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NOVARTIS

Global Clinical Development - General Medicine

FTY720/Fingolimod

Clinical Trial Protocol CFTY720D2409

Long-term, open-label, multicenter study assessing long-term cardiovascular risks in patients treated with fingolimod

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List of abbreviations

ADEM	Acute disseminated encephalomyelitis
AE	Adverse event
ATC	Anatomic therapeutic chemical
CFR	US code of federal regulations
CI	Confidence interval
CNS	Central nervous system
CRA	Clinical research associate
CRF	Case report/record form
CRO	Contract research organization
DMT	Disease modifying therapy
DS&E	Drug safety & epidemiology
ECG	Electrocardiogram
EDC	Electronic data capture
EDSS	Expanded disability status scale
EMA	European medicine agency
FDA	Food and drug administration
GCP	Good clinical practices
HDL	High density lipoprotein
ICF	Informed consent form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent ethics committee
IFN	Interferon
i.m.	intra-muscular
IN	Investigator notification
IR	Incidence rate
IRB	Institutional review board
ISS	Integrated safety summary
i.v.	Intra-venous
MedDRA	Medical dictionary for regulatory activities
MI	Myocardial infarction

MS	Multiple sclerosis
OCT	Optical coherence tomography
PFT	Pulmonary function test
PML	Progressive multiform leucoencephalopathy
PPMS	Primary progressive multiple sclerosis
PRES	Posterior reversible encephalopathy syndrome
PRMS	Progressive relapsing multiple sclerosis
RRMS	Relapsing remitting multiple sclerosis
SAE	Serious adverse event
SAP	Statistical analysis plan
s.c.	Sub-cutaneous
SPMS	Secondary progressive multiple sclerosis
SUSAR	Suspected unexpected serious adverse reaction
WBC	White blood cell
WHO	World health organization

Glossary of terms

Assessment	A procedure used to generate data required by the study
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Protocol	A written account of all the procedures to be followed in a trial, which describes all the administrative, documentation, analytical and clinical processes used in the trial.
Study treatment	Any single drug administered to the patient as part of the required study procedures
Subject Number	A number assigned to each patient who enrolls into the study
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study

Protocol summary

Protocol number	CFTY720D2409
Title	Long-term, open-label, multicenter study assessing long-term cardiovascular risks in patients treated with fingolimod
Brief title	Study assessing the long-term cardiovascular risks in patients treated with fingolimod
Sponsor and Clinical Phase	Novartis, Phase 4
Investigation type	Drug
Study type	Interventional
Purpose and rationale	This study is a post-authorization follow-up measure to assess the long-term cardiovascular risk of fingolimod in patients who experience a serious cardiovascular event during the first 24-hours of fingolimod treatment initiation in study FTY720D2406.
Primary Objective(s)	To estimate the long-term cardiovascular risk of fingolimod, as defined by the incidence of selected cardiovascular events over the course of the study, in patients who experienced a cardiovascular event during treatment initiation or re-initiation in the study D2406.
[redacted]	[redacted]
Study design	This is a single-arm, open-label, long-term safety study.
Population	The study will enroll MS patients who sustained a serious cardiovascular event during their fingolimod treatment initiation or re-initiation in the D2406 study.
Inclusion criteria	Patients in study D2406 who experience a cardiovascular event within 24-hours of fingolimod treatment initiation or re-initiation having led to overnight monitoring or met seriousness criteria
Exclusion criteria	Patients receiving an investigational drug except if this is part of a Novartis sponsored MS study lasting less than 1 month.
Study treatment	Fingolimod 0.5mg/day.
Efficacy assessments	None
Safety assessments	ECG, vital signs and adverse events
Other assessments	None
Data analysis	The proportion (with 95%CI) of patients with at least one selected cardiovascular adverse events will be summarized. Results will be compared with the proportion of D2406 patients who also experienced a selected cardiovascular event but who did not have a cardiovascular event during the first 24 hours after initiation of fingolimod treatment in D2406.
Key words	Long-term cardiovascular risks, fingolimod, MS

Amendment 1

Amendment rationale

Amendment 1 to protocol CFTY720D2409 is developed to align with the recent safety related updates to the Fingolimod label (SmPC) and to introduce administrative changes in the protocol to align with the language of D2406, the parent study from which patients are being enrolled into D2409 study.

Changes to the protocol

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

The changes applied are the following:

- Discontinuation section (5.5.9) has been updated to warn about the potential occurrence of severe exacerbation of disease upon fingolimod discontinuation.
- Pregnancy section (6.5.8) has been updated to inform about the contraindication in pregnancy (and in women of child bearing potential not applying highly effective measures of contraception) recently added to the SmPC
- [redacted]
- Clarification that First Dose Monitoring events qualifying for participation in FTY720D2406 can be considered during initiation or re-initiating of Fingolimod treatment
- Clarification that ECG reading should be done by a qualified physician
- Other minor editorial changes.

