Ponesimod / ACT-128800

Relapsing Multiple Sclerosis

Protocol AC-058B301

OPTIMUM: Oral Ponesimod versus Teriflunomide In relapsing MUltiple sclerosis

Multicenter, randomized, double-blind, parallel-group, active-controlled, superiority study to compare the efficacy and safety of ponesimod to teriflunomide in subjects with relapsing multiple sclerosis

Study Phase:	3 confirmatory
EudraCT Number:	2012-000540-10
Status and version:	Final Version 7
Date:	5 December 2018
Actelion document number (Doc No.):	D-18.388

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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-058B301, OPTIMUM, Multicenter, randomized, double-blind, parallel-group, active-controlled, superiority study to compare the efficacy and safety of ponesimod to teriflunomide in subjects with relapsing multiple sclerosis

I approve the design of this study.

	NAME (TITLE)	DATE	SIGNATURE
Clinical Trial Physician	Magdalena Pirozek-Lawniczek, MD	05 DEC 2018	PPD
Clinical Trial Statistician	Hilke Kracker, PhD	05 Dec 2018	PPD

INVESTIGATOR SIGNATURE PAGE

Treatment name / number

Ponesimod / ACT-128800

Indication

Relapsing Multiple Sclerosis

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AC-058B301, OPTIMUM, Multicenter, randomized, double-blind, parallel-group, active-controlled, superiority study to compare the efficacy and safety of ponesimod to teriflunomide in subjects with relapsing multiple sclerosis.

I agree to the terms and conditions relating to this study as defined in this protocol, the electronic Case Report Form (eCRF), 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 on 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
Site Principal Investigator					

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LIST OF ABBREVIATIONS AND ACRONYMS

9-HPT	9-Hole Peg Test
ACTH	Adrenocorticotropic hormone
AE	Adverse event
ALT	Alanine aminotransferase / serum glutamic pyruvic transaminase
ANCOVA	Analysis of covariance
AP	Alkaline phosphatase
ARR	Annualized Relapse Rate
AST	Aspartate aminotransferase / serum glutamic oxaloacetic transaminase
ATS	American Thoracic Society
AV	Atrioventricular
BCRP	Breast cancer resistant protein
BP	Blood pressure
Bpm	Beats per minute
CDA	Confirmed disability accumulation
CGI-C	Clinician's Global Impression of Change
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CID	Clinically Important Differences
CNS	Central nervous system
CRO	Contract Research Organization
CSF	Cerebrospinal fluid
CTCAE	Common terminology criteria for adverse events
CTT	Clinical trial team
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

DIR	Double inversion recovery
DL_{CO}	Diffusing capacity for the lungs measured using carbon monoxide
DMT	Disease-modifying therapy
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
eC-SSRS	Electronic self-rated version of the Columbia-Suicide Severity Rating Scale
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
FMS	FSIQ-RMS Measurement Set
FS	Functional system
FSIQ-RMS	Fatigue Symptom and Impact Questionnaire-Relapsing Multiple Sclerosis
FU	Follow-up
FVC	Forced vital capacity
GCP	Good Clinical Practice
Gd	Gadolinium
Gd+	Gadolinium-enhancing
Hb	Hemoglobin
HIV	Human immunodeficiency virus
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A

HR	Heart rate
i.m.	Intramuscular
i.v.	Intravenous
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
ICU	Intensive care unit
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN	Interferon
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive response technology
ISF	Investigator site file
JCV	John Cunningham Virus
MACE	Major Adverse Cardiovascular Events
MedDRA	Medical Dictionary for Regulatory Activities
MIAC	Medical Image Analysis Center
MID	Minimally Important Differences
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSFC	Multiple Sclerosis Functional Composite
MTR	Magnetization transfer ratio
NAWM	Normal appearing white matter
NEDA	No evidence of disease activity
NK	Natural killer
NMSS	US National Multiple Sclerosis Society
o.d.	Once a day
OAT	Organic anion transporter
OCT	Optical coherence tomography

OSB	Ophthalmology Safety Board
PASAT	Paced Auditory Serial Addition Test
PBH	Persistent black holes
PCBV	Percent change in brain volume
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PFT	Pulmonary function test
PGI-S	Patient's Global Impression of Severity
PK	Pharmacokinetic
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
RMS	Relapsing Multiple sclerosis
RNA	Ribonucleic acid
RR	Relapsing-remitting
RRMS	Relapsing-remitting multiple sclerosis
s.c.	Subcutaneous
S1P	Sphingosine-1-phosphate
SAC	Statistical Analysis Center
SAE	Serious adverse event
SAF	Safety Set
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure

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 Normalization, of Atrophy
SIV	Site initiation visit
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
WBC	White blood cell
WHO	World Health Organization
WOCBP	Woman of childbearing potential
WPAI:MS	Work Productivity and Activity Impairment: Multiple Sclerosis

SUBSTANTIAL GLOBAL AMENDMENT 6

Amendment rationale

This amendment rationale applies to global protocol AC-058B301 Version 6, dated 30 August 2017. The resulting amended global protocol is Version 7, dated 5 December 2018.

The main reason for this amendment is to revise the secondary endpoints multiple testing strategy as explained further below. This revision is not based on information collected in the OPTIMUM study and no analysis has been performed on the OPTIMUM data to develop this proposal. All data collected remain fully blinded to the sponsor:

i. Reduce the number of secondary endpoints in the OPTIMUM study from five to four to reduce the complexity of the testing strategy by including only the following:

   - Change from baseline to Week 108 in fatigue-related symptoms as measured by the symptoms domain of the Fatigue Symptom and Impact Questionnaire-Relapsing Multiple Sclerosis (FSIQ–RMS)
   - Cumulative number of Combined Unique Active lesions (CUAL) from baseline to Week 108
   - Time to 12-week Confirmed disability accumulation (CDA) from baseline to End of Study (EOS)
   - Time to 24-week CDA from baseline to EOS

   The "Time to 24-week CDA from baseline to EOS" endpoint will be moved from the exploratory endpoints to the category of secondary endpoints and the endpoints "Time to first confirmed relapse" and "Percent change in brain volume (PCBV) from baseline to Week 108" will be moved from the secondary endpoints list to the category of exploratory endpoints.

   The "Guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis" [EMA 2015], dated 26 March 2015, recommends confirmation of disability accumulation based on a confirmatory Expanded Disability Status Scale (EDSS) at least 6 months apart as a relevant endpoint. From a regulatory point of view and as per EMA feedback to the sponsor, the "Time to 24-week CDA from baseline to EOS" endpoint would be relevant to be included as a secondary endpoint.

   The endpoints "Time to first confirmed relapse" and "PCBV from baseline to Week 108" do not add substantial information on clinically important effects of the study drug on MS disease for the following reasons:

- The endpoint "Time to first confirmed relapse" is highly correlated to the primary endpoint of ARR. Thus, although this endpoint may provide some additional insight into the drug's effect on relapse activity, it is not expected to add relevant information to what is already available through the primary endpoint of ARR.
- The clinical significance of brain volume loss in MS and the relevance of the endpoint "PCBV from baseline to Week 108" remains unclear as the degree of change in whole brain volume measurement that results in a clinically meaningful benefit is not well defined due to several methodological limitations in brain volume measurements.

ii. Modify the multiple testing strategy for the control of the type I error by testing the secondary endpoints according to a fallback type method. As compared to the previously planned fixed-sequence hierarchical method, this will provide some opportunity to test an endpoint later in the sequence even if an endpoint tested earlier in the sequence has failed to show statistical significance. If statistical superiority of an endpoint tested earlier in the sequence can be shown the corresponding alpha can be passed on to endpoints later in the sequence. As a consequence, endpoints tested late in a fallback sequence are given a higher weight as compared to endpoints at the beginning of the sequence. This is in contrast to the previous planned hierarchical fixed sequence approach where endpoints at the beginning of the sequence receive a higher weight. To maintain the same weight ranking of the secondary endpoints it is proposed to change the order in the sequence.

The hypothesis for the primary endpoint of ARR is first tested with the full alpha. If the primary endpoint null hypothesis is rejected, the alpha will be split evenly (1/3 of alpha) between the following three secondary endpoints using the fallback procedure, allowing for passing on alpha as per the following sequence:

- Change from baseline to Week 108 in fatigue-related symptoms as measured by the symptoms domain of the FSIQ–RMS [Fatigue]
- Cumulative number of CUAL from baseline to Week 108 [CUALs]
- Time to 12-week CDA from baseline to EOS [12-week CDA]

If a secondary endpoint listed as part of the fallback procedure above is successful, the preserved alpha is passed along to the next secondary endpoint in the sequence and the summed alpha is used for testing that endpoint. Thus, as sequential tests are successful, the alpha accumulates for the endpoints later in the sequence; these endpoints are then potentially tested with a progressively larger alpha, but always with at least 1/3 of the alpha.

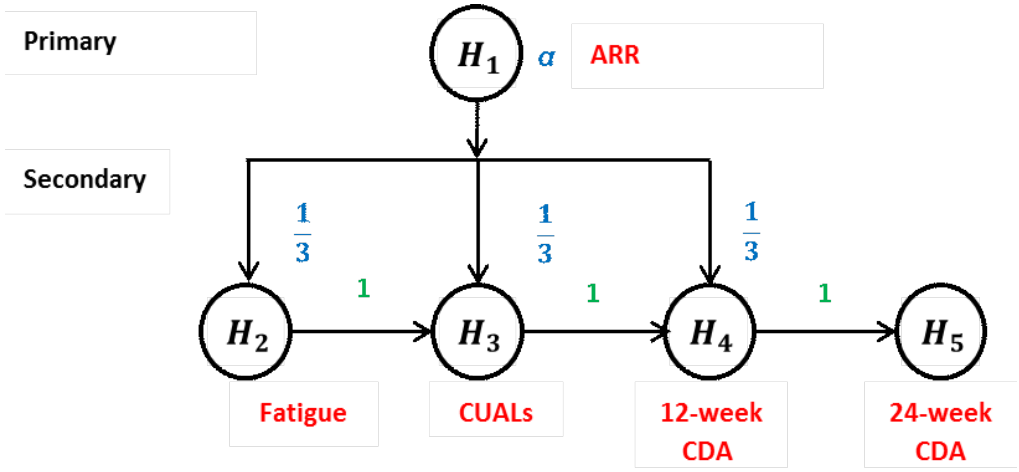
In a last step, the secondary endpoint

- Time to 24-week CDA from baseline to EOS [24-week CDA]

is tested in a subsequent stage following Time to 12-week CDA with the remaining alpha.

A graphical description of this testing strategy for the primary and secondary endpoints following the approach from Bretz, et al. [Bretz 2009] is provided in Figure 8 Overall testing strategy.

Figure 8 Overall testing strategy



Based on the latest published information from recent MS trials, the disability accumulation rate is expected to be lower than assumed in earlier protocol versions [Cohen 2018, Comi 2018]. This results in a lower than anticipated probability of the study providing a robust evaluation of the effect of ponesimod on disability accumulation and, consequently, would have limited the ability to assess the other secondary endpoints with the previously planned hierarchical multiple testing strategy. The sponsor considers that the introduced fallback type multiple testing strategy optimizes the ability of the trial to obtain conclusive results on key disease parameters.

Analyses for secondary endpoints will be conducted at an overall two-sided 5% alpha level, with multiplicity adjustment as per the above testing strategy. 95% confidence intervals will be presented. The statistical analyses sections and sample size calculations for the secondary endpoints have been updated accordingly.

Additional minor changes and clarifications were made to the protocol as follows:

- Cladribine was added to the list of orally administered disease-modifying therapies.
- It was clarified that oral taper of corticosteroids should not be administered in order to harmonize the treatment of relapses in the study and to minimize the risk of combined immunosuppression.
- It was clarified that No evidence of disease activity (NEDA) status will be considered up to EOS.
- It was corrected that health care utilization will be not be displayed by visit.
- The possibility of using a chiral assay for the analysis of selected plasma PK samples was added to the protocol. Rationale: Metabolism of ponesimod may hypothetically result in chiral inversion of the parent compound to its S-enantiomer (ACT-128818). In plasma samples from rat and dog it was confirmed that this inversion did not occur in measurable quantities, using a chiral bioanalytical assay [ponesimod IB] but chiral inversion was never tested in humans. The validated bioanalytical assay that is currently being used in the study for the quantification of ponesimod is a non-chiral assay, not able to separate the enantiomers.
- Wording was added to allow the analysis of biomarkers in the serum sample taken at Visit 2 (Baseline).
- The definition of confirmed relapses was clarified.
- It was clarified that the relapse assessment questionnaire may be completed during the additional safety blood draws (if applicable).
- It was clarified that specific assessments collected at the end of treatment visit may be conducted up to 7 days prior to the last intake of study drug.
- The definition of which EDSS assessment can qualify as confirmatory for 12- and 24-week CDA was clarified in order to maximally use data provided by the investigator and minimize the impact of short-term relapse-related disability.

Furthermore, some inconsistencies between sections in the protocol were corrected or clarified as follows:

- The threshold for HHH grading for lymphocytes in Appendix 6 was aligned to the specifications in Sections 7.3.14.1 and 5.1.5.2.
- The criteria leading to exclusion from the per-protocol set were aligned with the overall definition of the per protocol set regarding deviations that impact the

assessment of the primary or secondary endpoint leading to exclusion: Subjects developing discontinuation criteria that were not discontinued are not removed from per protocol analysis as these deviations are not considered to impact the assessment of the primary or secondary endpoint.

In the statistical analysis section the following minor updates were made:

- It was clarified that separate SAPs and reports will be prepared for the final analyses of PK data, the MRI sub-study and the Patient Preference sub-study.
- Definition of highly active relapsing multiple sclerosis has been aligned with the updated therapeutic indications of Gilenya® in EMA [Gilenya® SmPC].
- Treatment-emergent QTc > 450 ms, > 480 ms, > 500 ms are reported irrespective of gender to align with standard reporting.
- For PFT reporting the provided thresholds are clarified to include subjects with a decrease of = 200 mL or = 12% in FEV_1 or FVC.
- The number of supportive / sensitivity statistical analyses was reduced to focus on the analyses required for the regulatory submission.
- For the secondary endpoint change from baseline in FSIQ-RMS symptoms score to Week 108 reference to last observation carried forward has been removed and a repeated measurements ANCOVA using data from all scheduled visits (instead of an ANCOVA using only change from baseline to Week 108 data) will be applied to make use of all data collected at scheduled visits and make use of them in the analysis.
- For the secondary and exploratory efficacy endpoints statistical models have been updated to adjust for the baseline result (where available) instead of the number of relapses in the year prior to study entry to increase statistical rigor and align with health authority recommendations.
- For analyses of safety variables 95% CLs (not 99% CLs) are provided as they are considered descriptive analyses.
- For analyses of AEs of special interest, and MACE, reference to logistic regression has been removed to align with analysis of specific safety events described in the introduction of Section 11.3.5.

Finally, edits were done to correct typographical errors.

Changes to the protocol

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

Amended protocol sections

The main 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:

CONTRACT RESEARCH ORGANIZATIONS INFORMATION

1.1.4.2	**Orally administered disease-modifying therapies**
5.2.3	**Recommended concomitant therapy**
6.1.1	**Primary efficacy endpoint(s)**
6.1.2	**Secondary efficacy endpoints**
6.1.3	**Other efficacy endpoints**
6.2	**Safety endpoints**
6.4	**Pharmacoeconomic endpoints**
7.2.2	**Detection and evaluation of relapses**
7.3.14.2	**Laboratory tests**
7.7.1.4	**Bioanalysis**
8.2.10	**Visit 14 – EOT Visit**
11	**Statistical Methods**
11.1.3	**Per-Protocol Set**
11.2.2	**Secondary efficacy variables**
11.2.2.1	**Fatigue Symptoms and Impact Questionnaire (FSIQ-RMS)**
11.2.2.2	**Cumulative number of CUAL from baseline to Week 108**
11.2.2.3	**Time to 12-week CDA**
11.2.2.4	**Time to 24-week CDA**
11.2.3.1	**Exploratory efficacy variables**
11.2.4	**Safety variables**

Summary of previous amendments

Amendment	Date	Main reason(s)
1	29 April 2015	Addition of a sub-study assessing patient preferences for different outcomes in the treatment of multiple sclerosis using an electronic Multiple Sclerosis Patient Preference Questionnaire.
2	16 July 2015	Addressing the comments received after Voluntary Harmonization Procedure review for this Clinical Trial Application in the EU.
3	5 February 2016	Addressing a comment received from the US FDA regarding the assessments of relapses. For this purpose, a standardized step-wise procedure for the confirmation and reporting of relapses has been introduced.
4	14 November 2016	Modify the procedure for teriflunomide plasma concentration testing after the subject's discontinuation from study treatment.
5	30 August 2017	Allow the testing of teriflunomide plasma concentration in any subject who has discontinued study drug if deemed necessary for the subject's safety, at the discretion of the investigator.

PROTOCOL SYNOPSIS AC-058B301

TITLE	Multicenter, randomized, double-blind, parallel-group, active-controlled, superiority study to compare the efficacy and safety of ponesimod to teriflunomide in subjects with relapsing multiple sclerosis (RMS)
ACRONYM	OPTIMUM: **O**ral **P**onesimod vs **T**eriflunomide **I**n relapsing **MU**ltiple sclerosis
OBJECTIVES	**Primary objective** To determine whether ponesimod is more efficacious than teriflunomide in terms of reducing relapses in subjects with RMS. **Secondary objectives** 1. To assess the effect of ponesimod on disability accumulation and on other aspects of multiple sclerosis (MS) disease control 2. To assess the safety and tolerability of ponesimod in subjects with RMS.
DESIGN	Prospective, multicenter, randomized, double-blind, parallel-group, active-controlled, Phase 3, superiority study.
PERIODS	**Pre-randomization period** Up to 45 days before randomization. **Treatment period** The double-blind treatment period will last for 108 weeks. It will consist of a randomization visit, visits at two, four, and 12 weeks after randomization, and 12-weekly visits thereafter. **End-of-Treatment (EOT)** • The EOT visit will take place at Week 108 (or earlier in case of premature discontinuation of study drug). In all cases, the EOT visit should take place one day after the last dose of study drug but no later than 7 days after the last dose of study drug. • Subjects who have completed treatment until Week 108 will be proposed to enroll in an extension study conducted under a separate protocol. Subjects who discontinue study drug prematurely for any reason will not be eligible for the extension study.

	• Subjects who prematurely discontinue study drug treatment should be subsequently treated according to local standard of care at the investigator's discretion and will be followed in the post-treatment observation period. **Post-treatment safety follow-up (FU) period:** Teriflunomide is eliminated slowly from plasma. An accelerated elimination procedure must be used by all subjects after the last dose of study drug [see Section 5.1.14]. A safety FU after the last dose of study drug is mandated. All subjects will enter the safety FU period: • For subjects who enter the extension study, the FU period starts after the last dose of study drug and ends with a safety FU visit (FU1) 14–22 days after the last dose of study drug or with an abbreviated FU2 23–37 days after the last dose of study drug (if compliance to the teriflunomide accelerated elimination procedure was assessed as not sufficient at FU1). • For subjects who do not enter the extension study, the safety FU period lasts for 30 days after the last dose of study drug and includes two safety FU visits (FU1, FU2) at 14–22 and 30–37 days after the last dose of study drug, respectively. **Post-treatment observation period (PTOP):** Subjects who prematurely discontinue study treatment will enter the PTOP which lasts until 108 weeks after randomization (i.e., planned EOT period). It consists of an abbreviated schedule of assessments at the time of the originally scheduled 12-weekly visits. **End-of-Study (EOS)** • EOS is reached when treatment, safety FU, and, if applicable, PTOP have been completed. • For subjects who completed the 108-week treatment period and enter the extension study, the EOS visit corresponds to the FU visit (FU1) conducted 14–22 days after the last study drug dose or to the abbreviated FU2 visit conducted 23–37 days after the last study drug dose (if needed for compliance reasons with the teriflunomide accelerated elimination procedure).

