, were more common in fingolimod treated patients (in study D2301 8.0% on fingolimod vs. 3.6% on placebo for bronchitis and 0.5% on vs. 0.2% for pneumonia). There was no clear relationship between lymphocyte count and the incidence of infections on fingolimod treatment. In the clinical trial program, there were 3 cases of disseminated herpes infection with organ involvement other than skin in patients treated with fingolimod 1.25 mg. Two fatal cases: herpes simplex encephalitis in a

patient in whom initiation of acyclovir therapy was delayed by 1 week, and fulminant primary varicella infection with hepatitis in a sero-negative patient receiving concomitant high dose steroid therapy with taper for a MS relapse. The third case was a patient with disseminated herpes zoster with pulmonary involvement treated with fingolimod 1.25 mg who made a complete recovery after treatment with acyclovir therapy. In the post-marketing setting, one additional fatal case of disseminated varicella zoster virus (VZV) infection has been reported in a sero-positive patient treated with fingolimod 0.5 mg in the context of concomitant high dose steroid therapy with taper. Co-administration with a short course of corticosteroid did not increase the overall rate of infection in patients treated with fingolimod in the phase III clinical trials.

In addition, cases of lymphoma (cutaneous T-cell lymphoproliferative disorders or diffuse B-cell lymphoma) have been reported during the clinical studies in patients receiving fingolimod at doses of 0.5 mg or higher. Based on the small number of cases and short duration of exposure, the relationship to fingolimod remains uncertain.

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

Toxicology studies in neonatal and juvenile rats with special emphasis on potential effects on the reproductive system, developing immune system, and neurobehavioral aspects showed that treatment-related effects in neonatal/ juvenile animals were comparable to those seen in adult rats at comparable doses, with the exception of the absence of smooth muscle hypertrophy in the lungs of the juvenile rats. Repeated stimulations with Keyhole Limpet Hemocyanin showed a moderately decreased response during the treatment period, but fully functional immune reactions at the end of an 8-week recovery period. No adverse effects on postnatal development, including behavior and reproductive function were observed (for details on the non-clinical safety program see Investigators' Brochure).

Clinical experience with fingolimod in a pediatric population is limited; a single oral dose study (exposure corresponded to that of 5.0 mg in adults) in 7 renal transplant patients 11-16 years of age. This study showed that pharmacokinetics and pharmacodynamic responses to fingolimod (reduction in lymphocyte counts and in heart rate), were comparable to those seen in adults.

Currently, there is no experience with the use of fingolimod in pediatric MS patients. The present study will evaluate the efficacy and safety of fingolimod in children/adolescents aged 10 to less than 18 years to provide information that will help guide its use in this pediatric population.

1.2 Purpose

The purpose of study is to seek regulatory approval for use of fingolimod in a pediatric population with MS aged 10 to less than 18 years old. This study is conducted in line with the

Pediatric Investigational Plan agreed with the EMA (under EU pediatric regulation (EC) No 1901/2006) and the post-marketing requirements in the US.

2 Study objectives

2.1 Primary objectives: Core Phase

To evaluate the efficacy of fingolimod relative to intramuscular interferon β-1a (IFN β-1a) in reducing the frequency of relapses as assessed by the annualized relapse rate (ARR) in children/adolescent MS patients aged 10 to less than 18 years treated for up to 24 months.

2.2 Secondary objectives: Core Phase

Key secondary

To evaluate the efficacy of fingolimod relative to IFN β-1a in reducing the number of new/newly enlarging T2 (n/neT2) lesions in children/adolescent MS patients aged 10 to less than 18 years treated for up to 24 months.

Other secondary

- To evaluate the safety and tolerability of fingolimod relative to IFN β-1a in children/adolescent MS patients.
- To evaluate the effect of fingolimod relative to IFN β-1a in children/adolescent MS patients on other relapse-related parameters:
  - Time to first relapse
  - Proportion of patients relapse-free
- To evaluate the effect of fingolimod relative to IFN β-1a in children/adolescent MS patients on T1 Gd-enhancing lesions on brain MRI.
- To study the pharmacokinetics of fingolimod and fingolimod-P in children/adolescent MS patients treated for up to 24 months.
- To study the pharmacokinetic/pharmacodynamic relationship for key efficacy and safety outcomes in children/adolescent MS patients treated for up to 24 months.

2.3 Exploratory objectives: Core Phase

- To explore the effects of fingolimod relative to IFN β-1a on other MRI measures including change in total T2 hyperintense and [redacted] lesion volumes, [redacted] and brain volume change in children/adolescent MS patients.
- [redacted]
- [redacted]
- [redacted]

2.4 Objectives: Extension Phase

- To examine long-term safety, tolerability and efficacy parameters in patients treated with fingolimod
- To examine the effects of fingolimod on safety, tolerability and efficacy parameters in patients who were treated with inferferon-β-1a in the Core Phase.
- [redacted]

3 Investigational plan

3.1 Study design

The study is divided into a Core Phase, which includes the Pre-Randomization Period and the Double-Blind Treatment Period, and an Extension Phase in which all patients will be treated with fingolimod.

Core Phase:

The Core Phase is a 24-month, double-blind, randomized, active-controlled, parallel-group multicenter study phase to evaluate the efficacy and safety of fingolimod compared to IFN β-1a in children/adolescent patients aged 10-17 (i.e. have not yet had their 18th birthday at randomization) with MS. The end of the Core Phase of the study will be determined by a blinded sample size re-estimation (BSSR). The study shall maintain the required power of 80% to detect a 50% relative treatment effect on the annualized relapse rate (two-sided 5% alpha-level). Accordingly, Novartis proposes to change the trial design from a fixed 2-year study to an information-based flexible duration design study with study duration of up to 2 years:

[redacted]

After obtaining informed consent, patients will complete the screening and baseline assessments of the pre-randomization period to confirm eligibility for the study. On Day 1, the first visit in the double-blind treatment period, eligible patients will be randomized to one of the two treatment arms (fingolimod or IFN β-1a).

Patients will be required to remain at the site for at least 6 hours after the first dose of study drug (first dose monitoring on Day 1, see Appendix 2).

Post-randomization visits (after Day 1) are scheduled at 2 weeks, 1 month, 2 months, 3 months and then every 3 months during the double-blind treatment period. Additionally, blood sampling for liver function tests will be performed at 6 weeks and at 4 and 5 months.

Blood samples for the purposes of characterizing fingolimod and fingolimod-P pharmacokinetics in the study population will be collected on Day 1 before and approximately 5-6 hours after the first dose of oral study medication, and once at any time at all other visits. The only exception will be the Month 1 visit when two samples will be collected, one at pre-dose (i.e. before the oral capsule administration) and one approximately 5-6 hours post-dose for on-line PK assessment of exposure and determination of need for potential dose-adjustment as described below in Section 3.3.

Patients who prematurely discontinue study drug and remain in the study will be followed in an abbreviated schedule of assessments for the duration of the Core Phase. Upon discontinuation of the study drug, patients must complete the end of treatment visit assessments as soon as possible, followed by a 3-month follow-up visit, before continuing in the abbreviated schedule of assessments.

Patients who complete the double-blind treatment period (on or off study drug) may be eligible to enter a long-term Extension Phase to receive treatment with fingolimod. Patients who complete the double-blind treatment period on study drug, but do not enter the Extension Phase will return for a follow-up visit 3 months after Visit 14/End of Study-Core Phase (CP).

Fingolimod Extension Phase:

The Extension Phase is a 60-month (5 year) study phase for patients who complete the Core Phase of the study and meet all inclusion/exclusion criteria. All patients will be treated with fingolimod (either 0.5 mg/d or 0.25 mg/d based on body weight; see Section 5.1). To comply with local requirements if, in a specific country/site the Extension Phase is not allowed by the Health Authority/IRB then that country/site will not be required to participate in the Extension Phase.

The Core Phase treatment will remain blinded until the Core Phase database is locked.

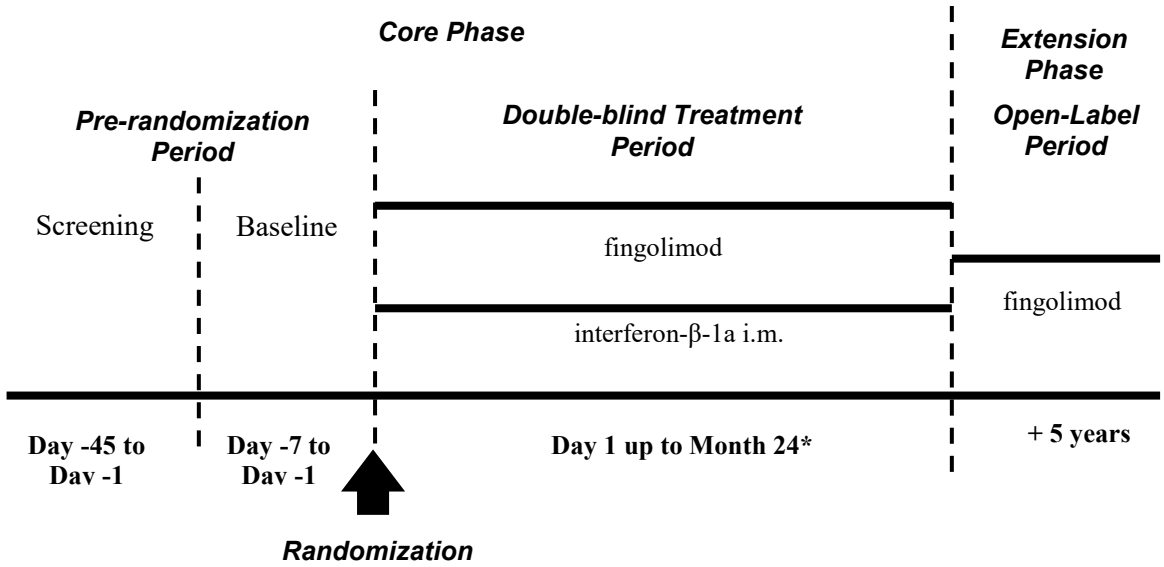
The first dose of study drug will be provided in the clinic at Visit 15 (the day after study completion of the Core Phase), following the first dose monitoring guidelines in Appendix 2. To prevent the risk of unblinding the first dose monitoring procedure for the first/second dose in the Extension Phase must be conducted by the independent first dose administration team and is required for all patients in order to maintain blinding of the Core Phase treatment. Subsequent re-initiation or dose increases in the Extension Phase may be conducted by the main study team.

Patients randomized in the Core Phase to receive fingolimod will continue to receive fingolimod. Patients randomized to receive interferon-β-1a during the Core Phase of the study will be assigned to receive fingolimod (0.5 or 0.25 mg/d based on body weight; see Section 5.1).

Visits after Extension Day 1 are scheduled in 2 weeks, 1 month, 2 months, 3 months, 6 months, 9 months, 12 months and then every 6 months for the duration of the Extension Phase.

All patients who prematurely discontinue study drug must complete the end of treatment visit assessments as soon as possible, followed by a 3-month follow-up visit.

Figure 3-1 Study design



*The 3-MFU visit will be required for those patients that do not go into the Extension Phase.

3.2 Rationale of study design

The Core Phase is designed to evaluate the potential of fingolimod as a treatment for MS in a pediatric patient population. The primary endpoint that will be used is the reduction in the annualized relapse rate (ARR), a widely used and accepted primary endpoint in Phase III studies in the adult population for the evaluation of new MS treatments.

The study uses a double-blind, double-dummy design with IFN β-1a i.m. once weekly as the comparator. A double-dummy design is necessary in order to blind the study drug (oral fingolimod and i.m. injections of IFN β-1a), This means that patients randomized to the fingolimod arm will also receive weekly placebo injections i.m. and patients in the IFN β-1a arm will take once daily oral placebo capsules.

The overall medical care of the patient will be provided by the treating physician ("treating physician") while the assessment of patients with neurological symptoms consistent with MS and the determination of the EDSS score will be performed by a blinded rater ("independent evaluating physician"), who is not otherwise involved in the patient's management or care. Given the well-characterized heart rate lowering effect of fingolimod on treatment initiation, first dose of study drug will be administered by a First Dose Administrator and not by the treating physician (refer to Section 5.5.13). The key secondary outcome, T2 lesion activity, on brain MRI is an objective measure of disease activity. Lesion counts will be established based on review by a central reader who will be blinded to the patients' treatment. These design features further reduce the potential for unblinding and bias in the assessments that may be

introduced by potentially unblinding effects of the study drugs. The measures taken to retain the rater blinding during the study are further detailed in Section 5.4.

The Extension Phase is designed to examine the long-term safety, tolerability and efficacy of fingolimod (up to 7 years for patients randomized to fingolimod in the Core Phase and up to 5 years for patients randomized to interferon-β-1a in the Core Phase) as a treatment for MS in a pediatric/ young adult patient population.

3.3 Rationale of dose/regimen, duration of treatment

The dose regimen has been selected based on the efficacy and safety results of the adult Phase III studies with the aim to yield systemic exposure comparable to that obtained in MS adult patients at the 0.5 mg dose. Based on the adult Phase III PK/PD data, it was shown that exposure levels were the best predictor of efficacy (i.e., reduction in ARR).

Clinical experience with fingolimod in a pediatric population comes from a single dose study in renal transplant patients 11-16 years of age. Administration of a single oral dose of fingolimod scaled for body weight yielded comparable total exposure to fingolimod and fingolimod-P in this group of children/adolescents versus adults receiving a fixed dose of 5.0 mg. As expected from previous clinical experience, pharmacodynamic responses to fingolimod, i.e., reduction in lymphocyte counts and in heart rate, were comparable in children/adolescents and adults.

It is known that cytochrome P450 (CYP450) activity, in children/adolescents aged 10-18 years, is comparable to that of adults (Kearns et al 2003). The relationship between body weight and elimination clearance of fingolimod-P has been investigated by integrating the evidence from two different and independent sources: a single dose PK study in renal transplant patients 11-16 years of age; an analysis of the pooled steady state concentrations from two Phase II and two Phase III studies in adult MS patients with relapsing MS. This analysis indicates that an allometric scaling method based on normalized body weight with an exponent of 0.53 is adequate to describe the relationship between body weight and elimination clearance of fingolimod-P. Using this method, fingolimod-P concentrations as a function of patient weight and dose were simulated and compared to the observed fingolimod-P concentrations from the Phase II/III studies in adult MS patients. The dose regimen yielding systemic exposure comparable to that obtained in MS adult patients was then selected.

Therefore the dose regimen chosen in this study, based on body weight, is:

- 0.5 mg/day for all patients weighing more than 40 kg (at treatment initiation and/or during the study);
- 0.25 mg/day for all patients weighing 40 kg or less. This dose may be increased based on the results of the Month 1 online pharmacokinetic analysis or if the patient has a sustained bodyweight increase to above 40 kg during the study (sustained over at least 2 visits 3 months apart).

This approach is expected to provide exposures considered safe and effective based on data available in adults. The majority of the study population, aged 10 to less than 18 years, is expected to have a bodyweight of at least 30 kg. Children below 20 kg are nonexistent in this age range, children below 25 kg occur with a 5% frequency at an age of 10 years.

All patients weighing 40 kg or less at start of Core and/or Extension Phase will have blood sampling for PK analysis conducted at Month 1 Core Phase and/or Month 1 Extension Phase, respectively. For patients treated with fingolimod, the Month 1 Core Phase and/or Month 1 Extension Phase pharmacokinetic samples will be analyzed as soon as possible (online analysis) to ensure the systemic exposure is adequate (see Section 6.7, online pharmacokinetics, for details). If the systemic exposure is below 65% of the target exposure, the dose for the individual patient will be increased to 0.5 mg at the Month 2 Core Phase and/or Month 2 Extension Phase visits via the Interactive Voice Response system (IVR system). This rapid turnover of the results and fast implementation of a dose adjustment will limit the period of potential under-exposure for the fingolimod-treated patient.

At the Month 2 Core Phase and/or Month 2 of the Extension Phase visit, all patients in the ≤40 kg group will again undergo the first dose monitoring procedure described in Section 3.1 and in Appendix 2.

Patients weighing 40 kg or less who have an increase in body weight over 40 kg, sustained over at least two visits, 3 months apart, will again undergo the first dose monitoring procedure described in Section 3.1 and in Appendix 2.

The flexible treatment duration of up to 24 months for the Core Phase has been chosen to allow for sufficient time to adequately assess the effects on disease activity, as measured by relapses and brain MRI, and to determine the safety and tolerability profile of chronic treatment in the pediatric MS population.

The treatment duration of 60 months (five years) for the Extension Phase is a regulatory requirement and was chosen to allow for adequate time to assess long-term safety, tolerability and look at efficacy parameters in patients treated with fingolimod.

3.4 Rationale for choice of comparator

The use of placebo as a control in the Core Phase of an agent already demonstrated to be effective in adults is for ethical reasons not deemed acceptable in the pediatric MS population (Ghezzi et al 2010, Banwell and Triplett 2005).

IFN β-1a once-weekly i.m. is the active comparator selected for the pediatric study. In the EU, it is approved for use in patients 12 years and older and is also used in younger patients in the absence of an approved treatment. Compared to the other two available IFN β agents, it is associated with less frequent injections, fewer injection site reactions and thus less burden for the patients. Furthermore, IFN β-1a was the active comparator included in the adult fingolimod Phase III program. Use of the same active comparator as in the adult program will allow for comparison of safety and efficacy outcomes in the pediatric population to those in the adults.

3.5 Purpose and timing of interim analyses/design adaptations

Interim analyses for the Data Monitoring Committee (DMC) may be performed (see Section 7.4).

A BSSR will be conducted during the study to provide estimation on ARR and the between-patient variability. The study shall maintain the required power of 80% to detect a 50%

relative treatment effect on the annualized relapse rate (two-sided 5% alpha-level). Accordingly, Novartis proposes to change the trial design from a fixed 2-year study to an information-based flexible duration design study with study duration of up to 2 years:

[redacted]

[redacted]

4 Population

Core Phase:

Male and female patients with multiple sclerosis (MS) aged 10 to less than 18 years will be included in this Core Phase study.

Patients will be recruited into two cohorts based on their puberty status (pre-pubertal, pubertal). The study will be conducted in centers worldwide. Approximately 190 patients will be randomized to receive either fingolimod or IFN β-1a. The maximum treatment duration in the Core Phase will not exceed approximately 2 years. There is no minimum duration for participation in the Core Phase.

Fingolimod Extension Phase:

The population of the Extension Phase will consist of patients who complete the double-blind treatment period on or off of study drug and meet the in/exclusion criteria for enrollment in the Extension Phase. If the study is stopped early then all patients that are enrolled in the Core Phase and that complete the EOS-CP visit will be considered to have completed the Core Phase of the study (see Section 9.6).

- Patients who complete the Core Phase on study drug will be allowed to enter the Extension Phase without any further criteria.
- Patients who complete the Core Phase but prematurely discontinued study drug during the Core Phase for any reason will be assessed for eligibility in the Extension Phase based on the exclusion criteria.

4.1 Inclusion criteria

Core Phase:

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

1. Written informed consent must be obtained before any assessment is performed.

2. Male and female patients aged 10-17 years old*, inclusive (i.e., have not yet had their 18th birthday) at randomization.
3. A diagnosis of MS as defined by the revised consensus definition for pediatric MS, (Krupp et al 2013, Polman et al 2011).
4. Central review of the diagnosis of pediatric MS will be required for all patients prior to randomization.
5. At least one MS relapse/attack during the previous year or two MS relapses in the previous two years prior to screening or evidence of one or more Gd enhancing lesions on MRI within 6 months prior to randomization (including screening MRI).
6. Expanded Disability Status Scale (EDSS) score of 0 to 5.5, inclusive.

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

Fingolimod Extension Phase:

Criterion applies to all patients entering the Extension Phase.

