Clinical Development

FTY720

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A 3-year multi-center study to describe the long term changes of optical coherence tomography (OCT) parameters in patients under treatment with Gilenya®

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Approved by the following

Signatures of Novartis Personnel:

Dr. [redacted] (Clinical Trial Leader)	signature	date
Dr. [redacted] (Trial Statistician)	signature	date
Dr. [redacted] [redacted]	signature	date

Signature of Coordinating Investigator:

Prof. Dr. [redacted]

(Coordinating Investigator) signature date

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I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with the principles outlined in the Declaration of Helsinki.

(Principal Investigator)	signature	date

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List of abbreviations

AE	adverse event
ACTH	adrenocorticotropic hormone
ALT	alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST	aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
AV	atrioventricular
bpm	beats per minute
BUN	blood urea nitrogen
BP	blood pressure
CRC	Central Reading Center
CRF	Case Report/Record Form
CSF	cerebrospinal fluid
CNS	central nervous system
CRO	Contract Research Organization
DMD	disease modifying drugs
DS&E	Drug Safety and Epidemiology
EAE	experimental autoimmune encephalomyelitis
ECG	Electrocardiogram
EDC	electronic data capture
EDSS	expanded disability status scale
FA	fluorescein angiography
FDA	First dose administration
GCLT	ganglion cell layer thickness
GGT	gamma-glutamyl-transferase
HCG	human chorionic gonadotropin
IB	investigator’s brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN	interferon
IRB	Institutional Review Board
i.m.	intramuscular(ly)
IUD	intrauterine device
i.v.	intravenous(ly)
LN	lymph node
MRI	magnetic resonance imaging

MS	multiple sclerosis
[redacted]	[redacted]
o.d.	omnia die/once a day
OCT	optic coherence tomography
ON	optic neuritis
[redacted]	[redacted]
[redacted]	[redacted]
PML	progressive multifocal leukoencephalopathy
PCR	polymerase chain reaction
p.o.	per os/by mouth/orally
PPMS	primary progressive multiple sclerosis
[redacted]	[redacted]
[redacted]	[redacted]
RBC	red blood cell
REB	Research Ethics Board
RMP	risk management plan
RNFL(T)	retinal nerve fiber layer (thickness)
RRMS	relapsing remitting multiple sclerosis
SAE	serious adverse event
s.c.	subcutaneously
[redacted]	[redacted]
SmPC	Summary of Product Characteristics
SPMS	secondary progressive multiple sclerosis
TMV	total macular volume
ULN	upper limit of normal range
VEP	visual evoked potential
WBC	white blood cell count
WHO	World Health Organization

Amendment 1

Amendment Rationale

The protocol is being amended to implement an update to the Gilenya® (fingolimod) label in the EU approved by the Committee for Medicinal Products for Human Use (CHMP), as well as in Switzerland as approved by Swissmedic.

The updates to the label provide refined guidance on when existing first dose monitoring procedures should be repeated.

The updates were submitted to both Health Authorities as a Type II Variation by Novartis. These recommendations are already included in the US Prescribing Information (PI) and are not related to any new safety reports.

In agreement with the FDA, both EMA and Swissmedic confirmed the positive benefit-risk profile for Gilenya when used in accordance with updated labels, which were announced earlier this year.

Novartis informed healthcare professionals in the European Union of these recommendations via a Direct Healthcare Professional Communication (DHPC) by January 11, 2013, in Switzerland Physicians were informed via a DHPC Letter on January 22nd 2013.

Changes to the protocol

- In patients who are re-initiated after a certain treatment interruption a repetition of first-dose-monitoring strategy is necessary.
- In patients who require pharmacological intervention during the first dose monitoring and are monitored overnight in a medical facility the first dose monitoring should be repeated after the second dose of fingolimod (For EU only; already implemented in Swiss label).

Additional changes to the protocol

- One center in Switzerland is added
- Section 7.6.4 “Pregnancy and assessments of fertility” is updated

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

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The protocol synopsis has been updated accordingly. In addition, as the changes herein affect the Informed Consent, a revised Informed Consent will also be submitted for approval to IRB/IEC.

Amendment 2

Amendment Rationale

The protocol is being amended to further define blood biomarker sampling and to define the period of one month as 28 days. Furthermore, the specifications for contraception and for elevated liver function tests are adjusted and some inconsistencies within the protocol are corrected.

Changes to the protocol

- Section 3.3, 7.5.5, and 10.5.7: wording has been adjusted to further define blood biomarker sampling. A subset of 50 patients was determined.
- Section 5.1, 6.5 and 7: One month was defined as 28 days and visit 2 is defined as inclusion date (section 5.1)
- Section 6.5 and Appendix 7: wording has been adjusted corresponding to the wording of the SmPC; study drug has to be discontinued if liver function tests are repeatedly >5x ULN.
- Section 7.6.3 and Appendix 3: some corrections were made to adjust inconsistencies within the protocol and to further define laboratory evaluations.
- Section 7.6.4: wording has been adjusted to permit also secondary and other forms of contraception (Pearl index <1).

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

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol require IRB/IEC approval prior to implementation.

In addition, as the changes herein affect the Informed Consent, a revised Informed Consent will also be submitted for approval to IRB/IEC.

Amendment 3

Amendment Rationale

The protocol is being amended to remove blood biomarker sampling from the protocol.

Changes to the protocol

- Section 1, 3.3, 7, 7.5.5, 10.5.7, 11, and Appendix 2: Blood biomarker sampling was completely removed and wording has been adjusted.
- Section 9.3: The responsible person for the OCT Quality Control, Dr. [redacted] has been added

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

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol require IRB/IEC approval prior to implementation.

In addition, as the changes herein affect the Informed Consent, a revised Informed Consent will also be submitted for approval to IRB/IEC.

Amendment 4

Amendment Rationale

The protocol is being amended to clarify the minimum pre-treatment with fingolimod as 28 days and to adapt the visit schedule to the recommended visit schedule in the fingolimod product information. The fingolimod product information recommends visits every 3 months of treatment. Therefore a month during the observational period of the study is defined as 28-31 days depending on the actual length of the respective month. The definition of one month as 28 days is removed.

Changes to the protocol

- Section 5.1 and table 7-1 are changed according to the amendment rationale.

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.

All changes in the protocol are classified as non-substantial. Therefore an Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) approval prior to implementation is not necessary.

Glossary of terms

Assessment	A procedure used to generate data required by the study
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e., prior to starting any of the procedures described in the protocol)
Patient number	A number assigned to each patient who enrolls in the study; when combined with the center number, a unique identifier for each patient in the study is created.
Phase	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study assessments; at this time no further assessments are planned
Stop study participation	Point/time at which patient came in for a final evaluation
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

1 Background

Multiple Sclerosis (MS) is a chronic, demyelinating, immune-mediated disease of the central nervous system affecting about 2.3 times as many women as men (Alonso & Hernan, 2008). With regard to disease pathogenesis, MS is characterized by inflammation and destruction of myelin and axons (Trapp et al., 1998, Sospedra & Martin, 2005). Typically recurrent acute episodes (relapses) of neurological symptoms, which are followed by a complete or partial recovery, can be observed during the relapsing remitting multiple sclerosis (RRMS) disease course (about 85% of patients at diagnosis). Approximately 50% of these patients progress to secondary progressive MS (SPMS) within 10 years, 90% within 25 years. In these SPMS patients a less inflammatory and more neurodegenerative course of disease appears to take precedence. Apart from these initially relapsing forms of MS 10-15% of patients present with primary progressive MS (PPMS), which is characterized by steady deterioration of impairment without prior experience of relapses (Keegan & Noseworthy, 2002).

The driving force of disability in MS is axonal loss. In MS, axonal loss seems to be associated with thinning of the retinal nerve fiber layer (RNFL). The RNFL contains ganglion cell axons that give rise to the optic nerve. Myelination of these fibers begins behind the eye, at the level of the lamina cribrosa (Frohman et al. 2008). The RNFL represents a unique region of the central nervous system because it lacks myelin and thus, allows for direct imaging of axons. It has therefore emerged as a highly interesting potential marker for the evaluation of axonal loss in MS. The thickness of the RNFL itself and the amount of change that may occur, however, are both very small (few microns) making a reliable assessment of RNFL thickness change challenging. Currently, optical coherence tomography (OCT) is the most accurate method to measure RNFL thickness.

Optical coherence tomography (OCT) is a validated, sensitive, non-invasive technique that uses low-coherence interferometry to obtain cross-sectional images of the retina. Commercially available OCT machines show good reproducibility of the measurement of RNFL thickness (Serbecic et al, 2010; Syc et al, 2010; Wu et al, 2010). With the latest technical improvements such as higher resolution and dual laser beam to overcome eye movements these instruments may have a high clinical utility in predicting MS disease course and determining treatment response.

