Ponesimod / ACT-128800

Relapsing Multiple Sclerosis

Protocol AC-058B302

POINT: POnesImod aNd Tecfidera

Multicenter, randomized, double-blind, parallel-group, add-on, superiority study to compare the efficacy and safety of ponesimod to placebo in subjects with active relapsing multiple sclerosis who are treated with dimethyl fumarate (Tecfidera®)

Study Phase:	3
EudraCT Number:	2012-000541-12
Status and version:	Final Version 6
Date:	21 December 2017
Actelion document number (Doc No.):	D-17.622

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SIGNATURE PAGE FOR ACTELION PHARMACEUTICALS LTD

Hereinafter called Actelion

Treatment name / number

Ponesimod / ACT-128800

Indication

Relapsing multiple sclerosis

Protocol number, study acronym, study title

AC-058B302, POINT, Multicenter, randomized, double-blind, parallel-group, add-on, superiority study to compare the efficacy and safety of ponesimod to placebo in subjects with active relapsing multiple sclerosis who are treated with dimethyl fumarate (Tecfidera®)

I approve the design of this study.

TITLE	NAME	DATE	SIGNATURE
Clinical Trial Physician	Ewa Lindenstrøm, MD, PhD	21-DEC-17	PPD
Clinical ~~Project~~ Statistician	PPD PPD PPD	22-Dec-2017	PPD

INVESTIGATOR SIGNATURE PAGE

Treatment name / number

Ponesimod / ACT-128800

Indication

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AC-058B302, POINT, Multicenter, randomized, double-blind, parallel-group, add-on, superiority study to compare the efficacy and safety of ponesimod to placebo in subjects with active relapsing multiple sclerosis who are treated with dimethyl fumarate (Tecfidera®)

I agree to the terms and conditions relating to this study as defined in this protocol, the electronic Case Report Form (CRF), and any other protocol-related documents. I fully understand that any changes instituted by the investigator(s) without previous agreement with the sponsor would constitute a protocol deviation, including any ancillary studies or procedures performed on study subjects (other than those procedures necessary for the wellbeing of the subjects).

I agree to conduct this study in accordance with the Declaration of Helsinki principles, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and applicable regulations and laws. I will obtain approval by an Institutional Review Board or Independent Ethics Committee (IRB/IEC) prior to study start and signed informed consent from all subjects included in this study. If an amendment to the protocol is necessary, I will obtain approval by an IRB/IEC and ensure approval by regulatory authorities (if applicable) have been obtained before the implementation of changes described in the amendment. I will allow direct access to source documents and study facilities to sponsor representative(s), particularly monitor(s) and auditor(s), and agree to inspection by regulatory authorities or IRB/IEC representative. I will ensure that the study treatment(s) supplied by the sponsor are being used only as described in this protocol. I will ensure that all subjects or legally designated representatives have understood the nature, objectives, benefits, implications, risks and inconveniences for participating in this study. During the conduct of the study, I will constantly monitor the risk/benefit balance for an individual subject. I confirm herewith that the sponsor is allowed to enter and utilize my professional contact details and function in an electronic database for internal purposes and for submission to Health Authorities worldwide.

	Country	Site number	Town	Date	Signature
Principal Investigator					

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9-HPT	9-Hole Peg Test
ACTH	Adrenocorticotropic hormone
AE	Adverse event
ALT	Alanine aminotransferase / serum glutamic pyruvic transaminase
ANOVA	Analysis of variance
ARR	Annualized relapse rate
ARS	All randomized set
AST	Aspartate aminotransferase / serum glutamic oxaloacetic transaminase
ATS	American Thoracic Society
AV	Atrioventricular
b.i.d.	Twice daily
BP	Blood pressure
bpm	Beats per minute
CDA	Confirmed disability accumulation
CI	Confidence interval
CIS	Clinically isolated syndrome
CNS	Central nervous system
CRO	Contract Research Organization
CSF	Cerebrospinal fluid
CUAL	Combined unique active lesion
CXR	Chest X-ray
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DL_{CO}	Diffusing capacity for the lungs measured using carbon monoxide
DMF	Dimethyl fumarate
DMT	Disease-modifying therapy
DWI	Diffusion-weighted imaging

ECG	Electrocardiogram
eCRF	Electronic case report form
eC-SSRS	Electronic self-rated version of the Columbia-Suicide Severity Rating Scale
ECTRIMS	European Committee for Treatment and Research in Multiple Sclerosis
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
EOS	End-of-Study
EOT	End-of-Treatment
ePRO	Electronic PRO
ERS	European Respiratory Society
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescence angiography
FAS	Full analysis set
FDA	Food and Drug Administration
FEF	Forced expiratory flow
FEV_1	Forced expiratory volume in 1 second
FLAIR	Fluid-attenuated inversion recovery
FS	Functional system
FSIQ-RMS	Fatigue Symptom and Impacts Questionnaire-Relapsing Multiple Sclerosis
FU7d	FU visit approximately 7 days after the last dose of study drug
FU	Follow-up
FVC	Forced vital capacity
GCP	Good Clinical Practice
Gd	Gadolinium
Gd+	Gadolinium-enhancing
Hb	Hemoglobin
HIV	Human immunodeficiency virus
HR	Heart rate
i.m.	Intramuscular

i.v.	Intravenous
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICU	Intensive care unit
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN	Interferon
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISAC	Independent Statistical Analysis Center
ISF	Investigator site file
JCV	John Cunningham Virus
MACE	Major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
MIAC	Medical Image Analysis Center
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSFC	Multiple Sclerosis Functional Composite
NEDA	No evidence of disease activity
NK	Natural killer
NMSS	US National Multiple Sclerosis Society
NOAEL	No-observed-adverse-effect level
NYHA	New York Heart Association
o.d.	Once a day
OCT	Optical coherence tomography
OSB	Ophthalmology Safety Board
PASAT	Paced Auditory Serial Addition Test
PCBV	Percent change in brain volume
PCR	Polymerase chain reaction

PD	Pharmacodynamic(s)
PEF	Peak expiratory flow
PFT	Pulmonary function test
PK	Pharmacokinetic(s)
PML	Progressive multifocal leukoencephalopathy
PP	Primary progressive
PPMS	Primary progressive multiple sclerosis
PPS	Per-protocol set
PRMS	Progressive relapsing multiple sclerosis
PRN	As needed
PRO	Patient-reported outcome
PTOP	Post-treatment observation period
QTc	QT corrected
QTcB	QT corrected for heart rate on the basis of Bazett's formula
QTcF	QT corrected for heart rate on the basis of Fridericia's formula
RBC	Red blood cell
RMS	Relapsing multiple sclerosis
RR	Relapsing-remitting
RRMS	Relapsing-remitting multiple sclerosis
s.c.	Subcutaneous
S1P	Sphingosine-1-phosphate
SAE	Serious adverse event
SAF	Safety set
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SCR	Screened analysis set
SDMT	Symbol Digit Modalities Test
SF-36v2™	36-Item Short Form Health Survey Version 2
SI	International system of units
SIENA	Structural Image Evaluation, using Normalisation, of Atrophy
SIV	Site initiation visit

SmPC	Summary of Product Characteristics
SOC	System organ class
SOP	Standard operating procedure
SPMS	Secondary progressive multiple sclerosis
SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
ULN	Upper limit of the normal range
USPI	United States Package Insert
WBC	White blood cell(s)
WHO	World Health Organization
WOCBP	Woman of childbearing potential
WPAI:MS	Work Productivity and Activity Impairment: Multiple Sclerosis

SUBSTANTIAL GLOBAL AMENDMENT 5

Amendment rationale

This amendment rationale applies to global protocol AC-058B302 Version 5, dated 8 December 2016. The resulting amended global protocol is Version 6, dated 21 December 2017.

The main reasons for this amendment are to make the following changes to inclusion criterion #6:

- To include the presence of at least one new or one unequivocally enlarging T2 lesion on magnetic resonance imaging (MRI) of the brain or spinal cord as an alternative criterion of disease activity. In order to assess this alternative criterion, two MRI scans have to be compared; the first MRI scan must be performed within 15 months prior to Visit 1 (Screening) and after at least 3 months of dimethyl fumarate (DMF) treatment; the second MRI scan must be performed prior to randomization (i.e., MRI performed at Visit 2 [Baseline] may be used). The presence of at least one new or one unequivocally enlarging MRI T2 lesion has to be confirmed by the central MRI reading facility prior to randomization of the subject.

  New or enlarging MRI T2 lesions are commonly accepted as a sign of multiple sclerosis (MS) disease activity [Lublin 2014] and as such are part of international and national MS treatment guidelines [ICER Report 2017, Goodin 2002, Montalban 2017, Torkildsen 2016]. T2 lesions are considered a predictor of MS clinical activity such as relapses [Sormani 2009] and disability progression [Sormani 2013]. This modification takes into account the "re-baseline" MRI performed after at least 3 months on DMF, and the window of 15 months reflects the anticipated visit window for yearly MRI scans (i.e., 12 + 3 months) at sites where yearly MRI monitoring is standard of care.

- To include the presence of MRI T1 gadolinium-enhancing (Gd+) lesions observed on the pre-randomization MRI scan of the brain as an alternative criterion of disease activity.

  The presence of at least one T1 Gd+ lesion was already included in the definition of disease activity; however, sites could only use an MRI prior to Visit 1 (screening) and not the pre-randomization MRI to qualify a subject for the study. With this modification, sites will have the possibility to detect radiological signs of disease activity at the pre-randomization MRI, which is in line with allowing pre-randomization T2 lesions to be part of inclusion criterion #6.

Adding T2 lesions to disease-activity criteria and allowing a pre-randomization MRI to be a qualifying MRI will not change the study population, which will still consist of subjects with active relapsing MS (RMS) while on Tecfidera® with disease activity criteria based on relapses and active MRI lesions; the change is pertaining solely to the method and the timing of detecting the active MRI lesions.

Additional modifications are being made to the study protocol as follows:

- The recommendation for treatment of relapses provided in Section 5.2.4 is being modified to include a standardized dose of oral corticosteroids. High-dose oral corticosteroids are frequently used for treatment of relapses and have been proven to be as effective as intravenous oral prednisolone [Burton 2009, Le Page 2015] while less burdensome for the patients.

- The text related to modification of treatment due to confirmed relapses and re-consenting is amended to ensure alignment within the different protocol sections. According to Sections 5.1.1, 7.1.1, 7.2.2 and 13.3, after each confirmed relapse, the subjects must be made aware of the potential risks and benefits of continuing in the study as well as alternative treatment options available and then provide re-consent if they wish to continue on study treatment.

  Re-consenting subjects after each confirmed relapse is a more conservative approach than re-consenting only after two confirmed relapses or after 48 weeks of treatment and at least one confirmed relapse. Since the subjects have to be re-consented after each confirmed relapse, the requirement for re-consenting after two confirmed relapses or after 48 weeks of treatment with at least one confirmed relapse [originally mentioned in Sections 3.2, 3.5.2.1 and 5.1.1] is removed since it is redundant.

- In accordance with the recent update of sections 4.4 and 4.8 of the Tecfidera® Summary of Product Characteristics [Tecfidera USPI], in which it is now stated that drug-induced liver injury cases have been reported in post-marketing experience following Tecfidera® administration, the liver was introduced as a target organ of potential toxicity of dimethyl fumarate (Tecfidera®) in protocol Section 1.4. This modification does not warrant any change to the current monitoring of the liver functions, as the frequency of the tests is deemed to be sufficient.

- To alleviate the burden on subjects and sites in case of re-screening, sites do not have to repeat all the pre-randomization assessments that were performed for the first screening attempt, as described in the guidance for re-screening in Appendix 15.

- Prior to re-screening, a re-consent has to be obtained (i.e., a new Informed Consent Form has to be signed by the subject and by the investigator). The pre-randomization period will then start from the date of this re-consent [see Sections 8, 13.3 and Appendix 15].

- As the results from the lymphocyte subsets sub-study carry an unblinding potential, it is clarified in Sections 3.6.1 and 7.7.2.2 that the results from this sub-study will be blinded to site staff and the sponsor until study closure.

- In case of a temporary interruption of study treatment that lasts more than 30 days and leads to a permanent treatment discontinuation, the safety FU visits can be combined with the End-of-Treatment (EOT) visit [see Sections 8.2.10, 8.3.1.1 and 8.3.1.2].

- Section 1.3.2.3 is updated with results from an interim analysis of studies AC-058B201/B202 with cut-off date of 1 September 2016, which were presented as a poster at the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) congress in 2017.

- It is now permitted to omit gadolinium administration prior to MRI T1 sequences in case of medical contraindication during the study; consequently allergy to gadolinium is being removed from exclusion criterion #19. This is justified because gadolinium sequences are not used for the evaluation of the primary or secondary endpoints of the study.

- Clarification regarding the need to perform a new dermatological examination in case the subject was re-screened following an excision of a pre-cancerous skin lesion or a basocellular carcinoma is added to the section on dermatological examination [Section 7.3.12]. In this case, the dermatological examination performed at re-screening will ensure that the lesions were successfully excised.

- Clarification on the time windows for the conduct of assessments and visits:
  - In-between visit telephone calls: As per Section 8.2.5, the calls are scheduled at Weeks 18, 30, 42, 54, 66, 78, 90, 102, 114, 126, 138 and 150 (± 7 days; with Day 1 as a reference). However, in the same section it was stated "*The site will contact the subject 6 weeks (± 7 days) after each of the 12-weekly visits (e.g., Visit 6 – Week 12, Visit 7 – Week 24, ...). The window for these telephone calls is ± 7 days*." Thus, the change in Sections 7.2.2 and 8.2.5 provides clarification that the time window to conduct the in-between telephone calls may be either Weeks 18, 30, 42, 54, 66, 78, 90, 102, 114, 126, 138 and 150 (± 7 days), or 6 weeks after the last 12-weekly visit (± 7 days).

- Hourly electrocardiograms (ECGs), blood pressure (BP), and pharmacokinetic (PK) assessments: Cardiac monitoring consisting of hourly ECG and BP assessments must be conducted after first dosing on Day 1 or on the first day of re-initiation of study drug when post-dose monitoring is required. In addition, PK samples are to be drawn 3 hours post-dose at Visits 3 and 6 (Day 1 and Week 12). At Visit 6 (Week 12), an ECG must also be conducted 3 hours post-dose. The time windows for the above-mentioned assessments have not been specified in the study protocol. A time window of ± 15 minutes around the scheduled time seems reasonable for the collection of the data pertaining to the data time point. Thus, the study protocol is amended in order to provide a recommendation to perform the hourly ECG, BP, and PK within 15 minutes from the scheduled time.
- Home urine pregnancy tests: The time windows for the 4-weekly urine pregnancy tests conducted at home during the treatment period have not been specified in the study protocol. This test should be conducted at home within 4 days from the scheduled time point.

- Active or latent tuberculosis can be assessed by chest X-ray (CXR) or interferon (IFN) Gamma release assay. As defined in Section 7.3.5 of the study protocol, only subjects with a negative IFN gamma release assay (QuantiFERON-TB-Gold®) test at Visit 1 (Screening) **and** without CXR findings at Visit 1 (Screening) or within 90 days suggestive of active or latent tuberculosis can be included in the study. Thus, exclusion criterion #15 is amended to clarify that subjects with active or latent tuberculosis as assessed by CXR **or** IFN gamma release assay test are excluded from the study.

- In order not to repeat an MRI so soon after a previous assessment, it is clarified in Section 7.2.3 that, in case of premature study treatment discontinuation, the MRI assessment at EOT does not need to be performed if the EOT visit occurs within 4 weeks after the latest scheduled MRI assessment.

- Since the ECG assessment will inform about heart rate, it is clarified in Section 7.3.11 that pulse rate assessment may be omitted in case a visit for relapse corresponds to a visit when 12-lead ECG is performed.

- Correction is made in Sections 8.3.2.1, 8.3.2.2 and 8.3.2.3 to clarify that post-treatment observation visits are not recorded in the Interactive Response Technology system.

- Clarification on the conduct of physical examination: The required examinations as part of the physical examination at pre-randomization and at subsequent visits are clarified in Section 7.3.9. It is the responsibility of the principal investigator or

treating neurologist to perform other exams if indicated, based on medical history and/or symptoms.

- As stated in Section 7.2.5, the Symbol Digit Modalities Test (SDMT) is administered along with the Multiple Sclerosis Functional Composite (MSFC) test. Since, depending on the site setting, the efficacy assessor may be in charge of administering the MSFC test, clarification is provided in Section 3.7.3 that the efficacy assessor may also administer the SDMT.

- Section 3.5.5 is added to the study protocol in order to provide clarifications on the visits and assessments that will have to be performed after the study closure announcement by the sponsor and the time frame for these.

- Sections 5.2.5 and 5.2.6 are amended to further clarify that short-term treatment with low dose of corticosteroids and inhaled corticosteroids for pulmonary conditions are allowed.

- Clarification is provided in Sections 7.3.13.1 and 7.3.13.2 that an additional blood sample may need to be collected if deemed necessary by the investigator in case of a lost or deteriorated sample.

- Adjustments are made to align Section 1.1.4 with recent changes in available therapies for MS.

- The definition of 24-week CDA was not present in the study protocol and is now added to Section 6.1.3.

- Text has been added to allow physician assistants and nurse practitioners to assume the role of efficacy assessor if adequately trained and certified [Section 3.7.3]. Physician assistants and nurse practitioners are trained in autonomous healthcare decision-making. The performing of examinations such as Expanded Disability Status Scale / Functional system (EDSS/FS) scoring is typically delegated to efficacy assessors by physicians. Any person acting as the efficacy assessor in this study will be trained and certified in EDSS scoring as defined in the study protocol. Qualification and certification of the person assigned to this role will be reviewed by the sponsor before she/he is allowed to make an efficacy assessment.

- Text has been added to allow physician assistants, nurse practitioners as well as any trained and qualified person as per local regulations to assume the role of dermatologist and first-dose administrator [Sections 3.7.10 and 3.7.4, respectively]. Physician assistants and nurse practitioners are trained in autonomous healthcare decision-making. Any person acting as the dermatologist or first-dose administrator in this study will have to be trained and qualified, as per local regulations, to assume

this role. For non-physicians the role of a dermatologist or first-dose administrator must be within the scope of the national and/or local authorization. The qualifications of non-physicians performing dermatological examinations or acting as first-dose administrator will need to be assessed by the sponsor prior to assignment.

- Clarity has been added in Section 5.1.12.7 that the decision to permanently discontinue a subject due to a macular edema is based on the confirmation of macular edema by the local ophthalmologist.
- In Sections 6.2 and 11.3.5.5.1, a safety endpoint has been added on John Cunningham Virus serology change from baseline up to End-of-Study.
- Text has been added to allow replacement of dilated funduscopy by funduscopy with ultra widefield imaging when pupil dilation is medically contraindicated [Section 7.3.6].

Finally, some inconsistencies between sections in the protocol were corrected as follows:

- Table 2 and Section 7.3.4 currently state that, in case of premature study treatment discontinuation, the chest X-ray at Visit 18 (EOT) does not need to be performed if the EOT visit occurs within 48 weeks of the pre-randomization chest X-ray. This requirement is made consistent in Section 8.2.10.
- At the unscheduled visit for relapses, the principal investigator / treating neurologist will need to perform a physical examination and vital signs including pulse rate and body temperature to exclude potential other reasons for the symptom(s) observed. In this event, systolic blood pressure (SBP) / diastolic blood pressure (DBP) assessment is not mandated. SBP/DBP assessment is therefore removed from the table of assessment and Section 8.4.1.
- Section 3.8.3 currently defines the process for review and evaluation of brain MRIs by the MRI safety board in case of a suspected opportunistic infection in the central nervous system (CNS). Therefore, the text in Section 5.1.12.3.1 is made consistent with Section 3.8.3.
- Section 4.5.2 currently states that if a hormonal method of contraception is chosen, then it must be initiated at least 30 days prior to randomization. Inclusion criterion #3 is modified to refer to Section 4.5.2 in which the time window for each acceptable method of contraception is described.
- Figure 2 is updated to align the definition of maintenance period with Section 5.1.9.
- Spirometry and physical examination are added to the list of assessments to be performed at Visit 6A (Week 12) and Visit 7A (Week 24), respectively, Sections

8.3.2.1 and Table 3, to have the same frequency for these two assessments in the post-treatment observation period than during the treatment period.

Changes to the protocol

Two versions of the amended protocol will be prepared: 1) a clean version and 2) a Word comparison document, showing deletions and insertions in comparison to the previous protocol version.

Amended protocol sections

The sections of the protocol affected by this amendment are listed below. Where applicable, the same changes have also been made to the corresponding sections of the protocol synopsis:

1.1.4	Treatment of MS
1.1.4.1	Injectable disease-modifying therapies
1.1.4.2	Orally administered disease-modifying therapies
1.3.2.3	Efficacy in humans
1.4	Purpose and rationale of the study
1.5	Summary of known and potential risks and benefits
3.4.1	Lymphopenia
3.5.2.1	Modification of treatment
3.5.3.2	Post-treatment observation period
Figure 1	AC-058B302 study design
3.5.5	Study closure
3.6.1	Lymphocyte subset
3.7.3	Efficacy assessor
3.7.4	First-dose administrator
3.7.7	Local radiologist or neurologist with MRI expertise
3.7.10	Dermatologist
3.8.4	Major adverse cardiovascular events adjudication board

8.4.2	Additional unscheduled visits for re-initiation of study drug (I1, I2, etc.)
11.3.5.5.1	Laboratory tests
13.3	Informed consent
13.12	Reporting of study results and publication
14	REFERENCES
Appendix 5	Adverse events of special interest
Appendix 6	Abnormalities for ECG, BP and laboratory variables
Appendix 15	Guidance for re-screening

Summary of previous amendments

Global Amendment	Date	Main reason(s)
1	4 December 2015	Addressing comments received during the special protocol assessment (SPA) review by the US FDA.
2	9 March 2016	Addressing comments received after the US FDA's review of the SPA.
3	17 June 2016	Addressing comments received during the Voluntary Harmonization Procedure review for this Clinical Trial Application in the EU.
4	8 December 2016	Clarifying that study subjects will be re-consented to continue receiving study drug (rather than re-consenting to participate in the study) if they meet one of the following conditions: • The subject has completed at least 48 weeks of treatment in the study AND has had at least one confirmed relapse that occurred after 12 weeks or more of treatment; • The subject has experienced two confirmed relapses while on study treatment; • The subject has experienced an event of 24-week confirmed disability accumulation while on study treatment.

PROTOCOL SYNOPSIS AC-058B302

TITLE	Multicenter, randomized, double-blind, parallel-group, add-on, superiority study to compare the efficacy and safety of ponesimod to placebo in subjects with active relapsing multiple sclerosis who are treated with dimethyl fumarate (Tecfidera®)
ACRONYM	POINT: **PO**nes**I**mod a**N**d **T**ecfidera
OBJECTIVES	**Primary objective** The primary objective of the study is to determine whether add-on therapy with ponesimod reduces relapse frequency as compared to placebo in subjects with active relapsing multiple sclerosis (RMS) who are treated with dimethyl fumarate (DMF; Tecfidera®). **Secondary objectives** • To assess the effect of add-on therapy with ponesimod vs placebo on disability accumulation and on other aspects of multiple sclerosis (MS) disease control in subjects with RMS who are treated with DMF (Tecfidera®); • To assess the safety and tolerability of add-on therapy with ponesimod vs placebo in subjects with RMS who are treated with DMF (Tecfidera®).
DESIGN	This is a prospective, multicenter, randomized, double-blind, parallel group, add-on, placebo-controlled, Phase 3, superiority study. The study is designed to compare the efficacy, safety, and tolerability of add-on therapy with ponesimod 20 mg vs placebo in adult subjects with active RMS who are treated with DMF (Tecfidera®).
PERIODS	**Pre-randomization period** This period commences up to 45 days before randomization at the time of the signature of the Informed Consent Form (ICF) and ends with subject randomization. It includes Visit 1 (Screening), Visit 2 (Baseline) and the pre-dose assessments of Visit 3 (Day 1). **Treatment period** This period consists of a double-blind treatment period, which starts after randomization with the first dose of study treatment

	during Visit 3 (Day 1 of study). The double-blind treatment period has a variable duration from a minimum of 60 weeks (for the last subject randomized) to a maximum of 156 weeks (3 years) for the first subjects randomized in the trial. Average duration is expected to be approximately 2 years. It includes a randomization visit, visits at 2, 4, and 12 weeks after randomization, and 12-weekly visits thereafter until 60 weeks after the randomization of the last subject or 156 weeks of treatment (whichever occurs first). For an individual subject, this period starts on the day of the first study treatment intake and continues until the premature discontinuation of study treatment, Week 156 or until 60 weeks after the randomization of the last subject (whichever occurs first). End-of-Treatment (EOT) visit: The EOT visit at an individual level should preferably take place 1 day after the last dose of study treatment, but no later than 7 days after the last dose of study treatment. ***Modification of treatment*** If a subject meets one of the following conditions: • The subject has experienced a confirmed relapse while on study treatment; • The subject has experienced an event of 24-week confirmed disability accumulation (CDA) while on study treatment; Then, the principal investigator / treating neurologist should consider and propose the following options to this subject: • Subject remains on study treatment. In this case, the subject will be asked to re-consent to continue receiving study treatment. • Subject prematurely discontinues study treatment and DMF background therapy, and begins treatment with an approved MS therapy at the discretion of the treating neurologist in accordance with local practices. In this case, the subject will enter the post-treatment observation period (PTOP) of the study.

	Subjects who prematurely discontinue study treatment for reasons other than lack of efficacy (e.g., safety or tolerability) will also enter the PTOP of the study. Treating neurologists may choose to continue DMF therapy or may begin treatment with an approved MS therapy at the discretion of the treating neurologist in accordance with local practices. Discontinuation of DMF treatment should be considered in accordance with prescribing information at the discretion of the treating neurologist and in accordance with local practices. Subjects who permanently discontinue DMF background therapy will discontinue study treatment and may begin treatment with an approved MS therapy in accordance to local practices. In this case, the subject will enter the PTOP of the study. **Post-treatment period and End-of-Study** This period starts immediately after the last dose of study treatment and ends when End-of-Study (EOS) visit has been completed. It comprises the post-treatment safety follow-up (FU) period and if applicable, is followed by the PTOP. ***Post-treatment safety follow-up period*** All subjects will enter the safety FU period which lasts for at least 30 days after the last dose of study treatment and includes a safety FU visit approximately 30 days after the last dose of study treatment. Subjects participating in the lymphocyte subset sub-study will have an additional FU visit approximately 7 days after the last dose of study drug. ***Post-treatment observation period*** Subjects who prematurely discontinue study drug and complete the 30-day safety follow-up including FU visit, will enter the PTOP which lasts until 60 weeks after randomization of the last subject (i.e., planned EOT visit) irrespective of treatment completion. It consists of an abbreviated schedule of assessments at the time of the originally scheduled 12-weekly visits. ***End-of-Study*** The study level EOS will occur after all subjects have completed the safety FU period or the last visit of the PTOP. For an individual subject, EOS is reached when treatment, post-

	treatment safety FU, and, if applicable, PTOP have been completed: • For subjects who complete the treatment period, and for subjects who prematurely discontinue study treatment and do not enter the PTOP, the EOS visit corresponds to the 30-day FU visit. • For subjects who prematurely discontinue study treatment and enter the PTOP period, the EOS visit corresponds to the last visit of the PTOP. The study closure will be communicated by the sponsor 60 weeks after the randomization of the last subject.
PLANNED DURATION	Assuming a subject recruitment time of 104 weeks (including the period from first subject, first visit (FSFV) to last subject, first visit (LSFV) and a 45-day pre-randomization period for the last randomized subject), the overall duration of the study from FSFV to last subject, last visit (LSLV) will consist of 104 weeks recruitment, followed by the minimum treatment time of 60 weeks, and 30 days post-treatment safety follow-up. This results in an anticipated study duration of approximately 168 weeks (3.3 years). The actual overall study duration or subject recruitment period may vary. For an individual subject, the maximum duration time will consist of a 45-day pre-randomization period followed by a maximal 156-week treatment period and a 30-day post-treatment safety follow-up. This results in a maximal total participation time of approximately 167 weeks (3.3 years).
SITE(S) / COUNTRY(IES)	100 sites in 15 countries (planned).
SUBJECTS / GROUPS	Approximately 600 subjects who have been receiving DMF twice daily (b.i.d.) for at least 6 months will be randomized in a 1:1 ratio to ponesimod 20 mg or placebo (approximately 300 subjects per arm). Randomization will be stratified by baseline Expanded Disability Status Scale (EDSS) score (EDSS $\leq$ 3.5, EDSS > 3.5).

INCLUSION CRITERIA	1. Signed informed consent prior to initiation of any study-mandated procedure. 2. Males and females aged 18 to 55 years (inclusive). 3. A woman of childbearing potential (WOCBP) is eligible only if the following applies: • must have a negative serum pregnancy test at Visit 1 (Screening) and a negative urine pregnancy test at Visit 2 (Baseline); • must agree to undertake monthly urine pregnancy tests during the study and up to 30 days after study treatment discontinuation; • must use reliable methods of contraception until 30 days after study treatment discontinuation as described in protocol Section 4.5.2; 4. Presenting with a diagnosis of MS as defined by the revised (2010) McDonald Diagnostic Criteria for MS [see Appendix 2] with relapsing course from onset (i.e., relapsing-remitting multiple sclerosis (RRMS), or secondary progressive multiple sclerosis (SPMS) with superimposed relapses). 5. Ongoing treatment with DMF for at least 6 months prior to Visit 1 (Screening); 6. Active disease after at least 3 months of DMF treatment defined by at least one of the following features: • At least one MS attack supported by objective neurological examination with onset within 12 months to 1 month prior to baseline EDSS assessment; • At least one gadolinium-enhancing (Gd+) lesion on an MRI of the brain or spinal cord, performed within 12 months prior to Visit 1 (Screening) or during the pre-randomization period (MRI assessed at Visit 2 [Baseline] may be the qualifying scan); • Presence of at least one new or one unequivocally enlarging T2 lesion on an MRI of the brain or spinal cord, assessed by comparing two MRI scans: the first MRI scan must be performed within 15 months prior to Visit 1 (Screening) and after at least 3 months of DMF treatment; the second MRI scan must be performed prior to randomization (MRI assessed at Visit 2 [Baseline] may be used). The presence of at least one new or one

	unequivocally enlarging T2 lesion has to be confirmed by the central MRI reading facility prior to randomization. 7. Ambulatory and with an EDSS score between 0 and 6.0 (inclusive) at Visit 1 (Screening) and Visit 2 (Baseline). 8. For subject with ongoing treatment with DMF ≥ 12 months prior to screening: • Lymphocyte count ≥ 0.8×10^9/L (≥ 800/mm^3) at Visit 1 (Screening) and Visit 2 (Baseline) (assessed at least 3 weeks apart) with the lymphocyte count at Visit 2 (Baseline) > 0.5-fold and < 2.0-fold of the count at Visit 1 (Screening). For subject with ongoing treatment with DMF ≥ 6 months (but < 12 months) prior to screening: • Lymphocyte count ≥ 0.9×10^9/L (≥ 900/mm^3) at Visit 1 (Screening) and Visit 2 (Baseline) (assessed at least 3 weeks apart) with the lymphocyte count at Visit 2 (Baseline) > 0.5-fold and < 2.0-fold of the count at Visit 1 (Screening).
EXCLUSION CRITERIA	**Pregnancy and Breastfeeding** 1. Lactating or pregnant women and women intending to become pregnant during the study. **MS disease** 2. Presenting with a diagnosis of MS with progressive course from onset (i.e., primary progressive MS or progressive relapsing MS). 3. Evidence of a relapse of MS with onset within 30 days prior to baseline EDSS assessment or between baseline EDSS assessment and randomization. **Treatments** 4. Treatment with the following medications: • Within 15 days prior to randomization: o β-blockers, diltiazem, verapamil, digoxin or any other anti-arrhythmic or heart rate (HR) lowering systemic therapy [non-exhaustive list of drugs provided in Appendix 3] • Within 30 days prior to randomization: o Adrenocorticotropic hormone (ACTH) or systemic corticosteroids (for any reason)

	○ Vaccination with live vaccines • Within 90 days prior to randomization: ○ Plasmapheresis, cytapheresis ○ Intravenous (i.v.) immunoglobulin ○ Treatment with an investigational drug (within 90 days or five half-lives of the drug, whichever is longer), except biological agents (see below) • Within 180 days prior to randomization: ○ IFN β-1a, IFN β-1b, glatiramer acetate, or daclizumab ○ Systemic immunosuppressive treatment (e.g., cyclosporine, sirolimus, mycophenolic acid, azathioprine, methotrexate or cyclophosphamide) ○ Fingolimod (Note: prior treatment with fingolimod anytime is an exclusion criterion if discontinuation was due to an adverse event (AE) or poor tolerability) • Within 12 months prior to randomization: ○ Natalizumab ○ Non-lymphocyte-depleting experimental biological agents • Within 24 months prior to randomization: ○ Lymphocyte-depleting biological agents such as rituximab or ocrelizumab ○ Cladribine • Any time prior to randomization: ○ Alemtuzumab ○ Mitoxantrone ○ Ponesimod ○ Other investigational S1P modulators ○ Stem cell transplantation ○ Leflunomide or teriflunomide unless adequate and successful wash-out is documented. **Infection and Infection Risk** 5. Ongoing known bacterial, viral or fungal infection (with the exception of onychomycosis and dermatomycosis), confirmed positive hepatitis B surface antigen test at Visit 1 (Screening; unless hepatitis B vaccination has occurred within 4 weeks prior to a positive screening test and a repeat hepatitis B surface antigen test performed ≥ 2 weeks after

	the initial test has been negative) or hepatitis C antibody tests at Visit 1 (Screening). 6. Congenital or acquired severe immunodeficiency or known human immunodeficiency virus (HIV) infection or positive HIV testing at Visit 1 (Screening). 7. Negative antibody test for varicella-zoster virus at Visit 1 (Screening). 8. Known progressive multifocal leukoencephalopathy (PML) infection or evidence of new neurological symptoms or MRI signs within 6 months prior to randomization which are compatible with a diagnosis of PML infection. **Malignancy** 9. History or presence of malignancy (except for surgically excised basal or squamous cell skin lesions), lymphoproliferative disease, or history of total lymphoid irradiation or bone marrow transplantation. 10. Presence of pre-cancerous (e.g., actinic keratosis, atypical moles) or cancerous skin lesions (e.g., basal cell carcinoma, squamous cell carcinoma) at Visit 2 (Baseline). **Ophthalmologic** 11. Presence of macular edema. **Cardiovascular** 12. Any of the following cardiovascular conditions: • Resting HR < 50 bpm as measured by the pre-randomization 12-lead ECG on Day 1; • Myocardial infarction within 6 months prior to randomization or current unstable ischemic heart disease; • Cardiac failure (NYHA class III or IV) or any severe cardiac disease at the time of Visit 1 (Screening) or randomization; • History or presence of valvular heart disease associated with significant symptoms or hemodynamic change according to investigator judgment; • History or presence of cardiac rhythm disorders (e.g., sino-atrial heart block, symptomatic bradycardia, atrial flutter or atrial fibrillation, ventricular arrhythmias, cardiac arrest); • Presence of second-degree atrioventricular (AV) block

	or third-degree AV-block or a QTcF interval > 470 ms (females), > 450 ms (males) as measured by 12-lead ECG at Visit 1 (Screening), Visit 2 (Baseline) or by the pre-dose ECG at Visit 3 (Randomization / Day 1); • History of syncope associated with cardiac disorders; • Systemic arterial hypertension not controlled by medication according to investigator judgment. **Metabolic** 13. Type 1 or 2 diabetes which is poorly controlled according to investigator judgment or diabetes complicated with organ involvement such as diabetic nephropathy or retinopathy. **Pulmonary** 14. Subjects with a clinically significant pulmonary condition including: • Asthma which is insufficiently controlled according to investigator judgment, or any hospitalization due to asthma exacerbation within 6 months prior to randomization; • Abnormal pulmonary function tests (PFTs): forced expiratory volume in 1 second (FEV_1) or forced vital capacity (FVC) < 70% of the predicted normal value at Visit 2 (Baseline). 15. Active or latent tuberculosis (TB), as assessed by chest X-ray performed at Visit 1 (Screening) or within 90 days prior to Visit 1 (Screening), or interferon gamma release assay (QuantiFERON-TB-Gold®) at Visit 1 (Screening), except if there is documentation that the subject has received adequate treatment for latent TB infection or TB disease previously. **Hematology** 16. Any of the following abnormal laboratory values at Visit 1 (Screening) or Visit 2 (Baseline): • Hemoglobin (Hb) < 100 g/L • White blood cells (WBC) count $< 3.5 \times 10^9$/L ($< 3500/mm^3$) • Neutrophil count $< 1.5 \times 10^9$/L ($< 1500/mm^3$) • Platelet count $< 100 \times 10^9$/L ($< 100{,}000/ mm^3$)

	Hepatic 17. Known and documented moderate or severe hepatic impairment. 18. Any of the following abnormal laboratory values at Visit 1 (Screening) or Visit 2 (Baseline): • Alanine aminotransferase (ALT/SGPT) > 3 × the upper limit of normal (ULN) • Aspartate aminotransferase (AST/SGOT) > 3 × ULN • Total bilirubin > 1.5 × ULN (unless in the context of known Gilbert's Syndrome) **Other categories** 19. Contraindications for MRI such as: • Pacemaker, certain metallic implants such as artificial heart valves, aneurysm/vessel clips and any metallic material in high-risk areas which are contraindicated for MRI according to the local procedures; • Severe renal insufficiency defined as a calculated creatinine clearance < 30 mL/min (Cockroft-Gault); • Claustrophobia if its nature or severity is prohibitive for performing MRI according to the investigator's judgment. 20. History of clinically significant drug or alcohol abuse. 21. Known allergy to any of the ponesimod formulation excipients. 22. Any other clinically relevant medical or surgical condition, which, in the opinion of the investigator, would put the subject at risk by participating in the study. 23. Subjects unlikely to comply with protocol, e.g., uncooperative attitude, inability to return for follow-up visits, or known likelihood of not completing the study including mental condition rendering the subject unable to understand the nature, scope, and possible consequences of the study.

<table>
<tr>
<td>STUDY TREATMENTS</td>
<td>
Investigational treatment
One tablet of ponesimod 20 mg or matching placebo, administered orally once daily preferably in the morning from Day 15 to EOT.

To reduce the first-dose effect of ponesimod, an up-titration scheme will be implemented from Day 1 to Day 14:

<table>
<tr><th>Duration</th><th>Dose regimen in the ponesimod group</th></tr>
<tr><td>Day 1 and 2</td><td>2 mg</td></tr>
<tr><td>Day 3 and 4</td><td>3 mg</td></tr>
<tr><td>Day 5 and 6</td><td>4 mg</td></tr>
<tr><td>Day 7</td><td>5 mg</td></tr>
<tr><td>Day 8</td><td>6 mg</td></tr>
<tr><td>Day 9</td><td>7 mg</td></tr>
<tr><td>Day 10</td><td>8 mg</td></tr>
<tr><td>Day 11</td><td>9 mg</td></tr>
<tr><td>Day 12 to 14</td><td>10 mg</td></tr>
<tr><td>Day 15 until EOT</td><td>20 mg</td></tr>
</table>
</td>
</tr>
<tr>
<td>CONCOMITANT THERAPY</td>
<td>
Concomitant background therapy
In order to be eligible for this study, subjects must have been treated with DMF (Tecfidera®) for at least 6 months prior to Visit 1 (Screening). Subjects should be treated with DMF as per prescribing information [Tecfidera USPI, Tecfidera SmPC] throughout the course of the study [see Section 3.5.2.1].

Allowed concomitant therapy
• Dalfampridine (synonymous with fampridine) on a stable dose for at least 90 days prior to randomization and during double blind treatment. Dalfampridine therapy must not be started or increased in dose during the study. Stopping or decreasing the dose of dalfampridine during the study should only take place if deemed absolutely necessary by the investigator;
• Administration of i.v. atropine in the event of symptomatic bradycardia;
• Short-acting β2-agonists for respiratory symptoms and/or reduced pulmonary function during study treatment (please refer to Sections 5.1.12.4 and 7.3.3 for guidance);
</td>
</tr>
</table>

	• QT-prolonging drugs with known risk of Torsades de Pointes should be used with caution since ponesimod may potentially enhance their effect on QT interval [guidance is provided in Appendix 4]; • Vaccination with non-live vaccines. Subjects receiving non-live vaccination while on study treatment will have 5 mL of blood drawn prior to and ≥ 3 weeks after vaccination in order to explore changes in vaccine-specific antibody titers from pre- to post-vaccination. Samples will be analyzed at the end of the study; • Low dose corticosteroid (up to 10 mg prednisone equivalent daily), given as short-term treatment (up to 2 weeks per treatment cycle with at least 8 weeks' interval between treatment cycles and no more than 8 weeks during the whole study duration); • Inhaled corticosteroids for pulmonary conditions; • Other treatments considered necessary for the subject's benefit and not categorized as prohibited concomitant medications. **Forbidden concomitant therapy** The below list of forbidden concomitant therapies is applicable to all subjects receiving study treatment, but not to the subjects who prematurely discontinued study treatment and participate in the PTOP. • Systemic corticosteroids and ACTH, except for: the treatment of MS relapses (see Recommended therapy below); short-term treatment with a low dose of corticosteroid; and inhaled corticosteroids for pulmonary conditions (see Allowed concomitant therapy above); • Disease-modifying drugs for MS other than prescribed as per protocol (e.g., interferon beta, glatiramer acetate, fingolimod, teriflunomide, natalizumab, or other monoclonal antibody therapy); • Immunosuppressive treatment (e.g., cladribine, mitoxantrone or other systemic immunosuppressive treatments such as azathioprine, cyclophosphamide, cyclosporine, methotrexate, or leflunomide); • Intravenous immunoglobulin; • Plasmapheresis, cytapheresis, or total lymphoid irradiation;

	• Vaccination with live vaccines; • β-blockers, diltiazem, verapamil, digoxin, or any other anti-arrhythmic or heart rate lowering systemic therapy [non-exhaustive list of drugs provided in Appendix 3]; • Any other investigational drug; • Any investigational therapeutic procedure for MS (e.g., stent placement or angioplasty for chronic cerebrospinal venous insufficiency (CCSVI), stem cell transplantation). In the event that a subject takes any of these forbidden medications, the investigator must contact the sponsor to discuss further FU actions including stopping/interrupting study treatment as appropriate. **Recommended therapy – treatment of relapses** • If a relapse requires treatment with corticosteroids, methylprednisolone 1 g i.v., oral methylprednisolone in the dose range of 1 g to 1.25 g or equivalent doses of oral prednisone or prednisolone daily for 3 to 5 days is recommended (without an oral taper). Treatment with other corticosteroids, another dose, other routes of administration, or ACTH is not recommended unless deemed necessary and must be documented in the patient charts by the investigator. • Treatment of relapses with plasma exchange (i.e., plasmapheresis, cytapheresis) is prohibited.
ENDPOINTS	**Primary efficacy endpoint** • Annualized relapse rate (ARR) defined as the number of confirmed relapses from randomization up to EOS, per subject-year. **Secondary efficacy endpoints** • Time to 12-week CDA from baseline up to EOS; • Time to first confirmed relapse up to EOS; • Mean number of combined unique active lesions (CUALs) per post-baseline scan up to EOS; • Longitudinal change over time in fatigue-related symptoms as measured by the symptom domain of the FSIQ–RMS from baseline up to EOS;

	• Longitudinal percent change over time in brain volume from baseline up to EOS. **Other efficacy endpoints** **MRI-based exploratory endpoints:** • Percent change in brain volume (PCBV) from baseline to Week 48, 96, 144, EOT, and EOS; • Mean number of CUALs per subject per scan from baseline up to Week 48, 96, 144, EOT, and EOS; • Mean number of Gd+ T1 lesions per subject per scan from baseline up to Week 48, 96, 144, EOT, and EOS; • Mean number of new or enlarging T2 lesions per subject per scan from baseline to Week 48, 96,144, EOT, and EOS; • Change from baseline to Week 48, 96, 144, EOT, and EOS in the volume of MRI lesions (T2 lesions, T1 hypointense lesions); • Absence of MRI lesions (Gd+ T1 lesions, new or enlarging T2 lesions, new T1 hypointense lesions) from baseline to Week 48, 96, 144, EOT, and EOS. **Clinical exploratory endpoints (disease activity, relapses, disability progression):** • Absence of confirmed relapses from baseline up to EOS; • Time to first 24-week CDA from baseline up to EOS; • Change in EDSS from baseline by visit to EOS; • No evidence of disease activity (NEDA) status at EOS (defined by the absence of confirmed relapse, Gd+ T1 lesions, new or enlarging T2 lesions, 12-week CDA, as well as absence of annual brain volume decrease $\geq 0.4\%$ from baseline to EOS and completing treatment as planned). **Other clinical exploratory endpoints:** • Change in Multiple Sclerosis Functional Composite (MSFC) Z-score from baseline by visit up to EOS; • Change in the Symbol Digit Modalities Test (SDMT) score from baseline by visit up to EOS; • Change from baseline by visit up to EOS in fatigue-related impacts as measured by the impact sub-scales of the FSIQ-RMS.

	Safety endpoints • Treatment-emergent AEs, serious adverse events, AEs of special interest[#], major adverse cardiovascular events (MACE), and AEs leading to premature discontinuation of study treatment; • Treatment-emergent morphological ECG abnormalities (as defined by the ECG provider); • Change in 12-lead ECG variables (HR, PR, QRS, QT, QT corrected for HR on the basis of Bazett's formula [QTcB], QT corrected for heart rate on the basis of Fridericia's formula [QTcF]) from pre-dose to selected post-doses assessments (1 h, 2 h, 3 h, 4 h) on Day 1 and on day of re-initiation of study treatment when post-dose monitoring is required; • Notable abnormalities* for selected 12-lead ECG variables (HR, PR, QT, QTc) at 3-hour post dose assessment on Day 1, Week 12 and at the re-initiation of study treatment when post-dose monitoring is required; • Treatment-emergent decrease of FEV_1 or FVC > 20% from baseline values or decrease of percent predicted FEV_1 or FVC > 20 percentage points from baseline values; • Change in FEV_1 or FVC from baseline, absolute and % of absolute change to all timepoints up to EOS; • Change from baseline to EOS versus change from baseline to EOT in FEV_1 or FVC (absolute and % of predicted); • Among subjects with a decrease of > 200 mL or > 12% in FEV_1 or FVC from baseline to EOT, reversibility defined as a decrease of < 200 mL or < 12% in FEV_1 or FVC from baseline to last available post-EOT follow-up • Treatment-emergent notable blood pressure abnormalities*; • Treatment-emergent notable laboratory abnormalities*; • Change in body weight from baseline to EOS; • Treatment-emergent electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) suicidal ideation score of 4 or above, or a "yes" response on the eC-SSRS suicidal behavior item. • Change in John Cunningham Virus serology from baseline up to EOS. [# #] The selection of AEs of special interest is based on the anticipated risks of treatment with ponesimod and on the events that may be related to MS

	co-morbidities (e.g., seizures or stroke) as described in Appendix 5; the final list of AEs of special interest will be defined in the Statistical Analysis Plan (SAP). * The selection of notable abnormalities considered for the analyses is based on standard definitions and the anticipated risks of treatment with ponesimod as described in Appendix 6; the final list of abnormalities will be defined in the SAP. **Quality of life endpoints** • Change from baseline by visit up to EOT in SF-36v2™ Health Survey domain and component scores. **Pharmacoeconomic endpoints** • Change from baseline by visit up to EOT in work productivity and activity impairment in MS (WPAI:MS) scores. • Health care resource utilization from baseline by visit up to EOT on-treatment visit (number of hospitalizations, length of stay, number of intensive care admissions for MS relapse and visits to an emergency medical services facility for MS). **Pharmacokinetic (PK) evaluations** • Plasma concentrations of ponesimod pre-dose at Week 12, Week 24, Week 48, Week 96, Week 144, EOT and FU, and 3 hours post-dose on Day 1 and at Week 12. **Pharmacodynamic (PD) evaluations** • Absolute and percent change in peripheral blood lymphocyte counts pre-dose by visit up to EOS. • Absolute and percent change in lymphocytes subsets by visit up to EOS (Sub-study). **PK/PD relationship** • Correlation of selected efficacy and safety variables with absolute lymphocyte counts and magnitude of reduction of lymphocyte counts may be analyzed.
ASSESSMENTS	Refer to the schedule of assessments in Table 1, Table 2, and Table 3.
STATISTICAL METHODOLOGY	The Statistical Analysis Plan (SAP) will be finalized prior to database lock for the final analyses. The SAP provides the full details of all analyses, data displays, and algorithms to be used

	for data derivations. **Screened analysis set** The screened analysis set (SCR) includes all subjects who were screened and received a subject number. **Full analysis set** The full analysis set (FAS) includes all randomized subjects who were treated with at least one dose of study treatment and have at least one post-baseline efficacy assessment. All primary statistical analyses of efficacy endpoints will be based on the FAS. **All-randomized set** The all-randomized set includes all randomized subjects. **Per-protocol set** The per-protocol set (PPS) comprises all subjects included in the FAS without any major protocol deviations. **Safety set** The safety set (SAF) includes all subjects who received at least one dose of study treatment. Subjects will be analyzed based on actual treatment taken. **Primary endpoint variable** The primary endpoint is the ARR defined as the number of confirmed relapses per subject-year. All confirmed relapses up to the EOS will be included in the analysis. **Secondary endpoint variables** There are five secondary efficacy endpoints, which will be analyzed in a hierarchical manner: • Time to 12-week CDA from baseline up to EOS; • Time to first confirmed relapse up to EOS; • Mean number of CUALs per subject per post-baseline MRI scan from baseline up to EOS; • Longitudinal absolute change over time in fatigue-related symptoms as measured by the symptom domain of the FSIQ-RMS from baseline up to EOS; • Longitudinal percent change over time in brain volume from baseline up to EOS;

Primary endpoint hypotheses

Two-sided hypotheses are expressed in terms of the model parameters $\mu_{Ponesimod}$ and $\mu_{Placebo}$. The primary null hypothesis is that the ARR (μ) does not differ between ponesimod and placebo. The alternative hypothesis is that the ARR differs between ponesimod and placebo.

$$H_{0,\,ARR}: \mu_{Ponesimod} - \mu_{Placebo} = 0$$

vs

$$H_{1,\,ARR}: \mu_{Ponesimod} - \mu_{Placebo} \neq 0$$

The null hypothesis will be tested by a two-sided Wald test within the negative binomial regression model, with a two-sided significance level of 0.05. Two-sided 95% Wald confidence intervals (CIs) will be calculated for the relative reduction in mean ARR for ponesimod compared to placebo.

Primary endpoint main analysis

The primary statistical analysis will be performed on the FAS using a negative binomial model for confirmed relapses, with the stratification variable EDSS category included as covariate in the model and the logarithm of the time on treatment up to EOS as an offset variable.

Secondary endpoint analysis

The secondary efficacy endpoints will be tested in a hierarchical manner in the order listed above on the FAS if the primary analysis on ARR has led to the rejection of the null hypothesis in favor of ponesimod. The hierarchical testing procedure starts from the top, and it stops when a null hypothesis cannot be rejected.

Analysis of the safety variables

The SAF will be used to perform all safety analyses.

If not otherwise stated, only treatment-emergent safety data (observations up to 30 days after study drug discontinuation) will be considered in tables and figures. All safety data will be included in listings, with flags for safety data not considered to be treatment-emergent.

Specific safety events (AEs, laboratory tests, ECG findings, etc.) will be considered. In general, they consist of one or more well-defined safety events which are similar in nature and for

	which there is a specific clinical interest in connection with ponesimod. **Sample size** The sample size for the study was determined by a simulation using the negative binomial distribution. A sample size of 600 subjects (300 per treatment group) will provide a power of approximately 90% for a significance level of 0.05, under the assumption that the ARR (for confirmed relapses up to EOS) is 0.50 for placebo and 0.325 for ponesimod (which corresponds to a risk reduction of 35%), and using a dispersion $k = 1.3$ (where the variance is $= \mu + k \mu^2$). A mean subject follow-up of 1.9 years is assumed with 3.3 years maximum follow-up.
STUDY COMMITTEES	**Independent Data Monitoring Committee** An Independent Data Monitoring Committee (IDMC) composed of physicians with relevant medical expertise in neurology, cardiology, infectious diseases, immunology and/or hematology, pulmonology, and a statistician, will review unblinded subject safety and efficacy data on an ongoing basis and is empowered to recommend modifications to the protocol. The composition and operation of the IDMC are described in the IDMC charter. **Ophthalmology Safety Board** An Ophthalmology Safety Board (OSB) composed of two independent ophthalmologists will review and evaluate in a blinded fashion any new or suspected cases of macular edema. Important findings will be communicated to the IDMC. The composition and operation of the OSB are described in the OSB charter. **MRI safety board** A MRI safety board composed of radiologists and/or neurologists with relevant MRI expertise will review and evaluate in a blinded fashion the brain MRIs selected by the local radiologists or neurologists with MRI expertise and exported to the Medical Image Analysis Center (MIAC) in cases of a suspected opportunistic infection in the central nervous system. The MRI safety board will communicate the results of the review to the site and important findings will be communicated to the IDMC. The composition and operation of the MRI safety board are described in the MRI safety board

	charter. **MACE adjudication board** A MACE adjudication board will review and evaluate in a blinded fashion the MACE reported in the study. The composition and operations of MACE adjudication board will be described in the MACE adjudication board charter.
SUB-STUDIES	**Lymphocyte subsets** A sub-study assessing lymphocyte subsets will be conducted in approximately 200 subjects [see Section 7.7.2.2]. Participation in the sub-study will be mandatory for all subjects until at least the first 200 subjects are randomized to the main study. T cell, B cell, and NK cell counts as well as T cell subsets (e.g., $CD4^+$ naïve, $CD4^+$ effector memory, $CD4^+$ central memory, $CD8^+$ naïve, $CD8^+$ effector memory, $CD8^+$ central memory, $CD8^+$ terminally differentiated effector memory, Th17 cells, Treg cells, and Th1 cells) will be analyzed at the central laboratory by fluorescence activated flow cytometry using a combination of cell surface markers. Other lymphocyte subsets may also be analyzed. Selected lymphocyte subsets may also be analyzed functionally *ex vivo*. Results will be provided regularly to the IDMC. Results from the lymphocyte subsets sub-study will be blinded to site staff and the sponsor until study closure. **Vaccination** Changes in vaccine-specific antibody titers from pre- to post-vaccination will be assessed at the end of the study for subjects having received a non-live vaccination while on study treatment.

Table 1 Visit and assessment schedule (Part 1)

Periods	Name	**PRE-RANDOMIZATION** (1)		**TREATMENT PERIOD**						
	Duration	Up to 45 Days		Up to 60 weeks after the randomization of the last subject						
Visits	Number	1	2	3	4	5	6	7	8,10, 12, 14, 16	11, 15
	Name	Screening (1)	Baseline (1)	Rand	W2	W4	W12	W24	W36,W60, W84, W108, W132	W72, W120
	Time	Day −45 to −1		Day 1	Day 15	Day 28	Week 12	Week 24	Week 36, 60, 84, 108, 132	Week 72, 120
	Visit window				± 1 day	± 5 days	± 7 days	± 7 days	± 7 days	± 7 days
Informed consent*		X								
Inclusion/exclusion criteria*		X	X	X						
Demographics*		X								
Medical history / smoking status*		X								
MS history & treatment*		X								
McDonald criteria (Revision 2010)		X								
EDSS/FS*		X	X				X	X	X	X
Relapse* (2)			X	X (2)	◄	―	―	―	―	X (2) ►
MSFC, SDMT*		X (3)	X (3)	X (3)			X	X		X
FSIQ-RMS** (4)			X				X	X		X
SF-36v2**			X				X	X		X
Health care resource utilization* (5)			X		X	X	X	X	X	X
WPAI:MS**			X				X	X		X
Chest X-ray* (6)		X								
eC-SSRS**			X							
MRI**			X					X		X
Concomitant medications*		X	X	X	X	X	X	X	X	X
Physical examination*		X	X					X		X
Body temperature*		X	X	X	X	X	X	X	X	X
Dermatological examination* (7)			X							
Body weight and height* (8)		X	X							
Systolic/diastolic blood pressure*		X	X	X (9)	X	X	X	X	X	X
12-lead ECG** (10)		X	X	X (11)	X	X	X (11)	X	X	X
Ophthalmological examination*(12)		X					X	X		
OCT*(12)			X				X	X		
Spirometry*			X				X			
Hematology/chemistry**		X	X		X	X	X	X	X	X

Urinalysis*	X					X	X		X
Lymphocytes** (13)	X	X		X	X (13) ◄——►		X (13)	X	X
Lymphocyte subsets** (14)		X				X	X		
Tuberculosis test**	X								
Viral serology**	X								
JCV serology**		X							
Additional serum sample for viral serology		X							
Pregnancy test*/**	X (15)	X		X	X	X	X	X	X
PK sampling (pre dose, except Visit 3)*			X (16)			X (16)	X		
Study treatment dispensing & accountability (17)			X	X	X	X	X	X	X
AE*/SAE* (18)	X	X	X	X	X	X	X	X	X

* Data collected in the eCRF

** Electronically transferred to sponsor.

Day 1 (date of randomization visit) is to be used as the reference date for the purpose of calculating the subsequent visit dates (and time windows).

(1) All pre-randomization assessments performed at Visit 1 (Screening) and Visit 2 (Baseline) may be conducted on days differing from the actual Visit 1 (Screening) date defined as the start of screening activities (i.e., signature of the Informed Consent Form) and Visit 2 (Baseline) date defined as the date of baseline EDSS assessment. However, all pre-randomization assessments performed at Visit 1 (Screening) that are repeated at Visit 2 (Baseline; e.g., physical examination, 12-lead ECGs, SBP/DBP) with the exception of hematology and blood chemistry laboratory assessments must be performed at least 7 days after the Visit 1 (Screening) assessments. Blood chemistry and hematology assessments at Visit 2 (Baseline) must be performed at least 21 days after the hematology and blood chemistry laboratory assessments performed at Visit 1 (Screening) [see Section 4.3]. Similarly, for women of childbearing potential, the serum pregnancy test at Visit 1 (Screening) must be performed at least 21 days before the urine pregnancy test performed at Visit 2 (Baseline). All baseline assessments, including the ECG and blood pressure performed pre-dose on first day of dosing at Visit 3 (Day 1) must be performed before randomization. The blood draw at Visit 2 (Baseline) should happen early enough in order to obtain the results from the central laboratory and confirm the eligibility prior to randomization.

(2) At every study visit, subjects are reminded to contact their principal investigator / treating neurologist at the clinical site immediately in the event of the appearance of any new or worsening neurological symptoms. In addition, the site will contact the subject in-between the 12-weekly visits (e.g., Visit 6 – Week 12, Visit 7 – Week 24) in order to proactively inquire about any new or worsened neurological symptoms. These telephone calls will be conducted either at Weeks 18, 30, 42, 54, 66, 78, 90, 102, 114, 126, 138 and 150 (± 7 days), or 6 weeks after the last 12-weekly visit (± 7 days). Whenever between visits a subject experiences any new or worsening neurological symptoms, he/she must contact the principal investigator / treating neurologist, study nurse or clinical coordinator as soon as possible in order to complete a telephone questionnaire for relapse assessment [see Appendix 12]. After the occurrence of each confirmed relapse, subjects will be asked to re-consent to continue receiving study treatment [see Section 13.3].

(3) During pre-randomization, two practice tests and a third test serving as baseline assessment will be performed. Ideally, the 3 tests should be performed ≥ 5 days apart (i.e., second test practice ≥ 5 days from first practice test and third test serving as baseline ≥ 5 days from second practice test). The first practice test may be done at Visit 1 (Screening), the second practice test may be done at Visit 2 (Baseline) and the third test serving as baseline may be performed pre-dose at Visit 3 (Randomization).

(4) The symptoms scale (with a 24-hour recall) will be completed for 7 consecutive days (the day of the visit and the 6 days after the visit) with an average score being taken across these 7 days. The completion of the FSIQ-RMS during the pre-randomization period will be done as follows: At Visit 1 (Screening),

subjects who appear eligible based on the assessments made during this visit will be provided with the FSIQ-RMS. Once the results from the laboratory tests confirm the subject's eligibility, and provided no other assessment performed in the meantime excludes the subject, the site coordinator will contact the subject to instruct him/her to start the completion of the FSIQ-RMS. At home, the subject will complete the symptom domain of the FSIQ-RMS for 7 days (i.e., section 1 of the questionnaire). On the 7th day, the subject will also complete the impacts domain of the FSIQ-RMS (i.e., section 2 of the questionnaire).