1. Patients that originally met Core Phase Inclusion criteria and completed the Core phase on or off of study drug.

4.2 Exclusion criteria

Core Phase:

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

1. Patients with progressive MS.
2. Patients with an active, chronic disease (or stable but treated with immune therapy) of the immune system other than MS (e.g. Sjögren's disease, systemic lupus erythematosus) or with a known immunodeficiency syndrome (AIDS, hereditary immune deficiency, drug induced immune deficiency) or tested positive for HIV at Screening.
3. Patients with widespread and symmetric white matter alterations in the Screening MRI suggestive of other demyelinating disorders (e.g. metabolic disorders, mitochondrial disorders).
4. Patients meeting the definition of ADEM (Krupp et al. 2013); patients meeting criteria for neuromyelitis optica (Wingerchuk et al 2006) or tested positive for aquaporin 4 (AQP4) at Screening.
5. Patients treated with:
   - Systemic corticosteroids or adrenocorticotropic hormone (ACTH) in the 30 days prior to Screening MRI scan
   - High dose intravenous immunoglobulin within 2 months prior to randomization
   - Natalizumab within 3 months or teriflunomide within 3 ½ months prior to randomization

- Immunosuppressive/immunomodulatory medications such as, azathioprine, methotrexate, laquinimod, ofatumumab, ocrelizumab within 6 months prior to randomization.
- Alemtuzumab, cladribine, cyclophosphamide, mitoxantrone or rituximab at any time
- Fingolimod at any time
- The following antiarrhythmic drugs at Screening: Class Ia (e.g. quinidine, disopyramide) or Class III (e.g. amiodarone, sotalol) anti-arrhythmics
- Concurrently treated with heart-rate-lowering drugs at Screening e.g.: Beta blockers, heart-rate lowering calcium channel blockers (e.g. verapamil, diltiazem or ivabradine), digoxin, anticholinesteratic agents, pilocarpine. Advice from a cardiologist should be sought regarding the switch to non-heart-rate lowering medicinal products.

6. Patients diagnosed with macular edema during the pre-randomization phase
7. Patients with active systemic bacterial, viral or fungal infections, including tuberculosis.
8. Patients without acceptable evidence of immunity to varicella-zoster virus, mumps, measles, rubella, diphtheria, tetanus and pertussis at Randomization (See Appendix 3 Guidance on vaccinations for guidance on acceptable evidence of immunity and requirements for serologic testing).
9. Patients who have received any live or live attenuated vaccines (including for varicella-zoster virus or measles) within one month prior to randomization.
10. Patients with a history or presence of malignancy.
11. Patients with any medically unstable condition, as assessed by the investigator.
12. Patients with any severe cardiac disease or significant findings on the screening ECG, such as:
    - History of symptomatic bradycardia or recurrent syncope
    - Known ischaemic heart disease
    - History of congenital heart disease (except conditions such as small patent ductus arteriosus, atrial septal defect, ventricular septal defect, or an ECG or rhythm abnormality, which have been assessed by a pediatric cardiologist and considered to be clinically insignificant).
    - Cerebrovascular disease
    - History of myocardial infarction
    - Congestive heart failure
    - History of cardiac arrest
    - Uncontrolled hypertension despite prescribed medications
    - Resting (sitting) heart rate <55 bpm (in patients 12 years or older) and <60 bpm (in patients below 12 years)
    - Severe untreated sleep apnea
    - Sick sinus syndrome or sino-atrial heart block
    - QTcF interval >450 msec in males and >460 msec in females or relevant risk factors for QT prolongation (e.g. hypokalaemia, hypomagnesemia, congenital QT

prolongation) or treatment with QT prolonging drugs with a known risk of Torsades de pointes (e.g. citalopram, chlorpromazine, haloperidol, methadone, erythromycin) or history of familial long QT syndrome or known family history of Torsades de Pointes.

- Second degree Mobitz type II or higher AV block

13. Patients with any pulmonary conditions, as determined by the investigator, including severe asthma defined as per the 2010 WHO uniform definition on severe asthma (Bousquet et al 2010).
14. Positive results of screening period testing for serological markers for hepatitis A, B, C and E indicating acute or chronic infection:
    - anti-HAV IgM
    - HBs Ag and/or anti-HBc IgM
    - anti-HCV IgG or HCV-RNA PCR
    - anti- HEV IgM or IgG (if positive IgG: do HEV-RNA PCR: if negative, patient can be included)
15. Patients with any of the following hepatic conditions:
    - Chronic liver or biliary disease, acute or chronic pancreatitis, with the exception of Gilbert's syndrome;
    - Liver enzymes
        - ALT, AST, alkaline phosphatase, GGT, >2 x upper limit of normal (ULN) range for age (for pre-pubertal patients > 1 X ULN or > 2X ULN if currently treated with IFN or glatiramer acetate). Elevations of alkaline phosphatase should not be used in isolation to exclude subjects, and would require Investigator discretion.
        - Bilirubin elevations not in the context of Gilberts Syndrome: Total and conjugated bilirubin >1.5 X ULN (for pre-pubertal patients >1 X ULN or > 1.5 X ULN if currently treated with IFN or glatiramer acetate).
16. Patients with severe renal insufficiency (GFR <30 ml/min/1.73 m^2).
17. Patients with lymphocyte count < 800 cells (mm^3).
18. Patients with any of the following neurologic/psychiatric disorder:
    - History of any type of epileptic seizure(s) as well as psychogenic non-epileptic seizure(s) during the past 12 months before screening;
    - History of substance abuse (drug or alcohol) or any other factor (i.e., serious psychiatric condition) that may interfere with the subject's ability to cooperate and comply with the study procedures;
    - Progressive neurological disorder, other than MS, which may affect participation in the study or require the use of medications not allowed by the protocol
19. Patients unable to undergo MRI scans, including claustrophobia or history of hypersensitivity to gadolinium-DTPA.
20. Pregnant or nursing females, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive HCG laboratory test.

21. Female patients of childbearing potential, defined as all females physiologically capable of becoming pregnant, unless they agree to abstinence or, if sexually active, the use of contraception as defined in Section 6.6.
22. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes.
23. Patients with a score of "yes" on item 4 or 5 of the Suicidal Ideation section of the C-SSRS, if this ideation occurred in the past 6 months, or with a score of "yes" on any item of the Suicidal Behavior section, except for "Non-Suicidal Self Injurious Behavior", if this behavior occurred in the past 2 years.
24. Patients who have received an investigational drug or therapy within 180 days or 5 half-lives of randomization, whichever is longer.

    No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

Fingolimod Extension Phase:

Criteria apply to patients who completed the Core Phase, but prematurely discontinued study drug.

1. Premature discontinuation of the study drug during the Core Phase due to:
   - an adverse event,
   - serious adverse event,
   - laboratory abnormality
   - other conditions leading to permanent study drug discontinuation due to safety reasons as described in protocol Section 5.5.9.

   Note: If a patient was discontinued due to lack of efficacy in the Core Phase, the patient may be offered the option to enter the extension trial if the investigator determines it is in the patient's best interest when considering all available treatment options.
2. Patients with known new events or concomitant medications (washout periods required prior to Visit 15) that would exclude them from the Core Phase exclusion criteria. Serological or other additional tests will not be required.

5 Treatment

5.1 Investigational and control treatment

Investigational drug: Core Phase and Fingolimod Extension Phase

Two dose-strengths will be used (depending on the patients' body weight) with the aim to achieve systemic exposure in the pediatric population that is comparable to that obtained in MS adult patients at the 0.5 mg dose:

- Fingolimod 0.5 mg capsule, administration orally once daily in patients weighing more than 40 kg

- Fingolimod 0.25 mg capsule, administration orally once daily in patients weighing 40 kg or less (patients weighing ≤ 40 kg at the start of the Extension Phase will receive the 0.5 mg/d dose if they had a dose increase at Month 2 during the Core Phase)

Dose adjustments to ensure exposure is appropriate may be implemented in patients with a body weight 40 kg or less based on online PK assessment (see Section 3.3). During the course of the study any patient receiving the lower fingolimod dose of 0.25 mg who reaches the weight of more than 40 kg (sustained over at least 2 visits, 3 months apart), will be automatically switched to the 0.5 mg dose strength. Dose adjustments for any other reason are not permitted. Patients in the IFN β-1a arm whose bodyweight increases to above 40 kg during the Core Phase (sustained over at least 2 visits, 3 months apart), will have a sham increase in their oral dose. The dose increases will be done in a blinded fashion (refer to Section 3.3).

Oral study drug may be taken with or without food, preferably at the same time every day.

Study medication will be dispensed at the randomization visit (Day 1).

Control treatment: Core Phase

Interferon β-1a (Avonex®), administration intramuscular (i.m.) injection once weekly

The first dose of IFN β-1a i.m. at Day 1 will be administered intramuscularly at the site by the First Dose Administrator or nurse. Site personnel will provide training to the patients and their parents/caregivers on the correct procedure for administration of i.m. injections. A patient leaflet and/or oral instructions will be provided. The patient leaflet and/or oral instructions describe information related to the i.m. study drug including storage information, precautions and instructions for administering i.m. injections. This information should be reviewed with the patient and his/her parents/caregivers to ensure that they understand the correct procedure.

Injectable study drug may be initiated at ¼ or ½ volume per clinical practice at the individual sites. Full dose should, however, be achieved by the fourth week of injections. Prophylaxis and treatment of flu-like symptoms with e.g. paracetamol/acetaminophen may be performed per clinical practice at the site.

Matching placebo capsules and syringes: Core Phase

- Matching fingolimod placebo capsules for oral administration once daily.
- Matching IFN β-1a placebo in pre-filled syringes for i.m. injection once weekly.

The fingolimod capsules (0.25 mg and 0.5 mg) and matching placebo capsules will be identical in appearance and will be packed in identical bottles. Both, the IFN β-1a and its matching placebo will be packed and supplied in pre-filled syringes.

5.2 Treatment arms

Core Phase:

Randomized patients will be assigned to fingolimod + matching IFN placebo injection or IFN β-1a injection + matching fingolimod placebo capsule in a ratio of 1:1.

Fingolimod Extension Phase:

All patients will receive fingolimod in the Extension Phase.

5.3 Treatment assignment

Core Phase:

At Visit 3, all eligible patients will be randomized via Interactive Voice Response (IVR) system to one of the two treatment arms. The investigator or his/her delegate will contact the IVR system after confirming that the patient fulfills all the inclusion/exclusion criteria. The IVR system will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study drug to be dispensed to the patient. The randomization number will not be communicated to the caller.

Fingolimod Extension Phase:

At Visit 15 (first Extension Phase visit), all eligible patients will be assigned via Interactive Voice Response (IVR) system to receive either 0.25 mg/d or 0.5 mg/d fingolimod.

Patients randomized in the Core Phase to receive fingolimod will continue to receive the same dose of fingolimod that they were receiving at Visit 14 / EOS-CP (End of Core Phase treatment) Note: A dose increase at Visit 15 is possible if the patient had a sustained increase in weight to >40 kg at two consecutive visits at least three months apart.

Patients randomized to receive interferon-β-1a during the Core Phase of the study will be assigned to receive fingolimod (0.5 or 0.25 mg/d based on body weight as described in Section 5.1. Note: The body weight of a patient must be sustained at >40 kg at two consecutive visits at least three months apart for a patient to receive the 0.5 mg/d dose of fingolimod at the start of the Extension Phase.

The randomization numbers for the Core Phase will be generated using the following procedure to ensure that treatment assignment is unbiased. A patient randomization list will be produced by the IVR system provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to study drug packs containing each of the study drugs.

Randomization will be stratified by region, due to the anticipated low number of patients that will be enrolled at each site, and by puberty status (pre-pubertal and pubertal).

The randomization scheme for patients will be reviewed and approved by a member of the Biostatistics Quality Assurance Group.

5.4 Treatment blinding

Core Phase:

This study will be conducted using a double-blind, double dummy design.

Patients randomized to one of the two treatment groups will be given the following medications:

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

IFN β-1a Group: IFN β-1a 30 µg i.m. injection once weekly +
fingolimod matching placebo capsule orally once daily

The study medication assignments will be blinded and will remain blinded for the entire double-blind Treatment Period and until the database lock for the Core Phase has been completed.

Patients, treating physician, site personnel, independent evaluating physician, First Dose Administrator and all Novartis personnel, involved in the study, with the exception of Novartis Drug Supply Management (DSM), Novartis on-line PK analyst, Novartis independent statistician and independent programmer for DMC, will remain blinded to the identity of the treatment from the time of randomization of the first patient until database lock. During this time period, the treatment codes will be accessible only to authorized personnel (those mentioned above and DMC members). The following measures will be taken to protect the blinding of the Independent Evaluating Physician ("rater"):

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

Fingolimod Extension Phase:

All patients in the Extension Phase will be treated with fingolimod, but the dose they received during the Core Phase (interferon or fingolimod) will remain blinded until the Core Phase database has been locked.

For any patient that is ≤ 40 kg at the start of the Core Phase the Extension Phase dose of fingolimod will remain blinded if the patient did not have a dose increase during the Core Phase due to sustained body weight increase to >40 kg at two consecutive visits at least 3 months apart . For these patients the Extension Phase dose will remain blinded until the Core Phase database lock or until the patient has a dose increase to 0.5 mg (increase in body weight to >40 kg sustained at 2 consecutive visits at least 3 months apart). This blinding is required in

order to maintain the blind of the Core Phase medication as some patients' may have had a dose increase during the Core Phase at the Month 2 visit based on the online PK results.

5.5 Treating the patient

5.5.1 Patient numbering

Each patient is uniquely identified in the study by a combination of his/her center number and patient number. The center number is assigned by Novartis to the investigative site. Upon signing the informed consent form, the patient is assigned a patient number by the investigator. At each site, the first patient is assigned patient number 1, and subsequent patients are assigned consecutive numbers (e.g. the second patient is assigned patient number 2, the third patient is assigned patient number 3). The investigator or his/her staff will contact the IVR system and provide the requested identifying information for the patient to register them into the IVR system. For studies using eCRFs, only the assigned patient number should be entered in the field labeled "Patient ID" on the electronic data capture (EDC) data entry screen (e.g. enter '1', '2', etc.). Once assigned to a patient, the patient number will not be reused. If the patient fails to be randomized for any reason, the IVR system must be notified within 2 days that the patient was not randomized. The reason for not being randomized will be entered on the Screening Log, and the Demography eCRF should also be completed. The patient will retain the same number throughout the Core and Extension Phase.

5.5.2 Dispensing the study treatment

Each study site will be supplied by Novartis with study drug.

The study drug packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the 2 treatment arms. Investigator staff will identify the study drug package(s) to dispense to the patient by contacting the IVR system and obtaining the medication number(s). Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique patient number.

5.5.3 Supply, storage and tracking of study treatment

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

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

The investigator must maintain an accurate record of the shipment and dispensing of study drug in a drug accountability ledger. Monitoring of drug accountability will be performed by the field monitor during site visits and at the completion of the trial. Patients will be asked to

return all unused study drug and packaging at the end of the study or at the time of study drug discontinuation.

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

5.5.4 Instructions for prescribing and taking study treatment

The study medication (fingolimod + matching placebo syringes or IFN β-1a + matching placebo capsules) will be dispensed starting at the Randomization Visit (Visit 3). Drug will then be dispensed at scheduled visits throughout the double-blind treatment period and Extension Phase according to Table 6-1 and Table 6-3.

Oral capsules (fingolimod or matching placebo) must be taken once a day, preferably at the same time every day, with or without food. Injectable study drug (IFN β-1a or matching placebo) must be injected intramuscularly (i.m.) once a week. Site personnel will provide training to the patients and their parents/caregivers on the correct procedure for administration of intramuscular injections. A patient leaflet and/or oral instructions will be provided. The patient leaflet describes information related to the IFN β-1a i.m. study drug including storage information, precautions and instructions for administering i.m. injections. This information should be reviewed with the patient and his/her parents/caregivers to ensure that they understand the correct procedure.

The first dose of the study drug (oral capsule and i.m. injection) at Visit 3 (Day 1), Visit 6 (Month 2, for patients ≤40 kg), Visit 15 (First dose in Extension Phase) and at Visit 18 (Month 2 of Extension Phase, for patients ≤40 kg) must be taken at the clinic. All patients will need to be monitored in the clinic for at least 6 hours or longer if discharge criteria are not met (see Appendix 2 for Guidance for monitoring of patients taking their first dose of the study drug). Subsequent doses can be taken at home, unless Day 2 monitoring is required as per Appendix 2.

For any patient that has been off oral study drug under the following durations:

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

The first dose of study drug administered either at the Randomization visit (Day 1, Visit 3) or after an interruption of treatment in the Core Phase must be administered in the clinic under the supervision of the independent first dose administrator.

Study medication must also be administered by the independent first dose administrator for the first dose visit in the Extension Phase (Visit 15). First dose monitoring will be required for study drug interruptions in the Extension Phase, but the 6 hour monitoring does not need to be conducted by the independent first dose administrator.

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

Throughout the study careful planning of patient visits is required to make sure that a patient will have enough study drug to last until the next scheduled visit. Particular care in planning of patient visits is required for the transition between the Core Phase and Extension Phase. The EOS-CP and first Extension Phase visit need to be scheduled to ensure that the patient has enough study drug to complete the Core Phase of the study and enter the Extension Phase without study drug interruption.

At the completion of the Core Phase (Visit 14/EOS-CP), after the patient takes the last dose of study drug in the Core Phase, the site will contact IVR to change the status of the patient to completed. No study drug will be dispensed at Visit 14/EOS-CP. At Visit 15 the site will need to call the IVR system to enroll the patient into the Extension Phase and to dispense study drug.

The investigator and/or study personnel should promote compliance by instructing the patient and his/her parents/caregivers to take the study drug exactly as prescribed and by stating that compliance is necessary for the patient's safety and validity of the study. The patient and his/her parent/caregiver should be instructed to contact the site if he/she is unable to take the study drug as prescribed for any reason. As a measure of compliance, all remaining capsules/unused syringes must be returned to the site at each visit for counting. The counts will be recorded in the eCRF.

All dosages prescribed and dispensed to the patient and all dose changes during the study will be recorded in the IVR system and Drug Administration Record in the eCRF.

5.5.5 Permitted dose adjustments and interruptions of study treatment

With the exception of the dose adjustments described in Section 5.1, study drug dose adjustments for any other reason are not permitted.

Conditions/events that may lead to the study drug interruptions based on investigator judgment and overall clinical assessment:

- reported serious adverse event;

- emergency medical condition, unplanned hospitalization, involving use of excluded concomitant medications;
- abnormal laboratory value(s) or abnormal test or examination result(s) (e.g. PFT, ECG, ophthalmic findings etc.);
- hypersensitivity to the study medication;
- patient's non-compliance.

Should the patient interrupt the study drug, both oral capsule and i.m. study drug must be interrupted. Should the investigator decide in agreement with the sponsor to re-initiate treatment with study drug, depending on the duration of the interruption, the first dose intake at re-start may need to take place at the study site to ensure at least 6-hour monitoring by the First Dose Administrator in a similar manner as the first intake of the study medication (Section 5.5.4 and Appendix 2). When re-starting study drug, monitoring (as for first dose) is mandatory in the following cases:

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

If study drug is interrupted for more than 2 weeks after the first month of treatment the effects on heart rate and atrio-ventricular conduction may recur on reintroduction of treatment and thus, for study drug interruption of this duration, the same procedures as for initial dosing will apply.

Re-start decision should be made on a case-by-case basis. A reason for the interruption of treatment and time of interruption should be appropriately documented in the source documents as well as in the Dosage Administration Record eCRF.

5.5.6 Recommendations for the treatment of MS relapses

MS relapses may be treated as follows:

A standard short course of corticosteroids (methylprednisolone) on an inpatient or outpatient basis is allowed for treatment of relapses as clinically warranted. Steroid treatment should consist of 20-30 mg/kg/day or up to a maximum of 1,000 mg methylprednisolone i.v. for 3-5 days (Kuntz et al 2010). Standard of care will be followed during treatment. Taper with oral steroids is not permitted.

The use of steroid therapy for the treatment of MS relapse must be recorded on the steroid specific eCRF.

Investigators should consider the added immunosuppressive effects of corticosteroid therapy and increase vigilance regarding infections during such treatment and in the weeks following administration. Should a patient show evidence or suspicion of infection, please refer to the Guidance on monitoring of patients with infections outlined in Appendix 3.