In MS, visible RNFL thinning by OCT may be seen when inflammation causes degeneration of axons within the optic nerve, e.g. as a result of optic neuritis (ON), a common manifestation in MS. However, RNFL thickness is reduced even in the absence of acute ON, making RNFL atrophy a potential structural biomarker of axonal injury or loss in the afferent visual pathway (Frohman et al, 2008; Barkhof et al,2009; Talman et al, 2010). Cross-sectional studies in patients with MS have shown that RNFL thickness by OCT correlates with clinically relevant measures of disability like brain atrophy (Petzold et al, 2010) and cognitive decline (Toledo et al, 2008). Limited available longitudinal OCT data indicate that progressive RNFL thinning occurs over time in the eyes of MS patients and that this may correlate with change in clinically relevant parameters (Costello et al, 2009; Talman et al, 2010). A recent study in 299 MS patients with a mean follow-up of 18 months showed that progressive RNFL thinning observed over time (in eyes with and without prior history of ON) was associated with significant visual loss (Talman et al, 2010). Further studies are needed to evaluate if changes in RNFL are correlated also with global measures of disability in more detail (e.g. EDSS, patient reported outcomes, etc.).

To address this and to describe the change in RNFL thickness over time a global study is planned that includes RRMS patients (either untreated or treated with any approved MS disease modifying therapy) and a group of reference subjects (without neurologic or ophthalmic disease). Since the global study is not powered to particularly detect changes under fingolimod treatment – fingolimod is not even approved in all participating countries – the present study focuses on this subpopulation.

Fingolimod (FTY720; Gilenya®) is an oral, once daily disease modifying drug which has been approved for the treatment of relapsing MS in the US (on 21-Sep-2010), Europe (on 17-03-2011) and other countries.

Pharmacologically, fingolimod targets a novel class of G protein-coupled receptors (GPCRs) which bind the pleiotropic sphingolipid mediator sphingosine 1-phosphate (S1P) and acts in large part by down-modulating S1P/S1P receptor responses in the immune- and the central nervous systems. It causes a reversible sequestration of a proportion of CD4+ and CD8+ positive T-cells and B-cells from blood and spleen into lymph nodes (LNs) and Peyer's patches, apparently without affecting many of the functional properties of these cells. Under normal circumstances, T-cells selectively require S1P1 activation for emigration from the thymus, and both T- and B-cells require this receptor to egress from peripheral lymphoid organs. FTY720-P acts as a super agonist of the S1P1 receptor on lymphocytes, inducing its uncoupling/internalization. The internalization of S1P1 renders these cells unresponsive to S1P, depriving them of the obligatory signal to egress from lymphoid organs and recirculate to peripheral inflammatory tissues. As a consequence, autoaggressive T-cells remain trapped in the lymphoid system, i.e. in the autoantigen-draining cervical LNs in experimental autoimmune encephalomyelitis (EAE)/MS, and this reduces their recirculation to the CNS and abrogates central inflammation.

Fingolimod has shown clinical efficacy in several stages of MS. There is indirect evidence of neuroprotection by this compound due to its unique mode of action. This study should elucidate what changes in RNFLT (retinal nerve fiber layer thickness) occur using late-stage spectral domain OCT during oral treatment with fingolimod. In parallel, investigations will include the safety of fingolimod and other OCT parameters like changes in total macular volume or papillomacular bundles.

In summary, the present study will provide important longitudinal data towards the development of the RNFL under fingolimod treatment as assessed by OCT as an outcome measure in MS over a period of 36 months.

2 Study purpose

This is a 3-year, prospective, multi-center, open-label study to describe the long term changes of optical coherence tomography (OCT) parameters in RRMS patients under treatment with Fingolimod. It is designed to longitudinally study the degeneration of retinal axons by measuring change in RNFL thickness by latest OCT-technology. Correlations of OCT findings with available MRI data and clinical findings may enhance our understanding of the relationship between CNS inflammation, tissue injury, regeneration and neurological deficit in the context of fingolimod therapy.

3 Objectives

3.1 Primary objective

To evaluate the change in average RNFL thickness (RNFLT) in RRMS patients treated with fingolimod over 36 months as assessed by OCT

3.2 Secondary objectives

To evaluate the change in average RNFLT under fingolimod therapy from baseline to months 12 and 24 as assessed by OCT

To evaluate change in quadrant RNFLT under fingolimod therapy from baseline to months 12, 24 and 36

To evaluate changes in total macular volume (TMV) under fingolimod therapy from baseline to months 12, 24 and 36

To evaluate changes in ganglion cell layer thickness (GCLT) under fingolimod therapy from baseline to months 12, 24 and 36

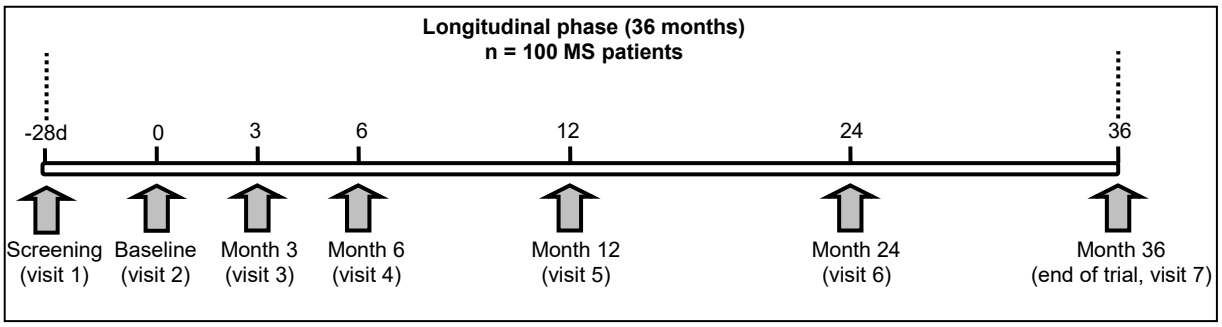
To compare changes in OCT parameters between eyes with and without history of optic neuritis and between right and left eye

To evaluate safety and tolerability of fingolimod in MS patients followed for up to 36 months and specifically to determine the frequency of macular edema under treatment with oral fingolimod in this patient population

4 Study design

This is a multi-center, open-label study in RRMS patients treated with fingolimod. After signing the informed consent, patients will enter a Screening Phase (day -28 to day 0) before starting the study at Baseline (day 0), followed by a 36-month longitudinal data collection phase (see Figure 4-1). Eligibility will be determined at Screening. OCT and other assessments will be performed according to the schedule in Table 7-1.

Figure 4-1 Study outline



5 Population

In this study approximately 100 patients with MS are expected to be enrolled in Germany and Switzerland.

The investigator must ensure that all patients who meet the following inclusion and do not fulfill any of the exclusion criteria are offered enrollment in the study. No additional exclusion parameters can be applied by the investigator, in order that the study population will be representative of all eligible patients.

Patients who drop out after baseline during the longitudinal phase will not be replaced.

The study is planned to be conducted at approximately 10 sites in Germany and approximately 1 site in Switzerland.

5.1 Inclusion/exclusion criteria

Inclusion Criteria

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

1. Written informed consent must be obtained before any assessment is performed.
2. Male or female subjects aged 18-65 years.
3. Subjects with relapsing remitting MS defined by 2010 revised McDonald criteria (see Appendix 4).
4. Patients with Expanded Disability Status Scale (EDSS) score of 0-6.0 inclusive (see Appendix 6).
5. Patients stable on immunomodulatory treatment with fingolimod for at least 28 days and at most 4 months prior to screening according to local label
6. Neurologically stable with no evidence of relapse within 30 days prior to inclusion date (visit 2)
7. Sufficient ability to read, write, communicate and understand

Exclusion Criteria

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

1. Patients who have been treated with:

- systemic corticosteroids or immunoglobulins within 1 month prior to screening;
- immunosuppressive medications such as azathioprine, cyclophosphamide, or methotrexate within 3 months prior to screening;
- monoclonal antibodies (including natalizumab) within 3 months prior to screening;
- mitoxantrone within 6 months prior to screening
- cladribine at any time.