(5) Healthcare resource utilization data, including number of hospital visits, length of stay, number of Intensive care unit admissions for MS relapses and emergency medical services facility visits for MS.
(6) Any CXR that has been performed within 90 days prior to Visit 1 (Screening) can be used (in this case, no need to repeat CXR at Visit 1 [Screening]).
(7) Dermatological examination to be performed by a dermatologist [see Section 7.3.12]. In case of re-screening, skin examination does not need to be repeated if skin examination from initial screening was performed within 90 days prior to the date of re-screening.
(8) Height only at Visit 1 (Screening).
(9) SBP/DBP: Pre-dose and hourly (± 15 minutes) for at least 4 hours post-dose and up to 12 hours.
(10) Only pre-dose ECGs at all visits except Visit 3 (Day 1), and Visit 6 (Week 12).
(11) Pre-dose and hourly (± 15 minutes) for at least 4 hours post-dose ECGs and up to 12 hours on Day 1. Pre-dose and 3 hour (± 15 minutes) post-dose at Week 12.
(12) OCT and/or ophthalmological examination to be performed at any visit in the presence of visual symptoms suggestive of macular edema or active uveitis.
(13) Total lymphocyte counts will be tested every 4 weeks (± 3 days) up to Week 24 (i.e., additional lymphocyte tests will be performed at Week 8, Week 16, and Week 20) and every 12 weeks thereafter.
(14) Lymphocyte subset analysis will be performed on a subset of at least 200 subjects randomized to the main study.
(15) Serum pregnancy test at Visit 1 (Screening), urine pregnancy test at all subsequent visits. Urine pregnancy tests (performed at home) on a 4-weekly basis (± 4 days) between the visits during the study (results of the pregnancy test to be communicated by telephone call to the principal investigator / treating neurologist).
(16) Three hours (± 15 minutes) post-dose at Visit 3 (Day 1); pre-dose and 3 hours (± 15 minutes) post-dose at Visit 6 (Week 12).
(17) Scheduled study medication dispensing/return procedures may be adapted according to the site practice.
(18) All AEs and SAEs that occur after signing the Informed Consent Form and up to 30 days after study treatment discontinuation must be reported.

AE = adverse event; CXR = chest X-ray; DBP= diastolic blood pressure; eCRF = electronic case report form; eC-SSRS = electronic self-rated version of the Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EDSS = expanded disability status scale; FS = functional system; FSIQ-RMS = fatigue symptoms and impacts questionnaire – relapsing multiple sclerosis; JCV = John Cunningham Virus; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSFC = multiple sclerosis functional composite; OCT = optical coherence tomography; PK = pharmacokinetics, SAE = serious adverse event; SBP = systolic blood pressure; SDMT = symbol digit modalities test; SF-36v2 = 36-Item Short Form Health Survey Version 2; WPAI:MS = work productivity and activity impairment in MS.

Table 2 Visit and assessment schedule (Part 2)

Periods	Name	**TREATMENT PERIOD**		**FOLLOW-UP**		**UNSCHEDULED**			
	Duration	Up to 60 weeks after randomization of the last subject		30 Days					
Visits	Number	9, 13, 17	18	19	20	I1, I2, …		R1, R2, …	U1, U2, …
						d1	d15		
	Name	W48, W96, W144	EOT	FU7d (16)	FU (17)	Re-initiation		Relapse	Unscheduled (15)
						Day 1 of re-initiation	Day 15 after re-initiation		
	Time	Week 48, 96, 144	Up to Week 156 or earlier in case of premature discontinuation	Last study treatment intake + 7 days	Last study treatment intake + 30 days	Any day between Day 1 and EOT		Any day between Day 1 and EOS	
	Visit window	± 7 days	+ 7 days	± 2 days	+ 7 days	NA	± 1 day	+ 7 days	NA
EDSS/FS*		X	X		X			X	X
Relapse* (1)		X (1) ◄			► X (1)			X	
MSFC, SDMT*		X	X						
FSIQ-RMS** (2)		X	X		X			X	X
SF-36v2**		X	X					X	
Health care resource utilization* (3)		X	X					X	
WPAI:MS**		X	X						
Chest X-ray* (4)			X						
eC-SSRS**		X	X						
MRI**		X	X						X
Concomitant medications*		X	X		X			X	X
Physical examination*		X	X					X	X
Body temperature*		X	X		X	X	X	X	X
Pulse rate*								X	X (18)
Dermatological examination* (5)		X	X						X
Body weight*		X	X						X
Systolic/diastolic blood pressure*		X	X		X	X (6)	X		X
12-lead ECG** (7)		X	X		X	X (7)	X		X
Ophthalmological examination* (8)		X	X		X				X
OCT* (8)		X	X						X
Spirometry*		X	X		X				X
Hematology/chemistry**		X	X		X				X
Urinalysis*		X	X		X				X
Lymphocytes**		X	X		X				X

Lymphocyte subsets** (9)	X	X	X	X				
JCV serology**	X	X						
Pregnancy test*/** (10)	X	X		X				X
Serum sample vaccination* (11)								X
PK sampling pre dose*	X	X		X				X(12)
Study treatment dispensing & accountability (13)	X	X			X	X		X
AE*/SAE * (14)	X	X	X	X		X	X	X

* Data collected in the eCRF

** Electronically transferred to sponsor.

Day 1 (date of randomization visit) is to be used as the reference date for the purpose of calculating the subsequent visit dates (and time windows).

(1) At every study visit, subjects are reminded to contact their principal investigator / treating neurologist at the clinical site immediately in the event of the appearance of any new or worsened neurological symptoms. In addition, the site will contact the subject in-between the 12-weekly visits (e.g., Visit 6 – Week 12, Visit 7 – Week 24) in order to proactively inquire about any new or worsened neurological symptoms. These telephone calls will be conducted either at Weeks 18, 30, 42, 54, 66, 78, 90, 102, 114, 126, 138 and 150 (± 7 days), or 6 weeks after the last 12-weekly visit (± 7 days). Whenever between visits a subject experiences any new or worsened neurological symptoms, he/she must contact the principal investigator / treating neurologist, study nurse or clinical coordinator as soon as possible in order to complete a telephone questionnaire for relapse assessment [see Appendix 12]. After the occurrence of each confirmed relapse, subjects will be asked to re-consent to continue receiving study treatment [see Section 13.3].

(2) The symptoms scale (with a 24-hour recall) will be completed for 7 consecutive days (the day of the visit and the 6 days after the visit) with an average score being taken across these 7 days. At Visit 20 (FU), the FSIQ-RMS will be completed at home prior to the visit, ideally, during the 7 consecutive days preceding the visit.

(3) Healthcare resource utilization data, including number of hospital visits, length of stay, number of Intensive care unit admissions for MS relapses and emergency medical services facility visits for MS.

(4) In case of premature study treatment discontinuation, the chest X-ray at EOT does not need to be performed if the EOT visit occurs within 48 weeks of the pre-randomization chest X-ray.

(5) Dermatological examination to be performed by a dermatologist [see Section 7.3.12].

(6) SBP/DBP: Pre-dose and hourly (± 15 minutes) for at least 4 hours post-dose and up to 12 hours.

(7) Only pre-dose ECGs at all visits (if applicable) except EOT and re-initiation visits. At re-initiation, pre-dose and hourly (± 15 minutes) for at least 4 hours post-dose ECGs and up to 12 hours.

(8) OCT and/or ophthalmological examination to be performed at any visit in the presence of visual symptoms suggestive of macular edema or active uveitis.

(9) Lymphocyte subset analysis will be performed on a subset of at least 200 subjects randomized to the main study.

(10) Serum pregnancy test at FU. Urine pregnancy tests at all other visits. Urine pregnancy tests (performed at home) on a 4-weekly basis (± 4 days) between the visits until 4 weeks after last study treatment intake (results of the pregnancy test to be communicated by telephone call to the principal investigator / treating neurologist).

(11) Pre and post-vaccination sampling for vaccine-specific antibody titers for subjects having received non-live vaccines while on study treatment (sub-study).

(12) When possible, collect PK sample upon experiencing a SAE. Preferably, sample will be collected pre-dose, as early as possible after SAE onset, and within 7 days after the last dose of study treatment.

(13) Scheduled study medication dispensing/return procedures may be adapted according to the site practice.

(14) All AEs and SAEs that occur after signing the Informed Consent Form and up to 30 days after study treatment discontinuation must be reported.

(15) Unscheduled visits may be performed at any time during the study and may include all or some of the indicated assessments, based on the judgment of the investigator.
(16) Visit performed only for subject participating in the lymphocyte subset sub-study
(17) If a total lymphocyte count $< 0.5 \times 10^9$/L is observed at FU an alert will be sent to the principal investigator and the sponsor. Discontinuation of DMF treatment should be considered in accordance with prescribing information [Tecfidera USPI, Tecfidera SmPC].
(18) Pulse rate to be assessed only if no 12-lead ECG is performed at this visit.

AE = adverse event; DBP= diastolic blood pressure; DMF = dimethyl fumarate; eCRF = electronic case report form; eC-SSRS = electronic self-rated version of the Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EDSS = expanded disability status scale; EOT = end-of-treatment; FU7d = FU visit approximately 7 days after the last dose of study drug; FS = functional system; FSIQ-RMS = fatigue symptoms and impacts questionnaire – relapsing multiple sclerosis; FU = follow-up; JCV = John Cunningham Virus; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSFC = multiple sclerosis functional composite; OCT = optical coherence tomography; PK = pharmacokinetics, SAE = serious adverse event; SBP = systolic blood pressure; SDMT = symbol digit modalities test; SF-36v2 = 36-Item Short Form Health Survey Version 2; SmPC = Summary of Product Characteristics; USPI = United States Prescribing Information; WPAI-MS = work productivity and activity impairment in MS.

Table 3 Visit and assessment schedule (Part 3)

Periods	Name	**Post-Treatment observation period (PTOP)** (to be performed after EOT, and FU)		
	Duration	Up to 60 weeks after randomization of the last subject		
Visits	Number	6A, 7A, 8A, 10A, 12A, 14A, 16A	11A, 15A	9A, 13A, 17A, 18A
	Name	W12A, W24A, W36A, W60A, W84A, W108A, W132A	W72A, W120A	W48A - W96A - W144A - W156A
	Time	Weeks 12, 24, 36, 60, 84, 108, 132	Weeks 72, 120	Weeks 48, 96, 144, 156
	Visit window	± 7 days	± 7 days	± 7 days
EDSS/FS*		X	X	X
Relapse* (1)		X (1) ◄	———	► X (1)
MRI**		X (Week 24 only)	X	X
FSIQ-RMS** (2)		X (only Weeks 12 and 24)	X	X
Concomitant medications*		X	X	X
Physical examination*		X (Week 24 only)	X	X
Body temperature*		X	X	X
Dermatological examination* (3)				X
Systolic/diastolic blood pressure*		X	X	X
12-lead ECG **				X
Spirometry*		X (Week 12 only)		X
Hematology/chemistry**		X	X	X
Urinalysis*		X	X	X
Lymphocytes**		X	X	X
Lymphocyte subsets**		X (only Weeks 12 and 24)		X
JCV serology**				X
Adverse events (AE)*		X	X	X
Serious adverse events (SAE)*		X	X	X

* Data collected in the eCRF

** Electronically transferred to sponsor.

Day 1 (date of randomization visit) is to be used as the reference date for the purpose of calculating the subsequent visit dates (and time windows).

(1) At every study visit, subjects are reminded to contact their principal investigator / treating neurologist at the clinical site immediately in the event of the appearance of any new or worsened neurological symptoms. In addition, the site will contact the subject in-between the 12-weekly visits (e.g., Visit 6A – Week 12, Visit 7A – Week 24) in order to proactively inquire about any new or worsened neurological symptoms. These telephone calls will be conducted either at Weeks 18, 30, 42, 54, 66, 78, 90, 102, 114, 126, 138 and 150 (± 7 days), or 6 weeks after the last 12-weekly visit (± 7 days). Whenever between visits a subject experiences any new or worsened neurological symptoms, he/she must contact the principal investigator / treating neurologist, study nurse or clinical coordinator as soon as possible in order to complete a telephone questionnaire for relapse assessment [see Appendix 12].

(2) The symptoms scale (with a 24-hour recall) will be completed for 7 consecutive days (the day of the visit and the 6 days after the visit) with an average score being taken across these 7 days. At Visit 18A (Week 156), the FSIQ-RMS will be completed at home prior to the visit, ideally, during the 7 consecutive days preceding the visit.
(3) Dermatological examination to be performed by a dermatologist [see Section 7.3.12].
ECG = electrocardiogram; EDSS = expanded disability status scale; EOT = End-of-Treatment; FS = functional system; FSIQ-RMS = fatigue symptoms and impacts questionnaire – relapsing multiple sclerosis; FU = Follow up; JCV = John Cunningham Virus; MRI = magnetic resonance imaging.

PROTOCOL

1 BACKGROUND

1.1 Multiple sclerosis

Multiple sclerosis (MS) is an inflammatory autoimmune disorder of the central nervous system (CNS) and the most common cause of progressive neurological disability in young adults [Compston 2008]. This chronic demyelinating disease is characterized by heterogeneous clinical expression, an unpredictable course and a variable prognosis. In MS, the frequent and major neurological disability has important personal, social, and financial consequences for patients, their families, and health care systems.

1.1.1 Pathogenesis

Although the etiology of MS is still unknown it is widely accepted that it is an immune-mediated, demyelinating process precipitated by unknown environmental factors in genetically susceptible people.

MS results from a cascade of events involving activation of the immune system, acute focal inflammatory demyelination, and axonal loss with limited remyelination, culminating in chronic multifocal sclerotic plaques in the brain and spinal cord.

1.1.2 Clinical course

The two main clinical features of MS are exacerbations (also called attacks or relapses) and progressive loss of neurological function. Relapses are considered the clinical expression of acute, inflammatory, focal lesions of the brain or spinal cord, corresponding to axonal demyelination, which leads to the slowing or blockade of axonal conduction at diverse affected sites of the brain and spinal cord. This inflammatory disease activity may translate to a large variety of clinical symptoms and signs and/or acute lesions visualized on magnetic resonance imaging (MRI). The acute MRI lesions may or may not be accompanied by clinical symptoms. The progressive loss of neurological function (called progression or accumulation of disability) may result from incompletely recovered relapses or may be independent from relapses [Lublin 2003]. It is thought to reflect mainly neurodegeneration corresponding to demyelination, axonal loss and gliosis.

The natural history of MS suggests that there are different patterns of disease course [Confavreux 2014, Compston 2008]. In relapsing-remitting MS (RRMS), patients have acute exacerbations with full or partial recovery [Lublin 2003] and are otherwise stable between exacerbations; this presentation is observed in the majority of MS patients (80–85% of the MS population).

Approximately 65–70% of RRMS patients experience gradual accumulation of disability and fewer relapses later in their disease, which evolves into a secondary progressive MS (SPMS) stage characterized by less inflammatory and more pronounced neurodegenerative features. The median time for patients with RRMS to progress into SPMS is about 10 years [Noseworthy 2000, Compston 2008]. In primary progressive MS (PPMS), patients experience progression of disability from onset (approximately 10–20% of patients with MS). In progressive relapsing MS (PRMS) occurring in approximately 5% of patients with MS, the disability progression starts from the onset of the disease and is associated with occasional relapses.

The classification of MS subtypes and the related terminology has been subject to changes over the last two decades. In 1996, the US National Multiple Sclerosis Society (NMSS) Advisory Committee on Clinical Trials in Multiple Sclerosis defined the clinical subtypes of MS and provided standardized definitions for four MS clinical courses: relapsing-remitting (RR), secondary progressive, primary progressive (PP), and progressive relapsing [Lublin 1996]. In 2011, the NMSS Advisory Committee proposed to redefine the MS course by taking into account disease activity and progression and eliminate the progressive relapsing MS (PRMS) category [Lublin 2014]. A patient with RRMS who has a gadolinium-enhancing (Gd+) lesion on a current MRI would be considered to be RR–active. Conversely, the term 'not active' could be used to indicate a patient with a relapsing course but no relapses, no Gd+ activity, or no new or unequivocally enlarging T2 lesions during the assessment period. A patient with PPMS who has an acute attack (thus fulfilling prior criteria for PRMS) would be considered to be PP-active. On the other hand, a patient with PPMS with no acute attacks and no MRI activity would be considered to be PP-not active. In terms of progressive disease, this new classification distinguishes between:

- progressive accumulation of disability from onset, which includes
  - non-active PPMS (previously known as PPMS) and
  - active PPMS (previously known as PRMS)
- progressive accumulation of disability after initial relapsing course (SPMS).

Further, the term 'disability progression' is only reserved for patients who are in the progressive phase of MS, while the term disability accumulation refers to worsening in Expanded Disability Status Scale (EDSS) score, which can either be due to incomplete recovery from relapses or occurring independently from relapses, disregarding the RR or progressive course of MS.

The Diagnostic Criteria for MS have been modified with the 2010 revised version of McDonald Criteria [Polman 2011]. Implementation of these Diagnostic Criteria allows for an earlier diagnosis of MS, with equivalent or improved specificity and sensitivity compared to the 2005 revision of McDonald Criteria [Polman 2005].

Historically, the term clinically isolated syndrome (CIS) applied to those patients who have experienced a single clinical event, who have had other possible diagnoses excluded, and who did not fulfill the Diagnostic Criteria for MS [Polman 2005]. With the 2010 revision of McDonald's Diagnostic Criteria, CIS patients with clinical and/or MRI signs of dissemination in space and MRI signs of dissemination in time are now diagnosed with relapsing MS (RMS).

1.1.3 Epidemiology

MS affects an estimated 2–2.5 million people worldwide, of whom approximately 630,000 are in Europe and 250,000 to 350,000 in the United States [Milo 2010, WHO 2008].

The incidence of MS is about 7 cases per 100,000 persons per year. The prevalence rate varies between races and geographical latitudes, ranging from 50 to 120 per 100,000 [Compston 2002, Milo 2010]. The prevalence is highest in Northern Europe, Southern Australia, New Zealand, and North America. The reason for the changing prevalence with geographical latitude is unknown but suggests the existence of environmental factors, in addition to genetic factors [Pugliatti 2002, Compston 2008]. The highest prevalence is observed in Northern European descendants (Scandinavia and Scotland) [Milo 2010], whereas MS is less common in Asian populations [Pugliatti 2002].

MS is the most common chronic neurologic disease in adults between 20 and 50 years of age with a peak onset of MS in the early thirties. Women are affected approximately twice as often as men [Confavreux 2014]. In 2 to 5% of patients, disease presents before the age of 16 [Compston 2002, Renoux 2007].

1.1.4 Treatment of MS

Current medical practice encourages early intervention with disease-modifying treatments, with the intent of optimizing long-term clinical outcomes [Gold 2012].

Key objectives in the management of MS are reducing the rate of relapses and preventing or at least delaying disease progression [Gold 2012]. Most of the disease-modifying drugs approved for MS have to be administered by injection or infusion (subcutaneous [s.c.], intramuscular [i.m.], or intravenous [i.v.] route). Recently, new disease-modifying drugs administered orally have been approved for RMS. Currently, there are 15 disease-modifying therapies (DMTs) approved in at least one country for the treatment of MS. Disease-modifying treatments for MS are ususally administered as monotherapy. If the disease continues to be active (relapses and/or inflammatory MRI lesions) in spite of the given treatment, a shift to a more effective compound (treatment escalation) is usually considered, however, the criteria for such treatment escalation vary between countries and physicians. At the top of the escalation hierarchy are the two monoclonal antibodies, natalizumab and alemtuzumab, and, in some cases, mitoxantrone, all of which

require i.v. infusion. An oral option with comparable or better risk-benefit profile is currently not available.

1.1.4.1 Injectable disease-modifying therapies

The following injectable drugs have been approved in at least one country for the treatment of MS:

- Interferon (IFN) β-1a 30 µg i.m. once weekly (Avonex®)
- IFN β-1a 22 or 44 µg s.c. 3 times weekly (Rebif®)
- IFN β-1b 250 µg s.c. every other day (Betaferon®, Betaseron®, Extavia®)
- Pegylated IFN β-1a 125 µg s.c. every 14 days (Plegridy®)
- Glatiramer acetate 20 mg s.c. once a day (o.d.) or 40 mg three times a week (Copaxone®)
- Glatiramer acetate 20 mg s.c. once a day (o.d.; Glatopa®)
- Natalizumab 300 mg i.v. every 4 weeks (Tysabri®)
- Mitoxantrone i.v. every 3 months (Novantrone®)
- Alemtuzumab concentrate for solution for infusion, 12 mg alemtuzumab in 1.2 mL (10 mg/mL) (Lemtrada®)
- Daclizumab 150 mg s.c. once a month (Zinbryta®)
- Ocrelizumab 600 mg i.v. every 6 months (Ocrevus®).

Additional injectable drugs are currently in late-stage development for the treatment of RMS, including AIN457 (secukinumab).

1.1.4.2 Orally administered disease-modifying therapies

Several oral drugs have been approved for MS:

- Fingolimod 0.5 mg orally o.d. (Gilenya®)
- Teriflunomide 7 mg, 14 mg o.d. (Aubagio®). NB: only 14 mg dose is approved in the EU
- Dimethyl fumarate (DMF, BG-12) gastro-resistant hard capsules 120/240 mg twice daily (b.i.d.) (Tecfidera®)
- Cladribine 3.5 mg/kg body weight over 2 years (Mavenclad®)

Oral drugs currently in late-stage development for the treatment of RRMS include laquinimod [Comi 2012], and a sphingosine 1-phosphate (S1P) receptor modulator, RCP1063. Siponimod, another $S1P_1$ receptor modulator, is currently being developed for the treatment of MS with relapsing onset.

1.1.4.3 Unmet need in relapsing multiple sclerosis

Despite multiple disease modifying therapies recently becoming available for the treatment of relapsing MS, a significant unmet need remains. Existing therapies are only

partly effective in reducing ongoing inflammatory tissue damage and clinical attacks and disability progression.

In recently completed Phase 3 trials with the most effective injectable (alemtuzumab) or oral therapies (fingolimod, DMF), up to one-third of MS patients experience an MS relapse, 10-20% experience a progression of their disability, and approximately 50% have either clinical or MRI manifestations of active disease over a 2-year treatment course [Kappos 2010, Gold 2012, Fox 2012, Cohen 2012, Coles 2012]. With availability of several first-line (e.g., IFN β, glatiramer acetate) and second-line (e.g., natalizumab, alemtuzumab) therapies, the choice of initial MS therapy and the switch from one therapy to another has become individualized and based on considerations of efficacy, safety, tolerability, and convenience of treatment administration. However, given the complexity of MS pathogenesis and heterogeneity among patients, combination therapy strategies that target distinct disease mechanisms might be more effective than medications used as monotherapy. Combination of two oral disease modifying therapies showing high efficacy and a favorable risk-benefit profile may represent an attractive alternative to currently available treatment escalation options which carry significant safety concerns for opportunistic infections and autoimmunity (e.g., natalizumab, alemtuzumab) and tolerability burden due to i.v. administration.

1.2 Sphingosine-1-phosphate receptors

S1P plays a central role in lymphocyte trafficking [Cyster 2005, Brinkmann 2007, Brinkmann 2010, Schwab 2007, and references therein]. S1P is synthesized and secreted by many cell types, including platelets, erythrocytes, and mast cells, and elicits a variety of physiological responses [Cyster 2005, Alvarez 2007]. Among other effects, lymphocyte egress from primary and secondary lymphoid organs is dependent on the $S1P_1$ receptor. $S1P_1$ receptor modulators block lymphocyte migration out of lymphoid tissue into the lymphatic and vascular circulation, thereby reducing peripheral lymphocyte counts and preventing lymphocyte recruitment to sites of inflammation. Following withdrawal of an $S1P_1$ receptor agonist, the functional lymphocytes return to the circulation from their sites of sequestration. Other functions that do not rely on homing mechanisms, such as antibody generation by B lymphocytes, first-line immunological protection by granulocytes and monocytes, and antigen-dependent T cell activation and expansion, are not affected by this mechanism [Pinschewer 2000].

S1P itself induces pleiotropic effects, which are mediated by a family of five G protein-coupled receptors, $S1P_1$-$S1P_5$, located on endothelial cells, vascular and cardiac smooth muscle cells, and cardiac myocytes [Alvarez 2007, Brinkmann 2007, Brinkmann 2010]. The first S1P receptor modulator, fingolimod (FTY720, Gilenya®), which has been approved by the FDA and the EMA for the treatment of MS, is not selective for the $S1P_1$ receptor but interacts with all five S1P receptors [Brinkmann 2007,

Brinkmann 2010]. $S1P_1$ selectivity is expected to maintain the therapeutic effects mediated via this receptor subtype while avoiding unwanted effects mediated by other receptor subtypes [Sobel 2013].

1.3 Ponesimod

Ponesimod, an iminothiazolidinone derivative, is an orally active, selective modulator of the $S1P_1$ receptor that induces a rapid, dose-dependent, and reversible reduction in peripheral blood lymphocyte count by blocking the egress of lymphocytes from lymphoid organs. T and B cells are most sensitive to ponesimod mediated sequestration. In contrast, monocyte, natural killer (NK) cell and neutrophil counts are not reduced by ponesimod. The effect of ponesimod on circulating effector T cells represents a promising therapeutic approach for diseases in which activated T cells play a critical role.

More detailed information can be found in the Investigator's Brochure (IB) [Ponesimod IB].

1.3.1 Nonclinical studies

The main findings in the nonclinical studies conducted with ponesimod are:

- Ponesimod causes a rapid and substantial reduction in circulating lymphocytes in rats and dogs, which is also rapidly and fully reversible. The effect correlates well with the plasma concentration of ponesimod.
- Studies with ponesimod in animal models of T cell-mediated diseases, such as MS, rheumatoid arthritis, type 1 diabetes and skin hypersensitivity, consistently indicated a therapeutic potential of ponesimod at oral doses that lower peripheral blood lymphocyte counts.
- Ponesimod shows an oral bioavailability of 35–74%, low clearance, and a tissue distribution greater than total body water in rats and dogs. Plasma protein binding is high (≥ 98.9%) in rats, dogs, and humans.
- The metabolism of ponesimod is comparable in rats, dogs, and humans. The main metabolite, ACT-338375 (M13), is present in plasma of mice, rats, and dogs at levels similar to or higher than steady-state exposures in humans at 40 mg/day.
- Based on available nonclinical data, the potential for drug-drug interactions (DDIs) is limited. The metabolite M13 has no liability for causing DDIs *via* inhibition of cytochrome P450 (CYP) enzymes or transport proteins. M13 is not a time-dependent inhibitor of CYP3A4, CYP2D6 or CYP2C9. Neither ponesimod nor the M13 metabolite approach plasma concentrations expected to inhibit CYP2C9 or CYP2C19 after daily doses of 20 mg at steady-state.
- The following main target organs for ponesimod-related toxicity were identified: lung (mouse, rat, dog), heart (dog), nervous system (clinical signs, dog), skin (dog), the red

blood cell (RBC) compartment (dog, rat), liver (all species), and adrenals (rat). The observed findings were in general dose-related in terms of incidence and/or degree of severity. Full or partial reversibility was seen for the majority of findings after 4 weeks of treatment followed by a 4-week recovery period and after 26 and 52 weeks of treatment followed by a 13-week recovery period. In the dog, the heart findings observed in the 26-week study were still observed after the 13-week recovery period. No-observed-(adverse)-effect levels (NO[A]ELs) were established at 2 mg/kg/day in rats and 0.4 mg/kg/day in dogs in the 4-week toxicity studies, at 30 mg/kg/day in rats and 2 mg/kg/day in dogs in the 26-week toxicity studies, and at 3 mg/kg/day in dogs in the 52-week study. In mice treated for 13 weeks, the NOAEL was established at 90 mg/kg/day.

- Embryo-fetal toxicity studies in rats and rabbits indicated that ponesimod has embryotoxic and teratogenic potential. In rat fertility studies, ponesimod had no effects on female and male fertility and did not produce any testicular morphologic changes.

More detailed information can be found in the IB [Ponesimod IB].

1.3.1.1 Efficacy of combined dimethyl fumarate and ponesimod in rats

Dimethyl fumarate is the active principle of the commonly prescribed psoriasis drug Fumaderm™ and the MS drug Tecfidera®.

Both neuroprotective and anti-inflammatory effects are induced by DMF through activation of the Nrf-2 pathway and disruption of the NF-κB pathway that is involved in the regulation of cytokines and lymphocyte apoptosis [Scannevin 2012]. In an experimental autoimmune encephalomyelitis (EAE) disease model of MS in mice, DMF dose-dependently inhibited disease symptoms, demyelination, neurodegeneration and inflammation [Linker 2011, Schilling 2006].

Ponesimod has been demonstrated to be beneficial in EAE mostly by inhibiting lymphocyte infiltration [Gergely 2012, Papadopoulos 2010, Gonzalez-Cabrera 2012, Kataoka 2005, Webb 2004]. Inhibitory effects on NF-κB and activation of Nrf-2 have not been described for $S1P_1$ modulators. By combining DMF with ponesimod, multiple different pathways (inhibition of NF-κB activation, activation of Nrf-2, and inhibition of lymphocyte infiltration) may result in increased efficacy such as preservation of neuromuscular function and prevention of disability progression in MS.

The combined administration of DMF and ponesimod was compared to DMF alone in a rat model of relapsing-remitting EAE. Sensory-motor deficits were assessed throughout the observation-time of 40 days. In contrast to DMF alone (40 mg/kg or 80 mg/kg orally, daily), the combination of DMF with ponesimod (100 mg/kg orally, daily) showed a reduction of clinical scores throughout the whole treatment-phase. This suggests that the

combination of DMF with ponesimod is more efficacious in this model of relapsing-remitting EAE as compared to DMF alone [Ponesimod IB].

1.3.1.2 Combination toxicity study of combined dimethyl fumarate and ponesimod in beagle dogs

The combined toxicity and systemic exposure of ponesimod and DMF was studied in beagle dogs who received oral administrations for 13 consecutive weeks as follows:

- ponesimod 3, 10, and 40 mg/kg/day (n = 4/sex/dose group)
- DMF 5, 25, and 50 mg/kg/day (n = 4/sex/dose group)
- ponesimod + DMF: 3+5, 10+25 and 40+50 mg/kg/day (n = 4/sex/dose group)
- a vehicle control group with (n = 4/sex)

Systemic exposure was evaluated after 1 week and 13 weeks. The toxicological assessment included clinical signs, food consumption, body weight, blood pressure, ECG, ophthalmology, hematology, clinical chemistry, urinalysis, organ weights, and macroscopic/microscopic evaluation. Possible effects on the immune system were assessed by immunophenotyping, histology of primary and secondary lymphoid organs and T cell dependent antigen response.

The safety profile of ponesimod treated dogs was in line with findings previously seen such as reduced white blood cell counts and lymphocytes, reduced protein and increased cholesterol. Histopathologically, arterial lesion in the heart was observed at the mid and high ponesimod dose. DMF treatment led mainly to the expected reduction in food consumption, body weight and creatinine at the mid and high dose.

The combination of ponesimod with DMF induced effects comparable with each compound alone; there was no evidence for new or synergistic toxicity. A NOAEL could be established at the low doses of 3 mg/kg/day ponesimod alone or combined with 5 mg/kg/day DMF and at 5 mg/kg/day for DMF alone. The ponesimod NOAEL of 3 mg/kg/day is in line with previous studies. At this dose level the exposure to ponesimod was 10400/21800 h·ng/mL (males/females) when given alone and 11500/13100 (males/females) when given in combination with DMF [Ponesimod IB].

1.3.2 Clinical studies

The human clinical experience with ponesimod to date consists of studies assessing single- and multiple-dose safety and tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) in healthy subjects treated with a single dose of up to 75 mg, or multiple doses of up to 100 mg o.d., for up to 22 days, as well as studies in subjects with RRMS treated for up to 5 years and in subjects with moderate-to-severe chronic plaque psoriasis treated for up to 28 weeks with doses up to 40 mg o.d. A proof-of-concept study (AC-058A200) and dose-finding study (AC-058A201) in moderate-to-severe plaque

psoriasis and a dose-finding study in RRMS (AC-058B201) have been completed. An extension study evaluating long-term effects of ponesimod in RRMS subjects who completed study AC-058B201 is ongoing (AC-058B202). Ponesimod is also being investigated in subjects suffering from chronic graft versus host disease.

For results of the Phase 1 studies and Phase 2 study in chronic plaque psoriasis, please refer to the IB [Ponesimod IB].

1.3.2.1 Clinical pharmacology

The PK profile of ponesimod is characterized by low variability. The terminal elimination half-life is about 32 h. There is approximately two-fold accumulation of the drug with repeated daily oral dosing, and steady-state is achieved within 4–5 days. There is a good correlation between the plasma concentration of ponesimod and the peripheral blood total lymphocyte count. Food, age, race or sex do not appear to relevantly affect the PK and PD of ponesimod. The PK DDI potential of ponesimod is judged to be low based on current nonclinical and clinical data.

More detailed information can be found in the IB [Ponesimod IB].

1.3.2.2 Pharmacodynamics in humans

Oral administration of ponesimod dose-dependently reduces the circulating lymphocyte count in humans. The maximum reduction from baseline of approximately 65–80% is achieved after a single dose of ≥ 50 mg, or 40 mg o.d. at steady-state. The nadir in lymphocyte count is attained within 6–10 hours following a given single dose. There is no evidence of tachyphylaxis on lymphocyte count. Peripheral blood counts of both T and B cells are reduced by ponesimod, while NK cells and neutrophils are not reduced. Food, race and sex do not appear to relevantly affect the PD of ponesimod. Upon discontinuation of ponesimod, the lymphocyte count generally returns to within the normal range within 1 week.

The magnitude of lymphocyte-count reductions seen with ponesimod in MS subjects was consistent with observations made after short-term treatment in healthy subjects. In the Phase 2 dose-finding study AC-058B201, at Week 24, the mean reductions from baseline in lymphocyte count were 49.8%, 65.3%, and 68.6% in the ponesimod 10 mg, 20 mg, and 40 mg groups, respectively, compared to a mean increase of 3.3% in the placebo group. Lymphocyte counts remained stable on treatment and returned to baseline levels within one week following ponesimod treatment discontinuation.

More detailed information can be found in the IB [Ponesimod IB].

1.3.2.3 Efficacy in humans

Study AC-058B201 was a prospective, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-finding Phase 2b study, in which efficacy, safety, and tolerability of three doses of ponesimod administered for 24 weeks were investigated in subjects with RRMS. A total of 464 subjects were randomized (1:1:1:1) to 10, 20, or 40 mg ponesimod as the capsule formulation, or placebo. Study medication was administered orally o.d., with a starting dose of 10 mg o.d. in all ponesimod arms and with up-titration to 20 and 40 mg on Days 8 and 15, respectively.

Treatment with ponesimod at doses of 10, 20, and 40 mg was associated with a statistically significant decrease in the cumulative number of new T1 Gd+ lesions at Weeks 12, 16, 20, and 24 (primary endpoint) compared to placebo. The observed effect was dose-dependent, reaching a risk reduction vs placebo of 77% ($p < 0.0001$), 83% ($p < 0.0001$) and 43% ($p < 0.05$) in the 40, 20, and 10 mg groups, respectively vs placebo.

The study was not powered to detect a significant effect of ponesimod on clinical endpoints such as annualized relapse rate (ARR) or time to first confirmed relapse. Treatment with ponesimod was associated with a reduction in the ARR up to Week 24. The ARR reduction in the 40 mg dose group was 52% (0.251 vs 0.525 for placebo; nominal $p < 0.05$), compared with 21% and 37% in the 20 mg and 10 mg groups, respectively. Treatment with ponesimod was associated with a delay in time to first confirmed relapse on treatment. The hazard ratio for subjects treated with 40 mg ponesimod was 0.42 (95% confidence interval [CI] 0.20–0.87, $p = 0.0189$). In the 20 mg and 10 mg groups, the hazard ratio was 0.79 (95% CI 0.43, 1.45) and 0.64 (95% CI 0.33, 1.22), respectively.

Study AC-058B202 is an ongoing randomized, double-blind, parallel-group extension to study AC-058B201, in which the long-term safety, tolerability, and efficacy of 10, 20, and 40 mg/day ponesimod in subjects with RRMS are being investigated. Subjects who completed 24 weeks of treatment with ponesimod in the core study were offered to continue treatment with the same dose of ponesimod. Subjects who completed 24 weeks of treatment with placebo were randomized in a 1:1:1 ratio to either 10, 20 or 40 mg ponesimod daily. After at least 48 weeks and up to 96 weeks of treatment in the extension study, subjects who were receiving 40 mg ponesimod daily were randomized in a 1:1 ratio to 10 or 20 mg ponesimod daily for continuation in the study.

The results from an interim analysis of study AC-058B201/B202 with cut-off date of 1 September 2016 [Havrdova 2017] (median treatment exposure > 5.5 years) have shown sustained low numbers of brain inflammatory lesions on MRI and low clinical disease activity with dose-dependent effects on relapse rate and disability accumulation. The model-adjusted ARR observed with ponesimod 20 mg was 0.153, a rate similar to that observed with the 1.25 mg dose of fingolimod after 5 years in the Phase 2 extension

study [Izquierdo 2013]. There was also a dose-dependent effect of ponesimod on disability accumulation, with a 49% (p = 0.024) relative risk reduction in the ponesimod 20 mg arm compared to the ponesimod 10 mg arm. The incidence of overall adverse event (AEs), serious adverse events (SAEs) and AEs leading to discontinuation over 6 years was similar in patients treated with ponesimod 20 mg compared to those treated with ponesimod 10 mg.

More detailed information can be found in the IB [Ponesimod IB].

1.3.2.4 Safety and tolerability

Clinical studies to date have identified transient changes in heart rate (HR) and atrioventricular (AV) conduction as the most prominent safety-related signal with ponesimod. Oral doses of ponesimod resulted in dose-dependent sinus rate reductions in all treated subjects; the changes were transient and resolved largely within 6–10 hours after dosing. In some subjects, these HR reductions were accompanied by a transient effect on AV conduction with prolongation of the PR interval on the electrocardiogram (ECG) and, occasionally, second degree AV-block. The effects on HR and AV conduction diminish with repeated administration of ponesimod, indicating desensitization. To minimize the first-dose effects on HR and AV conduction, a dose up-titration regimen was successfully tested and is implemented in current clinical trials.

Breathing difficulties and pulmonary function test (PFT) changes have also been detected in humans. Mild transient dyspnea/cough was noted frequently 2–6 hours after an oral dose of 40 mg or higher, and was associated with a clinically relevant forced expiratory volume in 1 second (FEV_1) decrease from baseline. Symptoms resolved spontaneously upon discontinuation of treatment with ponesimod, and PFTs returned to baseline upon drug discontinuation. In study AC-058B201, dyspnea AEs were reported in 6.1% of patients in the ponesimod 20 mg group as compared to 3.3% in the placebo group. Accordingly 13.5% of patients in the ponesimod 20 mg group had $FEV_1 < 80\%$ of their baseline measurements at least once during the treatment period compared to 3.3% in the placebo group. However, none of the patients in the 20 mg group discontinued treatment due to a respiratory AE. Doses higher than 20 mg were associated with decreased tolerability; there were increased discontinuation rates with 40 mg mainly due to more pronounced pulmonary function effects and an increased incidence of liver enzyme elevations.

Data from an interim analysis of the long-term extension study AC-058B201/B202 with a cut-off date of 31 October 2014 showed that dose-dependent decrease in FEV_1 remained stable in patients treated with ponesimod for up to approximately 4 years and were reversible after treatment discontinuation.

Elevations of aspartate transaminase (AST) and/or alanine aminotransferase (ALT) without any substantial bilirubin increase (i.e., total bilirubin > 2 times upper limit of normal [ULN]) have been noted with ponesimod; they have been reversible with or without discontinuation of dosing. The changes were asymptomatic.

Individual cases of macular edema associated with changes in visual acuity have been observed in subjects treated with ponesimod. These events resolved upon discontinuation of ponesimod.

Nonclinical safety testing of ponesimod indicates an embryotoxic and teratogenic potential. Pregnant or lactating women are excluded from clinical trials, and women of childbearing potential (WOCBP) must use reliable methods of contraception and must not become pregnant during a clinical study and for at least 30 days after study drug discontinuation. A hormonal contraceptive is allowed as one of the required methods of contraception, as the PK profile of hormonal contraceptives has been shown not to be substantially altered in the presence of ponesimod.

More detailed information can be found in the IB [Ponesimod IB].

1.3.3 Background treatment

Dimethyl fumarate (Tecfidera®) was approved by the FDA in 2013 for the treatment of patients with RMS and it was approved by EMA in January 2014 for the treatment of RRMS. In the two Phase 3 placebo-controlled 2-year studies DEFINE and CONFIRM, DMF reduced the ARR by 53% and 44% respectively, as compared to placebo at the approved dose of 240 mg b.i.d. [Gold 2012, Fox 2012]. Efficacy on disability progression has not been consistently demonstrated: in the DEFINE study, DMF reduced the risk of 3-month sustained disability progression as compared to placebo (hazard ratio = 0.62, 95% CI: 0.44, 0.87). In the CONFIRM study, the difference between the placebo group and the DMF treatment group on this endpoint was not statistically significant. The main side effects associated with DMF are abdominal pain, diarrhea, nausea, flushing, and lymphopenia.

1.4 Purpose and rationale of the study

None of the disease modifying therapies currently available for relapsing MS can fully suppress inflammatory activity in the CNS and halt clinical attacks or disability progression of the disease.

Patients who have active disease despite being treated with first line treatments for MS such as IFNs, glatiramer acetate, teriflunomide or DMF may need treatment escalation to more efficacious agents. The currently existing alternatives include monoclonal antibodies natalizumab or alemtuzumab, subject to availability in a given country. These agents provide high efficacy but require i.v. infusions, and are associated with potentially

serious and life threatening adverse reactions. In particular, the occurrence of opportunistic infections such as progressive multifocal leukoencephalopathy (PML) in patients treated with natalizumab, and autoimmune disorders in those treated with alemtuzumab have raised concern.

Ponesimod may represent a safer oral alternative for treatment escalation in RMS. A Phase 3 study (AC-058B301) is currently ongoing to assess the efficacy and safety of ponesimod monotherapy in patients with RMS.

Study AC-058B302 aims to expand the clinical utility of ponesimod by assessing the efficacy and safety of add-on treatment with ponesimod in patients whose RMS is not sufficiently controlled by DMF (Tecfidera®).

Tecfidera® is a recently approved first-line treatment of RMS which is already widely used across North America and Europe. Based on Phase 3 clinical trial results, during 2 years of treatment with DMF almost one-third of patients had a relapse and approximately 50% had ongoing radiological or clinical signs of disease activity, thus disease is not sufficiently controlled in many patients on DMF [Fox 2012, Gold 2012].

Both ponesimod and DMF have effects on the immune system, but neither compound has shown a profound immunosuppression. The target organs of potential toxicity of DMF do not generally overlap with those of ponesimod, with the exception of the immune system and liver. Although via different mechanisms, both compounds lead to a reduction of lymphocyte counts in peripheral blood, which are routinely monitored and can be used to guide treatment decisions in the clinical trial and in clinical practice. Thus, adding ponesimod to DMF might represent a safer treatment escalation with the added value of an oral administration when compared to current options for treatment escalation.

Nonclinical studies of this combination indicate improved efficacy of the combination when compared to DMF alone without new safety findings of concern [Sections 1.3.1.1 and 1.3.1.2]. These observations support the clinical testing of ponesimod add-on to DMF in patients with RMS. Nevertheless, as the addition of ponesimod to DMF has not yet being tested in humans, specific safety measures have been designed and will be implemented in this study as described in Section 3.4. Assuming high efficacy and acceptable safety are shown in humans, the add-on of ponesimod to DMF (Tecfidera®) may display a favorable benefit/risk balance and represent a valuable treatment option for RMS patients insufficiently controlled by DMF monotherapy.

1.5 Summary of known and potential risks and benefits

DMF (Tecfidera®) is an oral fumaric acid ester approved for the treatment of RMS. Phase 3 clinical studies with DMF have shown a significant reduction of a brain inflammatory

activity and relapse rate compared with placebo in patients with RMS [Gold 2012, Fox 2012].

Subjects treated with DMF with recent evidence of active disease may still benefit from continuation of DMF treatment in the proposed study, even if they are randomized to placebo for the following reasons:

- MS is a clinically heterogeneous disease with an underlying complex pathology and unpredictable course. At an individual subject level, disease activity and response to treatment may vary with time. Therefore, continuation of DMF treatment may still be beneficial even if subjects had recent evidence of active disease prior to entering the study and are randomized to placebo add-on therapy.
- Several lines of evidence indicate that the annualized relapse rate (ARR) for subjects assigned to the placebo arm in RMS clinical trials decreases substantially when compared to the pre-trial ARR [Steinvorth 2013]. Among other reasons, careful patient management and increased adherence to treatment may explain these findings and provide justification for a positive benefit/risk balance for subjects receiving placebo add-on therapy in the study.

Ponesimod is an oral, selective, and reversible modulator of the $S1P_1$ receptor under investigation for the treatment of RMS. In a large Phase 2 study performed in patients with RRMS, ponesimod has been shown to reduce the number of inflammatory lesions in the brain and the number of relapses compared with placebo [Olsson 2014]. Furthermore, in a long-term extension of the Phase 2 study (ongoing, blinded), there was also a trend towards a dose-dependent decrease in disability accumulation and in brain volume loss with ponesimod [Pozzilli 2013]. Ponesimod has therefore the potential to benefit patients with MS with residual disease activity by reducing relapses.

The mechanisms of action of DMF and ponesimod appear to be complementary and suggest potential additive or synergistic efficacy when combined. Indeed, both drugs have immunomodulatory and neuroprotective properties but they act on distinct molecular and cellular targets. While DMF decreases lymphocyte proliferation and inhibits pro-inflammatory cytokines, ponesimod inhibits migration and egress of T and B cells from secondary lymphoid organs. Similarly, while DMF may increase neural cell survival by reducing oxidative stress, ponesimod may activate astrocytes and oligodendrocytes promoting re-myelination. In a rat model of relapsing-remitting EAE, the combination of DMF with ponesimod showed a marked reduction of clinical scores throughout the whole treatment-phase [Ponesimod IB]. In summary, the combination of ponesimod with DMF may reduce inflammation and prevent disability accumulation, resulting in additive or synergistic efficacy in MS. Hence, this study has the ambitious aim to reduce disease activity to a level which is not achievable with monotherapy.

Additionally, subjects enrolled in the study may receive improved medical care for their RMS. Subjects who prematurely discontinue study treatment will enter the Post-treatment observation period (PTOP) in which they will be allowed to receive other approved MS therapies and will continue to receive improved medical care as part of the study. Their participation in the study will also allow collection and analysis of information that may help patients obtain better care in the future.

When considering combinations of different drugs, it is important to minimize risk of overlapping or increased toxicity. Side effects of ponesimod do not substantially overlap with those of DMF. The main side effects associated with DMF are abdominal pain, diarrhea, nausea, flushing and lymphopenia [Tecfidera SmPC, Tecfidera USPI]. A few cases of PML have also been reported after long-term treatment with DMF, the majority in association with sustained lymphopenia [see Section 3.4.2]. Clinical studies conducted to date with ponesimod in MS patients have identified first-dose effects on HR and AV conduction, blood pressure, pulmonary function effects, macular edema, and liver enzyme elevations as potential risks [see Section 1.3.2.4]. Both DMF and ponesimod can reduce lymphocyte counts, but the mechanisms and modalities of lymphocyte-lowering effects of the two drugs are different and are not expected to lead to a profound immune-suppression. In a 13-week treatment duration study in dogs [Ponesimod IB], the combination of ponesimod with DMF induced effects comparable to those observed with each drug alone with no evidence of new or increased toxicities.

The study includes several safety measures for monitoring and minimizing the potential risks of combining ponesimod with DMF. These include:

- Specific study inclusion and exclusion criteria to reduce the risk of high grade lymphopenia during the course of the study and select subjects without enhanced risk of opportunistic infections [see Section 4.3];
- Protocol-specific procedures, including criteria for interruption and premature discontinuation for minimizing and managing the risk of lymphopenia and opportunistic infection [see Sections 5.1.12.2 and 5.1.12.3];
- Criteria for premature discontinuation in the event of lack of efficacy during the study, allowing subjects to receive other treatments (rescue therapy) [see Section 3.5.2.1];
- An overview surveillance by two independent safety committees (i.e., an MRI safety board and an Independent Data Monitoring Committee (IDMC) [see Sections 3.8.1 and 3.8.3]).

During the study, MRI scanning will be performed every 6 months. These MRI scans will require the injection of a gadolinium (Gd)-containing contrast agent which may, in rare

cases, lead to serious allergic reactions. Gd administration may be omitted if medically contraindicated. In addition, chest X-rays will be performed at Visits 1 (Screening) and 18 (End-of-Treatment [EOT]) (i.e., at least 63 weeks apart, or 48 weeks in the event of premature discontinuation), thus exposing subjects to a limited quantity of radiation.

The above listed considerations, related to the known and potential risks, together with the risk mitigation measures planned for the study, and the expected improved efficacy of the ponesimod add-on therapy as compared to DMF alone, provide a rationale for a positive benefit/risk for subjects participating in the study.

It is the investigator's responsibility to monitor the risk-benefit ratio of study treatment administration, as well as the degree of distress caused by study procedures on an individual subject level, and to discontinue study treatment or the study if, on balance, he/she believes that continuation would be detrimental to the subjects' well-being.

2 STUDY OBJECTIVES

2.1 Primary objective

The primary objective of the study is to determine whether add-on therapy with ponesimod reduces relapse frequency as compared to placebo in subjects with active RMS who are treated with DMF (Tecfidera®).

2.2 Secondary objectives

- To assess the effect of add-on therapy with ponesimod vs placebo on disability accumulation and on other aspects of MS disease control in subjects with RMS who are treated with DMF (Tecfidera®);
- To assess the safety and tolerability of add-on therapy with ponesimod vs placebo in subjects with RMS who are treated with DMF (Tecfidera®).

3 OVERALL STUDY DESIGN AND PLAN

3.1 Study design

This is a prospective, multicenter, randomized, double-blind, parallel-group, add-on, placebo-controlled, Phase 3, superiority study. The study is designed to compare the efficacy, safety, and tolerability of add-on therapy with ponesimod 20 mg vs placebo in adult subjects with active RMS who are treated with DMF (Tecfidera®).

Approximately 600 subjects who have been receiving DMF b.i.d. for at least 6 months will be randomized in a 1:1 ratio to ponesimod 20 mg or placebo (approximately 300 subjects per arm). Randomization will be stratified by baseline Expanded Disability Status Scale (EDSS) score (EDSS $\leq$ 3.5, EDSS > 3.5).

The study will be conducted at approximately 100 sites in 15 countries. Randomization will proceed until the required number of subjects has been reached. Any eligible subject in screening at the time of randomization of the 600th subject will be recruited. Subject enrollment will be competitive across participating sites.

It is permitted to re-screen subjects once [see Section 8]. Actelion may wish to replace sites with no subject enrollment.

3.2 Study design rationale

The present study was designed to assess whether ponesimod as add-on therapy to DMF (Tecfidera®) is superior to add-on placebo to DMF (Tecfidera®) in reducing relapses in subjects with active RMS. Eligible subjects entering the study will have received DMF therapy for at least 6 months prior to study entry with clinical and/or MRI-documented disease activity after at least 3 months on DMF. The requirement for 6 months of DMF treatment prior to study entry aims to ensure a relatively stable effect of DMF on lymphocytes as well as better adherence to treatment during the study as most of flushing and gastrointestinal AEs occur during the initial months following initiation of DMF treatment. According to expert opinion, at least 6 months of DMF treatment would be necessary before the response to DMF can be considered insufficient and additional treatment justified.

The requirement for evidence of active MS disease after at least 3 months of DMF treatment is based on data from Phase 2 and Phase 3 clinical studies showing increased therapeutic efficacy of DMF after at least 3 months of treatment.

The requirements set in this study are considered to represent the earliest timepoints at which the treating neurologist would consider escalating the therapy if disease activity persists, avoiding the risk of a too early change in treatment.

The study includes a placebo comparator arm, but all subjects will remain on DMF background therapy throughout the treatment period. Moreover, during the study subjects who experience a confirmed relapse or an event of 24-week confirmed disability accumulation (CDA) will have the option to switch to an alternative treatment. During the study, several decisions and assessments including subjective judgment will have to be performed. In order to limit the considerable risk of bias, a double-blind design is warranted.

The study includes only one ponesimod treatment arm at the maintenance dose of 20 mg o.d. corresponding to the optimal dose when used as monotherapy based on the Phase 2 dose-finding trial and its ongoing extension [see also dose rationale Section 3.3].

No ponesimod monotherapy treatment arm has been included in the present study. Importantly, the clinical efficacy of ponesimod (20 mg o.d.) monotherapy is already

being evaluated against teriflunomide (14 mg o.d., Aubagio®) in the ongoing pivotal Phase 3 AC-058B301 study. The objective of this study is to assess ponesimod as add-on therapy in patients with active disease on DMF, with the ambitious aim at suppressing disease activity to a level which is not achieved with available therapies. Add-on studies can assess the superiority of active treatment over placebo on a background medication. The proposed add-on design without testing the add-on arm against each monotherapy is quite common in other therapeutic areas (e.g., in rheumatology in studies testing add-on design to disease modifying antirheumatic drugs [DMARD], in oncology, etc.) and has been also used in MS. The SENTINEL study tested natalizumab as add-on to IFN β-1a versus placebo add-on to IFN β-1a [Rudick 2006]. Two Phase 2 studies tested teriflunomide as add-on to either IFN β-1a or glatiramer acetate in comparison to placebo add-on and the Phase 3 study TERACLES was planned to confirm the benefit of add-on teriflunomide to IFN β-1a in comparison to placebo [Freedman 2012].

In order to evaluate the ARR over an estimated mean treatment duration of approximately 2 years, a study design with variable treatment duration was chosen. The minimum treatment time will be of at least 60 weeks. However, based on a projected recruitment time of approximately 2 years, prolonged study treatment exposure time of up to 3.3 years will be available for efficacy and safety analysis.

3.3 Dose rationale

Based on the available Phase 2 data, ponesimod 20 mg o.d. displayed the optimal benefit/risk balance and this dose was selected for Phase 3 studies.

Lower doses of ponesimod did not provide an adequate level of disease control and did not offer a relevantly improved safety profile. Consistent with a lower effect on lymphocytes, 10 mg ponesimod was unable to suppress MRI brain inflammatory activity to the level achieved with 20 mg and continued to show higher levels of clinical disease activity with more relapses and accumulation of disability after 4 years of treatment. While more efficacious, 20 mg showed similar rates of AEs and discontinuations when compared to 10 mg; the pulmonary function effects were lower with 10 mg but the difference was not clinically relevant. Ponesimod 40 mg was associated with decreased tolerability, leading to increased discontinuation rates, mainly due to pulmonary function effects and liver enzyme elevations. By contrast, there was a similar or only small incremental effect of 40 mg compared to 20 mg on lymphocytes, MRI brain inflammatory activity, and clinical disease activity.

Ponesimod will be added to DMF in patients who have active disease while on DMF therapy, thus it is expected that the full efficacy of ponesimod, as achieved with 20 mg, will be required to adequately control disease activity. Furthermore, given that the AE profiles of the two drugs are different, it is reasonable to expect that the safety profile of

the 20 mg dose will not substantially change and will also be acceptable when added-on to DMF.

3.4 Risk mitigation strategy

To minimize, assess, and manage potential risks to patients who will receive ponesimod and DMF or DMF alone, a risk mitigation strategy consisting of several components has been implemented in this study. These include: i) specific study inclusion and exclusion criteria to ensure that patients who have underlying characteristics that increase their risk for an adverse outcome are excluded; ii) protocol specific procedures, including criteria for interruption and premature discontinuation [see Section 5.1.12] for minimizing and managing certain AEs with particular emphasis on lymphopenia and opportunistic infections [see Sections 3.4.1 and 3.4.2], iii) an overview surveillance by two independent safety committees (i.e., an MRI safety board, and an IDMC, see Sections 3.8.1 and 3.8.3).

3.4.1 Lymphopenia

Both ponesimod and DMF have lymphocyte-lowering effects. Low lymphocyte counts can potentially increase the risk of infections including opportunistic infections, and need to be monitored. The mechanism and modality of lymphocyte count reduction by the two drugs are very different. DMF treatment slowly reduces lymphocyte counts by inducing apoptosis of lymphocytes with a nadir after one year of treatment. By contrast, ponesimod treatment induces lymphocyte count reduction within one week by reversible sequestration of lymphocytes in secondary lymphoid tissues. Discontinuation of DMF treatment is followed by a slow increase of lymphocyte counts over several weeks, while discontinuation of ponesimod is followed by recovery of lymphocyte counts within one week. In a 13-week treatment duration study in dogs, the combination of ponesimod with DMF induced effects on lymphocyte counts comparable to those observed with each drug alone. The effect on lymphocytes by adding ponesimod to DMF has not been investigated in humans. All these aspects represent important safety concerns that have been taken into account when designing appropriate safety measures as follows:

- To reduce the risk of high grade lymphopenia during the course of the study, only subjects with lymphocyte counts $\geq 0.8 \times 10^9$/L ($\geq 800/mm^3$) after at least 12 months of DMF treatment or subjects with lymphocyte counts $\geq 0.9 \times 10^9$/L ($\geq 900/mm^3$) after at least 6 months of DMF treatment (but < 12 months) will be enrolled [see inclusion criterion #8 in Section 4.3].
- To ensure a relatively stable effect of DMF on lymphocyte has been reached prior to study entry, subjects with large excursions in lymphocyte counts between screening and baseline assessments (at least 3 weeks apart) will not be included [see inclusion criterion #8 in Section 4.3].

- To ensure a prompt detection of high grade lymphopenia or unstable declining lymphocyte counts while on DMF or after adding ponesimod to DMF, lymphocyte counts will be monitored every 4 weeks (± 3 days) during the initial 24 weeks, and then every 12 weeks for the remainder of the study.
- To facilitate management of potential lymphopenia for patients who discontinue study treatment and enter the PTOP, lymphocyte counts will be made readily available to the treating neurologists. Upon discontinuation of ponesimod, lymphocytes generally return to within the normal range within one week. Lymphocyte counts are therefore expected to have returned to normal range during the 30-day follow up period preceeding the start of PTOP, unless the lymphopenia was due to DMF background treatment. Thus, there is no risk of unblinding to ponesimod treatment when providing lymphocyte count values during the PTOP.
- To ensure that any unexpected effect on lymphocytes by adding ponesimod to DMF is properly assessed in due time, the IDMC will perform a review of lymphocyte count data on an ongoing basis, starting with a cut-off corresponding to 12 weeks after randomization of the 20th subject in the study. Furthermore, the IDMC will continue to review lymphocyte count and other data at regular intervals approximately every 4 months during the study [see also Section 3.8.1].

3.4.2 Opportunistic infections

Both ponesimod and DMF have immune-modulating properties which may increase the risk of opportunistic infections. Opportunistic infections of the CNS require particular vigilance due to the risk of invalidating or fatal outcome. Although no cases of PML have been reported with ponesimod, single cases of this disease were reported in patients treated with fingolimod, another S1P receptor modulator, without previous treatment with natalizumab or immunosuppressants. Cases of PML with DMF (Tecfidera®) have also been reported, the majority in association with sustained lymphopenia. Add-on of ponesimod to DMF may potentially increase the risk of such infections. Therefore, several measures will be in place to select subjects without enhanced risk of such infections and to detect signs of infections as early as possible during the course of the study [see Section 5.1.12.3. Previous treatments with potential delayed risk of infection will be prohibited anytime prior to the study (i.e., alemtuzumab, mitoxantrone) or will be allowed only after appropriate wash-out period (e.g., natalizumab, rituximab, azathioprine, methotrexate). An MRI safety board will perform centralized expert evaluation of MRI images selected by the local radiologists or neurologists with MRI expertise in case of suspected opportunistic CNS infections including PML.

The risk of opportunistic infections should be seen in the perspective of expected benefit of ponesimod added-on to DMF and of the currently accepted benefit/risk profile of natalizumab where the approximate risk of PML is in the range of 1/10,000–1/100 and

varies with John Cunningham Virus (JCV)-specific antibody status, prior immunosuppression and duration of treatment [Calabrese 2015]. The overall incidence of PML in natalizumab-treated patients was 3.78/1000 as of 3 December 2014 [Kornek 2015]. The currently known risk of PML with fingolimod and DMF is substantially lower and it remains unclear whether it is significantly elevated compared to the general population [Van Schependom 2015]. These considerations, together with the risk mitigation measures planned for the study, and in light of expected improved efficacy of the ponesimod add-on therapy as compared to DMF alone [see Section 11.5.1] provide a rationale for an acceptable benefit/risk ratio for the trial.

3.5 Study periods

The study consists of the following study periods:

3.5.1 Pre-randomization period

This period commences up to 45 days before randomization at the time of the signature of the Informed Consent Form (ICF) and ends with subject's randomization. It includes Visit 1 (Screening), Visit 2 (Baseline) and the pre-dose assessments of Visit 3 (Day 1).

3.5.2 Treatment period

This period consists of a double-blind treatment period, which starts after randomization with the first dose of study treatment during Visit 3 (Day 1 of study).