	• For all other subjects, the EOS visit corresponds to the 30-day FU visit (FU2) or to the last visit of PTOP (i.e., Week 108 Visit of the PTOP), whichever is last.
PLANNED DURATION	Approximately 171 weeks (3.3 years) from first subject first visit to last subject last visit. For an individual subject, the maximum duration of the study will be approximately 118 weeks (2.2 years).
SITE(S) / COUNTRY(IES)	Approximately 200 sites in 25 countries in North America, South America, Eastern and Western Europe, Pacific (planned).
SUBJECTS / GROUPS	Approximately 1100 subjects will be randomized in 2 groups in a 1:1 ratio to receive ponesimod 20 mg (approximately 550 subjects) or teriflunomide 14 mg (approximately 550 subjects). Randomization will be stratified by prior use of MS disease-modifying treatment in the last two years prior to randomization (yes, no) and by baseline Expanded Disability Status Scale (EDSS) score (EDSS ≤ 3.5, EDSS > 3.5).
INCLUSION CRITERIA	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., relapsing-remitting multiple sclerosis and secondary progressive multiple sclerosis [SPMS] with superimposed relapses). The trial will include up to a maximum 15% of subjects with SPMS with superimposed relapses. Subjects must have active disease evidenced by one or more MS attacks with onset within the period of 12 to 1 months prior to baseline EDSS assessment, or by two or more MS attacks with onset within the 24 to 1 months prior to baseline EDSS assessment, or with one or more gadolinium-enhancing (Gd+) lesion(s) of the brain on an MRI performed within 6 months prior to baseline EDSS assessment. Enrolled subjects must be ambulatory with an EDSS score of up to 5.5 inclusive. The subjects may be treatment-naïve (i.e., no MS disease-modifying therapy received at any time in the past) or previously treated

	with interferon (IFN) β-1a, IFN β-1b, glatiramer acetate, dimethyl fumarate, or natalizumab. Women of childbearing potential (WOCBP) must have a negative pregnancy test during pre-randomization and must agree to use reliable methods of contraception from Visit 1 (Screening) until 6 weeks after the first of two tests showing teriflunomide level < 0.02 mg/L. Fertile male subjects participating in the study who are sexually active with WOCBP must agree to use a condom during the treatment period and for an additional 6 weeks after the first of two tests showing teriflunomide level < 0.02 mg/L. Eligible subjects must be able and willing to give informed consent for participation in the clinical study. For the complete list of inclusion criteria, please see Section 4.3.
EXCLUSION CRITERIA	Subjects with significant medical conditions or therapies for such conditions (e.g., cardiovascular, pulmonary, immunological, hepatic, ophthalmological, ocular) or lactating or pregnant women are not eligible to enter the study. Subjects with contraindications to MRI or with clinically relevant medical or surgical conditions that, in the opinion of the investigator, would put the subject at risk by participating in the study are not eligible to enter the study. Finally, subjects unlikely to comply with protocol are not eligible to enter the study. For the complete list of exclusion criteria, please see Section 4.4.
STUDY TREATMENTS	One capsule of ponesimod 20 mg, or teriflunomide 14 mg, 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: **_Ponesimod Group_** Days 1 and 2: 2 mg Days 3 and 4: 3 mg Days 5 and 6: 4 mg Day 7: 5 mg

	<table><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>Days 12, 13, and 14</td><td>10 mg</td></tr><tr><td>Day 15 until EOT</td><td>20 mg</td></tr></table>
CONCOMITANT THERAPY	**Treatment of relapses** • If a relapse requires treatment with corticosteroids, methylprednisolone 1 g intravenous (i.v.) daily for 3 to 5 days is recommended (without an oral taper). Treatment with other corticosteroids or another dose, or other routes of administration, or adrenocorticotropic hormone (ACTH) is not recommended, unless deemed absolutely necessary by the investigator who will document the rationale. • Treatment of relapses with plasma exchange (i.e., plasmapheresis, cytapheresis) is prohibited. **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 ß2-agonists for respiratory symptoms and/or reduced pulmonary function during study drug treatment. • 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. • 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 assess changes in vaccine-specific

	antibody titers from pre- to post-vaccination. Samples will be analyzed at the end of the study. • The following medication should be administered with caution and carefully monitored due to potential interactions with teriflunomide: medications metabolized by cytochrome P450 (CYP)2C8 and CYP1A2, potent CYP and transporters inducers, medications with a low therapeutic index such as warfarin, substrates of organic anion transporter 3 (OAT3), breast cancer resistant protein (BCRP) and the organic anion transporter polypeptide (OATP) family (especially 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors). • Other treatments considered necessary for the subject's wellbeing and not categorized as prohibited concomitant medications. **Prohibited concomitant therapy** • Systemic corticosteroids and ACTH, except for the treatment of MS relapses and for short-term treatment with low dose or inhaled corticosteroids for pulmonary conditions; • Disease-modifying drugs for MS other than prescribed as per protocol; • Immunosuppressive treatment; • i.v. immunoglobulin; • Plasmapheresis, cytapheresis, or total lymphoid irradiation; • Vaccination with live vaccines; • β-blockers, diltiazem, verapamil, digoxin, or any other anti-arrhythmic or heart rate (HR)-lowering systemic therapy; • Cholestyramine or activated charcoal unless needed for an accelerated elimination procedure [see Section 5.1.14]; • Any other investigational drug; • Any investigational therapeutic procedure for MS (e.g., stent placement or angioplasty for chronic cerebrospinal venous insufficiency, stem cell transplantation).

ENDPOINTS	**Primary efficacy endpoint** • Annualized relapse rate (ARR) defined as the number of confirmed relapses per subject-year. **Secondary efficacy endpoints** • Change from baseline to Week 108 in fatigue-related symptoms as measured by the symptoms domain of the Fatigue Symptoms and Impact Questionnaire – Relapsing Multiple Sclerosis (FSIQ–RMS); • Cumulative number of combined unique active lesions (CUAL; defined as new Gd+ T1 lesions plus new or enlarging T2 lesions [without double-counting of lesions]) from baseline to Week 108; • Time to 12-week confirmed disability accumulation (CDA) from baseline to EOS; • Time to 24-week CDA from baseline to EOS; **Exploratory endpoints** **MRI-based exploratory endpoints:** • Percent change in brain volume (PCBV) from baseline to Week 108; • Number of MRI lesions (Gd+ T1 lesions) at Week 60 and Week 108; • Cumulative number of new or enlarging T2 lesions from baseline to Week 108; • Change from baseline to Week 60 and Week 108 in the volume of MRI lesions (T2 lesions, T1 hypointense lesions); • Absence of MRI lesions (Gd+ T1 lesions, new or enlarging T2 lesions) at Week 60 and Week 108; • Proportion of Gd+ lesions at baseline evolving to persistent black holes (PBHs) by Week 108 (axonal loss); • Change of CCI [redacted] • Change in CCI [redacted] • Cumulative number of CCI [redacted]

	Clinical exploratory endpoints (disease activity, relapses, disability accumulation): • Time to first confirmed relapse; • Absence of relapses from baseline to Week 60 and Week 108; • Change from baseline by visit up to Week 108 in EDSS; • No evidence of disease activity status at Week 108 (defined by the absence of confirmed relapse, Gd+ T1 lesions, new or enlarging T2 lesions, 12-week CDA, and annual brain volume change $\geq -0.4\%$ from baseline to EOS, and completing treatment as planned). **Other exploratory endpoints:** • Change in Multiple Sclerosis Functional Composite (MSFC) Z-score from baseline by visit up to Week 108; • Change in the Symbol Digit Modalities Test (SDMT) score from baseline by visit up to Week 108; • Proportion of responders at Week 108 in fatigue-related symptoms as measured by the Fatigue Symptom and Impact Questionnaire-Relapsing Multiple Sclerosis (FSIQ-RMS); • Change from baseline by visit up to Week 108 in fatigue-related impacts as measured by the impact sub-scales of the FSIQ–RMS. • Change from baseline in Patient's Global Impression of Severity of Fatigue by visit up to Week 108; • Change from baseline in Clinician's Global Impression of Change of the patient's relapsing MS by visit up to Week 108; • Preferences for several treatment outcomes from MS subjects using the Measuring Attractiveness by a Categorical Based Evaluation Technique (MACBETH; sub-study, at selected sites only). **Safety endpoints:** • Treatment-emergent adverse events (AEs), serious adverse events, AEs of special interest, and major adverse cardiovascular events (MACE);

	• AEs leading to premature discontinuation of study treatment; • Treatment-emergent morphological electrocardiogram (ECG) abnormalities (as defined by the ECG provider); • Change in 12-lead ECG variables (HR, PR, QRS, QT, QTcB, and 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 drug; • Notable abnormalities for selected 12-lead ECG parameters (HR, PR, QT, QTcF) at 3-h post-dose assessment on Day 1, Week 12 and at the re-initiation of study drug when post-dose monitoring is required. • Treatment-emergent decrease of forced expiratory volume in 1 second (FEV_1) or forced vital capacity (FVC) > 20% from baseline values; • Treatment-emergent 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 vs 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 and < 12% in FEV_1 or FVC from baseline to last available FU; • Change in lung diffusion capacity as assessed by the diffusing capacity of the lung for carbon monoxide (DL_{CO}; at selected sites only), expressed in absolute change and % of predicted value from baseline to all timepoints up to EOS; • Change from baseline to EOS vs change from baseline to EOT in DL_{CO} (absolute and % of predicted) (at selected sites only); • 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. **Quality of life endpoints** • Change from baseline by visit up to Week 108 in SF-36v2™ Health Survey domain and component scores. **Pharmacoeconomic endpoints** • Change from baseline by visit up to Week 108 in work productivity and activity impairment in MS (WPAI:MS) scores. • Health care resource utilization from baseline up to Week 108 (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) endpoints** • Plasma concentrations of ponesimod pre-dose at Week 12, Week 60 and Week 108 and 3 h post-dose on Day 1 and at Week 12. **Pharmacodynamic (PD) endpoints** • Peripheral blood lymphocyte counts pre-dose (absolute and change from baseline counts) by visit up to Week 108; • Change from baseline to EOS vs change from baseline to EOT in lymphocyte counts (absolute and % change); • Post-treatment lymphocyte recovery at 15 days and 30 days after study drug discontinuation.
ASSESSMENTS	See schedule of assessments in Table 1, Table 2, Table 3.
STATISTICAL METHODOLOGY	The Full Analysis Set (FAS) includes all randomized subjects. In order to adhere to the intention-to-treat principle as much as possible, subjects will be evaluated according to the treatment they have been randomized to. The Per-Protocol Set (PPS) comprises data from all subjects included in the FAS without major protocol deviations as categorized in Section 11.1.3.

	The Safety Set (SAF) includes all randomized subjects who received at least one dose of study treatment. Subjects will be analyzed based on actual treatment taken, not randomized treatment. **Statistical model and hypotheses for primary efficacy endpoint** A generalized linear model with negative binomial distribution will be fitted for the primary efficacy endpoint ARR. Two-sided hypotheses are expressed in terms of the model parameters μ_{P20mg} and μ_{T14mg}. The primary null hypothesis is that the ARR (μ) does not differ between ponesimod 20 mg and teriflunomide 14 mg. The alternative hypothesis is that the ARR differs between ponesimod 20 mg and teriflunomide 14 mg. $H_{0, ARR}: \mu_{P20mg} - \mu_{T14mg} = 0$ vs $H_{1, ARR}: \mu_{P20mg} - \mu_{T14mg} \neq 0$ 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 0.01 for conclusive evidence and 0.05 for a positive study. Two-sided 99% and 95% Wald confidence intervals will be calculated for the relative reduction in mean ARR for ponesimod 20 mg compared to teriflunomide 14 mg. The primary statistical analysis of the ARR endpoint will be performed on the FAS using a negative binomial model for confirmed relapses, with the stratification variables prior use of disease-modifying therapies (DMTs) and EDSS category as well as the number of relapses in the year prior to study entry, included in the model and time in the study as an offset variable. Sensitivity analyses will be performed on the PPS and also based on different subgroups derived from baseline variables. The secondary efficacy endpoints will be tested if the primary analysis on ARR has led to the rejection of the null hypothesis in favor of ponesimod 20 mg at an overall two-sided significance level of 0.05. A fallback method will be used for testing the family of hypotheses related to the following three secondary endpoints:

	• Absolute change of FSIQ-RMS from baseline to Week 108. • Cumulative number of CUAL from baseline to Week 108; • Time to 12-week CDA from baseline up to EOS; This is followed in a hierarchical manner by testing • Time to 24-week CDA from baseline up to EOS; at the remaining alpha. The endpoints will be analyzed using the FAS population. All secondary endpoints will also be analyzed using the PPS population. The sample size was calculated based on the primary endpoint, and power calculations are provided for the secondary endpoints. **Sample size for the primary endpoint** The sample size for the study was determined by a simulation using the negative binomial distribution. A sample size of 1100 subjects (550 per treatment group) would provide a power of approximately 90% for a significance level of 0.01, under the assumption that ARR is 0.320 for teriflunomide 14 mg and 0.215 for ponesimod 20 mg (which corresponds to a risk reduction of 33%) and using a dispersion = 0.9. An annual dropout rate of approximately 15% for the first year and 7.5% for the second year has been assumed. The adjusted risk reduction for teriflunomide 14 mg in the fixed 2-year duration TEMSO study was 31.5%, and in the variable duration TOWER study it was 36%. An integrated analysis showed a pooled 34% reduction compared to placebo. A 33% reduction for ponesimod 20 mg compared to teriflunomide 14 mg gives a relative 55% reduction compared to placebo, which is similar to that observed in the fingolimod Phase 3 trials. The dispersion from the ponesimod Phase 2 study was 1.0, the calculated dispersion from the TEMSO study is 0.8; the chosen dispersion is the mean of the two. **Exploratory efficacy endpoints** No multiplicity adjustments will be made on exploratory efficacy endpoints. Any two-sided p-value < 0.05 will be

	identified as statistically significant but will only be considered as an exploratory result. **Safety endpoints** Safety endpoints will mainly be analyzed descriptively by treatment group on the SAF.
STUDY COMMITTEES	An Independent Data Monitoring Committee (IDMC) composed of physicians with relevant medical expertise (including a neurologist, a neurovirologist, a neurologist with MRI expertise or a neuroradiologist, a cardiologist, a pulmonologist) and a statistician will review unblinded subject safety and efficacy data on an ongoing basis and is empowered to recommend modifications to the protocol (to enhance subject safety) or to recommend early termination of the study. The composition and operation of the IDMC are described in the IDMC charter. A statistical analysis center (a Contract Research Organization not otherwise involved with study conduct or statistical analysis) will generate unblinded analysis reports, exclusively for review by the IDMC throughout the trial period. 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. The composition and operation of the OSB are described in the OSB charter. A MACE adjudication board will review and evaluate in a blinded fashion the MACE reported in the study. The selection of AEs that will be sent for adjudication will be based on a pre-defined list of preferred terms belonging to relevant Standardized Medical Dictionary for Regulatory Activities (MedDRA) Queries. For each AE sent for MACE adjudication, the MACE adjudication board will determine whether the event belongs or not to one of the pre-specified categories including cardiovascular death, myocardial infarction, and stroke. The composition and operations of MACE adjudication board are described in the MACE adjudication board charter.

SUB-STUDIES	**Pulmonary function monitoring** A sub-study assessing DL_{CO} will be conducted in approximately 400 subjects recruited at approximately 80 selected sites with appropriate equipment and experience. With the 1:1 randomization (20 mg ponesimod or 14 mg teriflunomide), this will represent approximately 200 subjects per treatment group. **Non-conventional MRI techniques** MTR has better histological specificity than conventional T2-weighted MRI. MTR is sensitive to change over time and to treatment effects on NAWM and on focal lesions. DIR is a method that allows better visualization of grey matter lesions than conventional T2-weighted imaging. Both methods can be applied in multicenter settings. A sub-study using these non-conventional MRI techniques will be implemented in approximately 300 subjects recruited at selected sites with appropriate equipment and experience. **Patient preferences** A sub-study assessing patient preferences in approximately 360 subjects recruited at selected sites will be conducted using an electronic questionnaire. The Multiple Sclerosis Patient Preference Questionnaire will be completed at home twice during the pre-randomization period (after Visits 1 and 2 [Screening, Baseline]), and once during the follow-up period (Visit 15, FU1). **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 non-live vaccination while on study treatment.
STUDY EXTENSION	**Extension study AC-058B303 (separate protocol)** Subjects who complete the 108-week treatment will be proposed to enroll in a non-comparative extension study conducted under a separate protocol.

Table 1 Visit and assessment schedule (Part 1)

Periods	Name	PRE-RANDOMIZATION (1)		TREATMENT PERIOD						
	Duration	Up to 45 Days		108 Weeks						
Visits	Number	1	2	3	4	5	6	7	8–9	10
	Name	Screening	Baseline	Rand	W2	W4	W12	W24	W36 – 48	W60
	Time	Day –45 to –1		Day 1	Day 15	Week 4	Week 12	Week 24	Week 36 – 48	Week 60
	Visit window				± 1 day	± 3 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	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), PGI-S**, CGI-C*			X(5)				X	X		X
SF-36v2**			X				X	X		X
Health care resource utilization* (6)					X	X	X	X	X	X
WPAI:MS**			X				X	X		X
Patient preference questionnaire** (7)		X	X							
Chest X-ray* (8)		X								
eC-SSRS**			X							X
MRI** (9)			X							X
Concomitant medications*		X	X	X	X	X	X	X	X	X
Physical examination*		X	X			X	X	X		X
Dermatological examination* (10)			X							X
Body weight and height* (11)		X								X
Body temperature*		X	X	X	X	X	X	X	X	X
SBP/DBP*		X	X	X(12)	X	X	X	X	X	X
12-lead ECG** (13)		X	X	X(14)	X	X	X(15)	X	X	X
Ophthalmological examination* / OCT* (16)		X					X	X		X
PFT** (17)			X			X	X			X
Hematology/Chemistry** (fasted)		X	X		X	X (18) <----------		> X (18)	X	X
Urinalysis		X				X	X	X		X
Tuberculosis test / Viral serology **		X								
Additional serum sample for viral serology			X							
Pregnancy test*/**		X (19)	X		X	X	X	X	X	X
PK sampling for ponesimod* (20)				X			X			X
Study drug dispensing & accountability (21)*/**				X	X	X	X	X	X	X

Study drug swallowing test (optional)		X							
AEs*/SAEs(22)	X	X	X	X	X	X	X	X	X

*Data collected in the eCRF

**Data 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 and repeated at Visit 2 (Baseline; e.g., hematology, blood chemistry, urinalysis, physical examination, central laboratory, 12-lead ECGs, and SBP/DBP) must be performed at least 7 days after the Visit 1 (Screening) assessments. For women of childbearing potential, the serum pregnancy test at Visit 1 (Screening) must be performed at least 3 weeks before the urine pregnancy test performed pre-randomization at Visit 2.The blood draw at Visit 2 (Baseline) should happen early enough in order 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, and 102 (+/− 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 relapse assessment questionnaire [see Appendix 17].

(3) During pre-randomization, 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 test practice ≥ 5 days from first practice test and third test serving as baseline ≥ 5 days from second practice test). The first test practice may be done at Visit 1 (Screening), the second test practice 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-h recall) will be completed for 7 consecutive days (the day of the visit and the 6 days after the visit). During pre-randomization, subjects during Visit 1 (Screening) will be provided with the FSIQ-RMS and will be instructed to complete the symptoms domain (i.e., section 1) of the FSIQ-RMS on 7 consecutive days prior to randomization at home (provided no other assessment performed in the meantime exclude the subject). Once the results from the laboratory tests confirm the subject's eligibility, the site coordinator will contact the subject to instruct him/her to start the completion of the symptoms domain of the FSIQ-RMS at latest 7 days before the randomization.

(5) No CGI-C assessment at Baseline.

(6) Health care resource utilization data, including number of intensive care unit admission for MS relapses and emergency medical services facility visits for MS

(7) Only for subjects participating in the patient preference substudy. The Multiple Sclerosis Patient Preference Questionnaire will be completed at home twice during pre-randomization (after Visits 1 and 2 [Screening and Baseline]).

(8) Any CXR that has been performed within 90 days prior to screening can be used (in this case, no need to repeat CXR at Screening). In case of re-screening, CXR does not need to be repeated if CXR was performed within 90 days prior to the date of re-screening.

(9) Brain MRI to be performed at any time an opportunistic infection in the central nervous system is suspected. In addition, non-conventional MRI techniques (MTR and DIR) will be performed at selected sites only.

(10) Dermatological examination to be performed by a dermatologist. 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

(11) Height only at Visit 1 (Screening).

(12) SBP/DBP: Pre-dose and hourly (+/− 15 min) for at least 4 h post-dose and up to 12 h.

(13) Only pre-dose ECGs at all visits except Day 1 and Week 12.
(14) Pre-dose and hourly (+/− 15 min) for at least 4 h post-dose and up to 12 h.
(15) Pre-dose and 3-h (+/− 15 min) post-dose ECGs.
(16) OCT and/or ophthalmological examination to be performed at any visit in the presence of visual symptoms or findings suggestive of macular edema or active uveitis [see Section 5.1.13.7].
(17) Pulmonary function tests include spirometry to be performed pre-dose in all subjects and DL_{CO} to be performed in a subset of approximately 400 subjects at selected sites only.
(18) In addition, liver tests (ALT, AST, INR, alkaline phosphatase and total bilirubin) at Weeks 6, 8, 10, 14, 16, 18, 20, and, 22 will be collected, sent to, and analyzed at the central laboratory. Furthermore, total white blood cell and total lymphocyte counts will be assessed at Weeks 8, 16, and 20. The test window is ± 3 days. Note: No relapse assessment questionnaire is needed when blood sample is drawn.
(19) Serum pregnancy test at Screening, urine pregnancy test at all subsequent visits. Urine pregnancy tests (performed at home) on a 4-weekly (+/− 4 days) basis between the visits during the study (results to be communicated by telephone call to the principal investigator / treating neurologist). At all visits and telephone calls, the methods of contraception will be reviewed and the contraceptive method form entered in the eCRF must be updated as applicable.
(20) Pharmacokinetic sampling pre-dose at Weeks 12, 60 and 108, and 3 h (+/− 15 min) post-dose on Day 1 and Week 12.
(21) Scheduled study medication dispensing/return procedures may be adapted according to the site practice.
(22) 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; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CGI-C = Clinician's Global Impression of Change of the patient's relapsing MS; CXR = chest X-ray; DBP = diastolic blood pressure; DIR = double inversion recovery; DL_{CO} = diffusing capacity for the lungs measured using carbon monoxide; eC-SSRS = electronic self-rated version of the Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; eCRF = electronic case report form; EDSS = Expanded Disability Status Scale; FS = functional system; FSIQ-RMS = Fatigue Symptom and Impact Questionnaire-Relapsing Multiple Sclerosis; INR = International Normalized Ratio; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSFC = Multiple Sclerosis Functional Composite; MTR = magnetization transfer ratio; OCT = optical coherence tomography; PFT = pulmonary function test; PGI-S = Patient's Global Impression of Severity of Fatigue; PI = principal investigator; PK = pharmacokinetics; SAE = serious adverse event; SBP = systolic blood pressure; SDMT = Symbol Digit Modalities Test; WPAI:MS = Work Productivity and Activity Impairment Index: Multiple Sclerosis.