2. Patients with any medically unstable condition, as assessed by the primary treating physician at each site.
3. Patients with any of the following cardiovascular conditions :
   - history of myocardial infarction or with current unstable ischemic heart disease;
   - Heart failure (NYHA III-IV) or any severe cardiac disease as determined by the Investigator (see Appendix 5);
   - history or presence of a second-degree AV block, Type II or a third-degree AV block
   - patients receiving Class Ia (ajmaline, disopyramide, procainamide, quinidine) or III antiarrhythmic drugs (e.g., amiodarone, bretylium, sotalol, ibulitide, azimilide, dofelitide);
   - proven history of sick sinus syndrome;
   - uncontrolled hypertension
4. Patients with severe respiratory disease, pulmonary fibrosis, or chronic obstructive pulmonary disease (Class III-IV).
5. Patients with history of specific MRI findings (tumor, subdural haematoma, post-contusional changes, territorial stroke, neurodegenerative disorders, aneurysm/arteriovenous malformation, evidence of past macroscopic haemorrhage, or other relevant MRI findings that would interfere with evaluation)
6. Any severe disability or clinical impairment that can prevent the patient to meet all study requirements at the investigator`s discretion
7. History of malignancy of any organ system, treated or untreated, within the past 5 years whether or not there is evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin
8. Patients who have received an investigational drug (excluding fingolimod) or therapy within 90 days or 5 half-lives of screening, whichever is longer.
9. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG test (serum)
10. Patients with any ophthalmologic reason for RNFL pathology other than MS, such as: optic neuropathy, active advanced glaucoma, injury of the optic nerve based on the ophthalmologist’s clinical judgment
11. history or presence of severe myopia

a. in patients who have not had refractive surgery, a refractive error of greater than 6.00 diopters

b. pathologic fundus changes of high myopia, such as retinal pigmentary atrophy, besides peripapillary atrophy (atrophy involving the macula) or a staphyloma

c. in patients that have had previous refractive surgery, an axial eye length of greater than 26 mm

12. Acute optic neuritis within the past 6 months before screening
13. Evidence of advanced, non-proliferative or proliferative diabetic retinopathy
14. Presence of retinal conditions associated with edema, subretinal fluid, cysts, etc.
15. Concomitant use of drugs that may directly affect retinal structure and function (e.g. chronic systemic corticosteroids [>30 consecutive days; doses higher than Cushing threshold e.g. prednisone 7.5mg/d], intraocular anti-angiogenic drugs [ranibizumab, bevacizumab], intraocular steroids etc.)

5.2 Premature patient withdrawal

Patients must be withdrawn from the study for any of the following reasons:

- Withdrawal of informed consent
- Investigator's decision (withdrawn in the best interest of the patient for any reason)
- Use of prohibited medication (see section 6.4 Prohibited Treatment)

Patients should be withdrawn at any time if the investigator concludes that it would be in the patient's best interest for any reason. Protocol violations should not lead to patient withdrawal unless they indicate a significant risk to the patient's safety.

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, or 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 determine the primary reason for a patient's premature withdrawal from the study and record this information on the Study Completion CRF.

For patients who are lost to follow-up (i.e., those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

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

6 Treatment

6.1 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). Once assigned to a patient, a patient number will not be reused. If the patient fails to be enrolled for any reason, the reason for not being enrolled will be entered in the CRF and demography should also be completed.

6.2 Investigational treatment

MS medication: Fingolimod (FTY720) 0.5 mg per capsule (hard gelatin capsules) is used to be taken p.o. once daily. Fingolimod will be prescribed according to local label. The decision to prescribe Fingolimod will be made independent of this study.

6.3 Concomitant treatment

All concomitant medications taken within 30 days prior to Screening (Visit 1) and during the study must be recorded on the appropriate CRFs. The investigator should instruct the MS patients to notify the study site about any new medications he/she takes after the start of the study.

6.4 Prohibited treatment

Patients who have met exclusion criteria for exclusionary medications will not be allowed to join the study. Concomitant use of drugs that may directly affect retinal structure and function (e.g. chronic [>30 consecutive days; doses higher than Cushing threshold e.g. prednisone 7.5 mg/day] systemic corticosteroids, intraocular anti-angiogenic drugs [ranibizumab, bevacizumab] etc.) is not allowed during the study and these participants will have to be withdrawn from the study.

Once the patient has entered the study at Visit 1 and while the patient is on fingolimod therapy, use of the following treatments are NOT allowed concomitantly:

- Immunosuppressive medication (e.g. cyclosporine, azathioprine, methotrexate, cyclophosphamide, mitoxantrone, cladribine);
- Other concomitant medications: immunoglobulins, monoclonal antibodies (including natalizumab), IFN- ß, glatiramer acetate, adrenocorticotropic hormone (ACTH)

The administration of any live or live attenuated vaccines (including for measles) is prohibited while patients are receiving fingolimod and for 12 weeks after fingolimod discontinuation. They may be administered thereafter, once there is confirmation that lymphocyte counts are in the laboratory normal range.

6.5 Discontinuation of study treatment and premature patient withdrawal

Study drug must be discontinued for a given patient if the investigator determines that continuing it would result in a significant safety risk for that patient. The following circumstances require study drug discontinuation:

- Intolerability of study medication (fingolimod)

- The occurrence of an adverse event or clinically significant abnormality that, in the judgment of the investigator, warrants discontinuation of treatment
- Use of prohibited medications, listed in section 6.4

In addition, the following conditions based on safety monitoring guidelines (See Appendix 7) should result in fingolimod interruption or discontinuation:

- Ophthalmic:
  - Diagnosis of macular edema
  - Decrease in visual acuity or cystic changes in the macula
- Hepatic:
  Repeated confirmation of an increase in ALT > 5 x ULN
  Repeated confirmation of an increase in AST > 5 x ULN
- Blood lymphocyte count less than 100/mm^3
- New neurological symptoms accompanied by MRI findings (according to local practice) unexpected for MS

In case of a decrease of visual acuity an immediate ophthalmologic assessment is required. After exclusion of a macula edema or cystic changes in the macula treatment can be continued.
Permanent study drug discontinuation **is required** upon diagnosis of cancerous skin disorders or pregnancy.

Furthermore, all criteria listed under 5.2 for premature patient withdrawal will automatically lead to study drug discontinuation.

In addition to these requirements for study drug discontinuation, the investigator should discontinue study drug for a given patient if, on balance, he thinks that continuation would be detrimental to the patient's well-being.

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

Document the date and primary reason for stopping the study drug on the appropriate page of the CRF.

For re-initiation after treatment interruption the same first dose monitoring as for treatment initiation should be repeated if treatment is interrupted for:

- One day or more during the first 2 weeks of treatment
- More than 7 days during weeks 3 and 4 of treatment
- More than 2 weeks after 4 weeks of treatment

If the treatment interruption is of shorter duration than the above, the treatment should be continued with the next dose as planned. It is recommended not to initiate or change dosages of digoxin, beta-blockers and calcium-channel blockers treatment due to a possible additive effect on heart rate reduction. In case these are already initiated advice from a cardiologist is necessary according to local label. If study medication is restarted as per protocol, a reason for the interruption of treatment and time of interruption should be appropriately documented in the source documents as well as in the CRF.

The following examinations regarding cardiac response observation have to be performed at re-start of study drug:

- 12-lead ECG prior to and after 6 hours of first administration
- Continuous 6-hour ECG is recommended
- measurement of blood pressure and heart rate (every hour)

In case of clinically significant abnormalities during or at the end of the 6 hours observation (criteria defined in the local label), cardiac monitoring will be prolonged and surveillance measures implemented as recommended in the label (see also Appendix 7). If study medication is restarted, the reason for the interruption of treatment and time of interruption should be appropriately documented in the source documents as well as in the CRF.

6.6 Treating the patient

6.6.1 Permitted drug dose adjustments and interruptions

Fingolimod dose adjustments are not permitted, although interruptions may be warranted according to label.

6.6.2 Rescue medication

Not applicable.

6.6.3 Recommendations on treatment of MS relapse

Following an onset of MS relapse the patient may have unscheduled visits in the investigator's discretion. Handling of MS relapses will be performed according to local practice and standard of care procedures.

A standard course of corticosteroids (methylprednisolone) on an inpatient or outpatient basis is allowed for treatment of relapses as clinically warranted and should be recorded in the CRF.

Steroid treatment should consist of 3-5 days and up to 1,000 mg methylprednisolone/day. Standard of care procedures will be followed during treatment.

Use of any oral tapering is not permitted.

The use of steroid for MS relapses therapy should be recorded on the "Prior-/concomitant medications" CRF.

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 actual Summary of product Characteristics.

In the event that steroids are administered patients 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) and appropriate antiviral therapy (e.g. acyclovir, valacyclovir) should be promptly initiated

and continued for up to 30 days after stopping high dose steroid treatment. An infectious disease specialist may be consulted to guide such therapy if needed.

Should a patient develop any neurological symptoms or signs, unexpected for MS in the opinion of the investigator or accelerated neurological deterioration, the investigator should immediately schedule an MRI according to local practice.

In case of acute optic neuritis or MS relapse the OCT assessment should be postponed for at least 30 days (at the discretion of the investigator) and the circumstance must be recorded in the corresponding CRF.