In the event that steroids are administered, patients and their parents/caregivers should be reminded of the importance of reporting any signs or symptoms of an infection. Special

consideration should be given to symptoms or signs of herpes simplex or zoster reactivation (e.g. lancinating pain, skin lesions). Appropriate therapy should be promptly initiated and patients should be closely followed up as clinically warranted. An infectious disease specialist may be consulted to guide such therapy if needed.

Should a patient develop any symptom or signs, unexpected for MS in the opinion of the investigator or accelerated neurological deterioration, the investigator should immediately schedule an MRI and follow Guidance on monitoring of patients with symptoms or signs or neurological deterioration inconsistent with MS outlined in Appendix 3.

5.5.7 Concomitant treatment

The investigator should instruct the patients and their parents/caregivers to notify the study site about any new medications he/she takes after the start of the study drug. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug must be listed on the Concomitant medications/Significant non-drug therapies after start of study drug eCRF.

The investigator should instruct the patient and his/her parents/caregivers to notify the study site about any new medications he/she takes after the start of the study drug. All medications and significant non-drug therapies (including physical therapy) administered after the patient starts treatment with study drug must be listed on the Concomitant medications/Significant non-drug therapies after start of study drug eCRF.

Patients with pre-existing dimethyl fumarate, IFN β or glatiramer acetate at Screening may continue drug intake up to the day before Day 1 of the study (i.e. there is no need for a washout period). There is also no washout period required for these drugs for enrollment in the Extension Phase for patients' that discontinued study drug during the Core Phase and were treatment with these agents.

Concomitant use of ketoconazole in patients treated with fingolimod may lead to an increase in fingolimod plasma concentrations. Patients who initiate ketoconazole during the study should be informed and the investigator should be vigilant as these patients may be at a higher risk of adverse events.

Special consideration should be given towards chronic treatment with medication which has a hepatotoxic potential and the investigator should be vigilant as these patients may be at a higher risk of liver adverse events.

Use of the treatments to manage potential bradycardia after first dose administration is allowed. For recommendations on the management of bradycardia, refer to Appendix 2.

5.5.8 Prohibited treatment

Patients who have met exclusion criteria for exclusionary medications will not be allowed to join the study. Once the patient has entered the study at Visit 3 and while the patient is on therapy, use of the following treatments are NOT allowed concomitantly with the study drug:

- Immunosuppressive medication (e.g. cyclosporine, azathioprine, methotrexate, cyclophosphamide, mitoxantrone, cladribine, rituximab, alemtuzumab);

- Other concomitant medications: immunoglobulins, monoclonal antibodies (including natalizumab), IFN ß, glatiramer acetate, teriflunomide, dimethyl fumarate, adrenocorticotropic hormone (ACTH).
- Class Ia (e.g. quinidine, disopyramide) or Class III (e.g. amiodarone, sotalol) anti-arrhythmics
- Heart-rate-lowering drugs (e.g.: Beta blockers); heart-rate lowering calcium channel blockers (e.g. verapamil, diltiazem or ivabradine)
- Digoxin, anticholinesteratic agents, pilocarpine

Careful planning is required if these medications are taken during the Core Phase (after the patient discontinued study drug treatment) then the patient must meet the washout exclusion criteria for these medications before entry into the Extension Phase. Washout of these medications must occur with adequate time to complete the full washout period prior to enrollment in the Extension Phase at Visit 15.

The administration of any live or live attenuated vaccine is prohibited while patients are receiving study drug and for 2 months after last dose of study drug.

5.5.9 Discontinuation of study treatment and premature patient withdrawal

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

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

Study drug must be discontinued for a given patient if the investigator determines that continuing it would result in a significant risk for that patient. The following conditions/events may be considered sufficient to support a decision about the study drug discontinuation in individual cases:

- Serious adverse event (e.g. diagnosed malignancy)
- Abnormal laboratory value(s) or abnormal test result(s); see below and Appendix 3 for guidance for safety monitoring
- Sexual activity in girls who do not agree to the use of contraception as defined in Section 6.6
- Use of prohibited medications (Section 5.5.8)
- Adverse events
- Protocol deviation
- Unsatisfactory therapeutic effect
- Patient's condition no longer requires study treatment
- Administrative problems (e.g. patient's non-compliance)

The following conditions must result in permanent study drug discontinuation:

- Hepatic (Appendix 3: Section 15.2)
  - Increase in ALT or AST >8 x ULN (with confirmed value on a repeat lab within 48 hours) or
  - "Hy's law" criterion is met or
  - The occurrence of new elevations greater than 5 X the ULN for ALT/AST in patients where study drug was re-initiated after drug stoppage for liver enzyme elevations.
- Ophthalmic (Appendix 3: Section 15.8)
  - Diagnosis of macular edema.
  - If systemic immunosuppressive treatment (other than corticosteroids) is required for treatment of uveitis.
- First/Redose Criteria (Appendix 2)
  - Any hemodynamically compromising cardiac arrhythmias.
  - Patients who meet the criteria requiring overnight hospitalization again on Day 2.
- ECG abnormalities (all visits including first/redose)
  - Absolute QTcF $\geq$ 500 msec, confirmed by repeat ECG measurements (within 24 hours).
  - New complete heart block (third degree AV block) or second degree AV block Mobitz type II.
- ECG abnormalities (non-first/redose visits)
  - Resting heart rate < 40 or > 120 bpm observed after 1st dose monitoring and confirmed on repeat measure.
  - Increase in QRS duration > 25% from Baseline (Day 1 pre-dose) observed after 1st dose monitoring and confirmed on repeat ECG measure (within 24 hours).
- Pregnancy
- Withdrawal of consent

Patients who discontinue study drug should not be considered withdrawn from the study, unless one of the reasons listed above for study withdrawal are met. Patients who discontinue the study drug should be treated according to the best standard of care and followed as indicated in Table 6-2.

A Study Drug Discontinuation eCRF should be completed, giving the date and primary reason for stopping the study drug.

5.5.10 Study completion and post-study treatment

The Core Phase will be considered completed for an individual patient when he/she completes the double-blind treatment period (up to Month 24 or earlier in case the Core Phase ends once 80% power has been obtained to detect a 50% difference for the primary endpoint (see Section 9.6), or in case of premature study discontinuation. A subset of patients may not have completed the full 3M FU data by the time of database lock for the Core Phase CSR; however this information will be reported in the Extension Phase CSR).

The results of the Core Phase and Extension Phase will be summarized and written in separate documents.

The Extension Phase will be considered completed for an individual patient when he/she completes the extension phase (Month 60 of Extension Phase [EOS visit], including any required 3 month follow-up visits or earlier in case of premature study discontinuation).

5.5.11 Early study termination

The study (overall study or just Core or Extension Phase**)** can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated as described in Section 6 for a prematurely withdrawn patient. If the Core Phase of the study is terminated then the patient may be eligible for participation in the Extension Phase if they satisfy the inclusion/exclusion criteria. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

5.5.12 Emergency breaking of assigned treatment code

Emergency treatment code breaks should only be undertaken when it is essential to treat the patient safely and efficaciously. Most often, investigational treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IVR System. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the Global Trial Lead (GTL) that the code has been broken.

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

5.5.13 Role of site personnel

In order to facilitate the required study contact at each investigational site, it is essential that the Primary Investigator will assign the following site personnel:

- Primary Treating Physician, a pediatrician specialized in neurology or a neurologist experienced in treating pediatric MS patients. The Primary Investigator usually serves as the Primary Treating Physician;
- Independent Evaluating Physician, a neurologist (experienced with assessing pediatric MS patients) not involved in the clinical care and management of the study patients;

- Pediatrician (unless the Primary Treating Physician is a pediatrician)
- Primary treating Nurse/Study Coordinator
- First Dose Administrator
- MRI technician
- Neuroradiologist
- Ophthalmologist
- Pulmonary function test (PFT) laboratory technician

Where specified, evaluations described in the protocol must be performed only by the personnel indicated.

Primary Treating Physician

The primary treating physician will be responsible for:

- Overall conduct of the study at the study site
- Management of the routine clinical care of the study patients
- Confirmation of patient's eligibility for randomization
- Assessment and treatment of adverse events and MS relapses
- Referral of patients with neurological symptoms consistent with MS relapse to the Independent Evaluating Physician for EDSS
- Monitoring of adverse events in subjects who have permanently discontinued study drug
- Ensuring that all treating site personnel are informed of concomitant medications excluded per protocol (e.g. the use of steroids other than for the treatment of MS relapses)
- Ensuring that the need for increased vigilance regarding infections during and in the weeks following administration of corticosteroids is explained to the patients and his/her parent/caregiver

It is strongly recommended that the Primary Treating Physician remains unchanged throughout the entire course of the study. Occasionally, the Primary Treating Physician may designate other medical personnel (i.e., a back-up physician or nurse) at the study site to perform some of the tests and evaluations listed above.

Independent Evaluating Physician: Required for Core Phase only

The Independent Evaluating Physician will be responsible for:

- Assessing patients with neurological symptoms consistent with MS relapse (as referred by the Primary Treating Physician) and obtaining an EDSS score needed for relapse confirmation.
- Obtaining an EDSS score based on detailed neurological examinations as per Table 6-1 or Table 6-2.

The Independent Evaluating Physician must not be involved in any other aspect of the patient's care and/or management.

To ensure consistency across sites, the Independent Evaluating Physician must participate in the standardized training session on EDSS scoring (unless already certified at required level in past 12 months) prior to enrollment of subjects at their site. Re-certification will be required annually.

The communication of new findings on the neurological examination from the Independent Evaluating Physician to the Primary Treating Physician is permitted. The roles of the Primary Treating Physician and the Independent Evaluating Physician, including their back-ups, are not interchangeable. The Independent Evaluating Physician must remain blinded to adverse events, concomitant medications, laboratory data and any other data that have the potential of revealing the treatment assignment. The patients and his/her parent/caregiver should be instructed to take care not to reveal the patient's treatment to the Independent Evaluating Physician.

It is strongly recommended that the Independent Evaluating Physician remains unchanged throughout the entire course of the study.

Pediatrician

The pediatrician will be responsible for:

- Serving as a consultant to the Primary Treating Physician for management of the routine care of the patient
- Guiding the assessment of the pubertal changes according to the Tanner stages, as well as bone age as applicable, refer to Section 6.5.5). These assessments may also be conducted by other health care professionals experienced with these assessments.
- Perform a skin examination at Screening and end of study (if not performed by a dermatologist, Section 6.5.1)

Primary Treating Nurse/Study Coordinator

The Treating Nurse/Study Coordinator will be responsible for:

- Assisting the primary treating physician in patient management, including the assessment and treatment of adverse events and disease relapses and the recording of adverse events, concomitant medications and monitoring of compliance (returned capsule and syringe counts)
- Scheduling visits and assessments as outlined in the protocol, maintaining proper source documentation and transcription of the data to the eCRFs
- Coordination with and between the study selected central labs, drawing and processing lab samples
- Assisting patients in the completion of questionnaires

First-dose Administrator

The First-dose Administrator will:

- Ensure that facilities for monitoring and treatment of symptomatic bradycardia are available if needed

  - Monitor1st dose intake of the assigned study medication, and if applicable monitor, at protocol required re-start or at oral dose increase according to the procedure outlined in Appendix 2. Administer first i.m. injection (IFN or dummy placebo).
- Review vital signs and ECG at 6 hours post-dose administration and make a decision regarding patients' eligibility for discharge as described in Appendix 2.
- Clinically monitor the patient for at least 6 hours post-dose, record vital signs, ECG findings, bradycardia events occurring post 1st dose administration. All other adverse events should be reported to the primary treating physician.
- Monitor the patient beyond 6 hours, if indicated (if discharge criteria are not met at 6 hours post-dose and prolonged monitoring is required)
- Determine whether the 2nd dose should also be administered in the clinic on the next day.
- Provide written instructions to the patient upon discharge with contact information for emergencies, instruct the patient to avoid driving by himself/ herself on the day of discharge
- Ensure that the patient or primary treating physician/nurse do not have access to or are informed of vital signs values to avoid unblinding of the patient or site personnel, unless it is medically warranted
- Maintain and ensure accuracy of completeness of eCRFs during 1st dose monitoring and transferring them directly to the Data Management (care must be taken to ensure that this data remains blinded from the site personnel)

The First-dose Administrator can be supported by a nurse or other health care professional as appropriate (not otherwise involved in the patient care).

MRI technician

An MRI technician will be responsible for:

- Familiarization with the MRI manual procedures and the study specific MRI protocol
- Performance of a "dry" or "dummy" run using the MRI parameters outlined by the MRI protocol
- Accommodation of patients for the MRI scan as per request of the treating nurse and performance of high-quality MRI scans using the study specific parameters stored in the designated MRI scanner for the duration of the study
- Submission of the MRIs in the appropriate format to the central MRI reader immediately upon completion

Neuroradiologist

A neuroradiologist will be responsible for:

- Previewing each MRI scan performed for the study patients
- Contacting the Primary Treating Physician in case of unexpected findings detected on the MRI scan

Ophthalmologist

- The Ophthalmologist will perform the ophthalmic examinations as per protocol

Pulmonary Function Test Laboratory Technician

- Pulmonary function test (PFT) technician will perform PFTs per local standard practice for pediatric patients

6 Visit schedule and assessments

The Core Phase will consist of two periods: a pre-randomization period consisting of screening and baseline visits, and a double-blind treatment period. The Extension Phase consists of a fingolimod treatment period.

The day of randomization in the Core Phase is defined as Day 1 of the study (Visit 3), which is the first day of study drug administration. Entry in the Extension Phase occurs at Visit 15 immediately following the completion of the Core Phase.

Table 6-1, Table 6-2 and Table 6-3 lists all assessments and indicates with an "X" the visits when they are performed.

Patients should follow the visit schedule with an allowed visit window as follows:

- ± 2 days for Visit 4 and Visit 16
- ± 5 days for Visit 5 and all monthly visits
- ± 10 days for all quarterly and biannual visits
- + 14 days for Visit 15 (should be completed within 14 days of completion of Visit 14 / EOS-CP). Date of completion of Core Phase should be entered in the Study phase completion eCRF (date entered should be 1 day before Visit 15; first Extension Phase visit). Study drug should not be interrupted between the end of the Core Phase and the start of the Extension Phase.

Visit windows can be extended on a case-by-case basis to accommodate scheduling (please consult Sponsor for approval). The pre-randomization period may be extended with approval from the sponsor on a case by case basis to accommodate additional time needed to complete the screening assessments (e.g., additional lab tests, time to be (re)vaccinated, time to allow lab parameters to come within protocol requirements, etc.).

In addition to the scheduled visits, patients may have unscheduled visits following an onset of an MS relapse or for safety follow-up.

Patients who prematurely discontinue study drug during the Core Phase should be encouraged to remain in the study. Patients who prematurely withdraw (PPW – Premature Patient Withdrawal) from the study for any reason should be scheduled for a final Visit 14 (EOS-CP) assessment at the time of discontinuation from study drug as outlined in Table 6-1). A follow-up visit should then be scheduled three months after the last dose of the study drug. If the patient is unable to return to the site for the Visit 14 / EOS-CP assessments, every effort should be made to contact the patient by telephone for safety evaluations during the 3 months

following the last dose of study drug, including a final contact at the 90-day point (3-month follow up).

Patients who prematurely discontinue study drug (SDD) during the Core Phase, and remain in the study will follow an abbreviated schedule of assessments (see Table 6-2). At the time of SDD, patients must complete the Visit 14 / EOS-CP assessments (as end of treatment assessments), followed by a 3-month follow-up visit prior to continuing in the abbreviated schedule of assessments. If a patient who is being followed in the abbreviated schedule of assessments prematurely withdraws from the study, the patient should be scheduled for a final visit (EOS-CP according to Table 6-2) at the time of study discontinuation.

Patients who have completed the Core Phase, as per Table 6-1 or Table 6-2, may be eligible to enter the long-term extension study (Table 6-3). Patients who complete the Core Phase on study drug, but choose not to enter the Extension Phase should return for a 3-month follow-up visit.

Patients who prematurely discontinue study drug (SDD) during the Extension Phase, may remain in the study and be followed at yearly visits (see Table 6-2). At the time of SDD, patients must complete the Visit 30 assessments (as end of treatment assessments), followed by a 3-month follow-up visit.

Table 6-1 Core Phase: Assessment schedule

Phase	Pre-Randomization		Double-blind Treatment Phase															
Period	Screening	Baseline																
Visit No.	1	2	3	4	5	51	6	7	71	72	8	9	10	11	12	13	14/ EOS-CP	FU #
Study month	-45 days	-7 days	Day 1	½	1	1 ½	2	3	4	5	6	9	12	15	18	21	24	+3 mo
Informed consent	X																	
Background, Demography	X																	
Incl/exclusion criteria	X	X																
Medical history	X																	
MS history/MS treatment	X																	
Concomitant medications	X	X	X	X	X		X	X			X	X	X	X	X	X	X	X
Pregnancy test**	X	X		X	X		X	X			X	X	X	X	X	X	X	X
Physical exam	X	X		X	X		X	X			X	X	X	X	X	X	X	X
Skin exam	X																X	
PK[1]			X	X	X		X	X			X		X		X		X	X
Ophthalmologic examination[2]	X							X			X	X*	X*		X*		X	
Tanner stages[5]	X	[redacted]																
Pulmonary Function Tests	X				X			X			X		X		X		X	
Vital signs	X	X	X	X	X		X	X			X	X	X	X	X	X	X	X
Hematology/ Blood chemistry[4]	X[14]	X		X	X	X[6]	X	X	X[6]	X[6]	X	X	X	X	X	X	X[14]	X
Serology	X																X[10]	
[redacted]																		
Urinalysis	X	X									X		X				X	
First Dose Administration monitoring			X				X[13]	As needed[11]										
Fingolimod drug supply			X				X	X			X	X	X	X	X	X		
IFN β-1a drug supply			X				X	X			X	X	X	X	X	X		

Phase	Pre-Randomization		Double-blind Treatment Phase															
Period	Screening	Baseline																
Visit No.	1	2	3	4	5	51	6	7	71	72	8	9	10	11	12	13	14/ EOS-CP	FU #
Study month	-45 days	-7 days	Day 1	½	1	1 ½	2	3	4	5	6	9	12	15	18	21	24	+3 mo
Capsule/syringe count							X	X			X	X	X	X	X	X	X	
ECG	X		X[7]		X								X				X	
MRI	X[8]										X		X		X		X[9]	
[redacted]																		
EDSS	X	X						X			X	X	X	X	X	X	X	X
MS relapse	X	X	X	X	X		X	X			X	X	X	X	X	X	X	X
C-SSRS[12]	X	X	X	X	X		X	X			X	X	X	X	X	X	X	X
IVR	X		X				X	X			X	X	X	X	X	X	X	
Adverse events/SAEs			X	X	X		X	X			X	X	X	X	X	X	X	X
Study Phase Completion																	X	

Phase	Pre-Randomization		Double-blind Treatment Phase															
Period	Screening	Baseline																
Visit No.	1	2	3	4	5	51	6	7	71	72	8	9	10	11	12	13	14/ EOS -CP	FU #
Study month	-45 days	-7 days	Day 1	½	1	1 ½	2	3	4	5	6	9	12	15	18	21	24	+3 mo

1. Two PK samples collected at Visit 3 (Randomization) and Visit 5 (Month 1) pre-oral dose and approximately 6 hours post-oral dose; one PK sample collected at other specified visits.

2. Ophthalmologic examination includes OCT at Screening and EOS visits.

[redacted]

4. Laboratory results must be available prior to randomization to evaluate inclusion/ exclusion criteria.

[redacted]

6. Blood sample for liver panel only (see Section 6.5.4 for patients with travel restrictions)

7. ECG to be obtained on Day 1 before first dose administration or if dose increase or restart of study drug after having been off treatment for the durations referenced in 11, 6 hours post-first dose and at discharge (if patient monitored longer than 6 hours).