The double-blind treatment period has a variable duration from a minimum of 60 weeks (for the last subject randomized) to a maximum of 156 weeks (3 years) for the first subjects randomized in the trial. Average duration is expected to be approximately 2 years. It includes a randomization visit, visits at 2, 4 and 12 weeks after randomization, and 12-weekly visits thereafter until 60 weeks after the randomization of the last subject or 156 weeks of treatment (whichever occurs first).

For an individual subject, this period starts on the day of the first study treatment intake and continues until the premature discontinuation of study treatment, Week 156, or until 60 weeks after the randomization of the last subject (whichever occurs first).

EOT visit: The EOT visit at an individual level should preferably take place 1 day after the last dose of study treatment, but no later than 7 days after the last dose of study treatment.

3.5.2.1 Modification of treatment

If a subject meets one of the following conditions:

- The subject has experienced a confirmed relapse while on study treatment;
- The subject has experienced an event of 24-week CDA while on study treatment;

Then, the principal investigator / treating neurologist should consider and propose the following options to this subject:

- Subject remains on study treatment. In this case, the subject will be asked to re-consent to continue receiving study treatment [see Section 13.3].
- Subject prematurely discontinues study treatment and DMF background therapy, and begins treatment with an approved MS therapy at the discretion of the treating neurologist in accordance with local practices. In this case, the subject will enter the post-treatment observation period (PTOP) of the study [see Section 3.5.3.2].

Subjects who prematurely discontinue study treatment for reasons other than lack of efficacy (e.g., safety or tolerability) will also enter the PTOP of the study [see Section 3.5.3.2]. Treating neurologists may choose to continue DMF therapy or may begin treatment with an approved MS therapy at the discretion of the treating neurologist in accordance with local practices. Discontinuation of DMF treatment should be considered in accordance with prescribing information [Tecfidera USPI, Tecfidera SmPC] at the discretion of the treating neurologist and in accordance with local practices.

Subjects who permanently discontinue DMF background therapy will discontinue study treatment [see Section 5.1.12.8] and may begin treatment with an approved MS therapy in accordance with local practices. In this case, the subject will enter the PTOP of the study [see Section 3.5.3.2].

3.5.3 Post-treatment period and End-of-Study

This period starts immediately after the last dose of study treatment and ends when End-of-Study (EOS) visit has been completed. It comprises the post-treatment safety follow-up (FU) period and if applicable, is followed by the PTOP.

3.5.3.1 Post-treatment safety follow-up period

All subjects will enter the safety FU period which lasts for at least 30 days after the last dose of study treatment and includes a safety FU visit approximately 30 days after the last dose of study treatment. Subjects participating in the lymphocyte subset sub-study will have an additional FU visit approximately 7 days after the last dose of study drug (FU7d) [see Section 3.6.1].

3.5.3.2 Post-treatment observation period

Subjects who prematurely discontinue study drug and complete the 30-day safety follow-up including the FU visit, will enter the PTOP which lasts until 60 weeks after randomization of the last subject or until Week 156, whichever is first (i.e., planned EOT visit) irrespective of treatment completion. It consists of an abbreviated schedule of assessments at the time of the originally scheduled 12-weekly visits. The aim is to

follow-up with the subjects after discontinuation of study treatment and to collect long-term data while the subject possibly receives other approved MS therapies.

While participating in the PTOP, subjects may not be enrolled in another clinical trial. They may, however, withdraw their consent to participate to this study at any time [see Section 9.2].

3.5.3.3 End-of-Study

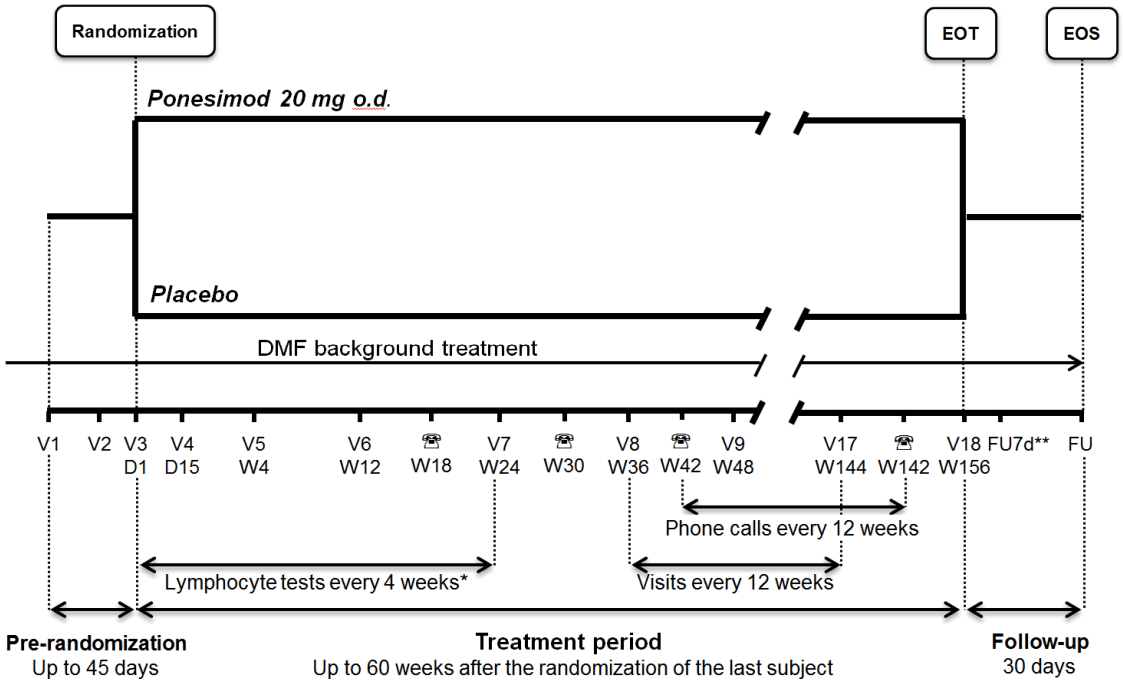
The study level EOS will occur after all subjects have completed the safety FU period or the last visit of the PTOP.

For an individual subject, EOS is reached when treatment, post-treatment safety FU, and if applicable, the PTOPs have been completed:

- For subjects who complete the treatment period, and for subjects who prematurely discontinue study treatment and do not enter the PTOP, the EOS visit corresponds to the 30-day FU visit (FU).
- For subjects who prematurely discontinue study treatment and enter the PTOP period, the EOS visit corresponds to the last visit of the PTOP.

The overall study design is shown in Figure 1.

Figure 1 AC-058B302 study design



D = day; DMF = dimethyl fumarate; EOS = End-of-Study; EOT = End-of-Treatment; FU = follow-up; V = visit; W = week; *Lymphocyte tests every 4 weeks (± 3 days) until Week 24; ** Subjects participating in the lymphocyte subset sub-study will have an additional FU visit approximately 7 days after the last dose of study drug (FU7d).

3.5.4 Study duration

Assuming a subject recruitment time of 104 weeks (including the period from first subject, first visit [FSFV] to last subject, first visit [LSFV] and a 45-day pre-randomization period for the last randomized subject), the overall duration of the study from FSFV to last subject, last visit (LSLV) will consist of 104 weeks recruitment, followed by the minimum treatment time of 60 weeks, and 30 days post-treatment safety follow-up. This results in an anticipated study duration of approximately 168 weeks (3.3 years). The actual overall study duration or subject's recruitment period may vary.

For an individual subject, the maximum duration time will consist of a 45-day pre-randomization period followed by a maximal 156-week treatment period and a 30-day post-treatment safety follow-up. This results in a maximal total participation time of approximately 167 weeks (3.3 years).

3.5.5 Study closure

The study closure will be communicated by the sponsor 60 weeks after the randomization of the last subject.

All subjects on study drug should perform the Visit 18 (EOT) assessments within 4 weeks after study closure is communicated by the sponsor, and then the post-treatment safety follow-up (i.e., Visit 19 [FU7d], if applicable, and Visit 20 [FU]). For these subjects, the EOS visit corresponds to Visit 20 (FU).

All subjects who prematurely discontinued from the study treatment and entered the PTOP should perform the Visit 18A (Week 156) assessments within 4 weeks after study closure is communicated by the sponsor. For these subjects, the EOS visit corresponds to Visit 18A (Week 156).

3.6 Sub-studies

Two sub-studies designed to evaluate specific safety variables will be conducted in a subset of sites and subjects.

3.6.1 Lymphocyte subset

Ponesimod decreases total lymphocyte counts but some lymphocyte subsets are more sensitive to this effect than others. DMF and other fumaric acid esters may also decrease total lymphocyte counts but the effect on lymphocyte subsets is not well understood. The effect of ponesimod add-on to DMF on lymphocyte subsets is not known. Analysis of blood lymphocyte subsets may provide a better understanding of the immunomodulatory effect of ponesimod when added on to DMF in subjects with RMS.

A sub-study assessing lymphocyte subsets will be conducted in approximately 200 subjects [see Section 7.7.2.2]. Participation in the sub-study will be mandatory for all subjects until at least the first 200 subjects are randomized to the main study. T cell, B cell, and NK cell counts as well as T cell subsets (e.g., $CD4^+$ naïve, $CD4^+$ effector memory, $CD4^+$ central memory, $CD8^+$ naïve, $CD8^+$ effector memory, $CD8^+$ central memory, $CD8^+$ terminally differentiated effector memory, Th17 cells, Treg cells, and Th1cells) will be analyzed at the central laboratory by fluorescence activated flow cytometry using a combination of cell surface markers. Other lymphocyte subsets may also be analyzed. Selected lymphocyte subsets may also be analyzed functionally *ex vivo*. Results will be provided regularly to the IDMC. Results from the lymphocyte subsets sub-study will be blinded to site staff and the sponsor until study closure.

3.6.2 Vaccination

In order to characterize the immune response in subjects receiving ponesimod add-on to DMF therapy, changes in vaccine-specific antibody titers from pre- to post-vaccination

will be assessed at the end of the study for subjects having received a non-live vaccination while on study treatment.

3.7 Site staff and their roles

In order to maintain the blind [see Section 5.1.4] throughout the study and to facilitate the performance of efficacy and safety assessments required by the protocol, it is essential that:

- the site personnel have the appropriate medical expertise to perform these assessments;
- the roles are defined clearly upfront.

It is recommended that the designated personnel remain unchanged throughout the entire course of the study and that an adequately trained back-up be designated to perform the assessments in case of absence of any of the staff listed below.

For each site, the study staff will consist of:

- A principal investigator
- A treating neurologist (who may be the principal investigator)#
- An efficacy assessor#
- A first-dose administrator#
- A clinical coordinator/study nurse (if required)
- MRI staff
- A radiologist/neuroradiologist
- An ophthalmologist
- A pulmonary function laboratory technician or expert
- A dermatologist

The roles of treating neurologist, efficacy assessor and first-dose administrator are irreconcilable and must be assumed by three distinct persons.

3.7.1 Principal investigator

The principal investigator must be an experienced neurologist or must name a sub-investigator who is an experienced neurologist. The principal investigator is responsible for the overall conduct of the study at the site. It is her/his responsibility to assign appropriate personnel to the protocol-requested assessments (including safety and efficacy) and define their roles. This includes the supervision of any external facility delegated with any study procedure/assessment for a subject. The principal investigator

oversees the accrual of appropriate subjects, the conduct of the study according to the trial protocol, and the collection of the required data.

3.7.2 Treating neurologist

The treating neurologist is an experienced neurologist who may be the principal investigator. The treating neurologist is responsible for subject clinical care and management, e.g., eligibility evaluation, supervision of study drug administration, assessing and reporting MS relapses on the specific MS relapses pages of the electronic case report form [eCRF; see Sections 7.2.2 and 10.1.6], monitoring of safety, including recording and treating of AEs (with the exception of non-serious AEs with onset after study drug intake and resolution prior to discharge from cardiac monitoring on Day 1 or on the first day of re-initiation of study drug when post-dose monitoring is required, which will be recorded by the first-dose administrator), physical examination, routine laboratory results (with the exception of WBC and lymphocyte counts), concomitant medications, blood pressure (BP), and ECGs (with the exception of BP and post-dose ECG on Visit 3 [Day 1] or on first day of re-initiation of study drug when post-dose monitoring is required, which will be performed by the first-dose administrator). Depending on the site setting, all BP and ECG assessments required by the protocol during the study may be conducted by the first-dose administrator [see Section 3.7.4]. The treating neurologist will not perform EDSS / FS assessment and will not alter the EDSS or FS scores obtained by the efficacy assessor [see Section 7.2.2]. The treating neurologist will not have access to MRI data throughout the study, unless necessary for safety reasons.

It is the responsibility of the treating neurologist to explain the study in all its aspects to the subject and obtain her/his informed consent. The treating neurologist will be responsible for emphasizing the need for reliable contraception methods and explaining such methods to the female participants who are WOCBP for the period defined in this protocol [Section 4.5].

The treating neurologist is responsible for the medical management of the subject experiencing cardiac events of clinical concern occurring at any time during the study treatment and not already evaluated by the first-dose administrator. In these events, the treating neurologist may consult with the first-dose administrator and/or a cardiologist. In case of acute cardiac events, she/he may refer the subject to a cardiologist to receive emergency care and treatment.

The same physician must maintain the role of the treating neurologist for a given subject throughout the study. A back-up treating neurologist may conduct a subject study visit only if the primary treating neurologist is not available.

3.7.3 Efficacy assessor

The efficacy assessor is a physician, physician assistant, or nurse practitioner who will perform the detailed neurological examination for obtaining the EDSS / Functional System (FS) scores using the "Neurostatus" scoring forms [see Appendix 1] according to the protocol schedule, as well as EDSS/FS scores at every unscheduled visit for confirmation of relapse. If other trained and certified personnel participate in EDSS/FS scoring, they must not be involved in the clinical care and management of the study subject.

Throughout the study, the efficacy assessor must remain unaware of AEs, concomitant medications, BP, ECG measurements, MRI and laboratory results, and any other data that have the potential to reveal the treatment assignment, in order to avoid potential bias due to unblinding. For that reason, all other members of the study staff, as well as the study subjects, must be instructed not to discuss clinical findings or safety issues with the efficacy assessor.

To ensure consistency across sites, the efficacy assessor must be trained and certified on EDSS/FS scoring prior to enrollment of the first subject at the study site. Through this training, the efficacy assessor will become familiar with the EDSS/FS scoring and "Neurostatus" scoring forms using an interactive "Neurostatus" Training DVD-ROM that will be provided to the site. Certification, consisting of the "Neurostatus e-Test" web-based interactive test, will be assessed prior to enrollment of the first subject at the study site and every 2 years thereafter.

The same person should preferably maintain the role of efficacy assessor for a given subject throughout the study. A back-up efficacy assessor may conduct neurological examination and EDSS/FS scoring if the primary efficacy assessor is not available. This back-up efficacy assessor must be trained and certified in EDSS/FS scoring (see above) and capable of ensuring consistency in EDSS/FS scoring with the primary efficacy assessor.

Depending on the site setting, the efficacy assessor may be in charge of administering the Multiple Sclerosis Functional Composite (MSFC) test and the Symbol Digit Modalities Test (SDMT).

3.7.4 First-dose administrator

The first-dose administrator must be a physician, physician assistant, nurse practitioner, or any trained and qualified person as per local regulations capable of making healthcare decisions based on ECG interpretation reports provided in a timely manner by the central ECG laboratory, and experienced in the evaluation of BP and clinical signs or symptoms. For non-physicians the role of first-dose administrator must be within the scope of the national and/or local authorization. If the first-dose administrator is adequately trained

and experienced in cardiology, she/he will make healthcare decisions solely based on her/his own interpretation of the ECG (in which case expedited central reading of the ECGs by the central ECG laboratory will not be required).

She/he is responsible for conducting all BP and ECG assessments requested by the protocol at Visit 3 (Day 1) and at visits for re-initiation of study drug when post-dose monitoring is required. This includes the close monitoring of the subject during the first 4 hours and up to 12 hours following study drug intake. While the exams themselves may be performed by a delegate (e.g., a study nurse), the review and interpretation must be performed by the first-dose administrator. She/he will independently assess eligibility for discharge from cardiac monitoring or continued subject management on Visit 3 and on visits for re-initiation of study drug when post-dose monitoring is required [see Sections 5.1.8, 5.1.9, and 5.1.10]. The confirmation of discharge of the subject will be documented in the source documents. Depending on the setting at the site, the first-dose administrator may also be responsible for the conduct of all BP and ECGs assessments requested by the protocol during the study. Depending on the setting at the site, study drug administration at Visit 3 (Day 1), or at visits for re-initiation of study drug following a temporary cessation of treatment when post-dose monitoring is required, may be performed under the supervision of the treating neurologist. In this case, the subject must be rapidly transferred to the first-dose administrator, who will supervise the post-dose monitoring.

On Day 1 and on the first day of re-initiation of study drug when post-dose monitoring is required, significant findings, which in view of the first-dose administrator meet the definition of AE, have an onset after the study drug intake and are resolved at the time of discharge from the cardiac monitoring, must be recorded directly on the Adverse Event page of the separate eCRF by the first-dose administrator / delegate. These AEs will not be visible to any of the blinded study personnel at the study site. During the study, all clinical records related to first-dose data (e.g., 12-lead ECG printouts, BP results, AEs, etc.) must be filed in a separate medical chart only visible to the first-dose administrator.

All other AEs (i.e., those with an onset prior to study drug intake or which are not resolved at the time of discharge from the cardiac monitoring or with an onset after discharge from the cardiac monitoring), as well as all SAEs and all AEs requiring study drug discontinuation must be reported to the principal investigator / treating neurologist, who will record these events on the AE page of the eCRF.

The 3-hour PK sample on Day 1 or on the first day of re-initiation of study drug when post-dose monitoring is required should be taken by the first-dose administrator, the first-dose administrator nurse or another person not involved in the clinical care and management of the study subject.

Any cardiac events of potential clinical concern on Day 1 and on the first day of re-initiation of study drug when post-dose monitoring is required must be assessed by the first-dose administrator for seriousness. In addition, the first-dose administrator should determine the need for medical management and assist the treating neurologist in deciding what actions should be taken on study treatment, if any. In case of such events, the first-dose administrator may consult with a cardiologist. In case of acute cardiac events, and if the first-dose administrator is not adequately trained and experienced in cardiology and is not equipped to provide emergency treatment, she/he will refer the subject to a cardiologist to receive emergency care and treatment.

The first-dose administrator must ensure that blinded study personnel at the study site, such as the treating neurologist and the efficacy assessor, clinical coordinator / study nurse, and other personnel involved in the clinical care and management of study subjects, do not have access to Day 1 or day of re-initiation of study drug post-dose BP assessment, or ECG interpretation reports or to AEs with onset after the study drug intake on Day 1 or on the first day of re-initiation of study drug when post-dose monitoring is required, and resolved at the time of discharge of the subject from the cardiac monitoring on that same day. When the exams themselves are performed by a delegate (e.g., a study nurse), this delegate must not be involved in the clinical care and management of the study subject (i.e., cannot be the clinical coordinator / study nurse of the study [see Section 3.7.5]).

In case the first-dose administrator is responsible for conducting **all** BP and ECGs assessments requested by the protocol during the study, he/she will report to the principal investigator / treating neurologist any significant findings on BP or ECGs which in his/her view meet the definition of an AE (with the exception of BP and ECG on Visit 3 [Day 1] or on first day of re-initiation of study drug when post-dose monitoring is required, which will be reported by the first-dose administrator as explained above). These must then be reported and recorded on the AE page of the eCRF by the principal investigator / treating neurologist.

3.7.5 Clinical coordinator / study nurse

Depending on the organization of the investigational site, a clinical coordinator / study nurse may be required to assist the principal investigator / treating neurologist in all aspects of subject's management. She/he will be responsible for scheduling visits and assessments as planned in the study protocol, recording concomitant medications, maintaining source documentation, and transcription of data into the eCRF. She/he will instruct the subjects on study drug administration, and collect, process, and send all blood and urine samples to the central laboratory. Additionally, she/he may be responsible for coordinating the conduct of:

- MRI

- PFTs
- Ophthalmological and cardiac examination (except cardiac assessment on Day 1 and on day of re-initiation of study drug when post-dose monitoring is required [see Section 3.7.4])
- MSFC score
- SDMT
- Patient-Reported Outcome (PRO) instruments:
  - Fatigue Symptom and Impacts Questionnaire-RMS (FSIQ-RMS)
  - 36-Item Short Form Health Survey version 2 (SF-36v2™)
  - Work Productivity and Activity Impairment: MS (WPAI:MS).

In the absence of a clinical coordinator / study nurse, the above tasks will be performed by the principal investigator or a co-investigator.

3.7.6 MRI staff

The MRI staff will be responsible for performing the MRI investigations according to the study MRI manual (separate document). Original data will be exported to the Medical Image Analysis Center (MIAC), c/o University Hospital Basel, Switzerland, and primary data will be stored at the study site.

3.7.7 Local radiologist or neurologist with MRI expertise

The local radiologist or neurologist with MRI expertise will review the MRI images for safety purposes and will inform the principal investigator / treating neurologist of any findings of concern for the subjects' safety, including non-MS-related findings detected on the MRI scan. She/he will not communicate any efficacy-related MRI results (e.g., lesion counts) to study staff or to the subject, unless deemed necessary for maintaining safety of the subject. Significant findings, which, in view of the local radiologist or neurologist with MRI expertise, meet the definition of an AE must be assessed for seriousness, reported to the principal investigator / treating neurologist and recorded on the AE page of the eCRF. In the event of safety findings of potential clinical concern observed on the MRI scans at any visit during the study, the local radiologist or neurologist with MRI expertise will conduct further examination, as per local standard practice, to rule out or confirm the diagnosis. In case of suspicion of PML, the local radiologist or neurologist with MRI expertise should perform MRI as described in the Section 7.2.3. She/he may support the principal investigator in making a decision on eligibility of the subject prior to randomization by reviewing MRIs performed up to 15 months prior to screening used to assess the eligibility of the subject in the study.

The local radiologist will review the chest X-ray (CXR) images. At Visit 1 (Screening), the local radiologist will assess CXRs in order to exclude any subject with findings

suggestive of active or latent tuberculosis (TB; any CXR that had been performed within 90 days prior to Visit 1 (Screening) can be used; if available, there is no need to repeat CXR at Visit 1 [Screening]). At Visit 18 (EOT), the local radiologist will assess CXRs in order to characterize any pulmonary structural changes that could have occurred during treatment. She/he will inform the principal investigator / treating neurologist of any findings of concern for the subjects' safety. Significant findings, which, in view of the local radiologist, meet the definition of an AE, must be reported to the principal investigator / treating neurologist and recorded on the AE page of the eCRF.

Depending on site setting, the same local radiologist may review MRI images and CXR images, or a local radiologist or neurologist with MRI expertise may review MRI images and another local radiologist may review CXR images.

3.7.8 Ophthalmologist

The ophthalmologist will review and interpret the ophthalmological examinations and optical coherence tomography (OCT) assessments as scheduled in the study protocol [see Sections 7.3.6 and 7.3.7]. In the event of suspected clinically significant findings (e.g., macular edema), an unscheduled OCT examination should be performed by the ophthalmologist, and the principal investigator / treating neurologist will be notified for reporting of an AE. In the event of findings observed at any visit during the study, the ophthalmologist will conduct further examination, as per local standard practice, to rule out or confirm the diagnosis.

3.7.9 Pulmonary function laboratory technician or expert

The PFTs must be performed by experienced staff, such as a pulmonary function technician or expert, according to the American Thoracic Society (ATS) / European Respiratory Society (ERS) guidelines [Miller 2005a].

3.7.10 Dermatologist

A dermatologist is a physician, physician assistant, nurse practitioner, or any trained and qualified person per local regulations who will perform complete skin examinations as scheduled in the study protocol [see Section 7.3.12]. For non-physicians the role of a dermatologist must be within the scope of the national and/or local authorization.

Significant findings, which in view of the dermatologist meet the definition of an AE, must be reported to the principal investigator / treating neurologist and recorded on the AE page of the eCRF. In the event of findings observed at any visit during the study, the dermatologist will conduct further examination, as per local standard practice, to determine the diagnosis.

3.8 Study committees

3.8.1 Independent Data Monitoring Committee

An IDMC has overall responsibility for safeguarding the interests of subjects by reviewing unblinded safety and efficacy data obtained in the study and making appropriate recommendations based on the reported data, thus ensuring that the study is being conducted in accordance with the International Council for Harmonisation (ICH) - Good Clinical Practice (GCP) guidelines.

The IDMC is composed of physicians with relevant medical expertise in neurology, cardiology, infectious diseases, immunology and/or hematology, pulmonology, and a statistician, and will be fully operational prior to enrolment of the first subject into the study. The composition and operation of the IDMC are described in the IDMC charter.

The IDMC will perform a review of all available data including lymphocyte counts on an ongoing basis, starting with a cut-off corresponding to 12 weeks after randomization of the 20th subject in the study. The IDMC will continue to review data at regular intervals (approximately every 4 months) during the study. The IDMC will be responsible for recommending actions which may include:

- continuation of the study as per protocol,
- modifications to the study protocol to preserve subject's safety and/or data integrity,
- termination of the study at any time if major concerns arise regarding the safety of the study subjects.

No interim analysis is planned for the study. An Independent Statistical Analysis Center (ISAC), not otherwise involved in study conduct or statistical analysis, will generate all unblinded analysis reports, throughout the trial period, exclusively for review by the IDMC. The unblinded reports will be generated from blinded efficacy and safety data periodically transferred to the ISAC.

3.8.2 Ophthalmology Safety Board

An Ophthalmology Safety Board (OSB) composed of two independent ophthalmologists will review and evaluate in a blinded fashion any new or suspected cases of macular edema. Important findings will be communicated to the IDMC. The composition and operation of the OSB are described in the OSB charter.

3.8.3 MRI safety board

An MRI safety board composed of radiologists and/or neurologists with relevant MRI expertise will review and evaluate in a blinded fashion the brain MRIs selected by the local radiologists or neurologists with MRI expertise and exported to the MIAC in cases of a suspected opportunistic infection in the CNS. The MRI safety board will

communicate the results of the review to the site and important findings will be communicated to the IDMC. The composition and operation of the MRI safety board are described in the MRI safety board charter.

3.8.4 Major adverse cardiovascular events adjudication board

A major adverse cardiovascular events (MACE) adjudication board will review and evaluate in a blinded fashion the MACE reported in the study. The selection of adverse events that will be sent for adjudication will be based on a pre-defined list of preferred terms belonging to relevant Standardized MedDRA Queries related to cardiovascular and stroke and recorded as serious in the eCRF. For each AE sent for MACE adjudication, the MACE adjudication board will determine whether the event does or does not belong to one of the pre-specified categories including, but not limited to, cardiovascular death, myocardial infarction and stroke.

The composition and operations of MACE adjudication board will be described in the MACE adjudication board charter.

4 SUBJECT POPULATION

4.1 Subject population description

This study will enroll adult male and female subjects aged 18 to 55 years with established diagnosis of MS, as defined by the 2010 revision of McDonald Diagnostic Criteria [Polman 2011], with relapsing course from onset (i.e., RRMS and SPMS with superimposed relapses).

Subjects must have been treated with DMF for at least 6 months and have active disease after at least 3 months of DMF treatment, defined by at least one of the following features:

- At least one MS attack with onset within 12 months to 1 month prior to baseline EDSS assessment;
- At least one Gd+ lesion on an MRI of the brain or spinal cord, performed either within 12 months prior to Visit 1 (Screening) or during the pre-randomization period (MRI assessed at Visit 2 [Baseline] may be the qualifying scan);
- Presence of at least one new or one unequivocally enlarging T2 lesion on an MRI of the brain or spinal cord, assessed by comparing two MRI scans: the firstMRI scan must be performed within 15 months prior to Visit 1 (Screening) and after at least 3 months of DMF treatment; the second MRI scan must be performed prior to randomization (MRI assessed at Visit 2 [Baseline] may be used). The presence of at least one new or unequivocally enlarging T2 lesion has to be confirmed by the MRI central reading facility prior to randomization.

Enrolled subjects must be ambulatory with an EDSS score of up to 6.0 inclusive. The subjects may have been previously treated with other MS disease modifying therapies including IFN β-1a, IFN β-1b, glatiramer acetate, leflunomide, teriflunomide, or natalizumab.

Subjects with significant medical conditions or therapies for such conditions (e.g., cardiovascular, pulmonary, immunological, hepatic, ophthalmological) are not eligible to enter the study.

Eligible subjects must be able and willing to give informed consent for participation in the clinical study.

4.2 Rationale for the selection of the study population

RMS is the most frequent presentation of MS. Despite multiple therapies available, many subjects continue to experience relapses and accumulate disability.

Subjects with SPMS represent a significant unmet medical need for new therapeutic options. According to the US label [Tecfidera USPI], these subjects can also be treated with Tecfidera®, but they have generally been less studied and have often not been included in pivotal trials of medications approved for the treatment of RMS. For these reasons, it is important to also evaluate the benefit/risk profile of ponesimod in subjects who are treated with Tecfidera® and have SPMS with superimposed relapses.

The clinical relevance of McDonald 2010 Diagnostic Criteria, including subjects with only one attack, in the presence of supplementary clinical and/or MRI criteria as well as the value of early treatment in MS is widely recognized.

The study will enroll subjects treated with DMF with recent evidence of active disease as determined by clinical or imaging criteria. Inclusion criteria for active disease consist of prognostic factors that identify patients not responding satisfactorily to treatment, and thus require more efficacious therapies. The requirement for at least 6 months of DMF treatment prior to study entry aims to ensure:

- A better adherence to treatment during the study as most of flushing and gastrointestinal AEs which lead usually to treatment discontinuation occur during the initial months following DMF treatment,
- the evaluation of patient's response to DMF treatment occurs at an appropriate time to avoid delaying additional treatment or a change in treatment,
- most of the effect of DMF on lymphocyte counts is established.

Furthermore, the requirement for imaging or clinical signs of disease activity after at least 3 months of DMF treatment is to ensure additional treatment is justified [see Section 3.2].

The study will recruit adult subjects, restricted to subjects between 18 and 55 years of age, which is the age range used in most contemporary clinical trials in MS. In older MS subjects presence of non-MS-specific white matter lesions on MRI can make patient selection and evaluation of disease activity during the study more difficult. In addition, the treatment effect is expected to be less pronounced in older MS patients and other co-morbidities, which appear in older age, may make the MS assessment difficult. The age range of the study population will be representative of the general RMS population.

Subjects with an EDSS score 0–6.0 may have developed mild to moderate impairment but are still ambulatory. The clinical care and management of these subjects is compatible with their inclusion in clinical trials. Outcomes measured in this study require ambulatory subjects (e.g., MSFC performance). The subjects with EDSS above 6.0 will often have SPMS with declining disease activity and would therefore make the study population too heterogeneous for testing a disease-modifying potential of a new MS compound.

Subjects with underlying characteristics that increase their risk for an adverse outcome will be excluded from this study. In particular, subjects with low or unstable lymphocyte counts while on DMF, subjects who have been previously treated or have only recently discontinued certain immunosuppressive or lymphocyte-depleting drugs, and subjects with ongoing infections or immunodeficiency will be excluded from the study.

Subjects with significant cardiovascular, pulmonary, immunological, hepatic, or ophthalmological medical conditions or therapies are excluded since such conditions/therapies have the potential to put the subject at increased risk of adverse drug reactions, and/or interfere with the treatment effect, study assessment and interpretation of study results.

4.3 Inclusion criteria

For inclusion in the study, all of the following inclusion criteria must be fulfilled. It is not permitted to waive any of the criteria for any subject:

1. Signed informed consent prior to initiation of any study-mandated procedure.
2. Males and females aged 18 to 55 years (inclusive).
3. A woman of childbearing potential (WOCBP) is eligible only if the following applies:
   - must have a negative serum pregnancy test at Visit 1 (Screening) and a negative urine pregnancy test at Visit 2 (Baseline);
   - must agree to undertake monthly urine pregnancy tests during the study and up to 30 days after study treatment discontinuation;
   - must use reliable methods of contraception until 30 days after study treatment discontinuation as described in Section 4.5.2;

   Definition of WOCBP and the acceptable methods of contraception for this study are described in Section 4.5.

4. Presenting with a diagnosis of MS as defined by the revised (2010) McDonald Diagnostic Criteria for MS [see Appendix 2] with relapsing course from onset (i.e., RRMS, or SPMS with superimposed relapses).
5. Ongoing treatment with DMF for at least 6 months prior to Visit 1 (Screening).
6. Active disease after at least 3 months of DMF treatment defined by at least one of the following features:
   - At least one MS attack supported by objective neurological examination with onset within 12 months to 1 month prior to baseline EDSS assessment;
   - At least one Gd+ lesion on an MRI of the brain or spinal cord, performed either within 12 months prior to Visit 1 (Screening) or during the pre-randomization period (MRI assessed at Visit 2 [Baseline] may be the qualifying scan);
   - Presence of at least one new or one unequivocally enlarging T2 lesion on an MRI of the brain or spinal cord, assessed by comparing two MRI scans: the first MRI scan must be performed within 15 months prior to Visit 1 (Screening) and after at least 3 months of DMF treatment; the second MRI scan must be performed prior to randomization (MRI assessed at Visit 2 [Baseline] may be used). The presence of at least one new or one unequivocally enlarging T2 lesion has to be confirmed by the MRI central reading facility prior to randomization.
7. Ambulatory and with an EDSS score between 0 and 6.0 (inclusive) at Visit 1 (Screening) and Visit 2 (Baseline).
8. For subjects with ongoing treatment with DMF ≥ 12 months prior to screening:
   - Lymphocyte count ≥ 0.8×10^9/L (≥ 800/mm^3) at Visit 1 (Screening) and Visit 2 (Baseline) (assessed at least 3 weeks apart) with the lymphocyte count at Visit 2 (Baseline) > 0.5-fold and < 2.0-fold of the count at Visit 1 (Screening).

   For subjects with ongoing treatment with DMF ≥ 6 months (but < 12 months) prior to screening:
   - Lymphocyte count ≥ 0.9×10^9/L (≥ 900/mm^3) at Visit 1 (Screening) and Visit 2 (Baseline) (assessed at least 3 weeks apart) with the lymphocyte count at Visit 2 (Baseline) > 0.5-fold and < 2.0-fold of the count at Visit 1 (Screening).

4.4 Exclusion criteria

Subjects must not fulfill any of the following exclusion criteria. It is not permitted to waive any of the criteria for any subject:

Pregnancy and Breastfeeding

1. Lactating or pregnant women and women intending to become pregnant during the study.

MS disease

2. Presenting with a diagnosis of MS with progressive course from onset (i.e., PPMS or PRMS).

3. Evidence of a relapse of MS with onset within 30 days prior to baseline EDSS assessment or between baseline EDSS assessment and randomization.

Treatments

4. Treatment with the following medications:
   - Within 15 days prior to randomization:
     - β-blockers, diltiazem, verapamil, digoxin or any other anti-arrhythmic or HR lowering systemic therapy [non-exhaustive list of drugs provided in Appendix 3]
   - Within 30 days prior to randomization:
     - Adrenocorticotropic hormone (ACTH) or systemic corticosteroids (for any reason)
     - Vaccination with live vaccines
   - Within 90 days prior to randomization:
     - Plasmapheresis, cytapheresis
     - Intravenous immunoglobulin
     - Treatment with an investigational drug (within 90 days or five half-lives of the drug, whichever is longer), except biological agents (see below)
   - Within 180 days prior to randomization:
     - IFN β-1a, IFN β-1b, glatiramer acetate, or daclizumab
     - Other systemic immunosuppressive treatment (e.g., cyclosporine, sirolimus, azathioprine, methotrexate, mycophenolic acid, or cyclophosphamide)
     - Fingolimod (Note: prior treatment with fingolimod at any time is an exclusion criterion if discontinuation was due to an adverse event (AE) or poor tolerability)
   - Within 12 months prior to randomization:
     - Natalizumab
     - Non-lymphocyte-depleting experimental biological agents
   - Within 24 months prior to randomization:
     - Lymphocyte-depleting biological agents such as rituximab or ocrelizumab
     - Cladribine
   - Any time prior to randomization:
     - Alemtuzumab
     - Mitoxantrone
     - Ponesimod
     - Other investigational S1P modulators
     - Stem cell transplantation
     - Leflunomide or teriflunomide unless adequate and successful wash-out is documented.

Infection and Infection Risk

5. Ongoing known bacterial, viral or fungal infection (with the exception of onychomycosis and dermatomycosis), confirmed positive hepatitis B surface antigen test at Visit 1 (Screening; unless hepatitis B vaccination has occurred within 4 weeks prior to a positive screening test and a repeat hepatitis B surface antigen test performed ≥ 2 weeks after the initial test has been negative) or hepatitis C antibody tests at Visit 1 (Screening).
6. Congenital or acquired severe immunodeficiency or known human immunodeficiency virus (HIV) infection or positive HIV testing at Visit 1 (Screening).
7. Negative antibody test for varicella-zoster virus at Visit 1 (Screening).
8. Known PML infection or evidence of new neurological symptoms or MRI signs within 6 months prior to randomization which are compatible with a diagnosis of PML infection.

Malignancy

9. History or presence of malignancy (except for surgically excised basal or squamous cell skin lesions), lymphoproliferative disease, or history of total lymphoid irradiation or bone marrow transplantation.
10. Presence of pre-cancerous (e.g., actinic keratosis, atypical moles) or cancerous skin lesions (e.g., basal cell carcinoma, squamous cell carcinoma) at Visit 2 (Baseline).

Ophthalmologic

11. Presence of macular edema.

Cardiovascular

12. Any of the following cardiovascular conditions:
    - Resting HR < 50 bpm as measured by the pre-randomization 12-lead ECG on Day 1;
    - Myocardial infarction within 6 months prior to randomization or current unstable ischemic heart disease;
    - Cardiac failure (NYHA class III or IV) or any severe cardiac disease at the time of Visit 1 (Screening) or randomization;
    - History or presence of valvular heart disease associated with significant symptoms or hemodynamic change according to investigator judgment;
    - History or presence of cardiac rhythm disorders (e.g., sino-atrial heart block, symptomatic bradycardia, atrial flutter or atrial fibrillation, ventricular arrhythmias, cardiac arrest);
    - Presence of second-degree AV-block or third-degree AV-block or a QTcF interval > 470 ms (females), > 450 ms (males) as measured by 12-lead ECG at Visit 1 (Screening), Visit 2 (Baseline) or by the pre-dose ECG at Visit 3 (Randomization / Day 1);

- History of syncope associated with cardiac disorders;
- Systemic arterial hypertension not controlled by medication according to investigator judgment.

Metabolic

13. Type 1 or 2 diabetes which is poorly controlled according to investigator judgment or diabetes complicated with organ involvement such as diabetic nephropathy or retinopathy.

Pulmonary

14. Subjects with a clinically significant pulmonary condition including:
    - Asthma which is insufficiently controlled according to investigator judgment, or any hospitalization due to asthma exacerbation within 6 months prior to randomization;
    - Abnormal PFTs: FEV_1 or forced vital capacity (FVC) < 70% of the predicted normal value at Visit 2 (Baseline).
15. Active or latent TB, as assessed by CXR performed at Visit 1 (Screening) or within 90 days prior to Visit 1 (Screening), or IFN gamma release assay (QuantiFERON-TB-Gold®) at Visit 1 (Screening), except if there is documentation that the subject has received adequate treatment for latent TB infection or TB disease previously.

Hematology

16. Any of the following abnormal laboratory values at Visit 1 (Screening) or Visit 2 (Baseline):
    - Hemoglobin (Hb) < 100 g/L
    - White blood cells (WBC) count < 3.5×10^9/L (< 3500/mm^3)
    - Neutrophil count < 1.5×10^9/L (< 1500/mm^3)
    - Platelet count < 100×10^9/L (< 100,000/mm^3)

Hepatic

17. Known and documented moderate or severe hepatic impairment.
18. Any of the following abnormal laboratory values at Visit 1 (Screening) or Visit 2 (Baseline):
    - ALT/SGPT > 3 × ULN
    - AST/SGOT > 3 × ULN
    - Total bilirubin > 1.5 × ULN (unless in the context of known Gilbert's Syndrome)

Other categories

19. Contraindications for MRI such as:

- Pacemaker, certain metallic implants such as artificial heart valves, aneurysm/vessel clips and any metallic material in high-risk areas which are contraindicated for MRI according to the local procedures;
- Severe renal insufficiency defined as a calculated creatinine clearance < 30 mL/min (Cockroft-Gault);
- Claustrophobia if its nature or severity is prohibitive for performing MRI according to the investigator's judgment.

20. History of clinically significant drug or alcohol abuse.
21. Known allergy to any of the ponesimod formulation excipients.
22. Any other clinically relevant medical or surgical condition, which, in the opinion of the investigator, would put the subject at risk by participating in the study.
23. Subjects unlikely to comply with protocol, e.g., uncooperative attitude, inability to return for follow-up visits, or known likelihood of not completing the study including mental condition rendering the subject unable to understand the nature, scope, and possible consequences of the study.

4.5 Women of childbearing potential

4.5.1 Definition of childbearing potential

A woman is considered to be of childbearing potential unless she meets at least one of the following criteria:

- Previous bilateral salpingectomy, bilateral salpingo-oophorectomy or hysterectomy.
- Premature ovarian failure confirmed by a specialist.
- XY genotype, Turner syndrome, uterine agenesis.
- Post-menopausal, defined as 12 consecutive months with no menses without an alternative medical cause (ICH M3 definition).

4.5.2 Acceptable methods of contraception

WOCBP [definition see Section 4.5.1] must follow the below contraception scheme up to at least 30 days after study treatment discontinuation:

- Two methods of contraception, one from Group 1 and one from Group 2, defined as follows:
  - Group 1: Oral, implantable, transdermal or injectable hormonal contraceptives, which are associated with inhibition of ovulation, or intrauterine devices. Methods of contraception from Group 1 must be taken for at least 30 days prior to randomization.
  - Group 2: Female or male condoms, diaphragm or cervical cap.

  OR

- True abstinence from intercourse with a male partner only when this is in line with the preferred lifestyle of the subject. If true abstinence from intercourse with a male partner is chosen, then it must be started at latest at Visit 1 (Screening).
  OR
- Permanent female sterilization (tubal occlusion/ligation at least 6 weeks prior to Visit 1 (Screening).
  OR
- Sterilization of the male partner with documented post-vasectomy confirmation (prior to randomization) of the absence of sperm in the ejaculate.

Rhythm methods or the use of a condom by a male partner alone are not considered acceptable methods of contraception for this study.

The methods of contraception used (including non-pharmacological methods) must be recorded in the eCRF.

4.6 Medical history

4.6.1 General Medical History

Relevant medical history, as defined below, must be recorded in the eCRF:

- Significant chronic medical conditions at any time prior to the study (in the opinion of the investigator);
- Significant (in the opinion of the investigator) cardiovascular, pulmonary, liver, renal, eye disorder, and skin conditions, serious infections leading to hospitalization, and malignant tumors at any time prior to the study;
- Medically significant new acute medical conditions in the past 12 months prior to the study (in the opinion of the investigator);
- Smoking status at the time of entry in the study;
- Episodes of anaphylaxis, angioedema, flushing in the past 12 months.

Previous and concomitant therapies at pre-randomization, as defined in Section 5.2, will be recorded in the previous/concomitant medication page of the eCRF.

4.6.2 MS history

MS disease characteristics, as defined below and evidenced by documentation in the patient charts, will be recorded on the MS history page of the eCRF:

- Date of first known MS symptoms;
- Date of MS diagnosis;
- MS type (e.g., RRMS, SPMS);

- Symptoms associated with MS (e.g., optic neuritis, numbness, spasticity, tremor, fatigue, dizziness, dysfunctional bladder, cognitive problems, etc.) within the last 24 months prior to the study;
- Number of documented MS relapses within the last 12 months and between 12 and 24 months prior to the study. The onset date and the duration of the relapse when available, and treatment of these relapses (corticosteroids, ACTH, plasmapheresis etc.) will be reported;
- Number of documented Gd+ lesions per scan and number of documented T2 hyperintense lesions per scan on any MRI scan performed within 24 months prior to the study. Additionally, the condition of the MRI scan will be collected (e.g., scanner type, manufacturer and strength, the type of T1 sequence and number of slices used to detect Gd+, contrast agent used [Gd type], dose of contrast agent and time of injection, time of T1 sequence, the type of T2 sequence and number of slices used to detect T2 hyperintense lesions);
- Previous MS disease-modifying treatments received at any time in the past. For treatments received in the last 24 months prior to the study, start date, end date, dose, route, frequency, and reason for discontinuation will be recorded in the previous/concomitant medication page of the eCRF [see Section 5.2.2].

5 TREATMENTS

5.1 Study treatment

The treatment period consists of an up-titration period (from Day 1 to 14) and a maintenance period (Day 15 until EOT).

In the maintenance period, the study treatment consists of the daily administration of one tablet containing ponesimod 20 mg [see Section 5.1.8] (or matching placebo).

5.1.1 Investigational treatment and matching placebo: description and rationale

Ponesimod is supplied as its free base, in oral film-coated tablets at the doses of 2, 3, 4, 5, 6, 7, 8, 9, 10, and 20 mg.

During the up-titration period (Day 1 to 14) and the maintenance period, one tablet of ponesimod 2, 3, 4, 5, 6, 7, 8, 9, 10, or 20 mg (or matching placebo) will be taken orally o.d. The matching placebos for the doses of 2, 3, 4, 5, 6, 7, 8, 9, 10, and 20 mg are supplied as identical tablets, formulated with the same excipients but without the active ingredient, ponesimod. The 20 mg tablets and their matching placebo dispensed during the treatment maintenance are identical and indistinguishable and will be packaged in the same way.

The proposed add-on design will assess the superiority of ponesimod over placebo on a background of DMF therapy, an approved disease modifying therapy for the treatment of

RMS. The use of a placebo comparator is additionally justified by the provision of the option to switch to an alternative treatment or to remain on study treatment for subjects who meet at least one of the following conditions:

- Subjects have experienced a confirmed relapse;
- Subjects have experienced an event of 24-week CDA.

In any of the above cases, the subject will be asked to re-consent to continue receiving study treatment [see Section 13.3].

5.1.2 Study treatment administration

One tablet of ponesimod (or matching placebo) will be taken orally o.d. During the titration, the tablet will be taken in the morning, either with breakfast or before or after breakfast. During maintenance, the tablet will preferably be taken in the morning (either with breakfast or before or after breakfast). Overall, it is preferable that the tablet is taken each day at approximately the same time. The tablet will be swallowed as a whole. The last administration date and time of study treatment prior to the study visits and the administration date and time of study treatment on the days of visits will be recorded in the eCRF.

5.1.2.1 Titration

A gradual up-titration of ponesimod from a 2 mg starting dose to a 20 mg maintenance dose over a period of 14 days was found to successfully mitigate first-dose effects on HR and AV conduction. This 2-week up-titration regimen will be implemented in the study on initiation of treatment (Day 1) and on days of re-initiation of treatment following treatment interruption of more than 3 days [see Section 5.1.9].

Table 4 Dosing scheme

Treatment period	*Duration*	*Dose regimen in the ponesimod group*
Titration	Day 1 and 2	2 mg
Titration	Day 3 and 4	3 mg
Titration	Day 5 and 6	4 mg
Titration	Day 7	5 mg
Titration	Day 8	6 mg
Titration	Day 9	7 mg
Titration	Day 10	8 mg
Titration	Day 11	9 mg
Titration	Day 12 to 14*	10 mg
Maintenance	Day 15 until EOT	20 mg

* Visit 4 is to take place at Day 15 ± 1 day.
EOT = End-of-Treatment; NA = not applicable.

Study treatment up-titration, other than described above, is prohibited. Study treatment down-titration is not foreseen in any situation and is prohibited.

5.1.2.2 Maintenance

On the day of the study visits, study treatment must be administered only after the completion of the pre-dose safety assessments (diastolic BP [DBP], systolic BP [SBP], ECGs, PFTs, laboratory tests) and PK sampling (if scheduled).

5.1.3 Treatment assignment

A total of 600 eligible subjects will be randomized in a 1:1 ratio to ponesimod 20 mg or placebo, stratified by baseline EDSS score (EDSS ≤ 3.5, EDSS > 3.5).

Each of the study sites will be assigned a unique site number, and every subject will receive a unique screening number (= subject number), which identifies the subject throughout the study. After having confirmed the eligibility of the subject and informed consent has been signed, the investigator/delegate contacts the Interactive Response Technology system (IRT) at Visit 3 to randomize the subject. The IRT assigns a randomization number to the subject, and assigns the treatment kit number which matches the treatment arm assigned by the randomization list to the randomization number.

The randomization list is generated by an independent Contract Research Organization (CRO) and kept strictly confidential.

5.1.4 Blinding

5.1.4.1 Study drug material related blinding

This study will be performed in a double-blind fashion. The investigator and study staff, the subjects, the monitors, Actelion staff, and CROs involved in the conduct of the study will remain blinded to the study treatment until study closure. Actelion staff responsible for clinical trial supply distribution may need to be unblinded to ensure adequate distribution of study treatment. These persons will be clearly identified, their unblinding will be documented in the trial master file and they will not take part in any Clinical Trial Team meetings after the IRT is activated.

Until the time of unblinding for final data analysis, the randomization list is kept strictly confidential, and accessible only to authorized persons, who are not involved in the conduct of the study.

The investigational treatment and its matching placebo are indistinguishable and all subject's kits will be packaged in the same way.

5.1.4.2 Functional blinding

First-dose effects on HR and AV conduction, and lymphocyte count reduction have been identified as potentially unblinding information. Access to this information by the site's staff and sponsor's study team will be restricted. The following measures will be taken to ensure that the efficacy assessments (i.e., EDSS/FS) are done independently and that cardiac safety assessments, and lymphocyte count assessments are performed and reviewed without potential to introduce a bias:

- The primary endpoint (ARR) and the first secondary endpoint (disability accumulation) are based on the evaluations of the EDSS and FS scores, assessed by an efficacy assessor, not involved in any other aspects of patient care and management throughout the study.
- The subject will be instructed not to discuss AEs (other than those required for EDSS assessments), HR, pulmonary function and/or concomitant medications and any other medical event that have the potential of revealing the treatment allocation with the efficacy assessor.
- The principal investigator / treating neurologist and first-dose administrator evaluating cardiac safety assessments must not discuss any issues related to patient care and management unless mandated for reasons of subject safety. On Day 1 and on the first day of re-initiation of study drug when post-dose monitoring is required, significant findings, which in view of the first-dose administrator meet the definition of an AE, have an onset after the study drug intake and are resolved at the time of discharge of the subject, must be recorded directly on the AE page of the separate eCRF by the first-dose administrator / delegate. These AEs, the ECGs interpretation

reports and BP data collected on these days will not be visible to any of the blinded study personnel at the study site. During the study, all clinical records related to first dose data (e.g., 12-lead ECG printouts, BP results, AEs, etc.) must be filed in a separate medical chart only visible to the first-dose administrator. At the sponsor's level, these events and ECGs and BP data will be entered into a separate eCRF and will only be visible to the site monitor and to the first-dose monitor. The site monitor will not reveal any potentially unblinding information to the rest of the site team or to the sponsor study team and will only discuss any of these data with the first-dose administrator or the first-dose monitor. The first-dose monitor is a role created by the sponsor for medical and scientific review of the BP and 12-lead ECG data assessed during cardiac monitoring after first dosing or after re-initiation. In order to keep the rest of the sponsor's team blinded the first-dose monitor will not reveal any potentially unblinding information to the site team or to the rest of the sponsor study team and will be clearly identified. Her/his access to potentially unblinding information will be documented in the trial master file.

- Results of the total WBC count and total lymphocyte count assessed during the double blind treatment period will not be communicated to the sites, sponsor, and CRO involved in the conduct of the study unless one of the below applies:
  - A total lymphocyte count $< 0.2 \times 10^9$/L is recorded by the central laboratory. In this event, an alert containing the total lymphocyte count result will be sent to the principal investigator / treating neurologist and the sponsor. FU monitoring must be provided as described in Sections 5.1.12.2 and 7.3.13.
  - A WBC count $> 20 \times 10^9$/L or a lymphocyte count $> 8.0 \times 10^9$/L is recorded by the central laboratory. In this event, an alert containing the total WBC or lymphocyte count result (as applicable) will be sent to the principal investigator / treating neurologist and the sponsor.
  - A total lymphocyte count decrease of > 50% from the value recorded at Visit 5 (Week 4) associated with a total lymphocyte count $< 0.5 \times 10^9$/L (< 500 cells/mm^3) is recorded at 2 consecutive scheduled visits after Visit 5 (Week 4). In this event, an alert containing the lymphocyte count result will be sent to the principal investigator / treating neurologist and the sponsor.
  - A total lymphocyte count $< 0.5 \times 10^9$/L is observed at FU. In this event, an alert containing the total lymphocyte count result will be sent to the principal investigator / treating neurologist. Discontinuation of DMF treatment should be considered in accordance with prescribing information [Tecfidera USPI, Tecfidera SmPC].
  - WBC and total lymphocyte counts measured at any of the visits in the PTOP. For subjects who have entered PTOP following study drug discontinuation,

lymphocyte count values recorded after entering the PTOP will be visible to the principal investigator / treating neurologist.

- All MRI scans collected for the assessment of efficacy endpoints are evaluated by a central reading center (MIAC) also in a fully blinded fashion.

Under no circumstances should potentially unblinding information be shared with the efficacy assessor.

5.1.5 Unblinding

5.1.5.1 Unblinding for final analyses

Full randomization information will be made available for data analysis only after database closure in accordance with Actelion standard operating procedures (SOPs).

5.1.5.2 Unblinding for IDMC review

An ISAC, not otherwise involved in the design, conduct and analysis of the study, will have access to the randomization code in order to prepare unblinded reports for review by the IDMC (for IDMC review meetings during the course of the trial). The randomization code will be made available to the ISAC in accordance with the sponsor's SOPs.

5.1.5.3 Unblinding for suspected unexpected serious adverse reactions

When a suspected unexpected serious adverse reaction (SUSAR) occurs for a subject participating in the study, Actelion Global Drug Safety will request the unblinding of the treatment assignment. The randomization code will not be communicated to the site staff or to the Actelion study team; unblinded SUSAR information will be anonymized and provided to Actelion Global Drug Safety, respective health authorities and Institutional Review Boards (IRBs) / Independent Ethics Committees (IECs) only. SUSARs will be reported to investigators in a blinded fashion.

5.1.5.4 Emergency procedure for unblinding

The investigator, study staff and sponsor staff must remain blinded to the subject's study treatment assignment. The identity of the study treatment may be revealed only if the subject experiences a medical event, the management of which would require knowledge of the blinded treatment assignment. In this case, the investigator can receive the unblinded randomization code for study treatment allocation through the IRT. In these situations, the decision to unblind resides solely with the investigator. Whenever it is possible and if it does not interfere with (or does not delay) any decision in the best interest of the subject, the investigator is invited to discuss the intended unblinding with Actelion.

The occurrence of any unblinding during the study must be clearly justified and explained by the investigator. In all cases, Actelion must be informed as soon as possible before or after the unblinding.

The circumstances leading to unblinding must be documented in the Investigator Site File (ISF) and eCRF.

5.1.6 Study treatment supply

Manufacture, labeling, packaging, and supply of study treatment will be conducted according to Good Manufacturing Practice (GMP), GCP, and any local or national regulatory requirements.

All study treatment supplies are to be used only in accordance with this protocol, and not for any other purpose.

5.1.6.1 Study treatment packaging and labeling

5.1.6.1.1 Study treatment packaging

Study treatment is provided as tablets and supplied in childproof blister packs.

5.1.6.1.2 Study treatment labeling

Study treatment is labeled to comply with the applicable laws and regulations of the countries in which the study sites are located.

5.1.6.2 Study treatment distribution and storage

Study treatment supplies must be kept in an appropriate, secure area and stored according to the conditions specified on the label.

5.1.6.3 Study treatment dispensing

The subjects will receive sufficient study treatment to cover the period up to the next scheduled visit. Alternatively, scheduled study medication dispensing/return procedures may be adapted according to the site practice (i.e., if the subject comes to the investigational site more frequently than the scheduled visits, it is then possible to dispense medication in smaller quantities). Subjects are asked to return all used, partially used and unused study treatment blister packs and unused tablets at each visit. If the subject forgets to bring the remaining study treatment to a study visit, she/he must be instructed not to take any tablet from the remaining study treatment and to bring it at the next visit.

An accurate record of the date and amount of study treatment dispensed to each subject must be available for inspection at any time.

5.1.6.4 Study treatment return and destruction

On an ongoing basis and/or on termination of the study, the monitor will collect used and unused subject kits and tablets, which will be sent to the warehouse where Actelion or a deputy will check treatment reconciliation.

5.1.7 Study treatment accountability and compliance

5.1.7.1 Drug accountability

Records of study treatment dispensed and returned, dosages administered, and intervals between visits are kept during the study. Study treatment accountability must be performed by the study staff on the day of the visit and before providing further study treatment, in order to ensure that the subject is compliant with study requirements. Study treatment accountability is checked by the monitor during site visits and at EOS.

5.1.7.2 Drug compliance

Subjects' compliance with study treatment intake will be recorded using an electronic diary. On each day, the subjects will be asked to enter the date, time, number of tablets taken, and the unique blister-card identifying number from which the tablets were taken. In addition, during the up-titration, the position of the well on the blister card will be recorded in order to check that tablets were taken in the correct sequence [see gradual up-titration in Section 5.1.2.1].

The electronic diary will give feedback and instruct the subject to contact the investigator as soon as possible before taking next dose, whenever one of the following is observed:

- Dose is taken in an incorrect sequence during the up-titration (e.g., tablet at position 6 taken before tablet at position 4 on the blister card);
- 1 or more tablets are missed during the up-titration;
- 4 or more doses are missed during the maintenance.

Additionally, feedback will be given to the subject whenever 1 to 3 dose(s) are missed during the maintenance.

At each visit, the site personnel will crosscheck the subject's compliance as indicated in the electronic diary against the study treatment accountability [see Section 5.1.7.1]. Subjects will be asked to explain the observed discrepancies. Interruptions with known dates will be recorded accordingly in the study treatment log of the eCRF [see Section 5.1.8]. Study treatment intake requirements will be re-explained to the subject each time an interruption is observed.

5.1.8 Study treatment dose adjustments and interruptions

Study treatment up-titration, other than described in Section 5.1.2.1, is prohibited. Study treatment down-titration is not foreseen in any situation and is prohibited.

Study treatment interruption should be avoided. If study treatment intake is interrupted by the subject for any reason, she/he must immediately inform the investigator / treating neurologist.

Study treatment may be temporarily interrupted (i.e., re-start of the study treatment is possible) in response to an AE, a diagnostic or therapeutic procedure, a laboratory abnormality, or for administrative reasons. Study-specific criteria for interruption of study treatment are described in Section 5.1.12. The duration of a temporary interruption is determined by the investigator and is not limited in time. At maximum, it will last until the investigator deems necessary to require another MS treatment for the subject, which would end the temporary interruption and trigger permanent discontinuation of the study treatment.

Detailed guidance on how to re-initiate study treatment in the event of drug interruption is provided in Section 5.1.9.

Study treatment dose adjustments/interruptions must be recorded in the eCRF.

5.1.9 Guidance for re-initiation of study treatment in the event of study treatment interruption

If study drug intake is interrupted by the subject for any reason, she/he must immediately inform the principal investigator / treating neurologist.

The following guidance is provided for re-initiation of investigational study drug after study drug interruptions.

A schematic overview of the re-initiation algorithm is given in Figure 2.

Depending on the day, time, and duration of study drug interruption, the following procedures will be followed.