6.6.4 Study completion, post-study treatment and early study termination

The study will be considered completed for an individual patient when he/she completes visit 7.

After premature withdrawal Visit 7 should be scheduled as soon as possible.

The study can be terminated for reasons stipulated in the study contract. Should this be necessary, the patients should be contacted and scheduled for their end of study assessments as described in Section 7. Novartis will be responsible for informing IRBs and/or IECs of the early termination of the study.

7 Visit schedule and assessments

Table 7-1 lists all of the assessments and indicates with an “X” the visits when they are performed and recorded in the clinical database.

Patients who prematurely withdraw from the study for any reason, should be scheduled for a final visit, at which time all of the assessments listed for the final visit will be performed.

Patients should be seen for all visits on the designated day with an allowed visit window of +/- 14 days for visits 3 to 7.

In addition to the scheduled visits, patients may have unscheduled visits following an infection, relapse or for other reasons as indicated in the protocol. All information should be collected.

Table 7-1 Assessment schedule

Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Time of Visit	**Screening (d-28 to d0)**	**Baseline**	**month 3**	**month 6**	**month 12**	**month 24**	**month 36**
Information & Informed consent	X						
Inclusion/exclusion criteria	X						
Background/ Demography	X						
Physical examination	X						X
Medical History incl. MS history	X						
Ophthalmologic examination[1]	X						
Previous MS treatment	X						
Vital signs	X	X	X	X	X	X	X
Hematology	X		X	X	X	X	X
Blood chemistry	X		X	X	X	X	X
SAE/ AEs	X	X	X	X	X	X	X
Concomitant treatment	X	X	X	X	X	X	X
OCT[2]		X	X	X	X	X	X
[redacted]							
[redacted]							

[1] exclusion of severe myopia, advanced, non-proliferative or proliferative diabetic retinopathy, and retinal conditions associated with edema, subretinal fluid, cysts, etc. Results have to be available at baseline

[2] after occurrence of acute optic neuritis or MS relapse OCT should be postponed for 30 days

To allow enough time for ophthalmologic examination by an ophthalmologist a screening phase of 28 days is scheduled.

7.1 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected for all patients include: date of birth, age, sex, ethnicity, pre-treatments and source of patient referral. Relevant medical history/current medical condition data includes data until the start of trial. Where possible, diagnoses and not symptoms will be recorded.

Previous MS history (including history of relapses) needs to be documented in the patient's medical chart and/or in documented dialog with the patient's referring physician. Information relating to a patients MS history will be collected in the study including: date of MS diagnosis, date of first MS symptoms, eye history (e.g. optic neuritis, uveitis), MS relapse history (past 12 months) and history of medications used to treat MS (past 12 months). These data will be collected and recorded in the medical History, Ophthalmology Screening and prior-/concomitant medication CRFs.

Medications used to treat MS may include glatiramer acetate (Copaxone®), interferon β-1a i.m. (Avonex®), interferon β-1a s.c. (Rebif®), interferon β-1b (Betaseron®/Betaferon®), natalizumab (Tysabri®), azathioprine, methotrexate or any other medications used as MS-disease-modifying agents. Patients are not allowed to take these medications during the study. Other medications to treat MS-related symptoms should be recorded in the Concomitant Medication CRF. MS history should be supplemented by review of the patient's medical chart and/or by documented dialog with the patient's referring physician.

7.2 Ophthalmologic examination

A complete ophthalmologic examination will be performed by an ophthalmologist as described in Table 7-1. The exam will include previous eye history and any new ophthalmic symptoms, best corrected visual acuity, dilated ophthalmoscopy and optical coherence tomography (OCT) for the measurement of central foveal thickness. Substitution of OCT with fluorescein angiography will not be permitted. Details on the ophthalmologic examinations are provided in the Guidance for Ophthalmic Monitoring Appendix 7.

[redacted]

An ophthalmological examination is regularly recommended 3-4 months after commencing fingolimod therapy (according to local label). If patients report visual disturbances at any time while on therapy, evaluation of the fundus, including the macula, should be carried out.

7.3 Optical coherence tomography

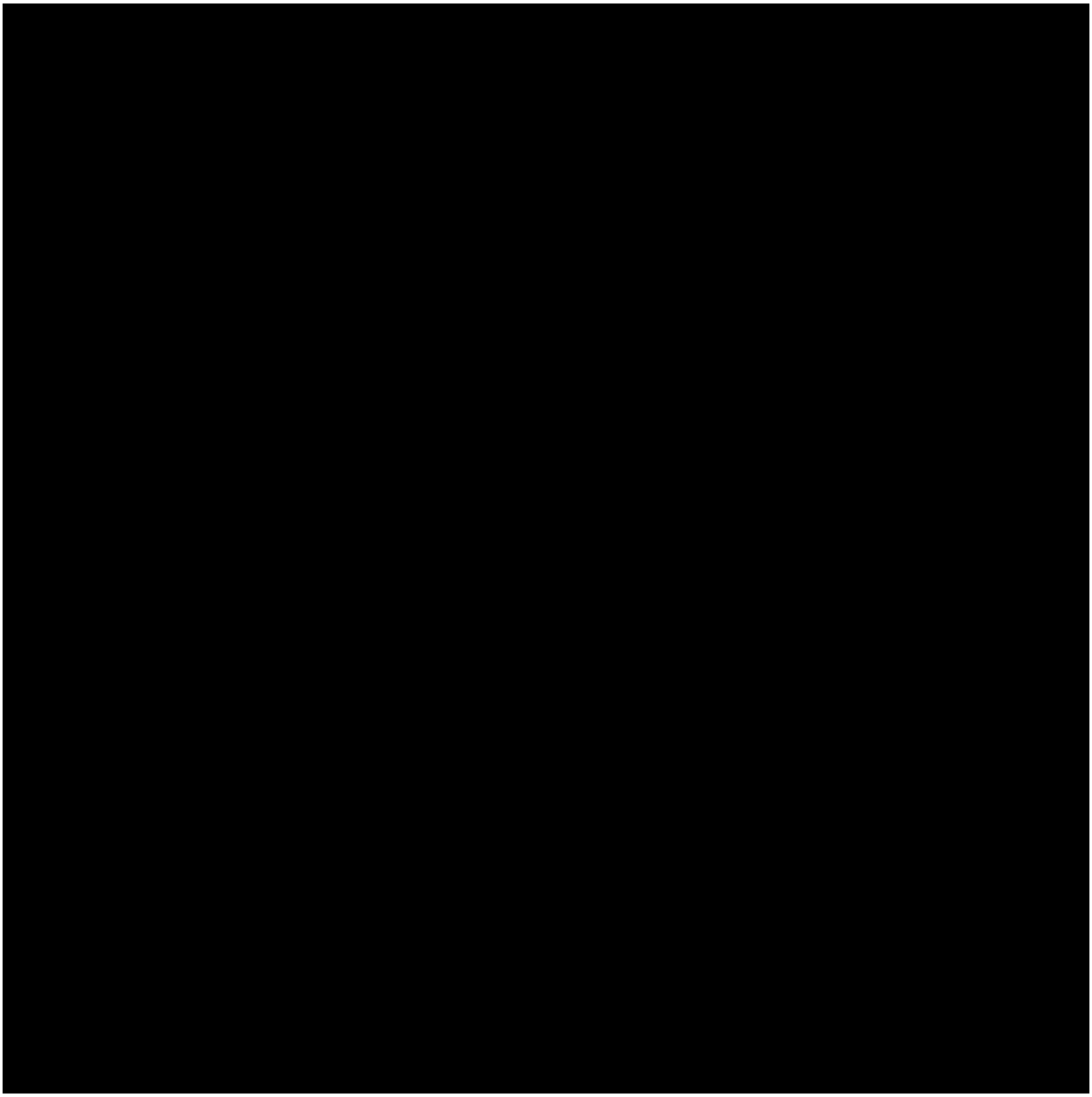
Optical Coherence Tomography (OCT) will be assessed for both eyes at Baseline (Visit 2), Visit 3, 4, 5, 6, and 7. Anxiety/Stress, Comfort and Satisfaction - Level (Appendix 8) will be recorded after the first scan. These assessments will be performed by trained personnel at each site. All OCT Scans will be analyzed and quality controlled by a Central Reading Center (CRC), see section 9.3. The patients identity will be masked for all information forwarded to the CRC during the study. A copy of the OCT images will be retained with the source documents at each investigative site.

7.4 Treatment exposure and compliance

In order to collect information about the medications taken, the following records should be maintained for each patient participating in this study: records of medication prescribed, interruptions in fingolimod intake and intervals between visits.

Compliance will be assessed by the investigator and/or study personnel at each visit using information provided by the patient.