8. MRI scan must be performed within 30 days prior to randomization.

9. EOS-CP MRI is not required for patients who discontinue within 4 weeks of a completed, scheduled scan.

10. IFN β neutralizing antibodies evaluated at Visit 14 / EOS-CP.

11. Patient who reaches the weight of 40 kg sustained over at least 2 visits (3 months apart) and needs to have dose increase or will reinitiate treatment after interruption of study drug (Section 5.5.5) for the following durations:

The treatment lasted for 14 days or less and was interrupted for 1 day or more, or

The treatment lasted for more than 14 days and less than 29 days and was interrupted for more than 7 consecutive days, or

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

12. To be completed at every visit including any unscheduled visits.

13. The patients with BW 40 kg or less potentially increase in dose based on on-line PK assessment. First-dose monitoring done.

14. T cell and B cell phenotyping

Patients who prematurely discontinue study drug should complete the 3 month follow-up visit and then be allowed to enter the abbreviated schedule of assessments at the next scheduled study visit (Table 6-2).
Patients who complete the Core Phase but do not enter the Extension Phase should complete the 3 month follow-up visit.

*Visits required only in patients with history of diabetes mellitus or uveitis, or newly diagnosed uveitis

**if applicable (please refer to Section 6.6. for details), plus monthly urine pregnancy tests (e.g. home test) between scheduled serum tests, if applicable.

Table 6-2 Core Phase: Abbreviated schedule of assessments for patients with SDD

Phase	Double-blind Treatment Phase						
Visit No.[1]	8	9	10	11	12	13	14/ EOS-CP
Study month	6	9	12	15	18	21	24
Physical exam	X		X		X		X
Skin exam							X
[redacted]							
Pulmonary Function Tests	X		X		X		X
MS relapses	X	X	X	X	X	X	X
MS treatment/Concomitant medications/Steroids	X	X	X	X	X	X	X
EDSS	X	X	X	X	X	X	X
MRI	X		X		X		X
[redacted]							
Vital signs	X	X	X	X	X	X	X
Hematology/Blood chemistry	X		X		X		X
[redacted]							
Urinalysis	X		X				X
C-SSRS[4]	X	X	X	X	X	X	X
AE/SAE reporting (if any)	X	X	X	X	X	X	X

1. The abbreviated schedule should be adopted at the appropriate visit after the 3 month follow-up visit.

[redacted]

4. To be completed at every visit including any unscheduled visits.

Table 6-3 Fingolimod Extension Phase: Assessment schedule

Phase	Fingolimod Treatment										
Visit No. #	15	16	17	18	19	20	21	22	23 to 29	Study Completion (Visit 30)***	FU [2]
Study month #	Day 1 [1]	½	1	2	3	6	9	12	every 6 months[15]	60	
Incl/exclusion criteria	X										
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test (serum) [3**]		X	X	X	X	X	X	X	X	X	X
Physical exam					X	X		X	1 / year	X	X
[redacted]											
Skin Exam									1 / 2 years	X	
Ophthalmologic Examination [6]					X	X		X	As Needed	X	
Pulmonary Function Tests			X		X	X		X	As Needed	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Hematology/ Blood chemistry		X	X	X	X	X	X	X	X	X	X
Urinalysis						X		X	1 / year	X	
Fingolimod drug supply [7]	X			X	X	X		X	X		
ECG	X [8]		X					X	1 / year	X	
MRI						X		X	1 / year [9]	X	
EDSS [10]					X	X	X	X	X	X	X
MS relapse [11]	X	X	X	X	X	X	X	X	X	X	X
C-SSRS[12]	X	X	X	X	X	X	X	X	X	X	X
[redacted]											
Adverse events/SAEs[13]	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetic sample FTY720/FTY720-P[14]			X								
First Dose Administration*	X			X [14]	As needed						

Phase	Fingolimod Treatment										
Visit No. #	15	16	17	18	19	20	21	22	23 to 29	Study Completion (Visit 30)***	FU [2]
Study month #	Day 1 [1]	½	1	2	3	6	9	12	every 6 months[15]	60	

1. Assessments and first dose administration will occur on day 1 of the Extension Phase (ideally the day after the completion of the Core Phase), visit should be completed within 14 days of Visit 14 / EOS-CP. For ease of scheduling, if needed, some Visit 14 / EOS-CP assessments may be completed in the morning prior to dosing at Visit 15

2. Follow-up visit should be scheduled 3 months (±10 days) after the last dose of study medication.

3. Additional pregnancy tests may be collected at Investigators discretion during the study.

[redacted]

6. Optical Coherence Tomography will be conducted at the Core Phase EOS-CP Visit and then at the end of the study.

7. Study drug dispensation will occur at scheduled visits.

8. ECG to be obtained before fingolimod first dose administration in the extension and 6 hours post-first-dose.

9. MRI assessments are required to be done annually. If MRI's would be conducted more frequently for routine medical practice then MRI's may be conducted as often as every 6 months.

10. Additional unscheduled EDSS assessments may be conducted to confirm relapse.

11. Unscheduled visits required to confirm MS relapse.

12. To be completed at every visit including any unscheduled visits.

13. Adverse events that happen prior to the first dose intake in the Extension Phase should be recorded as having occurred in the Core Phase of the study.

14. The patients with BW 40 kg or less potentially increase in dose based on on-line PK assessment. PK collected at Visit 17 and first-dose monitoring done at Visit 18.

15. Assessments occur at each biannual visit (every 6 months) unless specified otherwise.

Visit numbering is sequential following the Core Phase visit numbering. All patients will complete Visit 14 prior to entry in the Extension Phase. Study month reflects the time in the Extension Phase since patients may enter the Extension Phase after various durations of time in the Core Phase.

* The first dose monitoring at Visit 15 must be conducted by the independent first dose monitoring team in a blinded fashion. All additional first dose monitoring visits may be done by the main clinical team (monitoring is not blinded).

**if applicable (please refer to Section 6.6 of Core Phase protocol. for details), plus monthly urine pregnancy tests (e.g. home test) between scheduled serum tests.

*** Patients that discontinue treatment with fingolimod must complete the end of visit assessments (Visit 30) at the time of study drug discontinuation and then must complete the 3-month follow-up visit. Patients may then come back at the next yearly visit and have monitoring visits yearly at 36, 48, 60, 72 and 84 Months.

6.1 Information to be collected on screening failures

Patients who have signed the informed consent form, but fail to meet eligibility criteria for enrollment during the Screening Phase will be deemed screen failures and a reason will be documented on the Screening Log eCRF. Only demography data will be collected. . If a patient does not meet In/Ex criteria they may be re-screened. In general a patient should not be re-screened more than once, although in some circumstances, if the clinical situation warrants, a 2nd re-screening may be appropriate (please contact sponsor for approval).

6.2 Patient demographics/other baseline characteristics

Patient demographic data and baseline characteristic data to be collected on the Demography eCRF will include date of birth, age, sex, race, ethnicity and Tanner stage. Relevant medical history includes data until the start of study drug and will capture pre-existing medical conditions and any medications taken to treat these conditions. Where possible, diagnoses, and not symptoms should be recorded. MS history and previous MS treatment will also be collected.

6.3 Treatment exposure and compliance

In order to collect accurate information about the study drug exposure, the following records should be maintained for each randomized patient: records of study medication dispensed and returned, dosages administered and intervals between visits. These data should be transcribed on the Dosage Administration Record eCRF. Any events that are considered adverse events that do result in an interruption of dosing must be recorded on the Adverse Events eCRF page.

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

6.4 Efficacy

Efficacy assessments will include:

- MS relapse
- MRI
- EDSS
- [redacted]

6.4.1 Magnetic resonance imagining (MRI)

All patients will undergo MRI scanning of the brain according to Table 6-1, Table 6-2 and Table 6-3.

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

Each MRI scan performed during the Core Phase needs to be previewed by a local neuroradiologist (see Section 5.5.13). The Primary Treating Physician needs to be contacted in case of unexpected findings (e.g. not consistent with MS) detected on the MRI scan.

During the study, the quality of each scan performed will be assessed by the central blinded MRI reading center. The MRI scan should be sent to the central MRI reading center within 3 working days, if possible. As soon as the scan is received by the central MRI reading center, it will be evaluated for quality, completeness and adherence to the protocol. Confirmation of MRI quality or a description of the quality problems, if detected, will be communicated to the site. If scan is incomplete or incorrectly performed, the study center will be asked to repeat it as soon as possible. After completion of the quality check, all scans will be analyzed according to the MRI protocol.

The central blinded MRI reading center will provide MRI notifications during the Core Phase of the study if certain MRI activity criteria are met for a given patient. MRI notifications will be based on combined unique active (CUA) lesion counts (defined as Gd-enhancing lesions + new/enlarging T2 lesions not associated with Gd-enhancement for scans performed after Gd administration or just new/enlarging T2 lesions for scans done without Gd (Gd administration is optional for Month 18 scan).

The Investigator will be notified if the following criteria are met:

- 5 or more Gd-enhancing lesions on month 6 scan and 5 or more CUA lesions on month 12 scan – notification triggered at Month 12
- 5 or more CUA lesions on month 12 scan and 5 or more new/enlarging T2 lesions on month 18 scan – notification triggered at Month 18
- 5 or more new/enlarging T2 lesions on month 18 scan and 5 or more new/enlarging T2 lesions on month 24 scan - notification triggered at Month 24

Extension Phase MRI scans will be read by the central MRI reading center as was done in the Core Phase using the same procedure and study specific MRI sequences. During the Extension Phase the Investigator will also be allowed to review the Extension Phase MRI's for disease activity and safety findings. MRI alerts for disease activity will not be reported by the Central Reader during the Extension Phase.

Restrictions for MRI schedule

To avoid interferences caused by steroids for the treatment of MS relapse, the following restrictions apply for this study:

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

As a result of these restrictions, MRI scheduling can be adjusted accordingly. In case a visit is performed outside the visit window, any subsequent visits should be performed according to the original visit schedule.

Scanning

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

Sequences for T1 hypointense images (with and without contrast medium, gadolinium-DTPA [use of contrast medium is optional at Month 18 and for all Extension Phase MRI's; sites may use contrast medium if this would normally be done as part of the sites routine clinical practice]), T2-weighted (T2 and PD) images and brain volume will be performed.

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.

6.4.2 MS relapse

The initial assessment, management and reporting of MS relapse is made by the Primary Treating Physician.

MS relapse definition: 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 (McDonald et al 2001). The abnormality must have been present for at least 24 hours and occurred in the absence of fever (< 37.5°C) or known infection.

Diagnosing MS relapses during the study: a patient may report symptoms indicative of a relapse at a scheduled visit or at any other time. Patients will be instructed to immediately contact the Primary Treating Physician if he/she develops new or re-occurring or worsening neurological symptoms. At each scheduled visit, the patient will also be asked whether any such symptoms have occurred. If a patient reports new neurological symptoms or worsening of previous symptoms, an unscheduled visit is to be planned as soon as possible, ideally within 7 days. During this visit, the treating physician will first assess whether the new/worsening neurological abnormality is consistent with the definition of MS relapse above. If so, the standard neurological examination (for the EDSS score) should be performed by the Independent Evaluating Physician (EDSS rater). If there is any doubt in the opinion of the treating physician, the default must always be to refer the case to the Independent Evaluating Physician to perform an EDSS rating.

During the Extension Phase the EDSS assessment needs to be completed by a qualified EDSS rater. Blinding of EDSS ratings is not required during the Extension Phase since all patients will be treated with fingolimod. However, it is highly recommended that the EDSS rater used in the Core Phase continues to monitor the EDSS in the Extension Phase for consistency of readings. If a rater change is required then adjudication/discussion between "Core Phase Rater" and "Extension Phase Rater" should be done if there are differences between the last Core Phase evaluation and the first Extension Phase evaluation. Co-ratings are also recommended. Every effort should be made for the rater to remain the same throughout the study.

Confirmation of MS relapse: the definition of a confirmed MS relapse is one accompanied by a clinically relevant change in the EDSS performed by the Independent Evaluating Physician/EDSS rater for Core/Extension Phase respectively, i.e. an increase of at least 0.5 points on the EDSS score, or an increase of 1 point on two FSs or 2 points on one FS, excluding changes involving bowel/bladder or cerebral FS compared to the previous available rating (the last EDSS rating that did not occur during a relapse).

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

The severity of relapses will be calculated centrally according to criteria in Table 6-4.

Table 6-4 Severity of MS relapse

Mild relapse	Moderate relapse	Severe relapse
EDSS increase of 0.5 point	EDSS increase of 1 or 2 points	Exceeding Moderate criteria
Or	or	or
1 point FS change in one to three systems	2-point FS change in one or two systems	Exceeding Moderate criteria
	or	or
	1-point change in four or more systems	Exceeding Moderate criteria
(Panitch et al 2002)		

6.4.3 (Kurtzke's) Expanded Disability Status Scale (EDSS)

EDSS will be determined, based on neurological examination, by the Independent Evaluating Physician during the Core Phase and by a certified EDSS rater during the Extension Phase at scheduled visits according to Table 6-1, Table 6-2 and Table 6-3 and in case of a suspected MS relapse.

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. 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.

The Independent Evaluating Physician/EDSS rater is a neurologist or otherwise qualified healthcare professional who has successfully completed the EDSS certification (at the highest level) within the past 12 months. During the Core Phase the Independent Evaluating Physician conducts the EDSS ratings and is otherwise not involved in the treatment of the patient. During the Extension Phase EDSS ratings may be done by a qualified healthcare professional that has successfully completed the EDSS certification.

EDSS assessments are to be performed at scheduled visits according to Table 6-1,Table 6-2 and Table 6-3 and in case of an MS relapse.

[redacted]

6.4.5 Appropriateness of efficacy assessments

MS relapse, MRI and EDSS are standard efficacy assessments in MS and are used in both the adult and the pediatric populations. They serve to characterize the patient population included in this study as well as their disease activity and neurological status. [redacted]

6.5 Safety

Safety assessments will include:

- Physical examination (including skin)
- [redacted]
- Ophthalmologic examination including Optical Coherence Tomography (OCT)
- Pulmonary function tests (PFTs)
- Vital signs
- Laboratory evaluations
- Electrocardiogram (ECG)
- Columbia Suicide Severity Rating Scale (C-SSRS)

Medical history, including MS history and prior MS treatments will be assessed at Visit 1. Concomitant medications will be assessed at every visit following informed consent.

6.5.1 Physical examination

A physical examination will be performed according to Table 6-1, Table 6-2 and Table 6-3 and will include an assessment of skin, head and neck, lymph nodes, breast, heart, lungs, abdomen, back and comments on general appearance. A complete neurological examination will be part of the initial physical examination at screening. Investigators should ask the patient/guardian if they have any new or changed skin lesions as part of each physical examination. If skin lesions (suspected to be precancerous or cancerous) are identified during the physical examination, the patients should be referred to a dermatologist.

A complete examination of the skin will be performed by a dermatologist or the study pediatrician according to Table 6-1, Table 6-2 and Table 6-3.

Information for all physical examinations (including skin exams) must be included in the source documentation at the study site. Significant findings that are present prior to the start of study drug must be included in the Relevant Medical History/Current Medical Conditions screen on the patient's eCRF. Significant findings made after the start of study drug which meet the definition of an Adverse Event must be recorded on the Adverse Event eCRF.

6.5.2 Ophthalmologic examination

A complete ophthalmologic examination will be performed according to Table 6-1 or Table 6-3 by an ophthalmologist. At each scheduled visit the following assessments will be performed:

- Eye history (medical history at baseline, AEs during the study)
- Best corrected visual acuity measurements using a standard visual acuity chart with equal space between letters and between lines (results must be provided in Snellen equivalent or decimal score)
- Dilated ophthalmoscopy to examine the macula and optic disc (may include contact lens biomicroscopy)
- [redacted]

Optical coherence tomography (OCT) to measure central foveal thickness/center point thickness should be performed according to Table 6-1 or Table 6-3. An OCT should also be performed if there is suspicion of macular edema by dilated ophthalmoscopy at any visit. Further explorations, such as a fluorescein angiogram, to confirm/rule out macular edema should be performed at the discretion of the ophthalmologist

Patients with medical history of diabetes mellitus or uveitis or newly diagnosed uveitis at screening or during the study will require special evaluation and additional ophthalmic evaluation (see Appendix 3).

6.5.3 Vital signs

Vital signs will be recorded according to the schedule in Table 6-1, Table 6-2 and Table 6-3. Vital signs will include height, weight, sitting pulse rate, sitting systolic and diastolic blood pressure, and oral temperature (degrees Celsius).

Heart rate (pulse)

Sitting radial pulse after 5 minutes of rest should be measured just prior to blood pressure measurement.

At least 6 hour monitoring in the clinic will be required on Day 1 (Visit 3) and Visit 15 after first dose of study drug in the Core and Extension Phase, respectively. This is also required in the event of an increase in fingolimod dose from 0.25 mg to 0.5 mg (see Section 3.3) and at any restart of study drug dosing after an interruption as specified in Section 5.5.5. Details of the monitoring during treatment initiation, dose increase or study drug restart are provided in Appendix 2.

In the Extension Phase, Visit 15 first dose monitoring must be done by the independent first dose monitoring team. All subsequent monitoring visits required per protocol for dose increases or study drug interruptions may be performed by the main study team since all patients will be treated with fingolimod in the Extension Phase and thus blinding is not required after the first dose of Extension Phase medication has been provided to a patient.

Blood pressure

Sitting blood pressure will be recorded according to the schedule in Table 6-1, Table 6-2 and Table 6-3. Every effort should be made to have the same study personnel obtaining blood pressure readings for an individual patient at each visit at the same time of day with the same equipment. Using a calibrated standard sphygmomanometer with the appropriate cuff size, arterial blood pressure determinations will be made. With the arm supported at the level of the heart, systolic and diastolic blood pressure will be recorded. The cuff should not be deflated at a rate greater than 2 mmHg/sec.

At each visit after the patient has been resting (i.e., not active) for 5 minutes, systolic/diastolic blood pressure will be measured three times. For blood pressure measurements during first dose monitoring on Day 1, refer to Appendix 2.

6.5.4 Laboratory evaluations

Routine blood and urine samples will be analyzed by the central laboratory. Details about collection, shipment of samples, reporting of results, laboratory normal ranges and alerting abnormal values will be provided in the study laboratory manual, supplied to the site before site initiation. With the exception of total and differential white blood cell count, which will be blinded to the sites (refer also to Section 15.4), the results of the analysis will be made available to each center by the central laboratory at the earliest 48 hours after receipt of the samples by the central laboratory.

Hematology

Complete blood cell count (CBC) analysis including red blood cell (RBC) count, total and differential white blood cell (WBC) count (basophils, eosinophils, lymphocytes, monocytes, neutrophils, WBC segments), platelet count, hemoglobin, hematocrit, MCV, MCH, MCHC and RBC morphology will be performed according to Table 6-1, Table 6-2 and Table 6-3.

Additionally, phenotyping of T cells (naïve T cells, T central memory cells and T effector memory cells) and B cells using FACS flow cytometry will be performed according to Table 6-1.

Blood chemistry

All laboratory samples are preferred to be collected at the same time of the day. Fasting status should be clearly identified on the laboratory requisition form accompanying the samples.

Blood chemistry is to be obtained according to Table 6-1,Table 6-2 and Table 6-3 and will include sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen (BUN), uric acid, random glucose, albumin, alkaline phosphatase, creatinine, cystatin C, ALT, AST, GGT, amylase, total bilirubin, conjugated bilirubin, total cholesterol, triglycerides, HDL and LDL. Abnormal laboratory parameters should be repeated for accuracy. A blood sample for liver function tests only (ALT, AST, GGT, alkaline phosphatase, total bilirubin, conjugated bilirubin) will be obtained according to Table 6-1. Serum pregnancy testing and home pregnancy testing will be performed according to Table 6-1 and Table 6-3.

To assist for patients with travel restrictions blood samples for liver panel assessments as described in Table 6-1 (Visits at 6 weeks, 4 and 5 months) may be drawn by a local lab and the results report sent to the Investigator within 48 hours of obtaining the results.

If any significant findings are observed on these reports (See Appendix 3 Section 15.2 guidelines), a confirmatory blood sample should be drawn by the site and sent to the central laboratory.

If no significant findings are observed then the results of the local laboratory values (including reference ranges) should be included in liver eCRF to document the values.