Table 2 Visit and assessment schedule (Part 2)

Periods	Name	TREATMENT PERIOD				FOLLOW-UP		UNSCHEDULED			
	Duration	108 Weeks				30 Days					
Visits	Number	11	12	13	14	15	16	R1, R2, …	U1, U2, …	I1, I2, …	
										d1	d15
	Name	W72	W84	W96	EOT	FU1	FU2	Relapse	Unscheduled (19)	Re-initiation	
										Day 1 of re-initiation	Day 15 after re-initiation
	Time	Week 72	Week 84	Week 96	Week 108 or earlier in case of premature discontinuation (18)	Last study drug intake +15 days	Last study drug intake +30 days	Any day between Day 1 and EOS			
	Visit window	± 7 days	± 7 days	± 7 days	± 7 days	−1 day, +7days	+7 days (22)	+7 days	NA	NA	± 1 day
EDSS/FS*		X	X	X	X		X	X	X		
Relapse* (1)		X(1)<----------->X(1)				X	X	X	X (21)		
MSFC*, SDMT*			X		X						
FSIQ-RMS** (2), PGI-S**, CGI-C *			X		X			X	X		
SF-36v2**			X		X			X			
Health care resource utilization* (3)		X	X	X	X			X			
WPAI:MS**			X		X						
Patient preference questionnaire** (4)						X					
Chest X-ray* (5)					X						
MRI** (6)					X				X		
eC-SSRS**					X						
Concomitant medications*		X	X	X	X	X	X	X	X		
Physical examination*			X		X			X	X		
Dermatological examination* (7)					X				X		
Body weight*					X				X		
Body temperature*		X	X	X	X	X	X	X	X	X	X
SBP/DBP*		X	X	X	X	X	X		X	X(8)	X
12-lead ECG** (9)		X	X	X	X	X	X		X	X(9)	X
Pulse rate*								X	X(20)		
Ophthalmological examination / OCT* (10)					X				X		
Pulmonary function tests** (11)					X	X	X		X		
Hematology/Chemistry**(fasted)		X	X	X	X	X	X		X		
Urinalysis			X		X	X			X		
Viral serology									X		
Pregnancy test*/** (12)		X	X	X	X	X	X (12)		X		
Serum sample vaccination* (13)									X		

PK sampling for ponesimod*				X				X (14)		
Teriflunomide plasma concentration								X (23)		
Accelerated elimination procedure				X	X (15)					
Accelerated elimination procedure compliance review					X	X (24)				
Study drug dispensing/accountability (16)	X	X	X	X			X	X	X	X
AEs/SAEs* (17)	X	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) 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, and 102 (+/− 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 relapse assessment questionnaire [see Appendix 17].
(2) The symptoms scale (with a 24-h recall) will be completed for 7 consecutive days (the day of the visit and the 6 days after the visit).
(3) Health care resource utilization data, number of intensive care unit admission for MS relapses and emergency medical services facility visits for MS.
(4) Only for subjects-participating in the patient preference sub-study. The Multiple Sclerosis Patient Preference Questionnaire will be completed at home during follow-up period (before Visit 15 [FU1]).
(5) In case of premature study drug discontinuation, the chest X-ray at EOT does not need to be performed if the EOT visit occurs within less than 24 weeks of the pre-randomization chest X-ray.
(6) Brain MRI to be performed at any time an opportunistic infection in the CNS is suspected. In addition, non-conventional MRI techniques (MTR and DIR) will be performed at selected sites only. Note: in case of premature study treatment discontinuation, the MRI assessment at EOT does not need to be performed if the EOT visit occurs within less than 4 weeks of the MRI assessment at Visit 10 (Week 60).
(7) Dermatological examination to be performed by a dermatologist.
(8) SBP/DBP: Pre-dose and hourly (+/− 15 min) for at least 4 h post-dose and up to 12 h.
(9) Pre-dose ECGs at all visits (when applicable) except re-initiation visits. At re-initiation, pre-dose and hourly (+/− 15 min) for at least 4 h post-dose ECGs and up to 12 h.
(10) OCT and/or ophthalmological examination to be performed at any visit in the presence of visual symptoms suggestive of macular edema or active uveitis [see Section 5.1.13.7].
(11) PFTs include spirometry to be performed pre-dose in all subjects and DL_{CO} to be performed in a subset of approximately 400 subjects at selected sites only.
(12) Serum pregnancy test at FU2. Urine pregnancy test at all other visits. Urine pregnancy tests (performed at home) on a 4-weekly basis between the visits during the study and continued after last study drug intake on a 4-weekly basis (+/− 4 days) (performed at home) until 6 weeks after the first of two tests showing teriflunomide plasma level < 0.02 mg/L (results of the pregnancy tests to be communicated by telephone call to the principal investigator / treating neurologist). At all visits and telephone calls, the methods of contraception will be reviewed and the contraceptive method form entered in the eCRF must be updated as applicable.
(13) Pre- and post-vaccination sampling for vaccine-specific antibody titers for subjects having received non-live vaccination while on study treatment (sub-study)

(14) When possible, collect PK sample upon experiencing SAE. Preferably, sample will be collected pre-dose, as early as possible after SAE onset, and no later than 7 days after the last dose of study drug.
(15) If the subject was not compliant with the accelerated elimination procedure, the procedure must be repeated or missing intakes completed.
(16) Scheduled study medication dispensing/return procedures may be adapted according to the site practice.
(17) All AEs and SAEs that occur after signing the Informed Consent Form and up to 30 days after study treatment discontinuation must be reported.
(18) The EOT visit will take place at Week 108 (or earlier in case of premature discontinuation of study drug). In all cases, the EOT visit should take place 1 day after the last dose of study drug but no later than 7 days after the last dose of study drug.
(19) 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.
(20) Only if no 12-lead ECG is performed at this visit.
(21) Only at unscheduled visits when the subject meets with the treating neurologist (but not at other unscheduled visits (e.g., conducted for repeat ALT or AST testing, repeat PFT testing,…).
(22) For subjects not continuing in the AC-058B303 extension study, FU2 will be performed 30 to 37 days after last study drug intake. For subjects continuing in the AC-058B303 extension study, an abbreviated FU2 will be performed 23 to 37days after last study drug intake, if needed for compliance reasons. The abbreviated FU2 should include: Accelerated elimination procedure compliance review, AEs/SAEs, relapse, concomitant medications
(23) The testing of teriflunomide plasma concentration may be conducted for women of childbearing potential and fertile male subjects, if needed to confirm that contraception may be discontinued. Teriflunomide plasma concentration can also be assessed for any subjects not entering the extension study if deemed necessary for the subject's safety, at the investigator's discretion. Testing must not be conducted earlier than i) 20 weeks after last drug intake if the subject's compliance with the accelerated elimination procedure has been assessed as sufficient [see Section 5.1.14.2]; ii) 35 weeks (i.e., 8 months) after last drug intake or EOS, whichever is last, if the subject's compliance with the accelerated elimination procedure has not been assessed as sufficient.
(24) Only if the accelerated elimination procedure has been repeated or missing intake was completed after FU1.

AE = adverse event; ALT = Alanine aminotransferase; AST = aspartate aminotransferase; CGI-C = Clinician's Global Impression of Change of patient's relapsing MS; CNS = central nervous system; DBP = diastolic blood pressure; DL_{CO} = diffusing capacity for the lungs measured using carbon monoxide; DIR = double inversion recovery; eC-SSRS = electronic self-rated version of the Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; eCRF = electronic case report form; EDSS = Expanded Disability Status Scale; EOS = End-of-Study; EOT = End-of-Treatment; FS = functional system; FSIQ-RMS = Fatigue Symptom and Impact Questionnaire-Relapsing Multiple Sclerosis; FU1 = follow-up visit 1; FU2 = follow-up visit 2; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSFC = Multiple Sclerosis Functional Composite; MTR = magnetization transfer ratio; OCT = optical coherence tomography; PFT = pulmonary function test; PGI-S = Patient's Global Impression of Severity of Fatigue; PI = principal investigator; PK = pharmacokinetics; SAE = serious adverse event; SBP = systolic blood pressure; SDMT = Symbol Digit Modalities Test; WPAI:MS = Work Productivity and Activity Impairment Index: Multiple Sclerosis.

Table 3 Visit and assessment schedule (Part 3)

Periods	Name	POST-TREATMENT OBSERVATION PERIOD (PTOP) (to be performed after EOT)		
	Duration	Up to 108 Weeks		
Visits	Number	6A, 8A, 9A, 11A,13A	7A, 12A	10A, 14A
	Name	W12A, W36A, W48A, W72A, W96A	W24A, W84A	W60A, W108A
	Time	Week 12-36-48-72-96	Week 24 and 84	Week 60 and 108
	Visit window	±7 days	±7 days	±7 days
EDSS/ FS*		X	X	X
Relapse*(1)		X(1)<----------->X(1)		
MRI*				X
FSIQ-RMS** (2), PGI-S**, CGI-C *		X (only Week12)	X	X
Concomitant medications*		X	X	X
Physical examination*				X
Dermatological examination* (3)				X
SBP/DBP*		X	X	X
12-lead ECG **				X
Body temperature*		X	X	X
Pulmonary function tests** (4)				X (Week 108 only)
Hematology/Chemistry** (fasted)			X	X
Urinalysis*			X	X
Pregnancy test*/** (5)		X	X	X
AEs/SAEs *		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). If the first PTOP visit windows overlaps with FU1 or FU2 visits, visits and assessments can be combined.
(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 worsening neurological symptoms. In addition, the site will contact the subject 6 weeks (+/−7 days) after each of 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. 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 relapse assessment questionnaire [see Appendix 17].
(2) The symptoms scale (with a 24-h recall) will be completed for 7 consecutive days (the day of the visit and the 6 days after the visit, except for Visit 14A, see Section 8.3.2).

(3) Dermatological examination to be performed by a dermatologist.
(4) PFTs include spirometry to be performed in all subjects and DL_{CO} to be performed in a subset of approximately 400 subjects at selected sites only.
(5) Urine pregnancy test at all visits and performed at home on a 4-weekly basis between the visits until 6 weeks after the first of two tests showing teriflunomide plasma level < 0.02 mg/L (results of the pregnancy tests to be communicated by telephone call to the principal investigator / treating neurologist).

AE = adverse event; DBP = diastolic blood pressure; DL_{CO} = diffusing capacity for the lungs measured using carbon monoxide; ECG = electrocardiogram; eCRF = electronic case report form; EDSS = Expanded Disability Status Scale; EOT = End-of-Treatment; FS = Functional system; FU = follow-up; MRI = Magnetic resonance imaging; PI = principal investigator; PTOP = post-treatment observation period; SAE = serious adverse event; SBP = systolic blood pressure.

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 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 2014a, 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]. The Committee proposed to eliminate the PRMS category since it could reflect misclassification of other MS categories (e.g., SPMS without recognition of the initial relapsing course), but the term continued to be used by clinicians and in clinical trials. In 2011, the NMSS Advisory Committee, also sponsored by the European Committee for Treatment and Research in MS, proposed to define the MS course by adding modifiers based on disease activity and progression [Lublin 2014]. A patient with RRMS who had a new 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, Gd+ activity, or new or unequivocally enlarging T2 lesions during the assessment period. Inclusion of activity as a modifier also allows elimination of the PRMS category. 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) and 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 independent 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 has been 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, clinically isolated syndrome 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 2014a]. 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 10 disease-modifying therapies (DMTs) approved in at least one country for the treatment of MS.

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 mcg i.m. once weekly (Avonex®)
- IFN β-1a 22 or 44 mcg s.c. 3 times weekly (Rebif®)
- IFN β-1b 250 mcg s.c. every other day (Betaferon®, Extavia®)
- Pegylated IFN β-1a 125 mcg subcutaneously every 2 weeks (Plegridy®)
- Glatiramer acetate 20 mg s.c. once a day (o.d.) or 40 mg subcutaneously 3 times weekly (Copaxone®)
- Glatiramer acetate 20 mg s.c. 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®)

Additional injectable drugs are currently in late-stage development for the treatment of RMS, including ocrelizumab, daclizumab, and 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®)
- Dimethyl fumarate (BG-12) gastro-resistant hard capsules 120/240 mg twice daily (Tecfidera®)
- Cladribine 40 to 100 mg orally per treatment week (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/ozanimod. Siponimod, another $S1P_1$ receptor modulator, is currently being developed for the treatment of SPMS.

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 $S1P_3$, $S1P_4$, and $S1P_5$ [Brinkmann 2007, Brinkmann 2010].

1.3 Ponesimod

Ponesimod, an iminothiazolidinone derivative, is an orally active, selective modulator of the $S1P_1$ 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 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 main targets for ponesimod-related toxicity after treatment of up to 4 weeks were the lung (all species) and the nervous system (clinical signs in dogs). After 13, 26 and 52 weeks of treatment, the heart and skin were identified as additional target organs in dogs. No-observed-adverse-effect levels were established for all toxicologically relevant targets in rats, mice, and dogs after 4, 13, 26, and 52 weeks of treatment, and resulting safety margins are considered acceptable.
- 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].

1.3.2 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 4 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 may also be investigated in subjects suffering from other lymphocyte-mediated diseases.

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 h 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 gender 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 1 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 like aggregate Annualized Relapse Rate (ARR) or time to first confirmed relapse. Treatment with ponesimod was associated with a reduction in the aggregate 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 an increase 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 a 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 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.

The results from an interim analysis of study AC-058B201/B202 with cut-off date of 31 October 2014 have shown sustained low rates of MRI and clinical disease activity with dose-dependent effects on relapse rate and disability accumulation. The model-adjusted ARR observed with ponesimod 20 mg was approximately 0.170, 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 decreasing risk of 6-month confirmed disability accumulation (CDA) and lower rates of EDSS worsening observed with increasing doses of ponesimod.

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 h 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.

Difficulty in inspiration (dyspnea) and related pulmonary function test (PFT) changes have also been detected in humans. Mild transient dyspnea/cough was noted frequently 2–6 h 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. Data from an interim analysis of the long-term extension study AC-058B201/B202 with a cut-off date of 31 October 2013 showed that dose-dependent decrease in FEV_1 remained stable in patients treated with ponesimod for a median of more than 3 years and remains reversible over the long term.

Elevations of aspartate transaminase (AST) and/or alanine aminotransferase (ALT) without any bilirubin increase have been noted with ponesimod; they have been reversible upon 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 Comparator drug

Teriflunomide has been chosen as the active comparator. Teriflunomide is indicated for the treatment of patients with relapsing forms of MS [Aubagio® USPI, Aubagio® SmPC].

Teriflunomide is a selective and reversible inhibitor of mitochondrial dihydroorotate dehydrogenase, an enzyme that is necessary for pyrimidine synthesis. The inhibition of pyrimidine synthesis results in a cytostatic effect on peripheral T- and B-lymphocytes, decreasing the number of activated lymphocytes that enter the CNS, thus decreasing the inflammatory response known to be present in the CNS in patients with MS. Teriflunomide is the active metabolite of leflunomide, marketed as ARAVA® for the treatment of rheumatoid arthritis since 1998.

Teriflunomide is administered orally o.d. at the doses of 7 and 14 mg in the USA and 14 mg in EU and other countries such as Australia. The plasma levels of teriflunomide circulating

at the dose of teriflunomide of 14 mg/day are comparable to the circulating levels of teriflunomide when leflunomide is given at the recommended dose of 20 mg/day.

Efficacy of Aubagio® was established in two pivotal placebo-controlled trials that enrolled 2257 patients with RMS (TOWER and TEMSO) [Confavreux 2014b, O'Connor 2011]. In the TEMSO study, teriflunomide reduced the ARR (0.54 for placebo vs 0.37 for teriflunomide at either 7 or 14 mg), with relative risk reductions of 31.2% and 31.5%, respectively ($p < 0.001$ for both comparisons with placebo). Consistent results were obtained in the TOWER study. Compared to placebo, only teriflunomide at the dose of 14 mg significantly reduced the risk of confirmed accumulation of disability in TEMSO (HR 0.70 [95% CI (0.51–0.97)]) and in TOWER (HR 0.68 [95% CI (0.47-1.00)]). Both doses were also shown consistently superior to placebo on a range of MRI endpoints in the TEMSO study.

In the clinical studies with teriflunomide in patients with RRMS, the incidence of serious adverse events (SAEs) was similar among the teriflunomide group and placebo-treated patients. The most common adverse events (AEs) associated with teriflunomide in RRMS patients included increased ALT levels, alopecia, diarrhea, influenza, nausea and paresthesia. Severe liver injury including fatal liver failure has been reported in patients treated with leflunomide. As a similar risk would be expected for teriflunomide, it is recommended to monitor ALT levels at least bi-weekly for 6 months after starting treatment; teriflunomide is contraindicated in patients with severe hepatic impairment and patients with pre-existing acute or chronic liver disease should not be treated with teriflunomide.

Based on animal data, teriflunomide may cause major birth defects if used during pregnancy. Pregnancy must be excluded before starting treatment with teriflunomide, and teriflunomide is contraindicated in pregnant women or WOCB who are not using reliable methods of contraception.

Teriflunomide is eliminated slowly from the plasma. Without an accelerated elimination procedure, it takes on average 8 months from discontinuing the drug to reach plasma concentrations less than 0.02 mg/L, although because of individual variations in drug clearance it may take as long as 2 years. An accelerated elimination procedure must be used after study drug discontinuation [see Section 5.1.14].

More detailed information can be found in the prescribing information [Aubagio® USPI, Aubagio® SmPC].

Demonstration of superiority over teriflunomide in terms of ARR is clinically relevant, as it would provide evidence of significant benefit of the new investigational drug compared to a world-wide approved, effective, first-line oral therapy.

1.4 Purpose and rationale of the study

The central role of S1P in lymphocyte trafficking and the ability of an S1P receptor modulator to reduce the availability of circulating lymphocytes is a promising therapeutic approach for autoimmune diseases [see Section 1.2]. The non-selective S1P receptor modulator fingolimod has been proven effective in the treatment of MS, leading to an approval for the treatment of RMS.

The Phase 2 dose-finding study AC-058B201 demonstrated dose-dependent effects of the selective and orally active $S1P_1$ receptor modulator ponesimod on relevant MRI variables, and on the lymphocyte count reduction [see Section 1.3.2.2]. Altogether, the above elements support further development of ponesimod for the treatment of RMS and suggest, if this profile is confirmed in this study, that ponesimod may offer a new type of selective immunomodulation for the treatment of RMS.

This Phase 3 study is considered pivotal for the registration of ponesimod in the indication of relapsing forms of MS. The purpose of this study is to confirm the efficacy seen in the Phase 2 studies and to further evaluate the safety and tolerability of ponesimod in subjects with RMS. Ponesimod will be compared to the active comparator teriflunomide for its ability to reduce relapse rate, slow disability accumulation and reduce brain volume loss as detected by MRI during an overall treatment period of 108 weeks.

The present study was designed in accordance with the 2006 CHMP guidance for product development in MS [EMA 2006] and its draft revision, adopted by the CHMP for release for public consultation [EMA 2012].

2 STUDY OBJECTIVES

2.1 Primary objective(s)

The primary objective of the study is to determine whether ponesimod is more efficacious than teriflunomide in terms of reducing relapses in subjects with RMS.

2.2 Secondary objectives

- To assess the effect of ponesimod on disability accumulation and on other aspects of MS disease control;
- To assess the safety and tolerability of ponesimod in subjects with RMS.

3 OVERALL STUDY DESIGN AND PLAN

This is a prospective, multicenter, randomized, double-blind, active-controlled, parallel-group, Phase 3, superiority study. The study is designed to compare the efficacy, safety, and tolerability of ponesimod 20 mg vs teriflunomide 14 mg in adult subjects with relapsing forms of MS.

Approximately 1100 subjects will be randomized in two groups in a 1:1 ratio to receive ponesimod 20 mg (approximately 550 subjects) or teriflunomide 14 mg (approximately 550 subjects). Randomization will be stratified by use of MS disease-modifying treatment in the last two years prior to randomization (yes, no) and by baseline EDSS score (EDSS ≤ 3.5, EDSS > 3.5).

The study will be conducted at approximately 200 sites in 25 countries in North America, South America, Eastern and Western Europe, and Pacific. Randomization will proceed until the required number of subjects has been reached. Any eligible subject in screening at the time of randomization of the 1100th subject will be recruited. It will be competitive across participating sites. The trial will include up to a maximum of 15% of subjects with SPMS. Screening of the subjects with SPMS will be permitted until a maximum of 165 subjects with SPMS have been randomized. Any eligible subject with SPMS in screening at the time of randomization of the 165th subject with SPMS will be recruited. It is permitted to re-screen subjects once [see Section 8]. Actelion may wish to replace sites with no subject enrollment.

Subjects who have completed treatment until Week 108 will be proposed to enroll in an extension study with ponesimod, conducted under a separate protocol. Those who discontinue study drug prematurely will not be eligible for the extension study.

3.1 Study periods

The organization of the different study periods is shown in Figure 1, Figure 2, and Figure 3.

The study consists of the following periods:

3.1.1 Pre-randomization period

This period starts 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) and Visit 2 (Baseline).

3.1.2 Treatment period

This period consists of a double-blind treatment period from Day 1 to Week 108. This period starts on the day of randomization immediately after the 1st dose of study drug intake (Visit 3–Day 1 of the study) and continues until the premature discontinuation of study drug or the scheduled End-of-Treatment (EOT) at Week 108.

EOT visit: The EOT visit will take place at Week 108 or earlier in case of premature discontinuation of study drug. In all cases, the EOT visit should preferably take place 1 day, and not later than 7 days, after the last dose of study drug.

3.1.3 Post-treatment period and End-of-Study

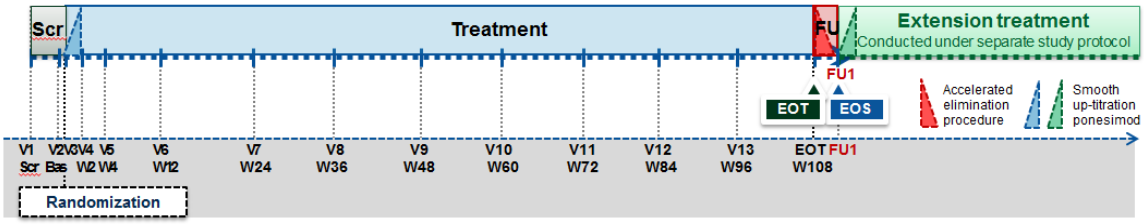
This period starts immediately after the last dose of study drug and ends when End-of-Study (EOS) visit has been completed. It comprises the post-treatment safety follow-up (FU) period and if applicable, the post-treatment observation period (PTOP).