[redacted]



7.6 Safety

- Physical/neurological examination
- Vital signs
- Laboratory evaluation

7.6.1 Physical examination

A complete physical examination will be performed at visits as described in Table 7-1 and will include an assessment of skin, head and neck, lymph nodes, breast, heart, lungs, abdomen, back and comments on general appearance. Initial neurological examination will be a part of the physical examination. All significant findings that are present prior to start of the trial must be reported on the Relevant Medical History/Current Medical Conditions CRF. Significant findings made after the start of study which meet the definition of an AE must be recorded on the Adverse Event CRF.

7.6.2 Vital signs

Vital signs will be recorded as described in Table 7-1. Vital signs will include sitting pulse rate, sitting systolic and diastolic blood pressure (3 measurements), oral temperature (degrees Celsius), body height (cm) and body weight (kg). Height and body weight will only be collected at Visit 2; see Appendix 3.

7.6.3 Laboratory evaluation

Routine blood samples (10 ml at each visit; also at unscheduled visits in case of an infection) will be collected at the visits described in Table 7-1 and analyzed by a local laboratory.

Investigators will be asked to comment on any abnormalities on the respective lab result page, including a notation of the clinical significance of each abnormal finding in the patient's source documents. The laboratory sheets will be filed with the patient source documents. Abnormal laboratory values should not be recorded on the adverse event CRF; however, any diagnoses (or signs or symptoms if a diagnosis is not possible) associated with the abnormal findings should be recorded on the adverse event CRF.

Hematology

Hematology parameters will be collected at the visits described in Table 7-1 and Appendix 2 and will include: RBC count, total WBC, differential blood count (lymphocytes), platelet count, hemoglobin, and hematocrit.

Chemistry

Blood samples will be collected at the visits described in Table 7-1 and Appendix 2. Measurements will include the following parameters: sodium, potassium, chloride, calcium, blood urea nitrogen (BUN), random glucose, alkaline phosphatase, creatinine, Bilirubin, ALT, AST, and GGT.

Notable abnormalities are defined in the Criteria for clinically notable laboratory values and vital signs further specified in Appendix 3.

Abnormal laboratory parameters, inconsistent with clinical presentation of MS or suspicious of underlying medical condition, should be repeated for accuracy.

7.6.4 Pregnancy and assessments of fertility

Serum pregnancy test will be performed for all women prior to inclusion. Additional pregnancy testing may be performed at the investigator's discretion during the trial. Patients becoming pregnant must discontinue the study.

Women of child bearing potential must use one of the below listed medically approved methods of contraception (Pearl Index <1):

Primary forms:

- hormonal contraception (combination oral contraceptives, hormonal transdermal patch, combined injected hormones, injected single hormone, implanted hormones, or hormonal vaginal ring)
- tubal sterilization
- partner's vasectomy
- intrauterine device (synthetic progestin containing IUDs, IUD copper T380)

Secondary forms: Barrier forms (always used with spermicide)

- latex condom
- diaphragm

- cervical cap

Others:

- vaginal sponge (contains spermicide)

Oral contraceptives without estrogen (e.g. "mini-pills"), nonsynthetic pregesterone only IUDs, female condoms, cervical shield, periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Reliable contraception should be maintained throughout the study and for 8 weeks after study drug discontinuation.

At the discretion of the investigator, total abstinence from sexual intercourse is acceptable in cases where the age, career, lifestyle, or sexual orientation of the patient ensures the prevention of pregnancy.

7.7 MS Relapse

A patient should report symptoms indicative of an MS relapse at a scheduled visit or any other time. Patients must be instructed to immediately contact the study site if he/she develops new, reoccurring or worsening neurological symptoms. Standard therapy with corticosteroids can be used. Following an onset of MS relapse the patient may have unscheduled visits at the discretion of the investigator. Handling of MS relapses will be performed according to local practice and standard of care procedures. Details of MS relapse handling will be recorded in the corresponding CRF.

7.8 Pharmacokinetics

Not applicable.

7.9 Pharmacogenetics/pharmacogenomics

Not applicable.

7.10 Other biomarkers

Not applicable.

8 Safety monitoring

8.1 Adverse Events (AEs)/Serious Adverse Events (SAEs)

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after first drug intake even if the event is not considered to be related to drug therapy. Medical conditions/diseases present before obtaining informed consent are only considered adverse events if they worsen after starting trial. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require medication discontinuation or require therapy.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the trial. 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 CRF with the following information:

1. its relationship to Fingolimod (suspected/not suspected)
2. its duration (start and end dates or if continuing at final exam)
3. 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)
  - 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 8.2.

Information about adverse reactions observed in relation to fingolimod can be found in the local product labeling.

All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e., further observation only); medication temporarily interrupted; medication 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 CRF.

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 medication, the interventions required to treat it, and the outcome.

Information about side effects already known about the investigational drug can be found in the Investigator's Brochure (IB) or will be communicated between IB updates in the form of SUSAR reports for the investigator and if applicable 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.

8.1.1 Reporting of ambulatory ECG (Holter-ECG)-related adverse device events

An adverse device event is any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient/subject, or user or of other persons or to a serious deterioration in their state of health.

For the purposes of compliance with the Medical Device Directive (MDD), adverse device events must be documented on the Adverse Device Event Report Form and submitted to the manufacturer of the ambulatory ECG (Holter-ECG) equipment used via fax or email within 24 hours of learning of the event. The contact details for reporting of ambulatory ECG (Holter-ECG)-related adverse device events are provided in the investigator folder provided to each site. The original copy of the Adverse Device Event Report Form and the confirmation of the submission must be kept in the study participant's file at the site.
Should an adverse event or Serious Adverse Event be connected to a device-related complication, the complication has to be documented and reported 1. to Novartis as AE /SAE via AE record and/or SAE report as well as 2. to the ECG manufacturer using the Adverse Device Event Report Form.

8.2 Serious adverse event reporting

To ensure patient safety, every SAE, regardless of suspected causality to a pharmaceutical product or procedure occurring in a study participant after the patient has provided informed consent and until 8 weeks after the patient has stopped study participation (defined as time last visit) must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 8-week period should only be reported to Novartis if the investigator suspects a causal relationship to fingolimod.

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 to fingolimod, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the local Novartis Drug Safety & Epidemiology Department. The telephone and telefax number of the contact persons in the local department of Drug Safety & Epidemiology, 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, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator’s Brochure (new occurrence) and is thought to be related to the Novartis drug, a Drug Safety & 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.

Exception: Progression of multiple sclerosis / MS relapse

Although disease progression of multiple sclerosis, including MS relapses, may be classified as medically significant, is often requiring hospitalization or results in a newly acquired disability / invalidity and therefore the criteria for an SAE can be met, these adverse events should only be documented in the source data and the CRF, respectively.

In case of a heavy or unexpected event (e.g. death) according to the investigators judgment a single case report may be required. The SAE form should then be filled as usual and the SAE reported to the company.

The responsible physician must verify all information given in the questionnaires of the patients for the presence of an adverse event and report this in the CRF respectively

8.3 Pregnancies

Pregnancies are not allowed by the study protocol and women of child bearing potential should be excluded from participation in the study unless they use effective contraception as described in 7.5.4. Any pregnancy that occurs during study participation should be reported by the investigator to the local Novartis Drug Safety & Epidemiology Department using a Clinical Trial Pregnancy Form for up to 2 months following the last visit.
Patients becoming pregnant while on FTY720 should be withdrawn from the study. To ensure patient safety each pregnancy must also 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 birth, and the presence or absence of any birth defects, congenital abnormalities or maternal and newborn complications. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

It is recommended that pregnant study participants, administered fingolimod, are registered (if they consent) in the fingolimod pregnancy registry.

8.4 Data Monitoring Board

Not applicable.

9 Data review and database management

9.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs 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 CRFs, the adherence to the protocol and to Good Clinical Practice, and the progress of enrollment. 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 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 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 CRFs are

performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

9.2 Data collection

Designated investigator staff must enter the information required by the protocol onto the Novartis CRFs that are printed on 3-part, non-carbon-required paper. Field monitors will review the CRFs for completeness and accuracy and instruct site personnel to make any required corrections or additions. The CRFs are forwarded to Data Management by field monitors, one copy being retained at the investigational site. Once the CRFs are received by Data Management, their receipt is recorded and they are reviewed prior to data entry.

9.3 Database management and quality control

Data from the CRFs are entered into the study database by Contract Research Organization staff following their own internal standard operating procedures that have been reviewed and approved by Novartis.