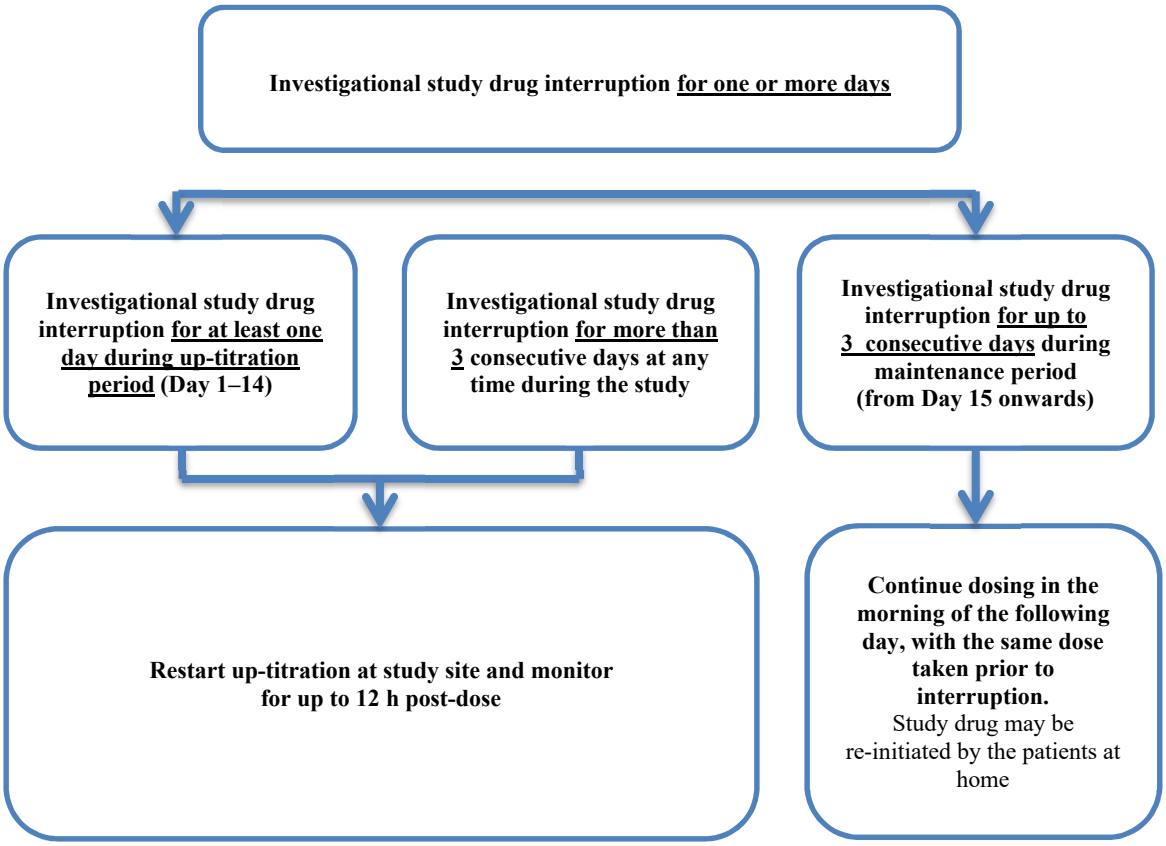
- If the subject missed taking the dose in the morning:
  - The dose should be taken at any time on the same day.
  - Regular dosing should be resumed with the morning dose on the following day.
- If the subject missed taking the dose for one or more days during treatment up-titration (from 1 to 14 days after the first-dose of initiation/re-initiation of the study drug):
  - The original up-titration scheme needs to be re-applied, with the initial dose and gradual up-titration steps for 14 days after the first-dose of re-initiation of the study drug.
  - On the day of the re-initiation of investigational study drug, the subject must be monitored for at least 4 hours post-dose by the first-dose administrator,

following the cardiac assessment schedule and applying the discharge criteria as described for Day 1 [see Section 5.1.10].

- If the subject missed taking the dose for up to three consecutive days during treatment maintenance (from Day 15 onwards after the first dose of initiation/re-initiation of the study drug):
  - Dosing should be resumed in the morning, with the same dose taken prior to study drug interruption.
  - Study drug intake may be re-initiated by the subject at home.
  - Subjects must be instructed to contact the investigator immediately if they experience any symptoms of bradycardia (e.g., dizziness, vertigo, syncope).
- If the subject missed taking the dose for four or more consecutive days during treatment maintenance (from Day 15 onwards after the first dose of initiation/ re-initiation of the study drug):
  - The original up-titration scheme for the investigational study drug needs to be re-applied.
  - On the day of the re-initiation of treatment, the subject must be monitored for at least 4 hours post-dose by the first-dose administrator, following the cardiac assessment schedule and applying the discharge criteria as described for Day 1 [see Section 5.1.10].

Whenever the investigator / treating neurologist becomes aware that the subject did not report having missed the study drug intake for one or more days during up-titration or four or more days during maintenance and has continued dosing, the subject should be interviewed by the investigator / treating neurologist for any symptoms related to bradycardia and further examinations (e.g., 12-lead ECG, BP measurement) may be performed at the discretion of the investigator / treating neurologist. Based on an assessment of the clinical findings and the likelihood of subject's adherence to treatment, the investigator / treating neurologist will determine whether the patient can continue regular dosing, needs to re-initiate treatment, or should permanently discontinue treatment.

Figure 2 Algorithm for management of treatment



5.1.10 Criteria for discharge from cardiac monitoring on Day 1, and on the first day of re-initiation of the investigational study drug following treatment interruptions

Discharge from cardiac monitoring on Day 1, and on the first day of re-initiation of study drug following drug interruptions, can occur at the earliest when the evaluation of the pre-dose and all the hourly (± 15 minutes) post-dose ECGs until 4 hours post-dose have been obtained, provided the following criteria have been met:

- ECG-derived resting HR > 45 bpm, and if HR < 50 bpm it must not be the lowest value post-dose;
- SBP > 90 mmHg;
- QT corrected for heart rate on the basis of Fridericia's formula (QTcF) < 500 ms and QTcF increase from pre-dose < 60 ms;

- No persisting significant ECG abnormality (e.g., AV-block second or third degree) or ongoing AE requiring continued hospitalization or prohibiting study continuation as an out-patient.

If the subject does not meet the discharge criteria (as described above) at 4-hour post-dose, the subject should be carefully monitored for an additional period of up to 8 hours, and a 12-lead ECG and a BP measurement must be performed every hour. The subject can be discharged from cardiac monitoring as soon as the above criteria are met.

Should the subject not meet the criteria for discharge from cardiac monitoring at 12 hours post-dose, she/he must be permanently discontinued from study drug. Subjects who are permanently discontinued should not be discharged from cardiac monitoring before vital signs return to near baseline values or until there is no persisting ECG abnormality (e.g., AV-block second degree or higher), ongoing AE requiring continued cardiac monitoring, or until medically indicated.

5.1.11 Premature discontinuation of study treatment

The decision to prematurely discontinue study drug may be made by the subject, the investigator, or Actelion. The main reason and whether discontinuation of study drug is the decision of the subject, the investigator, or Actelion, must be documented in the eCRF.

A subject has the right to prematurely discontinue study drug at any time by withdrawal from study drug only or by withdrawal from any further participation in the study (i.e., premature withdrawal from the study, see Section 9.3).

The investigator should discontinue study drug for a given subject if the risks outweigh the potential benefits.

Study drug may be discontinued in response to an AE, lack of efficacy (including disease progression, treatment failure, worsening of subject's condition), a protocol deviation (including eligibility failure, non-compliance with study requirements), a diagnostic or therapeutic procedure, a laboratory abnormality, or for administrative reasons.

Study-specific criteria for discontinuation of study drug are described in Section 5.1.12.

A subject who prematurely discontinues study drug is NOT considered as withdrawn from the study and will be followed in the PTOP until up to 60 weeks after the randomization of the last subject, provided that the subject's consent for this limited participation in the study has not been withdrawn.

Subjects will be asked to return for an EOT visit preferably 1 day after last dose of study drug, but no later than 7 days after last dose of study drug. Subjects will be asked to attend FU visit (FU) 30 days after last dose of study drug. Subjects participating in the

lymphocyte subset sub-study will have an additional FU visit approximately 7 days after the last dose of study drug (FU7d). Then, subjects will attend 12-weekly visits as part of the PTOP until EOS. The assessments that are performed at each visit are described in the 'Abbreviated visit and assessment schedule for subjects who prematurely discontinued study treatment' [Table 3].

A subject who prematurely discontinues study treatment and withdraws consent to participate in any further study assessments is considered as withdrawn from the study. Subjects who die or are lost to follow-up [see Section 9.2] are also considered as withdrawn from the study. Withdrawal from the study and follow-up medical care of subjects withdrawn from the study is described in Sections 9.2 and 9.4, respectively.

5.1.12 Study-specific criteria for interruption / premature discontinuation of study treatment

5.1.12.1 Cardiovascular

Subjects **must** be permanently discontinued from study drug if:

- the following change in HR is observed at any time throughout the study, as documented by 12-lead ECG:
  - HR < 30 bpm, or
  - HR < 40 bpm is sustained for at least 1 hour and is associated with symptoms of bradycardia (e.g., syncope, dizziness, or vertigo), or
- QTcF > 500 ms is observed at any time throughout the study, as documented by 12-lead ECG, or
- the subject does not meet the criteria for discharge from cardiac monitoring on Day 1, or on the first day of re-initiation of study drug following drug interruptions after 12 hours post-dose monitoring, or
- the subject needs to receive systemic chronic treatment with β-blockers, diltiazem, verapamil, digoxin, or any other anti-arrhythmic or HR lowering therapy [non-exhaustive list of drugs provided in Appendix 3].

FU monitoring will have to be provided until the event resolves, the condition is stable, or the change is regarded as no longer clinically relevant.

Continuous ECG monitoring is recommended for subjects who meet study drug discontinuation criteria related to bradycardia or other arrhythmia. Subjects who are permanently discontinued should not be discharged from the monitored setting before vital signs return to near baseline values and until there is no persisting ECG abnormality (e.g., QT prolongation, AV-block second degree or higher) or ongoing AE requiring (continued) cardiac monitoring, or until medically indicated. Any clinically relevant

finding meeting the definition of an AE will be recorded accordingly in the respective eCRF.

In case of any signs and symptoms of bradycardia or other arrhythmia (e.g., syncope, palpitations, etc.), at any time during the study treatment, the first-dose administrator and/or a cardiologist may be consulted. In case a cardiac origin is suspected, permanent discontinuation of study drug should be considered.

In case subjects experience sustained *de novo* or worsening of pre-existing hypertension during the course of the treatment with the study drug which, in the opinion of the investigator, cannot be adequately controlled by medications, study drug should be permanently discontinued.

5.1.12.2 Hematological abnormalities

Subjects **must** be permanently discontinued from study drug at any time throughout the study if one of the following occurs:

- Confirmed total lymphocyte count decrease of > 50% from the value recorded at Visit 5 (Week 4) associated with a total lymphocyte count $< 0.5 \times 10^9$/L (< 500 cells/mm^3) at 2 consecutive scheduled visits after Visit 5 (Week 4)
- Confirmed total lymphocyte count $< 0.2 \times 10^9$/L (< 200 cells/mm^3)

Confirmation will be done as follows:

Whenever one of the above conditions is met, an alert will be sent by the central laboratory to the principal investigator and the sponsor. The principal investigator will immediately contact the subject and ask her/him to return to the site either within 2 weeks if the total lymphocyte count is $< 0.5 \times 10^9$/L but $\geq 0.2 \times 10^9$/L or within 48 hours at the latest if the total lymphocyte count is $< 0.2 \times 10^9$/L to repeat the test at trough level (pre-dose) by the central laboratory (unless the clinical situation mandates immediate local testing). If the repeat test confirms that one of the above conditions is met, then the study drug must be discontinued.

Lymphocyte counts must be monitored at least once a week by the central laboratory until the lymphocyte count has returned to $\geq 0.8 \times 10^9$/L or ≥ 80% of the value recorded at Visit 2 (Baseline). Any clinically relevant finding meeting the definition of an AE will be recorded accordingly in the eCRF.

5.1.12.3 General guidance for monitoring of subjects for opportunistic infections during treatment

Heightened vigilance is required for opportunistic infections caused by virus, fungi and bacteria. In the event of an opportunistic infection, the subject must permanently

discontinue the study drug and must be referred to an expert in infectious diseases for further examination and treatment. Early antiviral treatment will be considered.

Opportunistic infections caused by the reactivation of human herpes viruses (herpes simplex viruses, varicella-zoster virus, Epstein-Barr virus, cytomegalovirus) may be primarily associated with neurological symptoms. The neurotropic herpes viruses (herpes simplex and varicella-zoster) are frequent human pathogens and their reactivation can cause serious infections of the CNS such as encephalitis and meningitis. The most frequent characteristics of these infections are an acute onset, associated with fever, headache, confusion, personality changes, and disorientation. Any suspicion of these infections must lead to immediate interruption of study drug treatment and to early initiation of antiviral treatment [Steiner 2007].

The thorough physical examination and blood tests on the routine visits should be focused on any potential sign of skin, mucosal surfaces, gastrointestinal tract, liver, hematological etc., abnormality and organ dysfunction suggesting a potential opportunistic infection.

Subjects should be advised to be proactive and alert in reporting any unusual neurological symptoms and any signs and symptoms indicative of systemic infections, such as fever, malaise and fatigue [Kappos 2007].

The diagnostic workup and management of subjects with suspicion of opportunistic infection accompanied by CNS symptoms is described in Section 5.1.12.3.1.

5.1.12.3.1 Guidance for screening, exclusion and on-treatment monitoring of subjects for progressive multifocal leukoencephalopathy / other opportunistic CNS infections

Subjects with known PML infection or evidence of new neurological symptoms or MRI signs within 6 months prior to randomization, which are compatible with a diagnosis of PML infection, will not be eligible for the study. Subjects in whom suspicion of PML or other opportunistic CNS infections has been raised after randomization by new or worsening neurological symptoms combined with results of objective neurological exam or by MRI findings will have the study drug and DMF interrupted, and will be referred to the local MRI department to perform MRI as described in Section 7.2.3 which will be reviewed by the MRI safety board [see Section 3.8.3]. The suspicion of PML or other opportunistic CNS infections will be raised if the subjective and objective findings cannot readily be explained by the subject's MS (e.g., a relapse) or another known condition (e.g., abnormal speech due to a dental intervention or limb weakness due to a trauma) not corresponding to exclusion criteria or if signs of PML / other opportunistic CNS infection are present on MRI. The additional diagnostic workup may include lumbar puncture for cerebrospinal fluid (CSF) analysis including test for JCV in CSF. If, based on the results

of the MRI safety board review, other diagnostic tests and clinical symptoms and signs, the suspicion of PML or other opportunistic CNS infections can be ruled out, the investigator will consider re-start of the study drug if the risk/benefit is still considered positive for the subject and if criteria for permanent discontinuation of the study drug have not been met. **NB:** In subjects with suspicion of acute CNS infection, early lumbar puncture and antiviral treatment should be considered.

Progressive multifocal leukoencephalopathy (PML) is an opportunistic infection of the CNS that can lead to death or severe disability. Active replication of the human polyoma JCV in glial cells of the brain, causing lytic death in oligodendrocytes, is the underlying pathobiology of PML. The infection typically arises in severely immunocompromised subjects, e.g., those with HIV infection, malignant disease, or transplanted organs. People with autoimmune rheumatic diseases, especially systemic lupus erythematosus, are also at higher risk of PML [Kappos 2011].

As mentioned in Section 3.4.2, MS subjects treated with natalizumab are at increased risk of developing PML. In addition to natalizumab, cases of PML have been reported in subjects treated with various drugs, usually in combination with corticosteroids, including alkylating agents (e.g., cyclophosphamide, carmustine, and dacarbazine), purine analogues (e.g., fludarabine, cladribine, and azathioprine), immunosuppressants (e.g., cyclosporin, tacrolimus, sirolimus, and mycophenolate), and therapeutic monoclonal antibodies (e.g., rituximab, infliximab, etanercept, basiliximab, daclizumab, efalizumab, alemtuzumab, and muromonab-CD3) [Kappos 2011]. Sporadic cases of PML have occurred in patients treated with DMF [FDA 2015] and with fingolimod [Gilenya USPI]. The diagnosis of PML is based on a combination of clinical, imaging and laboratory findings according to the consensus statement from the American Academy of Neurology published in 2013 [Berger 2013]. Among the common clinical findings are motor weakness, gait abnormalities, visual field deficits, speech and language disturbances, and incoordination. Sensory loss, seizures, headache, and diplopia occur less frequently. Although all these symptoms can be due to MS relapse, the time course often helps to distinguish PML from MS. While MS relapses tend to occur over hours to days, normally stabilize, and can resolve without treatment, PML tends to be progressive over days to weeks [Chalkley 2013].

In a retrospective study of MRI scans in 40 patients with MS treated with natalizumab and PML [Yousry 2012] the characteristic pattern of early PML lesions included:

- Subcortical localization
- MRI signal: T2- and DW-hyperintense and T1-hypointense lesions;
- Lesion border: sharp toward the grey matter and ill-defined toward the white matter.

In all but one patient the discrimination between new PML lesions and MS lesions could be done without problems.

The most useful laboratory finding for PML is demonstrating the presence of JCV in CSF using polymerase chain reaction (PCR). The sensitivity of the newer ultrasensitive techniques is 95% and the method is highly specific. However, a negative JCV PCR result should not exclude a possible diagnosis of PML.

Based on these three criteria (clinical, MRI and CSF), the diagnostic certainty of PML can be categorized into definite (all three criteria positive), probable (two out of three criteria positive), possible (one out of three criteria positive) and not PML (all criteria negative). Subjects with probable PML should be managed as those with definite PML.

Case 1: At Visit 1 (Screening).

The subjects in whom the suspicion of PML / other opportunistic CNS infection has been raised by the investigator based on evidence of new neurological symptoms or MRI signs within 6 months prior to Visit 1 (Screening), which are compatible with a diagnosis of PML infection, will have MRI performed as described in Section 7.2.3, and reviewed by the MRI safety board. Based on the relevant clinical findings, results of MRI review, and, if justified and indicated, CSF analyses, the investigator will determine the probability of PML. Only subjects in whom PML/other opportunistic CNS infection can be ruled out will be eligible for the study. Subjects with possible PML at Visit 1 (Screening) in whom this diagnosis has been later ruled out will be eligible for a single re-screening.

Case 2: Subject randomized in the study, coming to scheduled visits.

The subjects in whom the suspicion of PML/other opportunistic CNS infection has been raised by the investigator as described above, will have the study drug and DMF interrupted and will have MRI performed as described in Section 7.2.3, and the site can ask for a review of the MRI by the MRI safety board [see Section 3.8.3]. Further diagnostic workup (such as lumbar puncture for JCV) will be performed at investigator's discretion. Based on the relevant clinical and nonclinical findings, including the MRI evaluation by the MRI safety board if applicable, the investigator will determine the probability of PML/other opportunistic CNS infection. Subjects in whom PML/other opportunistic CNS infection can be ruled out will be eligible for re-start of the study medication. Subjects with definite or probable PML or diagnosis of other opportunistic CNS infection will have the study drug and DMF permanently discontinued and will be managed according to the local practice (e.g., immune reconstitution and high dose corticoids). Subjects with possible PML/other opportunistic CNS infection will be observed off-study drug and assessed with repeated clinical, imaging and/or laboratory exams at the investigator's discretion until the PML/other opportunistic CNS infection

has been ruled out or confirmed. The study drug may be re-started if PML / other opportunistic CNS infection has been ruled out at a later time point.

Case 3: Subject randomized in the study, reporting new or worsening neurological symptoms outside the scheduled visits.

In case a subject contacts the investigator because of new or worsening neurological symptoms, the investigator should see the subject at an unscheduled visit as soon as possible and perform a full neurological exam in order to decide if the symptoms can be explained by a relapse or can be otherwise explained, or if suspicion of PML/other opportunistic CNS infection should be raised. If the findings indicate a relapse, the subject will be referred to the efficacy assessor for EDSS assessment. If the findings raise suspicion of PML/ other opportunistic CNS infection, the subject will have the study drug and DMF interrupted and will have MRI performed as described in Section 7.2.3, and the site can ask for a review of the MRI by the MRI safety board. Further diagnostic workup (such as lumbar puncture for JCV) will be performed at investigator's discretion. The further process will be the same as for Case 2 above.

Case 4: MRI from a scheduled visit shows findings not typical for MS.

In case the MRI at a scheduled visit shows signs atypical for MS, detected by the neuroradiologist or during the central review by the MIAC, the site and the sponsor will be alerted and the site can ask for a review of the MRI by the MRI safety board. The subject will be invited for an unscheduled visit at which the investigator will interview the subject for neurological signs and symptoms and perform a full neurological exam. In the event of suspicion of PML, the study drug will be interrupted. Based on the full evaluation of the subject, relevant clinical findings and results of any additional investigations, such as lumbar puncture for JCV, the investigator will determine the probability of PML/other opportunistic CNS infection. Subjects in whom PML/other opportunistic CNS infection can be ruled out will be eligible for re-start of the study medication. Subjects with definite or probable PML or diagnosis of other opportunistic CNS infection will have the study drug and DMF permanently discontinued and will be managed according to the local practice (e.g., immune reconstitution and high dose corticoids). Subjects with possible PML/other opportunistic CNS infection will be observed off-study drug and assessed with repeated clinical, imaging and/or laboratory exams at the investigator's discretion until the PML/other opportunistic CNS infection has been ruled out or confirmed. The study drug may be re-started if PML / other opportunistic CNS infection has been ruled out at a later time point.

5.1.12.4 Respiratory system

In case of abnormal spirometry results or persistent respiratory symptoms (e.g., dyspnea), the subject will be closely observed, spirometry will be repeated, and study drug discontinuation should be considered, according to the guidance provided in Table 5.

Table 5 Guidance for subject monitoring and discontinuation for PFT decrease and persistent respiratory AEs

Item	Parameter	Guidance
1	If: > 30% decrease from the study baseline FEV_1 and/or FVC.	Repeat PFT within the next 2 weeks or earlier if clinically indicated. See item 1a, 1b.
1a	If at repeat PFT: > 30% decrease from the study baseline FEV_1 and/or FVC and, in the opinion of the investigator, this change is clinically significant.	Discontinue study drug and perform FU PFTs.
1b	If at repeat PFT: ≤ 30% decrease from the study baseline FEV_1 and/or FVC and the subject does not have respiratory symptoms (e.g., cough, dyspnea).	Resume regular PFTs schedule.

AE = adverse event; FEV_1 = forced expiratory volume in 1 second; FU = follow-up; FVC = forced vital capacity; PFT = pulmonary function test.

If clinically significant, persistent respiratory AEs (e.g., dyspnea) are reported, PFTs must be performed and study drug may be interrupted at the discretion of the investigator. In case of study drug interruption, the subject will be closely observed, FU PFTs will be performed, and further diagnostic work-up and consultation with a pulmonologist or other specialist should be considered according to local practice and the clinical situation. Following study drug interruption, if PFTs normalize and lung toxicity is unlikely, study drug may be re-initiated at the discretion of the investigator.

The decision to permanently discontinue study drug will be made after evaluation of all available information concerning concomitant medications, other potential causes of respiratory AEs, and the clinical status of the subject. Further diagnostic work-up and consultation with a pulmonologist or other specialist should be considered according to local practice and the clinical situation.

Subjects experiencing respiratory symptoms and/or reduced pulmonary function during the course of the treatment with the study drug may be prescribed short-acting β_2 agonist (to be used on an 'as needed' basis ['PRN' use]), at the investigator's discretion. If a subject fails to show symptom relief and/or reversibility, additional diagnostic work-up

(e.g., high-resolution computerized tomography, diffusing capacity for the lungs measured using carbon monoxide [DL_{CO}]) and/or permanent study drug discontinuation should be considered at the discretion of the investigator.

In all cases of permanent discontinuation, FU monitoring must be provided until respiratory AEs have resolved and changes in pulmonary function are no longer regarded as clinically relevant, or until medically indicated.

5.1.12.5 Pregnancy

If a subject becomes pregnant while on study drug, study drug **must** be permanently discontinued. The investigator must counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

5.1.12.6 Liver abnormalities

In case of abnormal liver tests or signs and symptoms suggestive of drug induced liver injury (DILI), the subject will be closely observed, liver tests will be repeated, and study drug discontinuation should be considered according to the guidance provided in Table 6.

Table 6 Guidance for subject monitoring and discontinuation for liver enzyme abnormalities

Item	Laboratory parameter	Guidance
1	ALT or AST ≥ 3 × ULN *	Start close observation. Repeat labs within 72 hours. See items 1a and 1b. * if ALT or AST ≥ 8 × ULN ***or*** ALT or AST ≥ 3 × ULN and TBL ≥ 2 × ULN or INR > 1.5 ***or*** ALT or AST ≥ 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%) and retest cannot be done within 72 hours, permanently discontinue study drug, and perform FU
1a	If at repeated labs, ALT or AST ≥ 3 × ULN < 8 × ULN	Continue close observation. Repeat labs twice weekly. See items 2a and 2b.
1b	If at repeated labs, ALT or AST < 3 × ULN	Resume regular labs schedule.
2a	If at repeated labs, ALT or AST ≥ 5 × ULN for > 2 weeks	Permanently discontinue study drug, and perform FU.
2b	If at repeated labs, ALT or AST ≥ 3 × ULN < 5 × ULN for > 2 weeks	Continue close observation. Repeat labs once or twice weekly.
3	If at repeated labs: ALT or AST ≥ 8 × ULN	Permanently discontinue study drug, and perform FU.

Item	Laboratory parameter	Guidance
	ALT or AST ≥ 3 × ULN and TBL ≥ 2 × ULN or INR > 1.5 ALT or AST ≥ 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)	

ALT = alanine aminotransferase; AST = aspartate aminotransferase; FU = follow-up; INR = International Normalized Ratio; ULN = upper limit of normal range.

Whenever AST or ALT ≥ 3 × ULN are recorded by the central laboratory, an alert will be sent to the principal investigator and the sponsor. The sponsor will contact the principal investigator to ensure that she/he will immediately contact the subject, and ask the subject about any potential symptoms. The subject will be closely observed and will be asked to return to the site as soon as possible after the time of receipt of the alert to repeat the liver enzyme and bilirubin tests by the central laboratory (unless the clinical situation mandates immediate local testing) according to the scheme illustrated in Table 6. Further diagnostic work-up and consultation with a hepatologist or other specialist should be considered, and adequate medical management should be provided according to local practice and the clinical situation. Any clinically relevant finding meeting the definition of an AE will be recorded accordingly in the eCRF.

In case of study drug interruption, the subject will be closely observed and FU liver tests will be performed. Following study drug interruption, if liver tests normalize and drug-related hepatotoxicity is unlikely, study drug may be re-initiated at the discretion of the investigator. Re-initiation following interruption according to the above criteria can only be done once during the study. The decision to permanently discontinue study drug will be made after evaluation of all available information concerning concomitant medications, other potential causes of hepatotoxicity, and the clinical status of the subject. **NB:** The re-initiation is not permitted for situations where study treatment should be permanently discontinued according to Table 6.

In all cases of permanent study drug discontinuation, FU monitoring must be provided until signs and symptoms have resolved and changes in liver function are no longer regarded as clinically relevant or until medically indicated.

5.1.12.7 Ocular abnormalities

In the event of suspected clinically significant findings (e.g., macular edema), an unscheduled OCT examination should be performed. In the case of macular edema confirmed by the local ophthalmologist, the subject must be permanently discontinued from study drug and will be managed and followed up until resolution. Any clinically relevant finding meeting the definition of an AE will be recorded accordingly in the

eCRF. The OSB will receive all information related to suspected cases of macular edema and will perform central review of OCT results and subject data.

Subjects with active uveitis but without macular edema may continue on the study drug but will require additional ophthalmologic assessments as detailed below.

5.1.12.7.1 Guidance for monitoring and management of subjects with uveitis

In case of suspicion of active uveitis (ocular pain, floaters, blurred vision, increased intraocular pressure) at Visit 1 (Screening) or during a scheduled ophthalmological assessment, fluorescence angiography (FA) should be performed (unless contra-indicated according to the ophthalmologist) in addition to the scheduled ophthalmological assessment and OCT, in order to characterize the uveitis. Subjects with suspicion of uveitis occurring during the study treatment but outside scheduled ophthalmological assessment should have a full ophthalmological assessment performed together with FA (unless contraindicated) as soon as possible. If active uveitis can be confirmed and macular edema can be ruled out, the subject may continue in the study without interrupting the study drug. Such subjects will need to be controlled by the ophthalmologist after 1 week, 2 weeks, and 4 weeks after the diagnosis of uveitis has been confirmed and then every 4 weeks throughout the study or until the condition has resolved. These ophthalmological exams should include full ophthalmological assessment (ophthalmological symptoms, assessment of best corrected visual acuity (Early Treatment Diabetic Retinopathy Study [ETDRS] charts), measurement of ocular pressure, preferably with Goldmann applanation tonometry, slitlamp examination of the anterior segment, and dilated indirect funduscopy) as well as OCT. FA may be repeated at the ophthalmologist's discretion. The ophthalmologist will decide what treatment should be given to the subject. If the subject needs to be treated by immunosuppressants prohibited by the protocol, the study treatment has to be discontinued. If uveitis is progressing in spite of treatment, the investigator may consider interrupting or permanently discontinuing the study drug.

5.1.12.8 Discontinuation of DMF background therapy

Subjects who permanently discontinue DMF background therapy must permanently discontinue study treatment and may begin treatment with an approved MS therapy in accordance to local practices.

5.2 Previous and concomitant therapy

5.2.1 Definitions

A previous therapy is any treatment for which the end date is prior to the start of study (i.e., signing of informed consent).

A study-concomitant therapy is any therapy which is ongoing or initiated after signing of informed consent, and initiated before EOS visit. All study-concomitant therapies must be captured in the eCRF [see Section 5.2.2.1].

Study concomitant therapies include study treatment-concomitant therapies, which is any therapy either ongoing at the start of study treatment or initiated during the study treatment period, or up to 30 days after the end of study treatment.

5.2.2 Reporting of previous/concomitant therapy in the eCRF

5.2.2.1 Study-concomitant therapies

The use of all study-concomitant therapy (including traditional and alternative medicines, i.e., plant-, animal-, or mineral-based medicines; see definition in Section 5.2.1) will be recorded in the Concomitant Medications form of the eCRF. Contraceptives will be recorded in a specific Contraceptive Methods form of the eCRF. The generic name, start/end dates of administration (as well as whether it was ongoing at start of treatment and/or EOS), route, dose, frequency, and indication will be recorded in the corresponding forms of the eCRF. DMF intake (i.e., the background concomitant therapy) will be recorded on a specific log of the eCRF [see Section 5.2.2.3]).

5.2.2.2 Previous MS therapies

Any previous administration of disease-modifying treatment for MS (e.g., IFN β-1a [Rebif® - Avonex®, Plegridy®], IFN β-1b [Betaferon®, Extavia®], glatiramer acetate [Copaxone®, Glatopa®], natalizumab [Tysabri®], teriflunomide [Aubagio®], mitoxantrone [Novantrone®], alemtuzumab [Lemtrada®], daclizumab [Zynbryta®], ocrelizumab [Ocrevus®], cladribine [Mavenclad®]), at any time prior to Visit 1 (Screening) will be recorded in the previous MS treatment form of the eCRF [see Section 1.1.4]. For treatments received in the last 24 months prior to the study, start date, end date and reason for discontinuation will be recorded in the eCRF. In addition, dose, route, and frequency should be recorded in the eCRF, if available. For treatments stopped before the last 24 months prior to the study, start date, end date, and reason for discontinuation may be reported only if known and evidenced in the source documents.

The therapies used for the treatment of relapses experienced by the subject in the past 24 months will be recorded in the previous MS treatment form of the eCRF (e.g., corticosteroids, ACTH). For each therapy, the start date, end date, reason for discontinuation, dose, route, and frequency of administration will be recorded in the eCRF.

5.2.2.3 Other previous therapies

Any previous relevant therapy as per principal investigator / treating neurologist judgment (e.g., therapies listed in exclusion criteria, therapies for relevant medical history) will be recorded in the Previous Medications form of the eCRF.

5.2.3 Concomitant background therapy

In order to be eligible for this study, subjects must have been treated with DMF (Tecfidera®) for at least 6 months prior to Visit 1 (Screening). Subjects should be treated with DMF as per prescribing information [Tecfidera USPI, Tecfidera SmPC] throughout the course of the study [see Section 3.5.2.1].

Any previous administration including, if applicable, the last initiation of DMF (Tecfidera®) prior to Visit 1 (Screening) as well as intake (start date, end date, dose change, and reason for interruption and/or discontinuation) during the study must be recorded in the DMF-specific log of the eCRF.

5.2.4 Recommended concomitant therapy

Treatment of relapses:

- If a relapse requires treatment with corticosteroids, methylprednisolone 1 g i.v., oral methylprednisolone in the dose range of 1 g to 1.25 g or equivalent doses of oral prednisone or prednisolone daily for 3 to 5 days is recommended (without an oral taper). These administrations will be reported in the eCRF. Treatment with other corticosteroids, another dose, other routes of administration, or ACTH is not recommended unless deemed necessary and must be documented in the patient charts by the investigator.
- Treatment of relapses with plasma exchange (i.e., plasmapheresis, cytapheresis) is prohibited. The effect of plasmapheresis on relapse recovery is not sufficiently well documented to justify its inclusion as part of the protocol. Allowing plasmapheresis as per investigator discretion would lead to inhomogeneous treatment of relapses which could affect the study outcome in an unpredictable direction.

5.2.5 Allowed concomitant therapy

- Dalfampridine (synonymous with fampridine) on a stable dose for at least 90 days prior to randomization and during double blind treatment. Dalfampridine therapy must not be started or increased in dose during the study. Stopping or decreasing the dose of dalfampridine during the study should only take place if deemed absolutely necessary by the investigator;
- Administration of i.v. atropine in the event of symptomatic bradycardia;

- Short-acting β2-agonists for respiratory symptoms and/or reduced pulmonary function during study treatment (please refer to Sections 5.1.12.4 and 7.3.3 for guidance);
- QT-prolonging drugs with known risk of Torsades de Pointes should be used with caution since ponesimod may potentially enhance their effect on QT interval (guidance is provided in Appendix 4);
- Vaccination with non-live vaccines. Subjects receiving non-live vaccination while on study treatment will have 5 mL of blood drawn prior to and ≥ 3 weeks after vaccination in order to explore changes in vaccine-specific antibody titers from pre- to post-vaccination. Samples will be analyzed at the end of the study;
- Low dose of corticosteroids (up to 10 mg of prednisone equivalent daily), given as short-term treatment (up to 2 weeks per treatment cycle with at least 8 weeks' interval between treatment cycles and no more than 8 weeks during the whole study duration)
- Inhaled corticosteroids for pulmonary conditions;
- Other treatments considered necessary for the subject's benefit and not categorized as prohibited concomitant medications.

5.2.6 Forbidden concomitant therapy

The below list of forbidden concomitant therapies is applicable to all subjects receiving study treatment, but not to the subjects who prematurely discontinued study treatment and participate in the PTOP.

- Systemic corticosteroids and ACTH, except for: the treatment of MS relapses [see Section 5.2.4]; short-term treatment with a low dose of corticosteroid; and inhaled corticosteroids for pulmonary conditions [see Section 5.2.5];
- Disease-modifying drugs for MS other than prescribed as per protocol (e.g., IFN β, glatiramer acetate, fingolimod, teriflunomide, natalizumab or other monoclonal antibody therapy);
- Immunosuppressive treatment (e.g., cladribine, mitoxantrone or other systemic immunosuppressive treatments such as azathioprine, cyclophosphamide, cyclosporine, methotrexate, or leflunomide);
- Intravenous immunoglobulin;
- Plasmapheresis, cytapheresis, or total lymphoid irradiation;
- Vaccination with live vaccines;
- β-blockers, diltiazem, verapamil, digoxin, or any other anti-arrhythmic or HR lowering systemic therapy [non-exhaustive list of drugs provided in Appendix 3];
- Any other investigational drug;

- Any investigational therapeutic procedure for MS (e.g., stent placement or angioplasty for chronic cerebrospinal venous insufficiency (CCSVI), stem cell transplantation).

In the event that a subject takes any of these forbidden medications, the investigator must contact the sponsor to discuss further FU actions including stopping/interrupting study treatment as appropriate.

6 STUDY ENDPOINTS

6.1 Efficacy endpoints

For each of the study efficacy endpoints, baseline is defined as the last value recorded prior to randomization (the actual visit used as baseline might be different across endpoints).

6.1.1 Primary efficacy endpoint

The primary endpoint is ARR. This endpoint is defined as the number of confirmed relapses from randomization up to EOS, per subject-year.

Definition of relapse

- A relapse is defined as new, worsening or recurrent neurological symptoms that occur at least 30 days after the onset of a preceding relapse, and that last at least 24 hours, in the absence of fever or infection.
- The new, worsening or recurrent neurological symptoms are to be evaluated by the treating neurologist and, if all the elements of the above definition have been verified, in the absence of another, better explanation of the subject's symptoms, the event is considered as a relapse [see Section 7.2.2]. The onset date of the relapse corresponds to the onset date of the symptoms.
- A relapse will be confirmed only when the subjects' symptoms are accompanied by an increase in EDSS/FS scores, which is consistent with the subject's symptoms, from a previous clinically stable EDSS/FS assessment (i.e., performed at least 30 days after the onset of any previous relapse), obtained by the efficacy assessor and consistent with the following:
  - an increase of at least half a step (0.5 point; unless EDSS = 0, then an increase of at least 1.0 point is required), or
  - an increase of at least 1.0 point in at least two FS scores, or
  - an increase of at least 2.0 points in at least one FS score (excluding bladder/bowel and cerebral).

6.1.2 Secondary efficacy endpoints

There are five secondary efficacy endpoints, which will be analyzed in a hierarchical manner:

- Time to 12-week CDA from baseline up to EOS.

Definition: A 12-week CDA is:

  - an increase of at least 1.5 in EDSS for subjects with a baseline EDSS score of 0, or
  - an increase of at least 1.0 in EDSS for subjects with a baseline EDSS score of 1.0 to 5.0, or
  - an increase of at least 0.5 in EDSS for subjects with a baseline EDSS score ≥ 5.5

which is to be confirmed after 12 weeks.

Baseline EDSS is defined as the last EDSS score recorded during pre-randomization. The initial EDSS increase, meeting the above criteria, is defined as the onset of disability accumulation. All EDSS measurements (with or without relapse, at a scheduled or unscheduled visit) will be used to determine the onset of disability accumulation. However, for the purpose of confirmation, only EDSS measured more than 30 days after the onset of a confirmed relapse will be used. This is to avoid a confirmation of disability accumulation caused by a relapse. In order to confirm that the EDSS increase is persistent, all EDSS measurements between the onset and the 12-week EDSS confirmation (minus visit time-window) need to show an increase in EDSS, meeting the criteria for accumulation of disability as defined above.

- Time to first confirmed relapse up to EOS.

Definition: Relapse definition is given in Section 6.1.1. Date of the first confirmed relapse is defined as the onset date of the first confirmed relapse.

- Mean number of combined unique active lesions (CUALs) per subject per post-baseline MRI scan up to EOS.

Definition: CUALs are new Gd+ T1 lesions plus new or enlarging T2 lesions (without double-counting of lesions).

- Longitudinal change over time in fatigue-related symptoms as measured by the symptoms domain of the FSIQ–RMS from baseline up to EOS.
- Longitudinal percent change over time in brain volume from baseline up to EOS.

Definition: Longitudinal brain volume measurements are derived from MRI scans by using Structural Image Evaluation, using Normalisation, of Atrophy methodology (SIENA) [Smith 2001, Smith 2002].

6.1.3 Other efficacy endpoints

MRI-based exploratory endpoints:

- Percent change in brain volume (PCBV) from baseline to Weeks 48, 96, 144, EOT, and EOS;
- Mean number of CUALs per subject per scan from baseline up to Weeks 48, 96, 144, EOT, and EOS;
- Mean number of Gd+T1 lesions per subject per scan from baseline up to Weeks 48, 96, 144, EOT, and EOS;
- Mean number of new or enlarging T2 lesions per subject per scan from baseline to Weeks 48, 96,144, EOT and EOS;
- Change in the volume of MRI lesions (T2 lesions, T1 hypointense lesions) from baseline to Weeks 48, 96, 144, EOT, and EOS;
- Absence of MRI lesions (Gd+ T1 lesions, new or enlarging T2 lesions, new T1 hypointense lesions) from baseline to Weeks 48, 96, 144, EOT, and EOS.

Clinical exploratory endpoints (disease activity, relapses, disability progression):

- Absence of confirmed relapses from baseline up to EOS;
- Time to first 24-week CDA from baseline up to EOS;

Definition: A 24-week CDA is:

- an increase of at least 1.5 in EDSS for subjects with a baseline EDSS score of 0, or
- an increase of at least 1.0 in EDSS for subjects with a baseline EDSS score of 1.0 to 5.0, or
- an increase of at least 0.5 in EDSS for subjects with a baseline EDSS score $\geq$ 5.5,

which is to be confirmed after 24 weeks.

Baseline EDSS is defined as the last EDSS score recorded during pre-randomization. The initial EDSS increase, meeting the above criteria, is defined as the onset of disability accumulation. All EDSS measurements (with or without relapse, at a scheduled or unscheduled visit) will be used to determine the onset of disability accumulation.

However, for the purpose of confirmation, only EDSS measured more than 30 days after the onset of a confirmed relapse will be used. This is to avoid a confirmation of disability accumulation caused by a relapse. In order to confirm that the EDSS increase is persistent, all EDSS measurements between the onset and the 24-week EDSS confirmation (minus visit time-window) need to show an increase in EDSS, meeting the criteria for accumulation of disability as defined above.

- Change in EDSS from baseline by visit up to EOS;
- No evidence of disease activity (NEDA) status at EOS (defined by the absence of confirmed relapse, Gd+ T1 lesions, new or enlarging T2 lesions, 12-week CDA, as well as absence of annual brain volume decrease ≥ 0.4% from baseline to EOS and completing treatment as planned).

Other clinical exploratory endpoints:

- Change in MSFC Z-score from baseline by visit up to EOS;
- Change in the SDMT score from baseline by visit up to EOS;
- Change from baseline by visit up to EOS in fatigue-related impacts as measured by the impact sub-scales of the FSIQ–RMS.

6.2 Safety endpoints

The treatment-emergent period is defined as the time from first study drug intake up to 30 days (inclusive) after last study drug intake. The following safety endpoints will be analyzed:

- Treatment-emergent AEs, SAEs, AEs of special interest[#], MACE, and AEs leading to premature discontinuation of study treatment;
- Treatment-emergent morphological ECG abnormalities (as defined by the ECG provider);
- Change in 12-lead ECG variables (HR, PR, QRS, QT, QT corrected for HR on the basis of Bazett's formula [QTcB], Fridericia's formula [QTcF]) from pre-dose to selected post-dose assessments (1 h, 2 h, 3 h, 4 h) on Day 1 and on day of re-initiation of study treatment when post-dose monitoring is required;
- Notable abnormalities* for selected 12-lead ECG variables (HR, PR, QT, QTc) at 3-hour post-dose assessment on Day 1, Week 12 and at the re-initiation of study treatment when post-dose monitoring is required;
- Treatment-emergent decrease of FEV_1 or FVC > 20% from baseline values or decrease of percent predicted FEV_1 or FVC > 20 percentage points from baseline values;
- Change in FEV_1 or FVC from baseline, absolute and % of absolute change to all timepoints up to EOS;

- Change from baseline to EOS versus change from baseline to EOT in FEV_1 or FVC (absolute and % of predicted);
- Among subjects with a decrease of > 200 mL or > 12% in FEV_1 or FVC from baseline to EOT, reversibility defined as a decrease of < 200 mL or < 12% in FEV_1 or FVC from baseline to last available post EOT follow-up;
- Treatment-emergent notable blood pressure abnormalities*;
- Treatment-emergent notable laboratory abnormalities*;
- Change in body weight from baseline to EOS;
- Treatment-emergent electronic self-rated version of the Columbia-Suicide Severity Rating Scale (eC-SSRS) suicidal ideation score of 4 or above, or a "yes" response on the eC-SSRS suicidal behavior item;
- Change in JCV serology from baseline up to EOS.

The selection of AEs of special interest is based on the anticipated risks of treatment with ponesimod and on the events that may be related to MS co-morbidities (e.g., seizures or stroke) as described in Appendix 5; the final list of AEs of special interest will be defined in the Statistical Analysis Plan (SAP).

* The selection of notable abnormalities considered for the analyses is based on standard definitions and the anticipated risks of treatment with ponesimod as described in Appendix 6; the final list of abnormalities will be defined in the SAP.

6.3 Quality of life endpoints

- Change from baseline by visit up to EOT in SF-36v2™ Health Survey domain and component scores.

6.4 Pharmacoeconomic endpoints

- Change from baseline by visit up to EOT in WPAI:MS scores.
- Health care resource utilization from baseline by visit up to EOT on-treatment visit (number of hospitalizations, length of stay, number of intensive care admissions for MS relapse and visits to an emergency medical services facility for MS).

6.5 Pharmacokinetic and pharmacodynamic endpoints

6.5.1 Pharmacokinetic evaluations

- Plasma concentrations of ponesimod pre-dose at Week 12, Week 24, Week 48, Week 96, Week 144, EOT and FU, and 3 hours post-dose on Day 1 and at Week 12.

6.5.2 Pharmacodynamic evaluations

- Absolute and percent change in peripheral blood lymphocyte counts pre-dose by visit up to EOS.
- Absolute and percent changes in lymphocytes subsets by visit up to EOS [sub-study; see Section 3.6.1].

6.5.3 PK/PD relationship

- Correlation of selected efficacy and safety variables with absolute lymphocyte counts and magnitude of reduction of lymphocyte counts may be analyzed.

7 STUDY ASSESSMENTS

All study assessments are performed by a qualified study staff member: medical, nursing, or specialist technical staff, and are recorded in the eCRF, unless otherwise specified. Study assessments performed during unscheduled visits will also be recorded in the eCRF.

If the principal investigator delegates any study procedure/assessment for a subject, e.g., ECG, MRI, blood sampling etc., to an external facility, she/he should inform Actelion to whom these tasks are delegated. The set-up and oversight will be agreed upon with Actelion. The supervision of any external facilities remains under the responsibility of the principal investigator.

Calibration certificates for the following devices used to perform study assessments must be available prior to the randomization of the first subject:

- Temperature measurement devices for study medication storage area and lab sample storage (e.g., freezer).
- Spirometer; in addition, a copy of the calibrations check (syringe check) of the day of measurement must be stored and a log of calibration check results must be maintained at the site [see Section 7.3.3].
- ECG recorder.
- BP monitoring device.
- MRI; in addition, prior to the start of the study, each MRI site must be qualified by the MIAC [see Section 7.2.3].

7.1 Screening/baseline assessments

7.1.1 Informed consent (Visit 1 [Screening])

Prior to performing any study-specific procedures or assessments, the subject must provide written informed consent to participate in the study. If the signing of informed consent and performance of the first study-specific procedures or assessments take place on the same day, it must be clear from the source documents that informed consent was obtained prior to any study-specific procedures being performed. If a study-specific procedure or assessment has been performed as part of routine assessments and the results are available prior to the subject's signing of informed consent, such procedure or assessment may be used to assess eligibility and does not have to be repeated (e.g., CXR [see Section 7.3.4]). In such cases, it must be clear from the source document when and for which reason the assessment was done prior to the signing of the informed consent. It

is the responsibility of the principal investigator / treating neurologist to explain the study in all its aspects to the subject and obtain her/his informed consent. The informed consent process will be documented in the investigator site file. The oral and written information about the trial, as well as the ICF, will be provided in a language that is fully understandable to the subject.

For subjects who provide informed consent but are subsequently not randomized into the study, the reasons for not being randomized will be recorded in eCRF.

In order to ensure subjects are made aware of potential risks and benefits of continuing in the study as well as alternative treatment options available, subjects who continue study treatment and DMF background therapy upon experiencing a confirmed relapse or a 24-week CDA while on study drug will be asked to re-consent to continue receiving study treatment.

7.1.2 Baseline demographics and disease characteristics

Baseline demographics (sex, age, race, ethnicity, body weight, height, and childbearing potential [if applicable]) are to be recorded in the eCRF at Visit 1 (Screening). Complete, clinically relevant medical history and current conditions, as well as smoking status and MS disease characteristics [see Section 4.6] are to be documented in the eCRF.

7.1.3 Study-concomitant therapies

All study-concomitant therapy (including contraceptives and traditional and alternative medicines, i.e., plant-, animal-, or mineral-based medicines) taken by the subject from the signing of informed consent until the end of their participation in the study (i.e., EOS) will be recorded in their respective forms (i.e., Concomitant Medications form or Contraceptive Methods form) of the eCRF. This includes all ongoing therapies and those initiated or stopped during this period. The corresponding dates of initiation and discontinuation will be recorded [see Section 5.2.2.1].

7.1.4 Previous MS therapies

Any previous administration of disease-modifying treatment for MS (e.g., IFN β-1a [Rebif® - Avonex®, Plegridy®], IFN β-1b [Betaseron®, Betaferon®, Extavia®], glatiramer acetate [Copaxone®, Glatopa®], natalizumab [Tysabri®], teriflunomide [Aubagio®], fingolimod [Gilenya®], mitoxantrone [Novantrone®], alemtuzumab [Lemtrada®], daclizumab [Zynbryta®], ocrelizumab [Ocrevus®], cladribine [Mavenclad®]), at any time prior to Visit 1 (Screening) will be recorded in the previous MS treatment form of the eCRF [see Sections 1.1.4 and 5.2.2.2].

7.2 Efficacy assessments

7.2.1 Neurological evaluation

EDSS and FS scores [Kurtzke 1983] are based on a standard neurological examination for assessing neurologic disability and impairment in MS. The seven FS scores are ordinal clinical rating scales ranging from 0 to 5 or 6, assessing visual, brain stem, pyramidal, cerebellar, sensory, bowel and bladder, and cerebral functions while ambulation is an ordinal scale ranging from 0 to 12 assessing walking distance and assistance. The ratings of the individual FS scores are then used, in conjunction with ambulation score, to obtain the EDSS score. EDSS is an ordinal clinical rating scale ranging from 0 (normal neurological examination) to 10 (death due to MS) in half-point increments.

EDSS and FS assessments will be performed at Visit 1 (Screening), Visit 2 (Baseline), Visit 6 (Week 12) and every 12 weeks thereafter until Visit 18 (EOT), Visit 20 (FU), and at any unscheduled visit in the event of relapses (R1, R2, etc.) or other unscheduled visits (U1, U2, etc.). If applicable, EDSS and FS will also be assessed at the corresponding visits in the PTOP (Visits 6A to 18A).

EDSS and FS assessments will only be performed by the efficacy assessor who should preferably maintain this role for a given subject throughout the study [see Section 3.7.3]. The efficacy assessor must not consult prior EDSS/FS scores when performing the current EDSS/FS assessment. In no case will the treating neurologist alter the EDSS/FS score obtained by the efficacy assessor. The examination will be based on the modified neurological examination 'Neurostatus' [Appendix 1] using the corresponding scoring documents. The EDSS/FS scoring will be recorded in the eCRF. **NB:** Fatigue, which is an optional part of the 'Neurostatus' assessment will not contribute to the Cerebral FS score.

7.2.2 Detection and evaluation of relapses

Detection and evaluation of relapses will be done as follows [see Figure 3]:

Step 1: At every study visit, subjects are reminded to contact their principal investigator / treating neurologist immediately in the event of the appearance of any new or worsening neurological symptoms. In addition, the site will contact the subject in-between the 12-weekly visits (e.g., Visit 6 – Week 12, Visit 7 – Week 24, …) even after possible premature discontinuation from the study treatment (e.g., Visit 6A – Week 12 in the PTOP, Visit 7A – Week 24 in the PTOP, …) in order to proactively inquire about any new or worsened neurological symptoms. These telephone calls will be conducted either at Weeks 18, 30, 42, 54, 66, 78, 90, 102, 114, 126, 138 and 150 (± 7 days), or 6 weeks after the last 12-weekly visit (± 7 days).

Whenever between visits a subject experiences any new or worsening neurological symptoms he/she must contact the principal investigator / treating neurologist, study nurse or clinical coordinator as soon as possible in order to complete a telephone questionnaire for relapse assessment [see Appendix 12].

If, during the call from the site inquiring about symptoms suggestive of potential new relapses, the subject reports occurrence of such symptoms, a telephone questionnaire for relapse assessment will also be completed.

If a relapse is suspected, the subject will be required to come to the site for an unscheduled relapse assessment visit. The completed telephone questionnaire will be collected in the eCRF.

Step 2: At every scheduled and unscheduled visit (limited to unscheduled visits when the subject will meet with the principal investigator / treating neurologist, but not at other unscheduled visits conducted for repeat testing (e.g., spirometry, liver enzymes), the principal investigator / treating neurologist will interview and examine the subject to determine whether or not a relapse may have occurred since last visit using a dedicated relapse assessment questionnaire [see Appendix 12] and the relapse symptom form [see Appendix 13].

Based on the interview and examination, the principal investigator / treating neurologist will determine if symptoms are likely to be due to a relapse (i.e., all elements from the relapse definition in Section 6.1.1 have been verified, in the absence of another, better explanation of the subject's symptoms). If so, the subject will be referred to the efficacy assessor for an EDSS assessment (Note: at scheduled visits the EDSS assessment planned for this visit will be used). The completed questionnaire [see Appendix 12] and the outcome of the examination [see Appendix 13] will be collected in the eCRF.

Step 3: The efficacy assessor will perform the EDSS/FS assessment within 7 days after the onset of new or worsening neurological symptom(s) [see Section 7.2.1]. **Important note:** EDSS and FS assessments will be performed only by the efficacy assessor. The efficacy assessor must not consult prior EDSS/FS scores when performing the current EDSS/FS assessment. In no case will the treating neurologist alter the EDSS/FS score obtained by the efficacy assessor. If the relapse requires treatment with corticosteroids [see Section 5.2.4], treatment should be initiated as early as recommended by local clinical practice. The blinded neurological examination by the efficacy assessor must always be performed prior to the treatment start.

Step 4: The treating neurologist will review the EDSS/FS score obtained by the efficacy assessor and determine presence or absence of qualifying increase in EDSS/FS (i.e., of the magnitude described in Section 6.1.1 from a previously clinically stable EDSS/FS score and consistent with the subject's new symptoms). Based on this review, the treating

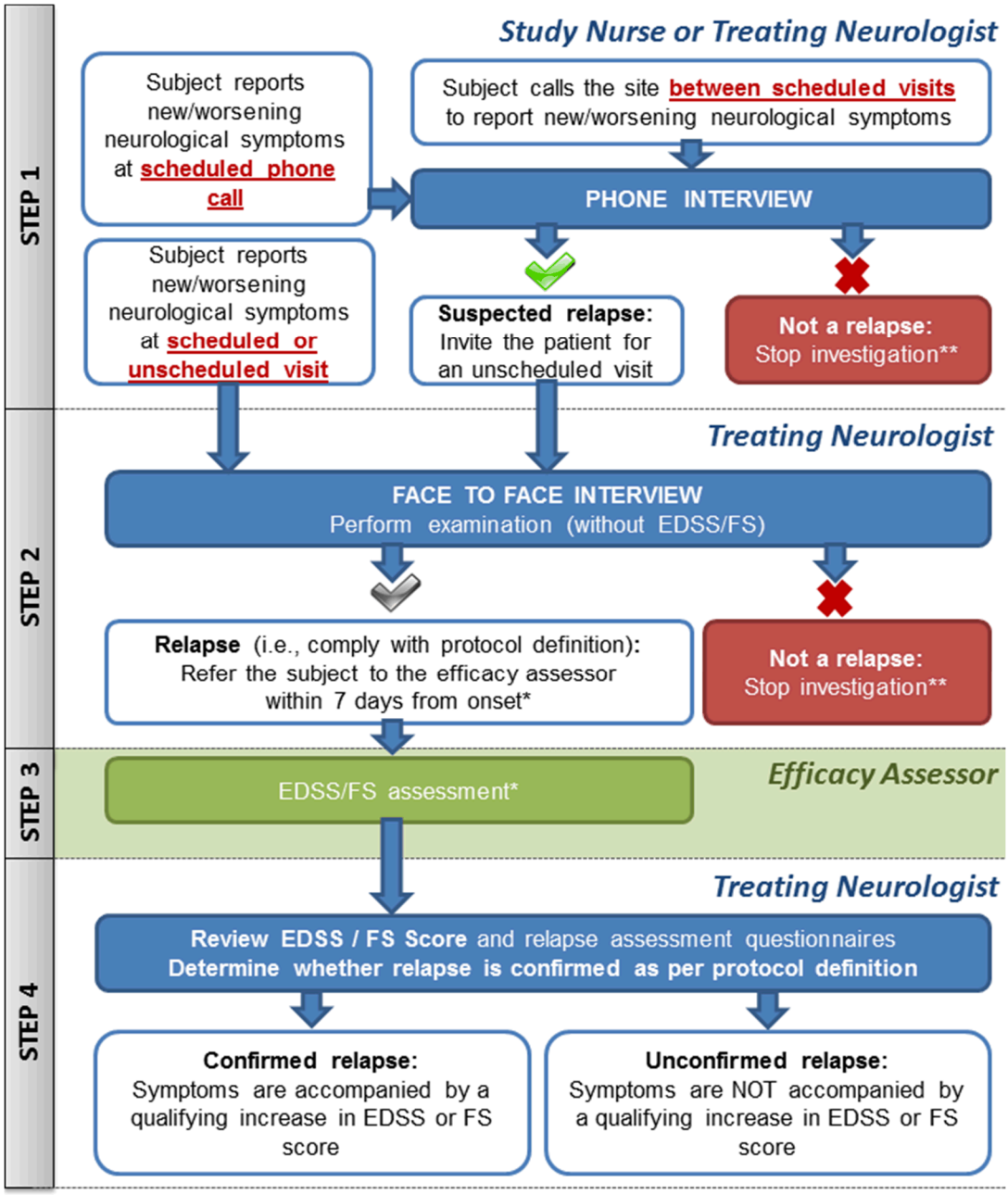
neurologist will decide if the relapse is confirmed or not, according to the protocol definition of confirmed relapse [see Section 6.1.1]. After the occurrence of each confirmed relapse, subjects will be asked to re-consent to continue receiving study treatment [see Section 13.3].

Once step 1 of the relapse detection has been initiated (whether by subject calling the site, by interview of the subject at scheduled visit, or by scheduled calls from the site to the subject), the final result of the relapse detection and confirmation process will be captured as one of the following three outcomes: no relapse, unconfirmed relapse, or confirmed relapse. New or worsened neurological symptoms reported by the subject and for which there is another better explanation for the subject's current symptoms than an MS relapse will be captured on an AE page.

All MS relapses, whether or not confirmed, must be reported on specific relapse pages of the eCRF. MS relapses and associated symptoms are not to be entered on the AE page of the eCRF with the following exceptions:

- MS relapses with fatal outcome (these must always be recorded as an AE on the AE page in addition to being reported as SAEs).
- MS relapses that, in the view of the investigator, warrant specific notice due to unusual frequency, severity or remarkable clinical manifestations (these should be reported as an AE on the AE page of the eCRF and, if applicable, on the SAE form).

Figure 3 Flow diagram for the detection and evaluation of relapses



* If time of onset of relapse is within 24 hours before the visit, then defer the neurological examination and EDSS/FS assessment by 24 hours.
** If appropriate (e.g., subject has a fever or an infection which can explain the symptoms, or if there is another and better explanation for the patient's current symptoms than an MS relapse), enter subject's symptoms or diagnosis on the AE page.

7.2.3 MRI evaluations

MRI scans will be performed at Visit 2 (Baseline), Visit 7 (Week 24), Visit 9 (Week 48) and every 24 weeks thereafter up to Visit 17 (Week 144) and at Visit 18 (EOT). In addition, MRI scans may be performed at any unscheduled visit (U1, U2, etc.) if deemed necessary for the subject safety. If applicable, MRI scans will also be performed at the corresponding 24 weekly visits in the PTOP. In case of premature study treatment discontinuation, the MRI at EOT does not need to be performed if the EOT visit occurs within 4 weeks after the latest scheduled MRI assessment.

MRI variables include the number and volume of new and total Gd+ lesions on T1-weighted MRI scans, number of new and enlarging lesions and lesion volume on T2-weighted MRI, and global measures of loss of brain tissue.

Fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI), T1-weighted imaging before and after i.v. administration of 0.1 mmol/kg body weight (= 0.2 mL/kg) of Gd as well as T2-weighted imaging will be performed. Gd may cause nausea and vomiting and in very rare cases allergic reactions that could require immediate anti-anaphylactic therapy (such as steroids, epinephrine/adrenaline, etc.). Gd administration may be omitted if medically contraindicated.

MRI data will be analyzed by the MIAC, c/o University Hospital Basel, Switzerland for MRI efficacy outcomes (i.e., T1-weighted images before and after Gd administration, and T2-weighted images). All FLAIR and DWI MRI scans will be exported to the MIAC. The MIAC will only analyze the images selected by the local radiologist or neurologist with MRI expertise upon notification for review by the site (i.e., in the event of a suspected opportunistic infection) [see Section 3.8.3]. MRI scans which are of unacceptable quality for central reading evaluation will be repeated.

Prior to the start of the study, each MRI site must be qualified by the MIAC. To be qualified, each MRI site will perform a dummy scan according to the parameter settings defined in the study MRI manual (separate document) and submit the image data to the MIAC who will assess the image quality, the quality of the data transfer, and the compatibility with the electronic data processing and will qualify the site accordingly. The dummy scan will not use contrast agent and will be performed on a volunteer or patient, having signed a specific informed consent for this MRI assessment. Once qualified, each MRI site must maintain all the study-specific parameter settings unchanged throughout the study.

Detailed instructions on procedures, standardization, qualification, recording, and transfer of data, etc., will be provided in the study MRI manual (separate document).

Lesion counts of MRIs performed within 24 months prior to the study will be recorded on the MS history page of the eCRF. These scans will not be analyzed by the MIAC, except when the MIAC's opinion is needed for T2-based eligibility criterion (i.e., when the inclusion criterion 6 is fulfilled only by potential presence of at least one new or one unequivocally enlarging T2 lesion based on historical MRI scans).