Blood samples for these visits may also be obtained by other methods as appropriate in a particular country or region and processed through the central laboratory (e.g., flying nurse, local phlebotomist etc.). Please follow Appendix 3 Section 15.2 guidelines of the protocol for liver safety monitoring for these visits.

Blood Chemistry criteria that require permanent study drug discontinuation are listed in Section 5.5.9.

Serology

Serology testing will be performed according to Table 6-1 and will include the following (for documentation of serology status or for assessment of exclusion criteria): herpes simplex virus-1, herpes simplex virus-2, hepatitis A, B, C and E, human immunodeficiency virus (HIV), Epstein Barr virus (EBV), cytomegalo virus (CMV), AQP4 auto-antibodies and IFN-β neutralizing antibodies. Varicella-zoster virus, mumps, measles, rubella, diphtheria, tetanus, pertussis may also be tested in patients without evidence of immunity. Please refer to Appendix 3 Guidance on Vaccinations and Guidance on monitoring of patients with infections for guidelines based on screening serology status and for general monitoring guidelines.

Endocrinology

The following parameters will be tested for according to Table 6-1, Table 6-2 and Table 6-3: Insulin-like growth factor 1 (IGF-1), insulin-like growth factor binding protein (IGFBP3); follicle stimulating hormone (3FSH) and stradiol (E-2) in girls, testosterone, LH (luteinizing hormone) in boys.

Urine measurements

Urinalysis will include urine protein, glucose, leucocytes, blood, specific gravity, pH, ketone, bilirubin and urobilinogen and will be obtained according to Table 6-1, Table 6-2 and Table 6-3.

Assessment of Tanner stages should be performed per local practice, guided by a pediatrician or health care professional experienced with this assessment. The Tanner scale assesses physical development in children, adolescents and adults (Marshall and Tanner 1970). The scale defines the physical measurements of development based on external primary and secondary sex characteristics. Tanner staging (breast development in girls and testes size in boys) is important for accurate interpretation of bone age and endocrine laboratory results. Patients with a Tanner Stage < II are considered pre-pubertal. [redacted]

[redacted]

6.5.6 ECG

A standard 12-lead ECG will be obtained as follows (Table 6-1 and Table 6-3):

- At Visit 1 to assess eligibility for study entry (all patients)
- Visit 3 and Visit 15 during first dose monitoring of the Core and Extension Phase: two ECGs will be performed. The first ECG will be performed prior to the study drug administration and the second ECG will be performed post-dose, approximately at the end of the 6-hour monitoring period.
- At any visit if a dose-increase or restart of study drug is to occur as specified in Section 5.5.5, with first dose monitoring as above and in Appendix 2.
- Other scheduled visits (all patients) according to Table 6-1 and Table 6-3.

Digital ECG devices will be provided to each clinical site by the central ECG reader for the duration of the study. Detailed information about recording and transmission of the studies will be outlined in the study specific manual provided by the center reader.

ECG criteria that require permanent study drug discontinuation are listed in Section 5.5.9.

6.5.7 Pulmonary Function Tests

Pulmonary function tests evaluating FEV_1, FVC and D_LCO will be performed according to the visit schedule in Table 6-1,Table 6-2 and Table 6-3. During the study, if the patient reports any respiratory symptoms such as dyspnea, shortness of breath, chest tightness or wheezing, or pulmonary function test abnormalities, please refer to Appendix 3 for monitoring guidance.

The tests will be conducted in all patients who are enrolled into the study and in the manner consistent with the standard laboratory practice.

Spirometry

The technician should demonstrate the appropriate technique to the subject and follow the standard procedure for the pediatric population. The quality of the tests must be accounted for including the technicians' comments (especially when, despite proper coaching of the subject, full collaboration cannot be achieved).

A minimum of 3 acceptable maneuvers will be performed at each visit. The acceptability criteria are a satisfactory start of test and a satisfactory end of test. In addition, the technician should observe that the subject understood the instructions and performed the maneuver with a maximum inspiration, a good start, a smooth continuous exhalation and maximal effort. The largest FVC and the largest FEV_1 will be recorded, after examining the data from all of the acceptable curves, even if the 2 values do not come from the same curve.

For each test (FEV_1, FVC, D_LCO), the absolute value as well as the percent of predicted value will be recorded in the eCRF. FEV_1/FVC ratio (expressed in %) will be calculated centrally.

Forced expiratory volume in 1 second (FEV_1) and Forced vital capacity (FVC):

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

The FVC denotes the volume of gas (in Liters) that is exhaled during a forced expiration starting from a position of full inspiration and ending at complete expiration. This parameter is normal or might be slightly decreased in obstructive disease, but shows a mild to severe decrease in restrictive disease.

Diffusion capacity of carbon monoxide (D_LCO):

Gas exchange is assessed by the carbon monoxide diffusing capacity (DLCO) 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.

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

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

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

All values must be corrected for hemoglobin concentration.

The DLCO can be expressed in both CI conventional units: ml CO/min/torr (or ml CO/min/mmHg), and SI units: mmol CO/min/kPa (Conversion factor: SI units x 2.986 = CI units).

6.5.8 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS, a questionnaire that prospectively assesses Suicidal Ideation and Suicidal Behavior using a semi-structured interview to probe patient responses, must be administered according to Table 6-1 and Table 6-3 and also at unscheduled visits.

If, at any time after screening and/or baseline, the score is yes" on item 4 or item 5 of the Suicidal Ideation section of the C-SSRS or "yes" on any item of the Suicidal Behavior section, the patient **must** be referred to a mental health care professional for further assessment and/or treatment. The decision on whether the study treatment should be discontinued is to be taken by the investigator in consultation with the mental health care professional to whom the patient is referred.

The C-SSRS will be administered by an IVR system with the patient entering responses directly into the IVR system. For patients unable/unwilling to do so or where self-reporting by minors is not permitted by the local regulatory authority, and for all patients below the age of 12, another individual (e.g. parent/other family member/caregiver/qualified site staff) will enter the answers to the C-SSRS questions into the IVR system on behalf of the patient.

The investigators must review reports received from the system for any answers indicative of suicidal ideation and adverse events on the Visit day the questionnaire was performed and before the patient is discharged. Adverse events ascertained through the administration of the C-SSRS will be documented.

6.6 Pregnancy and assessments of fertility

Females of child-bearing potential are defined as all females physiologically capable of becoming pregnant. This includes female children and adolescents who are menarchal or who become menarchal during the study.

Serum pregnancy test will be performed by the central laboratory for all females of child-bearing potential according to the schedule in Table 6-1 and Table 6-3.

Although it is expected that this study will enroll mostly girls who are not sexually active, some may be sexually active. All menarchal girls and their parents/caregivers should be informed about the potential risks of pregnancy and the need to prevent pregnancy during the study.

It is important to be sensitive in introducing this issue, as understanding and comprehension of a child about puberty, sexual activity, pregnancy and contraception varies with age. These discussions with the patient and her parents/caregivers are therefore best performed by investigators familiar with the child/adolescent and her family and are part of the circle of care. The investigator should also discuss the management of the pregnancy test results with the patient and her parents/caregivers. These discussions may vary across countries and regions and should be guided by requirements of the local regulatory authority.

Female patients of childbearing potential who are sexually active will perform a urine pregnancy test (e.g. via home pregnancy test kit) monthly (in the months between clinic Visits and serum pregnancy testing). In the event of a positive urine pregnancy test, the patient must immediately contact the investigator. Additional pregnancy tests may be performed at the investigator's discretion during the study. Patients becoming pregnant must discontinue study drug.

Female patients of child-bearing potential must be informed of the potential teratogenic risk with fingolimod and the need for highly effective contraception to prevent pregnancy while on study drug and for 2 months after stopping study drug should they be or become sexually active.

Use of a combination of any two of the following methods of contraception (a+b or a+c or b+c) should be used as appropriate:

a) use of oral, injected or implanted hormonal methods of contraception

b) placement of an intrauterine device or intrauterine system

c) barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

Contraception must be used during the study and for 2 months after stopping study drug. The decision on the contraceptive method should be reviewed at least every 3 months to evaluate the individual need and compatibility of the method chosen.

6.7 Other assessments

[redacted]

6.7.2 Pharmacokinetics

Blood collection and processing

All blood samples will be taken anytime during the visit except at Visit 3 (Randomization), Visit 5 (Month 1) and Visit 17 (Month 1 of Extension Phase).

At Visit 3, one blood sample will be collected before administration of the study drug (oral capsule), and another one approximately 6 hours post-dose (oral capsule).

At Visit 5 and Visit 17, one blood sample will be collected at pre-dose (24 hours post last dose of the study drug, and before the new administration) and a second collection approximately 6 hours post-dose. Patients should be instructed NOT to take the dose at home on this day of the visit. Instead they should be asked to bring the fingolimod capsule with them to the visit and take it after the pre-dose sample is drawn.

Blood samples (1.8 mL) will be collected into a sodium citrate vacuum tube, by either direct venipuncture or an insertion of an indwelling cannula into a forearm vein. Immediately after each tube of blood is drawn, it should be inverted gently several times to ensure the mixing of tube contents (e.g., anticoagulant). Prolonged sample contact with the rubber stopper should be avoided. The tube should be placed upright in a test tube rack surrounded by ice until transfer. Within 30 min of blood collection the tubes must be frozen at ≤ -18°C and must be transferred to a ≤ -70°C freezer within 3 months of collection pending analysis. Alternatively, the tubes can be transferred directly to a ≤ -70°C immediately after sample collection.

All samples will be given a unique sample number. The actual dosing date and time and actual sample collection date and time will be entered on the PK blood collection page of the eCRF. Sampling problems will be noted in the Notes field of the eCRFs.

Blood samples will be shipped to the central laboratory on a regular basis, except those from Visit 5 and Visit 17 that should be sent as soon as possible after collection to allow for the online pharmacokinetic analysis (i.e. those samples drawn from patients with a body weight of 40 kg or less).

Details on labeling of the pharmacokinetic samples and shipment instructions will be included in the laboratory manual provided by the Central Laboratory.

Analytical Method

Fingolimod and fingolimod-P will be measured in whole blood using a validated LC-MS/MS with a LLOQ of 0.020 ng/mL and of 0.025 ng/mL, respectively.

7 Safety monitoring

7.1 Adverse events

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Study drug includes the investigational drug under evaluation and the comparator drug or placebo that is given during any phase of the study. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

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

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

An SAE is defined as an event which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (e.g. hospitalization for relapse treatment)
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

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

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

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

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

7.2 Serious adverse event reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until 3 months after the patient has stopped study participation (defined as time of last dose of study drug taken or last visit whichever is later) must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 3 months period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug.

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

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

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

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study drug, a Drug Safety and

Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

Although MS relapses are considered medically significant and are frequently associated with hospitalization and thus, meet the definition for SAEs, these events will be reported on the MS relapse eCRF instead of the SAE form unless, in the judgement of the investigator, a MS relapse is unusually severe or unexpected and warrants specific notification as an SAE.

7.3 Pregnancies

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

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

7.4 Data Monitoring Committee

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

The DMC will be responsible for on-going review of enrollment, safety and, if requested by the DMC, efficacy data and will provide regular assessments on the safety and overall risk to benefit ratio of the study conduct, advise the sponsor of a need for protocol modification/amendment in order to minimize potential risk for patients, request additional information or make recommendation including stopping of enrollment and/or treatment, if needed.

A Novartis designee will be responsible for the timely coordination and delivery of the data to the DMC on a regular basis. The chair of the DMC will be responsible for providing summaries/executive reports of each DMC meeting to Novartis, arranging on-going communication between members of the DMC, arranging meetings and maintaining files with all correspondence pertaining to the study.

The responsibilities of the DMC may be terminated by Novartis once safety review by the DMC is no longer needed.

8 Data review and database management

8.1 Site monitoring

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

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

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

8.2 Data collection

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

8.3 Database management and quality control

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

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

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

ECG and CSSRS readings/values will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

MRI scans will be processed centrally and the results will be sent electronically to Novartis.

Randomization codes and data about all study drug(s) dispensed to the patient and all IVR recorded dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis.

The occurrence of any 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 by joint written agreement between the Global Head of Clinical Information Sciences and the Clinical Franchise Head.

9 Data analysis

The statistical models specified in this section may be modified by including fewer covariates in the models in case the pre-specified models do not converge.

9.1 Analysis sets

Core Phase:

All screened subjects (SCR): The SCR set comprises all subjects who were screened. The SCR will be used only for the summary of screening failures.

Randomized set (RAN): The RAN set comprises all subjects who were assigned a randomization number. The RAN will be used for the summaries of subject disposition, protocol deviation, demographic, baseline characteristics, and medical history data.

Full Analysis Set (FAS): The FAS comprises all randomized subjects with assigned treatments who took at least one dose of study medication. Subjects will be analyzed according to the randomized treatment assignment following the intention-to-treat principle, even if they actually received a different treatment. The FAS will be used for all efficacy analyses.

Per-protocol set: Consists of all patients in the full-analysis set who do not have any major protocol deviations that could confound the interpretation of analyses conducted on the FAS. Major protocol deviations will be determined according to the predefined protocol deviation criteria before treatment unblinding. Any efficacy data after study drug discontinuation will

be excluded. The per-protocol set will only be used for the supportive analyses of the primary efficacy variable.

Safety Set: The safety set includes all patients who received at least one dose of study medication. Subjects will be analyzed according to the actual treatment received. The Safety Set will be used for all safety analyses.

Fingolimod Extension Phase:

Extension Phase enrolled set: Includes all patients who were enrolled in the Extension Phase, whether or not they actually took any extension study medication. The Extension Phase enrolled set will be used for the summaries of subject disposition, protocol deviations, demographic, baseline characteristics, and medical history data.

Extension Phase FAS: All patients who *entered the Extension Phase* and received at least one dose of extension study medication. Patients will be analyzed according to the randomized treatment in the Core Phase. This analysis set will be used for all within-group efficacy analyses.

Fingolimod Treated FAS: All patients who received at least one dose of fingolimod (in the Core Phase for those who were randomized to fingolimod or in Extension Phase for those who were randomized to interferon β-1a in the Core Phase and switched to fingolimod in the Extension Phase). Patients will be analyzed according to the randomization treatment assignment in the Core Phase. This analysis set will be used for all long-term efficacy analyses.

Fingolimod Treated Safety Set: All patients who received at least one dose of fingolimod (in the Core Phase for those who were randomized to fingolimod or in Extension Phase for those who were randomized to interferon β-1a in the Core Phase and switched to fingolimod in the extension phase). Patients will be analyzed according to the actual treatment received in the Core Phase. This population will be used for overall exposure to study medication, long-term safety analyses and first dose administration summaries.

9.2 Patient demographics and other baseline characteristics

Patient demographics and other baseline characteristics, including Tanner stage, will be summarized using frequency distributions (for categorical variables) and descriptive statistics of mean, standard deviation, minimum, median and maximum (for continuous variables). Background information includes prior medication, past/current medical conditions, duration of the disease, pre-baseline relapse rate, baseline MRI assessments and baseline EDSS.

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

The duration (days) of exposure to study medication will be summarized by treatment group. Frequency distributions will be used to summarize patient disposition and reasons for discontinuation of study medication. Patients who prematurely discontinue the study medication will be listed along with the reason for discontinuation. The cumulative corticosteroid dose used after start of study medication for the treatment of multiple sclerosis

relapses will be summarized by treatment group in dose equivalent to prednisone (the conversion factors will be detailed in the statistical analysis plan). The cumulative duration of the corticosteroid use will be summarized similarly. The number of study drug capsules and syringes returned will be summarized by visits as a measure of compliance.

9.4 Analysis of the primary variable(s)

Core Phase:

The primary analysis pertaining to the primary efficacy objective will be based on the Full Analysis Set (FAS), following the intention-to-treat principle.

9.4.1 Variable

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

9.4.2 Statistical model, hypothesis, and method of analysis

The null hypothesis for the primary analysis states that: there is no reduction in the annualized relapse rate (ARR) in the patients treated with fingolimod compared to the ARR in patients treated with IFN β-1a, while the alternative hypothesis states there is a reduction in the ARR in fingolimod treated patients.

The test of the hypotheses will be based on a negative binomial regression model with log link, using treatment, number of relapses in the previous two years prior to screening, pubertal status, and region as covariates. Study centers are consolidated by country. In order to minimize the impact of low-enrolling countries on the analysis (such as non-convergence of the analysis model), countries will be pooled into regions based on geographical proximity. Details will be provided in the statistical analysis plan prior to database lock.

The response variable for this analysis is the number of confirmed relapses for each patient, and the quadratic variance estimate will be used. The natural log of (time in study for each patient) will be used as the offset to account for the varying lengths of patients' time in the study. The null hypothesis will be rejected if the observed p-value is less than the significance level of 0.05.

Model-based estimates of the ARR (aggregated over each treatment group) and its 95% confidence intervals, ARR ratio and its 95% confidence intervals and p-value comparing fingolimod vs. IFN β-1a will be provided.

9.4.3 Handling of missing values/censoring/discontinuations

All patients in the FAS will be included in the primary analysis, i.e., the number of confirmed relapses observed up to the end of patient's participation in the study. Relapses will be counted regardless of whether a patient is on or off study drug. Therefore it is expected that all

randomized patients can contribute to the primary analysis. The primary analysis model adjusts for missing information (early study discontinuations) under some statistical assumptions (non-informative dropouts and constant ARR).

9.4.4 Supportive analyses

To assess the impact of study drug discontinuation to the results observed, a supplementary analysis using the same negative binomial model as in the primary analysis to be performed on relapses on study drug (i.e., relapses will be counted only up to study drug discontinuation) in the per-protocol set will be performed.

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

9.5 Analysis of secondary variables

9.5.1 Key secondary variable(s)

Core Phase:

The key secondary variable is the annualized rate of the number of new/newly enlarged T2 lesions (n/neT2) from baseline to end of the study, with duration up to 24 months.

The null hypothesis for the key secondary analysis states that: there is no reduction in the neT2 lesion rate in patients treated with fingolimod 0.5 mg compared to patients treated with IFN β-1a, while the alternative hypothesis states there is a reduction in the neT2 lesion rate, in fingolimod 0.5 mg treated patients.

The test of the hypotheses will be based on a negative binomial regression model adjusted for treatment, pubertal status, number of T2 lesions at baseline and region. The natural log of (years in study for each patient) will be used as the offset.

For the key secondary analysis, there will be no imputations for missing data. The response variable for this analysis is the cumulative number of n/neT2 lesions based on the End of Study Core Phase MRI scan, for each patient. The quadratic variance estimate will be used and the natural log of time (in years) from randomization to the End of Study-Core Phase MRI assessment date for each patient will be used as the offset to account for the varying lengths of patients' time in study.

The above null hypothesis will be rejected if the observed p-value for treatment comparison (based on the n/neT2 rate ratio) is less than the significance level of 0.05. Model-based estimates of annualized rate of the number of n/neT2 lesions and their 95% confidence intervals, estimate of the n/neT2 annualized rate ratio (i.e., relative treatment effect) and its 95% confidence intervals and p-value for comparing fingolimod vs. IFN β-1a i.m. will be provided.

Summary statistics (mean, standard deviation, median, minimum and maximum) of the number of n/neT2 will also be provided.

Additional sensitivity analyses may be considered to further assess the robustness of the results.

Key efficacy variables data will be summarized for the overall population [redacted]

9.5.2 Efficacy variables

Core Phase:

Secondary and exploratory efficacy variables will be summarized by visit. Descriptive statistics (mean, standard deviation, median, minimum and maximum) will be provided for variables that are of the numeric or continuous type, while frequency distributions (with number and percent) will be provided for variables that of the categorical type.

P-values for the treatment comparisons will be provided. Each inferential analysis will be performed at a significance level of 0.05 with no adjustment for multiple analyses.

Secondary and [redacted] efficacy variables that are of the continuous or numeric type (such as the number of Gd-enhanced T1 lesions per scan, [redacted] will be analyzed via a negative binomial regression model adjusted for treatment, pubertal status, region, and relevant baseline value.

The volume of Gd-enhanced T1 lesions, change from baseline in T2 hyperintense and [redacted] lesion volume on MRI and percent brain volume change from baseline will be analyzed via a rank ANCOVA model adjusted for treatment, pubertal status, region and relevant baseline values. The percent brain volume change from baseline will also analyzed via an ANCOVA model with similar factor and covariates.