1 Introduction

1.1 Background

Multiple Sclerosis (MS) is a chronic, immune-mediated disease of the central nervous system characterized by inflammation, demyelination and axonal/neuronal destruction, ultimately leading to severe disability. MS affects ~ 2.5 million individuals worldwide. At diagnosis, approximately 85% of patients have relapsing-remitting MS (RRMS), characterized by recurrent, acute episodes (relapses) of neurological symptoms. After 6-10 years, 30-40% of patients with RRMS have progressed to secondary progressive MS (SPMS), when a less inflammatory, and more neurodegenerative, course of disease takes precedence. SPMS can also be segregated based on whether patients continue to experience relapses (relapsing form of SPMS) or not (purely progressive SPMS). About 10-15% of MS patients present with a primary progressive course (PPMS) defined by a continuous accumulation of neurological disability from symptom onset without superimposed exacerbations or remissions. Progressive relapsing MS (PRMS; chronic progressive from onset with infrequent relapses) is the least frequent form of MS.

Several therapies are approved for patients with RRMS and fall within 8 classes of products: interferon (IFN)β (1a and 1b), glatiramer acetate (amino acid copolymer), natalizumab (selective adhesion molecule inhibitor), mitoxantrone (chemotherapeutic), fingolimod (S1P receptor modulator), teriflunomide (pyrimidine synthesis inhibitor), dimethylfumarate (fumarates) and alemtuzumab (anti-CD52). All are considered as immunomodulatory or immunosuppressive medications. Beta interferons have multiple immune actions but the means by which the drugs are effective in MS remains unknown. They have shown modest (~30%) effect on relapses and in the case of IFNβ-1a, on disability (Goodin et al. 2002). Relatively minor differences in efficacy, based on dose frequency, exist between IFNβ products. Glatiramer acetate, a random mixture of amino acid copolymers has an effect on relapses similar to IFN-β but has not shown an effect on disability (Goodin et al. 2002). Natalizumab blocks lymphocyte migration into the CNS by inhibiting interaction of alpha-4 integrins on lymphocytes with the endothelial receptor VCAM-1 leading to significant reductions in relapse rate (68%) and disability (42%) (Polman et al. 2006). The risk of progressive multiform leucoencephalopathy (PML) limits use of this product predominantly to second-line situations (Ransohoff, 2007). Whether patients negative for antibodies to the JC virus (causal agent of PML) will have a lower risk of PML than those positive for antibodies (as appears likely based on preliminary reports) remains to be determined. Likewise, mitoxantrone, a chemotherapeutic agent, while demonstrating efficacy on relapses, is associated with risks of cardiac and hematological events that substantially restrict its use (Goodin et al. 2002). Interferon, glatiramer acetate, natalizumab and alemtuzumab are given by injection (SC, IM or IV) whereas fingolimod, teriflunomide and dimethylfumarate are oral medications.

Fingolimod (FTY720) 0.5 mg is an oral drug which has been approved in 90 countries for treatment of patients with relapsing of MS. Fingolimod 0.5 mg is an effective therapy to reduce the risk of relapses in patients with relapsing forms of MS.

The safety profile of fingolimod has been well characterized with over 284,000 MS patients treated with fingolimod in the context on clinical studies and in the post-marketing setting, comprising over 677,779 patient years of exposure by 31-May-2019.

Upon initiation of fingolimod there is activation of the S1P1 receptor that leads to transient negative chronotropy and dromotropy, which are the basis for the monitoring of heart rate and BP required for at least six hours upon the initiation of fingolimod. The incidence of bradyarrhythmic events and intolerance of these events that requires additional monitoring is infrequent. Whether or not such events within the first day of the initiation of fingolimod in MS patients have any association with long term risk for major adverse cardiovascular events is unknown.

As part of an EMA post-authorization follow-up measure and an FDA post-approval commitment a large observational post-authorization safety study CFTY720D2406 (D2406) is being conducted in several countries. This study will provide important information on the usage and the safety profile of fingolimod in a real life setting. However given its observational nature it does not allow to mandate procedures (e.g. ECG) which would be needed in order to properly evaluate whether or not serious cardiovascular events following fingolimod initiation have any association with long-term risk for serious cardiovascular events. Therefore the current study (D2409) is being implemented. This study will be conducted in D2406 patients who experienced such cardiovascular events. It will complement D2406 study by collecting all data in a similar manner as the D2406 study in addition to some extra mandated examinations.

For the purpose of this protocol, the term “fingolimod initiation” is used for first initiation as well as for re-initiation following fingolimod treatment interruption.

1.2 Purpose

This study is an additional EMA post-authorization follow-up measure to assess the cardiovascular risk of fingolimod in those patients who experience a cardiovascular event during the first 24-hours of fingolimod treatment initiation in study D2406 which leads to overnight monitoring or meets seriousness criteria.

In addition, this study will also explore the overall safety profile of fingolimod under conditions of routine medical practice as in protocol D2406.