Incidental, non-MS-related findings identified by central reading will be communicated to the principal investigator / treating neurologist. Furthermore, all MRI scans performed for the study must be reviewed and documented for safety by the local radiologist or neurologist with MRI expertise. The principal investigator / treating neurologist must be informed of any findings of concern for the subject's safety including non-MS-related findings detected on the MRI scan, but efficacy-related MRI results (e.g., lesion counts) will not be communicated to study staff or to the subject, unless deemed necessary for maintaining the safety of the subject. Study participants with clinically relevant findings on MRI will be followed up until establishing the final diagnosis and managed as per local medical practice. Other diagnostic procedures may be performed as a FU assessment according to local standard procedures when considered necessary by the investigator. Incidental clinically relevant findings on MRI will be reported in the Medical History or as AE, as applicable.

7.2.4 Multiple Sclerosis Functional Composite score

The MSFC score consists of three clinical examinations: the Timed 25-Foot Walk, the Paced Auditory Serial Addition Test (PASAT)-3" version, and the 9-Hole Peg Test (9-HPT). The Timed 25-Foot (7.62 meters) Walk is a quantitative measure of lower extremity function. The 9-HPT is a quantitative measure of upper extremity (arm and hand) function. The PASAT is a measure of cognitive function that specifically assesses auditory information processing speed and flexibility, as well as calculation ability.

MSFC will be assessed pre-randomization (see details below) and at Visit 6 (Week 12), Visit 7 (Week 24), Visit 9 (Week 48), and every 24 weeks thereafter until Visit 17 (Week 144), and at Visit 18 (EOT).

During the pre-randomization period, two practice tests and a third test serving as baseline assessment will be performed. Ideally, the three tests should be performed ≥ 5 days apart (i.e., second practice test ≥ 5 days from first practice test and third test serving as baseline ≥ 5 days from second practice test). The first practice test may be done at Visit 1 (Screening), the second practice test may be done at Visit 2 (Baseline) and the third test, serving as baseline, may be performed pre-dose at Visit 3 (Randomization). The MSFC results will be entered by the rater on a specific form which will serve as a source document and the relevant data will be transferred by the site to the eCRF.

MSFC will be administered in combination with the SDMT [see Section 7.2.5] in the following sequence:

1. Timed 25-Foot Walk (7.62 meter)
2. 9-HPT
3. PASAT
4. SDMT

A full description of the administration of the scale, sequence of tests and scoring will be given in a separate document provided to each site. The test administrator will be trained on the test administration before the initiation of the site. The test will only be administered by a trained administrator.

A more comprehensive description of the test and its administration is provided in Appendix 7.

7.2.5 Symbol Digit Modalities Test

The SDMT [Smith 1982, Benedict 2006] measures attention and processing speed much like the PASAT. It will be administered along with the MSFC at pre-randomization (see details below) and at Visit 6 (Week 12), Visit 7 (Week 24), Visit 9 (Week 48), and every 24 weeks thereafter until Visit 17 (Week 144), and at Visit 18 (EOT).

During the pre-randomization period, two practice tests and a third test serving as baseline assessment will be performed. Ideally, the three tests should be performed ≥ 5 days apart (i.e., second practice test ≥ 5 days from first practice test and third test serving as baseline ≥ 5 days from second practice test). The first practice test may be done at Visit 1 (Screening), the second practice test may be done at Visit 2 (Baseline) and the third test, serving as baseline, may be performed pre-dose at Visit 3 (Randomization).

The SDMT includes a reference key of nine symbols, each paired with a single digit. Below the reference key are rows of the symbols arranged randomly. The subject is given 90 seconds to say the number that corresponds to each symbol. The test administrator records the answers and the number of correct answers is recorded as the score.

The SDMT will be performed after the MSFC. Study personnel will be trained to administer and score the SDMT.

A sample of the SDMT is provided as Appendix 8. The rater will record the subject's responses on a validated paper form that will be collected and transcribed in the eCRF.

Actelion Pharmaceuticals has been granted a license agreement for the use of the SDMT. The individual questionnaires will be completed by all subjects in all countries as it does not require language translations.

7.2.6 Fatigue Symptom and Impacts Questionnaire-RMS

The FSIQ-RMS is a 20-item PRO measure that was developed by Actelion to evaluate fatigue-related symptoms and the impacts of those symptoms on the lives of people with RMS. The development of FSIQ-RMS is in accordance with the requirements set forth in the Final Guidance to the Industry on Subject Reported Outcomes: Use in Medical Product Development to Support Label Claims [FDA 2009a]. The questionnaire will be administered in an electronic format and consists of two separate domains:

- The **FSIQ-RMS symptom domain (FSIQ-RMS-S)** consists of seven items assessing fatigue-related symptoms with a recall period of 24 hours measured on an 11-point numeric rating scale; the symptom domain score ranges from 0 to 70 with a higher score indicating greater fatigue. This domain (i.e., section 1 of the questionnaire) will be completed on 7 consecutive days.

- The **FSIQ-RMS impacts domain (FSIQ-RMS-I)** consists of 13 items assessing impacts of fatigue-related symptoms with a recall period of 7 days measured on a 5-point scale, ranging from no impact to extreme impact; the impacts domain score ranges from 0 to 52 with a higher score indicating greater impact. As the impacts domain of the FSIQ-RMS (i.e., section 2 of the questionnaire) has a 7-day recall period, it will only be completed on the last day (i.e., 7th day) of completion of section 1.

FSIQ-RMS will be completed during the pre-randomization period, at Visit 6 (Week 12), Visit 7 (Week 24), Visit 9 (Week 48), and every 24 weeks thereafter until Visit 18 (EOT), Visit 20 (FU), and at unscheduled visits due to relapses (R1, R2, etc.) or other unscheduled visits (U1, U2, etc.) as described below. If applicable, FSIQ-RMS will also be performed at the corresponding visits in the PTOP.

The completion of the FSIQ-RMS during the pre-randomization period will be done as follows: at Visit 1 (Screening), subjects who appear eligible based on the assessments made during this visit (but prior to the results from the laboratory assessments being received) will be provided with the FSIQ-RMS.

Once the results from the laboratory assessments confirm the subject's eligibility, and provided no other assessment performed in the meantime excludes the subject, the site coordinator will contact and ask the subject to start the completion of the FSIQ-RMS. At home, the subject will complete the symptom domain of the FSIQ-RMS for 7 days (i.e., section 1 of the questionnaire). On the 7th day, the subject will also complete the impacts

domain of the FSIQ-RMS (i.e., section 2 of the questionnaire). The information captured from this assessment will be used as the baseline data for the FSIQ-RMS. Ideally, the FSIQ-RMS will be completed during the 7 consecutive days preceding the randomization.

After randomization, the symptom domain of the FSIQ-RMS (i.e., section 1 of the questionnaire) will be completed by the subject at home on a daily basis, starting in the evening of the day of a visit when the FSIQ-RMS is administered (Day 1 of questionnaire administration cycle) and during the 6 subsequent days (i.e., over 7 days in total). On the 7th day, the subject will also complete the impacts domain of the FSIQ-RMS (i.e., section 2 of the questionnaire). Subjects will return the completed FSIQ-RMS diary at the next scheduled visit. If applicable, the FSIQ-RMS will also be completed at home prior to Visit 20 (FU) and Visit 18A (Week 156), ideally during the 7 consecutive days preceding these visits.

The data from the electronic device will be collected by the vendor who will send the results to Actelion.

The individual questionnaires will be completed only in countries for which validated translations are available.

A sample of the FSIQ-RMS is provided as Appendix 9.

7.3 Safety assessments

The definitions, reporting and FU of AEs, SAEs and potential pregnancies are described in Section 10.

7.3.1 12-lead electrocardiogram

A standard 12-lead ECG will be recorded at all scheduled study visits with the subject in a fully rested supine position after the subject has been allowed to rest for a minimum of 5 minutes. Pre-dose ECG may also be performed at unscheduled visits (U1, U2, etc.).

Digital 12-lead ECG devices will be provided to each site by the central ECG laboratory for the duration of the study. Digital ECG recording must be performed for all subjects according to the study protocol schedule. The data records will be sent to the central ECG laboratory for central reading. The reports from the central ECG laboratory will be sent to the site within a few days. In addition, at all sites where the first-dose administrator is not adequately experienced in interpreting ECGs, at Visit 3 (Day 1) and on the day of re-initiation of study drug when post-dose monitoring is required, the pre-dose and post-dose ECGs required for evaluation of discharge criteria will be transmitted to the central ECG laboratory for expedited evaluation, and the ECG report will be returned to the site within approximately 1–2 hours from transmittal.

Details will be provided in the ECG laboratory manual.

At Visit 3 (Day 1) and visits for re-initiation of study drug when post-dose monitoring is required, the 12-lead ECG monitoring will be performed under the responsibility of the first-dose administrator. At all other visits it will be performed under the responsibility of the treating neurologist or the first-dose administrator, depending on the site setting [see Sections 3.7.2 and 3.7.4]. The first-dose administrator will ensure that blinded study personnel at the study site, such as the treating and evaluating neurologists, clinical coordinator / study nurse, and other personnel involved in the clinical care and management of study subjects, do not have access to post-dose ECGs at Visit 3 (Day 1) and at visits for re-initiation of study drug when post-dose monitoring is required (Visits I1, I2, etc.; see Section 8.4.2).

The following variables will be evaluated: HR (bpm), PR (ms), QRS (ms), QT (ms), QTc (ms), and any ECG findings. QTc (ms) will be calculated according to Bazett's and Fridericia's formula ($QTcB = QT/(RR)^{1/2}$ and $QTcF = QT/(RR)^{1/3}$, respectively).

At Visit 3 (Day 1), the pre-dose ECG must be performed prior to randomization and the applicable point from exclusion criterion #12 (e.g., HR < 50 bpm, presence of second-degree AV block or third degree AV block, or a QTcF interval > 470 ms [females], > 450 ms [males]; see Section 4.4) must be ruled out. The first-dose administrator must provide the ECG results and interpretation to the principal investigator / treating neurologist and support her/him, if requested, to make a final decision on the subject's eligibility according to the inclusion/exclusion criteria.

During the treatment period ECGs must be performed at pre-dose. Additionally, at Visit 6 (Week 12), an ECG must also be performed at 3 hours post-dose. In case concomitant treatment with a QT-prolonging drug with known risk of Torsades de Pointes is needed, additional ECGs will be performed according to the guidance provided in Appendix 4.

At Visit 3 (Day 1) and on the day of re-initiation of study drug when post-dose monitoring is required [see Section 5.1.9], ECGs must be performed at pre-dose, and hourly (± 15 minutes) thereafter for a minimum of 4 hours and up to 12 hours post-dose. Subjects may be discharged from the cardiac monitoring if they meet the discharge criteria before 12 hours post-dose but no sooner than the (report of) ECG at 4 hours post-dose has been evaluated by the first-dose administrator [see Section 5.1.10]. If the subject does not meet the defined discharge criteria at 12 hours post-dose, the subject will be permanently discontinued from the study drug but will continue to be monitored, and additional ECG measurements will be performed until changes in ECG variables are no longer clinically relevant (i.e., discharge criteria are met; see Section 5.1.10), or until medically indicated.

At Visit 3 (Day 1) and on the first day of re-initiation of study drug when post-dose monitoring is required, significant findings, which in view of the first-dose administrator meet the definition of a (non-serious) AE, have an onset after the study drug intake, and are resolved at the time of discharge of the subject from cardiac monitoring, must be recorded directly on the AE page of the separate eCRF by the first-dose administrator / delegate. These AEs will not be visible to any of the blinded study personnel at the study site. All other significant findings on Day 1 or on the first day of re-initiation of study drug when post-dose monitoring is required that are serious or unresolved at the time of discharge of the subject from cardiac monitoring or with an onset on any other day, which in her/his view meet the definition of an AE, must be reported to the principal investigator / treating neurologist who will record these events on the AE page of the eCRF.

7.3.2 Blood pressure

Blood pressure measurements, including SBP and DBP, will be performed at all scheduled study visits. In addition, unscheduled BP measurements may be performed at any time during the study (Visits U1, U2, etc.). At Visit 3 (Day 1), the pre-dose BP measurement must be performed prior to randomization. At Visit 3 (Day 1) and on days of re-initiation of study drug when post-dose monitoring is required [see Section 5.1.9], SBP and DBP will be measured at pre-dose and hourly (± 15 minutes) thereafter for a minimum of 4 hours and up to 12 hours post-dose. Subjects may be discharged from cardiac monitoring if they meet the discharge criteria before 12 hours post-dose but no sooner than 4 hours post-dose [see Section 5.1.10]. If the subject does not meet the defined discharge criteria at 12 hours post-dose, the subject will be permanently discontinued from the study drug but will continue the cardiac monitoring, and additional BP measurements will be performed until changes are no longer clinically relevant (i.e., discharge criteria are met; see Section 5.1.10), or until medically indicated.

BP monitoring will be performed using the same type of device throughout the study on the same arm with the subject in a fully rested supine position after the subject has been allowed to rest for a minimum of 5 minutes. At all assessments (except post-dose assessments after first dose on Day 1 or at re-initiation), SBP and DBP will be measured twice (i.e., two SBP measurements and two DBP measurements). The two obtained measurements (i.e., two SBP measurements and two DBP measurements) and the position and arm used are to be recorded in the eCRF. The means of the two obtained measurements will be calculated by the eCRF. Post-dose assessments at Visit 3 (Day 1) and at visits for re-initiation of study drug when post-dose monitoring is required will only be measured once at each timepoint. This single obtained SBP measurement is to be used for determining discharge criteria on Day 1 and on days of re-initiation of study drug when post-dose monitoring is required.

At Visit 3 (Day 1) and at visits for re-initiation of study drug when post-dose monitoring is required, the assessment of vital signs will be performed under the responsibility of the first-dose administrator who will also evaluate and interpret these assessments. At all other visits, it will be performed under the responsibility of the treating neurologist or the first-dose administrator, depending on the site setting [see Sections 3.7.2 and 3.7.4].

On Day 1 and on the first day of re-initiation of study drug when post-dose monitoring is required, significant findings, which in view of the first-dose administrator meet the definition of an AE, have an onset after the study drug intake, and are resolved at the time of discharge of the subject, must be recorded directly on the AE page of the separate eCRF by the first-dose administrator / delegate. These AEs will not be visible to any of the blinded study personnel at the study site. All other significant findings on Day 1 or on the first day of re-initiation of study drug when post-dose monitoring is required that are unresolved at the time of discharge of the subject from cardiac monitoring or with an onset on any other day which in her/his view meet the definition of an AEs must be reported to the principal investigator / treating neurologist who will record these events on the AE page of the eCRF.

7.3.3 Spirometry

Spirometry tests to assess pulmonary function will be performed at Visit 2 (Baseline), Visit 6 (Week 12), Visit 9 (Week 48) and every 48 weeks thereafter until Visit 17 (Week 144), Visit 18 (EOT), Visit 20 (FU), and at unscheduled visits (U1, U2, etc.) if clinically indicated. If applicable, spirometry tests will also be performed at the corresponding visits in the PTOP. In addition, unscheduled spirometry will have to be conducted in the event of persistent respiratory symptoms (e.g., dyspnea).

Prior to randomization, spirometry can be performed at Visit 2 (Baseline) or at any time during the pre-randomization period. It is highly recommended that all spirometry assessments are performed in the morning, and prior to study drug intake.

Subjects must refrain from taking short-acting beta-agonists (e.g., salbutamol) for 6 hours and long-acting beta-agonists for 24 hours prior to spirometry testing. If taken, the test should be rescheduled. To perform the spirometry test, subjects will be rested for a minimum of 5 minutes prior to start. Sufficient forced expiratory maneuvers (up to a maximum of eight) will be performed to produce a minimum of three technically acceptable and repeatable traces (according to American Thoracic Society (ATS) / European Respiratory Society (ERS) guideline criteria; see PFT manual). The best (largest) FEV_1 and FVC values from the three acceptable and repeatable tests will serve for the calculation of % of predicted values and used for the endpoint derivations. These values may come from separate maneuvers. The FEV_1 and FVC measures obtained at Visit 2 (Baseline) and selected as described above will be used as the study baseline.

Spirometry testing will consist of FVC and FEV_1 assessments. Further indices, part of the collected flow-volume curves, may be explored and/or used for spirometry quality control measures. The following flow-volume curve indices will be assessed at each timepoint: FEV_1; FVC; and the peak expiratory flow (PEF). An anonymized copy of these results, including all tracings (i.e., all flow volume curves, volume time curves (if available) and numeric values from every performed effort as additional parameters and quality check documents routinely collected by the PFTs site (i.e., calibration results and log) may be collected by the sponsor for quality control purposes.

The best (largest) FEV_1, FVC and PEF values from the three acceptable and repeatable tests will be recorded in the eCRF as absolute volume in liters and as flow in liters/second (rounded to two decimal places). These values may come from separate maneuvers. The FEV_1/FVC ratio will be derived from the FVC and FEV_1 values recorded in the eCRF.

Spirometry tests will be conducted according to the ATS/ERS guidelines [Miller 2005a, Miller 2005b]. The spirometer must fulfill the technical requirements and recommendations for range and accuracy for forced expiratory maneuvers from the ATS/ERS guidelines [Miller 2005b]. The pulmonary function testing laboratory will ensure that the spirometer is functioning properly and is calibrated according to manufacturer instruction and ATS/ERS guidelines. A copy of the calibrations from the day of test must be stored as source documents in the subject charts at each subject visit, and a log of calibration results must be maintained at the site.

Spirometry testing will be performed by a PFT technician, respiratory therapist or expert, or an equally experienced person according to the ATS/ERS guidelines (e.g., for the US, a registered pulmonary function technologist and/or a registered respiratory therapist). To the extent logistically feasible, attempts should be made to have the same tester throughout the study for a subject. For each test, the name of the tester must be stored as source documents in the patient charts. Back-up testers (PFT technician, respiratory therapist, or expert or an equally experienced person according to the ATS/ERS guidelines may conduct spirometry if the primary tester is not available). All PFT technicians or other experienced persons participating in the study will be trained on the specific requirements for the study and be reminded of ATS/ERS recommendations before study start and when compliance issues are identified. In addition, a specific PFT manual will describe the procedures to be implemented by the pulmonary function facility at each investigational site, in order to maintain high quality standards and in order to ensure the validity of the data collected.

Clinically relevant findings meeting the definition of an AE (new AE, or worsening of previously existing condition; see Section 10.1) must be recorded on the AE page of the eCRF.

Predicted normal values for FVC and FEV_1 will be used to determine exclusion criteria. Predicted normal values will be adjusted for subjects from ethnic groups other than white/Caucasian. The formulas for the calculation of the predicted normal values for FEV_1 and FVC and the ethnic group adjustments used in this study are those of the European Community for Coal and Steel [Quanjer 1993] (see details in PFTs manual).

Spirometry conduct, documentation, performance, training details (of the responsible PFT site personnel), and quality control procedures are described in the PFT manual.

7.3.4 Chest X-ray

CXR will be performed at Visit 1 (Screening) or at any time during the pre-randomization period and assessed by the local radiologist in order to exclude any subject with findings suggestive of active or latent TB. Any CXR performed within 90 days prior to Visit 1 (Screening) can be used; if available, there is no need to repeat CXR at Visit 1 (Screening). In case of re-screening, CXR does not need to be repeated if it was performed within 90 days prior to the date of re-screening.

CXR will be repeated at Visit 18 (EOT) in all subjects to characterize any pulmonary structural changes occurring during treatment. In case of premature discontinuation, the CXR at EOT does not need to be performed if the EOT visit occurs within 48 weeks of the pre-randomization CXR. All examinations will be documented in the source documents of the subject. Examination should also be recorded in the eCRF as normal or abnormal. If an abnormality is found, it should be specified on the corresponding eCRF page. Clinically relevant findings meeting the definition of an AE (new AE, or worsening of previously existing condition) [see Section 10.1] must be recorded on the AE page of the eCRF. Study participants, who experience clinically significant changes in CXR will be followed-up until establishing the final diagnosis and managed as per local medical practice. Other diagnostic procedures may be performed as a FU assessment according to local standard procedures when considered necessary by the investigator.

7.3.5 Test for tuberculosis

An IFN gamma release assay (QuantiFERON-TB-Gold®) will be performed at Visit 1 (Screening) to screen for active or latent TB. The test will be analyzed and interpreted at the central laboratory [see Section 7.3.13], and transferred to the eCRF database.

Only subjects with a negative test at Visit 1 (Screening) and without CXR findings [see Section 7.3.4] at Visit 1 (Screening) or within the previous 90 days suggestive of active or latent tuberculosis can be included in the study. If the test result is positive, subjects must not be included in the study, except if there is documentation that the subject has received adequate treatment for TB previously. If the test result is inconclusive (invalid, indeterminate, or borderline), the test may be repeated once and a negative result must be obtained prior to randomization in order to include the subject. If the result of the

repeated test is again inconclusive (invalid, indeterminate, or borderline), subjects must not be included in the study.

Details on the performance of the test for TB will be provided in the specific central laboratory manual.

7.3.6 Ophthalmologic assessments

Ophthalmologic assessments will be performed by an ophthalmologist at Visit 1 (Screening), Visit 6 (Week 12), Visit 7 (Week 24), Visit 9 (Week 48), and every 48 weeks thereafter until Visit 17 (Week 144), Visit 18 (EOT), Visit 20 (FU) and at unscheduled visits. The purpose of the assessment prior to randomization is to exclude subjects with macular edema or diabetic retinopathy from the study, and to document a baseline assessment.

Testing at Visit 1 (Screening) can be performed at any time during the pre-randomization period. At Visit 18 (EOT), testing may be performed up to 7 days prior to the visit date but no later than 7 days after the discontinuation of study drug. In addition, an unscheduled ophthalmological examination will be done in the event of visual symptoms or findings suggestive of active uveitis [see Section 5.1.12.7].

The safety ophthalmological assessment includes previous eye history and ophthalmic conditions, any new or current ophthalmological symptoms, assessment of best corrected visual acuity (ETDRS charts), measurement of ocular pressure with Goldmann applanation tonometry (recommended, if not available other tonometry methods are allowed), slitlamp examination of the anterior segment, and dilated indirect funduscopy. In cases where pupil dilatation is medically contraindicated then dilated funduscopy can be replaced by funduscopy with ultra widefield imaging. Additionally, the safety ophthalmological assessment will include FA in case of suspicion of active uveitis at Visit 1 (Screening) or during a scheduled ophthalmological assessment (unless contra-indicated according to the ophthalmologist) [see Section 5.1.12.7]. While the visual acuity and ocular pressure measurement themselves may be performed by a delegate (e.g., technician, optometrician), the review and interpretation must be performed by the ophthalmologist. Conduct, review, and interpretation of all other ophthalmological exams must be performed by the ophthalmologist. FA (if applicable) may be performed by a delegate (e.g., technician, optometrician) but always in the presence of the ophthalmologist who will review and interpret the results.

All ophthalmological examinations will be documented in the source documents of the subject. All variables assessed at the ophthalmological examination should also be recorded in the eCRF as normal or abnormal. If an abnormality is found on any of the assessed variable, it should be specified on the corresponding eCRF page. Clinically

relevant findings meeting the definition of an AE (new AE, or worsening of previously existing condition) [see Section 10.1], must be recorded on the AE page of the eCRF.

7.3.7 Optical coherence tomography

OCT will be assessed at Visit 2 (Baseline), Visit 6 (Week 12), Visit 7 (Week 24), Visit 9 (Week 48), and every 48 weeks until Visit 17 (Week 144), and at Visit 18 (EOT). OCT may also be performed at unscheduled visits (U1, U2, U3, etc.). Testing at Visit 2 (Baseline) can be performed at any time during the pre-randomization period. The purpose of the assessment prior to randomization is to exclude subjects with macular edema or diabetic retinopathy from the study, and to document a baseline assessment.

At Visit 18 (EOT), testing may be performed up to 7 days prior to the visit date but no later than 7 days after the discontinuation of study drug. In addition, unscheduled OCT examinations will have to be assessed in the event of visual symptoms or findings suggestive of macular edema according to the ophthalmologist's decision, or in case of active uveitis diagnosed during the study [see Section 5.1.12.7]. While the OCT exam may be performed by a delegate (e.g., technician, optometrician), the review and interpretation must be performed by the ophthalmologist.

The site will use the OCT device available locally and must ensure it is working properly. To the extent that is logistically feasible, the same OCT machine is to be used for each individual subject throughout the study.

All examinations will be documented in the source documents of the subject. OCT examination should also be recorded in the eCRF as normal or abnormal. If an abnormality is found, it should be specified on the corresponding eCRF page. Clinically relevant findings meeting the definition of an AE (new AE, or worsening of previously existing condition) [see Section 10.1.1], must be recorded on the AE page of the eCRF.

The OSB will receive all information related to suspected cases of macular edema and will perform a central, blinded review of OCT results and subject data of suspected cases of macular edema.

7.3.8 Weight and height

Body weight will be measured at Visit 1 (Screening), Visit 2 (Baseline), Visit 9 (Week 48), and every 48 weeks until Visit 17 (Week 144), and at Visit 18 (EOT). Height is only measured at Visit 1 (Screening). Data will be collected in the eCRF.

7.3.9 Physical examination

Physical examination is performed by the principal investigator or treating neurologist at Visit 1 (Screening), Visit 2 (Baseline), Visit 7 (Week 24), and every 24 weeks thereafter until Visit 17 (Week 144), at Visit 18 (EOT), and at unscheduled visits due to relapses

(R1, R2, etc.). If applicable, physical examination will also be performed at corresponding visits in the PTOP. In addition, unscheduled physical examination may be performed at any time during the study (Visits U1, U2, etc.) if deemed necessary by the investigator.

Physical examination includes the examination of the general appearance, head, eyes, ears, nose, throat, neck, heart, lungs, abdomen, lymph nodes, extremities, skin, neurological, and musculoskeletal functions. Other exams will be performed if indicated, based on medical history and/or symptoms.

Information for all physical examinations must be included in the source documentation at the study site. The observations should be reported by body system in the eCRF as normal or abnormal. If an abnormality is found, it should be specified on the corresponding eCRF page, describing the signs related to the abnormality (e.g., systolic murmur). Clinically relevant findings meeting the definition of an AE (new AE, or worsening of previously existing condition) must be recorded on the AE page of the eCRF.

Note:
The standardized neurological evaluation based on EDSS and FS scores conducted by the efficacy assessor [see Section 7.2.1] does not obviate the requirement for the examination of the neurological function as part of the physical examination by the treating neurologist.

7.3.10 Body temperature

Body temperature will be measured at all scheduled study visits. Body temperature will also be measured at unscheduled visits for relapses (Visits R1, R2, etc.). In addition, unscheduled body temperature measurements may be performed at any time during the study (Visits U1, U2, etc.).

All body temperature assessments will be documented in the source documents of the subject. All body temperature assessments should also be recorded in the eCRF as normal or abnormal. If an abnormality is found, it should be specified on the corresponding eCRF page. Clinically relevant findings meeting the definition of an AE (new AE, or worsening of previously existing condition; see Section 10.1) must be recorded on the AE page of the eCRF.

7.3.11 Pulse rate

Pulse rate will be assessed at unscheduled visits for relapses (Visits R1, R2, etc.). If the visit for relapse corresponds to a visit when 12-lead ECG is performed, pulse rate assessment may be omitted. Pulse rate may also be assessed at any time during the study,

as part of unscheduled visits (Visits U1, U2, etc.) when 12-lead ECG may not be performed.

All pulse rate examinations will be documented in the source documents of the subject. All pulse rates should also be recorded in the eCRF as normal or abnormal. If an abnormality is found on any of the assessed variables, it should be specified on the corresponding eCRF page. Clinically relevant findings meeting the definition of an AE (new AE, or worsening of previously existing condition) [see Section 10.1], must be recorded on the AE page of the eCRF.

7.3.12 Dermatological examination

A complete skin examination will be performed by a dermatologist at Visit 2 (Baseline), Visit 9 (Week 48), and every 48 weeks thereafter until Visit 17 (Week 144), and at Visit 18 (EOT). If applicable, dermatological examination will also be performed at corresponding visits in the PTOP. In addition, unscheduled complete skin examination may be performed by the dermatologist at any time during the study (Visits U1, U2, etc.).

The purpose of the skin examination prior to randomization is to record the pre-existing lesions, exclude subjects with suspicious skin lesions (pre-cancerous, cancerous) from the study, and to document a baseline assessment. In case of re-screening, skin examination does not need to be repeated if skin examination from initial screening was performed within 90 days prior to the date of re-screening unless the screen failure was due to a skin lesion. If the screen failure was due to a pre-cancerous skin lesion or basocellular carcinoma that was then completely excised, the subject may be re-screened, in which case a new dermatological examination with focus on the excised skin lesion(s) has to be performed during pre-randomization.

In the event of findings of suspicious or pre-cancerous or cancerous skin disorders observed at any visit during the study, the dermatologist will conduct further examination, as per local standard practice, including the taking of skin biopsies if required to rule out or confirm a diagnosis.

All examinations will be documented in the source documents of the subject. Dermatological examination should be recorded in the eCRF as normal or abnormal. If an abnormality is found, it should be specified on the corresponding eCRF page. Clinically relevant findings meeting the definition of an AE (new AE, or worsening of previously existing condition; see Section 10.1) will be recorded accordingly on the AE page of the eCRF.

7.3.13 Laboratory assessments

7.3.13.1 Type of laboratory

A central laboratory (see central laboratory manual for contact details) will be used for all protocol-mandated laboratory tests, including re-tests due to laboratory abnormalities and laboratory tests performed at unscheduled visits. Central laboratory data will be automatically transferred from the central laboratory database to Actelion's clinical database.

Under specific circumstances (e.g., if the subject lives far from the site and cannot return every 4 weeks (± 3 days) for the lymphocyte count assessments), laboratory samples may be collected at a laboratory close to where the subject lives (satellite laboratory), and sent to the central laboratory for analysis. In such a case, the satellite laboratory must be provided with the central laboratory sampling kits, which must be used for blood collection. The blood samples collected locally will be shipped by the local laboratory to the central laboratory for analysis. Such a local laboratory shall be identified as soon as possible, but no later than upon enrollment of the subject in the study.

In exceptional cases (e.g., subject is hospitalized in a different hospital from the study center due to a medical emergency, or missing central laboratory values) local laboratory results (with the corresponding normal ranges) will be entered into the clinical database via dedicated CRF pages.

If a central laboratory sample is lost or cannot be analyzed for whatever reason, the investigator may collect an additional sample as soon as possible for retest analysis, unless a local laboratory sample was collected within the same time-window and these test results are available.

The central laboratory will provide all laboratory results by fax or email to the site with the exception of the results of the total WBC count and total lymphocyte count. The lymphocyte count results obtained during treatment period will be communicated to the site only if one of the below applies:

- A total lymphocyte count $< 0.2 \times 10^9$/L is recorded by the central laboratory. In this event, an alert containing the total lymphocyte count result will be sent to the principal investigator / treating neurologist and the sponsor [see Section 5.1.12.2].
- A WBC count $> 20 \times 10^9$/L or a lymphocyte count $> 8.0 \times 10^9$/L is recorded by the central laboratory. In this event, an alert containing the total WBC or lymphocyte count result (as applicable) will be sent to the principal investigator / treating neurologist and the sponsor.
- A total lymphocyte count decrease of > 50% from the value recorded at Visit 5 (Week 4) associated with a total lymphocyte count $< 0.5 \times 10^9$/L (< 500 cells/mm^3) is

recorded at 2 consecutive scheduled visits after Visit 5 (Week 4). In this event, an alert containing the lymphocyte count result will be sent to the principal investigator / treating neurologist and the sponsor.

- A total lymphocyte count $< 0.5 \times 10^9$/L is observed at FU. In this event, an alert containing the total lymphocyte count result will be sent to the principal investigator / treating neurologist. Discontinuation of DMF treatment should be considered in accordance with prescribing information [Tecfidera USPI, Tecfidera SmPC].
- WBC and total lymphocyte counts measured at any of the visits in the PTOP. For subjects who have entered the PTOP following study drug discontinuation, lymphocyte count values recorded after entering the PTOP will be visible to the principal investigator / treating neurologist.

All laboratory reports must be signed and dated by the principal investigator or delegate within 5 calendar days of receipt and filed with the source documentation. The investigator/delegate must indicate on the laboratory report whether abnormal values are considered clinically relevant or not. Clinically relevant laboratory findings meeting the definition of an AE [see Section 10.1] must be reported as an AE or SAE as appropriate, and must be followed until the value returns to within the normal range or is stable, or until the change is no longer clinically relevant. Further laboratory analyses should be performed as indicated and according to the judgment of the investigator.

Details about the collection, sampling, storage, shipment procedures, and reporting of results and abnormal findings can be found in the laboratory manual.

7.3.13.2 Laboratory tests

When applicable, blood samples will be drawn before the morning administration of study medication at Visit 1 (Screening), Visit 2 (Baseline), Visit 4 (Week 2), Visit 5 (Week 4), Visit 6 (Week 12) and every 12 weeks thereafter up to Visit 18 (EOT), and at Visit 20 (FU) and, if applicable, at all corresponding visits in the PTOP (see anticipated total blood volume in Table 7). Unscheduled laboratory tests may be performed at any time during the study (Visits U1, U2, U3, etc.).

Additional lymphocyte count measurements will be performed every 4 weeks (± 3 days) up to Week 24.

During the pre-randomization period, hematology and clinical chemistry laboratory assessments at Visit 1 (Screening) must be performed a minimum of 21 days before the laboratory assessment at Visit 2 (Baseline).

If a laboratory sample cannot be evaluated (e.g., is lost or deteriorated), an additional sample may need to be taken if deemed necessary by the investigator.

Hematology

- RBC count
- Total and differential WBC counts (basophils, eosinophils, lymphocytes, monocytes, neutrophils, band forms)
- Platelet count
- Hb
- Hematocrit

Clinical chemistry

- Glucose
- ALT, AST, alkaline phosphatase (AP), total bilirubin, lactate dehydrogenase
- INR
- Creatinine
- Calculated creatinine clearance (Cockroft-Gault)
- Urea
- Uric acid
- Total cholesterol
- Triglycerides
- Sodium, potassium, chloride, calcium
- Total protein, albumin
- C-reactive protein

Virus serology

- Hepatitis B surface antigen, Hepatitis C antibodies, HIV1 and HIV2 antibodies, varicella-zoster virus antibodies at Visit 1 (Screening).

JCV serology testing

- JCV antibodies at Visit 2 (Baseline) and every 48 weeks up to Visit 18 (EOT), and, if applicable, at all corresponding visits in the PTOP. Aggregate data from this analysis will be reviewed by the IDMC and the sponsor, but will not be communicated to the sites until database closure unless deemed necessary for safety reasons (i.e., signs or symptoms raising suspicion of PML). In case of screening failure, the sample collected at Visit 2 (Baseline) will not be analyzed.

Additional analyses in the event of infections

- A serum sample will be taken at Visit 2 (Baseline) to be stored at the central laboratory for potential retrospective analyses of viral serology titers in the event of infections (e.g., suspected opportunistic infection) during the study.

Additional analyses in the event of a vaccination with non-live vaccines

- Subjects receiving non-live vaccination while on study treatment will have 5 mL of blood drawn prior to and ≥ 3 weeks after vaccination in order to explore changes in vaccine-specific antibody titers from pre- to post-vaccination. Samples are to be stored at the central laboratory to be analyzed at the end of the study.

Test for TB

- An IFN gamma release assay will be performed at Visit 1 (Screening) to screen for active or latent TB [see Section 7.3.5].

Pregnancy test

A serum pregnancy test for WOCBP will be performed at Visit 1 (Screening), Visit 20 (FU), and if pregnancy is suspected during the study. Urine pregnancy tests will be performed at Visit 2 (Baseline), Visit 4 (Week 2), Visit 5 (Week 4), Visit 6 (Week 12), and every 12 weeks thereafter up to Visit 17 (Week 144), and at Visit 18 (EOT). Additionally, urine pregnancy tests will be performed at home every 4 weeks (± 4 days) between the visits. Subjects will communicate the result (telephone call) of the tests to the principal investigator / treating neurologist.

In order for WOCBP to be randomized in the study, they must have a confirmed negative serum pregnancy test at Visit 1 (Screening) and a second confirmed negative urine pregnancy test at Visit 2 (Baseline) prior to randomization. **The two tests must be performed a minimum of 21 days apart.**

Serum pregnancy testing results will be automatically transferred from the central laboratory database to Actelion's clinical database. Urine pregnancy testing results will be recorded in the eCRF. In case of pregnancy, a Pregnancy Form must be completed [see Section 10.3].

Urinalysis

- pH
- Glucose
- Proteins
- Blood
- Leukocytes
- Bilirubin, urobilinogen

Urinalysis will be assessed using dipsticks at Visit 1 (Screening), Visit 6 (Week 12), Visit 7 (Week 24), and every 24 weeks thereafter up to Visit 17 (Week 144), Visit 18 (EOT), and Visit 20 (FU). If applicable, urinalysis will also be performed at all

corresponding visits in the PTOP. In addition, unscheduled urinalysis may be performed at any time during the study (Visits U1, U2, etc.).

Urine dipsticks provided by the central laboratory will be used to perform the urinalysis. The test should be performed and analyzed at the site. The results must be documented in the source documents / subject charts and should be recorded in the eCRF as normal or abnormal. If an abnormality is found, it should be specified on the corresponding eCRF page and the results for the abnormal variable will be reported in the eCRF. Clinically relevant findings meeting the definition of an AE (new AE, or worsening of previously existing condition) [see Section 10.1] will be recorded accordingly on the AE page of the eCRF.

7.4 Electronic self-rated version of the Columbia-Suicide Severity Rating Scale

The electronic self-rated version of the C-SSRS is used to reliably and consistently monitor subjects for suicidal ideation and behavior during the study.

The eC-SSRS assesses lifetime suicidality during an initial baseline evaluation (Visit 2 [Baseline]), and then prospectively monitors ideations and behaviors at subsequent follow-up assessments (Visit 9 [Week 48], Visit 13 [Week 96], Visit 17 [Week 144] and Visit 18 [EOT]). At each visit, the treating neurologist will review the responses provided by the subject and assess the findings. The eC-SSRS is a fully structured clinical interview designed and developed for electronic administration. Subjects will be asked to respond to standardized clinical questions aimed at measuring the severity of suicidal ideation (rated on a 5-point ordinal scale), the levels of suicidal behavior, and the category self-injurious behavior without suicidal intent. Any subject who reaches an eC-SSRS suicidal ideation score of 4 or above, or who responds “yes” on the eC-SSRS suicidal behavior item must be referred to an appropriate health professional who should make a decision on the management of the suicidal symptoms and recommend whether or not the subject should continue the treatment with the study drug.

It is recommended that the eC-SSRS is completed prior to any clinical assessments, after the WPAI:MS and SF-36v2™ have been completed. Preferably, subjects would complete the eC-SSRS while waiting for their appointment before any interaction with healthcare providers. It is recommended that the subject stays at site until the report has been reviewed by the PI / treating neurologist.

A sample of the eC-SSRS (in English) is provided as Appendix 14. The data will be collected via electronic data capture and processed centrally by a vendor who will send the results to Actelion.

Actelion has been granted a license agreement for the use of the eC-SSRS.

7.5 Quality of life assessments

7.5.1 36-Item Short Form Health Survey v2 (SF-36v2™)

The SF-36v2™ Questionnaire (SF-36v2™ Health Survey© 1996, 2000 by Medical Outcomes Trust and Quality Metric Incorporated) is used to assess the subject's quality of life. The SF-36v2™ will be completed by the subject at Visit 2 (Baseline), at Visit 6 (Week 12), Visit 7 (Week 24), Visit 9 (Week 48), and every 24 weeks thereafter up to Visit 17 (Week 144), and at Visit 18 (EOT) and at unscheduled visits due to relapses (R1, R2, etc.).

In the SF-36v2™ Questionnaire, subjects are instructed to rate their health and capacity to perform activities of daily living in eight domains including physical functioning, physical role limitations, bodily pain, general health, vitality, social functioning, emotional role limitations, and mental health during the last 4 weeks. Raw domain scores are determined and transformed to a 0–100 scale as described in the SF-36v2™ manual [Maruish 2011]. Individual domain scores are used to determine the physical and mental component summary scores as described in the SF-36v2™ manual [Maruish 2011].

It is preferable that the SF-36v2™ Questionnaire is completed prior to any clinical assessments, after the WPAI:MS have been completed. Preferably, subjects would complete the SF-36v2™ while waiting for their appointment before any interaction with health care providers to avoid any potential bias in their responses.

The SF-36v2™ with a 4-week recall period will be used. A sample of the SF-36v2™ (in English) is provided as Appendix 10. The questionnaire will be administered in an electronic format. The data from the electronic device will be collected by the vendor who will send the results to Actelion.

Actelion has been granted a license agreement for the use of the SF-36v2™ Questionnaire. The individual questionnaires will be completed only in countries for which validated translations are available.

7.6 Pharmacoeconomic assessments

7.6.1 Work Productivity and Activity Impairment Questionnaire: Multiple Sclerosis V2.0

The WPAI:MS is a six-question patient-reported quantitative assessment of the amount of absenteeism, presenteeism, work productivity loss and activity impairment attributable to MS during the previous 7 days.

Actelion has adapted the specific health version of the WPAI version 2, which was developed by Reilly Associates for MS.

The WPAI:MS will be completed by the subject at Visit 2 (Baseline), at Visit 6 (Week 12), Visit 7 (Week 24), Visit 9 (Week 48), and every 24 weeks thereafter up to Visit 17 (Week 144), and at Visit 18 (EOT).

WPAI:MS outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, i.e., worse outcomes.

It is preferable that the WPAI:MS Questionnaire is completed prior to any clinical assessments. Preferably, subjects would complete the WPAI:MS while waiting for their appointment before any interaction with health care providers to avoid any potential bias or impact of interventions in their responses.

A sample of the WPAI:MS (in English) is provided as Appendix 11. The questionnaire will be administered in an electronic format. The data from the electronic device will be collected by the vendor who will send the results to Actelion.

Actelion Pharmaceuticals has notified the developer about the use of the instrument in this study. No license is required for the administration of the instrument. The individual questionnaires will be completed only in countries for which validated translations are available.

7.6.2 Health care resource utilization

Health care resource utilization data, including number of intensive care unit (ICU) admissions for MS relapses and emergency medical facility visits for MS will be collected at Visit 2 (Baseline), Visit 4 (Day 15) and at every visit thereafter up to Visit 18 (EOT) as well as at unscheduled visits due to relapse (R1, R2, etc.).

Subjects will be asked to report any hospital visit, length of stay, any visits to emergency medical services facilities due to MS since the last study visit, the dates will be captured in the eCRF. Hospitalization due to MS relapses will be captured in the eCRF including the length of stay and any admissions to ICU.

7.7 Pharmacokinetic and pharmacodynamic assessments

7.7.1 Pharmacokinetic assessments

PK samples will be collected during this study for all subjects, in order to provide information about study drug exposure in the target population. Blood samples will be collected pre-dose at Visit 6 (Week 12), Visit 7 (Week 24), Visit 9 (Week 48), Visit 13 (Week 96), Visit 17 (Week 144), Visit 18 (EOT) and at Visit 20 (FU). Additionally, at Visits 3 and 6 (Day 1 and Week 12), PK samples will be drawn 3 hours (± 15 minutes) post-dose.

When possible, a PK sample will be collected for all subjects experiencing SAEs. In this event, the sample should be collected pre-dose, as early as possible after SAE onset, and no later than 7 days after the last dose of study drug.

Details of the collection and shipment of the samples will be described in the laboratory manual. The tubes and labels for the sampling will be provided by the central laboratory.

The date and the time of blood sample collection will be entered in the eCRF, as well as the status of the patient (fed or fasted). The date and time of the last study treatment dosing before blood draw will be entered in the eCRF.

The concentration of ponesimod in plasma will be determined by a validated liquid chromatography-tandem mass spectrometry assay by PRA Health Sciences – Early Development Sciences, bioanalytical laboratory. The lower limit of quantification is 1 ng/mL.

Note:
The 3-hour PK sample collected on Day 1 or on the first day of re-initiation of study drug when post-dose monitoring is required should be taken by the first-dose administrator, the first-dose administrator nurse or another person not involved in the clinical care and management of the study subject.

7.7.2 Pharmacodynamic assessments

7.7.2.1 Total lymphocytes

The main PD marker is total lymphocyte count, which will be measured as part of the hematology tests [see Section 7.3.13.2].

7.7.2.2 Blood lymphocyte subsets

Blood samples for lymphocyte subset analysis will be taken from approximately 200 subjects at Visit 2 (Baseline), Visit 6 (Week 12), Visit 7 (Week 24), Visit 9 (Week 48), Visit 13 (Week 96), Visit 17 (Week 144), Visit 18 (EOT), Visit 19 (FU7d), and at Visit 20 (FU). Participation in the sub-study will be mandatory for all subjects until at least the first 200 subjects are randomized [see Section 3.6.1] to the main study. If applicable, lymphocyte subsets will also be assessed at the corresponding visits in the PTOP (Visits 6A, 7A, 9A, 13A, 17A, and 18A).

The site staff will ship the blood samples to the central laboratory for analysis. T cell, B cell, and NK cell counts will be analyzed as well as T cell subsets (e.g., $CD4^+$ naïve, $CD4^+$ effector memory, $CD4^+$ central memory, $CD8^+$ naïve, $CD8^+$ effector memory, $CD8^+$ central memory, $CD8^+$ terminally differentiated effector memory, Th17 cells, Treg cells, and Th1 cells), will be analyzed by fluorescence activated flow cytometry using a combination of cell surface markers. Other lymphocyte subsets may also be analyzed.

Selected lymphocyte subsets may also be analyzed functionally *ex vivo* (e.g., production of cytokines). Results from the lymphocyte subsets sub-study will be blinded to site staff and the sponsor until study closure.

7.8 Total blood volume

The total blood volume to be drawn per subject during the entire course of the study is described in Table 7.

Table 7 Total blood volume to be drawn per subject

Main study

Test	Number of tests	Volume per test	Total volume per test throughout the study
Viral serology at Visit 1 (Screening)	1	7.5 mL	7.5 mL
Interferon gamma release assay for tuberculosis at Visit 1 (Screening)	1	3 × 1 mL	3 mL
Serum sample at Visit 2 (Baseline)[1]	1	5 mL	5 mL
Hematology[2]	19	2 mL	38 mL
Blood chemistry[3]	19	2.5 mL	47.5 mL
Lymphocytes[4]	3	2 mL	6 mL
INR	19	1.8 mL	34.2 mL
Ponesimod PK	9	3 mL	27 mL
Vaccine specific Antibody titers[5]	2	5 mL	10 mL
JCV serology	5	5 mL	25 mL
Total blood volume drawn throughout the main study: 203.2 mL[6,7]			

Lymphocyte subsets sub-study (approximately 200 subjects)

Test	Number of tests	Volume per test	Total volume per test throughout the study
Lymphocyte subsets	9	6 mL	54 mL
Additional blood volume drawn for the sub- study: 54 mL			

1. To be stored at the central laboratory for potential retrospective analyses of viral serology titers in the event of infections.
2. Additional samples may be needed in the event of lymphocytes < 200 cells/µL.
3. Includes serum pregnancy test at Visit 1 (Screening), if needed.
4. Blood samples for lymphocyte counts are required to obtain 4-weekly (± 3 days) lymphocyte counts up to Week 24.
5. Additional samples may be taken in the event of a vaccination with a non-live vaccine.

6. If the blood sample cannot be evaluated (e.g., is lost or deteriorated) additional samples may need to be taken if deemed necessary by the investigator.
7. In the event of a positive Hepatitis C antibody test, site can draw an additional confirmatory blood sample (2.5 mL) for testing of Hep C viral RNA.
INR = International Normalized Ratio; PK = pharmacokinetics

No genomic testing will be performed on any blood sample collected during this study.

8 SCHEDULE OF VISITS

A tabulated summary of all visits and assessments described in the following sections is provided in Table 1, Table 2 and Table 3. The schedule of visit dates should be established at the time of Visit 1 (Screening). To the extent possible, subjects will be expected to adhere to the established visit schedule.

The timepoint for every visit is defined taking as a reference Day 1 (Visit 3), which is the day of randomization.

When scheduling the different assessments for a subject visit, the following should be taken into account:

- When applicable, the subject must come to the clinic before the morning administration of study drug.
- At Visit 3 (Day 1) and on the days of re-initiation of study drug when post-dose monitoring is required (if applicable), the assessments during the visits will be divided into two parts: before (pre-dose) and after (post-dose) the administration of the study drug, which will be taken at the site on the day of visits.
- At other visits, ECGs, SBP/DBP, PFTs, blood drawings for hematology and biochemistry, along with all other assessments, are to be performed pre-dose.
- When applicable, PK sampling is to be done pre-dose. At Visit 3 (Day 1) PK sampling is to be drawn 3 hours post-dose. At Visit 6 (Week 12) PK sampling must be drawn on the same day as pre-and post-dose ECGs and SBP/DBP are performed.
- Resting time:
  - When the subject is to go to another department within the hospital for a specific test, sufficient time should be allowed for the subject to rest prior to the examination.
  - Sufficient resting time should be allowed between the walking assessments for MSFC and EDSS and other assessments (PFTs, ECGs, and BP).
  - Sufficient time between blood drawing and cardiac assessments (i.e., ECGs and/or BP measurement) is to be allowed.
- Preferably, questionnaires will be completed by the subject in the morning prior to any other protocol-mandated assessment and prior to any discussion with the

investigator or treating neurologist. Subjects will provide responses to the questionnaires while waiting for their appointment. Questionnaires should preferably be completed in the following order:

- WPAI:MS
- SF-36v2™
- eC-SSRS

To ensure compliance, at each visit the study personnel must remind WOCBP to use the methods of contraception defined for this study. The reminders must be documented in the hospital chart.

It is permitted to re-screen subjects once if the reason for non-eligibility was transient (e.g., abnormal laboratory test, insufficient wash-out period of a forbidden medication), provided that documented authorization has been received from Actelion. Re-screening requires re-consenting i.e., a new ICF must be signed by the subject and by the investigator. All pre-randomization assessments do not need to be repeated at the time of re-screening if they were performed within 90 days or within 37 days for laboratory (i.e., hematology, blood chemistry, and pregnancy test). The guidance indicating which test needs to be repeated at the time of the re-screening authorization is provided in Appendix 15.

The randomization must occur within 45 days from the date of Visit 1 (Screening; i.e., date of signature of the informed consent) or, in case of re-screening, within 45 days from the date of re-screening (i.e., date of signature of the new informed consent).

Unscheduled visits may be performed at any time during the study. Depending on the reason for the unscheduled visit (e.g., AE), appropriate assessments will be performed based on the judgment of the investigator and the results will be recorded in the CRF. After an unscheduled visit, the regular scheduled study visits must continue according to the planned visit and assessment schedule.

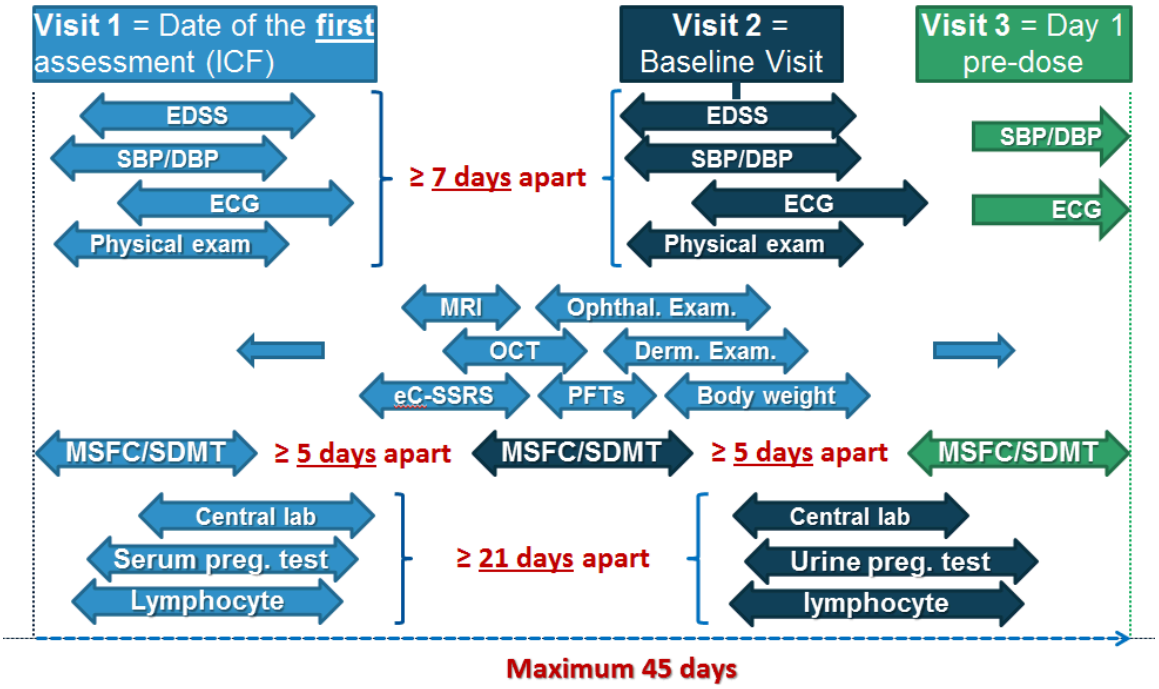
8.1 Pre-randomization period

The pre-randomization period must take place within 45 days prior to randomization and include the Visit 1 (Screening), Visit 2 (Baseline) and pre-dose assessments of Visit 3 (Day 1).

All pre-randomization assessments performed at Visit 1 (Screening) and Visit 2 (Baseline) may be conducted on days differing from the actual Visit 1 (Screening) and Visit 2 (Baseline) dates. All baseline assessments, including the ECG and blood pressure performed pre-dose on first day of dosing at Visit 3 (Day 1) must be performed before randomization [see Figure 4].

The start of screening occurs on the day the first screening assessment was performed (i.e., signature of informed consent).

Figure 4 Timing of the pre-randomization assessments



8.1.1 Visit 1 (Screening)

Visit 1 (Screening) will be performed at maximum 45 days prior to randomization. The Visit 1 (Screening) date is defined as the date of start of pre-randomization period (i.e., signature of the informed consent). During this visit, subject informed consent will be obtained, and the assessments required for the determination of subject eligibility will be performed. These assessments may generally be performed on separate days within the pre-randomization period.

Visit 1 (Screening) includes:

- After discussing the study with the investigator and after agreeing to study participation by signing the ICF, subjects will be assigned a subject number by the IRT provider. It is the responsibility of the investigator to obtain written informed consent prior to any screening assessment. The subject number will identify the subject throughout the study. In case of re-screening [see Section 8], the subject number assigned during the first screening procedure will be retained.
- Review of MS diagnosis and McDonald 2010 criteria.

- Recording of demographics, medical history, smoking status, and disease characteristics.
- Recording of previous and concomitant medications [see Section 5.2.2].
- EDSS/FS (performed by the efficacy assessor).
- SBP/DBP.
- Body weight and height.
- Physical examination.
- Body temperature.
- Ophthalmological examination (under the responsibility of the ophthalmologist).
- Hematology (including lymphocytes), blood chemistry, and serum pregnancy test for WOCBP.
- TB test.
- Viral serology.
- Urinalysis.
- 12-lead ECG.
- MSFC and SDMT (first test practice).
- FSIQ-RMS; subjects who appear eligible based on the assessments made during this visit will be provided with the FSIQ-RMS. Once the results from the laboratory assessments confirm the subject's eligibility, and provided no other assessment performed in the meantime excludes the subject, the site coordinator will contact the subject to instruct him/her to start the completion of the FSIQ-RMS [see Section 7.2.6].
- CXR (any CXR performed within 90 days prior to Visit 1 [Screening] can be used). In case of re-screening, CXR does not need to be repeated if it was performed within 90 days prior to the date of re-screening.
- Recording of AEs/SAEs: all AEs/SAEs occurring after signing of the ICF are to be reported in the eCRF and on an SAE form, if applicable.

The principal investigator / treating neurologist must check the inclusion/exclusion criteria. The next visit (Visit 2 [Baseline]) will only be scheduled if the subject meets all the eligibility criteria. If applicable, the date of screening failure will be collected in the IRT system and in the eCRF; additionally, the reasons for screening failure will be documented in the eCRF (screening information is collected for all screening failure subjects).

8.1.2 Visit 2 (Baseline)

Visit 2 (Baseline) will be performed anytime within the pre-randomization period. The date of EDSS assessment defines the date of the visit. During this visit, the inclusion and exclusion criteria will be confirmed, and baseline assessments will be performed and

recorded. While the assessments may generally be performed anytime during the pre-randomization period [see Figure 4], the following points should be considered:

- All Visit 1 (Screening) assessments repeated at Visit 2 (Baseline) with the exception of hematology and blood chemistry laboratory assessments (e.g., 12-lead ECGs, physical examination, SBP/DBP) must be performed at least 7 days after the Visit 1 (Screening) assessments.
- Hematology and blood chemistry laboratory assessments at Visit 2 (Baseline) must be performed at least 21 days after the hematology and blood chemistry laboratory assessments performed at Visit 1 [Screening; see Section 4.3].
- Similarly, for WOCBP, the urine pregnancy test at Visit 2 (Baseline) must be performed at least 21 days after the serum pregnancy test performed at Visit 1 (Screening).
- MSFC performed at Visit 2 (Baseline) must be performed at least 5 days after the assessment at Visit 1 (Screening) and at least 5 days before the assessment at Visit 3 (Randomization).

Visit 2 (Baseline) includes:

- WPAI:MS (subject completes the questionnaire prior to any clinical assessments or interaction with health care providers, preferably while waiting for their appointment).
- SF-36v2™ (subject completes the questionnaire after WPAI:MS, prior to any clinical assessments or interaction with health care providers, preferably while waiting for their appointment).
- eC-SSRS (subject completes the questionnaire after WPAI:MS and SF-36v2™ prior to any clinical assessments or interaction with health care providers, preferably while waiting for their appointment).
- Recording of change in previous and concomitant medications since Visit 1 [Screening; see Section 5.2].
- EDSS/FS (performed by the efficacy assessor).
- MS relapse.
- Health care resource utilization
- SBP/DBP.
- 12-lead ECG.
- Physical examination.
- Body temperature.
- Body weight.
- OCT (under the responsibility of the ophthalmologist).

- Dermatological examination (performed by the dermatologist). In case of re-screening, dermatological examination does not need to be repeated if dermatological examination from initial screening was performed within 90 days prior to the date of re-screening.
- Hematology (including lymphocytes), blood chemistry.
- Lymphocyte subsets (only at sites participating in sub-study).
- JCV serology.
- Urine pregnancy test for WOCBP.
- Additional serum sample for potential retrospective analysis of viral serology titers.
- Spirometry.
- MRI.
- MSFC and SDMT (second practice test).
- FSIQ-RMS.
- Recording of AEs/SAEs: all AEs/SAEs occurring after signing of the ICF are to be reported in the eCRF and on the SAE form, if applicable.

The principal investigator / treating neurologist must check all inclusion/exclusion criteria. The next visit (Visit 3) will only be scheduled if the subject meets all the eligibility criteria assessed at this time. Date of screen failure will be collected in the IRT system and in the eCRF; additionally, the reasons for screening failure are documented in the eCRF (screening information is collected for all screening failure subjects).

8.1.3 Visit 3 – Day 1 – pre-dose assessments

Visit 3 corresponds to the start of the treatment period and the date of randomization in the IRT system (Day 1 of the study). The assessments during Visit 3 will be divided into two parts: before (pre-dose) and after (post-dose) the administration of the first study drug dose [see Section 8.2.1]. The ECGs (pre- and post-dose), BP (pre- and post-dose), and first-dose administration must be performed on the same day and define the date of the visit.

The principal investigator / treating neurologist must check all inclusion/exclusion criteria. Pre-dose assessments include:

- Recording of change in previous and concomitant medications since Visit 1 [Screening; see Section 5.2].
- MS relapse.
- Body temperature.
- MSFC and SDMT (third test serving as baseline assessment).
- SBP/DBP (under the responsibility of the first-dose administrator).
- 12-lead ECG (under the responsibility of the first-dose administrator).
- Recording of methods of contraception (for WOCBP).

- Recording of AEs/SAEs: all AEs/SAEs occurring after signing of the ICF are to be reported in the eCRF and on an SAE form, if applicable.

8.2 Treatment period

The treatment period consists of the post-dose assessments at Visit 3 to Visit 18 (Randomization Day 1, Weeks 2, 4, 12, and every 12 weeks thereafter until EOT).

8.2.1 Visit 3 – Randomization Day 1 – Randomization and post-dose assessments

The treatment period starts with first dose taken during Visit 3 (Day 1 of the study).

The randomization must occur within 45 days from the date of Visit 1 (Screening; i.e., date of signature of the informed consent) or, in case of re-screening, within 45 days from the date of re-screening (i.e., date of the first assessment performed as part of the re-screening).