3.1.3.1 Post-treatment safety follow-up period

All subjects will enter the safety FU period:

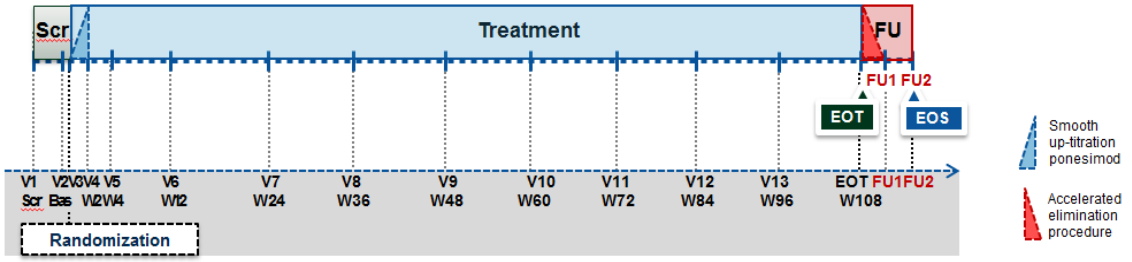
- For subjects who enter the extension study, the safety FU period lasts for 14–37 days after the last dose of study drug and includes a safety FU visit (FU1) 14–22 days after the last dose of study drug. If compliance to the teriflunomide accelerated elimination procedure is confirmed at FU1, the subjects will then be enrolled in the extension study. However, if compliance to the teriflunomide accelerated elimination procedure is not confirmed at FU1, the procedure may be repeated or missing intakes completed. In such cases an abbreviated FU2 will be conducted 23–37 days after the last dose of study drug. Provided sufficient compliance with the accelerated elimination procedure of teriflunomide [see Section 5.1.14.2] is documented, subjects will then be enrolled in the extension study.

Figure 1 Subjects who enter the extension study



- For subjects who do not enter the extension study, the safety FU period lasts for 30 days after the last dose of study drug and includes two safety FU visits (FU1, FU2) at 14–22 and 30–37 days after the last dose of study drug, respectively.

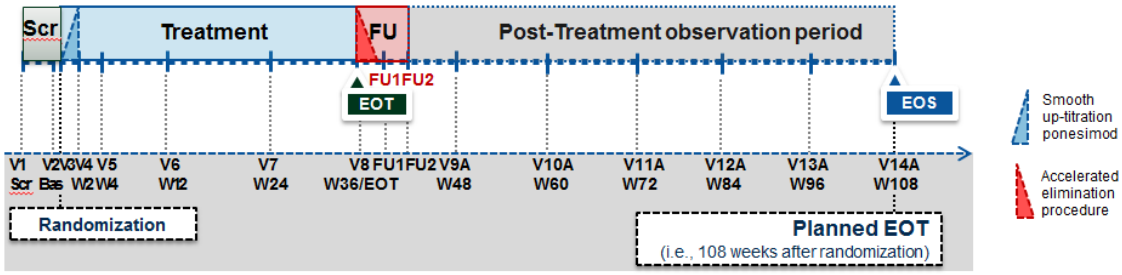
Figure 2 Subjects who complete the 108-week treatment but do not enter the extension study



3.1.3.2 Post-treatment observation period

Subjects who prematurely discontinue study treatment will enter the PTOP, which lasts from the last dose of study drug until 108 weeks after randomization (i.e., planned EOT period). The PTOP includes an abbreviated schedule of assessments at the time of the originally scheduled 12-weekly visits. The safety FU period lasts for 30 days after the last dose of study drug and includes two safety FU visits (FU1, FU2).

Figure 3 Subjects who prematurely discontinue study drug and enter the PTOP



3.1.4 End-of-Study

For an individual subject, EOS is reached when treatment, safety FU, and, if applicable, PTOP have been completed:

- For subjects who completed the 108-week treatment period and enter the extension study, the EOS visit corresponds to FU visit (FU1) conducted 14–22 days after the last study drug dose or to the abbreviated FU2 visit conducted 23–37 days after the last study drug dose.
- For all other subjects, the EOS visit corresponds to the 30-day FU visit (FU2) or to the last visit of PTOP (i.e., Week 108 Visit of the PTOP), whichever is last.

EOS at study level occurs at the time all subjects have completed their EOS visits, as described above and schematically presented in Figure 1, Figure 2, and Figure 3.

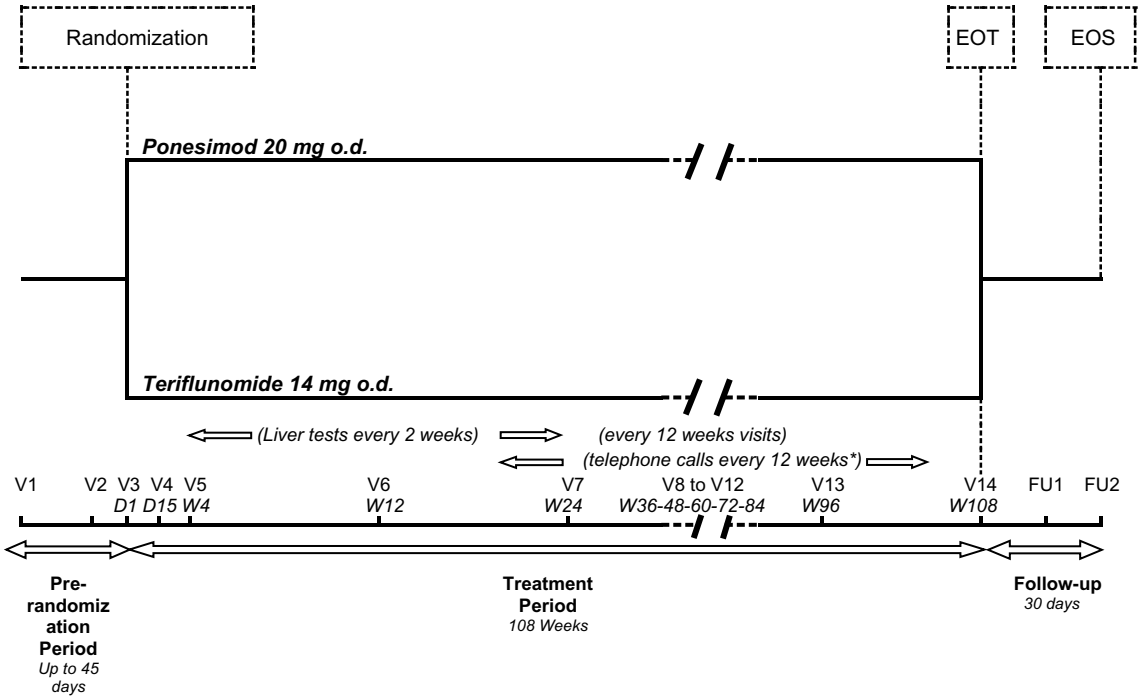
3.1.5 Study duration

For an individual subject, the maximum duration of the study will be approximately 118 weeks (2.2 years).

The overall duration of the study is expected to be 171 weeks (3.3 years). The actual overall study duration or subjects' recruitment period may vary.

The overall study design is shown in Figure 4.

Figure 4 AC-058B301 Study design



*Telephone calls in-between Visits 6 and Visit 14 (at Weeks 18, 30, 42, 54, 66, 78, 90, and 102). See Section 8.2.6. D = day; EOS = End-of-Study; EOT = End-of-Treatment; FU = follow-up; M = month; V = visit; W = week.

3.1.6 Sub-studies

Several sub-studies designed to evaluate specific safety and/or efficacy parameters will be conducted in a subset of sites and subjects.

3.1.6.1 Pulmonary function monitoring (DL_{CO})

A sub-study assessing the diffusing capacity of the lungs, measured using carbon monoxide (DL_{CO}), will be conducted in approximately 400 subjects at selected sites with appropriate equipment and experience. All subjects recruited at the selected sites will be proposed to participate in the sub-study.

3.1.6.2 Non-conventional MRI techniques

Magnetization transfer ratio (MTR) has better histological specificity than conventional T2-weighted MRI. MTR seems to be sensitive to disease-related changes over time and to treatment effects on normal appearing white matter (NAWM) and on focal lesions. Double inversion recovery (DIR) is a method that allows better visualization of grey matter lesions than conventional T2-weighted imaging. Both methods can be applied to multicenter settings.

A sub-study using these non-conventional MRI techniques will be implemented in approximately 300 subjects recruited at selected sites with appropriate equipment and experience. All subjects recruited at the selected sites will be proposed to participate in the sub-study.

3.1.6.3 Patient Preferences

The overall purpose of this sub-study is to capture patient preferences for selected treatment outcomes for use as an additional input to healthcare decisions. An increased understanding of individual values and preferences is the basis for shared decision-making, which in turn encourages patient compliance and health outcomes [Bowling 2001, Coyle 2001]. Patient preferences will be captured using a multi-criteria analysis model, Measuring Attractiveness by a Categorical Based Evaluation Technique (MACBETH). MACBETH uses a non-numerical questioning procedure to collect preference data. The responses are converted, by mathematical programming, to quantitative scores, thus allowing the construction of value function curves and the calculation of weights [Bana E Costa 1999, Fasolo 2014].

The sub-study will include a subgroup of approximately 360 patients who will be asked to complete the MS Patient Preference Questionnaire developed by Actelion [Appendix 14] at three different timepoints (twice during pre-randomization period [after Visits 1 and 2 (Screening, Baseline)], and once during the follow-up period [Visit 15, FU1]). The questionnaire will be administered in electronic format and will assess the patient preferences for nine outcomes including frequency of relapses, worsening of disability and specific adverse outcomes.

This sub-study has the following objectives: 1) To describe the value judgments of MS subjects within a clinical trial using the MACBETH methodology; 2) To assess the stability of MS subjects' value judgments over two timepoints; 3) To describe the impact of

treatment on the preferences of MS subjects; 4) To describe the relationship between demographics, disease characteristics, previous medical history and elicited preferences among MS subjects at all timepoints; 5) To construct a treatment-decision model using the elicited preference data; and 6) To assess the comprehension and ease of use of the preference elicitation instrument.

3.1.6.4 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 non-live vaccination while on study treatment.

3.1.7 Extension study AC-058B303 (separate protocol)

Subjects who complete the 108-week treatment period will be proposed to enroll in a non-comparative extension study with ponesimod treatment conducted under a separate protocol.

3.2 Study design rationale

This Phase 3 study is intended as pivotal for the registration of ponesimod for the treatment of relapsing forms of MS. This study is designed to assess superiority of ponesimod vs teriflunomide in reducing ARR in subjects with RMS. The design of this active-controlled study meets the requirements laid out by the relevant CHMP guideline [EMA 2006].

During the study, several decisions and assessments will have to be performed. In order to limit the considerable risk of bias, a double-blind design is warranted.

With the availability of efficacious disease-modifying treatments, long-term placebo-controlled trials have become increasingly difficult to conduct in RMS. In order to evaluate the benefit/risk ratio of a new treatment, active-control parallel-group trials comparing the new treatment to an already approved treatment are recommended. In this context, a superiority trial remains the most reliable means of efficacy demonstration.

Given the low ARR observed in RMS, a trial involving a large number of subjects treated for a 108-week duration is considered a minimum condition to observe a sufficient proportion of subjects experiencing relapses and allow for the demonstration of efficacy on ARR.

The size and scope of the resulting safety database for all subjects treated with ponesimod at the time of marketing authorization application is anticipated to meet the requirements of the ICH [ICH E1A 1995] and CHMP guidelines [EMA 2006; EMA 2012].

3.3 Site personnel and their roles

In order to maintain the blind [see Section 5.1.5] 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 pulmonologist (only at sites participating in the DL_{CO} sub-study)
- A dermatologist.

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

3.3.1 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.

3.3.2 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 Section 7.2.2 and Section 10.1.6], monitoring of safety including recording and treating of AEs (with the exception of 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 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 3.3.4]. The treating neurologist will not perform EDSS / FS assessment and will not alter the EDSS or FS scores obtained by the efficacy assessor. The treating neurologist will not have access to MRI 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 and for explaining to the fertile male participants the need for using condoms and the need for their female partners of childbearing potential to use reliable methods of contraception 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.

3.3.3 Efficacy assessor

The efficacy assessor is a physician with clinical experience in the medical treatment and care of patients with MS. She/he will perform the detailed neurological examination for obtaining the EDSS / Functional system (FS) scores using the "Neurostatus" scoring documents [see Appendix 2] 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 documents 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 physician 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 to ensure consistency in EDSS/FS scoring with the primary efficacy assessor.

The efficacy assessor may be in charge of administering the MSFC test.

3.3.4 First-dose administrator

The first-dose administrator must be a physician who is experienced in making health care decisions based on ECG interpretation reports provided in a timely manner by the central ECG laboratory, and experienced in the evaluation of BP and signs or symptoms. If the first-dose administrator is adequately trained and experienced in cardiology, she/he will make health care decisions solely based on her/his own interpretation of the ECG (i.e., in the case where the reading of the ECGs by the central ECG laboratory is not provided to the first-dose administrator in a timely manner).

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 will be required. This includes the close monitoring of the subject during the first 4 h and up to 12 h 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 physician. She/he will independently assess eligibility for discharge or continued subject management on Visit 3 and on visits for re-initiation of study drug when post-dose monitoring will be required [see Sections 5.1.9, 5.1.10, and 5.1.11]. 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 ECG assessments requested by the protocol during the study. Depending on the setting at the site, the study drug administration at Visit 3 (Day 1) or at visits for re-initiation of study drug when post-dose monitoring is required, may be performed under the supervision of the treating neurologist. In this instance, the subject must rapidly be transferred under first-dose administrator supervision for close 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 of the subject 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. All other significant findings on Day 1 and on the first day of re-initiation of study drug when post-dose monitoring is required that are not resolved at the time of discharge of the subject from the cardiac monitoring or with an onset on any other day, which in view of the first-dose administrator meet the definition of AEs, must be reported to the principal investigator / treating neurologist, who will record these events on the AE page of the eCRF.

The 3-h 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 these 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.

Any AEs with onset on Day 1 or on the first day of study drug re-initiation of study drug 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. Similarly, any SAEs with onset on Day 1 or on the first day of study drug re-initiation of study drug when post-dose monitoring is required must be reported by the first-dose administrator to the principal investigator / treating neurologist.

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 subject, 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 3.3.5]).

In case the first-dose administrator is responsible for conducting **all** BP and ECG assessments requested by the protocol during the study, he/she will report to the principal investigator / treating neurologist any significant findings in 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.

3.3.5 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 3.3.4])
- MS Functional Composite (MSFC) score
- Symbol Digit Modalities Test (SDMT)
- Patient-Reported Outcome (PRO) instruments
- Fatigue Symptom and Impact Questionnaire-RMS (FSIQ-RMS)
- 36-Item Short Form Health Survey version 2 (SF-36v2™)
- MS Patient Preference Questionnaire (if applicable)
- Patient's Global Impression of Severity (PGI-S) of Fatigue
- 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.

3.3.6 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.

3.3.7 Local neuroradiologist/radiologist

The local neuroradiologist 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 neuroradiologist, 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 neuroradiologist will conduct further examination, as per local standard practice, to rule out or confirm the diagnosis. She/he may support the principal investigator in making a decision on eligibility of the subject prior to randomization by reviewing historical MRI used to assess the eligibility of the subject in the study (i.e., active disease evidenced by one or more Gd+ lesion[s] of the brain on an MRI performed within 6 months prior to randomization).

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 screening can be used; if available, there is no need to repeat CXR at

Screening). At 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 may review MRI images and another local radiologist may review CXR images.

3.3.8 Ophthalmologist

The ophthalmologist will review and interpret the ophthalmological examinations and optical coherence tomography (OCT) assessments as scheduled in the study protocol [see Section 7.3.9 and 7.3.10]. 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.

3.3.9 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].

3.3.10 Pulmonologist

At sites participating in the DL_{CO} sub-study, a pulmonologist or a physician adequately trained in respiratory medicine will review DL_{CO} results. If clinically significant alterations in DL_{CO} variables indicating a pulmonary condition that could result in increased risk for the subject are observed, she/he may be prematurely discontinued from the study drug at the discretion of the principal investigator / treating neurologist. Significant findings, which in view of the pulmonologist 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 pulmonologist will conduct further examination, as per local standard practice, to rule out or confirm the diagnosis.

3.3.11 Dermatologist

A dermatologist will perform complete skin examination as scheduled in the study protocol [see Section 7.3.13].

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 rule out or confirm the diagnosis.

3.4 Study committees

3.4.1 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (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 with the highest scientific and ethical standards. The IDMC is also responsible for reviewing the data generated and for recommending on subsequent actions to be taken. These actions may include:

- Recommending modifications to the study protocol to enhance subject's safety.
- Recommending the termination of the study at any time if major concerns arise regarding the safety of ponesimod.

The IDMC is composed of physicians with relevant medical expertise (including a neurologist, a neurovirologist, a neurologist with MRI expertise or a neuroradiologist, a cardiologist, a pulmonologist), 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.

3.4.2 Statistical Analysis Center

A Statistical Analysis Center (SAC), a Contract Research Organization (CRO) 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 SAC.

3.4.3 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. The composition and operation of the OSB are described in the OSB charter.

3.4.4 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 AEs that will be sent for adjudication will be based on a pre-defined list of preferred terms belonging to relevant Standardized MedDRA Queries. For each AE sent for MACE adjudication, the

MACE adjudication board will determine whether the event belongs or not to one of the pre-specified categories including 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). The trial will include up to 15% of subjects with SPMS with superimposed relapses, but no forced randomization is planned.

Subjects must have active disease evidenced by one or more MS attacks within the period of 12 to 1 months prior to baseline EDSS assessment, or by two or more MS attacks within the 24 to 1 months prior to baseline EDSS assessment, or with one or more Gd+ lesion(s) of the brain on an MRI performed within 6 months prior to baseline EDSS assessment. The MRI assessed at Visit 2 (Baseline) may be serving as the qualifying scan. Enrolled subjects must be ambulatory with an EDSS score of up to 5.5 inclusive. The subjects may be treatment-naïve (i.e., no MS disease-modifying therapy received at any time in the past) or previously treated with IFN β-1a, IFN β-1b, glatiramer acetate, dimethyl fumarate, 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. These subjects have generally been less studied and have often not been included in pivotal trials of medications approved for treatment of RMS. For these reasons, it is important to also evaluate the benefit/risk profile of ponesimod in subjects with 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 are widely recognized.

The study will enroll subjects with recent evidence of active disease as determined by clinical or imaging criteria, as these are prognostic factors that identify a patient population in whom effective disease-modifying treatment is particularly indicated.

The study will recruit adult subjects, restricted to subjects between 18 and 55 years of age, as non-MS-specific MRI lesions can appear more frequently in older age. Such lesions and other CNS changes due to aging make the assessment of MS more difficult and may affect the response to treatment, which could result in inconclusive trial results. The age range of the study population will be representative of the general RMS population.

Subjects with an EDSS score 0–5.5 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). The subjects with EDSS above 5.5 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 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. Subjects of reproductive potential are eligible only if the following applies:
   - WOCBP:
     - 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 4-weekly urine pregnancy tests during the study and up to 6 weeks after the first of two tests showing teriflunomide plasma level < 0.02 mg/L;

  - must agree to use reliable methods of contraception from Visit 1 (Screening; see Section 4.5.1) until 6 weeks after the first of two tests showing teriflunomide level < 0.02 mg/L.
- Fertile male subjects participating in the study who are sexually active with WOCBP:
  - must agree to use a condom during the treatment period and for an additional 6 weeks after the first of two tests showing teriflunomide level < 0.02 mg/L.
- Definition of WOCBP, fertile male subjects and the reliable 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 1], with relapsing course from onset (i.e., RRMS, or SPMS with superimposed relapses).
5. Having experienced one or more documented MS attacks with onset within the period of 12 to 1 months prior to baseline EDSS assessment, or two or more documented MS attacks with onset within the period of 24 to 1 months prior to baseline EDSS assessment, or having one or more Gd+ lesion(s) of the brain on an MRI performed within 6 months prior to baseline EDSS assessment (MRI assessed at Visit 2 [Baseline] may be the qualifying scan).
6. Treatment-naïve or previously treated with IFN β-1a, IFN β-1b, glatiramer acetate, natalizumab, or dimethyl fumarate.
7. Ambulatory and with an EDSS score between 0 and 5.5 (inclusive) at Visit 1 (Screening) and Visit 2 (Baseline).
8. Agreeing to use an accelerated elimination procedure for teriflunomide after the last dose of study drug [see Section 5.1.14 for the description of the accelerated elimination procedure].

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.
2. Subjects wishing to parent a child during the study.

MS disease

3. Evidence of a relapse of MS with onset within 30 days prior to baseline EDSS assessment or between baseline EDSS assessment and randomization [see Section 6.1.1].
4. Presenting with a diagnosis of MS with progressive course from onset (i.e., primary progressive MS or progressive relapsing MS).