Time to event variables (such as the time to first confirmed relapse up to end of study-Core Phase) will be analyzed using the log-rank test (for comparing event-time distributions). In addition, a Cox regression model adjusted for treatment, number of relapses in the previous two year before study enrollment, pubertal status, and region will also be performed. Estimates of the hazard ratio and its 95% confidence intervals, and the p-value for treatment comparison from the Cox model will be provided. The Kaplan-Meier estimates of time to event variables and the relapse-free proportions at Month 24 will also be provided.

Fingolimod Extension Phase:

To examine long-term efficacy of continuous fingolimod treatment vs interferon β-1a switch to fingolimod treatment, the following endpoints will be analyzed by Core Phase treatment assignment and combined based on Fingolimod Treated FAS if not otherwise specified.

The efficacy variables will be summarized by visit or yearly intervals for the patients with continuous fingolimod treatment and the patients switched from IFN β-1a to fingolimod treatment. Descriptive statistics (mean, standard deviation, median, minimum and maximum)

will be provided for variables that are of the numeric or continuous type, while frequency distributions (with number and percent) will be provided for variables that are of the categorical type.

Nominal p-values will be provided as a measure of the strength of effect without declaring statistical significance.

ARR and time to relapse

The same negative binomial regression as used in the Core Phase (described in Section 9.4.2) will be employed for analyzing relapse rate. From this negative binomial model, ARR (95% CI) from Day 1 on fingolimod in Core Phase to end of the study (Core Phase and/or Extension Phase) will be obtained for the continuous fingolimod treatment and from Day 1 on fingolimod in the extension phase to end of the study for the IFN β-1a switch to fingolimod treatment; the ARR ratio (95% CI) and p-values for comparing the two treatment groups will also be reported. In addition, ARR will be analyzed by yearly intervals.

The Kaplan-Meier estimates (95% CI) of time to first relapse at Month 60 of Extension Phase will be provided for the continuous fingolimod treatment and the IFN β-1a switch to fingolimod treatment groups.

To further examine the fingolimod treatment effect on ARR reduction in patients who were treated with IFN β-1a in the Core Phase, a within group comparison will be done for patients switching from IFN β-1a to fingolimod based on Extension Phase FAS. A Poisson model with repeated measures having main effects for study phase (Core Phase, Extension Phase), number of relapses in the previous two year prior to Screening, pubertal status at core baseline, and region will be employed using generalized estimating equations. An exchangeable working correlation structure will be assumed to address the within subject repeated measures (i.e., measurements from Core Phase and Extension Phase). In addition, a robust variance estimator will be used to address any extra Poisson variability (i.e., over-dispersion) that may exist. The natural log of years in the corresponding study phase for each patient will be used as the offset. The ARR (95% CI) and ARR ratio (95% CI) defined as the ratio of the ARR estimates for the extension phase relative to the core phase will be presented along with the corresponding nominal p-value.

MRI endpoints

The annualized rate of new/newly enlarged T2 lesion (n/neT2) (95% CI), rate ratio (95% CI), and nominal p-value for treatment comparison will be provided using the same negative binomial model as specified in Section 9.5.1.

Other MRI endpoints, including patients free of new or newly enlarged T2 lesions, the number of Gd-enhanced T1 lesions, patients free of Gd-enhanced T1 lesions, [redacted] volume of Gd-enhanced T1 lesions, [redacted] and percent brain volume change, will be analyzed by visit using the same method as planned for the Core Phase.

9.5.3 Safety variables

Core Phase:

All safety analyses will be conducted on data from the Safety Analysis set. The assessment of safety will be based mainly on the incidence of adverse events and on the incidence of clinically notable laboratory abnormalities. Other safety assessments will include laboratory data summaries, vital signs, bradycardia events, pulmonary function tests, ophthalmic, and ECG data.

Adverse events will be summarized by presenting, for each treatment group, the number and percentage of patients having any adverse event by primary system organ class and preferred term. 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. Notable events will include death, non-fatal SAEs (including infections) and AEs (including infections) leading to discontinuation from the study. The summary will be tabulated by treatment group. The incidence rate (adjusted by treatment duration i.e., incidence rate per 100-patient years) will also be provided for any AE by system organ class and preferred term.

Laboratory data will be summarized by presenting summary statistics of raw data and change from baseline values, by presenting shift tables using clinically notable ranges (baseline to most extreme post-baseline value), and by flagging notable values in data listings. For liver function tests, the frequencies and percentages of patients with elevations of 1, 2, 3, 5, and 8 times upper limit normal will be summarized by visit and treatment group.

The incidence of patients with neutralizing antibodies (Nabs) to IFN at EOS-CP will be summarized by treatment group.

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

[redacted]

Pulmonary function test (PFT) data will consist of the following parameters: FEV_1, FVC, and D_LCO. Summary tables and listings will be produced for percentage of predicted value when applicable. For the purpose of the statistical analysis the percentage of predicted value will be calculated centrally and this centrally calculated value will be used for the study level analysis. The data will be summarized by presenting summary statistics of change from baseline. The frequency of patients who had PFT measurements below 80% of predicted, and shift tables presenting the frequency of patients with normal (≥80% of predicted when applicable) and abnormal (< 80% of predicted when applicable) will be presented.

The ophthalmic data will be summarized using the distribution tables, summary statistics, and change from baseline by visit and treatment group for visual acuity, OCT, and other ophthalmic parameters. The patient listing with these parameters will also be provided.

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

Frequency distribution of treatment-emergent suicidal ideation and behaviors from C-SSRS will be summarized. The proportion of patients who have completed suicide, suicide attempt, and preparatory actions toward imminent suicidal behavior, suicidal ideation, and self-injurious behavior without suicidal intent will be summarized by treatment group.

Safety data will be summarized for the overall population and listings provided for the pre-pubertal subgroup.

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

Fingolimod Extension Phase:

All safety endpoints, including adverse events (adjusted by the duration of fingolimod exposure), bradycardia events, laboratory tests, vital signs, pulmonary function tests, ophthalmic examinations, C-SSRS, ECG data, and [redacted] will also be summarized based on the long-term safety data during fingolimod treatment , by core treatment and combined using the Fingolimod Treated Safety Set. [redacted]

[redacted]

9.5.5 Pharmacokinetics

Online pharmacokinetics

All patients who have a body weight of 40 kg or less at study entry in the Core or Extension Phase will have samples taken at Month 1 of the Core Phase and/or Extension Phase, respectively for on-line pharmacokinetic analysis. Only patients in the fingolimod group in

the Core Phase or patients switched from interferon b-1a to fingolimod in the Extension Phase will have their samples analyzed.

The Month 1 Core Phase and/or Extension Phase pharmacokinetic samples from all patients treated with fingolimod weighing 40 kg or less will be evaluated for dose optimization (need for increase to 0.5 mg). These samples will be analyzed within one month (online analysis) to ensure the systemic exposure is adequate. The results should be available for the Month 2 Core Phase and/or Extension Phase visit where the dose adjustment, if needed, would take place.

The pre-dose concentration at Month 1 Core Phase and/or Extension Phase and the approximately 6-hour post-dose concentration (good marker of fingolimod-P peak concentration), will be averaged to provide a surrogate for the average concentration (Cav).

If in a patient weighing 40 kg or less, who has been receiving 0.25 mg/day fingolimod, Cav is greater than 65% of target concentration of 1.35 ng/mL, i.e. 0.9 ng/mL, the patient will continue on the 0.25 mg dose. If in such a patient Cav is smaller than 65% of the target concentration i.e. smaller than 0.9 ng/mL, the dose will be increased to 0.5 mg/day.

Population pharmacokinetic analysis

Core Phase:

A population pharmacokinetic analysis will be used to characterize the key pharmacokinetic parameters in this patient population. Additionally, this analysis will also determine whether there are population covariates that affect the pharmacokinetics of fingolimod-P when administered to this patient population.

The effect of covariates on pharmacokinetic parameters will be explored. Covariates examined will include age, weight, gender, and ethnicity, as well as comedications such as oral ketoconazole which has been shown to interact with fingolimod or fingolimod-P in adults (increase in fingolimod and fingolimod-P plasma concentrations). The choice of covariates to be included in the model will be guided by exploratory plots of random effects (inter-individual variability parameters) against covariates. Those that are judged to show evidence of a relationship with the random effects will be tested for entry into the model, using the likelihood-ratio test with $p < 0.05$. The final covariate model will be derived using a rigorous and acceptable model building procedure.

Population pharmacokinetic/pharmacodynamic analysis

Core Phase:

Population PK/PD modeling approaches will be used to relate the individual fingolimod PK parameter estimates to key efficacy measurements (MRI-related, relapse-related). A modeling plan will be prepared before final clinical data lock providing details for the proposed PK/PD analysis.

9.6 Sample size calculation

Core Phase:

The sample size calculations are based on the primary efficacy variable, the annualized relapse rate (ARR). The sample size calculations and power considerations follow the method outlined in Keene et al, 2007 with a constant dispersion parameter k and were programmed manually using the SAS software.

Different scenarios of the anticipated treatment effect between fingolimod 0.5 mg versus IFN β-1a, have been evaluated based on the available data on fingolimod and on IFN β-1a in the Phase III program in adults. In the TRANSFORMS study (FTY720D2302), a double-blind, one-year study, fingolimod 0.5 mg was directly compared to interferon beta-1a i.m. The ARR (0.21) in patients treated with fingolimod 0.5 mg was reduced by 52% compared to the ARR (0.43) in patient treated with IFN beta-1a.

The initial assumptions for this study (based on adult patient data) are as follows: Assuming a 50% relative reduction (from 0.72 to 0.36) in the relapse rate over 24 months (ARR: λ_1=0.18 for fingolimod, λ_2=0.36 for interferon beta-1a), a sample size of 95 patients per treatment group (or 190 total) would be needed for a 24-months study in order to provide 80% statistical power to detect such a reduction at a two-sided alpha level of 0.05 (with dispersion parameter of k=0.82). This corresponds to information I= 16.36 (equation 2 in Appendix 5).

The study duration can be revised based on BSSR; the power for the primary statistical test will be retained at 80%.

BSSR and End of Study:

Analysis based data reviews of the aggregate relapse data will be conducted to re-estimate the amount of information (I) generated by the study based on the relapse activity (λ) of the recruited patient population and the observed dispersion parameter (κ) in the accumulated study data. All patients will be treated as one group, and the treatment code will not be revealed in the process. Such BSSR's provide an adequate means to check assumptions that were made at the planning stage of a clinical study protocol. They do not pose a scientific risk in terms of bias or type-I-error control and can be used to modify the sample size or study duration if this is indicated by the results.

Designs which provide the same amount of information also provide the same power (for a constant treatment effect, λ_1/λ_2, and alpha). As in a BSSR (Friede and Schmidli 2010), fitting a negative binomial model to the aggregate data (i.e., the relapse data of all patients combined) provides an estimate of the overall ARR λ and the dispersion parameter κ. For an assumed rate ratio (clinically meaningful difference of 50%) of $\theta = \lambda_1/\lambda_2$, estimates can be obtained of the ARRs in the two groups, $\lambda_1 = 2*\lambda*\theta /(1+\theta)$ for fingolimod, and $\lambda_2=2*\lambda/(1+\theta)$ for interferon beta-1a. Based on the estimated values from the BSSR, the information (I) can be determined as follows (see equation 3 Appendix 5).

$$\text{Information } I_{review} = [2/ (\lambda_1 T_{total}) + 2/(\lambda_2 T_{total}) + 4 \kappa T2_{total}/T_{total}^2]^{-1}$$

where λ_1, λ_2, and κ are the re-estimated values assuming a rate ratio=50% at the BSSR.

- **If the Information from the BSSR ensures that the targeted 80% power for the primary analysis is maintained, then the Core Phase of the study will complete.** It means that the study has collected equivalent or more information than initially planned (≥80% power for the primary objective of the study). All patients can roll over into the Extension Phase.
- [redacted]
- Any data collected during follow up period but after the Core Phase data base lock will be reported in the Extension Phase.

Fingolimod Extension Phase:

The sample size for the Extension Phase can only be estimated on the basis of expected drop-out rate in the Core Phase. Assuming the drop-out rate to be 15%, we can expect to have approximately 162 patients eligible for the Extension Phase.

9.7 Power for analysis of key secondary variables

Core Phase:

For a 24-month study and assuming a fingolimod rate of n/neT2 lesions over 24 months of 2.3 a sample size of 95 per treatment group (or 190 total) will provide approximately 88% statistical power to detect a relative reduction of 50% (i.e., from 4.6 to 2.3) in the fingolimod group compared to the interferon beta-1a group. This sample size calculation assumes that the number of n/neT2 lesions over 24 months follows a negative binomial distribution. A negative binomial dispersion estimate of 2.0 was assigned which is within the 95% confidence interval. Using the same assumptions as above with a dispersion estimate of 2.67 will provide approximately 79% statistical power to detect a relative reduction of 50% (i.e., from 4.6 to 2.3) in the fingolimod group. These estimates were based on the FREEDOMS study (FTY720D2301).

As illustrated by the above sample size calculations, sample size requirements for the n/ne T2 endpoint are lower than those for the primary endpoint. It is therefore assumed that the power for the key secondary endpoint can be maintained at ≥80% even if the study duration is revised based on the results from the BSSR.

9.8 Interim analyses

Interim analyses for the Data Monitoring Committee (DMC) may be performed (see Section 7.4).

10 Ethical considerations

10.1 Regulatory and ethical compliance

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

10.2 Informed consent procedures

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

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

Females 16 years or older, or in case there is a concern that a female patient of child-bearing potential is or might become sexually active, as assessed by the investigator, the patient and her parents/caregivers should be informed about the potential risks of pregnancy and the need to prevent pregnancy during the study. Please also refer to Section 6.6.

Females of childbearing potential who are or might become sexually active, should also be informed that taking the study drug may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

10.3 Responsibilities of the investigator and IRB/IEC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to Novartis before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data

and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

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

11 Protocol adherence

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

11.1 Protocol Amendments

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

12 References (available upon request)

Banwell, B. Bar-Or A, Giovannoni G, et al. (2011) Therapies for multiple sclerosis: considerations in the pediatric patient. Nature Reviews Neurology, 7; 109–122.

Banwell B, Shroff M, Ness JM, et al (2007) MRI features of pediatric multiple sclerosis. Neurology; 68(Suppl 2):S46-53.

Benson LA, Healy BC, Gorman MP, et al (2014) Elevated relapse rates in pediatric compared to adult MS persist for at least 6 years. Mult Scler Relat Disord; 3(2):186-93.

Banwell B, Tremlett H (2005). Coming of age: The use of immunomodulatory therapy in children with multiple sclerosis. Neurology; 64(5):778-779.

Boiko A, Vorobeychik G, Paty D, et al (2002) Early onset multiple sclerosis – A longitudinal study. Neurology; 59:1006-1010.

Bousquet J, Mantzouranis E, Cruz AA, et al (2010) Uniform definitions of asthma severity, control and exacerbations: Document presented for the World Health Organization Consultation on Severe Asthma. J Allergy Clin Immunol; 126(5):926-938.

CDC (2012) Mumps: Chapter 9. VPD Surveillance Manual. 5th Edition: 1-18.

CDC (2013) Prevention of Measles, Rubella, Congenital Rubella Syndrome, and Mumps. Morbidity and Mortality Weekly Report (MMWR); 62(RR04):1-34.

Chitnis T, Glanz B, Jaffin S, et al (2009) Demographics of pediatric-onset multiple sclerosis in an MS center population from the Northeastern United States. Mult Scler; 15(5):627-631.

Chitnis T, Tardieu M, Amato MP, et al (2013). International Pediatric MS Study Group Clinical Trials Summit: Meeting report. Neurology; 80:1161–1168.

Cohen JA, Barkhof F, Comi G, et al (2010) Oral fingolimod or interferon for relapsing multiple sclerosis. N Engl J Med; 362(5):402-415.

De Sá J, Paulos A, Mendes H, et al (2006) The prevalence of multiple sclerosis in the District of Santarém, Portugal. J Neurol; 253(7):914-918.

Friede T, Schmidli H, (2010) Blinded Sample Size Reestimation with Negative Binomial Counts in Superiority and Non-inferiority Trials. Methods Inf Med; 6: 618-624.

Gadoth N (2003) Multiple sclerosis in children. Brain Dev; 25(4):229-232.

Ghezzi A, Banwell B, Boyko A, et al (2010) The management of multiple sclerosis in children: a European view. Mult Scler; 16(10):1258-1267.

Ghezzi A, Pozzilli C, Grimaldi LME, et al (2010) Safety and efficacy of natalizumab in children with multiple sclerosis. Neurology; 75(10):912-917.

Jacobs LD, Beck RW, Simon JH, et al (2000) Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS Study Group. N Engl J Med; 343(13):898-904.

Kappos L, Freedman MS, Polman CH, et al (2007) Effect of early versus delayed interferon beta-1b treatment on disability after a first clinical event suggestive of multiple sclerosis: a 3-year follow-up analysis of the BENEFIT study. Lancet; 370(9585):389-397.

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

Kearns GL, Abdel-Rahman S, Alander SW, et al (2003) Developmental Pharmacology-drug disposition, action and therapy in infants and children. N Engl J Med; 349(12):1157-1167.

Keene ON, Jones MR, Lane PW, et al (2007) Analysis of exacerbation rates in asthma and chronic obstructive pulmonary disease: example from the TRISTAN study. Pharm Stat; 6(2):89-97.

Krupp LB, Tardieu M, Amato MP, et al (2013) International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. Mult Scler 0(0) 1–7 (published online 9 April 2013)

Kuntz NL, Chabas D, Weinstock-Guttman B, et al (2010) Treatment of multiple sclerosis in children and adolescents. Expert Opin Pharmacother; 11(4):505-520.

Lurbe E, Cifkova R, Cruickshankd JK, et al (2009) Management of high blood pressure in children and adolescents: recommendations of the European Society of Hypertension. J Hypertens; 27(9):1719-1742.

Marshall WA, Tanner JM (1969) Variations in pattern of pubertal changes in girls. Arch Dis Child; 44(235):291-303.

Marshall WA, Tanner JM (1970) Variations in the pattern of pubertal changes in boys. Arch Dis Child; 45(239):13-23.

McDonald WI, Compston A, Edan G, et al (2001) Recommended diagnosis criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol; 50(1):121-127.

Melcon MO, Gold L, Carra A, et al (2008) Argentine Patagonia: prevalence and clinical features of multiple sclerosis. Mult Scler; 14(5):656-662.

NIH Clinical Center (Internet) Available from: http://cclnprod.cc.nih.gov/dlm/testguide.nsf>; 10th May 2012.

Panitch H, Goodin DS, Francis G, et al (2002) Randomized, comparative study of interferon beta-1a treatment regimens in MS: The EVIDENCE Trial. Neurology; 59(10):1496-1506.

Pinhas-Hamiel O, Sarova-Pinhas I, Achiron A (2001) Multiple sclerosis in childhood and adolescence: clinical features and management. Paediatr Drugs; 3(5):329-336.

Pohl D, Waubant E, Banwell B, et al (2007) Treatment of pediatric multiple sclerosis and variants. Neurology; 68(16 Suppl 2):S54-65.

Polman CH, Reingold S, Banwell B, et al. (2011) Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol; 68: 292-302.

Polman CH, Bertolotto A, Deisenhammer F, at al. (2010) Recommendations for clinical use of data on neutralizing antibodies to interferon-beta therapy in multiple sclerosis. Lancet Neurol; 9: 740–50.

Renoux C, Vukusic S, Mikaeloff Y, et al (2007) Natural history of multiple sclerosis with childhood onset. N Engl J Med; 356(25):2603-2613.

Ruggieri M, Pollizi A, Pavone L, et al (1999) Multiple sclerosis in children under 6 years of age. Neurology; 53(3):478-484.

Ruggieri M, Iannetti P, Polizzi A, et al (2004) Multiple sclerosis in children under 10 years of age. Neurol Sci; 25 (Suppl 4):S326-335.