2 Study objectives

2.1 Primary objective(s)

To estimate the long-term cardiovascular risk of fingolimod in patients who experienced a cardiovascular event during treatment initiation, as defined by the incidence of selected cardiovascular events over the course of the study.

[redacted]

3 Investigational plan

3.1 Study design

This is a multi-national, long-term safety study. Patients enrolled in study D2406 who experienced a cardiovascular event within 24-hours of fingolimod treatment initiation which led to overnight monitoring or met serious adverse event criteria, are eligible to participate in this study.

Patients eligible and consenting to study D2409 will discontinue their study D2406 participation and be followed in study D2409. Study D2409 enrollment period will be open until 1-year before the end of study D2406 and the study will last until the end of Study D2406 i.e. five years after the last patient has been enrolled in Study D2406.

Patients who experience a qualifying event in study D2406 should start study D2409 approximately 6 months after the occurrence of the D2406 qualifying event or as soon as possible after the site initiation.

As part of this study, patients will undergo mandatory assessments on a 6-monthly basis including 12-lead ECG, vital signs and a check list for the occurrence of selected events. Other assessments will be performed as per routine practice.

During the course of the study, patients switching to another MS therapy will remain in the study provided they fulfill the criteria defined in Section 5.5.9. These patients will have their last mandated evaluations 6 months after the discontinuation of fingolimod (see Table 6-1). After this time point, they will be followed according to routine practice without additional mandatory assessments.

3.2 Rationale of study design

This study is designed to assess the long-term cardiovascular risk of fingolimod in patients who experienced a cardiovascular event during fingolimod treatment initiation. As study D2406 provides a real-life population treated with fingolimod and allows easy identification and enrollment of patients, it was selected as the source of patients for D2409 study.

The data collection will be aligned to the study D2406 protocol apart from additional cardiovascular data in order to facilitate data pooling as well as to allow study D2406 patients who did not have any such first-dose event to be used as the comparator to study D2409 patients.

3.3 Rationale of dose/regimen and duration of treatment

Fingolimod 0.5 mg/day is the dose approved for the indication of relapsing forms of MS. The prescription of fingolimod, as well as the decision to discontinue treatment are at the sole discretion of the prescribing physicians and the patients and are not part of the study plan.

Patients will have different duration of follow-up based on when they join the study. Patients will be followed until 5 years after the last patient has been enrolled in Study D2406.

3.4 Rationale for choice of comparator

There is no comparator group enrolled in this study. Comparison will be made using fingolimod patients enrolled in Study D2406 who did not have any first-dose cardiovascular event as they provide a reasonable cohort with similar baseline data collection and allow an estimation of the risk of selected cardiovascular events.

3.5 Purpose and timing of interim analyses/design adaptations

A descriptive summary of the data of this study will be compiled on a periodic basis (at least yearly) in a pooled manner with data from Study D2406.

3.6 Risks and benefits

The safety profile of fingolimod has been well characterized with over 284,000 MS patients treated with fingolimod in the context of clinical studies and in the post-marketing setting, comprising over 677,779 patient years of exposure by 31-May-2019. During the course of the fingolimod clinical development, several areas were identified as safety areas of note: bradyarrhythmias upon treatment initiation, liver transaminase elevations, hypertension and macular edema; additional safety areas of interest include infections, malignancies and reproductive toxicity.

All risks related to fingolimod or other MS DMTs are described in the respective patient information leaflets.

Given that the treatment decision is independent from study participation, the additional risk for subjects to participate in this study is limited to the added procedures (i.e. a 6-monthly ECG) for which no risk is foreseen.

4 Population

This study will include patients with relapsing forms of MS who have been prescribed treatment with fingolimod by their treating physician as part of their MS treatment in accordance with the routine clinical practice and who in the context of the study D2406 experienced certain cardiovascular events during their fingolimod initiation.

4.1 Inclusion criteria

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

1. Written informed consent must be obtained before any assessment is performed
2. Patient experienced a cardiovascular event within 24-hours of fingolimod treatment initiation or re-initiation which led to overnight monitoring or met seriousness criteria
3. Patient experienced this cardiovascular event while participating in the study CFTY720D2406
4. Patient continues receiving fingolimod after the first dose event

4.2 Exclusion criteria

Patients treated with any investigational drug unless it is received as part of a Novartis sponsored MS study lasting less than 1 month.

5 Treatment

5.1 Protocol requested treatment

5.1.1 Study treatment

The study treatment is fingolimod.

Novartis will provide fingolimod 0.5 mg capsules supplies locally for the duration of the study participation ~~according to~~ if required by local regulations. Otherwise, local commercially available supplies will be used. Novartis will not provide any other MS treatment to patients who may discontinue fingolimod prior to the study end.

5.1.2 Additional study treatment

No additional treatment is requested for this trial.

5.2 Treatment arms

There is only one treatment arm with patients receiving fingolimod 0.5mg/day.

5.3 Treatment assignment, randomization

Not applicable.

5.4 Treatment blinding

Not applicable.

5.5 Treating the patient

5.5.1 Patient numbering

Each patient will retain the numbering they had in the study D2406.