Subsequently, the entered data are systematically checked by Data Management staff, using error messages printed from validation programs and database listings. Obvious errors are corrected by Data Management personnel preliminarily. However, a listing with these performed obvious corrections will be sent to the respective investigators for approval. Other errors or omissions are entered on Data Query Forms, which are returned to the investigational site for resolution. The signed original and resolved Data Query Forms are kept with the CRFs at the investigator site, and a copy is sent to Novartis so the resolutions can be entered into the database. Quality control audits of all key safety and efficacy data in the database are made prior to locking the database.

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.

OCT assessments (including last OCT measurement prior to first intake of fingolimod, if available) are evaluated and quality controlled centrally by Dr. [redacted], data will be recorded and stored at [redacted].

Laboratory samples will be processed locally.

At the conclusion of the study, the occurrence of any protocol violations 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 Trial Statistician and Statistical Reporting and the Clinical Trial Leader.

10 Data analysis

10.1 Populations for analysis

The safety set (SS) will consist of all enrolled patients for whom safety information was collected. Of note, the statement that a patient had no adverse events also constitutes a safety assessment.

The Full Analysis Set (FAS) will consist of all enrolled patients for whom data was collected and who have at least one post-baseline efficacy assessment. This will be analogous to the ITT population.

The Per Protocol Population will consist of all patients from the FAS-population, for whom no major protocol violations are reported. All reported protocol violations will be classified as minor or major in a data review meeting prior to data base lock.

10.2 Patient demographics/other baseline characteristics

Background and demographic characteristics will be presented using summary statistics.

Summary statistics will include n (number of observations), mean, standard deviation, median, minimum and maximum values for continuous variables, as well as frequencies and percentages for categorical variables.

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

All patients will receive a dose of 0.5 mg fingolimod daily according to local label. No study drug will be provided.

Concomitant therapy used both prior to and after start of study drug administration will be summarized by treatment group. The WHO Drug Reference Guide will be used for coding of medications.

10.4 Analysis of the primary objective(s)

10.4.1 Variable

The primary outcome of interest is the rate and pattern of change in RNFL thickness in RRMS patients treated with fingolimod from baseline to month 36 as assessed by OCT.

10.4.2 Statistical hypothesis, model, and method of analysis

The primary efficacy variable will be presented graphically to investigate the pattern of change over time. Change will be assessed from baseline to month 12, month 12 to month 24, month 24 to month 36. Change will be presented as absolute changes, as well as percent change. Pairwise comparisons will be performed using a t-test. No adjustment for multiple comparisons will be made. Additionally, change from baseline to month 12, 24, and 36 will be analyzed using a paired t-test under the assumption of normal distribution for the ITT population. In case of non-normality a Wilcoxon signed-rank test will be applied instead.

10.4.3 Handling of missing values/censoring/discontinuations

Due to the definition of the FAS-population, all patients in this population will have at least one post-baseline OCT assessment and hence, no imputation of data is necessary.

10.4.4 Supportive analyses

Additionally, the per-protocol population will be analyzed for the primary endpoint.

10.5 Analysis of secondary [redacted] objectives

10.5.1 Secondary [redacted] outcomes

Secondary endpoints like changes in quadrant RNFLT, changes in total macular volume (TMV), and changes in ganglion cell layer thickness (GCLT) from baseline to months 12, 24, and 36 will be evaluated with a paired t-test or Wilcoxon signed-rank test, as appropriate.

Changes in OCT parameters between eyes with and without history of optic neuritis will be evaluated with a paired t-test or Wilcoxon signed-rank test, as appropriate.

[redacted]

Additionally, means, standard deviations, median, minimum and maximum will be presented for each visit, as will be the change from baseline. These descriptive statistics will also be presented for the primary endpoint.

For all other [redacted] endpoints summary statistics will be presented. Summary statistics will include n (number of observations), mean, standard deviation, median, minimum and maximum values at each visit, as well as the change.

10.5.2 Tolerability

Not applicable.

10.5.3 Resource utilization

Not applicable.

[redacted]

10.5.5 Pharmacokinetics

Not applicable.

10.5.6 Pharmacogenetics/pharmacogenomics

Not applicable.

10.5.7 Biomarkers

10.5.8 Not applicable.PK/PD

Not applicable.

10.6 Interim analysis

No interim analysis is planned

10.7 Sample size calculation

Published data varies widely as to the average thinning of RNFL in MS patients and no data is available on patients treated with Fingolimod. As this is an explorative study to get a better understanding of RNFL thinning in RRMS treated with Fingolimod we will take a representative sample of approximately 100 patients with RRMS who are stable on Fingolimod.

10.8 Power for analysis of critical secondary variables

Not applicable.

11 Discussion and rationale for study design features

This study will describe the long-term changes of OCT parameters in RRMS patients treated with oral fingolimod.

This is a prospective, 3-year, open-label study in MS patients treated with fingolimod. It is designed to evaluate the change in average RNFL thickness in this patient population based on a disease modifying treatment with fingolimod. Approximately 100 patients will be enrolled to receive representative data from various centers. In the forefront of the study MS patients are screened for meeting eligibility criteria based on the defined criteria.

In detail, the primary objective of the study is to evaluate the change in average RNFL thickness (RNFLT) in RRMS patients treated with fingolimod from baseline to month 36 as assessed by OCT.

[redacted]

Design, study drug and control

As this trial aims to investigate changes in OCT parameters of RRMS patients treated with the disease modifying substance fingolimod, an open-label design was chosen. All patients will receive a dose of 0.5 mg fingolimod daily according to local label. No study drug will be provided.

Choice of control

Not applicable.

Choice of design

This is a prospective, multi-center, open-label study. An observation time of 3 years is needed to gain a better understanding of the long term changes of optical coherence tomography (OCT) parameters in RRMS patients under treatment with fingolimod. The study is designed to longitudinally investigate the degeneration of retinal axons by measuring change in RNFL thickness by latest OCT-technology. Correlations of OCT findings with available MRI data and clinical findings may enhance our understanding of the relationship between CNS inflammation, tissue injury, regeneration and neurological deficit in context of fingolimod therapy

Data analysis

A total of about 100 patients will be enrolled. Details on data analysis and the definition of the analysis sets are presented and discussed in section 10.

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Appendix 1: Administrative procedures

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.

Responsibilities of the investigator and IRB/IEC/REB

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/REB) before study start. Approval letters concerning protocol and informed consent will be filed by Novartis. 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.

Informed consent

Eligible patients may only be included in the study after providing written, IRB/IEC/REB-approved informed consent.

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.

Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, the Health Authority and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB 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/REB at the study site should be informed within 10 working days.

Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical trial agreement.

Appendix 2: Blood Collection Log

This is only an overview on the total volume of blood collected for local laboratory assessments at the study visits.

	Routine Laboratory = Total blood volume		
V1 (Screening)	10 ml		
V3	10 ml		
V4	10 ml		
V5	10 ml		
V6	10 ml		
V7	10 ml		

Appendix 3: Clinically notable vital signs

Only selected laboratory parameters which have been shown to be sensitive to fingolimod exposure are included.

CRITERIA FOR NOTABLE LABORATORY ABNORMALITIES

Notable Values		
Laboratory Variable	**Standard Units**	**SI Units**
LIVER FUNCTION AND RELATED VARIABLES		
SGOT (AST)	>3x ULN, <5x ULN F: > 105 U/L <175 U/L, M: >150 U/L <250 U/L>	F: > 105 U/L <175 U/L M: >150 U/L <250 U/L
Gamma Glutamyltransferase	> 130 U/L	> 130 U/L
SGPT (ALT)	>3x ULN, <5x ULN F: > 105 U/L <175 U/L, M: >150 U/L <250 U/L	F: > 105 U/L <175 U/L M: >150 U/L <250 U/L
Alkaline Phosphatase	> 280 U/L	> 280 U/L
Total bilirubin	≥ 2.0 mg/dL	≥ 34.2 μmol/L
RENAL FUNCTION / METABOLIC AND ELECTROLYTE VARIABLES		
Glucose	≥200 mg/dL	≥11.1 mmol/L
Creatinine	≥2.0 mg/dL	≥176 umol/L
Chloride	≤ 85 mEq/L ≥ 119 mEq/L	≤ 85 mmol/L ≥ 119 mmol/L
BUN	≤ 2 mg/dL ≥ 30 mg/dL	≤ 0.7 mmol/L ≥ 10.7 mmol/L
Sodium	< 130 mEq/L > 150 mEg/L	< 130 mmol/L >150 mmol/L
Potassium	≤ 3.0 mEq/L ≥ 6.0 mEq/L	≤ 3.0 mmol/L ≥ 6.0 mmol/L
Calcium	≤ 7.5 mg/dL ≥ 11.6 mg/dL	≤ 1.87 mmol/L ≥ 2.89 mmol/L
HEMATOLOGY VARIABLES		
Hemoglobin	≤10.0 g/dL	≤100 g/L
Platelets (Thrombocytes)	≤100 k/mm^3 ≥600 k/mm^3	≤100 x 10^9/L ≥600 x 10^9/L
Leukocytes (WBCs)	≤2.0 k/mm^3 ≥15 k/mm^3	≤2.0 x 10^9/L ≥15 x 10^9/L
Red blood cells RBCs	<3,300,000/mm³ >6,800,000/mm³	<3.3 x 10^{12}/L >6.8 x 10^{12}/L
HEMATOLOGY VARIABLES: DIFFERENTIAL		