If eligible, the subject should be randomized in the study, and take the first dose of study drug. The subject must be monitored for up to 12 hours post-dose. Starting at 4 hours post-dose, the first-dose administrator must check whether the subject fulfills the discharge criteria from cardiac monitoring [see Section 5.1.10]. Subjects may be discharged from cardiac monitoring if they meet the discharge criteria before 12 hours post-dose but no sooner than the (report of) 4 hours post-dose ECG has been evaluated by the first-dose administrator [see Section 5.1.10].

Visit 3 post-dose assessment includes:

- After confirmation of eligibility (i.e., verification of all entry criteria) by the investigator:
  - Randomization via IRT to obtain randomization and study treatment kit number.
  - Dispensing of study treatment.
- SBP/DBP hourly (± 15 minutes) for up to 12 hours post-dose with a minimum of 4 hours post-dose (under the responsibility of the first-dose administrator).
- 12-lead ECG hourly (± 15 minutes) for up to 12 hours post-dose with a minimum of 4 hours post-dose (under the responsibility of the first-dose administrator).
- PK sampling at 3 hours (± 15 minutes) post-dose (**NB:** this should be performed after the corresponding hourly 12-lead ECG and SBP/DBP measurement).
- Recording of AEs and SAEs (**NB:** On Day 1, significant findings that, in view of the first-dose administrator, meet the definition of an AE, have an onset after the study drug intake, and are resolved at the time of discharge of the subject from cardiac monitoring, must be recorded directly on the AE page of the separate eCRF by the first-dose administrator / delegate. These AEs will not be visible to any of the blinded study personnel at the study site.).

- Remind WOCBP to use the methods of contraception defined for this study. The reminders must be documented in the hospital chart.

Schedule an appointment for next visit and instruct subject to:

- not take study treatment on the day of study visit prior to coming to the site.
- contact their principal investigator / treating neurologist at the clinical site immediately in the event of the appearance of any symptoms suggestive of an MS exacerbation.

Subjects assigned to the ponesimod arm will need to gradually up-titrate from 2 mg to 10 mg during Day 1 to 14. As there is no site visit planned until Day 15, subjects will be instructed on how to perform the gradual up-titration / mock up-titration during Visit 3.

The subject will be instructed to contact the site if she/he has any questions or problems.

8.2.2 Four-weekly lymphocyte counts

Lymphocyte counts will be assessed every 4 weeks up to Week 24 (i.e., additional lymphocyte tests will be performed at Week 8, Week 16, and Week 20). (Thereafter, lymphocyte counts will be assessed every 12 weeks up to EOT.)

The test window is ± 3 days. Under specific circumstances (e.g., subject lives far away from the site and cannot return every 4 weeks), laboratory samples could be drawn in a local laboratory close to where the subject lives, and analyzed at the central laboratory [see Section 7.3.13].

8.2.3 Visit 4 – Day 15

The visit window for this visit is ± 1 day. The visit includes:

- MS relapse.
- Health care resource utilization since the last visit.
- Recording of changes in concomitant medications.
- Body temperature.
- SBP/DBP (pre-dose).
- 12-lead ECG (pre-dose).
- Hematology (including lymphocytes), blood chemistry.
- Assessment and recording in the eCRF of methods of contraception (for WOCBP only).
- Urine pregnancy test for WOCBP.
- Recording of AEs and SAEs.
- Study treatment accountability and compliance review.
- IRT call and study treatment dispensing.
- Remind WOCBP to use the methods of contraception defined for this study. The reminders must be documented in the hospital chart.

- Schedule an appointment for next visit and instruct subject to:
  - bring back any blister packs (used, partially used and unused blister packs) and any unused tablets.
  - not take study treatment on the day of study visit prior to coming to the site.
  - contact their principal investigator / treating neurologist at the clinical site immediately in the event of the appearance of any symptoms suggestive of an MS exacerbation.

8.2.4 Visit 5 – Week 4

The visit window for these visits is ± 5 days. The visits include:

- Recording of changes in concomitant medications.
- Assessment and recording in the eCRF of methods of contraception (for WOCBP only).
- SBP/DBP (pre-dose).
- 12-lead ECG (pre-dose).
- MS relapse.
- Health care resource utilization since the last visit.
- Body temperature.
- Hematology (including lymphocytes), blood chemistry.
- Urine pregnancy test for WOCBP.
- Recording of AEs and SAEs.
- Study treatment accountability and compliance review.
- IRT call and study treatment dispensing.
- Remind WOCBP to use the methods of contraception defined for this study. The reminders must be documented in the hospital chart.
- Schedule an appointment for next visit and instruct subject to:
  - bring back any blister packs (used, partially used and unused blister packs) and any unused tablets.
  - not take study treatment on the day of study visit prior to coming to the site.
  - contact their principal investigator / treating neurologist at the clinical site immediately in the event of the appearance of any symptoms suggestive of an MS exacerbation.

8.2.5 In-between-visit telephone calls until Week 156 (Weeks 18, 30, 42, 54, 66, 78, 90, 102, 114, 126, 138, and 150)

The site will contact the subject in-between the 12-weekly visits (e.g., Visit 6 – Week 12, Visit 7 – Week 24, …) even after possible premature discontinuation from the study treatment (e.g., Visit 6A – Week 12 in the PTOP, Visit 7A – Week 24 in the PTOP, …). These telephone calls will be conducted either at Weeks 18, 30, 42, 54, 66, 78, 90, 102,

114, 126, 138 and 150 (± 7 days), or 6 weeks after the last 12-weekly visit (± 7 days). During these telephone calls, the site will proactively inquire about any new or worsened neurological symptoms.

8.2.6 Visits 6 and 7 – Weeks 12 and 24

The visit window for these visits is ± 7 days. The EDSS must be assessed during this visit window (i.e., ± 7 days). The date of drug dispensing, preferably corresponding to the date of registration of the visit in the IRT system, defines the date of the visit. All other assessments may be performed up to 7 days prior to or after this visit date. The visits include:

- WPAI:MS (subject completes the questionnaire prior to any clinical assessments or interaction with health care providers, preferably while waiting for their appointment).
- SF-36v2^{TM} (subject completes the questionnaire after the WPAI:MS, prior to any clinical assessments or interaction with health care providers, preferably while waiting for their appointment).
- EDSS/FS (performed by the efficacy assessor).
- MS relapse.
- MSFC/SDMT.
- Health care resource utilization since the last visit.
- MRI (Visit 7 only).
- Recording of changes in concomitant medications.
- Assessment and recording in the eCRF of methods of contraception (for WOCBP only).
- Physical examination (Visit 7 only).
- Body temperature.
- SBP/DBP (pre-dose).
- 12-lead ECG pre-dose (and 3 hours (± 15 minutes) post-dose at Visit 6 only).
- OCT (under the responsibility of the ophthalmologist).
- Ophthalmological examination (under the responsibility of the ophthalmologist).
- Spirometry (pre-dose; Visit 6 only).
- Hematology (including lymphocytes), blood chemistry.
- Urinalysis.
- Lymphocyte subsets (only at sites participating in sub-study).
- PK sampling pre-dose (and 3 hours (± 15 minutes) post-dose at Visit 6 only; NB: this should be performed after the corresponding hour 12-lead ECG and SBP/DBP measurement).
- Urine pregnancy test for WOCBP.
- Recording of AEs and SAEs.

- Study medication accountability and compliance review.
- IRT call and study treatment dispensing.
- Dispense two urine pregnancy tests for WOCBP, remind to test for pregnancy on a 4-weekly basis (± 4 days) and to communicate the results to the principal investigator / treating neurologist (by telephone).
- Remind WOCBP to use the methods of contraception defined for this study. The reminders must be documented in the hospital chart.
- Schedule an appointment for next visit and instruct subject to:
  - bring back any blister packs (used, partially used and unused blister packs) and any unused tablets.
  - not take study treatment on the day of study visit prior to coming to the site.
  - contact their principal investigator / treating neurologist at the clinical site immediately in the event of the appearance of any symptoms suggestive of an MS exacerbation.
- Dispense the FSIQ-RMS and give instructions for completion.

8.2.7 Visits 8, 10, 12, 14, and 16 – Weeks 36, 60, 84, 108, 132

The visit window for these visits is ± 7 days. The EDSS must be assessed during this visit window (i.e., ± 7 days). The date of drug dispensing, preferably corresponding to the date of registration of the visit in the IRT system, defines the date of the visit. All other assessments may be performed up to 7 days prior to or after this visit date. The visits include:

- MS relapse.
- EDSS/FS (performed by the efficacy assessor).
- Health care resource utilization since the last visit.
- Recording of changes in concomitant medications.
- Assessment and recording in the eCRF of methods of contraception (for WOCBP only).
- Body temperature.
- SBP/DBP (pre-dose).
- 12-lead ECG (pre-dose).
- Hematology (including lymphocytes), blood chemistry.
- Urine pregnancy test for WOCBP.
- Recording of AEs and SAEs.
- Study treatment accountability and compliance review.
- IRT call and study treatment dispensing.
- Dispense two urine pregnancy tests for WOCBP, remind to test for pregnancy on a 4-weekly basis (± 4 days) and to communicate the results to the principal investigator / treating neurologist (by telephone).

- Remind WOCBP to use the methods of contraception defined for this study. The reminders must be documented in the hospital chart.
- Schedule an appointment for next visit and instruct subject to:
  - bring back any blister packs (used, partially used and unused blister packs) and any unused tablets.
  - not take study treatment on the day of study visit prior to coming to the site.
  - contact their principal investigator / treating neurologist at the clinical site immediately in the event of the appearance of any symptoms suggestive of an MS exacerbation.

8.2.8 Visits 11 and 15 – Weeks 72 and 120

The visit window for these visits is ± 7 days. The EDSS must be assessed during this visit window (i.e., ± 7 days). The date of drug dispensing, preferably corresponding to the date of registration of the visit in the IRT system, defines the date of the visit. All other assessments may be performed up to 7 days prior to or after this visit date. The visits include:

- WPAI:MS (subject completes the questionnaire prior to any clinical assessments or interaction with health care providers, preferably while waiting for their appointment).
- SF-36v2^{TM} (subject completes the questionnaire after WPAI:MS, prior to any clinical assessments or interaction with health care providers, preferably while waiting for their appointment).
- EDSS/FS (performed by the efficacy assessor).
- MS relapse.
- MSFC/SDMT.
- Health care resource utilization since the last visit.
- Recording of changes in concomitant medications.
- MRI.
- Assessment and recording in the eCRF of methods of contraception (for WOCBP only).
- Physical examination.
- Body temperature.
- SBP/DBP (pre-dose).
- 12-lead ECG (pre-dose).
- Hematology (including lymphocytes), blood chemistry.
- Urinalysis.
- Urine pregnancy test for WOCBP.
- Recording of AEs and SAEs.
- Study treatment accountability and compliance review.

- IRT call and study treatment dispensing.
- Dispense two urine pregnancy tests for WOCBP, remind to test for pregnancy on a 4-weekly basis (± 4 days) and to communicate the results to the principal investigator / treating neurologist (by telephone).
- Remind WOCBP to use the methods of contraception defined for this study. The reminders must be documented in the hospital chart.
- Schedule an appointment for next visit and instruct subject to:
  - bring back any blister packs (used, partially used and unused blister packs) and any unused tablets.
  - not take study treatment on the day of study visit prior to coming to the site.
  - contact their principal investigator / treating neurologist at the clinical site immediately in the event of the appearance of any symptoms suggestive of an MS exacerbation.
- Dispense the FSIQ-RMS and give instructions for completion.

8.2.9 Visits 9, 13, 17 – Weeks 48, 96, and 144

The visit window for these visits is ± 7 days. The EDSS must be assessed during this visit window (i.e., ± 7 days). The date of drug dispensing, preferably corresponding to the date of registration of the visit in the IRT system, defines the date of the visit. All other assessments may be performed up to 7 days prior to or after this visit date. The visits include:

- WPAI:MS.
- SF-36v2™.
- eC-SSRS.
- EDSS/FS.
- MS Relapse.
- MSFC, SDMT.
- Health care resource utilization.
- MRI.
- Recording of changes in concomitant medications.
- Assessment and recording in the eCRF of methods of contraception (for WOCBP only).
- Physical examination.
- Body temperature.
- Dermatological examination.
- Body weight.
- SBP/DBP (pre-dose).
- 12-lead ECG (pre-dose).
- OCT (under the responsibility of the ophthalmologist).

- Ophthalmological examination.
- Spirometry.
- Hematology (including lymphocytes), blood chemistry.
- Urinalysis.
- Lymphocyte subsets (only at sites participating in sub-study).
- PK sampling.
- JCV serology.
- Urine pregnancy test for WOCBP.
- Recording of AEs and SAEs.
- Study treatment accountability and compliance review.
- IRT call and study treatment dispensing.
- Dispense two urine pregnancy tests for WOCBP, remind to test for pregnancy on a 4-weekly basis (± 4 days) and to communicate the results to the principal investigator / treating neurologist (by telephone).
- Remind WOCBP to use the methods of contraception defined for this study. The reminders must be documented in the hospital chart.
- Schedule an appointment for next visit and instruct subject to:
  - bring back any blister packs (used, partially used and unused blister packs) and any unused tablets.
  - not take study treatment on the day of study visit prior to coming to the site.
  - contact their principal investigator / treating neurologist at the clinical site immediately in the event of the appearance of any symptoms suggestive of an MS exacerbation.
- Dispense the FSIQ-RMS and give instructions for completion.

8.2.10 Visit 18 – EOT

This visit will be conducted after at least 60 weeks of treatment and up to Week 156 or earlier in case of premature discontinuation of study treatment (+ 7 days). When study closure is communicated by the sponsor, all subjects on study drug should perform the Visit 18 (EOT) assessments for this study within 4 weeks [see Section 3.5.5].

The EOT visit must take place after the last dose of study drug. Preferably, the visit and all assessments will take place 1 day after the last dose of study drug, but no later than 7 days after the last dose of study drug. If a study treatment temporary interruption leads to permanent premature discontinuation, the EOT visit should be done as soon as possible, but no later than 7 days after the decision to discontinue was made. If the study treatment interruption leading to the permanent premature discontinuation lasts more than 30 days, then Visit 19 (FU7d), if applicable, and Visit 20 (FU) can be combined with Visit 18 (EOT). The date of EDSS assessment, preferably corresponding to the date of registration of the visit in the IRT system, defines the date of the visit. The visit includes:

- WPAI:MS.
- SF-36v2.
- eC-SSRS.
- EDSS/FS.
- MS Relapse.
- MSFC, SDMT.
- Health care resource utilization.
- CXR (in case of premature study treatment discontinuation, the CXR at EOT does not need to be performed if the EOT visit occurs within 48 weeks of the pre-randomization CXR).
- MRI.
- Recording of changes in concomitant medications.
- Assessment and recording in the eCRF of methods of contraception (for WOCBP only).
- Physical examination.
- Body temperature.
- SBP/DBP.
- Dermatological examination.
- Body weight.
- 12-lead ECG.
- Ophthalmological examination.
- OCT (under the responsibility of the ophthalmologist).
- Spirometry.
- Hematology (including lymphocytes), blood chemistry.
- Urinalysis.
- Lymphocyte subsets (only at sites participating in sub-study).
- PK sampling.
- JCV serology.
- Urine pregnancy test for WOCBP.
- Recording of AEs and SAEs.
- Study treatment accountability and compliance review.
- IRT call.
- Remind WOCBP to use the methods of contraception defined for this study. The reminders must be documented in the hospital chart.
- Schedule an appointment for next visit and instruct subject to:
  - bring back any blister packs (used, partially used and unused blister packs) and any unused tablets.

- contact their principal investigator / treating neurologist at the clinical site immediately in the event of the appearance of any symptoms suggestive of an MS exacerbation.

- Dispense the FSIQ-RMS and give instructions for completion.

8.3 Post-treatment period

8.3.1 Post-treatment safety follow-up period

- The safety FU period lasts 30 days and includes Visit 19 (FU7d; only for subjects participating in the lymphocyte sub-study), and Visit 20 (FU).

8.3.1.1 Visit 19 – FU7d

If a temporary interruption of study treatment lasts more than 30 days and leads to permanent premature discontinuation, Visit 19 (FU7d) can be combined with the EOT visit.

The FU7d visit will take place 7 days after the last dose of study treatment (± 2 days). Only subjects participating in the lymphocyte subset sub-study will have this additional FU visit. The visit includes:

- Lymphocyte subsets (only at sites participating in sub-study).
- Recording of AEs and SAEs.

8.3.1.2 Visit 20 – FU

If a temporary interruption of study treatment lasts more than 30 days and leads to permanent premature discontinuation, Visit 20 (FU) can be combined with the EOT visit.

The FU visit will take place at least 30 days after the last dose of study treatment, but no later than 37 days after last dose of study treatment. The visit includes:

- EDSS/FS.
- MS Relapse.
- FSIQ-RMS. At Visit 20 (FU), the FSIQ-RMS will be completed at home prior to the visit, ideally, during the 7 consecutive days preceding the visit.
- Recording of changes in concomitant medications.
- Body temperature.
- SBP/DBP.
- 12-lead ECG.
- Ophthalmological examination.
- Spirometry.
- Urinalysis.
- Hematology (including lymphocytes*), blood chemistry.
- PK sampling.

- Lymphocyte subsets (only at sites participating in sub-study).
- Serum pregnancy test for WOCBP.
- Recording of AEs and SAEs.

* If a total lymphocyte count < 0.5×10^9/L is observed at FU, an alert will be sent to the principal investigator and the sponsor [see Section 7.3.13.1]. Discontinuation of DMF treatment should be considered in accordance with prescribing information [Tecfidera USPI, Tecfidera SmPC].

8.3.2 Post-treatment observation period

Subjects who prematurely discontinue study treatment will perform the EOT and safety FU visits (FU7d [if applicable], FU) and will enter the PTOP which lasts until 60 weeks after randomization of the last subject (i.e., scheduled EOT period). It consists of an abbreviated schedule of assessments at the time of the originally scheduled 12-weekly visits. The timepoints and visit windows are the same as the corresponding visits during the treatment period but the number of assessments is reduced [see Section 3.5.3.2]. After FU has been performed, the study visits must continue according to the original visit and assessment schedule. If the first PTOP visit window overlaps with FU7d (if applicable) or FU visits, visits and assessments can be combined.

8.3.2.1 Visits 6A, 7A, 8A, 10A, 12A, 14A, and 16A – Weeks 12, 24, 36, 60, 84, 108, and 132

The visit window for these visits is ± 7 days. The EDSS must be assessed during this visit window (i.e., ± 7 days). The date of EDSS assessment defines the date of the visit. All other assessments may be performed up to 7 days prior to or after this visit date. The visits include:

- EDSS/FS.
- MS relapse.
- MRI (Visit 7A – Week 24 – only).
- Recording of changes in concomitant medications.
- Physical examination (Visit 7A – Week 24 – only).
- Body temperature.
- SBP/DBP.
- Spirometry (Visit 6A – Week 12 – only).
- Hematology (including lymphocytes), blood chemistry.
- Urinalysis.
- Lymphocyte subsets (only at sites participating in sub-study; Visits 6A and 7A – Weeks 12 and 24 only).
- Recording of AEs and SAEs.

- Dispense the FSIQ-RMS and give instructions for completion (Visit 6A – Week 12 and Visit 7A – Week 24 only).

8.3.2.2 Visits 11A – Week 72 and Visit 15A – Week 120

The visit window for these visits is ± 7 days. The EDSS must be assessed during this visit window (i.e., ± 7 days). The EDSS assessment defines the date of the visit. All other assessments may be performed up to 7 days prior to or after this visit date. The visits include:

- EDSS/FS.
- MS relapse.
- MRI.
- Recording of changes in concomitant medications.
- Physical examination.
- Body temperature.
- SDP/DBP.
- Hematology (including lymphocytes), blood chemistry.
- Urinalysis.
- Recording of AEs and SAEs.
- Dispense the FSIQ-RMS and give instructions for completion.

8.3.2.3 Visits 9A, 13A, 17A, and 18A – Weeks 48, 96, 144, and 156

When study closure is communicated by the sponsor, all subjects who prematurely discontinued from the study treatment and entered the PTOP should perform the Visit 18A (Week 156) assessments within 4 weeks [see Section 3.5.5].

The visit window for these visits is ± 7 days. The EDSS must be assessed during this visit window (i.e., ± 7 days). The EDSS assessment defines the date of the visit. All other assessments may be performed up to 7 days prior to or after this visit date. The visits include:

- EDSS/FS.
- Relapse.
- MRI.
- Recording of changes in concomitant medications.
- Physical examination.
- Body temperature.
- Dermatological examination.
- SBP/DBP.
- 12-lead ECG.
- Spirometry.

- Hematology (including lymphocytes), blood chemistry.
- Urinalysis.
- Lymphocyte subsets (only at sites participating in the sub-study).
- JCV serology.
- Recording of AEs and SAEs.
- Dispense the FSIQ-RMS and give instructions for completion. At Visit 18A (Week 156), the FSIQ-RMS will be completed at home prior to the visit, ideally, during the 7 consecutive days preceding the visit.

8.4 Unscheduled visits

An unscheduled site visit may be performed at any time during the study (between scheduled visits), as necessary, at the investigator's discretion. These visits include (but are not limited to) those performed due to safety (e.g., occurrence of an AE, laboratory abnormalities), administration of study treatment (e.g., re-initiation, return of unused study medication, need to initiate treatment with a QT-prolonging drug), and/or MS related issues (e.g., relapses).

The date of the visit and the reason for such visits as well as any data related to study assessments performed at unscheduled visits will be recorded in the eCRF.

8.4.1 Unscheduled visits for relapses (Visits R1, R2, etc.)

Subjects will be reminded to contact their treating neurologist at the clinical site immediately in the event of appearance of any new or worsened neurological symptoms. Whenever a subject contacts the principal investigator / treating neurologist reporting the appearance of any symptoms suggestive of an MS exacerbation, the principal investigator / treating neurologist will interview the subject and determine the necessity of an unscheduled visit for relapse. An unscheduled visit will be organized as soon as possible after onset or worsening of the symptom(s) as follows:

- The principal investigator / treating neurologist will interview and examine the subject to determine whether or not a relapse may have occurred since last visit using the dedicated relapse assessment questionnaire [see Appendix 12] and the relapse symptoms form [see Appendix 13] and decide whether the subject has to be referred to the efficacy assessor.
- In order to exclude potential other reasons for the symptom(s) observed, the principal investigator / treating neurologist will need to perform the following assessments:
  - Physical examination,
  - Vital signs: pulse rate, body temperature.
- In the event of the subject's referral to the efficacy assessor, the latter will perform the EDSS and FS within 7 days after onset or worsening of the symptom(s). The decision regarding whether the new or worsened neurological symptoms are

considered as confirmed or unconfirmed relapse will be made by the principal investigator / treating neurologist by assessing the compatibility of the symptoms reported by the patient and the presence or absence of a qualifying increase in the EDSS/FS (i.e., of the magnitude described in Section 6.1.1) resulting from comparison between the current and previous, clinically stable EDSS/FS assessment performed by the blinded efficacy assessor.

All MS relapses, whether confirmed or unconfirmed during the study, must be reported on specific relapse pages of the eCRF. MS relapses and associated symptoms are not to be entered on the AE page of the eCRF with the following exceptions:

- MS relapses with fatal outcome (these must always be recorded as an AE on the AE page in addition to being reported as SAEs).
- MS relapses that, in the view of the investigator, warrant specific notice due to unusual frequency, severity or remarkable clinical manifestations (these should be reported as an AE on the AE page of the eCRF and, if applicable, on the SAE form).

Additionally, the following assessments must be done during those visits:

- EDSS/FS (performed by the efficacy assessor).
- MS relapse.
- Health care resource utilization since the last visit.
- SF-36v2™ (subject completes the questionnaire prior to any clinical assessments or interaction with health care providers, preferably while waiting for their appointment).
- Recording of changes in concomitant medications.
- Recording of AEs and SAEs.
- Schedule an appointment for next visit and instruct subject to:
  - bring back any blister packs (used, partially used and unused blister packs) and any unused tablets.
  - not take study treatment on the day of study visit prior to coming to the site.
  - contact their principal investigator / treating neurologist at the clinical site immediately in the event of the appearance of any symptoms suggestive of an MS exacerbation.
- Dispense the FSIQ-RMS and give instruction for completion.

If a relapse visit is within 5 days prior to the date of a regular visit where MRI is assessed, efforts should be made to perform the MRI assessments prior to the start of treatment with i.v. corticosteroids. However, if this is not possible, then the MRI should be delayed until at least 14 days after the last dose of corticosteroids.

These visits for relapses are additional unscheduled visits. The regular scheduled study visits must be resumed according to the original visit and assessment schedule. If the visit

is within the visit window of a regular visit, the assessments for the relapse unscheduled visit are the ones of this regular visit.

8.4.2 Additional unscheduled visits for re-initiation of study drug (I1, I2, etc.)

As described in detail in Section 5.1.9, subjects may need to be monitored at the study site when re-initiating study drug following a study drug treatment interruption.

In such cases, there will be two visits; one visit on the day of re-initiation (d1) and an additional visit 14 days (± 1 day) after the day of re-initiation (d15).

The following assessments/procedures must be done during the visit on the day of re-initiation (d1):

- Body temperature.
- 12-lead ECG pre-dose and hourly (± 15 minutes) for up to 12 hours post-dose (under the responsibility of the first-dose administrator).
- SBP/DBP pre-dose and hourly (± 15 minutes) for up to 12 hours post-dose (under the responsibility of the first-dose administrator).
- Recording of AEs and SAEs.
- IRT call and study drug dispensing.

The discharge criteria will be applied as described for Day 1. Subjects may be discharged from cardiac monitoring if they meet the discharge criteria before 12 hours post-dose but no sooner than 4 hours post-dose [see Section 5.1.10].

The following assessments need to be done during the visit 14 days after the day of re-initiation:

- Body temperature.
- SBP/DBP (pre-dose).
- 12-lead ECG (pre-dose).
- Recording of AEs and SAEs.
- IRT call – return of study drug blisters and unused medication, and dispensing of new blisters, if appropriate.

The date of visit and any data related to study assessments performed during this visit (12-lead ECGs, SBP/DBP) will be reported on the specific eCRF pages for unscheduled visit for re-initiation of study drug when post-dose monitoring is required.

These visits for the cardiac monitoring of the subjects for re-initiating study drug when post-dose monitoring is required are additional unscheduled visits. The regular scheduled study visits must be resumed according to the original visit and assessment schedule. If the visit occurs at the same time as a regular visit, all assessments of the regular visit have to be perfomed in addition.

8.4.3 Unscheduled visits (any other assessment;U1, U2, U3, etc.)

An unscheduled site visit may be performed at any time during the study (between scheduled visits), as necessary, at the investigator's discretion. The date of the visit and the reason for such visits as well as any data related to study assessments performed at unscheduled visits will be recorded in the eCRF. During such visits, any of the following assessments may be performed at the investigator's discretion:

- EDSS/FS.
- FSIQ-RMS.
- MRI.
- Assessment of concomitant medications.
- Physical examination.
- Body temperature.
- Pulse rate (to be assessed only if no 12-lead ECG is performed at this visit)
- SBP/DBP.
- 12-lead ECGs (e.g., in case concomitant treatment with a QT-prolonging drug with known risk of Torsades de Pointes is needed [see Appendix 4]).
- Ophthalmological examination (e.g., presence of visual symptoms suggestive of active uveitis [see Section 5.1.12.7]).
- OCT (e.g., presence of visual symptoms suggestive of macular edema or active uveitis [see Section 5.1.12.7]).
- Spirometry.
- Complete laboratory tests including: hematology including lymphocytes, blood chemistry, viral serology, urinalysis, or serum pregnancy test (for WOCBP only).
- Assessment of AEs and SAEs.
- Dermatological examination.
- Assessment of methods of contraception (for WOCBP only).
- Measurement of body weight.
- IRT call – return of study drug blisters and unused medication, and dispensing of new blisters, if appropriate.
- PK – when possible, a PK sample will be collected for all subjects experiencing SAEs. In this event, a sample will preferably be collected pre-dose (trough), as early as possible after SAE onset, and no later than 7 days after the last dose of study drug.

Additional unscheduled spirometry will have to be conducted in the event of respiratory symptoms (e.g., dyspnea) during the course of the study. An inhaled short-acting β2 agonist (e.g., albuterol/salbutamol) for symptom relief may be administered at the discretion of the investigator. Administration of any short-acting β2 agonist will be recorded in the eCRF.

If any of the laboratory variables listed in Section 7.3.13.2 needs to be analyzed, this must be done at the Central Laboratory, except in case of emergency; if it has been done at a local laboratory, results must be recorded in the eCRF [see Section 7.3.13].

9 STUDY COMPLETION AND POST-STUDY TREATMENT/MEDICAL CARE

9.1 Study completion

For an individual subject, EOS is reached when treatment, safety FU period and, if applicable, the PTOP period have been completed:

- For subjects who remained under study treatment as defined per protocol (i.e., Week 156 or 60 weeks after randomization of the last subject [whichever occurs first]) and for subjects who prematurely discontinue study treatment and do not enter the PTOP, the EOS visit corresponds to Visit 20 (FU) 30 days after the last dose of study treatment.
- For subjects who prematurely discontinued study treatment (for whatever reason) and entered the PTOP, the EOS corresponds to the last PTOP visit performed.

The reason(s) for discontinuing the study along with who made the decision, if applicable (i.e., subject, investigator or Actelion) must be recorded in the eCRF.

EOS on a study level occurs at the time all subjects have completed their safety FU period and, if applicable, PTOP period as described above.

9.2 Premature withdrawal from study

Subjects may voluntarily withdraw from the study for any reason at any time. Subjects are considered withdrawn if they state an intention to withdraw further participation in all components of the study (i.e., withdrawal of consent), die or are lost to FU for any other reason. If a subject withdraws consent, no further data will be collected in the eCRF from the date of withdrawal onward. The investigator may withdraw a subject from the study (without regard to the subject's consent) if, on balance, they believe that continued participation in the study would be contrary to the best interests of the subject. Withdrawal from the study may also result from a decision by Actelion for any reason, including premature termination or suspension of the study [see Section 9.3].

A subject who prematurely discontinues study drug is not considered as withdrawn from the study and will enter the PTOP period consisting of an abbreviated schedule of assessments, at the time of the originally scheduled 12-weekly visits.

Subjects are considered as lost to FU if all reasonable attempts by the investigator to communicate with the individual fail. The site must take preventive measures to avoid a subject being lost to FU (e.g., document different ways of contact such as telephone

number, home address, e-mail address, person to be contacted in case the subject cannot be reached). If the subject cannot be reached, the site must make a reasonable effort to contact the subject, document all attempts and enter the loss of FU information into the eCRF. The following methods must be used: at least three telephone calls must be placed to the last available telephone number, and one registered letter must be sent by post to the last available home address. Additional methods may be acceptable if they are compliant with local rules/regulations (e.g., site staff visit to the subject's home), respecting the subject's right to privacy. If the subject is still unreachable after all contact attempts listed above, she/he will be considered to be lost to FU.

If premature withdrawal occurs for any reason, the reason for premature withdrawal from the study along with who made the decision (subject, investigator or Actelion) must be recorded in the eCRF.

If for whatever reason (except death or loss to FU) a subject was withdrawn from the study, the investigator should make efforts to conduct a last visit/contact to assess the safety and wellbeing of the subject, collect unused study drug and discuss FU medical care. Data obtained during this last appointment / telephone call will be recorded in the subjects' medical records. No data will be collected in the eCRF, except the vital status, if the subject agrees. The investigator must provide FU medical care for all subjects who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care, as described in Section 9.4.

9.3 Premature termination or suspension of the study

Actelion reserves the right to terminate the study at any time globally or locally. Investigators can terminate the participation of their site in the study at any time.

If the study is suspended or prematurely terminated, Actelion will promptly inform the investigators, the IRBs/IECs and health authorities as appropriate and provide the reasons for the suspension or termination.

If the study is suspended or prematurely terminated for any reason, the investigator in agreement with Actelion must promptly inform all enrolled subjects and ensure their appropriate treatment and FU, as described in Section 9.2. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subjects' interests.

In addition, if the investigator suspends or terminates the study without prior agreement from Actelion, the investigator must promptly inform Actelion and the IRB/IEC, and provide both with a detailed written explanation of the termination or suspension.

If the IRB/IEC suspends or terminates its approval/favorable opinion of the study, the investigator must promptly notify Actelion and provide a detailed written explanation of the termination or suspension.

Any suspension or premature termination of the study must be discussed with the IDMC.

9.4 Medical care of subjects after study completion / withdrawal from study

After the subject's study completion or premature withdrawal from the study, whichever applies, the investigator/delegate will explain to subjects what treatment(s) / medical care is necessary and available according to local regulations.

In making choices for treatment after withdrawal from the study or the study completion, the investigator should consider that subjects may have been treated with two immunomodulators concomitantly (i.e., DMF and ponesimod) for variable periods of time. This is particularly relevant when switching treatment to powerful immunosuppressive drugs such as natalizumab. Particular attention should be given to monitoring immune system function (e.g., lymphocyte counts, vaccination responses) and occurrence of opportunistic infections in these patients as the risk may potentially be increased.

Open label ponesimod (alone or as add-on to Tecfidera) may be offered to the subjects after study withdrawal/completion as compassionate treatment when allowed by local regulations.

The initial treatment allocation should remain blinded until after database closure [see Section 5.1.4] unless emergency unblinding is required [see Section 5.1.5.4].

10 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

10.1 Adverse events

10.1.1 Definitions of adverse events

An AE is any adverse change, i.e., any unfavorable and unintended sign, including an abnormal laboratory finding, symptom or disease that occurs in a subject during the course of the study, whether or not considered by the investigator as related to study treatment.

A treatment-emergent AE is any AE temporally associated with the use of study treatment (from study treatment initiation until 30 days after study treatment discontinuation), whether or not considered by the investigator as related to study treatment.

AEs include:

- Exacerbation of a pre-existing disease with the exception of MS relapse and associated symptoms [see Section 10.1.6].
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition.
- Disease or medical condition detected or diagnosed during the course of the study even though it may have been present prior to the start of the study.
- Continuous persistent disease or symptoms present at study start that worsen following the start of the study.
- Abnormal assessments, e.g., change on physical examination, ECG findings, if they represent a clinically significant finding that was not present at study start or worsened during the course of the study.
- Laboratory test abnormalities if they represent a clinically significant finding, symptomatic or not, that was not present at study start or worsened during the course of the study or led to dose reduction, interruption or permanent discontinuation of study treatment.

Overdose, misuse and abuse of the study treatment should be reported as an AE and, in addition, study treatment errors must be documented in the study drug log of the eCRF.

10.1.2 Intensity of adverse events

The intensity of clinical AEs is graded on a three-point scale – mild, moderate, severe – and is reported on specific AE pages of the eCRF.

If the intensity of an AE worsens during study treatment administration, only the worst intensity should be reported on the AE page. If the AE lessens in intensity, no change in the severity is required.

If the intensity of an AE with an onset date between informed consent signature and start of study treatment and which is ongoing at the start of treatment worsens after the start of study treatment, a new AE page must be completed. The onset date of this new AE corresponds to the date of worsening in intensity.

The three categories of intensity are defined as follows:

- **Mild**

The event may be noticeable to the subject. It does not influence daily activities and does not usually require intervention.

- **Moderate**

The event may make the subject uncomfortable. Performance of daily activities may be influenced, and intervention may be needed.

- **Severe**

The event may cause noticeable discomfort and usually interferes with daily activities. The subject may not be able to continue in the study, and treatment or intervention is usually needed.

A mild, moderate, or severe AE may or may not be serious [see Section 10.2]. These terms are used to describe the intensity of a specific event. Medical judgment should be used on a case-by-case basis.

Seriousness, rather than severity assessment, determines the regulatory reporting obligations.

10.1.3 Relationship to study treatment

Each AE must be assessed by the investigator as to whether or not there is a reasonable possibility of causal relationship to the study treatment, and reported as either related or unrelated. The determination of the likelihood that the study drug caused the AE will be provided by an investigator who is a qualified physician.

10.1.4 Adverse events associated to study design or protocol-mandated procedures

An AE is defined as related to study design or protocol-mandated procedures if it appears to have a reasonable possibility of a causal relationship to either the study design or to protocol-mandated procedures. Examples include discontinuation of a subject's previous treatment during a washout period leading to exacerbation of underlying disease.

10.1.5 Reporting of adverse events

All AEs occurring after study start (i.e., signing of informed consent) and up to 30 days after study treatment discontinuation or up to the last visit of the PTOP (i.e., Week 156 visit of the PTOP) (whichever is latest) must be recorded on specific AE pages of the eCRF. Actelion may contact the investigator to obtain further information.

Cardiac events

The first-dose administrator [see Section 3.7.4] must ensure that blinded study personnel at the study site, such as the treating neurologist, efficacy assessor, clinical coordinator / study nurse, and other personnel involved in the clinical care and management of the subject, do not have access to Day 1 and day of re-initiation of study drug post-dose BP assessments or ECGs interpretation reports, or to AEs with onset after the study drug intake on Day 1 or on the first day of re-initiation of study drug and which are resolved at the time of discharge.

However, significant findings (e.g., new ECG abnormalities, bradycardia) that meet the definition of an AE must be recorded on the AE page of the eCRF.

On Day 1 and on the first day of re-initiation of study drug when post-dose monitoring is required, significant findings that, in view of the first-dose administrator, meet the definition of an AE, have an onset after the study drug intake, and are resolved at the time of discharge of the subject from cardiac monitoring, must be reported directly on the AE page of the separate eCRF by the first-dose administrator / delegate. These AEs will not be visible to any of the blinded study personnel at the study site. All other significant findings on Day 1 and on the first day of re-initiation of study drug when post-dose monitoring is required but unresolved at the time of discharge from cardiac monitoring of the subject, which in her/his view meet the definition of an AE, must be reported to the principal investigator / treating neurologist who will record these events on the AE page of the eCRF. Similarly, any AEs with onset on Day 1 or on the first day of study drug re-initiation when post-dose monitoring is required leading to the premature discontinuation of study drug must be reported by the first-dose administrator to the principal investigator / treating neurologist who will record these events on the AE page of the eCRF.

10.1.6 Reporting of MS relapse

All MS relapses during the study must be reported on specific relapse pages of the eCRF.

MS relapses and associated symptoms are not to be entered on the AE page of the eCRF with the following exceptions:

- MS relapses with fatal outcome (these must always be recorded as an AE on the AE page in addition to being reported as SAEs).
- MS relapses that, in the view of the investigator, warrant specific notice due to unusual frequency, severity or remarkable clinical manifestations (these should be reported as an AE on the AE page of the eCRF and, if applicable, on the SAE form).

10.1.7 Follow-up of adverse events

AEs still ongoing more than 30 days after study treatment discontinuation must be followed up until they are no longer considered clinically relevant, or until the event outcome is provided.

10.2 Serious adverse events

10.2.1 Definitions of serious adverse events

10.2.1.1 Serious adverse events

An SAE is defined by the ICH guidelines as any AE fulfilling at least one of the following criteria:

- Fatal.
- Life-threatening: refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death had it been more severe.
- Requiring inpatient hospitalization or prolongation of existing hospitalization.
- Resulting in persistent or significant disability or incapacity.
- Congenital anomaly or birth defect.
- Medically significant: refers to important medical events that may not immediately result in death, be life-threatening, or require hospitalization but may be considered to be SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.

The following reasons for hospitalization are exempted from being reported:

- Hospitalization for cosmetic elective surgery, or social and/or convenience reasons.
- Hospitalization for MS relapse (with the exceptions described in Section 10.1.6).
- Hospitalization for pre-planned (i.e., planned prior to signing informed consent) surgery or standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for coronary angiography in a subject with stable angina pectoris.

However, complications that occur during hospitalization are AEs or SAEs (e.g., if a complication prolongs hospitalization).

10.2.1.2 Serious adverse events associated with the study design or protocol-mandated procedures

An SAE is defined as related to study design or protocol-mandated procedures if it appears to have a reasonable possibility of a causal relationship to either the study design or to protocol-mandated procedures. Examples include discontinuation of a subject's previous treatment during a washout period leading to exacerbation of underlying disease or a complication of an invasive procedure that is specifically required by the protocol.

10.2.2 Reporting of serious adverse events

All SAEs occurring after study start (i.e., signing of informed consent) up to 30 days after study treatment discontinuation must be reported on AE pages in the eCRF and on SAE forms, regardless of the investigator-attributed causal relationship with study treatment or study-mandated procedures.

10.2.3 Follow-up of serious adverse events

SAEs still ongoing at the EOS visit must be followed up until resolution or stabilization, or until the event outcome is provided, e.g., death.

10.2.4 After the 30-day follow-up period

10.2.4.1 During the PTOP period (if applicable)

All SAEs, regardless of investigator-attributed causal relationship, that occur during the PTOP period must be reported on AE pages in the eCRF and on SAE forms.

10.2.4.2 After the PTOP period

New SAEs occurring after the 30-day FU period, or after the last visit of the PTOP (whichever applies and is the latest) must be reported to the Actelion drug safety department within 24 hours of the investigator's knowledge of the event, **only** if considered causally related to previous exposure to the study treatment by the investigator.

10.2.5 Reporting procedures

All SAEs must be reported by the investigator to the Actelion drug safety department within 24 hours of the investigator's first knowledge of the event.

The MS relapses and associated symptoms are exempt from being reported on an SAE form by the investigator to the Actelion drug safety department with the exceptions described in Section 10.1.6.

All SAEs must be recorded on an SAE form, irrespective of the study treatment received by the subject, and whether or not this event is considered by the investigator to be related to study treatment.

The SAE forms must be faxed to the Actelion drug safety department (contact details are provided on the SAE form). The investigator must complete the SAE form in English, and must assess the causal relationship of the event to study treatment.

FU information about a previously reported SAE must also be reported within 24 hours of receiving it. The Actelion drug safety department may contact the investigator to obtain further information.

If the subject is hospitalized in a hospital other than the study site, it is the investigator's responsibility to contact this hospital to obtain all SAE relevant information and documentation.

The reference safety document to assess expectedness of a suspect serious adverse reaction and reported by the sponsor to health authorities, IRBs/IECs and investigators, is the reference safety information section of the IB [Ponesimod IB].

MS relapses and associated symptoms are commonly seen with the underlying disease and are therefore expected to occur in this subject population. The MS relapses and associated symptoms reported as serious (unless fatal) are waived and will be treated as expected and will therefore not require systematic unblinding or expedited reporting to health authorities, IRBs/IECs, and investigators. However, all MS relapses (irrespective of seriousness) will be collected on the specific relapse pages of the eCRF in the clinical trial database and monitored during the study by the sponsor and by the IDMC.

10.3 Pregnancy

If a woman becomes pregnant while on study treatment, study treatment must be discontinued. The investigator must counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

10.3.1 Reporting of pregnancy

Irrespective of the treatment received by the subject, any pregnancy occurring during the study including during 30 days following study treatment discontinuation must be reported within 24 hours of the investigator's knowledge of the event.

Pregnancies must be reported on the Actelion Pregnancy form, which is faxed to the Actelion drug safety department (see contact details provided on the Actelion Pregnancy form), and on the AE page in the eCRF.

10.3.2 Follow-up of pregnancy

Any pregnancy must be followed to its conclusion and its outcome must be reported to the Actelion drug safety department.

Any AE associated with the pregnancy occurring during the FU period after study drug discontinuation must be reported on separate AE pages in the eCRF. Any SAE occurring during the pregnancy must be reported on an SAE form as described in Section 10.2.2.

10.4 Study safety monitoring

Clinical study safety information (AEs, SAEs, laboratory values, ECGs, vital signs, and project-specific labs/examinations as required) is monitored and reviewed on a continuous basis by the Actelion clinical team (in charge of ensuring subjects' safety as

well as data quality) by periodically monitoring clinical study activities from protocol conception to database closure. In addition, an IDMC is monitoring safety data [see Section 3.8.1].

11 STATISTICAL METHODS

All statistical analyses will be conducted by Actelion or by designated CROs supervised by Actelion.

The Statistical Analysis Plan (SAP) will be approved prior to database lock for the final analyses. The SAP provides the full details of all analyses, data displays, and algorithms to be used for data derivations.

All data will be listed and endpoints will be summarized by appropriate descriptive statistics (tables or figures), typically including:

- Number of non-missing observations, number of missing observations, mean, standard deviation, median, Q1, Q3, minimum and maximum for continuous endpoints;
- Number of non-missing observations, number of missing observations and frequency with percentage per category (percentages based on the number of non-missing observations) for categorical endpoints;
- Number of subjects at risk, cumulative number of events, cumulative number of censored observations and Kaplan-Meier estimates of the survival function for time-to-event endpoints.

Absolute change from baseline is defined as post-baseline value minus baseline value, i.e., a positive sign indicates an increase as compared to baseline.

A percentage (relative) change from baseline is defined as the absolute change from baseline divided by the baseline value (if the baseline value does not = 0) multiplied by 100.

The baseline value for efficacy is defined as the last non-missing value recorded prior to randomization for each endpoint and each subject individually. The baseline value for safety is defined as the last non-missing value recorded prior to first study drug intake for each endpoint and each subject individually.

The EOS is defined as the date on the end-of-study eCRF page. If this date is missing the last recorded visit on the eCRF is considered as the EOS date.

The EOT date is defined as the date of the last dose of study treatment intake.

11.1 Analysis sets

11.1.1 Screened analysis set

The screened analysis set (SCR) includes all subjects who were screened and received a subject number.

11.1.2 Full analysis set

The full analysis set (FAS) includes all randomized subjects who were treated with at least one dose of study treatment and have at least one post-baseline efficacy assessment.

- In order to preserve the randomization, subjects will be evaluated according to the treatment they have been randomized to (which may be different to the treatment they have received) and stratum information used for randomization as recorded in the IVRS system (which may be different to the information available on the eCRF after data validation);
- Unless otherwise stated, all available efficacy data for the primary and secondary endpoints up to the EOS visit will be included in the analysis, regardless of study treatment discontinuation and/or switches to alternative MS treatments.

11.1.3 All-randomized set

The all-randomized set (ARS) includes all subjects that were randomized.

11.1.4 Per-protocol set

The per-protocol set (PPS) comprises all subjects included in the FAS without any major protocol deviations that impact the assessment of the primary/secondary endpoints, occurring prior to or at randomization. Due to the nature of the primary endpoint which is assessed over the entire study period rather than at a fixed timepoint, only the data for a subject collected after a major protocol deviation for subjects developing protocol deviations during the study will be excluded for the PPS analysis.

All reportable protocol deviations will be evaluated before unblinding and classified into the five categories below.

Subjects will be excluded from the PPS if:

- Subject is randomized and did not satisfy certain eligibility criteria;

Data will be excluded for subjects after the occurrence of one of the following criteria:

- Subject developed treatment discontinuation criteria during the study but was not discontinued;
- Subject received the wrong study treatment or incorrect dose;
- Subject took an unauthorized concomitant medication;

- Key study procedures missed or performed out of window (e.g., Randomization code was broken).

Additional details regarding the definition of the reasons for subject/data exclusion from the PPS will be defined in the final SAP.

11.1.5 Safety set

The safety set (SAF) includes all subjects who received at least one dose of study treatment. Subjects will be analyzed based on actual treatment taken.

11.1.6 Other analysis sets

Other analysis datasets will be defined in the SAP (or corresponding SAPs), e.g., PK set, PD set, sub-study sets, and subgroups of interest.

11.1.7 Usage of the analysis sets

The FAS, ARS, and the PPS are used for the analysis of the primary and the secondary endpoints. Results for the primary and secondary efficacy endpoints based on the PPS and ARS will supplement those based on the FAS and assess the robustness of treatment effects.

Other MRI, clinical exploratory endpoints and other exploratory endpoints will be analyzed using the FAS.

All safety data will be analyzed using the SAF.

The usage of other analysis sets will be described in the SAP.

11.2 Variables

Variables are defined only for the primary and secondary endpoints. Variables for exploratory and other endpoints will be defined in the SAP.

11.2.1 Primary efficacy endpoint variable

The primary endpoint is the ARR defined as the number of confirmed relapses per subject-year. All confirmed relapses from randomization up to EOS will be included in the analysis. For the statistical analysis of the ARR, the following variables will be used:

- The subject's number of confirmed relapses up to EOS;
- Length of observation expressed in years, defined as: [EOS date minus date of randomization + 1] divided by 365.25.

For the definition of relapses and confirmed relapses, see Section 6.1.1.

11.2.2 Secondary efficacy endpoint variables

There are five secondary efficacy endpoints, which will be analyzed in a hierarchical manner:

- Time to 12-week CDA from baseline up to EOS;
- Time to first confirmed relapse from baseline up to EOS;
- Mean number of CUALs per subject per post-baseline MRI scan up to EOS;
- Longitudinal change over time in fatigue-related symptoms as measured by the symptoms domain of the FSIQ-RMS from baseline up to EOS;
- Longitudinal percent change over time in brain volume from baseline up to EOS.

11.2.2.1 Time to 12-week CDA from baseline up to EOS

Time to 12-week CDA from baseline up to EOS is defined as an:

- Increase of at least 1.5 in EDSS for subjects with a baseline EDSS score of 0; or
- Increase of at least 1.0 in EDSS for subjects with a baseline EDSS score of 1.0 to 5.0; or
- Increase of at least 0.5 in EDSS for subjects with a baseline EDSS score ≥ 5.5;

confirmed after 12 weeks.

Time to first 12-week CDA is defined as the start date of the first 12-week CDA minus date of randomization + 1 in days. For a subject without a 12-week CDA, the censored time to 12-week CDA is defined as:

- [Date of last EDSS assessment up to EOS for subjects without an EDSS increase (as defined above) at their last visit or date of EDSS visit prior to the last visit if there is an increase at the last visit] minus date of randomization + 1.

This will constitute a right-censored observation. Further details of the derivation of this variable will be provided in the SAP.

11.2.2.2 Time to first confirmed relapse up to EOS

The time to first confirmed relapse is defined as:

- Date of first confirmed relapse minus date of randomization + 1 in days.

Subjects without any relapses will be censored at the EOS date, and the time is defined as EOS date minus date of randomization + 1 in days.

11.2.2.3 Mean number of CUALs per subject per post-baseline MRI scan up to EOS

The mean number of CUALs [defined in Section 6.1.3] per subject per post-baseline MRI scan up to EOS is calculated per subject as the sum of the lesions at all post-baseline MRI scans up to EOS divided by the number of MRI scans.

11.2.2.4 Longitudinal change over time in fatigue-related symptoms as measured by the symptoms domain of the FSIQ-RMS from baseline up to EOS

The variables required for this endpoint are the visit identifier and the absolute change in the FSIQ–RMS fatigue-related symptoms at each visit defined as the value at each visit up to EOS minus the value at baseline. Additional details for dealing with missing data will be provided in the SAP.

11.2.2.5 Longitudinal percent change over time in brain volume (PCBV) from baseline up to EOS

PCBV will be calculated at each visit using the skull as scaling constraint by performing halfway registration between images from the MRI assessments from baseline up to EOS:

- Percent change from the mean brain surface displacement between the MRI scans (SIENA method).

Further details of the derivation of this variable will be provided in the SAP.

11.3 Description of statistical analyses

11.3.1 Overall testing strategy

The primary endpoint (ARR using confirmed relapses) will be tested using a negative binomial regression model, comparing ponesimod with placebo. The five secondary endpoints will be tested, in order as listed in Section 11.2.2, using a hierarchical testing approach. The primary null hypotheses will be tested at a two-sided 5% alpha level, and if this is rejected, the study will be declared to show conclusive evidence of efficacy.

11.3.2 Analysis of the primary efficacy variable

11.3.2.1 Hypotheses and statistical model

A generalized linear model with negative binomial distribution for the number of confirmed relapses will be assumed.

t_j denotes the length of observation for subject j
Y_j denotes the number of relapses for subject j during t_j
μ_j denotes the mean of the negative binomial distribution of Y_j.

The mean for the distribution of the ARR for subject j, denoted by μ_j / t_j, will be modeled by the following equation:

$$\log(\mu_j / t_j) = \mathbf{x}'_j\boldsymbol{\theta}, \textit{ i.e., } \log(\mu_j) = \mathbf{x}'_j\boldsymbol{\theta} + \log(t_j), \text{ where}$$

$\mathbf{x}_j$ is the vector denoting study treatments and covariates for subject j

$\boldsymbol{\theta}$ is the vector of unknown fixed model parameters.

Two-sided hypotheses are expressed in terms of the model parameters $\mu_{Ponesimod}$ and $\mu_{Placebo}$. The primary null hypothesis is that the ARR (μ) does not differ between ponesimod and placebo. The alternative hypothesis is that the ARR differs between ponesimod and placebo.

$$H_{0,\,ARR}: \mu_{Ponesimod} - \mu_{Placebo} = 0$$

vs

$$H_{1,\,ARR}: \mu_{Ponesimod} - \mu_{Placebo} \neq 0$$

The null hypothesis will be tested by a two-sided Wald test within the negative binomial regression model [see Section 11.3.2.3], with a two-sided significance level of 0.05.

11.3.2.2 Handling of missing data

11.3.2.2.1 Main analysis of the primary endpoint

All confirmed relapses from randomization up to the EOS visit for subjects in the FAS will be used in the main analysis of the primary endpoint regardless of study drug compliance, therefore no data will be excluded from the analysis. No missing data imputation is used for the main analysis of the primary analysis.

Every effort will be made to collect as complete relapse information as possible, with a focus on collecting all start dates and all EDSS/FS data required for the relapses to make a correct evaluation of relapse confirmation. All relapses with missing or incomplete start dates will be included in the primary efficacy analysis, unless it is clear that they have occurred prior to randomization.

11.3.2.2.2 Sensitivity analysis of the primary endpoint

Missing data will be assessed in a number of ways to test the robustness of the primary endpoint results and to ensure that selection bias / informative drop-outs have not had an influence on the results.

<u>New or Worsening Neurological Symptoms Considered as Relapses:</u>

New or worsening neurological symptoms are reported via a telephone interview or at the site in a face-to-face interview and at both these stages a decision must be taken by the

treating neurologist to refer the subject to the efficacy assessor. Only at this point is the symptom considered a relapse and is assessed for confirmation. To ensure no bias in the selection of symptoms considered as relapses between treatments, an analysis will compare the proportion of these new or worsening neurological symptoms that are considered as relapses and as confirmed relapses. If there is an imbalance in the selection between treatments, this will be explored further.

Early Study Withdrawal:

To assess the impact of subjects withdrawing from the study prior to the Study Closure (60 weeks after the last subject is randomized or Week 156) a number of sensitivity analyses will be performed. These include the imputation of confirmed relapses using various assumptions for the period with missing data. The proportion of missing data will be calculated as

$$1 - \frac{\text{cumulative time between randomization and EOS}}{\text{cumulative time between randomization and Study Closure or Week 156}}$$

A worst case imputation will impute the observed ARR for ponesimod subjects up to EOS during the period EOS up to Study Closure and impute 0 relapses for placebo subjects during this period. A second imputation method will impute the observed placebo ARR up to EOS for the period EOS up to SC for both treatments, using simulations and bootstrapping techniques to calculate the 95% CI. A third more conservative approach will impute the observed individual treatment ARR up to EOS for the period EOS up to SC in a similar manner.

11.3.2.3 Main analysis

The primary statistical analysis will be performed on the FAS using the model described in Section 11.3.2.1 for confirmed relapses, with the stratification variable EDSS category included as covariate in the model and the logarithm of time on treatment up to EOS as an offset variable. The effect size will be measured by the relative reduction in the model estimated mean ARR for ponesimod compared to placebo including two-sided 95% Wald CIs.

11.3.2.4 Supportive/sensitivity analyses

The main supportive analysis will count all confirmed relapses up to EOT + 30 days using the FAS. In addition to the missing data sensitivity analysis described in Section 11.3.2.2, the following sensitivity analyses (based on the FAS, if not otherwise stated) are planned using the model described in Section 11.3.2.1:

- Analysis with treatment as the only covariate in the model for all confirmed relapses up to EOS and up to EOT +30 days;
- Analysis adjusting for the stratification covariate using the actual EDSS recorded at baseline on the eCRF up to EOS and up to EOT + 30 days;

- Analysis adjusting for additional baseline characteristics up to EOS and EOT + 30 days;
- Analysis counting only confirmed relapses up to starting alternative MS treatments or EOS for subjects not switching;
- Analyses using different methods of relapse imputation between EOT + 30 days and EOS (PTOP) to further assess the impact of switching to alternative MS treatments;
- Analyses based on the PPS counting confirmed relapses up to EOS;
- Analysis using all relapses (confirmed or unconfirmed) up to EOS and EOT + 30 days;

Further sensitivity analyses will be described in the SAP.

11.3.2.5 Subgroup analyses

The ARR within each level of each subgroup will be analyzed using an unadjusted negative binomial model. Subgroups of interest (including the stratification factor) are:

- Baseline EDSS (≤ 3.5, > 3.5);
- MS subtype (relapsing remitting, secondary progressive);
- Gender (male, female);
- Age (< 40, ≥ 40);
- Prior MS treatment other than DMF (yes, no);
- Relapse in the previous 6 month prior to study entry while on treatment with DMF (≤ 1, ≥ 2);
- Gd+ T1 lesions at baseline (absent, present);

Further subgroup analyses might be performed using other baseline characteristics and other variables. The analyses including interaction tests will be specified in more detail in the SAP.

11.3.3 Analysis of the secondary efficacy variables

The secondary efficacy endpoints will be tested in a hierarchical manner if the primary analysis on ARR has led to the rejection of the null hypothesis in favor of ponesimod. The hierarchical testing procedure starts from the top, and it stops when a null hypothesis cannot be rejected. The order of testing is as follows:

- Time to 12-week CDA from baseline up to EOS;
- Time to first confirmed relapse up to EOS;
- Mean number of CUALs per subject per post-baseline MRI scan up to EOS;
- Longitudinal change over time in fatigue-related symptoms as measured by the symptoms domain of the FSIQ-RMS from baseline up to EOS.
- Longitudinal percent change over time in brain volume from baseline up to EOS.

All hypotheses need to be rejected at a two-sided alpha-level of 0.05. The endpoints will be analyzed using the FAS. All secondary endpoints will also be analyzed using the PPS.

11.3.3.1 Time to 12-week CDA from baseline up to EOS

11.3.3.1.1 Hypothesis

Hypotheses are formulated in terms of "survival" functions S(t), i.e., the probability that time to 12-week CDA is ≥ t for a day t relative to the date of randomization. Two-sided hypotheses are expressed in terms of the survival functions $S_{Ponesimod}(t)$ and $S_{Placebo}(t)$.

$$H_{0,CDA}: S_{Ponesimod}(t) = S_{Placebo}(t) \text{ for all } t \geq 0$$

vs

$$H_{1,CDA}: S_{Ponesimod}(t) \neq S_{Placebo}(t) \text{ for all } t \geq 0$$

The null hypothesis will be tested using a two-sided stratified log-rank test.

11.3.3.1.2 Analyses

The primary analysis of Time to 12-week CDA will be performed on the FAS using a two-sided stratified log-rank test with stratification factor EDSS category. Kaplan-Meier estimates for the survival functions will be plotted using Kaplan-Meier curves and will be tabulated by 12-week intervals. The treatment effect will be measured by means of a hazard ratio calculated using a Cox's proportional hazard model with treatment, and baseline EDSS category as covariates.

11.3.3.1.3 Supportive analyses

Supportive analyses will include an unstratified log-rank test, adjusted and unadjusted Cox's proportional hazards models, analyses based on the PPS and analyses up to EOT + 30 days. A worst case analysis where all unconfirmed disability accumulations at EOS are considered as confirmed will also be performed.

11.3.3.2 Time to first confirmed relapse up to EOS

11.3.3.2.1 Hypothesis

The two-sided hypothesis is expressed in terms of "survival functions" $S_{Ponesimod}(t)$ and $S_{Placebo}(t)$.

$$H_{0,TTFR}: S_{Ponesimod}(t) = S_{Placebo}(t) \text{ for all } t \geq 0$$

vs

$$H_{1,TTFR}: S_{Ponesimod}(t) \neq S_{Placebo}(t) \text{ for all } t \geq 0$$

The null hypothesis will be tested using a two-sided stratified log-rank test.

11.3.3.2.2 Analyses

The primary analysis for this variable will be performed on the FAS using a two-sided stratified log-rank test, stratified by baseline EDSS category. Kaplan-Meier estimates for the survival functions will be plotted using Kaplan-Meier curves and will be tabulated by 12-week intervals. The treatment effect will be measured by means of a hazard ratio calculated using a Cox's proportional hazard model with treatment, baseline EDSS category as covariates.

11.3.3.2.3 Supportive analyses

Supportive/sensitivity analyses will include an unstratified log-rank test, adjusted and unadjusted Cox's proportional hazards models, analyses based on the PPS and analyses counting all confirmed relapses up to EOT + 30 days. An analysis using all relapses (confirmed and unconfirmed) will also be included. Missing data will be assessed using different censoring rules based on each subject's status at EOT + 30 days and EOS.