5.5.2 Dispensing the study treatment

Each study site will be supplied if required by local regulations. Otherwise, local commercially available supplies will be used.

5.5.3 Handling of study treatment

5.5.3.1 Handling of study treatment

Study treatment will be handled as per local procedures.

5.5.3.2 Handling of other study treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

All dose changes during the study must be recorded on the MS disease modifying therapy records eCRF.

The investigator should promote compliance by instructing the patient to take the study treatment exactly as prescribed. The patient should be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Study treatment dose adjustments and/or interruptions are permitted as per investigator judgment.

These changes must be recorded on the MS disease modifying therapy records eCRF.

5.5.6 Rescue medication

Not applicable.

5.5.7 Concomitant treatment

The investigator should instruct the patient to notify the study site about any new medications he/she takes after being enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded Concomitant Medications eCRF.

5.5.8 Prohibited Treatment

During the course of the study, if a patient switches to an unapproved MS DMT (i.e. marketed drug used as MS DMT without however being approved for MS indication), this patient will have to stop study participation. If possible, data should then be captured at the time of this change in MS therapy independently of the 6-monthly protocol scheduled visit and 6 months later. This last time point will constitute the end-of-study data collection point for this patient.

Patients who start treatment with any investigational drug (MS DMT or not) will have to stop the study participation from the day they start this investigational drug.

Table 5-1 Prohibited treatment:

Medication	Action to be taken
Unapproved MS DMT	Discontinuation from study 6 months after the end of the approved MS DMT
Investigational drugs	Discontinuation from study on the day investigational drug is started

5.5.9 Discontinuation of study treatment

During the course of the study, a patient may discontinue fingolimod:

- If this patient then starts another approved MS DMT or does not start any DMT at all (i.e. remains off DMT), he/she remains in the study. If possible, data should then be captured at the time of this change in MS therapy (either to another DMT or stopping DMTs entirely), 6 months later and thereafter as per the recommended data collection schedule until the end of the study (see Table 6-1).
- If this patient switches to an unapproved MS DMT, this patient will have to stop study participation as described above in Section 5.5.8.

Patients may voluntarily discontinue study treatment for any reason at any time.

The investigator should discontinue study treatment for a given patient if he/she believes that continuation would be detrimental to the patient's well-being.

Cases of severe exacerbation of the disease have been reported after discontinuation of fingolimod in the post-marketing setting. These cases were generally observed within 12 weeks after stopping fingolimod, but in some cases up to 24 weeks after Gilenya discontinuation. Therefore, caution is indicated when stopping Gilenya therapy. If discontinuation of Gilenya is deemed necessary, patients should be monitored for relevant signs and symptoms and appropriate treatment should be initiated as required.

5.5.10 Withdrawal of consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent occurs only when a patient does not want to participate in the study anymore and does not want any further visits or assessments and does not want any further study related contacts.

If a patient withdraws consent, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information in accordance with local regulations. Upon withdrawal of study participation, study treatment (i.e. fingolimod) will no longer be supplied and the patient will return to the prescribed medication as decided together with the treating physician. For patients visiting their sites infrequently, the site staff should contact the patient by phone at least once per year until study completion to collect his/her vital status (i.e. dead or alive, occurrence of SAEs and any change in MS treatment. See also section 5.5.9

5.5.11 Loss to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient. The treating physician should try to contact the patient or one of his/her relatives or the general practitioner (if such is known) in order to collect the patient's vital status, including when applicable, the cause of death.

If, despite three attempts spread over a 6-month period using different modalities (e.g. phone, fax, registered receipt letter), the treating physician is not successful in making contact with the patient, the patient will be considered lost to follow-up. Patients will be considered lost to follow-up from the date of the last successful contact.

5.5.12 Emergency breaking of assigned treatment code

Not applicable.

5.5.13 Study completion and post-study treatment

The study will be considered completed five years after the enrollment of the last patient in the study D2406.

A patient is considered to have completed the study when he/she will have been followed until that time-point.

The study might be prematurely terminated for several reasons see Section 5.5.14.

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

5.5.14 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, study patients should be seen as soon as possible. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

6 Visit schedule and assessments

As part of this study, patients will have mandatory assessments on a 6-monthly basis (i.e. ECG and vital signs) as long as they are treated with fingolimod and up to 6 months after a potential fingolimod permanent discontinuation. Frequency and nature of other data will be captured as per routine practice as described below in Table 6-1.

The study entry visit should be scheduled approximately 6 months after the patient experienced his/her cardiovascular event in the study D2406.

At this visit the patient will sign the Study D2409 informed consent and any new data pertaining to this patient will need to be captured in the D2409 eCRF. The end of Study D2406 will be on the day Study D2409 informed consent is signed.

For patients who experienced this qualifying event more than 6 months prior to Study D2409 implementation at the site, the study entry visit should be scheduled as soon as possible after site initiation.

The study recommends a visit window of +/- 1 month for all mandatory evaluations.