Notable Values		
Lymphocytes	<100/mm^3 ≥8000/mm^3	<0.1 x 10^9/L ≥8 x 10^9/L

NOTABLE VITAL SIGNS	
Vital Sign Variable	**Notable Criteria**
Pulse (beats/min)	>120bpm or Increase of ≥15 bpm from baseline Or < 50bpm or Decrease of ≥15 bpm from baseline
Systolic BP (mmHg)	≥140 mmHg or Increase of ≥20 mmHg from baseline Or ≤ 90 mmHg or Decrease of ≥ 20 mmHg from baseline
Diastolic BP (mmHg)	≥ 90 mmHg or Increase of ≥ 15 mmHg from baseline Or ≤ 50 mmHg or Decrease of ≥ 15 mmHg from baseline

Appendix 4: 2010 Revisions to the McDonald diagnosis criteria for MS

Guidelines from International Panel on the diagnosis of MS

(Polman et. al, 2011)

Clinical Presentation	Additional Data Needed for MS Diagnosis
2 or more attacks[a]; objective clinical evidence of 2 or more lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack[b]	None[c]
2 or more attacks[a]; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by • ≥ 1 T2 lesion in at least two out of four MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)[d] OR • Await a further clinical attack[a] implicating a different CNS site
1 attack[a]; objective clinical evidence of 2 or more lesions	Dissemination in time, demonstrated by • Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time. OR • A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan. OR • Await a second clinical attack[a]
1 attack[a]; objective clinical evidence of 1 lesion (clinically isolated syndrome)	Dissemination in space and time, demonstrated by: For DIS • ≥ 1 T2 lesion in at least two out of four MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)[d] OR • Await a second clinical attack[a] implicating a different CNS site **AND** For DIT • Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time. OR

	• A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan. **OR** • Await a second clinical attack[a]
Insidious neurological progression suggestive of MS (PPMS)	One year of disease progression (retrospectively or prospectively determined) **PLUS** Two out of the three following criteria[d] 1. Evidence for DIS in the brain based on ≥ 1 T2+ lesions in the MS-characteristic periventricular, juxtacortical or infratentorial regions 2. Evidence for DIS in the spinal cord based on ≥ 2 T2+ lesions in the cord 3. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

If the Criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is MS; if suspicious, but the Criteria are not completely met, the diagnosis is "possible MS"; if another diagnosis arises during the evaluation that better explains the clinical presentation, then the diagnosis is "not MS."

a. An attack (relapse; exacerbation) is defined this as patient-reported or objectively observed events typical of an acute inflammatory demyelinating event in the CNS, current or historical, with duration of at least 24 hours, in the absence of fever or infection. It should be documented by contemporaneous neurological examination, but some historical events with symptoms and evolutionm characteristic for MS, but for which no objective neurological findings are documented, can provide reasonable evidence of a prior demyelinating event. Reports of paroxysmal symptoms (historical or current) should, however, consist of multiple episodes occurring over not less than 24 hours. Before a definite diagnosis of MS can be made, at least one attack must be corroborated by findings on neurological examination, visual evoked potential (VEP) response in patients reporting prior visual disturbance, or MRI consistent with demyelination in the area of the CNS implicated in the historical report of neurological symptoms.

b. Clinical diagnosis based on objective clinical findings for two attacks is most secure. Reasonable historical evidence for one past attack, in the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristics for a prior inflammatory demyelinating event; at least one attack, however, must be supported by objective findings.

c. No additional tests are required. However, it is desirable that any diagnosis of MS
be made with access to imaging based on these Criteria. If imaging or other tests

[d]Gadolinium-enhancing lesions are not required; symptomatic lesions are excluded from consideration in subjects with brainstem or spinal cord syndromes.

MS = multiple sclerosis; CNS = central nervous system; MRI = magnetic resonance imaging; DIS = dissemination in space; DIT = dissemination in time; PPMS = primary progressive multiple sclerosis; CSF = cerebrospinal fluid; IgG = immunoglobulin G

Appendix 5: New York Heart Association Functional Classification

(The Criteria Committee of the New York Heart Association, 1994)

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

Appendix 6: EDSS Assessment Criteria

EXPANDED DISABILITY STATUS SCALE

0 = normal neurological exam (all FS grade 0)

1.0 = no disability, minimal signs in one FS (one FS grade 1)

1.5 = no disability, minimal signs in more than one FS (more than one FS grade 1)

2.0 = minimal disability in one FS (one FS grade 2, others 0 or 1)

2.5 = minimal disability in two FS (two FS grade 2, others 0 or 1)

3.0 = moderate disability in one FS (one FS grade 3, others 0 or 1) though fully ambulatory; or mild disability in three or four FS (three/four FS grade 2, others 0 or 1) though fully ambulatory

3.5 = fully ambulatory but with moderate disability in one FS (one FS grade 3) and mild disability in one or two FS (one/two FS grade 2) and others 0 or 1; or fully ambulatory with two FS grade 3 (others 0 or 1); or fully ambulatory with five FS grade 2 (others 0 or 1)

4.0 = ambulatory without aid or rest for >500 meters; up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps

4.5 = ambulatory without aid or rest for >300 meters; up and about much of the day, characterized by relatively severe disability usually consisting of one FS grade 4 and combination of lesser grades exceeding limits of previous steps

5.0 = ambulatory without aid or rest for >200 meters (usual FS equivalents include at least one FS grade 5, or combinations of lesser grades usually exceeding specifications for step 4.5)

5.5 = ambulatory without aid or rest >100 meters

6.0 = unilateral assistance (cane or crutch) required to walk at least 100 meters with or without resting

6.5 = constant bilateral assistance (canes or crutches) required to walk at least 20 meters without resting

7.0 = unable to walk 5 meters even with aid, essentially restricted to wheelchair; wheels self and transfers alone; up and about in wheelchair some 12 hours a day

7.5 = unable to take more than a few steps; restricted to wheelchair; may need some help in transferring and in wheeling self

8.0 = essentially restricted to bed or chair or perambulated in wheelchair, but out of bed most of day; retains many self-care functions; generally has effective use of arms

8.5 = essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions

9.0 = helpless bed patient; can communicate and eat

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

10.0 = death due to MS

Appendix 7: Guidance on safety monitoring

Patients with recorded elevated blood pressure values (systolic BP >140 and/or diastolic BP > 90 mmHg) should have their blood pressure controlled during the same visit. Patients who have two readings of elevated blood pressure (systolic BP >140 and/or diastolic BP >90 mmHg) should be followed up in one month by an unscheduled visit if the scheduled visit is not due. Should systolic BP >140 and/or diastolic BP >90 mmHg values will be confirmed in the next visit, the patient should be referred to his primary care physician, an independent internist or to the specialty hypertension clinic for evaluation, diagnosis and treatment of hypertension.

Patients with BP values of >160/100 mmHg on any visit during the study should be immediately referred as above for evaluation, diagnosis and treatment of hypertension.

Newly diagnosed hypertension as well as an aggravation of a preexisting condition must be reported as an AE and discontinuation of the study drug must be considered by the investigator.

After a treatment interruption of fingolimod for more than 14 days, patients have to be observed for cardiac events as described in the recommendations for first dose monitoring.

Recommendations for first dose monitoring (also in case of re-initation of fingolimod after treatment interruption)

Clinicians should be particularly mindful of patients who have a low pulse at baseline (spontaneously or through drug induced ß-receptor blockade), prior to administration of the study drug.
Be aware that fingolimod causes transient heart rate lowering and may cause AV conduction delays following initiation of treatment. This also applies to recommencing treatment after an interruption of more than 14 days.
All patients will be monitored for a period of at least 6 hours for signs and symptoms of bradycardia. The monitoring includes a 12-lead ECG prior and 6 hours after the first dose, continuous 6-hour ECG recording (recommended) after the first dose as well as blood pressure and heart rate measurement every hour. Should post-dose bradyarrhythmia-related symptoms occur, appropriate clinical management should be initiated and observation should be continued until the symptoms have resolved.
If the patient's heart rate at the end of the 6-hour period is the lowest following first dose administration, the monitoring should be extended by at least 2 hours and until the heart rate increases.
In those patients with evidence of clinically important cardiac effects during the first 6 hours, monitoring should be extended according to local label.