11.3.3.3 Mean number of CUALs per subject per post-baseline scan from baseline up to EOS

11.3.3.3.1 Hypothesis

Two-sided hypotheses are expressed in terms of the model parameters $\mu_{Ponesimod}$ and $\mu_{Placebo}$ similar to the primary endpoint. The null hypothesis is that the mean CUALs (μ) per subject per scan does not differ between ponesimod and placebo. The alternative hypothesis is that the mean CUALs per subject per scan differ between the two treatments.

$$H_{0,\,CUAL}: \mu_{Ponesimod} - \mu_{Placebo} = 0$$

vs

$$H_{1,\,CUAL}: \mu_{Ponesimod} - \mu_{Placebo} \neq 0$$

The null hypothesis will be tested by a two-sided Wald test within the negative binomial regression model at a two-sided alpha of 0.05 [see Section 11.3.2.1].

11.3.3.3.2 Analyses

The primary analysis of the mean number of CUALs per scan will be performed on the FAS using a similar model as described in Section 11.3.2.1 for the primary endpoint, with the baseline EDSS category included in the model. The log of the number of scans will be used as an offset variable so that estimates will be displayed as mean CUALs per scan. Two-sided 95% Wald CIs will be calculated for the relative reduction in mean CUALs per scan for ponesimod compared to placebo.

11.3.3.3.3 Supportive analyses

Supportive/sensitivity analyses will include a model with no adjustment for any baseline characteristics, models adjusting for additional baseline characteristics, subgroup analyses, analysis excluding MRI scans performed within 30 days after treatment with corticosteroids and analyses based on the PPS. Different methods of imputation for subjects with missing lesion counts will be considered in the SAP.

11.3.3.4 Longitudinal change over time in the fatigue related symptoms domain of the FSIQ-RMS from baseline up to EOS

11.3.3.4.1 Hypothesis

FSIQ-RMS-S is a score ranging from 0 to 70 with a higher score indicating more pronounced fatigue. This endpoint will be analyzed using a generalized linear mixed model to account for repeated measures, to compare the overall absolute change in the fatigue score between the two treatment groups. The hypotheses are expressed as a linear combination of the fixed-effects and are tested at a two-sided significance level of 0.05:

$$H_{0,\,FSIQ}: \mu_{Ponesimod} - \mu_{Placebo} = 0$$

Vs

$$H_{1,\,FSIQ}: \mu_{Ponesimod} - \mu_{Placebo} \neq 0$$

The null-hypothesis will be tested by an F-test.

11.3.3.4.2 Analyses

The primary analysis of change over time in FSIQ-RMS will be performed on the FAS using an adjusted generalized linear mixed model with treatment, time, baseline EDSS category as fixed effect and subject as a random effect. An F-test will be used to compare the overall mean percent change over time in ponesimod compared to placebo. The difference in treatment means and a two-sided 95% CI will also be used to measure the overall treatment effect. The differences at each visit, the effect of time and the interaction between treatment and time will be assessed within the same model. The compound symmetry covariance matrix will be used in the model, however the suitability of this structure will be assessed visually and also compared to an unstructured or autoregressive covariance matrix by assessing the Akaike's information criteria.

11.3.3.4.3 Supportive analyses

Supportive analysis will include an unadjusted model excluding the baseline stratification variable, an adjusted model including additional baseline covariates, model based on the PPS. Missing data imputation will be discussed in the SAP.

11.3.3.5 Longitudinal percent change from baseline over time in brain volume from baseline up to EOS

11.3.3.5.1 Hypothesis

The secondary endpoint percent change from baseline over time in brain volume up to EOS will be analyzed using a generalized linear mixed model to account for repeated measures, to compare the overall percent change in brain volume between the two treatment groups. The hypotheses are expressed as a linear combination of the fixed-effects and are tested at a two-sided significance level of 0.05:

$$H_{0,\,PCBV}: \mu_{Ponesimod} - \mu_{Placebo} = 0$$

vs

$$H_{1,\,PCBV}: \mu_{Ponesimod} - \mu_{Placebo} \neq 0$$

11.3.3.5.2 Analyses

The primary analysis of percent change from baseline in brain volume will be performed on the FAS using an adjusted generalized linear mixed model using the same approach as for the FSIQ-RMS secondary endpoint above [Section 11.3.3.4.2].

11.3.3.5.3 Supportive analyses

Supportive analyses will be similar to those described in Section 11.3.3.4.3 for FSIQ-RMS.

11.3.4 Analysis of the other efficacy variables

The analyses of all exploratory variables will be based on the FAS and described in detail in the SAP. If required, exploratory variables will also be analyzed by subgroups. Each null hypothesis will be tested with a two-sided significance level set to 0.05 in an exploratory manner. All statistical models used will be stratified by baseline EDSS category. For analyses by visit, the observed data will be used as primary analysis and a supportive analysis will use last observation carried forward (LOCF) or other imputation methods where appropriate.

11.3.4.1 Mean number of Gd+ T1, CUAL and new or enlarging T2 lesions by visit

The mean number of Gd+ T1, CUAL and new or enlarging T2 lesions per subject per scan up to Week 48, Week 96, Week 144, EOT and EOS will be analyzed using a negative binomial regression model similar to that described in Section 11.3.3.4.

11.3.4.2 Change in volume of T2 lesions, volume of T1 hypointense lesions and EDSS from baseline to each visit

All variables related to change in lesion volume and change in EDSS at Week 48, Week 96, Week 144, EOT and EOS will be analyzed using an analysis of variance

(ANOVA) with treatment, baseline EDSS category as covariate. Changes to other visits will be summarized descriptively.

11.3.4.3 Absence of Gd+ T1 lesions, absence of new or enlarging T2 lesions, absence of new T1 hypointense lesions and subjects relapse-free

Absence of Gd+ T1 lesions, new T1 hypointense and new or enlarging T2 lesions at Week 48, Week 96, Week 144, EOT and EOS will be analyzed using a logistic regression model with treatment as a factor, including baseline EDSS category as covariate. Subjects that are relapse-free at EOT + 30 days will be analyzed in a similar manner.

11.3.4.4 Time to first 24-week CDA from baseline to EOS

The analysis for this variable follows the same approach as described in Section 11.3.3.2.

11.3.4.5 NEDA status at EOS

NEDA status at EOS is defined by the absence of confirmed relapses, Gd+ T1 lesions, new or enlarging T2 lesions, 12-week CDA, and an annual brain volume decrease of $\leq 0.4\%$ from baseline to EOS. If at least one of the five criteria is not fulfilled or the subject discontinues treatment prematurely, the subject is not considered to have achieved NEDA. NEDA will be analyzed using a logistic regression model with treatment as a factor and baseline EDSS category included in the model.

11.3.4.6 Change of MSFC Z-score and SDMT score from baseline to EOS by visit

The changes from baseline by visit up to the EOS assessment of both scores are analyzed using an ANOVA, similar to the analyses described in Section 11.3.4.2.

11.3.4.7 Change of FSIQ-RMS fatigue-related impacts from baseline to EOS by visit

The changes from baseline by visit up to the EOS assessment of fatigue-related impacts as measured by the impact sub-scales of the FSIQ–RMS will be analyzed similarly to fatigue-related symptoms in Section 11.3.3.4.

11.3.5 Analysis of the safety variables

The SAF will be used to perform all safety analyses.

If not otherwise stated, only treatment-emergent safety data (observations up to 30 days after study drug discontinuation) will be considered in tables and figures. All safety data will be included in listings, with flags for safety data not considered to be treatment-emergent.

Specific safety events (AEs, laboratory tests, ECG findings, etc.) will be considered. In general, they consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with ponesimod.

11.3.5.1 Adverse events

All AEs will be coded using the latest version of MedDRA available at the time of database closure.

11.3.5.1.1 Treatment-emergent AEs and SAEs

Treatment-emergent AEs and SAEs will be tabulated by study treatment, system organ class (SOC) and preferred terms within each SOC: the number and percentage of subjects who experienced at least one (S)AE, at least one (S)AE within each SOC and at least one S(AE) within each preferred term will be displayed. (S)AEs will also be summarized by decreasing frequency of preferred term. (S)AEs will also be tabulated by maximum intensity and relationship to ponesimod or placebo.

11.3.5.1.2 AEs of special interest and MACE

AEs of special interest and MACE will be summarized in the same way as stated in the previous section and compared between treatments using logistic regression. The definition of those AEs is provided in Appendix 5.

AEs of special interest and MACE will also be summarized with point estimates and 95% CIs for event incidences adjusted for time on treatment and the relative risk ratio of ponesimod compared to placebo will be provided without adjustment for multiplicity.

In some cases, time to first onset of AEs of special interest or MACE will be displayed by Kaplan-Meier estimates. Subjects not experiencing the safety event will be censored at the minimum of the EOS date and 30 days after last dose of study drug. Where applicable, ponesimod will be compared to placebo using hazard ratios and corresponding 95% CIs from a Cox's regression model. For specific safety events where recurrence and/or duration are of interest, appropriate event history analysis such as an Andersen-Gill model for recurrent events will be described in the SAP.

11.3.5.1.3 AEs leading to premature discontinuation of study drug

(S)AEs leading to premature discontinuation of study drug will be summarized in a similar manner as that described in Section 11.3.5.1.1.

11.3.5.1.4 Post-treatment AEs and SAEs

Post-treatment (S)AEs occurring over 30 days after treatment discontinuation will be summarized in a similar manner as described in Section 11.3.5.1.1.

11.3.5.1.5 Deaths

Fatal SAEs occurring any time after the start of treatment will be summarized in a similar manner as described in Section 11.3.5.1.1.

11.3.5.2 Cardiac safety

Descriptive summary statistics by visit and study treatment will be provided for observed treatment-emergent values and absolute changes from baseline in numeric 12-lead ECG values (HR, PR, QRS, QT, QTcB, and QTcF). Data will be summarized from pre-dose to the post-dose assessments at 1 h, 2 h, 3 h, and 4 h on Day 1 and also at the re-initiation of study drug.

Notable abnormalities for selected 12-lead ECG variables (HR, PR, QT and QTc) will be summarized for all data of the 3-hour post-dose assessments on Day 1, Week 12 and also at the re-initiation of study drug.

In addition treatment-emergent morphological ECG abnormalities will be summarized that were not present before first study drug intake (using data from the ECG provider).

Cardiac safety events will be summarized as categorical variables.

11.3.5.3 Pulmonary safety

Descriptive summary statistics by visit and study treatment will be provided for observed treatment-emergent values and changes from baseline by visit in FEV_1 and FVC (all expressed in absolute change, % change and % of predicted value).

The number and proportion of treatment-emergent decreases of percent predicted FEV_1 or FVC > 20% from baseline at any time up to EOT + 30 will be summarized by treatment.

The trend effect of treatment of the percent predicted FEV_1 over time will be analyzed by treatment using a regression analysis with time as the independent variable and % predicted FEV_1 calculated with the age at the time of the assessment as the dependent variable. Assessments during up-titration and after the subject discontinues treatment will not be included in this analysis.

The mean (and 95% CIs), change and % change from baseline to EOS and from baseline to EOT in FEV_1 or FVC (absolute and % of predicted) will be plotted by treatment. A scatter plot will display the change from baseline to EOS versus the change from baseline to EOT on an individual subject level by study treatment.

For the subset of subjects with a decrease of > 200 mL or > 12% in FEV_1 or FVC from baseline at EOT, the number and percentage of subjects with a decrease of ≤ 200 mL and ≤ 12% from baseline to last available FU in FEV_1 or FVC will be summarized by treatment.

Pulmonary safety events will be summarized as categorical variables.

11.3.5.4 Vital signs

Descriptive summary statistics by visit and study treatment will be provided for observed treatment-emergent values and absolute changes from baseline in HR, BP and body weight.

Treatment-emergent notable BP abnormalities will also be summarized descriptively. The definition for notable abnormalities is provided in Appendix 6.

11.3.5.5 Laboratory endpoints

11.3.5.5.1 Laboratory tests

Descriptive summary statistics by visit and study treatment will be provided for observed treatment-emergent values and absolute and percentage changes from baseline for laboratory tests (hematology, blood chemistry, urinalysis). Data will be displayed in SI units whenever possible and graphical approaches will be applied for certain variables.

The lymphocyte count reversibility after EOT will be summarized by plotting the mean (and 95% CIs) change from baseline to EOT and change from baseline to EOS by treatment. A scatter plot will display the change from baseline to EOS versus the change from baseline to EOT on an individual subject level by study treatment.

Change in JCV serology from baseline up to EOS will be summarized descriptively.

11.3.5.5.2 Laboratory safety events

Laboratory safety events will include:

- Treatment-emergent laboratory test abnormalities based on normal ranges of the central laboratory, project-specific ranges, and common terminology criteria for adverse events (CTCAE) [CTCAE 2010];
- Treatment-emergent laboratory test abnormalities based on FDA guidance for DILI [FDA 2009b] (for ALT / AST / total bilirubin).

Laboratory safety events will be summarized as categorical variables. The definition for notable abnormalities is provided in Appendix 6.

11.3.6 eC-SSRS

The number of subjects (including percentages) with a treatment-emergent eC-SSRS suicidal ideation score of 4 or above, or a “yes” response on the eC-SSRS suicidal behavior item will be summarized descriptively, by treatment arm.

11.3.7 Analysis of other variable(s)

11.3.7.1 PK

Trough level (pre-dose) plasma concentrations of ponesimod at each visit and at EOT, and plasma concentrations of ponesimod at 3 hours post-dose at Day 1 and Week 12 will be analyzed by descriptive statistics, including arithmetic mean, standard deviation, minimum, maximum, and median.

11.3.7.2 PD

The relationship between ponesimod concentration and total lymphocyte counts will be investigated by modeling and simulation.

11.3.7.3 Quality of Life Questionnaire (SF-36v2™)

Data in the health survey domain and component scores will be summarized descriptively by visit and study treatment up to EOS in the FAS.

11.3.7.4 WPAI:MS Questionnaire

Data in the pharmacoeconomic WPAI:MS Questionnaire will be summarized descriptively by visit and study treatment, up to EOS in the FAS.

11.3.7.5 Health care resource utilization

Data on health care resource utilization will be summarized descriptively by visit and study treatment, up to EOT in the FAS.

11.4 Interim analyses

No interim analysis is planned for the study.

11.5 Sample size

The sample size is calculated based on the primary endpoint, and the power is calculated for the time to 12-week CDA secondary endpoint.

11.5.1 Primary endpoint

The sample size for the study was determined by a simulation using the negative binomial distribution. A sample size of 600 subjects (300 per treatment group) will provide a power of approximately 90% for a significance level of 0.05, under the assumption that the ARR (for confirmed relapses up to EOS) is 0.50 for placebo and 0.325 for ponesimod (which corresponds to a risk reduction of 35%), and using a dispersion $k = 1.3$ (where the variance is $= \mu + k\ \mu^2$). A mean subject follow-up of 1.9 years is assumed with 3.3 years maximum follow-up.

The dispersion from the ponesimod Phase 2 study was 1.0; a higher dispersion is assumed here due to the potentially higher disease activity in this subject population.

11.5.2 Secondary endpoints

Assuming 12-week CDA rate at 2 years for placebo of 0.3 and a hazard ratio of 0.55 (i.e., 2-year progression of 0.165 for ponesimod), a maximum number of 120 events are required to attain an approximate power of 90% for a two-sided significance level of 0.05.

11.5.3 Sample size sensitivity

The power for varying different assumptions of placebo ARR, % reduction, dispersion and mean follow-up time is presented in the table below.

Annualized Relapse Rate		% Reduction	Dispersion	Mean FU Time	Power
Placebo	Ponesimod				
Varying Placebo ARR up to EOS					
0.400	0.260	35.0%	1.3	1.9	86.5%
0.600	0.390	35.0%	1.3	1.9	92.5%
Varying % Reduction					
0.500	0.375	25.0%	1.3	1.9	60.1%
0.500	0.350	30.0%	1.3	1.9	77.7%
0.500	0.288	42.5%	1.3	1.9	98.4%
Varying Dispersion					
0.500	0.325	35.0%	0.5	1.9	97.3%
0.500	0.325	35.0%	2.0	1.9	82.3%
Varying Follow-Up Time					
0.500	0.325	35.0%	1.3	1.4	84.9%
0.500	0.325	35.0%	1.3	2.5	93.4%

11.5.4 Sample size re-estimation

There is no sample-size re-estimation planned.

12 DATA HANDLING

12.1 Data collection

The investigator/delegate is responsible for ensuring the accuracy, completeness, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of the data. Data reported in the eCRF derived from source documents must be consistent with the source documents.

Electronic CRF data will be captured via electronic data capture (using the Rave system provided by Medidata Solutions, Inc., a web-based tool). The investigator and site staff will be trained to enter and edit the data via a secure network, with secure access features

(username, password and identification – an electronic password system). A complete electronic audit trail will be maintained. The investigator/delegate will approve the data (i.e., confirm the accuracy of the data recorded) using an electronic signature (refer to 21 CFR Part 11). In addition to the main eCRF, a separate eCRF will be used to collect data with unblinding potential generated on Day 1 and on the first day of re-initiation of study drug when post-dose monitoring is required. This data will only be visible to the site monitor, the first-dose monitor and to an Independent Data Management Team [see Sections 5.1.4.2 and 10.1.5].

Entries recorded by the subject in the electronic diary (FSIQ-RMS, SF-36v2^{TM}, and WPAI:MS) and the eC-SSRS are considered source data. The site staff will review and ensure completeness and readability (if applicable) of the subject's entries.

Subject screening and enrollment data will be completed for all subjects (i.e., eligible and non-eligible) through the IRT system and eCRF.

For each subject enrolled, regardless of study treatment initiation, a eCRF must be completed and signed by the investigator/delegate. This also applies to those subjects who fail to complete the study. If a subject withdraws from the study, the reason must be noted on the eCRF.

12.2 Maintenance of data confidentiality

The investigator/delegate must ensure that data confidentiality is maintained. On CRFs or other documents submitted to Actelion, subjects must be identified only by number and never by name or initials, hospital numbers or any other identifier. The investigator/delegate must keep a subject identification code list at the site, showing the randomization number, the subject's name, date of birth and address or any other locally accepted identifiers. Documents identifying the subjects (e.g., signed ICFs) must not be sent to Actelion, and must be kept in strict confidence by the investigator/delegate.

12.3 Database management and quality control

Electronic CRFs will be used for all subjects. The investigator will have access to the site eCRF data until the database is locked. Thereafter, they will have read-only access. The eCRF must be kept current to reflect subject status at any timepoint during the course of the study.

While entering the data, the investigator/delegate will be instantly alerted to data queries by validated programmed checks. Additional data review will be performed by Actelion on an ongoing basis to look for unexpected patterns in data and study monitoring. If discrepant data are detected, a query specifying the problem and requesting clarification will be issued and visible to the investigator/delegate via the eCRF. All electronic queries visible in the system either require a data correction (when applicable) and a response

from the investigator/delegate to clarify the queried data directly in the eCRF, or simply a data correction in the eCRF. The investigator/delegate must, on request, supply Actelion with any required background data from the study documentation or clinical records. This is particularly important when errors in data transcription are suspected. In the case of health authority queries, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

This process will continue until database closure.

Laboratory samples, ECGs, eDiary, SF-36v2™, FSIQ-RMS, eC-SSRS and WPAI:MS assessments will be processed centrally through their respective central laboratory/provider, and the results will be sent electronically to Actelion. If local laboratory date is obtained as may be required per protocol in certain instances, it must be entered in the eCRF by the site.

After the database has been declared complete and accurate, the database will be closed. Any changes to the database after that time may only be made as described in the appropriate SOP. After database closure, the investigator will receive the eCRF of the subjects of her/his site (including all data changes made) on electronic media or as a paper copy.

13 PROCEDURES AND GOOD CLINICAL PRACTICE

13.1 Ethics and Good Clinical Practice

Actelion and the investigators will ensure that the study is conducted in full compliance with ICH-GCP guidelines, the principles of the "Declaration of Helsinki" and with the laws and regulations of the country in which the research is conducted.

13.2 Independent Ethics Committee / Institutional Review Board

The investigator will submit this protocol and any related document provided to the subject (such as Subject Information Leaflet used to obtain informed consent) to an IRB or IEC. Approval from the committee must be obtained before starting the study, and must be documented in a dated letter to the investigator, clearly identifying the study, the documents reviewed, and the date of approval.

Modifications made to the protocol after receipt of the approval must also be submitted as amendments by the investigator to the IRB/IEC in accordance with local procedures and regulations [see Section 13.6].

A list of members participating in the IRB/IEC meetings must be provided, including the names, qualifications and functions of these members. If that is not possible, the attempts made to obtain this information along with an explanation as to why it cannot be obtained

or disclosed must be documented in the study documentation. If a study staff member was present during a meeting, it must be clear that this person did not vote.

13.3 Informed consent

It is the responsibility of the investigator/delegate to obtain informed consent according to ICH-GCP guidelines and local regulations from each individual participating in this study and/or legal representative. The investigator/delegate must explain to subjects that they are completely free to refuse to enter the study or to withdraw from it at any time for any reason.

The ICF will be provided in the country's local language(s) and will be translated to the subject's preferred language if requested by the subject due to difficulties understanding the local language.

Site staff authorized to participate in the consent process and/or to obtain consent from the subject and/or legal representative will be listed on an Actelion Delegation of Authority form. A study physician must always be involved in the consent process.

The subject and/or legal representative must sign, personally date and time (if appropriate) the ICF before any study-related procedures (i.e., any procedures required by the protocol) begin. The ICF must also be signed, personally dated and timed (if the first study-mandated procedure was performed on the same day informed consent was obtained) by the authorized site staff listed on the Actelion Delegation of Authority form.

A copy of the signed and dated ICF is given to the subject and/or legal representative; the original is filed in the site documentation.

The informed consent process must be fully documented in the subject's medical records, including study reference, subject number, date/time (if applicable) when the subject was first introduced to the Actelion clinical study, date/time (if applicable) of consent, who participated in the consent discussion, who consented the subject and any additional person present during the consent process (e.g., subject family member), copy of the signed ICF given to the subject / legal representative.

Re-screening requires re-consenting i.e., a new ICF must be signed by the subject and the investigator.

Re-consent

In order to ensure subjects are made aware of potential risks and benefits of continuing in the study as well as alternative treatment options available, subjects who continue study treatment and DMF background therapy upon experiencing a confirmed relapse or a 24-week CDA while on study drug will be asked to re-consent to continue receiving study treatment.

13.4 Compensation to subjects and investigators

Actelion provides insurance in order to indemnify (with both legal and financial coverage) the investigator/site against claims arising from the study, except for claims that arise from malpractice and/or negligence.

The compensation of the subject in the event of study-related injuries will comply with applicable regulations.

13.5 Protocol adherence/compliance

The investigator must conduct the study in compliance with the approved version of the protocol and must not implement any deviation/change from the protocol, except when deviation is necessary to eliminate an immediate hazard to the subject.

If a protocol deviation occurs, the investigator/delegate will inform Actelion or its representative, in a timely manner. The investigator/delegate must document and explain any deviation from the approved protocol. IRB/IEC and regulatory authorities must be informed, according to their requirements, but no later than 15 calendar days after the event.

13.6 Protocol amendments

Any change to the protocol can only be made through a written protocol amendment. A protocol amendment must be submitted to an IRB/IEC and regulatory authorities, according to their requirements.

13.7 Essential documents and retention of documents

The investigator/delegate must maintain adequate records necessary for the reconstruction and evaluation of the study. A number of attributes are considered of universal importance to source data and the records that hold those data. These include that the data and records are accurate, legible, contemporaneous, original (or certified copy), attributable, complete, consistent, enduring and available when needed.

These records are to be classified into two different categories of documents: investigator's file, and subject clinical source documents.

These records must be kept by the investigator for as long as is necessary to comply with Actelion's requirements (e.g., as specified in the clinical study agreement), and national and/or international regulations, whichever would be the longest period. If the investigator cannot guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements respecting the data confidentiality must be made between the investigator and Actelion to store these documents outside the site, so that they can be retrieved in case of a regulatory inspection. No study document should be destroyed without prior written approval from Actelion. Should the investigator wish

to assign the study records to another party or move them to another location Actelion must be notified in advance.

If the site is using an electronic/computerized system to store subject medical records, it can be used for the purpose of the clinical study if it is validated (as per 21 CFR Part 11 or equivalent standard) and if the monitor has been provided personal and restricted access to study subjects only, to verify consistency between electronic source data and the eCRF during monitoring visits.

If the site is using an electronic/computerized system to store subject medical records but it could not be confirmed that the system is validated or if the monitor could not be provided access to the system, the site is requested to print the complete set of source data needed for verification by the monitor. The print-outs must be numbered, stapled together with a cover sheet, signed and dated by the investigator/delegate to confirm that these certified copies are exact copies having the same information as the original subject's data. The printouts will be considered as the official clinical study records and must be filed either with the subject medical records or with the subject's eCRF.

In order to verify that the process the site uses to prepare certified copies is reliable, the monitor must be able to observe this process and confirm that the comparison of the source documents and the certified copy did not reveal inconsistencies. The monitor does not need to verify this process for all data of all subjects but at least for some of them (e.g., first subject, regular check during the study of critical data like inclusion/exclusion criteria, endpoints for some subjects) as per Actelion's instructions. If it were not possible for the monitor to observe this process, it would not be possible to rely on the site's certified copies and therefore the site cannot be selected for the clinical study. The printouts should be filed either with the subject medical records or with the subject's eCRF.

13.8 Monitoring

Prior to study start, a site initiation visit (SIV) will be performed after the required essential study documents are approved by Actelion. The study treatment will be shipped to the site upon approval of the required essential documents.

The principal investigator must ensure that all site personnel involved in the study will be present during the SIV and will dedicate enough time to it. Site information technology support should also be available during the initiation visit.

The SIV must be completed before the site can start the screening of study subjects. Following the SIV, a copy of the completed initiation visit report and FU letter will be provided to the principal investigator and filed in the ISF.

During the study, the monitor will contact and visit the investigational site regularly, and on request must be permitted to have access to trial facilities and all source documents needed to verify adherence to the protocol and the completeness, consistency and accuracy of the data being entered in the CRFs and other protocol-related documents. Actelion monitoring standards require full verification that informed consent has been provided, and verification of adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of the main efficacy, safety and tolerability endpoints. Additional checks of the consistency of the source data with the CRFs will be performed according to the study-specific monitoring plan. The frequency of the monitoring visits will be based on subject recruitment rate and critical data collection times.

The principal investigator and first-dose administrator must ensure that the eCRF is completed after a subject's visit to the site, and that all requested subject files (e.g., ICFs, medical notes/charts, other documentation verifying the activities conducted for the study) are available for review by the monitor. The required site personnel must be available during monitoring visits and allow adequate time to meet with the monitor to discuss study-related issues.

The investigator agrees to cooperate with the monitor(s) to ensure that any issues detected in the course of these monitoring visits are resolved. If the subject is hospitalized or dies in a hospital other than the study site, the investigator is responsible for contacting that hospital in order to document the SAE, in accordance with local regulations.

A close-out visit will be performed for any initiated site and when there are no more active subjects and after all study data have been accepted by medical review and all FU issues have been resolved. In case a site does not enroll any subjects, the close-out visit may be performed prior to study database closure at the discretion of Actelion.

13.9 Investigator site file

Each site will be provided with an ISF prior to the initiation visit. It will contain all the essential documents that are required to always be up-to-date and filed at site as per ICH-GCP section 8.

The ISF will include a table of contents listing the essential documents. All study related documentation must be maintained in the ISF.

In some cases, exceptions can be discussed with the monitor regarding the filing of the study documents outside the ISF. It should be clearly documented where each document is filed. This note to file should be present in the specific tab of the document in the ISF.

The ISF must be stored in a secure and access-restricted area during and after the study. It must be kept by the site for as long as needed to comply with any applicable rules and regulations, ICH-GCP as well as instructions from Actelion. If the site needs to transfer

the ISF to another location and/or if the site facility can no longer store the ISF, the principal investigator must inform Actelion immediately.

If the principal investigator will change, or if the site will relocate, the monitor must be notified as soon as possible.

13.10 Audit

Actelion's Global Quality Management representatives may audit the investigator site (during the study or after its completion). The purpose of this visit will be to determine the investigator's adherence to ICH-GCP, the protocol, and applicable regulations; adherence to Actelion's requirements (e.g., SOPs) will also be verified. Prior to initiating this audit, the investigator will be contacted by Actelion to arrange a time for the audit.

The investigator and staff must cooperate with the auditor(s) and allow access to all study documentation (e.g., subject records) and facilities.

13.11 Inspections

Health authorities and/or IRBs/IECs may also wish to conduct an inspection of Actelion's clinical study (during the study or after its completion).

Should an inspection be requested by a health authority and/or IRB/IEC, the investigator must inform Actelion immediately (usually via the monitor) that such a request has been made.

The investigator and staff must cooperate with inspector(s) and allow access to all study documentation (e.g., subject records) and study facilities.

13.12 Reporting of study results and publication

Study results will be documented in a clinical study report that will be signed by Actelion representatives and the coordinating investigator (or principal investigator for single-center studies).

The coordinating investigator and the steering committee / advisory board, if any, will have the opportunity to review the analysis of the data and to discuss the interpretation of the study results with Actelion prior to publication.

Actelion will post results from its clinical studies on Actelion's clinical trial disclosure system Clinical Trial Register (VICTOR) and on external/national registries, as required by law.

Actelion's policy on disclosure of clinical research information can be found at:
http://www.actelion.com/documents/corporate/policies-charters/policy-clinical-research-information.pdf

In accordance with the Good Publication Practices and ethical practice, the results of the study will be submitted for publication in a peer-reviewed journal. Study results can be submitted for presentation at a congress before publication in a peer-reviewed journal.

Authorship will be determined in accordance with the International Committee of Journal Editors criteria, and be based on:

- Substantial contributions to: the conception or design of the study, or the acquisition, analysis or interpretation of data; and
- Drafting of the publication or critical review for important intellectual content; and
- Providing final approval of the version to be published; and
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The list of authors of any publication of study results may include representatives of Actelion and will be determined by mutual agreement.

Any study-related publication written independently by investigators must be submitted to Actelion for review at least 30 days prior to submission for publication or presentation. Upon review, Actelion may provide comments and may also request alterations and/or deletions for the sole purpose of protecting its confidential information and/or patent rights. Neither the institution nor the investigator should permit publication during such a review period.

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15 APPENDICES

Appendix 1 Neurostatus® scoring sheet

neurostatus scoring

Scoring Sheet for a standardised, quantified neurological examination and assessment of Kurtzke's Functional Systems and Expanded Disability Status Scale in Multiple Sclerosis

STUDY NAME

PERSONAL INFORMATION

Patient	
Date of Birth (04-Jun-1980)	- -
Centre Nr/Country	
Name of EDSS rater	
Date of Examination	- - 2 0

SYNOPSIS

1. Visual	[1]	Ambulation Score	
2. Brainstem			
3. Pyramidal		EDSS Step	
4. Cerebellar			
5. Sensory			
6. Bowel/Bladder	[1]	Signature	
7. Cerebral			

1. VISUAL (OPTIC) FUNCTIONS

OPTIC FUNCTIONS	OD	OS			
Visual acuity ☐ CC ☐ SC			Scotoma		
Visual fields			* Disc pallor		
			FUNCTIONAL SYSTEM SCORE	→	[1]

2. BRAINSTEM FUNCTIONS

CRANIAL NERVE EXAMINATION			
Extraocular movements (EOM) impairment		Dysarthria	
Nystagmus		Dysphagia	
Trigeminal damage		Other cranial nerve functions	
Facial weakness		FUNCTIONAL SYSTEM SCORE	

3. PYRAMIDAL FUNCTIONS

REFLEXES	R	><	L			
Biceps				Knee extensors		
Triceps				Plantar flexion (feet/toes)		
Brachioradialis				Dorsiflexion (feet/toes)		
Knee				* Position test UE, pronation		
Ankle				* Position test UE, downward drift		
Plantar response				* Position test LE, sinking		
Cutaneous reflexes				* Able to lift only one leg at a time (grade in *)	*	*
* Palmomental reflex				* Walking on heels		

LIMB STRENGTH	R	L			
Deltoid			* Walking on toes		
Biceps			* Hopping on one foot		
Triceps			SPASTICITY		
Wrist/finger flexors			Arms		
Wrist/finger extensors			Legs		
Hip flexors			Gait		
Knee flexors			OVERALL MOTOR PERFORMANCE		
			FUNCTIONAL SYSTEM SCORE		

CC = corrected
SC = without correction
* = optional part of the examination
[1] = converted FS Score

4. CEREBELLAR FUNCTIONS

CEREBELLAR EXAMINATION			Rapid alternating movements UE impairment		
Head tremor			Rapid alternating movements LE impairment		
Truncal ataxia			Tandem walking		
	R	L	Gait ataxia		
Tremor/dysmetria UE			Romberg test		
Tremor/dysmetria LE			Other, e. g. rebound		
			FUNCTIONAL SYSTEM SCORE		

5. SENSORY FUNCTIONS

SENSORY EXAMINATION	R	L	Position sense UE		
Superficial sensation UE			Position sense LE		
Superficial sensation trunk			* Lhermitte's sign		
Superficial sensation LE			* Paraesthesiae UE		
Vibration sense UE			* Paraesthesiae trunk		
Vibration sense LE			* Paraesthesiae LE		
			FUNCTIONAL SYSTEM SCORE		

6. BOWEL/ BLADDER FUNCTIONS

Urinary hesitancy/retention		Bowel dysfunction	
Urinary urgency/incontinence		* Sexual dysfunction	
Bladder catheterisation		FUNCTIONAL SYSTEM SCORE	→ [1]

7. CEREBRAL FUNCTIONS

MENTAL STATUS EXAMINATION		Decrease in mentation	
° Depression		' Fatigue	
° Euphoria		FUNCTIONAL SYSTEM SCORE	

AMBULATION

Distance reported by patient (in meters)		Assistance	
Time reported by patient (in minutes)		Distance measured (in meters)	
		AMBULATION SCORE	

* = optional part of the examination
[1] = converted FS Score
° Depression and Euphoria are not taken into consideration for FS and EDSS calculation.
' Because fatigue is difficult to evaluate objectively, in some studies it does not contribute to the Cerebral FS score or EDSS step. Please adhere to the study's specific instructions.

UE = upper extremities
LE = lower extremities

Standardised Neurological Examination and Assessment of Kurtzke's Functional Systems and Expanded Disability Status Scale
Slightly modified from J.F. Kurtzke, Neurology 1983:33,1444-52
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Appendix 2 Diagnostic criteria for MS (2010 Revised McDonald Criteria)

Clinical Presentation	Additional Data Needed for MS Diagnosis
≥ 2 attacks[a]; objective clinical evidence of ≥ 2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack[b]	None[c]
≥ 2 attacks[a]; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by: ≥ 1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)[d]; or Await a further clinical attack[a] implicating a different CNS site
1 attack[a]; objective clinical evidence of ≥ 2 lesions	Dissemination in 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 dissemination in space (DIS): ≥ 1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord); or Await a second clinical attack[a] implicating a different CNS site; and For dissemination in time (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)	1 year of disease progression (retrospectively or prospectively determined) plus 2 of 3 of the following criteria[d]: 1. Evidence for DIS in the brain based on ≥ 1 T2 lesions in the MS-characteristic (periventricular, juxtacortical, or infratentorial) regions 2. Evidence for DIS in the spinal cord based on ≥ 2 T2 lesions in the cord 3. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

If the criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is "MS"; if suspicious, but if 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 as patient-reported or objectively observed events typical of an acute inflammatory demyelinating event in the CNS, current or

historical, with duration of at least 24 hours, in the absence of fever or infection. It should be documented by contemporaneous neurological examination, but some historical events with symptoms and evolution characteristic for MS, for which no objective neurological findings are documented, can provide reasonable evidence of a prior demyelinating event. Reports of paroxysmal symptoms (historical or current) should, however, consist of multiple episodes occurring over not less than 24 hours. Before a definite diagnosis of MS can be made, at least 1 attack must be corroborated by findings on neurological examination, visual evoked potential response in subjects reporting prior visual disturbance, or MRI consistent with demyelination in the area of the CNS implicated in the historical report of neurological symptoms.

[b]Clinical diagnosis based on objective clinical findings for 2 attacks is most secure. Reasonable historical evidence for 1 past attack, in the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristics for a prior inflammatory demyelinating event; at least 1 attack, however, must be supported by objective findings.

[c]No additional tests are required. However, it is desirable that any diagnosis of MS be made with access to imaging based on these criteria. If imaging or other tests (for instance, CSF) are undertaken and are negative, extreme caution needs to be taken before making a diagnosis of MS, and alternative diagnoses must be considered. There must be no better explanation for the clinical presentation, and objective evidence must be present to support a diagnosis of MS.

[d]Gadolinium-enhancing lesions are not required; symptomatic lesions are excluded from consideration in 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.

[Polman 2011**]**

Appendix 3 Prohibited anti-arrhythmic and HR-lowering drugs

The following anti-arrhythmic and HR-lowering drugs (systemic administration) are prohibited during the study [see Section 5.2.6]:

- Adenosine
- Acebutolol
- Ajmaline
- Amiodarone
- Aprinidine
- Atenolol
- Azimilide
- Bepridil
- Betaxolol
- Bisoprolol
- Bretylium
- Bunaftine
- Carvedilol
- Cibenzoline
- Disopyramide
- Dofetilide
- Dronedarone
- Encainide
- Esmolol
- Flecainide
- Ibutilide
- Ivabradine
- Lidocaine
- Lorajmine
- Lorcainide
- Metoprolol
- Mexiletine
- Moracizine
- Nadolol
- Phenytoin
- Pilocarpine
- Prajmaline
- Procainamide
- Propafenone
- Propranolol
- Quinidine
- Sotalol
- Sparteine
- Tedisamil
- Timolol
- Tocainide
- Vernakalant

If, in the judgment of the investigator, it is in the best interests of the subject to receive any of the drugs listed above, study drug must be permanently discontinued. This list is not exhaustive, other anti-arrhythmic or HR-lowering drugs are also prohibited. In case of doubt, please discuss with the sponsor the use of any potential anti-arrhythmic or HR-lowering drug.

Appendix 4 Guidance for concomitant treatment with QT-prolonging drugs with known risk of Torsades de Pointes

QT-prolonging medications with known risk of Torsades de Pointes (e.g., azithromycin, citalopram, clarithromycin, erythromycin, escitalopram, moxifloxacin, etc.) should be administered with caution since ponesimod may potentially enhance their effect on QT interval. A list of QT-prolonging medications with known risk of TdP is published by AZCERT [University of Arizona CERT http://crediblemeds.org/]. The investigator should also take into account other relevant risk factors such as hypokalemia when considering treatment with a QT-prolonging drug. If treatment with such drugs is considered necessary, the principal investigator / treating neurologist should always discuss with the first-dose administrator and/or a cardiologist the appropriateness of combining such drugs with the study drug and may interrupt or permanently discontinue study drug. If the principal investigator determines in the best interest of the subject to concomitantly administer a QT-prolonging drug with known risk of Torsades de Pointes the following recommendations must be adhered to:

a) For a need to start treatment or to increase the dose of a QT-prolonging drug with known risk of Torsades de Pointes during the up-titration, treatment with study drug must be interrupted.

- Study drug can only be re-initiated [see Section 5.1.9] after the QT-prolonging drug has been stopped or once the QT-prolonging drug has reached the steady-state.
  - Once the QT-prolonging drug has reached the steady-state and prior to re-initiation of study drug, the QTcF interval obtained pre-dose on the day of the planned re-initiation must be ≤ 450 ms for males or ≤ 470 ms for females.
  - Following re-initiation of study drug, at next visit (scheduled or unscheduled occurring after completion of the up-titration), perform ECG measurements pre-dose.

b) For a need to start treatment or to increase the dose of a QT-prolonging drug with known risk of Torsades de Pointes during the study excluding the up-titration (i.e., after 2 weeks of study drug initiation or re-initiation).

- At visit (scheduled or unscheduled) prior to initiation or dose increase of QT-prolonging drug with known risk of Torsades de Pointes, perform ECGs measurements pre-dose.
  - If prior to initiation or dose increase of QT-prolonging drug with known risk of Torsades de Pointes, the QTcF interval is > 450 ms for males or > 470 ms for females, treatment with study drug must be interrupted.

- At next visit (scheduled or unscheduled occurring once the QT-prolonging drug has reached the steady-state [approximately after 5 half-lives of the QT-prolonging drug]) following initiation or dose increase of QT-prolonging drug with known risk of Torsades de Pointes, perform ECGs measurements pre-dose.

Appendix 5 Adverse events of special interest

Adverse events of special interest (AESIs) will include the anticipated risks of treatment with ponesimod and the events that may be related to MS comorbitities (e.g., seizures or stroke), and will address the following safety areas:

- Effect on heart rate and rhythm AESIs (including hypotension)
- Hepatobiliary disorders / Liver enzyme abnormality AESIs
- Pulmonary AESIs
- Macular edema AESIs
- Infection AESIs
- Herpetic infection AESIs
- Skin malignancy AESIs
- Non-skin malignancy related AESIs
- Cardiovascular AESIs
- Hypertension AESIs
- Stroke AESIs
- Seizure AESIs

A list of AESIs (MedDRA preferred terms) will be defined in the SAP.

Appendix 6 Abnormalities for ECG, BP and laboratory variables

Notable abnormalities for ECG and BP that are related to the potential effects of ponesimod will address the following variables:

- Morphological ECG findings (defined as any abnormal finding not present prior to start of treatment).
- HR outliers (bpm), based on ECG
- PR interval (ms)
- QT/QTc interval (ms), QTcB or QTcF
- BP (mmHg)

The definition of the abnormal values to be reported will be described in the SAP.

Laboratory abnormalities

Laboratory values below or above the normal range will be graded at three levels (H, HH, HHH for values above normal range and L, LL, LLL for values below the normal range) where L stands for "low", H for "high".

The term "marked abnormality" describes laboratory values above or below the thresholds, with grading of abnormalities at two levels: LL/HH and LLL/HHH. These thresholds have been defined by the sponsor in order to flag and/or communicate abnormal laboratory results from the central laboratory to the investigators, and for the purpose of standardized data analysis and reporting by the sponsor. The definitions of marked abnormal values are based mainly on the Common Terminology Criteria for Adverse Events (CTCAE) [CTCAE 2010] grading system and, in specific cases (e.g., lymphocyte levels), are adjusted based on the known PD effect of the study drugs (e.g., LLL threshold for lymphocytes).

The term ALERT here corresponds to protocol-defined test result threshold requiring an action from the investigator as described in the protocol (e.g., repeat the test; interrupt or discontinue the study drug) and should not be confused with the term "call alert" used by the central laboratory for laboratory results, which will be communicated to the investigator. Not all ALERTS listed in this table will be "call alerts" from the central laboratory and vice versa.

PLEASE NOTE: Thresholds for abnormality of level L or H are not provided in this appendix but will be provided in the central laboratory manual. Parameters for which no threshold is defined in the table below may be defined in the central laboratory manual.

Thresholds for marked laboratory abnormalities

Parameter (SI unit)	LL	LLL	HH	HHH
Hemoglobin (g/L)	< 100	< 80	Increase in > 20 g/L above ULN or above baseline (if baseline is above ULN)	Increase in > 40 g/L above ULN or above baseline (if baseline is above ULN)
MCH (pg/Cell)	ND	ND	ND	ND
MCV (fL)	ND	ND	ND	ND
Hematocrit (L/L)	< 0.28 (female) < 0.32 (male)	< 0.20	> 0.55 (female) > 0.60 (male)	> 0.65
Platelet count (10^9 /L)	< 75	< 50	> 600	> 999
RBC count (10^{12} /L)	ND	ND	ND	ND
WBC count (10^9 /L)	NA	< 1.9	> 20.0 **ALERT:** **> 20.0**	> 100.0
Lymphocyte (10^9 /L)	ND	< 0.2 **ALERT:** **< 0.2** **Decrease of > 50 % from the value of total lymphocyte count recorded at Visit 5 (Week 4) associated with a total lymphocyte count < 0.5 × 10^9/L recorded at two consecutive visits after Visit 5 (Week 4)**	> 4.0	≥ 8
Neutrophils (10^9 /L)	< 1.5	< 1.0	ND	ND

Parameter (SI unit)	**LL**	**LLL**	**HH**	**HHH**
Eosinophils (10^9 /L)	ND	ND	> 5.0	ND
Monocytes (10^9 /L)	ND	ND	ND	ND
Basophils (10^9 /L)	ND	ND	ND	ND
Polymorphonuclear leucocyte/Band cells (%)	ND	ND	> 90%	> 95%
AST (U/L)*	ND	ND	≥ 3 ULN **ALERT:** **≥ 3 ULN**	≥ 5 ULN **ALERT:** **≥ 5 ULN** **≥ 8 ULN**
ALT (U/L)*	ND	ND	≥ 3 ULN **ALERT:** **≥ 3 ULN**	≥ 5 ULN **ALERT:** **≥ 5 ULN** **≥ 8 ULN**
Total bilirubin (umol/L)	ND	ND	≥ 2 ULN **ALERT:** **≥ 2 ULN combined with ALT or AST ≥ 3 ULN**	≥ 5 ULN
Alkaline Phosphatase (U/L)	ND	ND	> 2.5 ULN	> 5 ULN
INR*	ND	ND	> 1.5 ULN or > 1.5 times above baseline if on anticoagulation **ALERT:** **> 1.5 combined with ALT or AST ≥ 3 ULN**	> 2.5 ULN or > 2.5 times above baseline if on anticoagulation
Lactate deshydrogenase	ND	ND	ND	ND
Creatinine (umol/L)*	ND	ND	>1.5 ULN or >1.5 x baseline	> 3 ULN or >3 x baseline
Creatinine clearance (mL/min)	< 60	< 30	ND	ND
Urea (mmol/L)	ND	ND	> 2.5 ULN	> 5 ULN

Parameter (SI unit)	LL	LLL	HH	HHH
Albumin (g/L)	< 30	< 20	ND	ND
Protein total (g/L)	ND	ND	ND	ND
C-reactive protein (mg/L)	ND	ND	ND	ND
Glucose (mmol/L)	< 3.0	< 2.2	> 8.9	>13.9
Potassium (mmol/L)	< 3.2	< 3.0	> 5.5	> 6.0
Sodium (mmol/L)	ND	< 130	> 150	> 155
Calcium (mmol/L)	< 2.0	< 1.75	> 2.9	> 3.1
Chloride (mmol/L)	ND	ND	ND	ND
Triglyceride (mmol/L)	ND	ND	> 3.42	> 11.4
Cholesterol (mmol/L)	ND	ND	> 7.75	> 12.92
Serum pregnancy test	ND	ND	ND	Positive **ALERT:** **Positive**

* HH and HHH based on CTCAE 2010 v4.03 [CTCAE 2010]. An ALERT wil be sent when INR ≥ 1.5 based on the guidance for monitoring liver test abnormalities from FDA [FDA 2009b]

ALERT = study-specific alerts that trigger specific actions by the investigator [see Section 7.3.13.1]; ALT = alanine aminotransferase; AST = aspartate aminotransferase; NA = not applicable; INR = International Normalized Ratio; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; ND = not defined; may be complemented by definitions provided by the central laboratory (see central laboratory manual); RBC = red blood count; SI = international system of units; ULN = upper limit of normal; WBC = white blood cell.

Appendix 7 Multiple Sclerosis Functional Composite

The MSFC consists of the three following assessments:

1) Timed 25-Foot walk;

The Timed 25-Foot Walk is a quantitative measure of lower extremity function. It is the first component of the MSFC administered at each visit. The subject is directed to one end of a clearly marked 25-foot course and is instructed to walk 25 feet as quickly as possible, but safely. The task is immediately administered again by having the subject walk back the same distance. Subjects may use assistive devices when doing this task. In clinical trials, it is recommended that the treating neurologist select the appropriate assistive device for each subject.

2) 9-Hole Peg Test (9-HPT);

The 9-HPT is a quantitative measure of upper extremity (arm and hand) function. The 9-HPT is the second component of the MSFC to be administered. Both the dominant and non-dominant hands are tested twice (two consecutive trials of the dominant hand, followed immediately by two consecutive trials of the non-dominant hand). It is important that the 9-HPT be administered on a solid table (not a rolling hospital bedside table) and that the 9-HPT apparatus be anchored.

3) Paced Auditory Serial Addition Test (PASAT-3" version).

The PASAT is a measure of cognitive function that specifically assesses auditory information processing speed and flexibility, as well as calculation ability. The PASAT is presented on audiocassette tape or compact disc to control the rate of stimulus presentation. Single digits are presented every 3 seconds and the subject must add each new digit to the one immediately prior to it. The test score is the number of correct sums given (out of 60 possible) in each trial. To minimize familiarity with stimulus items in clinical trials and other serial studies, two alternate forms have been developed; the order of these should be counterbalanced across testing sessions. The PASAT is the last measure of the MSFC that is administered at each visit.

Test administration:

The MSFC should be administered as close to the beginning of a study visit as possible but definitely before the subject does a distance walk. MSFC components should be administered in the following order:

1. Trial 1, Timed 25-Foot Walk

2. Trial 2, Timed 25-Foot Walk

3. Trial 1, Dominant Hand, 9-HPT

4. Trial 2, Dominant Hand, 9-HPT

5. Trial 1, Non-Dominant Hand, 9-HPT

6. Trial 2, Non-Dominant Hand, 9-HPT

7. PASAT-3"

Scoring:

There are three components to the MSFC: (1) the average scores from the four trials on the 9-HPT (the two trials for each hand are averaged, converted to the reciprocals of the mean times for each hand and then the two reciprocals are averaged); (2) the average scores of two Timed 25-Foot Walk trials; (3) the number correct from the PASAT-3. The MSFC is based on the concept that scores for these three dimensions – arm, leg, and cognitive function – are combined to create a single score (the MSFC) that can be used to detect change over time in a group of MS subjects. This is done by creating Z-scores for each component of the MSFC.

MSFC Score = {Zarm, average + Zleg, average + Zcognitive} / 3.0

Where Zxxx = Z-score

Nine Hole Peg Test

Name:_____

Dominant Hand (circle one): Right Left

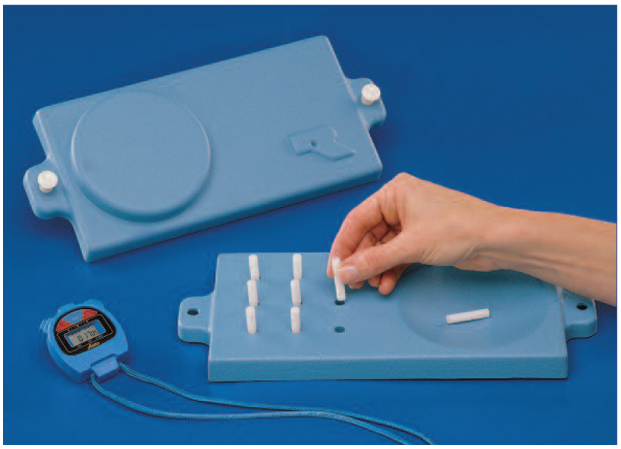
Time to complete the test in seconds:

Date: _____ Dominant Hand: _____ Non-Dominant Hand: _____

Date: _____ Dominant Hand: _____ Non-Dominant Hand: _____

Date: _____ Dominant Hand: _____ Non-Dominant Hand: _____

Date: _____ Dominant Hand: _____ Non-Dominant Hand: _____



PASAT - Form A

Name_____ Date_____

PRACTICE	9+1	3	5	2	6	4	9	7	1	4
	10__	4 __	8 __	7 __	8 __	10__	13__	16__	8 __	5 __
RATE #1	1+4	8	1	5	1	3	7	2	6	9
(3″)	5 __	12__	9 __	6 __	6 __	4 __	10__	9 __	8 __	15__
	4	7	3	5	3	6	8	2	5	1
	13__	11__	10__	8 __	8 __	9 __	14__	10__	7 __	6 __
	5	4	6	3	8	1	7	4	9	3
	6 __	9 __	10__	9 __	11__	9 __	8 __	11__	13__	12__
	7	2	6	9	5	2	4	8	3	1
	10__	9 __	8 __	15__	14__	7 __	6 __	12__	11__	4 __
	8	5	7	1	8	2	4	9	7	9
	9 __	13__	12__	8 __	9 __	10__	6 __	13__	16__	16__
	3	1	5	7	4	8	1	3	8	2
	12__	4 __	6 __	12__	11__	12__	9 __	4 __	11__	10__

Total Correct (raw) = _____ Percent Correct = _____

PASAT - Form B

Name_____ Date_____

PRACTICE	9+1	3	5	2	6	4	9	7	1	4
	10__	4 __	8 __	7 __	8 __	10__	13__	16__	8 __	5 __
RATE #1	2+7	5	8	2	9	6	4	1	3	6
(3")	9 __	12__	13__	10__	11__	15__	10__	5 __	4 __	9 __
	3	6	2	8	4	9	1	6	7	2
	9 __	9 __	8 __	10__	12__	13__	10__	7 __	13__	9 __
	4	1	5	7	3	9	7	2	6	8
	6 __	5 __	6 __	12__	10__	12__	16__	9 __	8 __	14__
	4	2	5	8	5	9	3	7	1	4
	12__	6 __	7 __	13__	13__	14__	12__	10__	8 __	5 __
	2	4	3	6	1	7	3	8	3	9
	6 __	6 __	7 __	9 __	7 __	8 __	10__	11__	11__	12__
	1	3	5	2	6	4	9	7	1	4
	10__	4 __	8 __	7 __	8 __	10__	13__	16__	8 __	5 __

Total Correct (raw) = _____ Percent Correct = _____

Appendix 8 Symbol Digit Modalities Test

The SDMT [Smith 1982, Benedict 2006] measures attention and processing speed much like the PASAT. The SDMT includes a reference key of 9 symbols, each paired with a single digit. Below the reference key are rows of the symbols arranged randomly. The subject is given 90 seconds to say the number that corresponds with each symbol. The test administrator records the answers and the number of correct answers is recorded as the score.

The SDMT will be performed after the MSFC. Study personnel will be trained to administer and score the SDMT. A sample of the SDMT is provided below. Subjects will complete the test on a validated paper form that will be collected and transcribed in the eCRF.

Appendix 9 Fatigue Symptoms and Impacts Questionnaire – Relapsing Multiple Sclerosis

INSTRUCTIONS

This questionnaire asks about your experience with your Relapsing Multiple Sclerosis (relapsing MS).

- This section of the questionnaire asks about your **fatigue-related symptoms** of relapsing MS over the **past 24 hours**.

Please select the response that best describes your experience. Please answer all of the questions and do not skip any. There are no right or wrong answers to any of the questions.

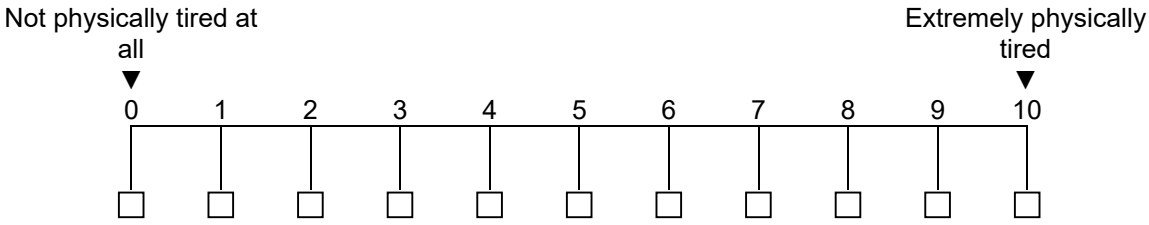
Section 1

Please enter today's date: DD/MM/YYYY

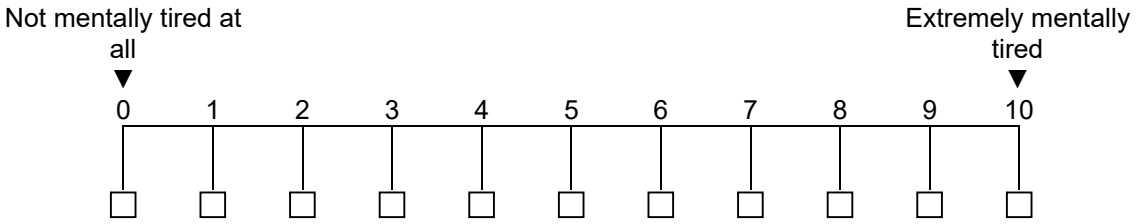
Instructions:

Please select the response that best describes your experience with **relapsing MS symptoms** in the **past 24 hours** while doing routine daily activities (e.g. housework, yard work, shopping, working).

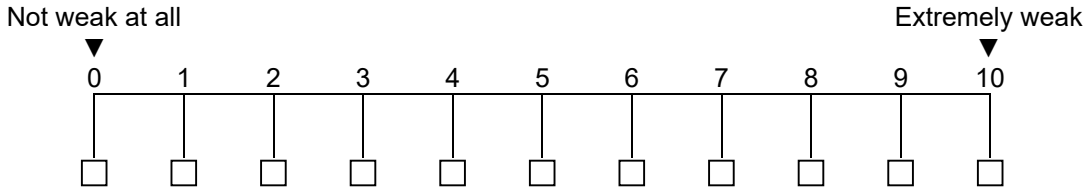
1. In the past 24 hours, while doing routine daily activities, how **physically tired did you feel**?



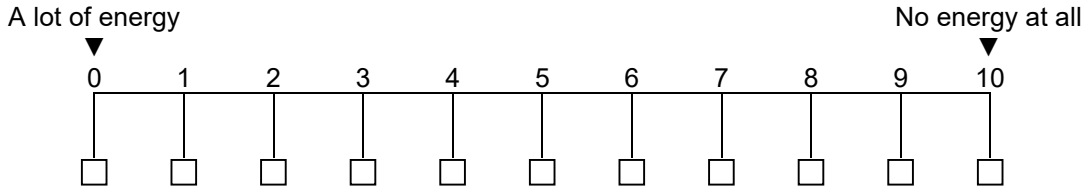
2. In the past 24 hours, while doing routine daily activities, how **mentally tired did you feel**?



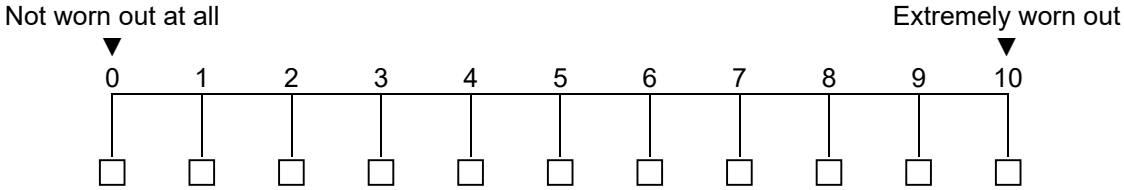
3. In the past 24 hours, while doing routine daily activities, how **physically weak did you feel**?



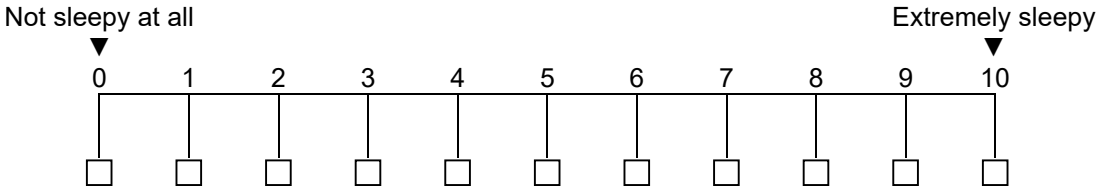
4. In the past 24 hours, how would you rate your **energy** while doing routine daily activities?



5. In the past 24 hours, while doing routine daily activities, how **worn out did you feel**?



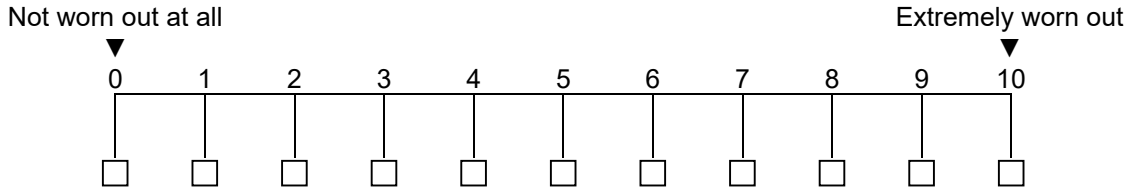
6. In the past 24 hours, while doing routine daily activities, how **sleepy did you feel**?



Instructions:

Please select the response that best describes your experience with **relapsing MS symptoms** in the **past 24 hours <u>while at rest</u>** (e.g. reading a book, watching TV).

7. In the past 24 hours, how **<u>worn out did you feel while at rest</u>**?



Section 2

INSTRUCTIONS

This questionnaire asks about your experience with your Relapsing Multiple Sclerosis (relapsing MS).

This section of the questionnaire asks about **how your life was affected** by fatigue-related symptoms of relapsing MS in the **past 7 days**.

Please select the response that best describes your experience. Please answer all of the questions and do not skip any. There are no right or wrong answers to any of the questions.