Treatments

5. Treatment with the following medications within 7 days prior to randomization:
   - IFN β-1a, IFN β-1b, or glatiramer acetate
6. 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 4]
   - Cholestyramine or activated charcoal
7. Treatment with the following medications within 30 days prior to randomization:
   - Adrenocorticotropic hormone (ACTH) or systemic corticosteroids (for any reason)
   - Dimethyl fumarate
   - Vaccination with live vaccines
8. Treatment with the following medications within 90 days prior to randomization:
   - Plasmapheresis, cytapheresis
   - 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)
9. Treatment with the following medications within 180 days prior to randomization:
   - Azathioprine, methotrexate, or cyclophosphamide
   - Natalizumab
   - Other systemic immunosuppressive treatment (e.g., cyclosporine, sirolimus, mycophenolic acid)
   - Non-lymphocyte-depleting experimental biological agents (e.g., daclizumab)
10. Treatment with the following medications within 24 months prior to randomization:
    - Lymphocyte-depleting biological agents such as rituximab or ocrelizumab
    - Cladribine
11. Treatment with the following medications at any time prior to randomization:
    - Alemtuzumab
    - Mitoxantrone, leflunomide, or teriflunomide
    - Fingolimod
    - Ponesimod
    - Other investigational S1P modulators
    - Stem-cell transplantation

Infection and Infection Risk

12. Ongoing known bacterial, viral or fungal infection (with the exception of onychomycosis and dermatomycosis), 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).

13. Congenital or acquired severe immunodeficiency or known human immunodeficiency virus (HIV) infection or positive HIV testing at Visit 1 (Screening).
14. Negative antibody test for varicella-zoster virus at Visit 1 (Screening).
36. 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

15. 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.
16. 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

17. Presence of macular edema.

Cardiovascular

18. 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 ongoing unstable ischemic heart disease
    - Cardiac failure (New York Heart Association 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 symptoms or significant 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 Mobitz Type II 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) or 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 the investigator's judgment

Metabolic

19. Type 1 or 2 diabetes that is poorly controlled according to the investigator's judgment, or diabetes complicated with organ involvement such as nephropathy or retinopathy.

Pulmonary

20. Subjects with a clinically significant pulmonary condition including:
    - Asthma that is insufficiently controlled according to the investigator's 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)
21. 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

22. Any of the following abnormal laboratory values at Visit 1 (Screening) or Visit 2 (Baseline):
    - Hemoglobin (Hb) < 100 g/L
    - White blood cell (WBC) count < 3.5×10^9/L (< 3500/mm^3)
    - Neutrophil count < 1.5×10^9/L (< 1500/mm^3)
    - Lymphocyte count < 0.8×10^9/L (< 800/mm^3)
    - Platelet count < 100×10^9/L (< 100,000/mm^3)

Hepatic

23. Known history of active hepatitis B or C any time prior to randomization or known history of active hepatitis A within 3 years prior to randomization.
24. Presence of chronic liver or biliary disease.
25. Moderate or severe hepatic impairment defined as Child Pugh Score B or C, respectively, based on measurement of total bilirubin, serum albumin, International Normalized Ratio (INR) and as well as on presence/absence and severity of ascites and hepatic encephalopathy [Appendix 15].
26. Any of the following abnormal laboratory values at Visit 1 (Screening) or Visit 2 (Baseline):
    - ALT/SGPT > 2 × the upper limit of normal (ULN)
    - AST/SGOT > 2 × ULN
    - Total bilirubin > 1.5 × ULN (unless in the context of known Gilbert's Syndrome).

Renal

27. Hypoproteinemia (e.g., in case of severe liver disease or nephrotic syndrome) with serum albumin < 3.0 g/dL.
28. Severe renal insufficiency defined as a calculated creatinine clearance < 30 mL/min (Cockroft-Gault) at Visit 1 (Screening) or Visit 2 (Baseline).

Other categories

29. Known history of clinically significant drug or alcohol abuse.
30. Known allergy to any of the ponesimod formulation excipients.
31. Known allergy to any of the Aubagio® formulation excipients.
32. Known hereditary problems of galactose intolerance (e.g., Lapp lactase deficiency, glucose-galactose malabsorption).
33. 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.
34. Contraindications for MRI such as:
    - Pacemaker, any 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
    - Known allergy to any gadolinium (Gd)-containing contrast agent
    - Claustrophobia if its nature or severity is prohibitive for performing MRI according to the investigator's judgment
35. Subjects unlikely to comply with protocol, e.g., uncooperative attitude, inability to return for FU 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 Subjects of reproductive potential

WOCBP and fertile male subjects participating in the study must agree that they will take means to reduce reproductive risk as defined in the following sections.

4.5.1 Women of childbearing potential

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

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

WOCBP participating in the study must agree to use one of the following reliable methods of contraception from the Visit 1 (Screening) until 6 weeks after the first of two consecutive tests showing teriflunomide plasma level < 0.02 mg/L:

- 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 or intrauterine devices. If a hormonal contraceptive is chosen from this group,

it must be taken for at least 30 days prior to randomization. Non hormonal methods of contraception (e.g., intrauterine device) should be in place no later than Visit 2 (Baseline).

- 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.

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 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. At all visits and 4-weekly telephone calls the methods of contraception will be reviewed and the contraceptive method form entered in the eCRF must be updated as applicable.

4.5.2 Fertile male subject

A fertile male is defined as physiologically capable of conceiving an offspring.

Since teriflunomide is detected in semen [Aubagio® USPI, Aubagio® SmPC], fertile male subjects participating in the study who are sexually active with WOCBP must agree to use a condom during the treatment period and for up to 6 weeks after the first of two tests showing teriflunomide plasma level < 0.02 mg/L and agree not to father a child during this period. The female partners of the fertile male subjects, if WOCBP, will need to use effective methods of contraception [Aubagio® USPI, Aubagio® SmPC], as assessed by the investigator during the same period.

4.6 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)
- Cardiac, cardiovascular, pulmonary, liver, renal, eye disorder, and skin conditions, peripheral edema, serious infections leading to hospitalization, and malignant tumors at any time prior to the study

- Medically significant new acute medical conditions in the past 24 months prior to the study (in the opinion of the investigator)
- Smoking status at the time of entry in the study.

Previous and concomitant therapies at Baseline, as defined in Section 5.2, will be recorded in the eCRF.

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

- Date of first MS symptoms
- Date of MS diagnosis
- MS type (e.g., RRMS, SPMS)
- Complication or 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 and resolution date, and treatment of these relapses (corticosteroids, ACTH, plasmapheresis etc.) will also 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. The start date, end date, dose, route, frequency, and reason for discontinuation will be recorded in the eCRF.

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).

During an initial phase of the study, the study drugs in the up-titration period will be administered in a double-dummy fashion. Ponesimod (or matching placebo) will be presented as tablet, and teriflunomide 14 mg (or matching placebo) will be presented as capsule (i.e., daily administration of one tablet and one capsule). At a later phase, the

double-dummy material (tablet and capsule) will be replaced by the daily administration of one capsule containing either ponesimod or teriflunomide.

In the maintenance period, the study treatment consists of the daily administration of one capsule containing ponesimod 20 mg or teriflunomide 14 mg.

If the subject expresses any concern regarding her/his ability to swallow the medicine, she/he will be shown an example of a capsule to be used in the study and will be given the option to perform a swallowing test with a placebo capsule at Visit 2 (Baseline) in order to test future compliance with study drug intake requirements. The test is to be done under the supervision of the site personnel.

5.1.1 Investigational treatment: 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. The 20-mg tablet is over-encapsulated. During an initial phase of the study, one tablet of ponesimod 2, 3, 4, 5, 6, 7, 8, 9, or 10 mg (or matching placebo) will be taken orally o.d. during the up-titration period (Day 1 to 14). The matching placebos for the doses of 2, 3, 4, 5, 6, 7, 8, 9, and 10 mg are supplied as identical tablets, formulated with the same excipients but without the active ingredient, ponesimod. At a later phase, once the development of the over-encapsulated forms of the ponesimod tablets for the up-titration is completed, one capsule of 2, 3, 4, 5, 6, 7, 8, 9, and 10 mg ponesimod (or matching teriflunomide 14 mg) will be taken orally o.d. during the up-titration period. During the maintenance period, one capsule of ponesimod 20 mg (or matching teriflunomide 14 mg) will be taken orally o.d.

Based on the available data and considering the currently available therapeutic options, ponesimod 20 mg displays the optimal benefit-risk balance for further development in RMS.

Lower doses of ponesimod are unlikely to provide an adequate level of disease control and do 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 3 years of treatment. While less efficacious, 10 mg showed similar rates of AEs and discontinuations when compared to 20 mg [see Sections 1.3.2.3 and 1.3.2.4].

Doses higher than 20 mg were associated with decreased tolerability; there were increased discontinuation rates with 40 mg mainly due to higher pulmonary function effects and increased incidence of liver enzyme elevations. By contrast, there was a similar or small incremental effect of 40 mg compared to 20 mg on lymphocytes, MRI brain inflammatory activity, and clinical disease activity [see Sections 1.3.2.3 and 1.3.2.4].

5.1.2 Comparator and matching placebo: description and rationale

Teriflunomide is supplied for this study as film-coated tablets as the commercially available Aubagio® tablets. Each tablet contains 14 mg of teriflunomide and excipients. Teriflunomide tablets are over-encapsulated. The study treatments of the up-titration period are administered in a double-dummy fashion, one capsule of teriflunomide or matching placebo will be taken orally o.d. during up-titration (Days 1 to 14). Matching placebo capsules will contain only a filling excipient.

In the maintenance period, study treatment always consists of the daily oral administration of one capsule containing teriflunomide or ponesimod (i.e., no double-dummy). The dose and regimen of teriflunomide are in accordance with the product labeling of Aubagio® [Aubagio® USPI, Aubagio® SmPC]. Aubagio® is manufactured by Sanofi.

Two dosage forms of Aubagio®, 7 mg and 14 mg, have been approved in US, while only 14 mg has been approved in the EU and other countries such as Australia. The reduction in relapse rates observed in the Phase 3 studies were comparable between the two doses, but the 7 mg dose has failed to demonstrate an effect on accumulation of disability. Teriflunomide 14 mg appears to be an appropriate comparator for ponesimod 20 mg. Demonstration of superiority over teriflunomide 14 mg in terms of ARR is clinically relevant, as it would provide evidence of significant benefit of the new investigational drug compared to a world-wide approved, effective, first-line oral therapy that has been shown to reduce relapse rate and accumulation of disability.

5.1.3 Study treatment administration

5.1.3.1 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. 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].

In order to keep the blind of the study, subjects randomized to teriflunomide will undergo a mock up-titration.

Table 4 Dosing scheme

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

* = Visit 4 is to take place at Day 15 ± 1 day. The titration kit will therefore include an additional capsule and tablet (if applicable) for treatment on Day 15 (i.e., dose regimen in the ponesimod group = 10 mg).
EOT = End-of-Treatment; NA = not applicable.

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

One tablet and one capsule (during the double-dummy phase) or one capsule will be taken orally o.d., in the morning, either with breakfast or before or after breakfast, preferably at approximately the same time each day. The capsule and tablet will be swallowed as a whole. When applicable, the tablet and the capsule (during double-dummy phase) will be taken in the shortest time from each other with no predefined order (tablet or capsule can be taken first). The last administration date and time of study drug (tablets and capsules) prior to the study visits and the administration date and time of study drug (tablets and capsules) on the days of visits will be recorded in the eCRF.

5.1.3.2 Maintenance

One capsule of ponesimod or teriflunomide will be taken orally o.d., preferably in the morning, either with breakfast or before or after breakfast. It is preferable that the capsule be taken each day at approximately the same time. The capsule will be swallowed as a whole. The last administration date and time of study drug (capsule) prior to the study visits and the administration date and time of study drug (capsule) on the days of visits will be recorded in the eCRF.

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

5.1.4 Treatment assignment

A total of 1100 eligible subjects will be randomized in a 1:1 ratio to ponesimod 20 mg or teriflunomide 14 mg, stratified by prior use of MS disease-modifying treatment in the last two years prior to randomization (yes, no) and 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 prior to the start of study treatment, the investigator/delegate contacts the interactive response technology (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 of each subject.

The randomization list is generated by an independent CRO (ALMAC Clinical technologies–see contact details in the IRT manual) and kept strictly confidential.

5.1.5 Blinding

5.1.5.1 Study drug material related blinding

This study will be performed in a double-blind fashion. The investigator and study staff, the subjects, the monitors, all Clinical Trial Team (CTT) members at Actelion and CROs involved in the conduct of the study will remain blinded to the treatment until study closure. Actelion staff responsible for clinical trial supply distribution will need to be unblinded to ensure adequate study oversight. These persons will be clearly identified, their unblinding will be documented in the trial master file and they will not take part in any CTT meeting after study set-up has been completed.

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 active comparator, and their respective matching placebos (if applicable, during the initial stage when the up-titration study drug treatments are administered in a double-dummy fashion) are indistinguishable, and all subject's kits will be packaged in the same way.

5.1.5.2 Functional blinding

First-dose effects on HR and AV conduction, lymphocyte counts reduction, and teriflunomide plasma concentration 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, lymphocyte count and teriflunomide plasma concentration assessment are performed and reviewed without potential to introduce a bias:

- The primary endpoint (ARR) and the second key secondary endpoint (disability accumulation) are based on the evaluations of the EDSS and FSs, 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 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 eCRF by the first-dose administrator/delegate. These AEs, the ECG interpretation reports and BP data collected on these days will not be visible to any of the blinded study personnel at the study site. 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 the purpose of keeping the rest of the sponsor's team blinded and assigned to (a) specific individual(s). 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 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 will not be communicated to the sites, sponsor, and CRO 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 and the sponsor. FU monitoring must be provided as described in Sections 5.1.13 and 7.3.14.

- A WBC count > 20×10^9/L or a lymphocyte count > 8.0×10^9/L is recorded by the central laboratory [see Appendix 6]. In this event, an alert containing the total WBC or lymphocyte count result (as applicable) will be sent to the principal investigator and the sponsor.
- WBC and total lymphocyte counts measured at Visit 1 (Screening), 2 (Baseline), and any of the visits in the PTOP (if applicable) will be visible to the treating neurologist. Upon discontinuation of ponesimod, lymphocytes counts return to within normal ranges within one week. Lymphocytes counts are therefore expected to have returned to normal range during the 30 days safety follow up period preceding the start of PTOP.

- Teriflunomide plasma concentration will be assessed after study treatment discontinuation for women of childbearing potential and fertile male subjects not entering the extension study and willing to discontinue contraception [see Section 4.5]. Teriflunomide plasma concentration can also be assessed for any subjects not entering the extension study if deemed necessary for the subject's safety, at the investigator's discretion. The following rules will apply:
  - For subjects entering the AC-058B303 extension study, no teriflunomide plasma testing will be conducted as part of the AC-058B301 study. The timing of teriflunomide plasma concentration testing and procedures are described in the AC-058B303 study protocol (separate protocol).
  - For subjects not entering the AC-058B303 extension study, teriflunomide plasma concentration testing should not occur before:
    - 20 weeks after last drug intake, if the subject's compliance with the accelerated elimination procedure has been assessed as sufficient [see Section 5.1.14.2].
    - 35 weeks (i.e., 8 months) after last drug intake or EOS, whichever is last, if the subject's compliance with the accelerated elimination procedure has not been assessed as sufficient [see Sections 5.1.14.1 and 5.1.14.4].
  - In all cases, the results will not be communicated to the sponsor (except site monitor). Sites will receive the following notifications:
    - if plasma concentration was < 0.02 mg/L: notification that the teriflunomide test was successfully performed

- if plasma concentration was ≥ 0.02 mg/L: full test results and notification that the subject should either repeat the accelerated elimination procedure [see Section 5.1.14] or wait an additional time period before another test may be performed.

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

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

5.1.6 Unblinding

5.1.6.1 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).

5.1.6.2 Unblinding for IDMC

A SAC, 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 SAC in accordance with the sponsor's SOPs.

5.1.6.3 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.

5.1.6.4 Emergency procedure for unblinding

The investigator, study staff and sponsor staff must remain blinded to the subject's 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 code break with Actelion.

The occurrence of any code break during the study must be clearly justified and explained by the investigator. The investigator must not disclose the unblinded treatment in the eCRF or to the sponsor or its delegates. In all cases, Actelion must be informed as soon as possible before or after the code break.

The circumstances leading to the code break must be documented in the site study file and eCRF.

Refer to the IRT guidelines for complete information regarding the IRT procedures for randomization, study drug assignment, and unblinding.

5.1.7 Study treatment supply

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

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

5.1.7.1 Study treatment packaging and labeling

5.1.7.1.1 Study treatment packaging

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

5.1.7.1.2 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.

5.1.7.2 Study treatment distribution and storage

Treatment supplies must be kept in an appropriate, secure area and stored according to the conditions specified on the medication labels. The study drug must be stored below 25 °C. The study drug must not be refrigerated.

5.1.7.3 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 quantity). Subjects are asked to return all used, partially used and unused study treatment blister packs 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/capsules 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.

5.1.7.4 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, which will be sent to the warehouse, where Actelion or a deputy will check treatment reconciliation.

5.1.8 Drug accountability and compliance

5.1.8.1 Drug accountability

Records of study drug 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.

5.1.8.2 Drug compliance

Subjects' compliance with study drug intake will be recorded using an electronic diary. On each day, the subjects will be asked to enter the date, time, number of capsules (and tablets, if applicable) taken, and the unique blister-card identifying number from which the capsules (and tablets, if applicable) are (were) taken from. In addition, during the up-titration, the position of the well on the blister card will be recorded in order to check that capsules and tablets (if applicable) were taken in the correct sequence [see gradual up-titration in Section 5.1.3.1].

The electronic diary will give feed-back 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., capsule at position 6 taken before capsule at position 4 on the blister card);
- 1 or more dose(s) (capsule and/or tablet if applicable) 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 drug accountability [see Section 5.1.8.1]. Subjects will be asked to explain the observed discrepancies. Interruptions with known dates will be recorded accordingly in the study drug log [see Section 5.1.9]. Study drug intake requirements will be re-explained to the subject each time an interruption is observed.

5.1.9 Study treatment dose adjustments and interruptions

Study drug up-titration, other than described in Section 5.1.3, is prohibited. Study drug down-titration is not foreseen in any situation and is prohibited.

Study drug 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 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 5.1.13. The duration of an interruption is determined by the investigator and is not limited in time. At maximum, it will last until the investigator deems the subject necessary to require another MS treatment. In this event, it is recommended performing an accelerated elimination procedure [see Section 5.1.14] before a new immunomodulatory treatment for MS is started.

Detailed guidance on how to re-initiate study drug in the event of drug interruption is provided in Section 5.1.10.

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

5.1.10 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 below in Figure 5.

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

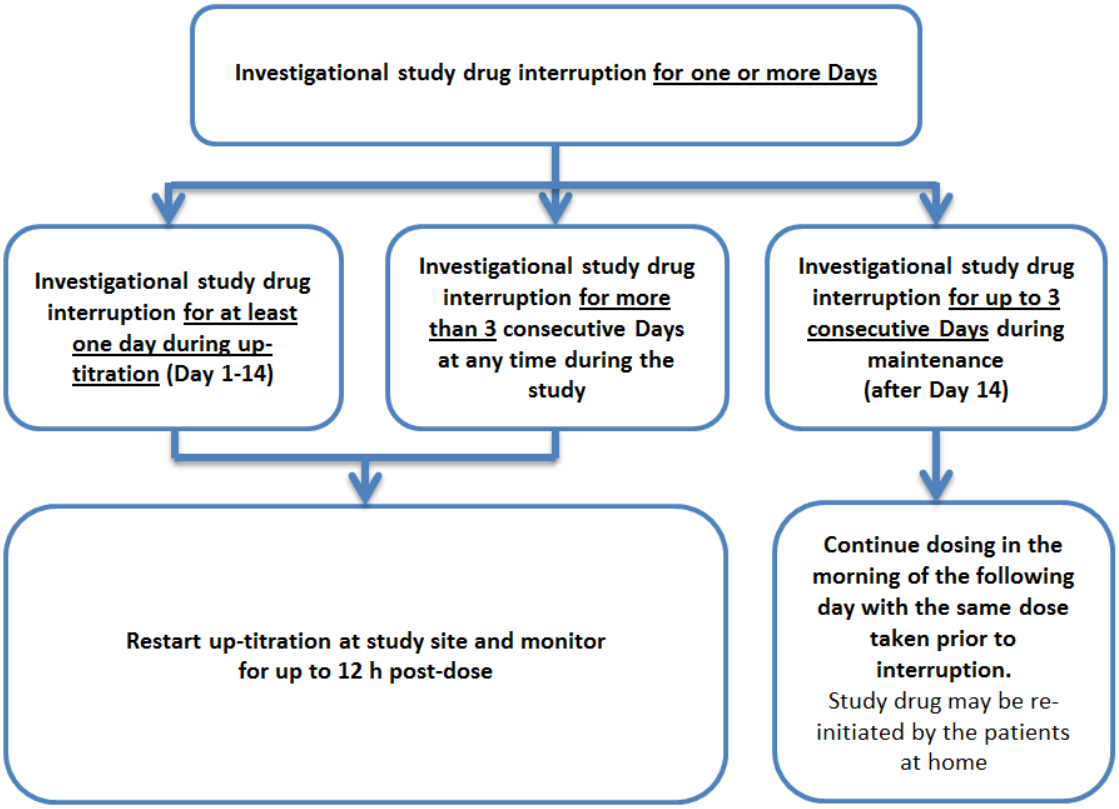
- If the subject missed taking the dose in the morning:
  - The dose should be taken at any time on the same day.
  - Regular dosing should be continued with the morning dose on the following day.
- If the subject missed taking the dose for one or more days during treatment up-titration (from 1 to 14 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 h post-dose by the first-dose administrator, following the cardiac assessment schedule and applying the discharge criteria as described for Day 1 [see Section 5.1.11].

- If the subject missed taking the dose for up to three consecutive days during treatment maintenance (from 14 days after the first dose of initiation/re-initiation of the study drug onwards):
  - Dosing should be continued in the morning following the last day without investigational study drug intake, 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 14 days after the first dose of initiation/re-initiation of the study drug onwards):
  - 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 h post-dose by the first-dose administrator, following the cardiac assessment schedule and applying the discharge criteria as described for Day 1 [see Section 5.1.11].