In the study eCRF, fingolimod discontinuation and 6-month follow-up time-points will be documented under routine study visits.

Table 6-1 Recommended assessment schedule, including mandatory evaluations

Visit/ study time-points	Study entry visit	Routine study visit (Every 6 months)	Fingolimod discontinuation[8]	6-months fup[9]	Abbreviated Routine visit[10]	End of study
Assessments and data collection page						
Informed consent	**X**					
Vital signs	**X**	**X**	**X**	**X**	X	**X[11]**
12-lead ECG	**X**	**X**	**X**	**X**		**X[11]**
Selected Adverse Events[1]	**X**	**X**	**X**	**X**	X	**X[11]**
MS status[2]	X	X	X	X	X	X
Laboratory results[3]	**X**	Record as needed				
Ophthalmic examination[4]	Record as needed					
1st dose observation[5]	Record as needed					
Pregnancy status (female of childbearing potential only)	Record as needed					
Dermatological examination	Record as needed					
Additional examination[6]	Record as needed					
Adverse events[7]	Record as needed					
Serious Adverse Events[7]	Record as needed					
MS disease-modifying therapy record	**X**	Record as needed				
Concomitant medication	Record as needed					
Study completion						**X**

Bold denotes mandatory evaluations

1 Selected AEs include cardiac and vascular events (e.g. stroke, myocardial infarction, angina pectoris and peripheral

Visit/ study time-points	Study entry visit	Routine study visit (Every 6 months)	Fingolimod discontinuation[8]	6-months fup[9]	Abbreviated Routine visit[10]	End of study
Assessments and data collection page						

vascular disease, second and third degree AV block, hypertension), symptomatic bradyarrhythmias on treatment initiation or on re-starting after an interruption in fingolimod therapy, eye events (e.g. macular edema), liver events, any infection, pulmonary events (e.g. dyspnea, asthma), malignancies (e.g. lymphoma), seizures, atypical MS relapse, other atypical severe neurological events (e.g. ADEM, PRES) and sudden/unexplained death.

2. MS status will capture when available, MS relapses, EDSS.

3. i) If total and HDL-cholesterol results were not collected as part of the D2406 baseline laboratory results, a sample will need to be drawn and analyzed for these 2 parameters. This is the only mandatory laboratory evaluation required for this study. ii) Only local laboratory results are being captured. Results of lymphocyte count, total WBC count and liver function tests whether normal or abnormal should be captured systematically in the CRF, whenever available. Other laboratory parameter results are to be captured when considered clinically relevant (whether abnormal or not). For ischemic type of events, results of prothrombin time/partial thromboplastin time, homocysteine, Activated protein C Resistance, lupus anticoagulant, antiphospholipid antibody, protein C, protein S fibrinogen and antithrombin III should be collected if performed.

4. Ophthalmic evaluation will capture, when available, visual acuity and macular edema status.

5. To be documented only for patients who re-start fingolimod after an interruption of dosing.

6. Additional examination (e.g. Chest X-Ray, PFT, Echocardiography…) performed in order to characterize an adverse event should be documented.

7. All events meeting the criteria for an AE or SAE should be reported on the “Adverse events” eCRF page.

8. Any evaluation performed at the time stopping fingolimod should be documented.

9. Patients who stopped fingolimod and switched to another approved MS DMT will have the 6 month follow-up visit with the mandatory ECG.

10. Patients discontinuing fingolimod will remain in the study. Only data captured per routine practice will reported. See Section 5.5.9

11. Evaluations are mandatory for patients still on fingolimod at the time of the study completion. These are not mandatory for patients who stopped fingolimod prior to this time-point.

6.1 Information to be collected on screening failures

Not applicable.

6.2 Patient demographics/other baseline characteristics

Patient demographics, baseline laboratory results, medical history in particular cardiac medical history and fingolimod first-dose-monitoring data will be captured as part of the study D2406 eCRF.

Data required to calculate the Framingham Point Score for 10-Year risk for coronary heart disease as well as the European cardiovascular risk score will be collected at study entry visit if they were not already captured in study D2406. These are age, gender, smoking status, systolic blood pressure and total & HDL cholesterol.

6.3 Treatment exposure and compliance

Although it is expected that patients will receive fingolimod 0.5 mg daily per local prescribing information, it is recognized that in a clinical setting, dosing may be delayed or interrupted due to personal reasons, physical reasons, physical conditions, or co-morbidities. Any change in fingolimod treatment (e.g. interruption, change in dose or change in drug) and the reason for change should be documented in the MS treatment eCRF. This will allow measurement of treatment compliance.

6.4 Effectiveness

In order to document the disease evolution of the study population, MS status including number of relapses and EDSS, should be collected whenever available.