The Fourth Report on the Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents (2005) US. Department of Health and Human Services. NIH Publication No. 05-5267.

Trojano M, Liguori M, Boscoe Zimatore G, et al (2002) Age related disability in multiple sclerosis. Ann Neurol; 51(4):475-480.

Turan S, Topcu B, Gökce I et al (2011) Serum Alkaline Phosphatase Levels in Healthy Children and Evaluation of Alkaline Phosphatase z-scores in Different Types of Rickets. J Clin Res Ped Endo; 3(1):7-11

Venkateswaran S, Banwell B (2010) Pediatric multiple sclerosis. Neurologist; 16(2):92-105.

Weinshenker BG, Bass B, Rice GP, et al (1989a) The natural history of multiple sclerosis: a geographically based study. I. Clinical course and disability. Brain; 112(Part 1):133-146.

Weinshenker BG, Bass B, Rice GP, et al (1989b) The natural history of multiple sclerosis: a geographically based study. 2. Predictive value of the early course. Brain; 112(Part 6):1419-1428.

Waubant E, Chabas D, Okuda DT, et al (2009) Difference in disease burden and activity in pediatric patients on brain magnetic resonance imaging at time of multiple sclerosis onset vs adults. Arch Neurol; 66(8):967-971.

Wingerchuk DM, Lennon VA, Pittock SJ, et al. (2006) Revised diagnostic criteria for neuromyelitis optica. Neurology; 66: 1485-1489.

Yeh EA, Chitnis T, Krupp L, et al (2009) Pediatric multiple sclerosis. Nat Rev Neurol; 5(11):621-631.

Yeh EA, Weinstock-Guttman B (2010) Natalizumab in Pediatric multiple sclerosis. Ther Adv Neurol Disord; 3(5):293-299.

Yeh EA; Waubant E, Krupp L et al. (2011) Multiple Sclerosis Therapies in Pediatric Patients With Refractory Multiple Sclerosis. Archives Neurology; 68(4): 437-444.

13 Appendix 1: Clinically notable laboratory values and vital signs

The clinically notable laboratory and vital sign values to be used for this study are listed below.

Table 13-1 Hematology and blood chemistry notable values

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

Table 13-2 Urinalysis clinically notable values

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

Table 13-3 Vital sign clinically notable values

Vital Sign	Age group	Notable criteria
Heart Rate	<12 years	>130 bpm or increase of ≥15 bpm from baseline Or <70 bpm or decrease of ≥15 bpm from baseline
	≥12 years	>120 bpm or increase of ≥15 bpm from baseline Or <50 bpm or decrease of ≥15 bpm from baseline
Systolic Blood Pressure	<12 years	≥125 mmHg or increase of ≥20 mmHg from baseline Or ≤70 mmHg or decrease of ≥20 mmHg from baseline
	≥12 to <18 years	≥160 mmHg or increase of ≥20 mmHg from baseline Or
	≥12 years	≤90 mmHg or decrease of ≥20 mmHg from baseline
	≥18 years	≥180 mmHg or increase of ≥20 mmHg from baseline
Diastolic Blood Pressure	<12 years	≥85 mmHg or increase of ≥15 mmHg from baseline Or ≤50 mmHg or decrease of ≥15 mmHg from baseline
	≥12 to <18 years	≥95 mmHg or increase of ≥15 mmHg from baseline Or
	≥12 years	≤50 mmHg or decrease of ≥15 mmHg from baseline
	≥18 years	≥105 mmHg or increase of ≥15 mmHg from baseline
Temperature		>38.3 °C or a change of 1.1 °C

Vital Sign	Age group	Notable criteria
		from baseline
Weight		≥7% decrease from baseline weight

14 Appendix 2: Guidelines for first dose monitoring

Patients must have their first intake/injection of study drug in the Core and Extension Phase at the site and monitored by the independent First-dose Administrator. An ECG must be obtained and evaluated prior to the first dose of study drug and 6 hours after. Baseline or pre-dose ECG should be available for comparison to the post-dose ECG. Sitting heart rate and blood pressure must be measured prior to the first dose of the study drug and then every hour for at least 6 hours thereafter.

When obtaining the sitting heart rate the patient should be allowed to rest for 5 minutes. Prior to the first dose of study drug, the sitting heart rate and blood pressure measurements should be repeated twice to produce three readings for both heart rate and blood pressure.

Patients should receive the first dose of study drug before 12:00 PM (noon) at the site.

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

- Heart rate (sitting) at discharge must be at least 55 bpm (in patients 12 years or older) or 60 bpm (in children below 12)
- Heart rate (sitting) at discharge must not be the lowest hourly value measured during the observation period (which would be suggestive of a continuing progressive decline in heart rate)
- Patients must have no symptoms in sitting or standing position associated with decreased heart rate or received treatment for bradycardia
- ECG at 6 hours should not show any new significant abnormalities, other than asymptomatic sinus bradycardia, not observed at the patient's pre-dose ECG (e.g. prolongation of QT/QTcF interval, persistent new onset 2nd degree (Mobitz Type I (Wenkebach) or higher AV block, 3rd degree AV block at any time during monitoring).

The same monitoring procedure applies also to the re-initiation of study drug after interruption (Section 5.5.5) and at the time of individual dose-increase (Section 3.3). In the Core Phase, re-initiation of study drug monitoring must be done by the independent first dose monitoring team in order to maintain the blind. However, in the Extension Phase monitoring for re-initiation of study drug or dose increases may be conducted by the main study team.

Patients who are off study drug treatment for the following durations:

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

Patients should have written instruction on when to return to the clinic and a 24 hour contact phone number to call in the event of any new or warranted symptoms (chest pain, dizziness, palpitations, syncope, nausea, vomiting, etc.).

If the above discharge criteria are not met, patients should continue to be observed until they are met (the observation must last for at least 2 hours even if the criteria are met earlier).

However, patients experiencing any symptomatic event associated with reduction of the heart rate, a heart rate of < 45 bpm at the end of the 6-hour monitoring, received treatment for bradycardia, or had relevant changes on the ECG, not resolving by the end of the 6-hour monitoring (e.g. ECG at 6 hours shows a QTcF interval ≥500 msec), must be hospitalized overnight. For those patients, the Day 2 dose of study drug should be given in the hospital according to monitoring and discharge criteria described above.

First/redose study drug discontinuation criteria are listed below and all ECG and other reasons requiring permanent study drug discontinuation are described in Section 5.5.9:

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

Patient with symptomatic events or relevant changes on ECG should be followed until symptoms/ECG finding have resolved or condition has stabilized.

In addition to the above described first dose monitoring and discharge criteria required per protocol, additional monitoring post first dose may be required in some countries/regions per the local product information for Gilenya for the treatment of adult RRMS. Of note, in some regions, like in the EU, the Product Information recommends to perform additional continuous (real time) ECG monitoring during the first 6 hours post first dose.

Recommendations for the management of bradycardia

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

15 Appendix 3: Guidance on safety monitoring

15.1 Guidance on the monitoring of patients with elevated blood pressure

In children and adolescents, the normal range of blood pressure (BP) is determined by body size and age. Standardized BP norms, based on sex, age and height, as well as recommendations for diagnosing, management and treatment of high blood pressure in children and adolescents have been published (NIH Publication No. 05-5267, Lurbe et al. 2009).

Using the standardized reference tables as described in these reference, if the BP is greater than the 95th percentile, BP should be staged.

- If BP is Stage 1 (95th percentile to 99th percentile plus 5 mmHg), BP measurements should be repeated within 1 month
- If BP is Stage 2 (>99th percentile plus 5 mmHg), prompt referral should be made for evaluation and treatment.
- If the patient is symptomatic, immediate referral and treatment are indicated.

The study drug should not be discontinued, unless the physician has a reason to do so. A newly diagnosed hypertension as well as an aggravation of a preexisting condition must be reported as an AE.

15.2 Guidance on monitoring of patients with elevated liver function tests

ALT/AST

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

In case of detection of elevated ALT/AST values >3 times ULN which are accompanied by symptoms (general malaise, fatigue, abdominal pain, nausea or vomiting, rash with eosinophilia) study drug needs to be discontinued immediately; hospitalize patient if clinically appropriate; establish causality. Further follow-up should include ALT, AST, TBL, Alb, PT/INR, AP and GGT until resolution[c] (see below definition; frequency at investigator discretion).

In case of detection of elevated ALT/AST values ≥5 times the ULN, Blood chemistry liver panel including ALT, AST, AP, GGT, Alb, PT/INR, total and conjugated bilirubin must be performed within 48 hours. If ALT/AST elevation persists for more than 2 weeks, study drug administration must be interrupted. The patient should be followed up bi-weekly, until no further increase in AST/ALT is observed. Further follow-up should include ALT, AST, TBL, Alb, PT/INR, AP and GGT until resolution[c] (frequency at investigator discretion).

If ALT/AST values reach 8 times the ULN, and the value is confirmed on a repeat lab within 48 hours, the study drug must be permanently discontinued (Section 5.5.9). Follow-up should include ALT, AST, TBL, Alb, PT/INR, AP and GGT until resolution[c] (frequency at investigator discretion).

Alkaline phosphatase (AP)

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

Bilirubin

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

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

Follow-up on ALT, AST, TBL, Alb, PT/INR, AP and GGT until resolution[c] (frequency at investigator discretion) and also test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin).

Concomitant elevation of ALT/AST and bilirubin (Potential Hy's Law case)

In case of elevation of ALT/AST >3 times the ULN and total bilirubin >2 times the ULN but without increase in AP >2 times the ULN (i.e. "Hy's law" criterion is met), study drug must be discontinued immediately and patient be hospitalized if clinically indicated; causality should be determined and the event reported as an AE/SAE as appropriate. The follow-up should include ALT, AST, TBL, Alb, PT/INR, AP and GGT until resolution[c] (frequency at investigator discretion).

Patients with clinical symptoms; jaundice; reinitiation of study drug

Patients who develop symptoms suggestive of hepatic dysfunction, such as, but not limited to, unexplained vomiting, abdominal pain, fatigue, anorexia, dark urine, should have liver enzymes checked, and study drug should be discontinued if significant liver injury is confirmed.

In case of jaundice the patient must discontinue the study drug immediately, should be hospitalized and causality established. The follow-up should include ALT, AST, TBL, Alb, PT/INR, AP and GGT until resolution[c] (frequency at investigator discretion).

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.

Re-initiation of the study drug should only be considered once the ALT/AST decrease is below 2 times the ULN. In case of re-starting the study drug, it is recommended that ALT/AST is assessed weekly for the 1st month and then monthly for the 2nd and 3rd months. The occurrence of new elevations greater than 5 times the ULN for the ALT/AST values will lead to permanent discontinuation of the study drug (Section 5.5.9). In cases of confirmed diagnosis of hepatic dysfunction, patients should be followed until symptom resolution (see below for definition)[c] or until the condition stabilizes.

Liver-specific events must be recorded in the appropriate eCRF. SAEs must be filed as appropriate.

Any interruption or discontinuation of the study drug should be clearly documented in the Dosage Administration Record eCRF. AE/SAEs must be filed as appropriate.

[c] Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

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

Should a patient develop any unexpected neurological or psychiatric symptoms/signs or accelerated neurological deterioration, the investigator should schedule a complete physical and neurological examination and an MRI as soon as possible. Discontinuation of study drug should be considered. In case of new unexpected findings in the MR images, mainly if not compatible with MS lesions, it is recommended to obtain a CSF sample for cellular, biochemical and microbiological analysis (e.g. herpes virus, JC virus). Further diagnostic evaluations should be performed at discretion of the investigator. Steroid treatment should only be started once an infectious origin has been excluded or properly treated.

The MRI must be evaluated by the local neuroradiologist. A copy of the unscheduled MRI should be sent to the central MRI reading center as soon as possible. AE/SAEs need to be filed as appropriate. The investigator will contact the Medical Advisor at Novartis to discuss findings and diagnostic possibilities as soon as possible.

Only when the differential diagnosis evaluations have excluded other possible diagnosis than MS the study drug may the restart of study drug be considered.

15.4 Guidance on monitoring of patients with notable lymphopenia

The absolute total WBC, neutrophil and lymphocyte counts will be measured at each visit by the central laboratory and will be blinded from the sponsor and the investigator and will only be communicated to the site in case of a notable abnormality (refer to Appendix 1 for notable abnormalities). For lymphocyte count this is defined as $<0.2 \times 10^9$/L, in which case the lymphocyte count should be repeated in two weeks by the central lab to confirm the reading. If the repeat test confirms the lymphocyte count is below 0.2×10^9/L or 200 cells/mm^3, the study drug must be discontinued and the lymphocytes count needs to be monitored monthly until levels return back to normal limits (by local laboratory for monitoring levels). If monthly site visits create a logistical burden for the patient, local lymphocyte testing can be performed, and ideally an additional sample should also be sent to central laboratory for analysis. In the

event that central laboratory analysis is not available, the results of the local laboratory values (including reference ranges) should be included in the eCRF to document recovery of values. The patient should be evaluated and monitored for infections on a regular basis. Re-initiation of the study drug can only be considered once the lymphocyte counts are back within normal limits.

15.5 Guidance on monitoring of patients with infections

The investigator should be vigilant for risk of infections, including opportunistic infections, with bacterial (e.g. atypical mycobacteria) viral (e.g. HSV, VZV, JCV or fungal (e.g. cryptococcus agents) and should remind the patient of the risk of infections and to instruct them to promptly report any symptoms of infections to the investigator. Investigators are requested to specifically ask about infections at each visit. All infections that develop during the study will be reported as AEs. The investigator will be notified in case of notably abnormal values for total WBC (<3000 cells/mm^3), neutrophil (<1000 cells/mm^3) and lymphocyte (<200 cells/mm^3) counts. The patient should be evaluated and monitored for infections on a regular basis. The investigator should consider early treatment with specific antimicrobial therapy on the basis of clinical diagnosis or suspicion thereof in consultation with infections disease experts, as appropriate. The infectious disease expert may conduct additional evaluations, including laboratory, if deemed necessary for treatment decisions. Investigators should consider the added immunosuppressive effects of corticosteroid therapy for treatment of MS attack/relapse and increase vigilance regarding infections during such therapy and in the weeks following administration.

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

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

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

- HSV-1 IgG positive: Cold sores
- HSV-2 IgG positive: Herpes genitalis

The investigator should instruct the patient to be alert to and report any symptoms or signs suggestive of cold sores, genital ulcers or shingles, so that appropriate anti-viral treatment can be initiated in consultation with a local infectious disease expert (if needed). A negative IgG antibody test result for HSV-1 and HSV-2 places patient at risk for more severe and atypical manifestations of primary infection in the event they are exposed to these viruses while they are immunosuppressed (taking study drug and/or corticosteroids). Patients should be instructed to promptly report any exposure to these viruses e.g. to a person with cold sores, herpes genitalis, or measles, respectively. In case of exposure, early treatment with appropriate antiviral drugs and/or post exposure prophylaxis with immunoglobulin should be considered in consultation with a local infectious disease expert.

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.

The Investigator should consider early treatment with specific therapy on the basis of clinical diagnosis of infection or suspicion thereof (e.g., antiviral treatment for herpes simplex or varicella zoster virus [VZV]; treatment for cryptococcus) in consultation with infectious disease experts, as appropriate. Investigators should be aware that in the post-marketing setting with Gilenya, isolated cases of cryptococcal meningitis have been reported. Patients reporting symptoms and signs (such as, but not limited to, headache accompanied with stuff neck, sensitivity to light, fever, confusion, tiredness, body aches, chills, vomiting, and/or nausea) consistent with meningitis should undergo prompt diagnostic evaluation. If cryptococcal meningitis is diagnosed, appropriate treatment should be initiated as soon as possible. The Investigator should inform the Novartis and CRO medical experts of any such cases. See also section 15.3 for guidance on JC virus

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

15.6 Guidance on vaccinations

Guidance on Screening serology:

Proof of immunity is required for VZV, measles, mumps, rubella, diphtheria, pertussis and tetanus.

Varicella-zoster virus (VZV):

Patients must have evidence of immunity to varicella which includes any of the following:

- Documentation of age appropriate varicella vaccination (2 doses of varicella vaccine for school-age children and adolescents)
- Laboratory evidence of immunity or laboratory confirmation of disease.
- Diagnosis or verification of a history of varicella or herpes zoster by a health care provider

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

- an epidemiologic link to another typical varicella case or to a laboratory confirmed case, or
- evidence of laboratory confirmation, if testing was performed at the time of acute disease.

With this evidence patients may enter the study without testing for antibodies.

- Patients who do not have evidence of immunity may still be screened for participation in the study, but will need to be tested for antibodies to VZV antigen as part of the screening labs and may enter the study if they receive the full course of VZV vaccine.
- A patient may be randomized in the trial 1 month after the last dose of vaccination without further serology testing for VZV.

Measles, Mumps and Rubella (MMR):

Patients must have evidence of immunity to MMR which includes any of the following:

- Documentation of age appropriate MMR vaccination (2 doses of MMR for school-age children and adolescents)
- Laboratory evidence of immunity or laboratory confirmation of prior disease.

With this documentation patients may enter the study without testing for antibodies to these antigens.

- Patients who do not have evidence of immunity to MMR may still be screened for participation in the study, but will need to be tested for antibodies to MMR antigens as part of the screening labs and if negative will need to be vaccinated prior to enrollment in the study. Once vaccinated no further testing is required.

The last dose of the vaccine should be given at least 4 weeks prior to randomization

Diphtheria, tetanus and pertussis (DTP):

Patients must have evidence of immunity to DTP which includes any of the following:

- Documented proof of age appropriate vaccination (including boosters).

With this documentation patients may enter the study without testing for antibodies to these antigens.

- Patients who do not have evidence of immunity may still be screened for participation in the study, but will need to be tested for DTP antibodies as part of the screening labs and if negative will need to be vaccinated prior to enrollment in the study. Once vaccinated no further testing is required.
- Booster dose for diphtheria, tetanus and pertussis may be given at least 2 weeks prior to randomization. Once vaccinated no further serology testing is required.

Hepatitis:

- Patients who are positive for any of the following serology markers for hepatitis A, B, C and E are excluded from the study:
  - anti-HAV IgM
  - HBs Ag and/or anti-HBc IgM
  - anti-HCV IgG or HCV by RNA PCR
  - anti-HEV IgM or IgG (if IgG positive, HEV-RNA PCR should be performed, if PCR is negative patient can be included).

  Note: Patients who have been vaccinated against HBV (only anti-HBs-IgG would be detectable from the HBV serologic markers) and patients cured from previous HAV or HBV infection with normal liver transaminases values are not excluded.

Herpes simplex virus-1, herpes simplex virus-2:

- Patients who are negative for anti-herpes simplex virus-1 IgG or anti-herpes simplex virus-2 IgG antibodies are not excluded but should be informed of their status (refer to Appendix 3 Section 15.5 above).

Epstein Barr virus (EBV), cytomegalo virus (CMV)

- Patients are not excluded from participation. Serology is obtained for documentation purposes.

General Guidance:

In addition, any live or live attenuated vaccine that, as per the local vaccination schedule, would be scheduled during the duration of the study must be administered at least one month prior to entering the study to allow the full effect of the vaccination to occur. Vaccinations with live or live attenuated vaccines are prohibited while the patients are taking study drug and for two months after study drug discontinuation.

Vaccines containing dead or inactivated microorganisms or derived purified products can be administered while the patient is on study drug (e.g., inactivated seasonal influenza vaccine, tetanus, inactivated hepatitis B, DTP). Data from a vaccination study have shown that subjects treated with fingolimod are able to mount an immune response to influenza vaccine (refer to fingolimod Investigators Brochure for further details).

15.7 Guidance on monitoring of pulmonary function

Patients reporting any respiratory symptoms such as dyspnea, shortness of breath, chest tightness or wheezing should be scheduled to be seen for a clinical assessment. In case of clinically relevant respiratory symptoms, the patient should be referred to a pulmonologist for assessment and treatment, if warranted. It is recommended to perform a spirometry for evaluation of pulmonary function, including FEV_1, FVC and DLCO for comparison to the baseline assessment. Further exploratory evaluations should be performed at the discretion of the pulmonologist.