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 subject can continue regular dosing, need to re-initiate treatment, or should permanently discontinue treatment.

Figure 5 Algorithm for management of treatment interruptions



5.1.11 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

At the time of discharge from cardiac monitoring (i.e., when the evaluation of the pre-dose and all the hourly post-dose ECGs until 4 h post-dose have been obtained) on Day 1, and on the first day of re-initiation of study drug following drug interruptions, the following criteria must be met:

- ECG-derived resting HR > 45 bpm, and if HR < 50 bpm it must not be the lowest value post-dose;
- SBP > 90 mmHg;
- QTcF < 500 ms and QTcF increase from pre-dose < 60ms;

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

If the subject does not meet the discharge criteria (as described above) at 4 h post-dose, the subject should be carefully monitored for an additional period, 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 h 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.

5.1.12 Premature discontinuation of study treatment

In the study, the premature discontinuation of study treatment is defined as a permanent discontinuation of study treatment earlier than the planned treatment duration of 108 weeks. The decision to prematurely discontinue study treatment may be made by the subject, the investigator or Actelion.

A subject has the right to prematurely discontinue study treatment at any time by withdrawal from treatment only or by withdrawal from treatment and any further participation in the study.

The investigator should discontinue study treatment for a given subject if, on balance, she/he believes that continued administration would be contrary to the best interests of the subject. In case of clinically significant progression of the disease as judged by the investigator, the investigator should consider switching to another potentially more effective therapy, discuss alternative treatment options with the subject, and document the outcome of this discussion in the medical records.

Premature discontinuation of study treatment may also result from a decision by Actelion, e.g., in case of premature termination or suspension of the study [see Section 9.3].

The main reason and whether discontinuation of study treatment is the decision of the subject, the investigator, or Actelion must be documented in the eCRF.

A subject who prematurely discontinues study treatment is NOT considered as withdrawn from the study and will be followed up until Week 108 in the PTOP or until the end of the safety FU period (30 days after study drug discontinuation), whichever comes last [see

Section 3.1.3], provided that the subject's consent for this limited participation in the study has not been withdrawn.

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

In the event of permanent discontinuation from study drug due to any reason, the investigator should consider prescribing appropriate treatment for MS according to the local clinical practice and availability. The investigator should exercise caution when considering the switch to another immunomodulatory MS treatment. Initiation of immunomodulatory therapies is best avoided during the FU period of 15 days and until an accelerated elimination procedure for teriflunomide has been conducted to minimize the risk of immunosuppression.

5.1.13 Study-specific criteria for interruption / premature discontinuation of study treatment and management of clinically relevant events

An accelerated elimination procedure must be used by all subjects permanently discontinued, after the last dose of study drug [see Section 5.1.14].

5.1.13.1 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 h 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 h 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 4].

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.

5.1.13.2 Hematological abnormalities and infections

Subjects **must** be permanently discontinued from study drug at any time throughout the study in the event of:

- Confirmed neutrophil count $< 1.0 \times 10^9$/L (< 1000 cells/mm^3)
- Confirmed platelet count $< 50 \times 10^9$/L (< 50 000 cells/mm^3)
- Confirmed total lymphocyte count $< 0.2 \times 10^9$/L (< 200 cells/mm^3)

Confirmation will be done as follows:

Whenever a neutrophil count $< 1.0 \times 10^9$/L, a platelet count $< 50 \times 10^9$/L, or a total lymphocyte count $< 0.2 \times 10^9$/L, is recorded by the central laboratory, an alert will be sent to the principal investigator and the sponsor. The principal investigator will immediately contact the subject and ask her/him to return to the site within 48 h at the latest 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 a neutrophil count $< 1.0 \times 10^9$/L, a platelet count $< 50 \times 10^9$/L, or a total lymphocyte count $< 0.2 \times 10^9$/L the study drug must be discontinued. Neutrophil, platelet, or lymphocyte counts must be monitored at least once a week by the central laboratory until the neutrophils or platelets have returned to $\geq$ 80% of the baseline value or the lymphocyte count has returned to

$\geq 0.8 \times 10^9$/L or $\geq$ 80% of the baseline value. Any clinically relevant finding meeting the definition of an AE will be recorded accordingly in the eCRF.

In the event of a decrease of neutrophil or platelet not reaching the above alert levels, test at trough level (pre-dose) may be repeated. Upon confirmation of the decline over time of neutrophil or platelet counts, study drug may be interrupted at the discretion of the investigator. Possible causes for this decline including signs and symptoms suggestive of an infection should be assessed.

In the event of a suspected opportunistic infection of the CNS, the study drug must be interrupted and the subject referred to an expert in infectious diseases for further examination and treatment. For any other infection the subject should be treated as clinically indicated and study drug may be interrupted or permanently discontinued at the discretion of the investigator. In case of study drug interruption the subject will be closely observed and if the infection is resolved or not confirmed and the benefit/risk balance is considered acceptable for the subject to resume study treatment, the study drug may be re-initiated at the discretion of the investigator.

In the event of permanent discontinuation from study drug due to infection, adequate treatment needs to be provided and the subject must be monitored until complete resolution of the infection.

A guidance for screening and monitoring of subjects for opportunistic infection is provided in Sections 5.1.13.2.1 and 5.1.13.2.2. Subjects must be advised to be proactive and alert in reporting any unusual neurological symptom and any signs and symptoms indicative of systemic infections, such as fever, malaise and fatigue.

In the event of a suspected opportunistic infection in the CNS, unscheduled brain MRI scans may be performed at the investigator's request.

5.1.13.2.1 Guidance for screening, exclusion and on-treatment monitoring of subjects for progressive multifocal leukoencephalopathy

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 John Cunningham Virus (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. Development of PML is extremely rare in immunocompetent individuals. People with autoimmune rheumatic diseases, especially systemic lupus erythematosus, are also at higher risk of PML [Kappos 2011].

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., cyclosporine, tacrolimus, sirolimus, and mycophenolate), and therapeutic monoclonal antibodies (e.g., rituximab, infliximab, etanercept, basiliximab, daclizumab, efalizumab, alemtuzumab, and muromonab-CD3) [Kappos 2011].

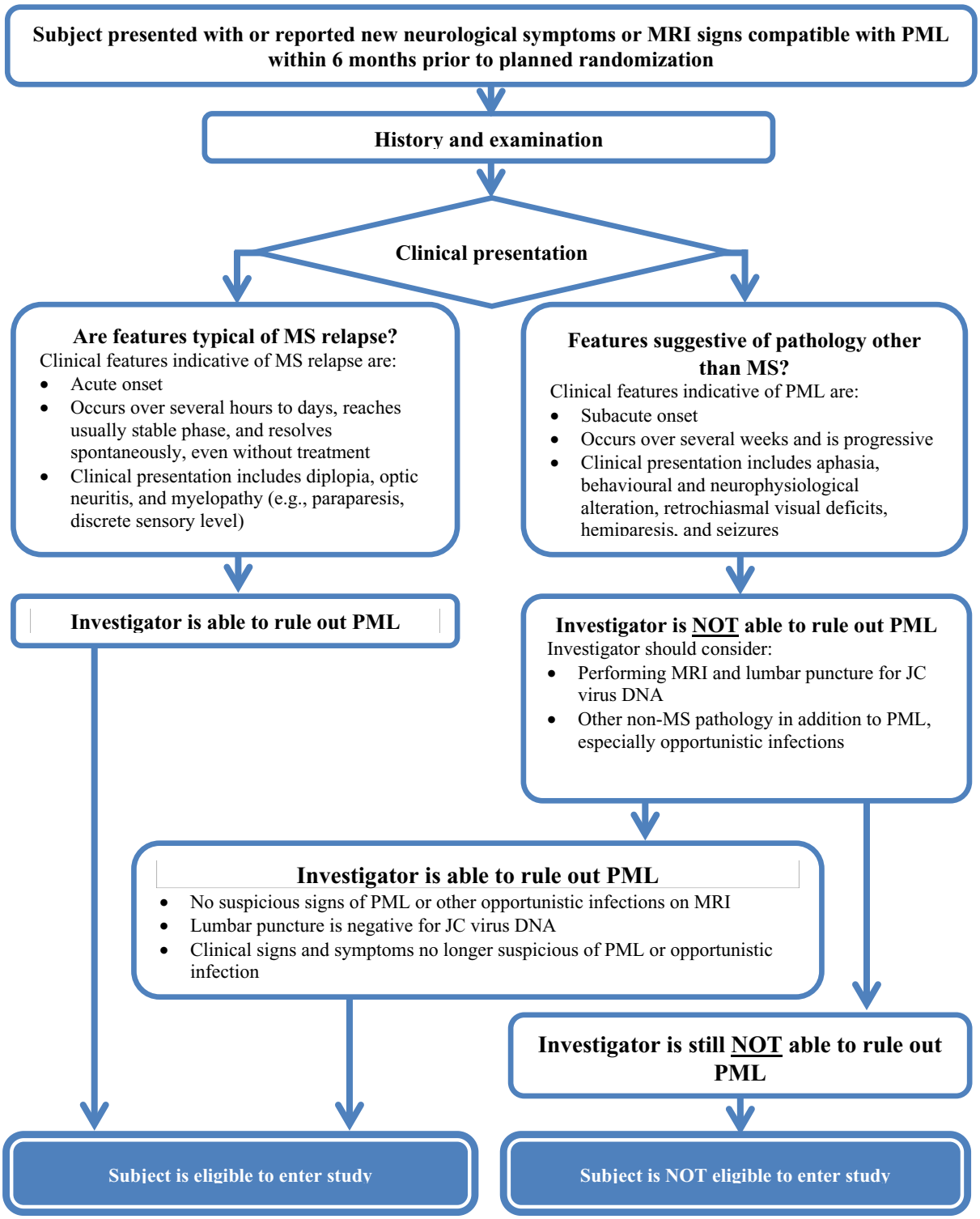
Clinical features indicative of PML are:

- Subacute onset
- Occurs over several weeks and is progressive
- Clinical presentation includes aphasia, behavioral and neurophysiological alteration, retrochiasmal visual deficits, hemiparesis, and seizures.

In order to facilitate the recognition of potential PML infection in MS subjects and to minimize the risk of enrolling subjects with undiagnosed or unrecognized PML infection in the clinical study of ponesimod, the following guidance is provided. The proposed algorithm is based on the updated experts' panel recommendation for monitoring subjects who receive treatment with natalizumab [Kappos 2011].

Subjects with known PML infection or evidence of new neurological symptoms or MRI signs within 6 months prior to randomization that are compatible with a diagnosis of PML infection are not be eligible for the study. The proposed algorithm should be applied for all subjects with evidence of new neurological symptoms or MRI signs compatible with PML within 6 months prior to randomization [Figure 6].

Figure 6 Clinical assessment for potential PML



For subjects who have been enrolled in the study and who, under the study treatment, present new neurological symptoms suggestive of pathology other than MS, the investigator should consider PML or another opportunistic infection of the CNS (especially in case of prior exposure to natalizumab or other immunosuppressive agents) and, in case of clinical features indicative of these conditions, the following diagnostic procedures are recommended:

- Perform MRI including T1 sequences with Gd (and additional MRI sequences if needed) and include comparison with the previous MRI images in the interpretation of the MRI results;
- Interrupt study drug until PML or other opportunistic CNS infection has been excluded with confidence;
- Perform lumbar puncture and send cerebrospinal fluid (CSF) for JCV DNA testing by polymerase chain reaction (PCR) with an ultrasensitive assay. The JCV DNA assay should be based on quantitative real-time PCR to maximize sensitivity and specificity for detection, and an assay with a maximum lower limit of quantification of 50 DNA copies per mL should be used.

Detection of JCV DNA in the CSF of a symptomatic subject confirms the diagnosis. However, a negative JCV PCR result should not exclude a possible diagnosis of PML.

In case the CSF is negative but clinical signs and symptoms and/or MRI are still suggestive of PML:

- Consider repeating CSF analysis;
- Consider other opportunistic infections with CNS manifestations;
- Manage the subject on suspicion of PML or other opportunistic CNS infections according to local guidelines.

If,

- There are no suspicious signs of PML or other opportunistic infections on MRI and
- Lumbar puncture, if done, is negative for JC DNA, and
- The neurological signs and symptoms show improvement and are no longer suspicious of PML and can be explained by MS or an alternative, not-infectious etiology,

the suspicion of PML is not supported. Other causes of the atypical neurological signs or symptoms or MRI findings need to be considered. Re-starting of the study drug should be considered if the benefit/risk is still favorable, according to the investigator.

However, if the investigator is still NOT able to rule out PML or another CNS opportunistic infection, the study drug should be permanently discontinued, the case should be reported

to the sponsor as an SAE and the subject should be managed according to the local standard of care.

In case the MRI at scheduled visit shows signs atypical for MS, PML or other opportunistic infection should be considered based on the clinical signs and symptoms, MRI results, previous exposure to natalizumab or immunosuppressants, and laboratory tests including CSF analysis, if indicated. As long as there is suspicion of PML or other opportunistic infection, the study drug should be interrupted and should not be re-introduced until this suspicion has been ruled out.

5.1.13.2.2 General guidance for monitoring of subjects for opportunistic infections other than PML during treatment

Heightened vigilance is required for opportunistic infections, with particular attention to be paid to viral infections. However, investigators and physicians following subjects should also be alert to potential systemic infections caused by fungi and bacteria. In the event of an opportunistic infection, the subject must be referred to an expert in infectious diseases for further examination and treatment. The study drug must be permanently discontinued in case of opportunistic CNS infections. For any other opportunistic infections, the study drug may be interrupted or permanently discontinued at the discretion of the investigator.

It is important to recognize that opportunistic infections caused by the reactivation of human herpes viruses (herpes simplex viruses, varicella-zoster virus, Epstein-Barr virus, cytomegalovirus) may be associated with neurological symptoms primarily. 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 discontinuation of study drug treatment and to early initiation of antiviral treatment [Steiner 2007].

Particular vigilance is required for rare and unusual neurological symptoms, as their recognition is crucial for the early diagnosis of neurotropic herpes viruses infections.

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].

5.1.13.3 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 vapacity; 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 '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, 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.

5.1.13.4 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. If the subject wishes to continue pregnancy, Actelion Global Drug Safety will request the unblinding of the treatment assignment and only the subject allocated to teriflunomide will perform an accelerated elimination procedure [see Section 5.1.14].

If a female partner to a male study participant becomes pregnant while the study participant is on study drug, the study drug in the male subject **must** be permanently discontinued. Actelion Global Drug Safety will request the unblinding of the treatment assignment. In case the male subject has been on teriflunomide, the investigator must counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. If the subject was on ponesimod, there is no risk for the female partner to continue pregnancy. The accelerated elimination procedure will be performed in the male subject only if the subject was on teriflunomide.

Male and female subjects participating in the study and wishing to father a child or wishing to become pregnant during the study must discontinue study drug, perform an accelerated elimination procedure, and continue contraception as indicated per protocol until 6 weeks after the first of two tests indicating serum teriflunomide level < 0.02 mg/L.

5.1.13.5 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 h, 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 • ALT or AST ≥ 3 × ULN and TBL ≥ 2 × ULN or INR > 1.5 × ULN • ALT or AST ≥ 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)	Permanently discontinue study drug, and perform FU.

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 the study drug 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.

5.1.13.6 Renal function

Subjects **must** be permanently discontinued from study drug at any time throughout the study in the event of a rapid serum creatinine increase to > 150 µmol/L or rapid decrease in calculated creatinine clearance to < 30 mL/min (Cockroft-Gault) that cannot be rapidly reversed (by volume repletion or relief of urinary tract obstruction [according to etiology]). Any clinically relevant finding meeting the definition of an AE will be recorded accordingly in the eCRF.

5.1.13.7 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. The OSB will receive all information related to suspected cases of macular edema and will perform central review of OCT results and subject data. Any clinically relevant finding meeting the definition of an AE will be recorded accordingly in the eCRF.

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

5.1.13.7.1 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 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.

5.1.13.8 Skin reactions

Subjects **must** be permanently discontinued from study drug at any time throughout the study in the event of Stevens-Johnson syndrome or toxic epidermal necrolysis or drug reaction with eosinophilia and systemic symptoms. Subjects will be managed and followed-up until resolution.

5.1.13.9 Peripheral neuropathy

In case of development of symptoms suggestive of peripheral neuropathy such as bilateral numbness or tingling of hands or feet, the investigator should evaluate the subject and decide whether the diagnosis of peripheral neuropathy is likely. Such evaluation may include further clinical and/or neurophysiological diagnostic work-up for peripheral neuropathy according to the local practice. If, as a result of such evaluation, diagnosis of peripheral neuropathy is likely according to the investigator, the subject must be permanently discontinued from study drug, managed and followed up until resolution. Any clinically relevant finding meeting the definition of an AE will be recorded accordingly in the eCRF.

5.1.14 Elimination of teriflunomide

5.1.14.1 Accelerated elimination procedure for teriflunomide

Teriflunomide is eliminated slowly from plasma. Without an accelerated elimination procedure, it takes on average 8 months to reach plasma concentrations less than 0.02 mg/L, although because of individual variations in drug clearance it may take as long as 2 years.

At EOT, all subjects will have to undergo an accelerated elimination procedure consisting of either of the following procedures:

- Administration of cholestyramine 8 g three times a day (i.e., every 8 h) for 11 days. If cholestyramine 8 g three times a day is not well tolerated, cholestyramine 4 g three times a day can be used.
- Administration of 50 g oral activated charcoal two times a day (i.e., every 12 h) for 11 days.

If either elimination procedure is poorly tolerated, treatment days do not need to be consecutive unless there is a need to lower teriflunomide plasma concentration rapidly. It is permissible to switch from cholestyramine to activated charcoal (or vice versa) for reasons of tolerability.

5.1.14.2 Compliance with accelerated elimination procedure

Subjects' compliance with the elimination procedure will be reviewed and assessed after each elimination procedure. The recommended compliance should include intake of 33 doses of cholestyramine (8 g or 4 g) or 22 doses of activated charcoal (50 g). Plasma concentration of teriflunomide should not serve to assess compliance. Please refer to Sections 5.1.5.2 and 5.1.14.4 for timing of teriflunomide testing after EOT.

Note: At FU1 and (abbreviated) FU2, plasma concentration of teriflunomide will not be measured. The testing should occur as described in Section 5.1.14.4.

For subjects not entering the AC-058B303 extension study, subjects compliance will be reviewed at FU1. If the compliance has been assessed by the investigator as not sufficient at FU1, the subject will be asked to complete missing intakes or repeat the procedure. In such a case a new compliance assessment will be performed at FU2. If the compliance has been assessed as not sufficient at FU2, washout may be obtained through additional elimination procedures or by waiting for several months of natural elimination according to the subject's preferences. Duration of continued contraception and timing of teriflunomide testing are described in Section 5.1.14.4.

For subjects entering the AC-058B303 extension study, compliance will be reviewed at FU1. If the compliance has been assessed as not sufficient at FU1, the investigator will

decide if the elimination procedure should be repeated or missing intakes completed. In such a case a new compliance assessment will be performed at an abbreviated FU2. The abbreviated FU2 should be scheduled to allow enough time for completing the elimination procedure. The subject will only be eligible to enter the extension study AC-058B303 if the compliance was assessed as sufficient at FU1 or abbreviated FU2. Duration of continued contraception and timing of teriflunomide testing are described in the AC-058B303 extension study protocol. If the compliance has been assessed as not sufficient at abbreviated FU2, the subject will not be eligible to enter the extension study AC-058B303. In such a case, teriflunomide washout may be obtained through additional elimination procedures or by waiting for several months of natural elimination according to the subject's preferences. Duration of continued contraception and timing of teriflunomide testing are described in Section 5.1.14.4.

5.1.14.3 Accountability of accelerated elimination procedure treatment

At FU1 and FU2 (if accelerated elimination procedure was repeated after FU1), the number of bottles (activated charcoal) or sachets (cholestyramine) dispensed and returned, and the dosages administered are recorded on the non-IMP accountability log by the site staff. The accelerated elimination procedure treatment accountability is checked by the monitor at EOS. If the accountability cannot be performed (e.g., subject doesn't return bottles or sachets), compliance will be evaluated based on discussions with the subject.

5.1.14.4 Duration of continued contraception after EOT

Contraception measures as described in Section 4.5, must be continued until at least 6 weeks after the first of two consecutive tests showing a teriflunomide concentration < 0.02 mg/L. The testing of teriflunomide plasma concentration may be conducted for WOCBP and fertile male subjects, if needed, to confirm that contraception can be discontinued.

For subjects not participating in the AC-058B303 extension study, plasma concentration of teriflunomide must not be measured earlier than 20 weeks after the last study drug intake, and provided the subject has been compliant with the accelerated elimination procedure of teriflunomide [see Section 5.1.14.2]. If the subject has not been compliant with the accelerated elimination procedure, testing for teriflunomide must not be done before 35 weeks (i.e., 8 months) after last dose of study drug or EOS, whichever comes last.

- If teriflunomide plasma concentration is as anticipated less than 0.02 mg/L, the site will receive notification that the test was successfully performed and that teriflunomide concentration is < 0.02 mg/L (actual concentration will not be displayed). A second test will be performed approximately 15 days after the first test to confirm the result.
- If plasma teriflunomide concentration is more than 0.02 mg/L, site will receive notification that teriflunomide plasma level is ≥ 0.02 mg/L and the actual concentration will be displayed on the report. In such a case, the accelerated elimination procedure

may be repeated at the discretion of the investigator and the subject will be instructed to continue contraception until at least 6 weeks after the first of two consecutive tests that show teriflunomide plasma concentration level below 0.02 mg/L.

For subjects continuing into the extension study AC-058B303 the applicable procedures for teriflunomide tests/retests and for continuation of contraception will be described in the AC-058B303 study protocol (separate protocol).