6.5 Safety

The following information should be collected in the context of this study in line with the different local label recommendations and whenever available:

- Physical and neurological examination findings, together with the occurrence of selected adverse events
- Fingolimod first dose monitoring data
- Vital signs
- ECG
- Laboratory evaluations results
- Ophthalmologic examinations results
- Dermatological examination result
- Other examination (e.g. Chest X-ray, Pulmonary function test…)

6.5.1 Physical and neurological examination

A physical examination may be performed at a routine clinical visit and may include an assessment of skin, head and neck, lymph nodes, breast, heart, lungs, abdomen, back and/or comments on general appearance. A neurological examination may also be a part of the physical examination. Significant findings that occur during the study which meet the definition of an AE as defined per this protocol (see Section 7.1) should be recorded on the Adverse Event eCRF.

6.5.2 Fingolimod first-dose monitoring

For any patient stopping and re-starting fingolimod, first-dose monitoring should be fully documented in the eCRF for each patient (e.g. vital signs, ECG, documentation in any event if available).

6.5.3 Vital signs

Vital signs are to be recorded at each half-year visit as long as the patient is on fingolimod therapy and if applicable, 6 months after discontinuation from fingolimod. After this time-point, vital signs may be recorded at routine clinical visits. Vital signs may include sitting pulse rate, sitting systolic and diastolic blood pressure.

6.5.4 Height and weight

Body weight may be recorded at each routine clinical visit while height is collected in study D2406 and will not be collected again in study D2409.

6.5.5 Laboratory evaluations

Patients for whom total and HDL-cholesterol results were not collected at the time of the study D2406 baseline will need to have a sample drawn and analyzed. Results will be collected in the eCRF.

All available results for lymphocyte counts, total WBC counts, and liver function tests, whether or not clinically significant should be recorded.

Additionally, results from tests performed to characterize an adverse event should be collected to properly document the event irrespective of normal or abnormal. This might include but is not limited to a complete white blood cell differential count or antibody titers for serious infections.

In this context, in case of ischemic type of events, results of prothrombin time/partial thromboplastin time, homocysteine, Activated protein C Resistance, lupus anticoagulant, antiphospholipid antibody, protein C, protein S fibrinogen and antithrombin III should also be recorded if available.

6.5.6 Electrocardiogram (ECG)

A standard 12-lead ECG will be performed on a 6-monthly basis. Interpretation of the tracing shall be made by a qualified physician and documented on the ECG section of the eCRF.

Each ECG tracing should be labeled with the study number, patient number, date, and kept in the source documents at the study site.

Clinically significant abnormalities should be recorded on the relevant section of the AE eCRF page as appropriate.

6.5.7 Ophthalmic evaluations

Any ophthalmic evaluations performed as part of routine clinical practice, should be recorded. Ophthalmic evaluation may include but is not limited to fundoscopy, visual acuity and OCT, if needed. Ophthalmic examinations should be performed according to the local label for the purpose of detecting macular edema.

6.5.8 Pregnancy and assessments of fertility

According to the updated SmPC, Fingolimod is contraindicated for pregnant women and women of childbearing potential (WOCBP) not using effective contraception. Females who are pregnant or nursing a child cannot participate in this trial. It must be confirmed that the subject is not pregnant at the time of study entry.

For a female patient of childbearing potential, defined as physiologically capable of becoming pregnant, participating in the study, it is mandatory for them to use an appropriate form of birth control. Contraception is required as described below. These highly effective methods of birth control have a less than 1% chance of unwanted pregnancy during one year, if used appropriately according to the instructions of the manufacturer.

- Use of a combination of any two of the following (a+b or a+c or b+c):

a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception (in case of oral contraception you should have been using the same pill on a stable dose for a minimum of 3 months before taking study treatment),

b. Placement of an intrauterine device (IUD) or intrauterine system (IUS),

c. Use of an occlusive cap (diaphragm or cervical/vault cap) by you, or a condom by your male partner combined with a spermicidal foam/gel/film/cream/vaginal suppository.

Since it takes approximately 2 months to eliminate fingolimod from the body after stopping treatment, a potential risk to the fetus may persist and contraception should be pursued for 2 months after finishing study treatment.

If WOCBP becomes pregnant during the study while being treated with fingolimod, they must discontinue the treatment and shall immediately inform the treating physician to discuss management options. In addition, the event should be reported as per Section 7.5.

6.5.9 Appropriateness of safety measurements

The safety measurements collected in this study were selected based on actual or potential signals identified as part of the fingolimod clinical development program as well as the risk management plan.

6.6 Other assessments

There is no other assessment performed in the context of this study.

6.6.1 Resource utilization

Not applicable.

6.6.2 Pharmacokinetics

Not applicable.

6.6.3 Pharmacogenetics/pharmacogenomics

Not applicable.

6.6.4 Other biomarkers

Not applicable.

7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the

study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal product.

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 tests, or other assessments.

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

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

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events.

Adverse events should be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information.

- the severity grade
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
- its relationship to the study treatment
- its duration (start and end dates)
- whether it constitutes a serious adverse event (SAE - see Section 7.2 for definition of SAE)
- action taken regarding study treatment

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 treatment dosage adjusted/temporarily interrupted
- study treatment permanently discontinued due to this adverse event
- concomitant medication given
- non-drug therapy given
- patient hospitalized/patient’s hospitalization prolonged

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 and the interventions required to treat it.