Should a patient require pharmacologic intervention during the first dose observation, overnight monitoring with continuous ECG in a medical facility should be instituted and the first dose monitoring strategy should be repeated after the second dose of fingolimod.

Because of additive effects on heart rate, Fingolimod is not recommended in patients receiving beta blockers or other substances which may decrease heart rate. Fingolimod should not be co-administered [for Switzerland: is contraindicated] with Class Ia (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrythmic medicinal products).

Recommendations for management of bradycardia

Be aware that fingolimod causes transient heart rate lowering and may cause AV conduction delays following initiation of treatment. This also applies to recommencing treatment after an interruption of more than 14 days.
All patients should be observed for a period of at least 6 hours for signs and symptoms of bradycardia (according to local label). Should post-dose bradyarrhythmia-related symptoms occur, appropriate clinical management should be initiated and observation should be continued until the symptoms have resolved.
Monitoring measures will be implemented as foreseen by the local label

Clinicians should be particularly mindful of patients who have a low pulse (<55bpm) at baseline (spontaneously or through drug induced ß-receptor blockade), prior to administration of the study drug.

Atropine (s.c. or i.v.) is recommended as the first line treatment of bradycardia, up to a maximum daily dose of 3 mg.

Furthermore, the common guidelines for treatment of bradycardia (e.g. ACLS guidelines) should be followed as appropriate:

- In case of clinical symptoms or hypotension, administration of atropine 1 mg, repeated administration in 3-5 minutes
- If heart rate and/or blood pressure remains unresponsive, consider administration of dopamine drip 5-20 µg/kg/min or epinephrine drip 2-10 µg/min
- Performance of transcutaneous pacing may also be considered

In the setting of decreased blood pressure, isoproterenol should be avoided/used with caution.

Guidance on monitoring of patients with elevated liver function tests

In case of detection of elevated ALT/AST values > 5 times the upper limit of the normal range (ULN), additional blood chemistry panel including ALT, AST, AP, GGT, total and conjugated bilirubin, albumin should be performed.

If ALT/AST values are repeatedly 5 times the ULN, the study drug must be suspended and not resumed until values have normalized. Patients who develop symptoms suggestive of hepatic dysfunction such as unexplained vomiting or jaundice, should have liver enzymes checked and fingolimod should be discontinued if significant liver injury is confirmed.

In case of isolated elevation of bilirubin over 2.0 mg/dl (34.2 umol/L), the investigator must discontinue fingolimod administration. Additional evaluations may be performed at the discretion of the investigator.

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

Guidance on monitoring of patients with notable lymphopenia

Fingolimod results in sequestration of a proportion of the circulating lymphocytes in lymph nodes with resultant reduction in circulating lymphocyte counts. Average circulating lymphocytes counts are expected to be around 0.5 -0.6 $x10^9$ /L or 500- 600 cells/mm^3. As such, the absolute total WBC, neutrophil and lymphocyte counts will be measured at each visit by the local laboratory. In case of lymphocyte alert, lymphocyte count should be

repeated in two weeks by the local laboratory. If the repeat test confirms the lymphocyte count is below $0.1x10^9$/L or 100 cells/mm^3, the study drug must be discontinued and the lymphocytes count needs to be monitored every two weeks until levels reach $0.6x10^9$/L values. Recovery of lymphocyte counts is expected to take several weeks given the long half-life of fingolimod. The patient should be evaluated and monitored for infections on a regular basis during this period. As shown recently (data presented at AAN 2011: S30.001 Lymphocytes and Fingolimod-Temporal patterns and relationship with infections) a lymphocyte count between 100-200 cells/mm^3 is not associated with a higher infection risk. Therefore, a cut-off of 100 cells/mm^3 is regarded as appropriate for this study. After termination of the study the recommendations defined in the local label will prevail, in Germany a limit of 200 cells/mm^3 will be considered in agreement with the SmPC.

Re-initiation of the study drug can only be considered once the lymphocyte counts increase above 600 cells/mm^3 as confirmed by the local lab after discussion with the Clinical Trial Leader at Novartis.

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

Should a patient develop any manifestations that, in opinion of the investigator, are atypical for multiple sclerosis including unexpected neurological or psychiatric symptom/signs (e.g. rapid cognitive decline, behavioral changes, cortical visual disturbances or any other neurological cortical symptoms/sign), or any symptom/sign suggestive of an increase of intracranial pressure or accelerated neurological deterioration, the investigator should schedule a complete physical and neurological examination and an MRI as soon as possible and before beginning any steroid treatment. Conventional MRI as defined in the protocol as well as Fluid-attenuated Inversion Recovery (FLAIR) and Diffusion-weighted imaging (DWI) sequences are recommended for differential diagnosis of Posterior reversible encephalopathy syndrome. The MRI must be evaluated by the local neuroradiologist. The investigator will contact the Clinical Trial Leader at Novartis to discuss findings and diagnostic possibilities as soon as possible. AE/SAEs need to be filed as appropriate.

In case of new findings in the MRI images in comparison with the previous available MRI which are not compatible with MS lesions, the study drug will be discontinued and other diagnostic evaluations need to be performed at the discretion of the investigator. In case of presence of new hyperintense T2-weighted lesions in the MRI which may be infectious in origin it is recommended to collect a cerebrospinal fluid sample if indicated. Analysis of the CSF sample including cellular, biochemical and, microbiological analysis (e.g. herpes virus, JC virus), to confirm/exclude an infection (e.g. PML) should be performed. In the event of suspected CNS infection, a CSF aliquot should in consultation with the sponsor be sent to a central laboratory (to be designated by the sponsor) for confirmatory testing.

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

Guidance on monitoring of patients with infections

All infections that develop during the study will be reported as AEs. Investigators are requested to specifically ask about infections at each visit. In case of infections an

unscheduled visit should be conducted. Treatment and additional evaluations will be performed at discretion of the investigator.

The investigator should remind the patient of the risk of infections and to instruct them to promptly report any symptoms of infections to the investigator. The patients must also be reminded to always carry their Patient Information Card (with site contact information and which identifies them as participants in a clinical study with an investigational agent with potential immunosuppressive effects) and to show this to any local healthcare provider they may consult and ask that the investigator be contacted.

When evaluating a patient with a suspected infection, the most sensitive tests available should be used (i.e. that directly detect the pathogen, as with PCR).

The investigator should consider early treatment with specific antimicrobial therapy on the basis of clinical diagnosis or suspicion thereof (e.g. antiviral treatment for herpes simplex or zoster) in consultation with infectious disease experts, as appropriate. The investigator should inform the Novartis medical expert of any such cases.

Investigators should consider the added immunosuppressive effects of corticosteroid therapy for treatment of MS attack/relapse and increase vigilance regarding infections during such therapy and in the weeks following administration.

Guidance for Ophthalmic Monitoring

Fingolimod has previously been associated with a two-fold increase in the risk of macular edema in renal transplant patients receiving cyclosporine. Although there have been no confirmed cases of macular edema in the multiple sclerosis Phase II study, careful ophthalmic monitoring is being implemented to permit early detection of this event, should it occur. A complete ophthalmic examination by an ophthalmologist will be conducted in accordance with Table 7-1. Similar assessments must be performed at an unscheduled ophthalmology visit for any patient who presents with new visual symptoms or decrease in visual acuity. The following assessments will be performed at the ophthalmic examinations:

1. Best corrected visual acuity using a visual acuity chart with equal spacing between letters and between lines
2. Dilated ophthalmoscopy for inspection of the macula and the optic disc
3. Optical Coherence Tomography (OCT)

Guidance on monitoring patients for possible macular edema

At baseline, if there is a suspicion of macular edema by dilated ophthalmoscopy or OCT (increased central foveal thickness or cystic changes in the fovea), the patient not be enrolled. A fluorescein angiogram may be performed to rule out vascular leakage in such cases. Based on ophthalmic monitoring during the study, study drug must be discontinued in any patient who meets one of the following criteria:

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

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

These patients must be followed-up 1 month and 3 months after diagnosis of macular edema and more frequently if needed based on the ophthalmologist's judgment. Further ophthalmologic evaluations until such time as resolution is confirmed or no further improvement is expected by the ophthalmologist (based on a follow-up period of not less than

3 months). These evaluations will include repeat best-corrected visual acuity, fundus examination, and OCT. Fluorescein angiography (FA) is 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.

An interruption or discontinuation of the study drug should be clearly documented and reflected on Dosage Administration Record eCRF. AE/SAEs need to be filed as appropriate. For patients discontinuing study drug for any of the above ophthalmic reasons, copies of the colored OCT and fluorescein angiography (if performed) as well as source documents of ophthalmic examination should be kept at the site as source documents. These documents may need to be submitted for review by in independent panel if needed.