Instructions:

Please read and answer each of the following questions by selecting the response that best describes your **experience** in the **past 7 days**.

1. Thinking about your **fatigue-related symptoms** over the past 7 days, how much difficulty did you have **running errands** (such as grocery shopping or going to the bank or ATM)?

   ☐0 No difficulty

   ☐1 A little difficulty

   ☐2 Moderate difficulty

   ☐3 Quite a bit of difficulty

   ☐4 Extreme difficulty

2. Thinking about your **fatigue-related symptoms** over the past 7 days, how much difficulty did you have **communicating clearly**?

   ☐0 No difficulty

   ☐1 A little difficulty

   ☐2 Moderate difficulty

   ☐3 Quite a bit of difficulty

   ☐4 Extreme difficulty

3. Thinking about your **fatigue-related symptoms** over the past 7 days, how much difficulty did you have **thinking clearly**?

   ☐0 No difficulty

   ☐1 A little difficulty

   ☐2 Moderate difficulty

   ☐3 Quite a bit of difficulty

   ☐4 Extreme difficulty

4. Thinking about your **fatigue-related symptoms** over the past 7 days, how difficult was it for you to **motivate yourself to do routine daily activities**?

   ☐0 Not difficult

   ☐1 A little difficult

   ☐2 Moderately difficult

   ☐3 Quite difficult

   ☐4 Extremely difficult

5. Thinking about your **fatigue-related symptoms** over the past 7 days, how much difficulty did you have doing **indoor household chores**?

   ☐0 No difficulty

   ☐1 A little difficulty

   ☐2 Moderate difficulty

   ☐3 Quite a bit of difficulty

   ☐4 Extreme difficulty

6. Thinking about your **fatigue-related symptoms** over the past 7 days, how much difficulty did you have **walking**?

- ☐0 No difficulty
- ☐1 A little difficulty
- ☐2 Moderate difficulty
- ☐3 Quite a bit of difficulty
- ☐4 Extreme difficulty

7. Thinking about your **fatigue-related symptoms** over the past 7 days, how much difficulty did you have **maintaining relationships with people you are close to**?

- ☐0 No difficulty
- ☐1 A little difficulty
- ☐2 Moderate difficulty
- ☐3 Quite a bit of difficulty
- ☐4 Extreme difficulty

8. Thinking about your **fatigue-related symptoms** over the past 7 days, how much difficulty did you have **taking part in social activities** (such as going to the movies or going out to eat)?

- ☐0 No difficulty
- ☐1 A little difficulty
- ☐2 Moderate difficulty
- ☐3 Quite a bit of difficulty
- ☐4 Extreme difficulty

9. Thinking about your **fatigue-related symptoms** over the past 7 days, how **frustrated** were you?

- ☐0 Not at all
- ☐1 A little bit
- ☐2 Somewhat
- ☐3 Quite a bit
- ☐4 Extremely

10. Thinking about your **fatigue-related symptoms** over the past 7 days, how often were you **forgetful**?

- ☐0 Never
- ☐1 Rarely
- ☐2 Some of the time
- ☐3 Most of the time
- ☐4 Almost all of the time

11. Thinking about your **fatigue-related symptoms** over the past 7 days, how often did you have to **take a nap**?

- ☐0 Never
- ☐1 Rarely
- ☐2 Some of the time
- ☐3 Most of the time
- ☐4 Almost all of the time

12. Thinking about your **fatigue-related symptoms** over the past 7 days, how often did you have to **take a break**?

- ☐0 Never
- ☐1 Rarely
- ☐2 Some of the time
- ☐3 Most of the time
- ☐4 Almost all of the time

13. Thinking about your **fatigue-related symptoms** over the past 7 days, how often did you have to **rearrange your plans**?

- ☐0 Never
- ☐1 Rarely
- ☐2 Some of the time
- ☐3 Most of the time
- ☐4 Almost all of the time

Appendix 10 SF-36v2™

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey!

For each of the following questions, please select the one response that best describes your answer.

In general, would you say your health is:

Excellent
Very good
Good
Fair
Poor

Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago
Somewhat better now than one year ago
About the same as one year ago
Somewhat worse now than one year ago
Much worse now than one year ago

The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?
Does <u>your health now limit you</u> in <u>vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
Does <u>your health now limit you</u> in <u>moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
Does <u>your health now limit you</u> in lifting or carrying groceries? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
Does <u>your health now limit you</u> in climbing <u>several</u> flights of stairs? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
Does <u>your health now limit you</u> in climbing <u>one</u> flight of stairs? If so, how much?

Yes, limited a lot Yes, limited a little No, not limited at all
Does your health now limit you in bending, kneeling, or stooping? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
Does your health now limit you in walking more than a mile? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all Does your health now limit you in walking several hundred yards? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
Does your health now limit you in walking one hundred yards? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
Does your health now limit you in bathing or dressing yourself? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all

During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?
During the past 4 weeks, how much of the time have you cut down on the amount of time you spent on work or other activities as a result of your physical health? All of the time Most of the time Some of the time A little of the time None of the time
During the past 4 weeks, how much of the time have you accomplished less than you would like as a result of your physical health? All of the time Most of the time Some of the time A little of the time None of the time During the past 4 weeks, how much of the time were you limited in the kind of work or other activities as a result of your physical health? All of the time Most of the time Some of the time A little of the time None of the time
During the past 4 weeks, how much of the time have you had difficulty

performing the work or other activities as a result of your physical health (for example, it took extra effort)? All of the time Most of the time Some of the time A little of the time None of the time
During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?
During the past 4 weeks, how much of the time have you cut down on the amount of time you spent on work or other activities as a result of any emotional problems (such as feeling depressed or anxious)? All of the time Most of the time Some of the time A little of the time None of the time
During the past 4 weeks, how much of the time have you accomplished less than you would like as a result of any emotional problems (such as feeling depressed or anxious)? All of the time Most of the time Some of the time A little of the time None of the time During the past 4 weeks, how much of the time have you done work or other activities less carefully than usual as a result of any emotional problems (such as feeling depressed or anxious)?

All of the time Most of the time Some of the time A little of the time None of the time
During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups? Not at all Slightly Moderately Quite a bit Extremely
How much bodily pain have you had during the past 4 weeks? None Very mild Mild Moderate Severe Very severe
During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? Not at all A little bit Moderately Quite a bit Extremely
These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that

comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u> did you feel full of life? All of the time Most of the time Some of the time A little of the time None of the time
How much of the time during the <u>past 4 weeks</u> have you been very nervous? All of the time Most of the time Some of the time A little of the time None of the time
How much of the time during the <u>past 4 weeks</u> have you felt so down in the dumps that nothing could cheer you up? All of the time Most of the time Some of the time A little of the time None of the time
How much of the time during the <u>past 4 weeks</u> have you felt calm and peaceful? All of the time Most of the time Some of the time A little of the time None of the time

How much of the time during the past 4 weeks did you have a lot of energy? All of the time Most of the time Some of the time A little of the time None of the time How much of the time during the past 4 weeks have you felt downhearted and depressed? All of the time Most of the time Some of the time A little of the time None of the time
How much of the time during the past 4 weeks did you feel worn out? All of the time Most of the time Some of the time A little of the time None of the time
How much of the time during the past 4 weeks have you been happy? All of the time Most of the time Some of the time A little of the time None of the time
How much of the time during the past 4 weeks did you feel tired? All of the time

Most of the time Some of the time A little of the time None of the time
During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)? All of the time Most of the time Some of the time A little of the time None of the time How TRUE or FALSE is <u>each</u> of the following statements for you?
I seem to get sick a little easier than other people. Definitely true Mostly true Don’t know Mostly false Definitely false
I am as healthy as anybody I know. Definitely true Mostly true Don’t know Mostly false Definitely false
I expect my health to get worse. Definitely true

Mostly true Don’t know Mostly false Definitely false
My health is excellent. Definitely true Mostly true Don’t know Mostly false Definitely false

Appendix 11 Work Productivity and Activity Impairment Questionnaire: Multiple Sclerosis

Work Productivity and Activity Impairment Questionnaire: Multiple Sclerosis V2.0 (WPAI:MS)

The following questions ask about the effect of your multiple sclerosis on your ability to work and perform normal daily activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____NO _____YES
   If NO, tick "NO" and skip to question 6.

The next questions refer to the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your multiple sclerosis? *Include hours you missed on sick days, times you went in late, left early, etc., because of your* multiple sclerosis . *Do not include time you missed to participate in this study.*

   _____HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as annual leave, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", skip to question 6)*

5. During the past seven days, how much did your multiple sclerosis affect your productivity while you were working?

   Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If multiple sclerosis affected your work only a little, choose a low number. Choose a high number if multiple sclerosis affected your work a great deal.

   Consider only how much multiple sclerosis affected productivity while you were working.

Multiple sclerosis had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Multiple sclerosis completely prevented me from working

   CIRCLE A NUMBER

6. During the past seven days, how much did your multiple sclerosis affect your ability to perform your normal daily activities, other than work at a job?

   By normal activities, we mean the usual activities you perform, such as working around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could perform and times you accomplished less than you would like. If multiple sclerosis affected your activities only a little, choose a low number. Choose a high number if multiple sclerosis affected your activities a great deal.

   Consider only how much multiple sclerosis affected your ability to do your normal daily activities, other than work at a job.

Multiple sclerosis had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Multiple sclerosis completely prevented me from doing my daily activities

   CIRCLE A NUMBER

Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. PharmacoEconomics 1993; 4(5): 353-65.

Appendix 12 Relapse assessment questionnaire

TO BE FILLED OUT BY THE TREATING NEUROLOGIST AND/OR STUDY NURSE

*When applicable, for each of the Questions 1 to 5 below, complete **either** the phone interview or visit interview questions.*

Phone interview ☎	**Visit interview** *During a visit at the study site (scheduled or unscheduled)*
❑ Subject calling the site to report new/worsened symptoms ❑ Scheduled call from the site to the subject for relapse detection	
Date of phone interview _ _ . _ _ _ . _ _ dd mmm yy	Date of visit _ _ . _ _ _ . _ _ dd mmm yy
1. Is / was the subject having new neurological symptom(s) or an acute worsening of pre-existing neurological symptom(s)?	
☎	**Visit**
❑ Yes → *Go to Question 2*	❑ Yes → *Go to Question 2*
❑ No → *STOP Relapse investigation*	❑ No → *STOP Relapse investigation*
2. Are / were symptoms suggestive of a relapse (e.g. rapid onset, typically hours or days as opposed to weeks/months, symptom type)?	
☎	**Visit**
❑ Yes/possibly → *Go to Question 3*	❑ Yes/possibly → *Go to Question 3*
❑ Definitely not → *STOP Relapse investigation and enter subject's symptoms or diagnosis on the eCRF AE page*	❑ Definitely not → *STOP Relapse investigation and enter subject's symptoms or diagnosis on the AE eCRF page*
3. Did the symptoms last > 24 hours?	
☎	**Visit**

❑ Yes/possibly → *Go to Question 5 and complete date and time of start of symptoms*	❑ Yes/possibly → *Go to Question 5 and complete date and time of start of symptoms*
❑ No → *Go to Question 4 and complete date and time of start of symptoms*	❑ No → *Go to Question 4 and complete date and time of start of symptoms*
Date of start of symptoms _ _ . _ _ _ . _ _ dd mmm yy	Date of start of symptoms _ _ . _ _ _ . _ _ dd mmm yy
Time of start of symptoms _ _ . _ _ hh mm	Time of start of symptoms _ _ . _ _ hh mm
4. Have the symptoms started within the last 24 hours? ***(To be answered only if answer to question 3 was "No")***	
☎	**Visit**
❑ Yes → *Go to Question 5*	❑ Yes → *Go to Question 5*
❑ No → *STOP Relapse investigation and enter subject's symptoms or diagnosis on the AE eCRF page*	❑ No → *STOP Relapse investigation and enter subject's symptoms or diagnosis on the AE eCRF page*
5. Does / did the subject have concomitant fever or an infection and, if yes, are/were the symptoms more likely due to fever/infection than to a relapse?	
☎	**Visit**
❑ Yes→ *STOP Relapse investigation and enter subject's symptoms or diagnosis on the AE eCRF page*	❑ Yes → *STOP Relapse investigation and enter subject's symptoms or diagnosis on the AE eCRF page*

❑ No / not sure → *Invite the subject to an unscheduled relapse assessment visit as soon as possible but at least 24 hours after the onset of symptom(s).* *→ Go to Question 7 but if answer to question 4 was "Yes", answer additionally question 6 at the visit performed at least 24 hours after symptom onset*	❑ No / not sure → *If this visit occurs < 24 hours from symptom onset, invite the subject to an unscheduled relapse assessment visit as soon as possible but at least 24 hours after the onset of symptom(s)* *→ Go to Question 7, but if answer to question 4 was "Yes", answer additionally question 6 at the visit performed at least 24 hours after symptom onset*

*Question 6 - 8 **<u>can only be asked during a visit at the study site</u>** (scheduled or unscheduled) which occurs at least 24 hours after the symptoms onset.*

<u>Visit interview</u>
during a visit at the study site (scheduled or unscheduled)

Date of visit
(complete only if different from the one reported for question 1 to 5)

_ _ . _ _ _ . _ _
dd mmm yy

6. Did the symptoms last > 24 hours?
(To be answered <u>only</u> at a visit performed at least 24 hours after onset of symptoms and if answer to question 4 was "Yes" during an earlier interview (i.e. an interview conducted within 24 hours from symptom onset)):

❑ Yes / possibly → *Go to Question 7*

❑ Definitely not → *STOP Relapse investigation and enter subject's symptoms or diagnosis on the AE eCRF page*

7. Prior to the onset of this event, were the MS symptom(s) stable or improving over the last 30 days?

❑ Yes / possibly → *Go to Question 8*

❑ No → *Choose one option below*
- ❑ The previous symptoms corresponded to a relapse, which is recorded in the eCRF

→ STOP the relapse investigation for the new episode and enter the symptoms on the AE eCRF page unless the current symptoms are considered as part of the most recent relapse. Note: New or recurrent symptoms that occur less than 30 days following onset of a protocol-defined relapse should be considered part of the same relapse.

- ❑ The previous symptoms were not due to a relapse
  → Go to Question 8 and make sure that those previous symptoms are recorded on the AE eCRF page

8. Is there other and better explanation for the patient's current symptoms than an MS relapse?

- ❑ Yes → *STOP Relapse investigation and enter patient's symptoms or diagnosis on the AE page*

- ❑ No → *Enter symptoms in the "Relapse symptom form ".*
  → The subject should undergo EDSS assessment by the efficacy assessor within 7 days from the relapse onset (Note: no referral is needed at scheduled visits where EDSS/FS score is assessed as part of the scheduled assessment for this visit - in this event, the EDSS assessment planned for this visit will be used as part of the relapse assessment)

Appendix 13 Relapse symptom form

TO BE FILLED OUT BY THE TREATING NEUROLOGIST

Relapse symptom Form		
Visual (optic) functions		
Did the patient report any new or worsening symptoms belonging to the visual functions?	❑ Yes *If yes, complete the below*	❑ No
❑ Decreased vision		
❑ Changed vision (excl. double vision) e.g. blurred vision		
❑ Decreased visual field		
❑ Scotoma		
❑ Ocular pain		
❑ Other If other, please specify:		
Brainstem functions		
Did the patient report any new or worsening symptoms belonging to the brain stem functions?	❑ Yes *If yes, complete the below*	❑ No
❑ Double vision		
❑ Sudden hearing decrease or loss		
❑ Oscillopsia		
❑ Numbness in the face		
❑ Symptoms of facial nerve weakness (e.g. problems with eye or mouth closure, facial asymmetry)		
❑ Dysarthria		
❑ Dysphagia		
❑ Vertigo		
❑ Other If other, please specify:		
Pyramidal functions		

Did the patient report any new or worsening symptoms belonging to the pyramidal functions?	❑ Yes *If yes, complete the below*	❑ No
❑ Weakness in any extremity ❑ Muscle stiffness/spasticity ❑ Impaired walking or hopping ❑ Other If other, please specify:		
Cerebellar functions		
Did the patient report any new or worsening symptoms belonging to the cerebellar functions?	❑ Yes *If yes, complete the below*	❑ No
❑ Difficulties keeping balance while sitting, standing or walking ❑ Tremor ❑ Vertigo ❑ Clumsy movements ❑ Other If other, please specify:		
Sensory functions		
Did the patient report any new or worsening symptoms belonging to the sensory functions?	❑ Yes *If yes, complete the below*	❑ No
❑ Any abnormal sensation ❑ Tingling ❑ Central pain syndrome ❑ Other If other, please specify:		
Bowel and Bladder functions		

Did the patient report any new or worsening symptoms belonging to the bowel and bladder functions?	❑ Yes *If yes, complete the below*	❑ No
❑ Urinary retention		
❑ Urinary urgency		
❑ Urinary incontinence		
❑ Constipation		
❑ Bowel incontinence		
❑ Other If other, please specify:		
Cerebral functions		
Did the patient report any new or worsening symptoms belonging to the Cerebral functions?	❑ Yes *If yes, complete the below*	❑ No
❑ Problems with cognition (e.g. memory, concentration)		
❑ Fatigue		
❑ Mood disorders		
❑ Other If other, please specify:		
Ambulation		
Did the patient report any new or worsening symptoms belonging to the ambulation?	❑ Yes *If yes, complete the below*	❑ No
❑ Reduced walking distance		
❑ Need for increased/new assistance (e.g. from no assistance to unilateral assistance)		
❑ Reduced walking speed		

- ❑ Other
  If other, please specify:

Other new or worsening symptoms attributed to relapse but difficult to classify into functional systems		
Did the patient report any other symptoms attributable to a relapse?	❑ Yes	❑ No

- If yes, please specify:

Appendix 14 Electronic self-rated version of the Columbia-Suicide Severity Rating Scale

eC-SSRS 2.0 Web Script – Lifetime (Corresponding to Visit 2 [Baseline] assessment)

Core Language: US-English Web
Introduction
NRT01
In this interview, we are going to ask questions about thoughts you may have had and actions you may have done related to wanting to be dead or killing yourself.   First we will ask about thoughts regarding wanting to be dead or killing yourself that you have not actually acted on.   Later we will ask about any actions you may have actually done or preparations you have made. We will let you know when we switch from thoughts to actions.
Passive Suicide Ideation
Q01
At any time in your life, have you wished you were dead or wished you could go to sleep and not wake up?
Yes
No
Ideation Level = 1
Active Suicide Ideation
Q02
Have you actually had any thoughts of killing yourself, at any time?
Yes
No
Ideation Level = 2
Q03
Have you thought about how you might do this?

Yes
No
Ideation Level = 3
Q03.1
What way of killing yourself did you think of most often?
with medication
by hanging
by jumping
with a gun
by some other method
Q04
At any time, have you ever had any intention of acting on these thoughts of killing yourself?   As opposed to, you have the thoughts, but you definitely would not act on them?
Yes
No
Ideation Level = 4
Q05
At any time, have you ever started to work out, or actually worked out, the specific details of how to kill yourself?
Yes
No
Q05q
Did you actually intend to carry out the details of your plan?
Yes

No
Ideation Level = 5
Q05r
How did you intend to kill yourself?
with medication
by hanging
by jumping
with a gun
by some other method
Ideation Probing
Q01aNRT
You just indicated that you, at some point, had wished you were dead or wished that you could go to sleep and not wake up. We want to ask you a few more questions about that.   When responding to these questions, we want you to think about the time when these thoughts were most severe.
Q01a
When your wishes to be dead or to go to sleep and not wake up were most severe, how often did the thoughts occur?
less than once a week
about once a week
2 to 5 times a week
daily or almost daily
many times a day
Q01b
How long did the thoughts last?
fleeting\\, lasting seconds to minutes
less than an hour

between 1 and 4 hours
between 4 and 8 hours
more than 8 hours
Q01c
Did you make any attempt to try to control these thoughts about wanting to die or going to sleep and not waking up, whether you were successful in controlling them or not?
Yes
No
Q01d
How easily could you control or stop these thoughts?
easily controlled these thoughts
with a little difficulty
with some difficulty
with a lot of difficulty
unable to control these thoughts
Q01e.1
Did you think about things like family, religion, or fear of pain or death that might affect your wish to be dead or going to sleep and not waking up?
Yes
No
Q01e
Choose one of the following statements that best describes whether anyone or anything did or did not stop you from wishing you were dead or that you could fall asleep and not wake up.
something definitely stopped you

something probably stopped you
you are uncertain whether something stopped you
something most likely did not stop you
something definitely did not stop you
Q01f.1
When you thought about wishing to be dead or going to sleep and not waking up, did you have a reason in mind like ending your pain or getting attention or revenge?
Yes
No
Q01f
What sort of reasons did you have for thinking about wanting to die? Was it to end the pain or stop the way you were feeling?   In other words, you could not go on living with this pain or how you were feeling? Was it to get attention, revenge or a reaction from others? Or both?
it was completely to get attention\\, revenge or a reaction from others
it was mostly to get attention\\, revenge or a reaction from others
equally to get attention\\, revenge or a reaction from others and to end or stop the pain
mostly to end or stop the pain \\(that is\\, you could not go on living with the pain or how you were feeling\\)
completely to end or stop the pain
Q02aNRT
You indicated before that you had thought of killing yourself. We want to ask you a few more questions about that.   When responding to these questions, we want you to think about the time you were feeling most suicidal.

Q02a
When you were feeling most suicidal, how often did you think of killing yourself?
less than once a week
about once a week
2 to 5 times a week
daily or almost daily
many times a day
Q02b
How long did these thoughts of killing yourself last?
fleeting\\, lasting seconds to minutes
less than an hour
between 1 and 4 hours
between 4 and 8 hours
more than 8 hours
Q02c
Did you make any attempt to try to control or stop these thoughts, whether you were successful in controlling them or not?
Yes
No
Q02d
How easily could you control or stop thinking about killing yourself?
easily controlled these thoughts
with a little difficulty
with some difficulty
with a lot of difficulty
unable to control these thoughts

Q02e.1
Did you think about things like family, religion, or fear of pain or death that might affect your decision about killing yourself?
Yes
No
Q02e
Choose one of the following statements that best describes whether anyone or anything did or did not stop you from acting on your thoughts of committing suicide.
something definitely stopped you
something probably stopped you
you are uncertain whether something stopped you
something most likely did not stop you
something definitely did not stop you
Q02f.1
When you thought about killing yourself, did you have a reason in mind like ending your pain or getting attention or revenge?
Yes
No
Q02f
What sort of reasons did you have for thinking about wanting to kill yourself? Was it to end the pain or stop the way you were feeling?   In other words, you could not go on living with this pain or how you were feeling? Or was it to get attention, revenge or a reaction from others? Or both?
it was completely to get attention\\, revenge or a reaction from others

it was mostly to get attention\\, revenge or a reaction from others
equally to get attention\\, revenge or a reaction from others and to end or stop the pain
mostly to end or stop the pain \\(that is\\, you could not go on living with the pain or how you were feeling\\)
completely to end or stop the pain
Q03aNRT
You indicated before that you had thought about how you might kill yourself. We want to ask you a few more questions about that.   When responding to these questions, we want you to think about the time you were feeling the most suicidal.
Q03a
When you were feeling most suicidal, how often did you think about how you might kill yourself?
less than once a week
about once a week
2 to 5 times a week
daily or almost daily
many times a day
Q03b
When you had these thoughts, how long did they last?
fleeting\\, lasting seconds to minutes
less than an hour
between 1 and 4 hours
between 4 and 8 hours
more than 8 hours

Q03c
Did you make any attempt to try to control or stop these thoughts, whether you were successful in controlling them or not?
Yes
No
Q03d
How easily could you control or stop thinking about how you might kill yourself?
easily controlled these thoughts
with a little difficulty
with some difficulty
with a lot of difficulty
unable to control these thoughts
Q03e.1
Did you think about things like family, religion, or fear of pain or death that might affect your decision about killing yourself?
Yes
No
Q03e
Choose one of the following statements that best describes whether anyone or anything did or did not stop you from acting on your thoughts of committing suicide.
something definitely stopped you
something probably stopped you
you are uncertain whether something stopped you
something most likely did not stop you
something definitely did not stop you

Q03f.1
When you thought about killing yourself, did you have a reason in mind like ending your pain or getting attention or revenge?
Yes
No
Q03f
What sort of reasons did you have for thinking about wanting to kill yourself? Was it to end the pain or stop the way you were feeling?   In other words, you could not go on living with this pain or how you were feeling? Or was it to get attention, revenge or a reaction from others? Or both?
it was completely to get attention\\, revenge or a reaction from others
it was mostly to get attention\\, revenge or a reaction from others
equally to get attention\\, revenge or a reaction from others and to end or stop the pain
mostly to end or stop the pain \\(that is\\, you could not go on living with the pain or how you were feeling\\)
completely to end or stop the pain
Q04aNRT
You indicated before that you had thought about killing yourself and that you had some intention of acting on these thoughts. We want to ask you a few more questions about that.   When responding to these questions, we want you to think about the time you were feeling the most suicidal.
Q04a
When you were feeling most suicidal and had some intention of acting on those thoughts of killing yourself, how often did those thoughts occur?

less than once a week
about once a week
2 to 5 times a week
daily or almost daily
many times a day
Q04b
How long did the thoughts last?
fleeting\\, lasting seconds to minutes
less than an hour
between 1 and 4 hours
between 4 and 8 hours
more than 8 hours
Q04c
Did you make any attempt to try to control or stop these thoughts about actually killing yourself, whether you were successful in controlling them or not?
Yes
No
Q04d
How easily could you control or stop thinking about killing yourself?
easily controlled these thoughts
with a little difficulty
with some difficulty
with a lot of difficulty
unable to control these thoughts
Q04e.1
Did you think about things like family, religion, or fear of pain or death that might affect your decision about killing yourself?

Yes
No
Q04e
Choose one of the following statements that best describes whether anyone or anything did or did not stop you from acting on your thoughts of committing suicide.
something definitely stopped you
something probably stopped you
you are uncertain whether something stopped you
something most likely did not stop you
something definitely did not stop you
Q04f.1
When you thought about killing yourself, did you have a reason in mind like ending your pain or getting attention or revenge?
Yes
No
Q04f
What sort of reasons did you have for thinking about wanting to kill yourself? Was it to end the pain or stop the way you were feeling?   In other words, you could not go on living with this pain or how you were feeling? Or was it to get attention, revenge or a reaction from others? Or both?
it was completely to get attention\\, revenge or a reaction from others
it was mostly to get attention\\, revenge or a reaction from others
equally to get attention\\, revenge or a reaction from others and to end or stop the pain

mostly to end or stop the pain \\(that is\\, you could not go on living with the pain or how you were feeling\\)
completely to end or stop the pain
Q05aNRT
You indicated before that you had started working on plans or had actually worked out the details of how to kill yourself and had some intention to act on them. We want to ask you a few more questions about that.   When responding to these questions, we want you to think about the time you were feeling the most suicidal.
Q05a
When you were feeling the most suicidal and started planning or worked out details of how to kill yourself, how often did you think about killing yourself?
less than once a week
about once a week
2 to 5 times a week
daily or almost daily
many times a day
Q05b
How long did the thoughts last?
fleeting\\, lasting seconds to minutes
less than an hour
between 1 and 4 hours
between 4 and 8 hours
more than 8 hours
Q05c
Did you make any attempt to try to control or stop these thoughts about actually killing yourself, whether you were successful in controlling them or not?
Yes

No
Q05d
How easily could you control or stop thinking about killing yourself?
easily controlled these thoughts
with a little difficulty
with some difficulty
with a lot of difficulty
unable to control these thoughts
Q05e.1
Did you think about things like family, religion, or fear of pain or death that might affect your decision about killing yourself?
Yes
No
Q05e
Choose one of the following statements that best describes whether anyone or anything did or did not stop you from acting on your thoughts of committing suicide.
something definitely stopped you
something probably stopped you
you are uncertain whether something stopped you
something most likely did not stop you
something definitely did not stop you
Q05f.1
When you thought about killing yourself, did you have a reason in mind like ending your pain or getting attention or revenge?
Yes
No

Q05f
What sort of reasons did you have for thinking about wanting to kill yourself? Was it to end the pain or stop the way you were feeling?   In other words, you could not go on living with this pain or how you were feeling? Or was it to get attention, revenge or a reaction from others? Or both?
it was completely to get attention\\, revenge or a reaction from others
it was mostly to get attention\\, revenge or a reaction from others
equally to get attention\\, revenge or a reaction from others and to end or stop the pain
mostly to end or stop the pain \\(that is\\, you could not go on living with the pain or how you were feeling\\)
completely to end or stop the pain
If Recent Ideation is required, go to Recent Ideation Section
Recent Ideation
Level 1 Ideation
You indicated that at some time in your life you have wished you were dead or that you could go to sleep and not wake up.   Have you had any thoughts like that in the past I months?
Have you wished you were dead or that you could go to sleep and not wake up in the past I months?
Yes
No

Level 2 Ideation
You indicated that there has been a time in your life when you had thought of killing yourself.   Have you had any thoughts like that in the past I months?
Have you had any thoughts of killing yourself in the past I months?
Yes
No
Level 3 Ideation
You indicated that there has been a time in your life when you thought about how you might kill yourself.   Have you thought about how you might kill yourself in the past I months?
Have you thought about how you might kill yourself in the past I months, even though you did not intend to act on the thoughts?
Yes
No
Level 4 Ideation
You indicated that there has been a time in your life when you thought about how you might kill yourself and that you had some intention of acting on those thoughts.   Have you had any intentions of acting on thoughts about killing yourself in the past I months?
Have you had any intentions of acting on a method to kill yourself in the past I months?
Yes
No

Level 5 Ideation
You indicated that there was a time in your life when you worked on a plan or had worked out details for killing yourself and that you had some intention to carry out the plan.   Have you made specific plans or worked out the details for killing yourself with the intention of carrying them out in the past I months?
Yes
No
Midpoint Transition (NRT02)
We are almost finished.   So far we have been asking about thoughts and feelings you may have had.   Now we would like to know about things you may have done to try to hurt yourself.
Suicidal Behavior
Q06a
At any time in your life, have you made a suicide attempt?
Yes
No
Q06b
Use the number keys to enter the number of suicide attempts you have made.
Q06cNRT01
If attempts >= 3
Consider your most recent attempt, your first attempt, and your most serious attempt separately.
Q06cNRT02
If attempts = 2
Consider your most recent attempt and your first attempt separately.

Q06c
If loop = 1
When you made your most recent attempt, were you trying to end your life?
Yes
No
If loop = 2
When you made your first attempt, were you trying to end your life?
Yes
No
If loop = 3
When you made your most serious attempt, were you trying to end your life?
Yes
No
Q06e
Did you think it was possible that you could have died from what you did?
Yes
No
Q06d
So then
you wanted to die\\, even a little\\, when you did this
you did it purely for other reasons\\, like to relieve stress\\, feel better\\, get sympathy\\, or get something else to happen to you\\, without any intention of killing yourself

Q07a
Have you ever done anything to intentionally hurt or harm yourself?
Yes
No
Q07b
Use the number keys to enter the number of times you have intentionally hurt or harmed yourself. If you cannot remember the exact number, enter your best estimate.
Q07cNRT01
Just consider the three most recent times you have intentionally harmed or hurt yourself.
Q07c_Attempt
If loop = 1
Think about the time you intentionally hurt or harmed yourself most recently
If loop > 1
Consider the time you hurt or harmed yourself before that
Q07c
Were you trying to end your life?
Yes
No
Q07e
Did you think it was possible that you could have died from what you did?

Yes
No
Q07d
So then
you wanted to die\\, even a little\\, when you did this
you did it purely for other reasons\\, like to relieve stress\\, feel better\\, get sympathy\\, or get something else to happen to you\\, without any intention of killing yourself
Q08a
Have you done anything dangerous where you could have died?
Yes
No
Q08b
Use the number keys to enter the number of times you have done dangerous activities where you could have died.
Q08c_NRT01
Just consider the three most recent times you have done something dangerous where you could have died.
Q08c_Attempt
If loop = 1
Think about the most recent time you did a dangerous activity where you could have died
If loop > 1
Consider the time you did something dangerous before that

Q08c_1
Were you trying to harm yourself when you did this?
Yes
No
Q08c
Were you trying to end your life?
Yes
No
Q08d
So then
you wanted to die\\, even a little\\, when you did this
you did it purely for other reasons\\, like to relieve stress\\, feel better\\, get sympathy\\, or get something else to happen to you\\, without any intention of killing yourself
Lethality
Q09
If Q06a = YES
As a result of your most serious attempt, were you injured more seriously than surface scratches or mild nausea?
Yes
No
If Q06a = NO
As a result of the most serious time you tried to hurt yourself, were you injured more seriously than surface scratches or mild nausea?
Yes

No
Q09RB
Did this occur within the past B months?
Yes
No
Q09a
Were you hospitalized for medical treatment of the physical injury you suffered?   For example, were you comatose from an overdose, or did you suffer extensive blood loss that required a transfusion, or severe damage to your head or a vital organ?   If you were hospitalized for psychiatric evaluation, but not for medical treatment of a severe physical injury, answer No.
Yes
No
Q09b
Were you injured so severely that you would have died without treatment in an intensive care unit, or did you suffer permanent physical damage from which you will never completely recover, such as paralysis or disfigurement?
Yes
No
Q09c
Did your injury cause you to be extremely drowsy, or result in broken bones, or severe bleeding?
Yes
No

Q09.1NRT
Earlier, you indicated that there were two times when you intended to kill yourself or thought you could have died from what you did.   We want to know if you suffered any physical injuries.
Q09.1
If Q06a = YES
As a result of your most recent attempt, were you injured more seriously than surface scratches or mild nausea?
Yes
No
If Q06a = NO
As a result of the most recent time you tried to hurt yourself, were you injured more seriously than surface scratches or mild nausea?
Yes
No
Q09.1RB
Did this occur within the past B months?
Yes
No
Q09.1a
Were you hospitalized for medical treatment of the physical injury you suffered?   For example, were you comatose from an overdose, or did you suffer extensive blood loss that required a transfusion, or severe damage to your head or a vital organ?   If you were hospitalized for psychiatric evaluation, but not for medical treatment of a severe physical injury, answer No.

Yes
No
Q09.1b
Were you injured so severely that you would have died without treatment in an intensive care unit, or did you suffer permanent physical damage from which you will never completely recover, such as paralysis or disfigurement?
Yes
No
Q09.1c
Did your injury cause you to be extremely drowsy, or result in broken bones, or severe bleeding?
Yes
No
Q09.2
If Q06a = YES
As a result of your first attempt, were you injured more seriously than surface scratches or mild nausea?
Yes
No
If Q06a = NO
As a result of the first time you tried to hurt yourself, were you injured more seriously than surface scratches or mild nausea?
Yes
No

Q09.2RB
Did this occur within the past B months?
Yes
No
Q09.2a
Were you hospitalized for medical treatment of the physical injury you suffered?   For example, were you comatose from an overdose, or did you suffer extensive blood loss that required a transfusion, or severe damage to your head or a vital organ?   If you were hospitalized for psychiatric evaluation, but not for medical treatment of a severe physical injury, answer No.
Yes
No
Q09.2b
Were you injured so severely that you would have died without treatment in an intensive care unit, or did you suffer permanent physical damage from which you will never completely recover, such as paralysis or disfigurement?
Yes
No
Q09.2c
Did your injury cause you to be extremely drowsy, or result in broken bones, or severe bleeding?
Yes
No

Q09.4NRT
Earlier, you indicated that there were three or more times you intended to kill yourself or thought you could have died from what you did.   Now we want to know if you suffered any physical injuries each time.
Q09.4
If Q06a = YES
As a result of your most recent attempt, were you injured more seriously than surface scratches or mild nausea?
Yes
No
If Q06a = NO
As a result of the most recent time you tried to hurt yourself, were you injured more seriously than surface scratches or mild nausea?
Yes
No
Q09.4RB
Did this occur within the past B months?
Yes
No
Q09.4a
Were you hospitalized for medical treatment of the physical injury you suffered?   For example, were you comatose from an overdose, or did you suffer extensive blood loss that required a transfusion, or severe damage to your head or a vital organ?   If you were hospitalized for psychiatric evaluation, but not for medical treatment of a severe physical injury, answer No.

Yes
No
Q09.4b
Were you injured so severely that you would have died without treatment in an intensive care unit, or did you suffer permanent physical damage from which you will never completely recover, such as paralysis or disfigurement?
Yes
No
Q09.4c
Did your injury cause you to be extremely drowsy, or result in broken bones, or severe bleeding?
Yes
No
Q09.5
If Q06a = YES
As a result of your first attempt, were you injured more seriously than surface scratches or mild nausea?
Yes
No
If Q06a = NO
As a result of the first time you tried to hurt yourself, were you injured more seriously than surface scratches or mild nausea?
Yes
No

Q09.5a
Were you hospitalized for medical treatment of the physical injury you suffered?   For example, were you comatose from an overdose, or did you suffer extensive blood loss that required a transfusion, or severe damage to your head or a vital organ?   If you were hospitalized for psychiatric evaluation, but not for medical treatment of a severe physical injury, answer No.
Yes
No
Q09.5b
Were you injured so severely that you would have died without treatment in an intensive care unit, or did you suffer permanent physical damage from which you will never completely recover, such as paralysis or disfigurement?
Yes
No
Q09.5c
Did your injury cause you to be extremely drowsy, or result in broken bones, or severe bleeding?
Yes
No
Q09.6
If Q06a = YES
As a result of your most serious attempt, were you injured more seriously than surface scratches or mild nausea?
Yes
No

If Q06a = NO
As a result of the most serious time you tried to hurt yourself, were you injured more seriously than surface scratches or mild nausea?
Yes
No
Q09.6a
Were you hospitalized for medical treatment of the physical injury you suffered?   For example, were you comatose from an overdose, or did you suffer extensive blood loss that required a transfusion, or severe damage to your head or a vital organ?   If you were hospitalized for psychiatric evaluation, but not for medical treatment of a severe physical injury, answer No.
Yes
No
Q09.6b
Were you injured so severely that you would have died without treatment in an intensive care unit, or did you suffer permanent physical damage from which you will never completely recover, such as paralysis or disfigurement?
Yes
No
Q09.6c
Did your injury cause you to be extremely drowsy, or result in broken bones, or severe bleeding?
Yes
No
Q09.8RB
Did this occur within the past B months?

Yes
No
Q09.8
Although you were not injured most recently, how serious could your injuries have been?
what you did was not likely to cause injury
what you did was likely to cause physical injury\\, but probably not death
what you did was likely to cause death with or without medical help\\, for example trying to shoot yourself in the head but the gun failed to fire
Q09.9
Although you were not injured the first time, how serious could your injuries have been?
what you did was not likely to cause injury
what you did was likely to cause physical injury, but probably not death
what you did was likely to cause death with or without medical help, for example trying to shoot yourself in the head but the gun failed to fire
Q09.10RB
Did this occur within the past B months?
Yes
No
Q09.10
Although you were not injured during the most serious time, how serious could your injuries have been?

what you did was not likely to cause injury
what you did was likely to cause physical injury\\, but probably not death
what you did was likely to cause death with or without medical help\\, for example trying to shoot yourself in the head but the gun failed to fire
Interrupted Attempts
Q10
Has there ever been a time when you started to do something to end your life, but someone or something stopped you before you actually did anything?
Yes
No
Q10a
About how many times have you been stopped from ending your life by someone or something?
Please enter the number.
Q10RB
Was the last time you were stopped from trying to end your life by someone or something in the past B months?
Yes
No
Aborted Attempts
Q11
Has there been a time when you started to do something to try to end your life, but you stopped yourself before you actually did anything?
Yes

No
Q11a
About how many times have you stopped yourself from ending your life?
Please enter the number.
Q11RB
Was the last time you stopped yourself from trying to end your life in the past B months?
Yes
No
Preparatory Acts or Behaviors
Q12NRT
Asses prior responses and present introduction:
Other than the times you have already told us about when you did things intending to kill yourself or thought you might have died, when you started to do something to end your life but someone or something stopped you, and when you started to do something to end your life but stopped yourself,
Other than the times you have already told us about when you did things intending to kill yourself or thought you might have died, and when you started to do something to end your life but stopped yourself,
Other than the times you have already told us about when you did things intending to kill yourself or thought you might have died and when you started to do something to end your life but someone or something stopped you,
Other than the times you have already told us about when you started to do something to end your life but someone or something stopped you and when you started to do something to end your life but stopped yourself,

Other than the times you have already told us about when you did things intending to kill yourself or thought you might have died,
Other than the times you have already told us about when you started to do something to end your life but someone or something stopped you,
Other than the times you have already told us about when you started to do something to end your life but stopped yourself,
Q12
Have you ever taken any steps toward making a suicide attempt or preparing to kill yourself, such as collecting pills, getting a gun, giving valuables away or writing a suicide note?
Yes
No
Q12a
About how many times?
Please enter the number.
Q12RB
Was the last time you took steps toward making a suicide attempt or preparing to kill yourself in the past B months?
Yes
No
Exit
You have completed your interview. Thank you and Good bye.

eC-SSRS Web Script – Since Last Call (Corresponding to Visit 9 [Week 48], Visit 13 [Week 96], Visit 17 [Week 144] and Visit 18 [EOT] assessments)

Usage Notes:
When the interval between calls exceeds 120 days the number of days since the last call is not repeated to the subject.
Core Language: US-English Web
Introduction
NRT01
The last time you were interviewed about thoughts or actions related to wanting to be dead or killing yourself was [day] [date]. That was [num] days ago.   During this interview we want you to only consider thoughts or actions that have occurred since that date.   In answering the following questions, only report your thoughts and actions over the past [num] days or since [day] [date].
If days SLC > 120
The last time you were interviewed about thoughts or actions related to wanting to be dead or killing yourself was [day] [date].   During this interview we want you to only consider thoughts or actions that have occurred since that date.   In answering the following questions, only report your thoughts and actions since [day] [date].
Passive Suicide Ideation
Q01
Since your last interview, have you wished you were dead or wished you could go to sleep and not wake up?
Yes
No
Ideation Level = 1

Active Suicide Ideation
Q02
Since your last interview on [day] [date], [num] days ago have you actually had any thoughts of killing yourself?
If days SLC > 120
Since your last interview on [day] [date], have you actually had any thoughts of killing yourself?
Yes
No
Ideation Level = 2
Q03
Have you thought about how you might do this?
Yes
No
Ideation Level = 3
Q03.1
What way of killing yourself did you think of most often?
with medication
by hanging
by jumping
with a gun
by some other method

Q04
Since your last interview, have you had any intention of acting on these thoughts of killing yourself?   As opposed to, you have the thoughts, but you definitely would not act on them?
Yes
No
Ideation Level = 4
Q05
Have you started to work out, or actually worked out, the specific details of how to kill yourself since your last interview?
Yes
No
Q05q
Did you actually intend to carry out the details of your plan?
Yes
No
Ideation Level = 5
Q05r
How did you intend to kill yourself?
with medication
by hanging
by jumping
with a gun
by some other method

Ideation Probing
Q01aNRT
You just indicated that since your last interview, you had wished you were dead or wished that you could go to sleep and not wake up. We want to ask you a few more questions about that.   When responding to these questions, we want you to think about the time when these thoughts were most severe in the past [num] days.
If days SLC > 120
You just indicated that since your last interview, you had wished you were dead or wished that you could go to sleep and not wake up. We want to ask you a few more questions about that.   When responding to these questions, we want you to think about the time when these thoughts were most severe since your last interview.
Q01a
When your wishes to be dead or to go to sleep and not wake up were most severe, how often did the thoughts occur?
less than once a week
about once a week
2 to 5 times a week
daily or almost daily
many times a day
Q01b
How long did the thoughts last?
fleeting\\, lasting seconds to minutes
less than an hour
between 1 and 4 hours
between 4 and 8 hours
more than 8 hours

Q01c
Did you make any attempt to try to control these thoughts about wanting to die or going to sleep and not waking up, whether you were successful in controlling them or not?
Yes
No
Q01d
How easily could you control or stop these thoughts?
easily controlled these thoughts
with a little difficulty
with some difficulty
with a lot of difficulty
unable to control these thoughts
Q01e.1
Did you think about things like family, religion, or fear of pain or death that might affect your wish to be dead or going to sleep and not waking up?
Yes
No
Q01e
Choose one of the following statements that best describes whether anyone or anything did or did not stop you from wishing you were dead or that you could fall asleep and not wake up.
something definitely stopped you
something probably stopped you
you are uncertain whether something stopped you
something most likely did not stop you
something definitely did not stop you

Q01f.1
When you thought about wishing to be dead or going to sleep and not waking up, did you have a reason in mind like ending your pain or getting attention or revenge?
Yes
No
Q01f
What sort of reasons did you have for thinking about wanting to die? Was it to end the pain or stop the way you were feeling?   In other words, you could not go on living with this pain or how you were feeling? Was it to get attention, revenge or a reaction from others? Or both?
it was completely to get attention\\, revenge or a reaction from others
it was mostly to get attention\\, revenge or a reaction from others
equally to get attention\\, revenge or a reaction from others and to end or stop the pain
mostly to end or stop the pain \\(that is\\, you could not go on living with the pain or how you were feeling\\)
completely to end or stop the pain
Q02aNRT
You indicated before that since your last interview you had thought of killing yourself. We want to ask you a few more questions about that.   When responding to these questions, we want you to think about the time you were feeling most suicidal in the past [num] days.
If days SLC > 120
You indicated before that since your last interview you had thought of killing yourself. We want to ask you a few more questions about that.   When responding to these questions, we want you to think about the time you were feeling most suicidal since your last interview.

Q02a
When you were feeling most suicidal, how often did you think of killing yourself?
less than once a week
about once a week
2 to 5 times a week
daily or almost daily
many times a day
Q02b
How long did these thoughts of killing yourself last?
fleeting\\, lasting seconds to minutes
less than an hour
between 1 and 4 hours
between 4 and 8 hours
more than 8 hours
Q02c
Did you make any attempt to try to control or stop these thoughts, whether you were successful in controlling them or not?
Yes
No
Q02d
How easily could you control or stop thinking about killing yourself?
easily controlled these thoughts
with a little difficulty
with some difficulty
with a lot of difficulty
unable to control these thoughts

Q02e.1
Did you think about things like family, religion, or fear of pain or death that might affect your decision about killing yourself?
Yes
No
Q02e
Choose one of the following statements that best describes whether anyone or anything did or did not stop you from acting on your thoughts of committing suicide.
something definitely stopped you
something probably stopped you
you are uncertain whether something stopped you
something most likely did not stop you
something definitely did not stop you
Q02f.1
When you thought about killing yourself, did you have a reason in mind like ending your pain or getting attention or revenge?
Yes
No
Q02f
What sort of reasons did you have for thinking about wanting to kill yourself? Was it to end the pain or stop the way you were feeling?   In other words, you could not go on living with this pain or how you were feeling? Or was it to get attention, revenge or a reaction from others? Or both?
it was completely to get attention\\, revenge or a reaction from others
it was mostly to get attention\\, revenge or a reaction from others
equally to get attention\\, revenge or a reaction from others and to end or stop the pain

mostly to end or stop the pain \\(that is\\, you could not go on living with the pain or how you were feeling\\)
completely to end or stop the pain
Q03aNRT
You indicated before that since your last interview you had thought about how you might kill yourself. We want to ask you a few more questions about that.   When responding to these questions, we want you to think about the time you were feeling the most suicidal in the past [num] days.
If days SLC > 120
You indicated before that since your last interview you had thought about how you might kill yourself. We want to ask you a few more questions about that.   When responding to these questions, we want you to think about the time you were feeling the most suicidal since your last interview.
Q03a
When you were feeling most suicidal, how often did you think about how you might kill yourself?
less than once a week
about once a week
2 to 5 times a week
daily or almost daily
many times a day
Q03b
When you had these thoughts, how long did they last?
fleeting\\, lasting seconds to minutes
less than an hour
between 1 and 4 hours
between 4 and 8 hours
more than 8 hours

Q03c
Did you make any attempt to try to control or stop these thoughts, whether you were successful in controlling them or not?
Yes
No
Q03d
How easily could you control or stop thinking about how you might kill yourself?
easily controlled these thoughts
with a little difficulty
with some difficulty
with a lot of difficulty
unable to control these thoughts
Q03e.1
Did you think about things like family, religion, or fear of pain or death that might affect your decision about killing yourself?
Yes
No
Q03e
Choose one of the following statements that best describes whether anyone or anything did or did not stop you from acting on your thoughts of committing suicide.
something definitely stopped you
something probably stopped you
you are uncertain whether something stopped you
something most likely did not stop you
something definitely did not stop you

Q03f.1
When you thought about killing yourself, did you have a reason in mind like ending your pain or getting attention or revenge?
Yes
No
Q03f
What sort of reasons did you have for thinking about wanting to kill yourself? Was it to end the pain or stop the way you were feeling?   In other words, you could not go on living with this pain or how you were feeling? Or was it to get attention, revenge or a reaction from others? Or both?
it was completely to get attention\\, revenge or a reaction from others
it was mostly to get attention\\, revenge or a reaction from others
equally to get attention\\, revenge or a reaction from others and to end or stop the pain
mostly to end or stop the pain \\(that is\\, you could not go on living with the pain or how you were feeling\\)
completely to end or stop the pain
Q04aNRT
You indicated before that since your last interview you thought about killing yourself and that you had some intention of acting on these thoughts. We want to ask you a few more questions about that.   When responding to these questions, we want you to think about the time you were feeling the most suicidal in the past [num] days.
If days SLC > 120
You indicated before that since your last interview you thought about killing yourself and that you had some intention of acting on these thoughts. We want to ask you a few more questions about that.   When responding to these questions, we want you to think about the time you were feeling the most suicidal since your last interview.

Q04a
When you were feeling most suicidal and had some intention of acting on those thoughts of killing yourself, how often did those thoughts occur?
less than once a week
about once a week
2 to 5 times a week
daily or almost daily
many times a day
Q04b
How long did the thoughts last?
fleeting\\, lasting seconds to minutes
less than an hour
between 1 and 4 hours
between 4 and 8 hours
more than 8 hours
Q04c
Did you make any attempt to try to control or stop these thoughts about actually killing yourself, whether you were successful in controlling them or not?
Yes
No
Q04d
How easily could you control or stop thinking about killing yourself?
easily controlled these thoughts
with a little difficulty
with some difficulty
with a lot of difficulty

unable to control these thoughts
Q04e.1
Did you think about things like family, religion, or fear of pain or death that might affect your decision about killing yourself?
Yes
No
Q04e
Choose one of the following statements that best describes whether anyone or anything did or did not stop you from acting on your thoughts of committing suicide.
something definitely stopped you
something probably stopped you
you are uncertain whether something stopped you
something most likely did not stop you
something definitely did not stop you
Q04f.1
When you thought about killing yourself, did you have a reason in mind like ending your pain or getting attention or revenge?
Yes
No
Q04f
What sort of reasons did you have for thinking about wanting to kill yourself? Was it to end the pain or stop the way you were feeling?   In other words, you could not go on living with this pain or how you were feeling? Or was it to get attention, revenge or a reaction from others? Or both?
it was completely to get attention\\, revenge or a reaction from others
it was mostly to get attention\\, revenge or a reaction from others

equally to get attention\\, revenge or a reaction from others and to end or stop the pain
mostly to end or stop the pain \\(that is\\, you could not go on living with the pain or how you were feeling\\)
completely to end or stop the pain
Q05aNRT
You indicated before that since your last interview you had started working on plans or had actually worked out the details of how to kill yourself and had some intention to act on them. We want to ask you a few more questions about that.   When responding to these questions, we want you to think about the time you were feeling the most suicidal in the past [num] days.
If days SLC > 120
You indicated before that since your last interview you had started working on plans or had actually worked out the details of how to kill yourself and had some intention to act on them. We want to ask you a few more questions about that.   When responding to these questions, we want you to think about the time you were feeling the most suicidal since your last interview.
Q05a
When you were feeling the most suicidal and started planning or worked out details of how to kill yourself, how often did you think about killing yourself?
less than once a week
about once a week
2 to 5 times a week
daily or almost daily
many times a day
Q05b
How long did the thoughts last?
fleeting\\, lasting seconds to minutes

less than an hour
between 1 and 4 hours
between 4 and 8 hours
more than 8 hours
Q05c
Did you make any attempt to try to control or stop these thoughts about actually killing yourself, whether you were successful in controlling them or not?
Yes
No
Q05d
How easily could you control or stop thinking about killing yourself?
easily controlled these thoughts
with a little difficulty
with some difficulty
with a lot of difficulty
unable to control these thoughts
Q05e.1
Did you think about things like family, religion, or fear of pain or death that might affect your decision about killing yourself?
Yes
No
Q05e
Choose one of the following statements that best describes whether anyone or anything did or did not stop you from acting on your thoughts of committing suicide.
something definitely stopped you
something probably stopped you

you are uncertain whether something stopped you
something most likely did not stop you
something definitely did not stop you
Q05f.1
When you thought about killing yourself, did you have a reason in mind like ending your pain or getting attention or revenge?
Yes
No
Q05f
What sort of reasons did you have for thinking about wanting to kill yourself? Was it to end the pain or stop the way you were feeling?   In other words, you could not go on living with this pain or how you were feeling? Or was it to get attention, revenge or a reaction from others? Or both?
it was completely to get attention\\, revenge or a reaction from others
it was mostly to get attention\\, revenge or a reaction from others
equally to get attention\\, revenge or a reaction from others and to end or stop the pain
mostly to end or stop the pain \\(that is\\, you could not go on living with the pain or how you were feeling\\)
completely to end or stop the pain
Midpoint Transition (NRT02)
We are almost finished.   So far we have been asking about thoughts and feelings you may have had.   Now we would like to know about things you may have done to try to hurt yourself since your last interview.
Suicidal Behavior
Q06a
Since your last interview on [day] [date] have you made a suicide attempt?

Yes
No
Q06b
Use the number keys to enter the number of suicide attempts you have made since your last interview.
Q06cNRT01
If attempts >= 3
Consider your most recent attempt, your first attempt, and your most serious attempt separately.
Q06cNRT02
If attempts = 2
Consider your most recent attempt and your first attempt separately
Q06c
If loop = 1
When you made your most recent attempt, were you trying to end your life?
Yes
No
If loop = 2
When you made your first attempt, were you trying to end your life?
Yes
No
If loop = 3
When you made your most serious attempt, were you trying to end your life?
Yes
No

Q06e
Did you think it was possible that you could have died from what you did?
Yes
No
Q06d
So then
you wanted to die\\, even a little\\, when you did this
you did it purely for other reasons\\, like to relieve stress\\, feel better\\, get sympathy\\, or get something else to happen to you\\, without any intention of killing yourself
Q07a
Since your last interview, have you done anything to intentionally hurt or harm yourself?
Yes
No
Q07b
Use the number keys to enter the number of times you have intentionally hurt or harmed yourself since your last interview. If you cannot remember the exact number, enter your best estimate.
Q07cNRT01
Just consider the three most recent times you have intentionally harmed or hurt yourself.
Q07c_Attempt
If loop = 1
Think about the time you intentionally hurt or harmed yourself most recently.

If loop > 1
Consider the time you hurt or harmed yourself before that
Q07c
Were you trying to end your life?
Yes
No
Q07e
Did you think it was possible that you could have died from what you did?
Yes
No
Q07d
So then
you wanted to die\\, even a little\\, when you did this
you did it purely for other reasons\\, like to relieve stress\\, feel better\\, get sympathy\\, or get something else to happen to you\\, without any intention of killing yourself
Q08a
Since your last interview, have you done anything dangerous where you could have died?
Yes
No
Q08b
Use the number keys to enter the number of times you have done dangerous activities where you could have died in the past [num] days.

If days SLC > 120
Use the number keys to enter the number of times you have done dangerous activities where you could have died since your last interview.
Q08c_NRT01
Just consider the three most recent times you have done something dangerous where you could have died.
Q08c_Attempt
If loop = 1
Think about the most recent time you did a dangerous activity where you could have died
If loop > 1
Consider the time you did something dangerous before that
Q08c_1
Were you trying to harm yourself when you did this?
Yes
No
Q08c
Were you trying to end your life?
Yes
No
Q08d
So then
you wanted to die\\, even a little\\, when you did this

you did it purely for other reasons\\, like to relieve stress\\, feel better\\, get sympathy\\, or get something else to happen to you\\, without any intention of killing yourself
Lethality
Q09
If Q06a = YES
As a result of your most serious attempt since your last interview, were you injured more seriously than surface scratches or mild nausea?
Yes
No
If Q06a = NO
As a result of the most serious time you tried to hurt yourself since your last interview, were you injured more seriously than surface scratches or mild nausea?
Yes
No
Q09a
Were you hospitalized for medical treatment of the physical injury you suffered?   For example, were you comatose from an overdose, or did you suffer extensive blood loss that required a transfusion, or severe damage to your head or a vital organ?   If you were hospitalized for psychiatric evaluation, but not for medical treatment of a severe physical injury, answer No.
Yes
No
Q09b
Were you injured so severely that you would have died without treatment in an intensive care unit, or did you suffer permanent physical damage from which you will never completely recover, such as paralysis or disfigurement?

Yes
No
Q09c
Did your injury cause you to be extremely drowsy, or result in broken bones, or severe bleeding?
Yes
No
Q09.10
Although you were not injured during the most serious time, how serious could your injuries have been?
what you did was not likely to cause injury
what you did was likely to cause physical injury\\, but probably not death
what you did was likely to cause death with or without medical help\\, for example trying to shoot yourself in the head but the gun failed to fire
Interrupted Attempts
Q10
Since your last interview, was there a time when you started to do something to end your life, but someone or something stopped you before you actually did anything?
Yes
No
Q10a
About how many times have you been stopped from ending your life by someone or something since your last interview?
Please enter the number.

Aborted Attempts
Q11
Since your last interview, has there been a time when you started to do something to try to end your life, but you stopped yourself before you actually did anything?
Yes
No
Q11a
About how many times have you stopped yourself from ending your life in the last [num] days, since your last interview?
If days SLC > 120
About how many times have you stopped yourself from ending your life since your last interview?
Please enter the number.
Preparatory Acts or Behaviors
Q12NRT
Asses prior responses and present introduction:
Other than the times you have already told us about since your last interview when you did things intending to kill yourself or thought you might have died, when you started to do something to end your life but someone or something stopped you, and when you started to do something to end your life but stopped yourself,
Other than the times you have already told us about since your last interview when you did things intending to kill yourself or thought you might have died, and when you started to do something to end your life but stopped yourself,
Other than the times you have already told us about since your last interview when you did things intending to kill yourself or thought you might have died and when you started to do something to end your life but someone or something stopped you

Other than the times you have already told us about since your last interview when you started to do something to end your life but someone or something stopped you and when you started to do something to end your life but stopped yourself,
Other than the times you have already told us about since your last interview when you did things intending to kill yourself or thought you might have died,
Other than the times you have already told us about since your last interview when you started to do something to end your life but someone or something stopped you,
Other than the times you have already told us about since your last interview when you started to do something to end your life but stopped yourself,
Q12
Have you taken any steps toward making a suicide attempt or preparing to kill yourself, such as collecting pills, getting a gun, giving valuables away or writing a suicide note?
Yes
No
Q12a
About how many times?
Please enter the number.
Exit
You have completed your interview. Thank you and Good bye.

Appendix 15 Guidance for re-screening

It is permitted to re-screen subjects once if the reason for non-eligibility was transient (e.g., abnormal laboratory test, insufficient wash-out period of a forbidden medication), provided that documented authorization has been received from Actelion. Re-screening requires re-consenting i.e., a new Informed Consent Form must be signed by the subject and the PI.

- If the screening failure was due to a laboratory result (i.e., one or more hematology variables and/or one or more biochemistry variables were out of eligibility range) from Visit 1 (Screening):
    - All hematology and/or blood chemistry assessments from Visit 1 (Screening) need to be repeated and will then be used for assessing eligibility.
    - Other pre-randomization assessments do not need to be repeated if performed within 90 days (with the exception of 12-lead ECG and pregnancy test which should be performed within 37 days) prior to the date of re-screening and if their outcome was not exclusionary.
- If the screening failure was due to a laboratory result from Visit 2 (Baseline):
    - Laboratory assessments from Visit 2 (Baseline) must be repeated.
    - Laboratory assessments from Visit 1 (Screening) must be repeated unless performed within 37 days prior to the re-screening. In this case, laboratory assessments at Visits 1 and 2 (re-screening) must be performed at least 21 days apart.
    - Other pre-randomization assessments do not need to be repeated if performed within 90 days (with the exception of 12-lead ECG and pregnancy test which should be performed within 37 days) prior to the date of re-screening and if their outcome was not exclusionary.
- If the reason for screening failure was due to an assessment other than laboratory tests:
    - The assessment leading to the screening failure has to be repeated.
    - Other pre-randomization assessments do not need to be repeated if performed within 90 days prior to the date of re-screening (with the exception of 12-lead ECG, hematology, blood chemistry and pregnancy test which should be performed within 37 days) and if the outcome was not exclusionary.

- If the screening failure wais due to more than one assessment (e.g., laboratory and dermatological assessments) and the re-screening was authorized by Actelion:
    - All pre-randomization assessments have to be repeated.