Information about common side effects already known about the study treatment can be found in the respective patient information leaflets. Investigators should inform study patients at the most nearest subsequent protocol visit about most updated safety information (adverse drug reaction) updated in the local label.

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

7.2 Serious adverse events

7.2.1 Definition of SAE

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

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (e.g. hospitalization for relapse treatment)
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - 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.

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

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

All AEs (serious and non-serious) are captured on the eCRF, SAEs also require individual reporting to DS&E as per Section 7.2.2.

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 12 weeks after the patient has stopped study participation (defined as time of last visit) must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after the 12 weeks period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

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 (*either initial or follow up information)* is collected and recorded on the paper Serious Adverse Event Report Form. The investigator must assess the relationship to the study treatment, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours after awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department. The telephone and fax 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 should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE.

Follow- up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the patient continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Package Insert (new occurrence) and is thought to be related to the study treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

7.3 Liver safety monitoring

Not applicable

7.4 Renal safety monitoring

Not applicable

7.5 Pregnancy reporting

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

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

Any SAE experienced during pregnancy must be reported on the SAE Report Form.

7.6 Prospective suicidality assessment

Not applicable.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol and to Good Clinical Practice. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

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

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

8.2 Data collection

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

8.3 Database management and quality control

Novartis staff and a CRO working on behalf of Novartis review the data entered into the CRFs 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. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff that will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

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

8.4 Data Monitoring Committee

Not required.

8.5 Adjudication Committee

Not required.

9 Data analysis

This section describes the analyses which will be performed to specifically address the study D2409 objectives. In addition all data from studies D2406 and D2409 will be analyzed and summarized in a pooled manner. These analyses are described as part of the study D2406 protocol and are not always repeated here.

The purpose of this study is to estimate the long-term cardiovascular risk of fingolimod in patients who sustained a significant cardiovascular event during treatment initiation in study D2406. Descriptive summary statistics (incidence and incidence rates, with respective 95% confidence intervals (CI)) will be generated when applicable and be included in the annual periodic safety updates that are required by the health authorities.

9.1 Analysis sets

The D2409 Safety set will consist of all patients who signed Study D2409 informed consent.

9.2 Patient demographics and other baseline characteristics

Patient demographic and baseline characteristics, as recorded in the Study D2406 database, will be summarized for the D2409 Safety set.

Patient demographic and baseline characteristic data will be described by means of absolute and relative frequencies for categorical variables and mean, standard deviation, minimum and maximum for continuous variables. Categorical variables will include sex, race, ethnicity, country, year of birth (grouped) and age. Continuous variables will include age, height and weight.

In addition, Framingham score as well as the European cardiovascular risk score will be summarized separately for D2409 Safety set, and for the D2406 fingolimod patients who did not experience a cardiovascular event during treatment initiation.

Relevant medical history/current medical condition data; MS history and MS treatment data will also be summarized by frequency of such conditions and treatments. Duration of MS and duration of previous MS treatment at D2406 study entry will be described with mean, median, standard deviation, minimum and maximum.

9.3 Treatments

Overall exposure to treatments will be presented for the D2409 Safety set.

Duration of exposure the study treatment is the number of days from the day of first dose at or after D2406 study entry until the last day of this treatment in the D2409 study. The days when the patient did not take any treatment of interest will be excluded, i.e. duration of exposure will exclude periods of temporary interruption of treatment.

Patients will be considered as being on continuous fingolimod therapy if their fingolimod treatment interruption is less than 45 consecutive days.

Duration of exposure to the study treatment will be described with mean, standard deviation, minimum and maximum. Frequency and percentage of patients exposed for a minimum

duration (i.e. ≥ 1 week, ≥1 month, ≥3 months, ≥6 months, etc.) will be reported along with the summary statistics of duration of exposure.

Percentage of patients discontinuing fingolimod as well as the reason for discontinuation will be reported.

Concomitant medications/significant non-drug therapies will be summarized by ATC code and preferred term.

9.4 Analysis of the primary variable(s)

The primary objective is to estimate the long-term cardiovascular risk, as measured by the proportion of patients experiencing at least one selected cardiovascular event, in patients with long-term exposure to fingolimod once they have been identified as being at risk during treatment initiation in study D2406.

9.4.1 Variable(s)

The primary variable will be the proportion of patients in the D2409 Safety Set who experienced at least one selected cardiovascular events.

Selected cardiovascular events include, but are not limited to, sudden unexplained death, cardiovascular death, myocardial infarction (MI), Q-wave MI, stroke (ischemic or hemorrhagic), unstable angina requiring hospitalization, congestive heart failure requiring hospitalization, complete heart block, ventricular fibrillation, torsade de pointes, hypertensive emergency and any other suspected life threatening cardiovascular condition. An exhaustive list of MedDRA preferred terms will be part of the analysis plan.