In case of persistent respiratory symptoms or pulmonary function abnormalities over a 3-month period, despite appropriate treatment, the Primary Treating Physician should consider an interruption/discontinuation of the study drug. Patient should be followed until symptoms resolved or condition has stabilized.

Any patient with abnormal pulmonary function tests (PFTs), including patients that have discontinued study drug, should be followed until PFTs return to within the normal range for the age or until the condition has stabilized.

15.8 Guidance for ophthalmic examination

Unscheduled ophthalmic examinations in case of visual complaints/worsening of vision

During the study, if there are visual complaints or any worsening of visual acuity then an ophthalmic examination should be scheduled to evaluate visual acuity and the macula and optic disc by dilated ophthalmoscopy (may include lens biomicroscopy). An OCT should be performed if there is objective evidence of worsening visual acuity equal to two or more lines on a standard eye chart using best corrected vision or if the ophthalmologist determines that an OCT should be conducted. If patients report visual disturbances at any time while on therapy, evaluation of the fundus, including the macula, should be carried out by an

ophthalmologist. Further explorations, such as fluorescein angiography (FA), should be performed at the discretion of the ophthalmologist.

Guidance on monitoring of patients with diagnosis of macular edema

Patients with diagnosis of macular edema must permanently discontinue the study drug (Section 5.5.9).

These patients must be followed up with monthly ophthalmologic evaluations until such time when resolution is confirmed or no further improvement is expected by the ophthalmologist (based on a follow up period of not less than 3 months). These evaluations will include repeat best-corrected visual acuity, fundus examination, and OCT. Fluorescein angiography (FA) is repeated at the discretion of the ophthalmologist. If the patient does not show definite signs of improvement on examination by specialist testing (e.g. OCT, FA) after 6-8 weeks after discontinuation of study drug, then therapy for macular edema in conjunction with an ophthalmologist experienced in the management of this condition should be initiated. Patients should be followed until symptom resolution or until the condition stabilizes.

Discontinuation of the study drug should be clearly documented and reflected on Dosage Administration Record eCRF and AE/SAEs must be reported as appropriate. For patients diagnosed with macular edema copies of the colored OCT and FA images, if available, should be kept by the investigative site as source documents.

Guidance on monitoring of patients with diabetes mellitus or uveitis

Each patient with a history of diabetes mellitus, history of uveitis and/or findings in the screening ophthalmic evaluations compatible with uveitis (e.g., significant anterior chamber cell or flare, vitreous cell or flare, pars planitis, vasculitis, chorioretinitis) must undergo more frequent and extensive ophthalmic examinations, as follows:

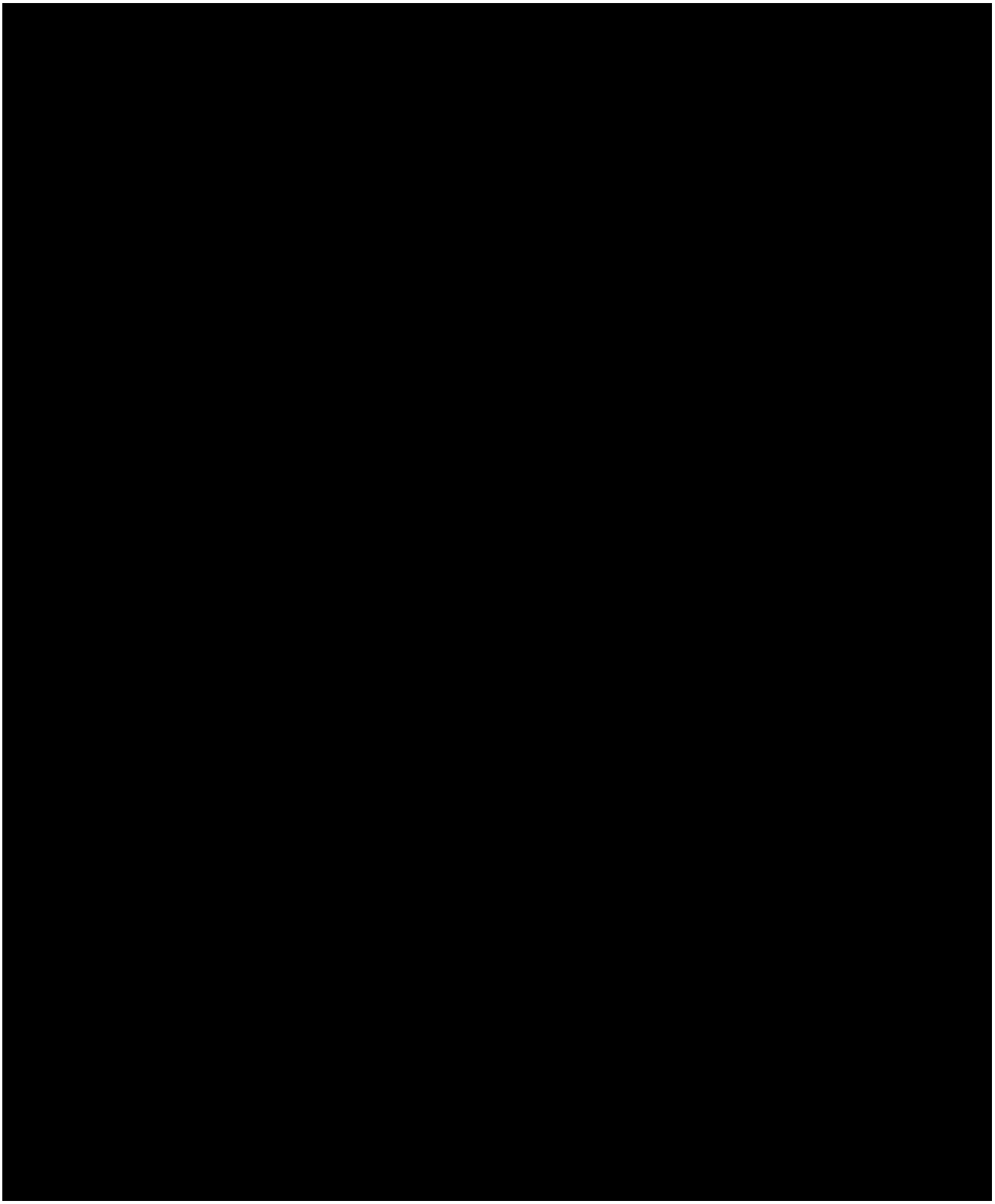
Ophthalmic visits should be scheduled at Months 3, 6 and every 3 months for the first year and then every 6 months thereafter per protocol. In addition to the assessments performed in the ophthalmic scheduled visits (i.e., best corrected visual acuity and dilated ophthalmoscopy), an OCT should be performed at each visit to evaluate the macula.

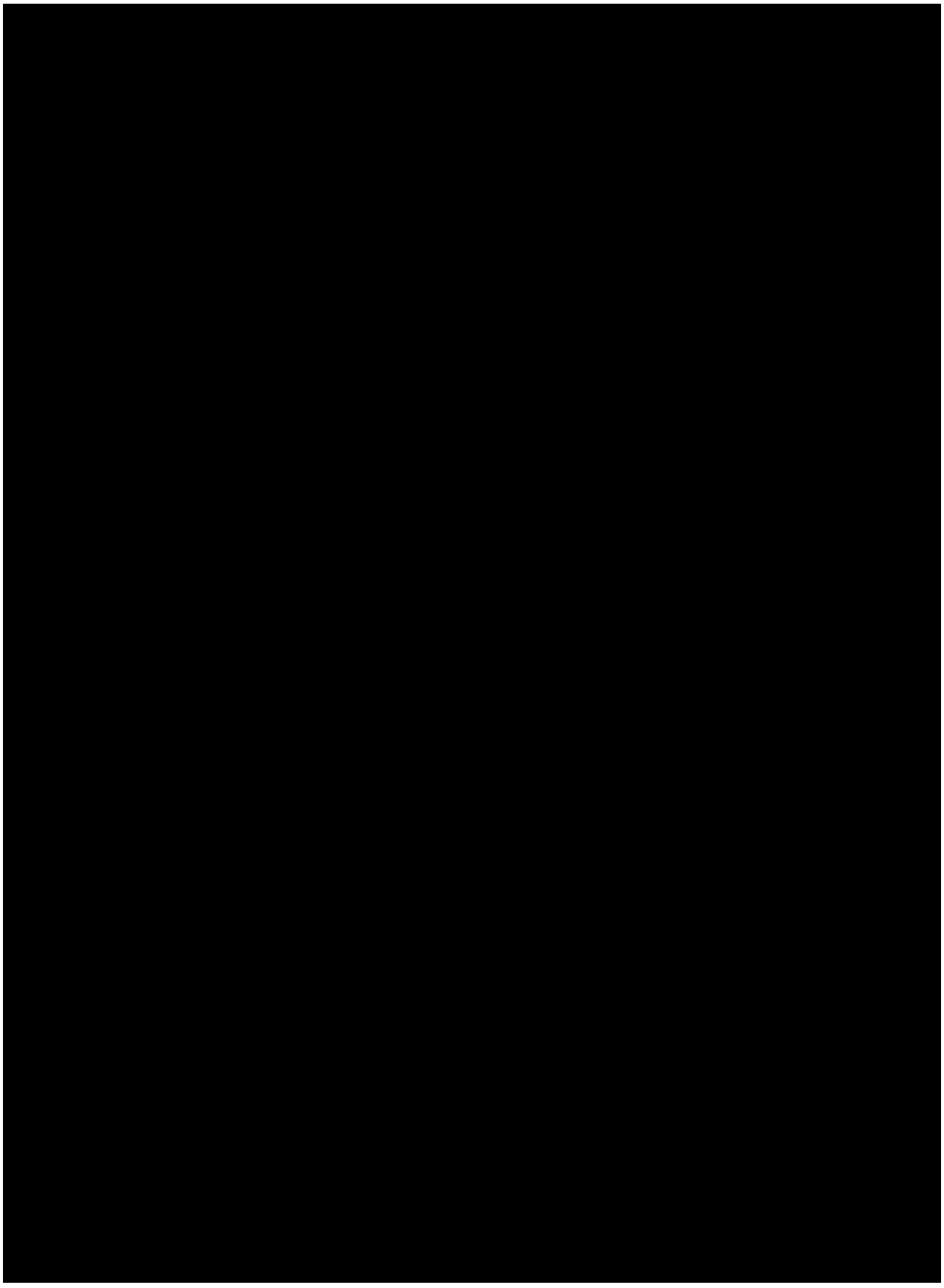
In case of visual complaints or worsening of vision in patients with history of diabetes mellitus or uveitis, please refer to the previous guidance on monitoring patients presenting with visual complaints or worsening of vision.

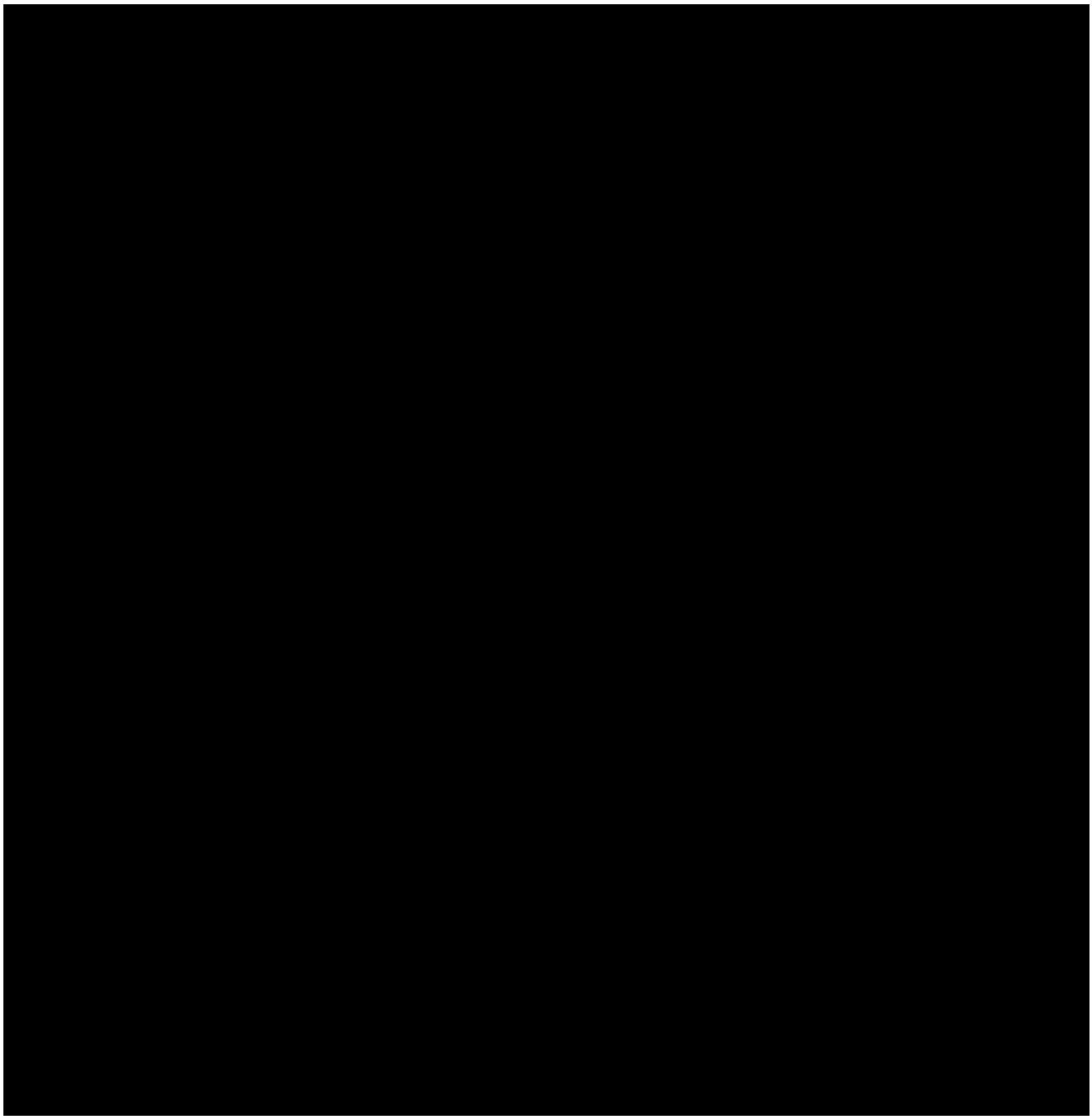
If a patient with or without previous history of uveitis presents with active uveitis without macular edema during the study, the patient may stay on study drug and will receive treatment at the discretion of the local ophthalmologist. Patients with active uveitis must have a follow up ophthalmic examinations at one month after uveitis diagnosis, three months later, then every 3 months up to one year, and every 6 months thereafter until symptom resolution or until the condition stabilizes.

If systemic immunosuppressive treatment (other than corticosteroids) is required for treatment of uveitis, the study drug must be permanently discontinued.

The diagnosis of macular edema will lead to permanent study drug discontinuation (refer to guidance for monitoring of patients with macular edema above).







Appendix 5: Statistical appendix (Information from a controlled clinical trial with count data)

Background

The ARR is the primary clinical endpoint in Study D2311. The trial compares fingolimod with a IFN beta-1a.

Objective

To mathematically derive the information obtained from a clinical trial in MS on the ARR ratio of test vs. control, on the log-scale based on a negative binomial distribution. The information is defined as the reciprocal of the estimate's variance, as in group sequential designs.

Model

We assume that the number of relapses follows a negative binomial distribution, which is a common assumption in MS trials. More specifically, the available data for patient i in treatment arm j is:

Y_{ij} = number of relapses in follow-up time T_{ij},

for $i=1,\ldots n_j$ and j=1,2 (1=test, 2=control).

The negative binomial model is then written as:

$Y_{ij} \sim \text{NegBin}(\lambda_j T_{ij} , \kappa)$,

with annual relapse rate λ_j (>0) and over-dispersion parameter κ (>0).

With this parametrization,

$E(Y_{ij}) = \mu_{ij}$ and $\text{Var}(Y_{ij}) = \mu_{ij} (1 + \kappa \mu_{ij})$, where $\mu_{ij} = \lambda_j T_{ij}$.

An estimate of λ_j is given by $r_j = Y_{.j} / T_{.j}$, where $Y_{.j} = \Sigma_i Y_{ij}$ and $T_{.j} = \Sigma_i T_{ij}$.

Using the delta-method (see details in a next section), a normal approximation for the logarithm of the estimated relapse rate ratio is obtained:

$\log(r_1 / r_2) \sim N(\log(\lambda_1 / \lambda_2) , 1/(\lambda_1 T_{.1}) + 1/(\lambda_2 T_{.2})$

$+ \kappa \{ \Sigma_i T_{i1}^2 / T_{.1}^2 + \Sigma_i T_{i2}^2 / T_{.2}^2 \})$

The information is the reciprocal of the variance, ie Information:

Equation 1: $I = [1/(\lambda_1 T_{.1}) + 1/(\lambda_2 T_{.2}) + \kappa \{ \Sigma_i T_{i1}^2 / T_{.1}^2 + \Sigma_i T_{i2}^2 / T_{.2}^2 \}]^{-1}$

For the case where $T_{ij} = T$, $n_j = n$,

Equation 2: Information $I = [1/n \{ 1/(\lambda_1 T) + 1/ (\lambda_2 T) + 2 \kappa \}]^{-1}$

Of note: Study designs with different parameterizations, but an equivalent amount of information also have an equivalent power for the detection of the specified treatment effect at a fixed alpha-level.

BSSR of the information

As in a BSSR (Friede and Schmidli 2010), fitting a negative binomial model to the aggregate data (ie the relapse data of all patients combined) provides an estimate of the overall annual relapse rate λ and of the dispersion κ. For an assumed rate ratio of $\theta = \lambda_1/\lambda_2$, we obtain estimates of the annual relapse rates in the two groups, λ_1 and λ_2.

We also make the assumption that the follow-up times in the two groups are the same, ie that $T_{.1} = T_{.2} = T_{total}/2$, where T_{total} is the total of the follow-up times at the review time. We further assume that the sum of the squared follow-up times is the same in both groups. ie that $\Sigma_i T_{i1}^2 = \Sigma_i T_{i2}^2 = \Sigma_j \Sigma_i T_{ij}^2 / 2 = T2_{total}/2$.

The evaluation of the Information (1) based on blinded information is then

Equation 3: Information $I = [\ 2/(\lambda_1 T_{total}) + 2/(\lambda_2 T_{total}) + 4 \kappa\ T2_{total}/T_{total}^2\ ]^{-1}$

where λ_1, λ_2, and κ are the re-estimated values at the BSSR.

Note: if $T_{ij} = T$, $n_j = n$, then $T_{total} = 2\ n\ T$, and $T2_{total} = 2\ n\ T^2$, and one obtains again (2).

Additional details (delta-method)

For a random variable X with expectation μ and variance σ^2 , the transformed random variable g(X) has approximatly expectation $g(\mu)$ and variance $\sigma^2\ g'(\mu)^2$ (delta-method).

For the estimate of λ_j given by $r_j = Y_{.j} / T_{.j}$, we have

$E(r_j) = \lambda_j$ and $Var(r_j) = \lambda_j / T_{.j} + \kappa\ \lambda_j^2\ \Sigma_i T_{ij}^2 / T_{.j}^2$

Using the delta-method, the log-transformed annual relapse rate estimate has expectation and variance

$E(\log(r_j)) = \log(\lambda_j)$

$Var(\log(r_j)) = 1/(\lambda_j\ T_{.j}) + \kappa\ \Sigma_i T_{ij}^2 /\ T_{.j}^2$

Hence, approximately:

$\log(r_j) \sim N(\ \log(\lambda_j)\ ,\ 1/(\lambda_j\ T_{.j}) + \kappa\ \Sigma_i T_{ij}^2 /\ T_{.j}^2\ )$

Note that for the special case of $T_{ij} = T$, we obtain:

$\log(r_j) \sim N(\ \log(\lambda_j)\ ,\ 1/(\lambda_j\ n\ T) + \kappa / n\ )$

This approximation is used for sample size calculation and re-calculation with negative binomial count data (Keene 2007; Friede and Schmidli 2010).