The duration of contraception after EOT should follow the following rules:

- **For subjects continuing in the extension study AC-058B303 (separate protocol)**: the duration of contraception will be described in the AC-058B303 study protocol.
- **For subjects <u>not</u> continuing in the extension study AC-058B303 (both males and females)**: the duration of contraception should always be until at least 6 weeks after the first of two consecutive tests that show teriflunomide plasma concentration level below 0.02 mg/L. Subjects who leave the study before achieving this should be instructed to follow this requirement outside the study.

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).

All therapy that is study concomitant (i.e., ongoing or initiated after signing of informed consent, and initiated before EOS visit) must be captured in the eCRF.

A therapy that is concomitant to study-treatment is any treatment that is either ongoing at the start of study treatment or is 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

The use of all study-concomitant therapy (including contraceptives or traditional and alternative medicines, i.e., plant-, animal-, or mineral-based medicines) will be recorded in 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, and indication will be recorded in the eCRF.

Any previous administration of disease-modifying treatment for MS (IFN beta 1a [Rebif® - Avonex®, Plegridy®], IFN beta 1b [Betaseron®], glatiramer acetate [Copaxone®, Glatopa®], fingolimod [Gilenya®], dimethyl fumarate/BG-12 [Tecfidera®], natalizumab [Tysabri®], alemtuzumab [Lemtrada®]) at any time prior to screening will be recorded in

the previous MS treatment form of the eCRF. The start date, end date, dose, route, frequency, and reason for discontinuation will be recorded in the eCRF.

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.

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 therapy form of the eCRF.

5.2.3 Recommended concomitant therapy

Treatment of relapses:

- If a relapse requires treatment with corticosteroids, methylprednisolone 1 g i.v. daily for 3 to 5 days is recommended. Treatment with other corticosteroids, another dose, other routes of administration, or ACTH is not recommended unless deemed absolutely necessary and must be documented in the patient charts by the investigator. Oral taper with corticosteroids should not be administered in any case.
- Treatment of relapses with plasma exchange (i.e., plasmapheresis, cytapheresis) is prohibited.

5.2.4 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 and must be documented in the patient charts by the investigator;
- Administration of i.v. atropine in the event of symptomatic bradycardia;
- Short-acting ß2-agonists for respiratory symptoms and/or reduced pulmonary function during study drug treatment;
- 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 3];
- 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 assess changes in vaccine-specific antibody titers from pre- to post-vaccination. Samples will be analyzed at the end of the study [see Section 3.1.6.4].

- The following medications should be administered with caution due to potential interaction with teriflunomide:
  - Teriflunomide is an inhibitor of cytochrome P450 (CYP)2C8 *in vivo*: CYP2C8 substrates such as repaglinide, paclitaxel, pioglitazone, or rosiglitazone should be carefully monitored when co-administered with study drug treatment as they may have higher exposure;
  - Teriflunomide may be a weak inducer of CYP1A2 *in vivo*: medicinal products metabolized by CYP1A2 such as duloxetin, alosetron, theophylline and tizanidine should be used with caution during study drug treatment, as reduction of the efficacy of these products may be observed;
  - A 25% decrease in peak INR was observed when teriflunomide was co-administered with warfarin as compared with warfarin alone. Therefore, when warfarin is co-administered with study drug treatment, close INR FU and monitoring is recommended;
  - Teriflunomide is an inhibitor of organic anion transporter (OAT)3 *in vivo*: when study drug treatment is co-administered with substrates of OAT3, such as cefaclor, benzylpenicillin, ciprofloxacin, indometacin, ketoprofen, furosemide, cimetidine, zidovudine, caution is recommended;
  - Co-administration of substrates of breast cancer resistant protein (e.g., topotecan, sulfasalazine, daunorubicin, doxorubicin) and the OAT polypeptide family (e.g., nateglinide, repaglinide, rifampicin) and especially HMG-CoA reductase inhibitors (e.g., rosuvastatin, simvastatin, atorvastatin, pravastatin) with the study drug treatment should be undertaken with caution. Subjects should be closely monitored for signs and symptoms of excessive exposure to these medicinal products, and reduction of the dose of these medicinal products should be considered;
  - Rifampicin and other known potent CYP and transporter inducers such as carbamazepine, phenobarbital, phenytoin and St John's Wort may result in a decrease in teriflunomide exposure. Co-administration of these drugs with study drug treatment should be used with caution.
- Other treatments considered necessary for the subject's wellbeing and not categorized as prohibited concomitant medications.

5.2.5 Forbidden study-treatment-concomitant therapy

- Systemic corticosteroids and ACTH, except for the treatment of MS relapses [see Section 5.2.3] and for 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) with low dose of corticosteroid (up to 10 mg of prednisone equivalent daily) or inhaled corticosteroids for pulmonary conditions;

- Disease-modifying drugs for MS other than prescribed as per protocol;
- Immunosuppressive treatment (e.g., cladribine, mitoxantrone or other systemic immunosuppressive treatments such as azathioprine, cyclophosphamide, cyclosporine or methotrexate);
- i.v. 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 4];
- Cholestyramine or activated charcoal unless needed for an accelerated elimination procedure;
- Any other investigational drug;
- Any investigational therapeutic procedure for MS (e.g., stent placement or angioplasty for chronic cerebrospinal venous insufficiency, 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

For each of the study 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 Efficacy endpoints

6.1.1 Primary efficacy endpoint(s)

The primary endpoint is ARR. This endpoint is based on the number of confirmed relapses 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 h, 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, and 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 by the treating neurologist 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 points; unless EDSS = 0, then an increase of at least 1.0 points 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 four secondary efficacy endpoints, which will be analyzed as per the statistical testing strategy outlined in Section 11.3.1:

- **Change from baseline to Week 108 in fatigue-related symptoms as measured by the symptoms domain of the FSIQ–RMS**

- **Cumulative number of combined unique active lesions (CUAL) from baseline to Week 108**

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

- **Time to 12-week CDA from baseline 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 0.0 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 prior to 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, EDSS scores used for confirmation of disability accumulation must be obtained at a scheduled visit (i.e., unscheduled visits cannot be used as confirmatory visits) outside any ongoing relapse. In this context, relapse duration is defined as period between start and end dates if available

and limited to 90 days from onset if end date is not available or duration is longer than 90 days.

In order to confirm that the EDSS increase is persistent, all EDSS measurements between the onset and the 12-week EDSS confirmation (minus 7-day visit time-window) need to show an increase in EDSS, meeting the criteria for accumulation of disability as defined above.

- **Time to 24-week CDA from baseline 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 0.0 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 24 weeks.

Baseline EDSS is defined as the last EDSS score recorded prior to 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, EDSS scores used for confirmation of disability accumulation must be obtained at a scheduled visit (i.e., unscheduled visits cannot be used as confirmatory visits) outside any ongoing relapse. In this context, relapse duration is defined as period between start and end dates if available and limited to 90 days from onset if end date is not available or duration is longer than 90 days.

In order to confirm that the EDSS increase is persistent, all EDSS measurements between the onset and the 24-week EDSS confirmation (minus 7-day visit time-window) need to show an increase in EDSS, meeting the criteria for accumulation of disability as defined above.

6.1.3 Other efficacy endpoints

MRI-based exploratory endpoints:

- Percent change in brain volume (PCBV) from baseline to Week 108

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

- Number of MRI lesions (Gd+ T1 lesions) at Week 60 and Week 108
- Cumulative number of new or enlarging T2 lesions from baseline to Week 108
- Change from baseline to Week 60 and Week 108 in the volume of MRI lesions (T2 lesions, T1 hypointense lesions)

- Absence of MRI lesions (Gd+ T1 lesions, new or enlarging T2 lesions) at Week 60 and Week 108
- Proportion of Gd+ lesions at baseline evolving to persistent black holes (PBHs) by Week 108 (axonal loss)
- Change of CCI
- Change in CCI
- Cumulative number of CCI

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

- Time to first confirmed relapse
  Definition: Time from randomization to first confirmed relapse. 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.
- Absence of confirmed relapses from baseline to Weeks 60 and 108
- Change from baseline by visit up to Week 108 in EDSS
- No evidence of disease activity (NEDA) status up to EOS (defined by the absence of confirmed relapse, Gd+ T1 lesions, new or enlarging T2 lesions, 12-week CDA, and annual brain volume decrease ≥ 0.4% from baseline to EOS and completing treatment as planned)

Other exploratory endpoints:

- Change in MSFC Z-score from baseline by visit up to Week 108
- Change in the SDMT score from baseline by visit up to Week 108
- FSIQ-RMS patient improvement response (clinically important difference, defined as a reduction in the FSIQ-RMS score ≥ a threshold value anchored on the PGI-S of Fatigue scale, which will be determined by a blinded analysis of the data, as described in Section 11.4);
- Change from baseline by visit up to Week 108 in fatigue-related impacts as measured by the impact sub-scales of the FSIQ–RMS
- Change from baseline in PGI-S of Fatigue by visit up to Week 108;
- Change from baseline in Clinician's Global Impression of Change (CGI-C) of patient's relapsing MS by visit up to Week 108;
- Preferences for several treatment outcomes from MS subjects using the MACBETH methodology (sub-study, at selected sites only).

6.2 Safety endpoints

Treatment-emergent period is defined as the time from first study drug intake up to 15 days (inclusive) after last study drug intake. The following safety endpoints will be analyzed:

- Treatment-emergent AEs, SAEs, AEs of special interest[#], and MACE

- AEs leading to premature discontinuation of study treatment
- Treatment-emergent morphological ECGs abnormalities (as defined by the ECG provider)
- Change in 12-lead ECG variables (HR, PR, QRS, QT, QTcB, QTcF) from pre-dose to selected post-dose assessments (1h, 2h, 3h, 4h) on Day 1 and on day of re-initiation of study drug
- Notable abnormalities* for selected 12-lead ECG variables (HR, PR, QT, QTcF) at 3-hpost-dose assessment on Day 1, Week 12, and at the re-initiation of study drug when post-dose monitoring is required
- Treatment-emergent decrease of FEV_1 or FVC > 20% from baseline values
- Treatment-emergent 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 vs 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 and < 12% in FEV_1 or FVC from baseline to last available FU
- Change in lung diffusion capacity as assessed by DL_{CO} (at selected sites only), expressed in absolute change and % of predicted value from baseline to all timepoints up to EOS
- Change from baseline to EOS vs change from baseline to EOT in DL_{CO} (absolute and % of predicted; at selected sites only)
- Treatment-emergent notable BP 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

[#] The selection of AEs of special interest is based on the anticipated risks of treatment with ponesimod or teriflunomide (e.g., liver enzyme abnormalities) and on the events that may be related to MS comorbidities (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 or teriflunomide 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 Week 108 in SF-36v2™ Health Survey domain and component scores.

6.4 Pharmacoeconomic endpoints

- Change from baseline by visit up to Week 108 in WPAI:MS scores
- Health care resource utilization from baseline up to Week 108 (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 endpoints

- Plasma concentrations of ponesimod pre-dose at Weeks 12, 60, and 108 and 3 h post-dose on Day 1 and at Week 12.

6.5.2 Pharmacodynamic endpoints

- Peripheral blood lymphocyte counts pre-dose (absolute and change from baseline counts) by visit up to Week 108
- Change from baseline to EOS vs change from baseline to EOT in lymphocyte counts (absolute and % change)
- Post-treatment lymphocyte recovery at 15 days and 30 days after study drug discontinuation

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 7.3.5].
- DL_{CO} gas analyzer (if applicable); in addition, a copy of the calibrations of the day of test must be stored and a log of calibration results must be maintained at the site. Frequent testing involving the same healthy subject control (biological quality check) or a DL_{CO} simulator will ensure continuous monitoring of the gas analyzer measurement accuracy over time [see Section 7.3.6].
- ECGs.
- BP monitoring device.
- MRI; in addition, prior to the start of the study, each MRI site must be qualified by MIAC [see Section 7.2.3].

7.1 Baseline assessments, including demographics

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 (CXR [see Section 7.3.7]). 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 (ISF). The language used in the oral and written information about the trial, and including the ICF, will be provided in a language that is fully understandable to the subject.

Separate informed consent must be obtained from those subjects participating in the DL_{CO}, non-conventional MRI, and patient preference sub-studies.

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.

7.1.2 Baseline demographics and disease characteristics

Baseline demographics (sex, age, race, body weight, and height) 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 the Concomitant Therapies pages 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.

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 Visits 1 (Screening), 2 (Baseline), 6 to 13 (Week 12 and every 12 weeks thereafter), 14 (EOT), 16 (FU2), 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 14A).

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 3.3.3]. 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 2] 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 [Figure 7]:

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, and 102 (+/− 7 days), or 6 weeks after the last 12-weekly visit (+/− 7 days). If applicable, the contacts may occur on site during blood sampling visits.

Whenever a subject experiences any new or worsening neurological symptoms between visits, 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 17].

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., ALT or AST PFT …), the principal investigator / treating neurologist will interview the subject to determine whether or not a relapse may have occurred since last visit using a dedicated relapse assessment questionnaire [see Appendix 17] and the relapse symptom form [see Appendix 18].

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 and, in the absence of another, better explanation of the subject's symptoms), 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 from 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 5.2.3], 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.

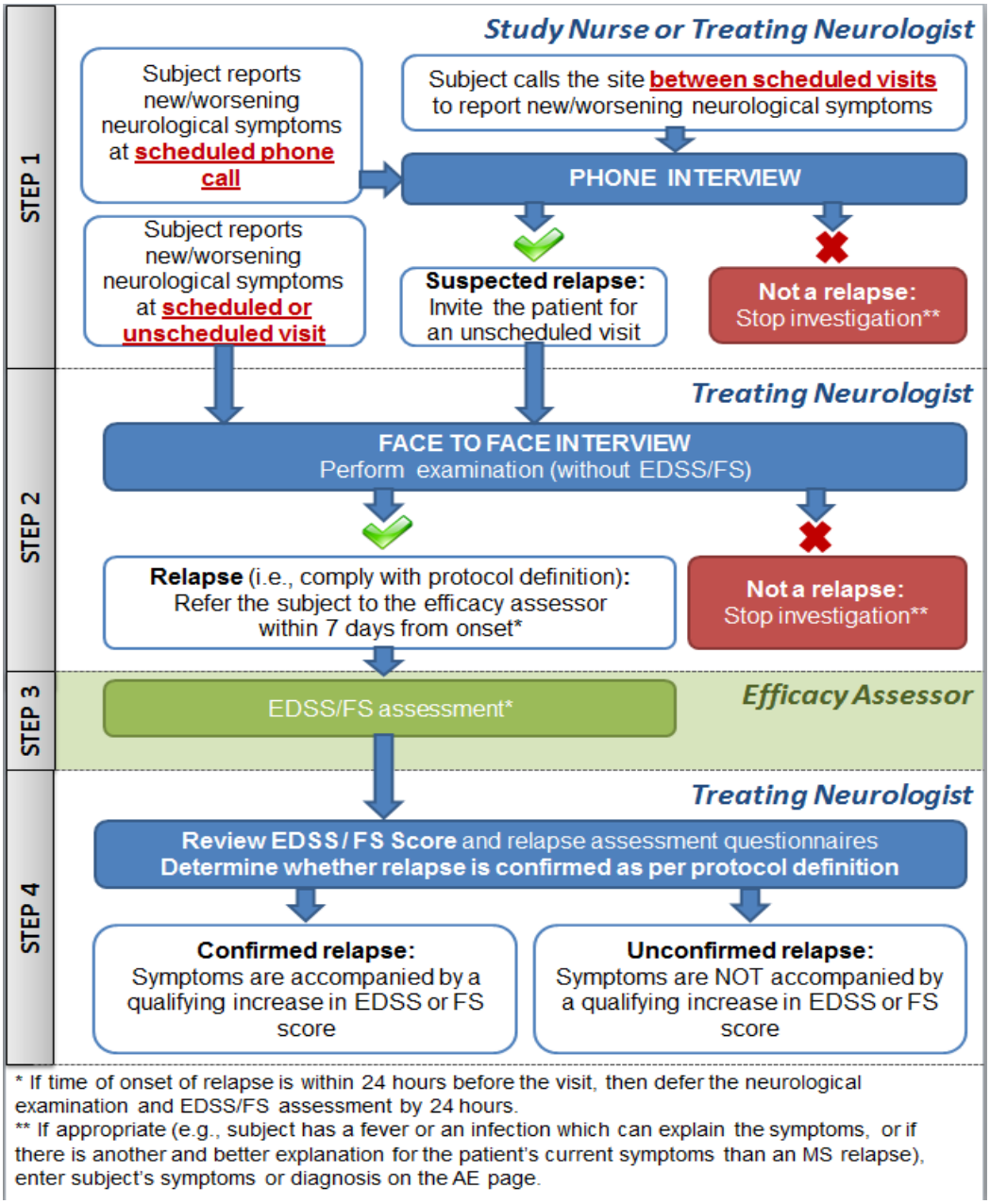
Step 4: The treating neurologist will review the EDSS/FS score obtained by the efficacy assessor and determine presence or absence of qualifying increase in EDSS/FS (i.e., an increase of the magnitude described in Section 6.1.1 from a previously clinically stable EDSS/FS score and consistent with the 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].

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 3 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 AEs 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 AEs on the AE page of the eCRF and, if applicable, on the SAE form).

Figure 7 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 Visits 2 (Baseline), 10 (Week 60), and 14 (EOT) and at any unscheduled visit (U1, U2, etc.). If applicable, MRI scans will also be performed at the corresponding visits in the PTOP (Visits 10A and 14A). Testing at all visits may be performed up to 7 days prior to or after the visit date. In case of premature study treatment discontinuation, the MRI at EOT does not need to be performed if the EOT visit occurs within less than 4 weeks of the MRI assessment at Visit 10 (Week 60).

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.

T_1-weighted imaging before and after i.v. administration of 0.1 mmol/kg body weight (= 0.2 mL/kg) of Gd as well as PD-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.).

All MRI data will be analyzed by the MIAC, c/o University Hospital Basel, Switzerland. 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 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 count of MRI 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.

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 neuroradiologist. 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 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 Supplementary non-conventional MRI sub-study

Supplementary non-conventional MRI scans assessing MTR and DIR will be performed at selected sites with adequate equipment and expertise at the same timepoints as the conventional MRI scan described above. Only subjects who consent under a separate informed consent for non-conventional MRI will participate in the sub-study. It is anticipated that up to 300 subjects will participate to the sub-study.

Similarly to the conventional MRI scans, data will be interpreted by MIAC.

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

7.2.5 MSFC

The MSFC score consists of 3 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 and at Visits 6, 7, 10, 12 (Weeks 12, 24, 60, and 84), and 14 (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 test practice ≥ 5 days from first practice test and third test serving as baseline ≥ 5 days from second practice test). The first test practice may be done at Visit 1 (Screening), the second test practice may be done at Visit 2 (Baseline) and the third test, serving as baseline, may be performed pre-dose at Visit 3 (Randomization).

MSFC will be administered in combination with SDMT [see Section 7.2.6] 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.

7.2.6 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 and at Visits 6, 7, 10, 12 (Weeks 12, 24, 60, 84), and 14 (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 test practice ≥ 5 days from first practice test and third test serving as baseline ≥ 5 days from second practice test). The first test practice may be done at Visit 1 (Screening), the second test practice 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.

7.2.7 FSIQ-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 h measured on an 11-point numeric rating scale; the symptom domain score ranges from 0 to 77 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 impact 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 Likert scale, ranging from no impact to extreme impact; the impact domain score ranges from 0 to 65 with a higher score indicating greater impact. As the impact 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., seventh day) of completion of section 1.

FSIQ-RMS will be completed during the pre-randomization period, at Visits 6, 7, 10, and 12 (Weeks 12, 24, 60, 84), 14 (EOT), 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 are received) will be provided with the electronic device containing 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 seventh day, the subject will also complete the impact 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 symptoms 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). Subjects will return the completed FSIQ-RMS diary at the next scheduled visit. On the seventh day, the subject will also complete the impact domain of the FSIQ-RMS (i.e., section 2 of the questionnaire). If applicable, at the end of the PTOP, the FSIQ-RMS will be completed prior to Visit 14A (Week 108), ideally, during the 7 consecutive days preceding the visit.

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.

7.2.8 Patient preferences

Patient preferences for several treatment outcomes will be assessed in a subset of approximately 360 subjects using an electronic questionnaire developed by Actelion. Subjects will be recruited at selected sites in countries for which translations are available. Only subjects who consent under a separate informed consent for MS Patient Preference Questionnaire will participate in the sub-study. The MS Patient Preference Questionnaire will be completed at home twice during the pre-randomization period (after Visits 1 and 2 [Screening, Baseline]), and during the follow-up period (before Visit 15, FU1) using an electronic device. All questionnaire responses will be electronically transferred to the Actelion database. Support for navigating the questionnaire will be provided as a tutorial within the electronic device. No guidance as to the content of the responses will be provided to the subject.

A sample of the MS Patient Preference Questionnaire is provided as Appendix 14.

7.2.9 Patient's Global Impression of Severity of Fatigue

The PGI-S of Fatigue assesses the subject's fatigue severity on a given day. The scale is scored by the subject on an 11-point numeric rating scale ranging from 0 to 10, anchored at 0 = "Not severe at all" and 10 = "Very severe". The questionnaire will be administered in an electronic format.

PGI-S of Fatigue will be completed during the pre-randomization period at Visit 2 (Baseline), at Visits 6, 7, 10, and 12 (Weeks 12, 24, 60, 84), 14 (EOT), and at unscheduled visits due to relapses (R1, R2, etc.) or other unscheduled visits (U1, U2, etc.). If applicable, PGI-S will also be performed at the corresponding visits in the PTOP.

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

It is recommended that the PGI-S of Fatigue is completed prior to any clinical assessments and before study drug exposure on the day of the visit. Preferably, subjects would complete the PGI-S of Fatigue 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 PGI-S of Fatigue is provided as Appendix 12.