9.4.2 Statistical model, hypothesis, and method of analysis

The proportion of patients with at least one selected cardiovascular adverse events post treatment initiation will be summarized for the D2409 Safety Set. Corresponding exact 95% confidence interval (Clopper-Pearson 1934) will be calculated.

9.4.3 Handling of missing values/censoring/discontinuations

Reasonable attempts should be made to limit the amount of missing data related to safety and patient outcomes to ensure that important information related to the primary objective of the study, evaluation of the long-term safety of fingolimod, is captured. No imputation will be made on the eCRFs for missing data and further details of how missing data will be handled will be outlined in the SAP.

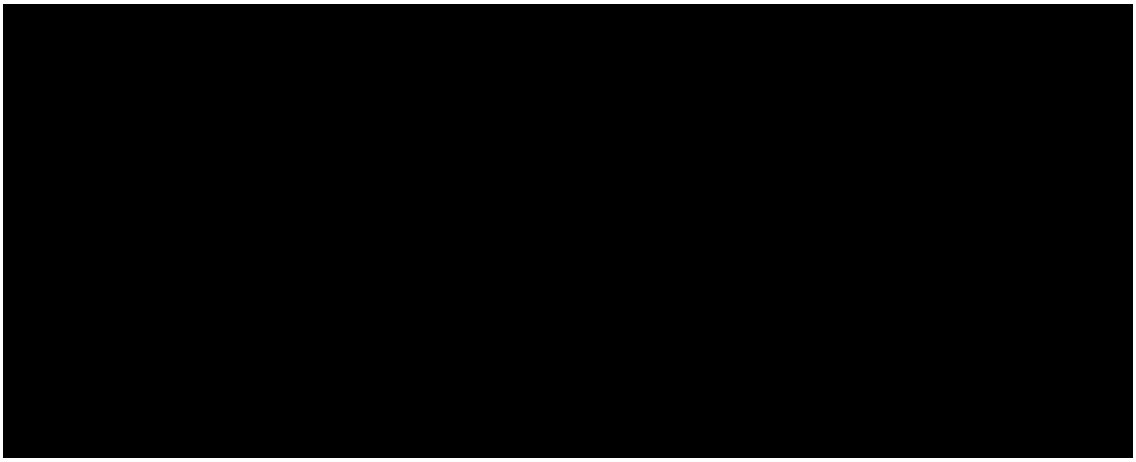
9.4.4 Supportive analyses

In order to put the D2409 data into perspective, a comparison will be made with the patients in D2406 who did not experience a D2409 qualifying event. Specifically, the proportion of patients in this latter subset who subsequently experience at least one selected cardiovascular adverse events will be summarized along with corresponding exact 95% confidence interval (Clopper-Pearson 1934) and compared with that of D2409.

[redacted]

Furthermore, matching techniques will be used to identify a sample from the other DMT cohort in the D2406 study which shares same background cardiac risk as the D2409 patients. Background variables used in the matching will include the Framingham score (10 year risk) for cardiovascular disease. The proportion of patients experiencing at least one selected cardiovascular adverse events post treatment initiation will be summarized for this matched sample, along with corresponding exact 95% confidence interval (Clopper-Pearson).

[redacted]



9.6 Interim analyses

Interim reports will be generated yearly according to reporting requirements using data pooled from D2406 and D2409 studies. The enrolment numbers, baseline characteristics of patients as well as incidence of events reported will be described in a pooled manner.

9.7 Sample size calculation

There is no sample size calculation since patient number will be driven by the proportion of fingolimod patients in D2406 study experiencing a cardiovascular event during treatment initiation which leads to overnight monitoring or meets seriousness criteria, and consenting to participate into this D2409 study. Based on observed incidence of such cardiovascular event occurring during the fingolimod first initiation in the clinical trial setting (1.4% based on patients from ISS January 2012 submission, Group D and Group E), it is estimated that approximately 40 patients may be enrolled in this study.

This small sample size and its associated power constitute the limitation to this study.

Table 9-1 provides the operating characteristics of this study based on a sample size of 40 patients, that is, it gives the probability of seeing at least one selected cardiovascular event in the D2409 study, for a range of *a priori* true proportions.

Table 9-1 Probability of seeing at least one serious cardiovascular event in D2409

True proportion	Sample size	Probability of seeing at least one event
0.001	40	0.039
0.003	40	0.113
0.005	40	0.182
0.007	40	0.245
0.01	40	0.331
0.025	40	0.637
0.05	40	0.871
0.1	40	0.985

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 CFR 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible patients 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(s) of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

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

Women of child bearing potential should be informed that taking the study treatment may involve unknown risks to the fetus.

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution should obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

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

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented. 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 prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented immediately provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety Monitoring should be followed.

12 References

Goodin DS, Frohman EM, Garmany GP, et al (2002). Disease modifying therapies in multiple sclerosis: Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. Neurology; 58: 169-78

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Clopper CJ, Pearson ES (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika, 26; 404–413.