7.2.10 Clinician's Global Impression of Change of patient's relapsing multiple sclerosis

The CGI-C of patient's relapsing MS requires the clinician to assess the change in subject's relapsing MS severity compared to Baseline (Visit 2). The question is scored by the investigator on a 7-point Likert scale ranging from 1 to 7, anchored at 1 = "Very much improved" and 7 = "Very much worse". The questionnaire will be completed on a paper form and subsequently transcribed in the eCRF.

CGI-C of patient's relapsing MS will be completed at Visits 6, 7, 10, and 12 (Weeks 12, 24, 60, 84), 14 (EOT), and at unscheduled visits due to relapses (R1, R2, etc.) or other unscheduled visits (U1, U2, etc.). If applicable, CGI-S will also be performed at the corresponding visits in the PTOP.

A sample of the CGI-C of patient's relapsing MS is provided as Appendix 13.

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 min prior to the measurement. 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 will be required, the pre-dose and post-dose ECGs required for evaluation of discharge criteria will be transmitted to the central ECG laboratory for expedite evaluation, and the ECG report will be returned to the site within approximately 1–2 h 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 will be 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

Section 3.3.2 and Section 3.3.4]. 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 subject, do not have access to post-dose ECG interpretation reports at Visit 3 (Day 1) and at visits for re-initiation of study drug when post-dose monitoring will be required (Visits I1, I2, etc.).

The following variables will be evaluated: HR (bpm), PR (ms), QRS (ms), QT (ms), QTc (ms), and any ECG findings. QT_C (ms) will be calculated according to Bazett's and Fridericia's formula (QTcB = QT/(RR) ½ and QTcF = QT/(RR) ⅓, respectively).

At Visit 3 pre-dose (Day 1), 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. At Visit 3 (Day 1), the pre-dose ECG must be performed prior to randomization and the applicable points from exclusion criterion #18 (e.g., HR < 50 bpm, presence of second-degree AV block Mobitz Type II or third-degree AV block, or a QTcF interval > 470 ms (females), > 450 ms (males), see Section 4.4) must be ruled out.

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

At Visit 3 (Day 1) and on the day of re-initiation of study drug when post-dose monitoring is required [see Section 5.1.10], ECGs must be performed at pre-dose, and hourly (+/− 15 min) thereafter for a minimum of 4 h and up to 12 h post-dose. Subjects may be discharged from the cardiac monitoring if they meet the discharge criteria before 12 h post-dose but no sooner than the (report of) ECG at 4 h post-dose has been evaluated by the first-dose administrator [see Section 5.1.11]. If the subject does not meet the defined discharge criteria at 12 h 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 5.1.11], or until medically indicated.

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 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 eCRF by the first-dose administrator. 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

BP measurements include SBP and DBP.

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 min prior to the measurement. 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 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 day 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 will be 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 Section 3.3.2 and Section 3.3.4].

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 eCRF by the first-dose administrator. 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.

BP measurements 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) and on days of re-initiation of study drug when post-dose monitoring is required, [see Section 5.1.10], SBP and DBP will be measured at pre-dose and hourly (+/− 15 min) thereafter for a minimum of 4 h and up to 12 h post-dose. Subjects may be discharged from cardiac monitoring if they meet the discharge criteria before 12 h post-dose but no sooner than 4 h post-dose [see Section 5.1.11]. If the subject does not meet the defined discharge criteria at 12 h 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 5.1.11], or until medically indicated.

7.3.3 Body temperature

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

All body temperature assessments will be documented in the source documents of the subject. All body temperature values 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.

7.3.4 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, 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.

7.3.5 Spirometry

Spirometry tests will be performed at Visits 2, 5, 6, 10, 14, 15, and 16 (Baseline, Week 4, Week 12, Week 60, EOT, FU1 and FU2). If applicable, spirometry tests will also be performed at Visit 14A 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 or at any time during the pre-randomization period. Spirometry at Visits 5, 6, 10, 15, and 16 (Week 4, 12, 60, FU1, and FU2) may be performed up to 7 days prior to or after the visit date. At Visit 14 (EOT), spirometry may be performed up to 7 days prior to the visit date but no later than 7 days after the discontinuation of study drug. It is highly recommended that all spirometry assessments are performed in the morning, preferably between 06:00 and 10:00, at approximately the same time to avoid diurnal variation. When applicable, it is also highly recommended that all spirometry assessments are performed prior to study drug intake.

Spirometry testing will consist of assessing FVC and FEV_1. 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 collected at each timepoint: FEV_1; FVC; the instantaneous forced expiratory flow (FEF) at 25%, 50% and 75% of the FVC ($FEF_{25\%}$, $FEF_{50\%}$, $FEF_{75\%}$, respectively); the mean FEF between 25% and 75% of the FVC ($FEF_{25–75\%}$); and the peak exploratory flow.

Spirometry tests will be conducted according to the ATS / ERS guidelines [Miller 2005a, Miller 2005b]. A central vendor will provide equipment and detailed instructions for use, calibration and validation of spirometers. The provided 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 facility will ensure that the spirometer is functioning properly and is calibrated according to manufacturer instruction and ATS/ERS guidelines. A copy of the calibrations of 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. 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 studies will be trained on the specific requirements for the studies and have refreshment on 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.

Subjects must refrain from taking short-acting-beta-agonists (e.g., salbutamol) for 6 h and long-acting-beta-agonists for 24 h 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 min 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 ATS/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.

All recorded spirometry values will be transmitted to the centralized reader, and will be reviewed by independent readers. Quality of the assessments will be evaluated for compliance with ATS/ERS criteria, and queries may be sent to the sites for clarification. If quality issues are identified, additional training will be provided. PFT values that trigger study drug discontinuation will be flagged. 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. Assessments may need to be repeated if results are of poor quality and/or inconclusive as per central reading.

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.

7.3.6 DL_{CO} sub-study

DL_{CO} will be assessed in a subset of approximately 400 subjects at selected sites with appropriate and established PFT expertise. Only subjects who consent under a separate informed consent for DL_{CO} will participate in the sub-study. The assessment will be conducted at Visits 2, 5, 6, 10, 14, 15, and 16 (Baseline, Week 4, Week 12, Week 60, EOT, FU1, and FU2). If applicable, DL_{CO} tests will also be performed at Visit 14A in the PTOP. In addition, unscheduled DL_{CO} tests may be performed at any time during the study (Visits U1, U2, etc.).

Prior to randomization, DL_{CO} can be performed at Visit 2 or at any time during the pre-randomization period. DL_{CO} at Visit 5, 6, 10, 15, and 16 (Week 4, 12, 60, FU1, and FU2) may be performed up to 7 days prior to or after the visit date. At Visit 14 (EOT), DL_{CO} may be performed up to 7 days prior to the visit date but no later than 7 days after the discontinuation of study drug.

DL_{CO} tests will be performed by a PFT technician, respiratory therapist or expert or an equally experienced person according to the ATS/ERS guidelines [Miller 2005a]. DL_{CO} results will be reviewed by a pulmonologist or a physician adequately trained in pulmonology. All PFT technicians or other experienced participating persons will be trained on the specific requirements and have refreshment on ATS/ERS recommendations before starting on the study and will receive additional training when non-compliance issues are identified.

DL_{CO} tests will be conducted according to the ATS/ERS guidelines and will be assessed by the single breath method [Macintyre 2005]. DL_{CO} efforts, up to a maximum of five, will be performed to produce at least two technically acceptable and repeatable traces (according to ATS/ERS guideline criteria; see DL_{CO} manual). There must be a minimal interval of at least 4 min between each effort performed. Data from all DL_{CO} efforts collected during a session will be captured in the eCRF.

All recorded DL_{CO} values will be transmitted to a centralized reader and will be reviewed by independent readers. Quality of the assessments will be evaluated for compliance with ATS/ERS criteria and will be reported in the eCRF; queries may be sent to the sites for clarification. If quality issues are identified, additional training will be provided to the site. Assessments may need to be repeated if results are of poor quality and/or inconclusive as per central reading facility. The selection of the DL_{CO} values to be used for the main endpoint derivations will be validated by the independent readers. The mean of two best within-session DL_{CO} efforts that meet the acceptability criteria according to the independent reader assessment will be selected and calculated by the sponsor as the value for this session. If only one acceptable effort is achieved, this will be selected by the sponsor for this session. If no acceptable effort is achieved, the effort with the highest inspiratory vital capacity will be selected by the sponsor for this session. For the analysis, the results will be corrected for Hb concentration and reported at a standard Hb concentration using the Cotes method [Macintyre 2005] (calculated by the sponsor in the database using the Hb value from the central laboratory).

The sites participating in the sub-study will use their own DL_{CO} gas analyzer and must ensure it is calibrated and working properly. The gas analyzer will need to fulfill the technical requirements and recommendations for range and accuracy for DL_{CO} assessment from the ATS/ERS guidelines [Macintyre 2005]. A copy of the calibrations of the day of a 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. In addition, frequent testing involving the same healthy subject control (biological quality check) or a DL_{CO} simulator will ensure continuous monitoring of the gas analyzer measurement accuracy over time (see details in PFT manual).

If clinically significant alterations in DL_{CO} variables indicating a pulmonary condition that could result in increased risk for the subject are observed, she/he may be prematurely discontinued from the study drug at the discretion of the investigator. 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.

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 to ensure validity of the data collected. To the extent logistically feasible, all within-subject DL_{CO} should preferably be done by the same tester. A back-up tester (PFT technician, respiratory therapist, or expert or an equally experienced person according to the ATS/ERS guidelines [Miller 2005a]) may conduct DL_{CO} if the primary tester is not available. This back-up tester must be trained on the specific requirements and have had refreshment on ATS/ERS recommendations before starting on the study. DL_{CO} conduct, documentation, performance, training details (of the responsible PFT site personnel), and quality control procedures are described in the PFT manual.

7.3.7 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 screening can be used; if available, there is no need to repeat CXR at 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 the EOT visit 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 less than 24 weeks of the pre-randomization CXR. All examinations will be documented in the source documents of the subject. Examinations 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.

7.3.8 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 7.3.14], and transferred to the eCRF database.

Only subjects with a negative test at Screening and without CXR findings [see Section 7.3.7] at 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.

7.3.9 Ophthalmologic assessments

Ophthalmologic assessments will be performed by an ophthalmologist at Visits 1 (Screening), 6 (Week 12), 7 (Week 24), 10 (Week 60), and 14 (EOT). Testing at Visit 1 can be performed at any time during the pre-randomization period. Testing at Visits 6, 7, 10 (Weeks 12, 24, and 60) may be performed up to 7 days prior to or after the visit date. At Visit 14 (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 ophthalmological examination will be done in the event of visual symptoms or findings suggestive of active uveitis [see Section 5.1.13.7].

The safety ophthalmological assessment includes previous eye history and ophthalmic condition, 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. Additionally, the safety ophthalmological assessment will include fluorescence angiography in case of suspicion of active uveitis at Screening or during a scheduled ophthalmological assessment (unless contra-indicated according to the ophthalmologist) [see Section 5.1.13.7]. 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. Fluorescence angiography (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.

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. All ophthalmological examinations will be documented in the source documents of the subject. All parameters 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 parameters, 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.

7.3.10 Optical Coherence Tomography

OCT will be assessed at Visits 1 (Screening), 6 (Week 12), 7 (Week 24), 10 (Week 60), and 14 (EOT). Testing at Visit 1 can be performed at any time during the pre-randomization period. Testing at Visits 6 and 10 (Week 12 and 60) may be performed up to 7 days prior to or after the visit date. At Visit 14 (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 examination 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 5.1.13.7]. 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 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. 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], 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.

7.3.11 Weight and height

Body weight will be measured at Visits 1 (Screening), 10 (Week 60) and 14 (EOT). In addition, unscheduled body weight measurement may be performed at any time during the study (Visits U1, U2, etc.). Body height is only measured at Visit 1 (Screening). Data will be collected in the eCRF.

7.3.12 Physical examination

Physical examination is performed by the principal investigator or treating neurologist at Visits 1 (Screening), 2 (Baseline), 5, 6, 7, 10, and 12 (Weeks 4, 12, 24, 60, and 84), 14 (EOT), and at unscheduled visits due to relapses (R1, R2, etc.). If applicable, physical examination will also be performed at Visits 10A and 14A 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.

7.3.13 Dermatological examination

A complete skin examination will be performed by a dermatologist at Visits 2 (Baseline), 10 (Week 60), and 14 (EOT). If applicable, dermatological examination will also be performed at Visits 10A and 14A 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.

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.

7.3.14 Laboratory assessments

7.3.14.1 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., subject lives far away from the site and cannot return every 2 weeks during the first 24 weeks), laboratory samples could be drawn in a local laboratory close to where the subject lives and analyzed at the central laboratory. In such circumstances, the local laboratory must be provided with the central laboratory 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.

Local laboratory results will only be collected in exceptional cases (e.g., subject is hospitalized in a different hospital from the study center due to a medical emergency). In cases where a local laboratory is used for the collection **and** analysis of blood samples, the local laboratory results (with the corresponding normal ranges) will be entered into the clinical database via dedicated eCRF pages. In all cases, testing of total lymphocytes count at a local laboratory is not to be assessed and collected unless deemed absolutely necessary by the investigator for maintaining safety of the subject.

If a central laboratory sample is lost, has deteriorated or cannot be analyzed for whatever reason, the investigator may collect an additional sample as soon as possible for retest analysis if still clinically relevant.

The central laboratory will provide all laboratory results by fax or normal mail to the site with the exception of the results of the total WBC count, total lymphocyte count, and teriflunomide plasma concentration.

- Total WBC count and total lymphocyte count: WBC and lymphocyte count results during treatment period will not be communicated to the site unless 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 5.1.13].

- Teriflunomide plasma concentration:
  - For subjects not entering the AC-058B303 extension study: Teriflunomide plasma concentration may be assessed if needed to determine if contraception can be discontinued [see Section 5.1.14.4]. Teriflunomide plasma concentration can also be assessed for any subjects not entering the extension study if deemed necessary for the subject's safety, at the investigator's discretion. Sites will receive notification if teriflunomide plasma level is < 0.02 mg/L. Sites will also receive notification if teriflunomide plasma level is ≥ 0.02 mg/L; In this event, the principal investigator / treating neurologist will decide whether the accelerated elimination procedure should be repeated (e.g., if rapid elimination is needed, such as a wish to become pregnant or father a child [see Section 5.1.14] or whether physiological elimination alone is warranted).
  - For subjects who enter the AC-058B303 extension study: The timing of teriflunomide test and procedures are described in the AC-058B303 study protocol (separate protocol).

- A WBC count $> 20 \times 10^9$/L or a lymphocyte count $> 8.0 \times 10^9$/L is recorded by the central laboratory [see Appendix 6]. In this event, an alert containing the total WBC or lymphocyte count result (as applicable) will be sent to the principal investigator and the sponsor.

- WBC and total lymphocyte counts measured at Visit 1 (Screening), 2 (Baseline), and any of the visits in the PTOP (if applicable) will be visible to the 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.

7.3.14.2 Laboratory tests

Blood samples will be drawn preferably in a fasted condition and, when applicable, before the morning administration of study medication at Visit 1 (Screening), Visit 2 (Baseline), Visits 4 to 13 (Week 2, 4, 12 and every 12 weeks thereafter), Visit 14 (EOT), Visit 15 (FU1), and Visit 16 (FU2) and, if applicable, at the corresponding visits in the PTOP (Visits 7A, 10A, 12A, and 14A). **In addition, ALT, AST, INR, alkaline phosphatase (AP), and total bilirubin will be assessed on a bi-weekly basis until Week 24 (i.e., at Week 6, 8, 10, 14, 16, 18, 20, and 22). Furthermore, total WBC and total lymphocyte counts will be assessed on a 4-weekly basis until Week 24 (i.e., at Week 8, 16, and 20).** Unscheduled laboratory tests may be performed at any time during the study (Visits U1, U2, etc.).

Urinalysis will be assessed using dipsticks at Visit 1 (Screening), Visits 5, 6, 7, 10, and 12 (Week 4, 12, 24, 60, and 84), Visit 14 (EOT), and Visit 15 (FU1) and, if applicable, at the corresponding visits in the PTOP (Visits 7A, 10A, 12A, and 14A). In addition, unscheduled urinalysis may be performed at any time during the study (Visits U1, U2, etc.).

Laboratory assessments at Visit 1 must be performed a minimum of 7 days before the laboratory assessment at Visit 2.

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

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

Clinical chemistry

- Fasting glucose
- ALT, AST, 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).

*In the event of a positive Hepatitis C antibody test, site can draw an additional confirmatory blood sample for testing of Hepatitis C viral RNA.

Biomarkers and 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 or for analysis of biomarkers.

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 7.3.8].

Pregnancy test

A serum pregnancy test for WOCBP will be performed at Visit 1 (Screening) and at Visit 16 (FU2) and if pregnancy is suspected during the study. Urine pregnancy tests will be performed at Visit 2 (Baseline), Visits 4 to 12 (Weeks 2, 4, 12, and every 12 weeks thereafter), Visit 14 (EOT), and Visit 15 (FU1). 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. Urine pregnancy testing, performed at home every 4 weeks, will be continued after last study drug intake on a 4-weekly basis until 6 weeks after the first of two tests showing teriflunomide plasma level < 0.02 mg/L (results to be communicated by telephone call 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 and a second confirmed negative urine pregnancy test prior to randomization. The two tests must be performed a minimum of 3 weeks 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

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 parameter 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.

Evaluation of teriflunomide elimination:

The testing of teriflunomide plasma concentration may only be conducted for women of childbearing potential and fertile male subjects, if needed, to confirm that contraception can be discontinued.

For subjects not entering the AC-058B303 study, teriflunomide plasma levels will be determined by the central laboratory if necessary to determine if contraception can be discontinued. Teriflunomide plasma concentration can also be assessed for any subjects not entering the extension study if deemed necessary for the subject's safety, at the investigator's discretion. The testing should not occur before 20 weeks after last drug

intake (if accelerated elimination procedure has been completed) or not before 35 weeks (i.e., 8 months) after last drug intake or EOS, whichever is last (if accelerated elimination procedure has not been completed) [see Sections 5.1.14.1 and 5.1.14.4] by a previously described high-performance liquid chromatography method [Sobhani 2010]. The possibility to test teriflunomide by the central laboratory after EOS will be offered. In this case, the results will only be communicated to the site.

For subjects who enter the AC-058B303 extension study: the timing of teriflunomide tests is described in the separate AC-058B303 study protocol.

7.4 Electronic self-rated version of the Columbia-Suicide Severity Rating Scale (eC-SSRS)

The electronic self-rated version of the eC-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 10-Week 60 and Visit 14-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 computer administration. Subjects will be asked to respond to standardized clinical questions aiming 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 subjects 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 PGI-S of Fatigue, WPAI:MS and SF-36v2™ have been completed. Preferably, subjects would complete the eC-SSRS while waiting for their appointment before any interaction with health care providers.

A sample of the eC-SSRS (in English) is provided as Appendix 16. The scale will be administered using a telephone-based system. The clinical site will provide a telephone to be used during above mentioned visits and the subject will respond to the questions with the telephone keypad. The data 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 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 Visits 6, 7, 10, 12 (Weeks 12, 24, 60, and 84), and 14 (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 recommended that the SF-36v2™ Questionnaire is completed prior to any clinical assessments, after the PGI-S of Fatigue and 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 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 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 6 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 Visits 6, 7, 10, 12 (Weeks 12, 24, 60, and 84), and 14 (EOT).

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

It is recommended that the WPAI:MS Questionnaire is completed prior to any clinical assessments, after the PGI-S of Fatigue has been completed. 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 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 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 Visits 4 to 13 (Weeks 2, 4, 12, 24, 36, 48, 60, 72, 84, and 96), and 14 (EOT) as well as at unscheduled visits due to relapse (R1, R2,…).

Subjects will be asked to report any visits to emergency medical services facilities due to MS since the last study visit, and 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

These assessments are done to investigate PD and PK effects of ponesimod.

7.7.1 Pharmacokinetic assessments

7.7.1.1 Timing for sampling

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 Visits 6, 10 and 14 (EOT; Week 12, 60 and 108). Additionally, at Visits 3 and 6 (Day 1 and Week 12), PK samples will be drawn 3 h (+/− 15 min) 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.

7.7.1.2 Procedures for sampling

Up to 3 mL of blood must be collected in tubes containing ethylenediaminetetraacetic acid. Immediately following collection of the required blood volume, the tubes must be slowly tilted backwards and forwards (no shaking) to bring the anti-coagulant into solution, and immediately cooled on ice. Within 30 min of collection, the tubes must be centrifuged at approximately 1500 g for 10 min at 2 to 8 °C. When a centrifuge that can be cooled is not available, the blood samples and the bucket of the centrifuge must be cooled on ice prior to centrifugation. The plasma must be transferred into one labeled opaque polypropylene tube to avoid carry-over of erythrocytes. All samples must be stored in an upright position ≤ –20 °C (Freezer settings: intended temperature –25 °C; upper limit –20 °C). The exact time of collection of the blood sample must be entered in the eCRF, as well as the status of the subject (fed or fasted), and the time of last previous study drug intake. Blood samples for PK analysis must be drawn prior to study drug intake on the day of the visit (except at Visits 3 and 6, when a sample will be drawn 3 h post-dose).

To prevent degradation of ponesimod in the plasma samples, exposure to light should be minimized. After centrifugation, plasma samples should be kept in the dark.

Note:

The 3-h 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.

7.7.1.3 Labeling

Details of the collection and shipment of the samples can be found in the laboratory manual provided to the investigator. The tubes and labels for the samples will be provided to the investigator and/or staff by the central laboratory.

7.7.1.4 Bioanalysis

The concentration of ponesimod in plasma will be determined by a validated liquid chromatography-tandem mass spectrometry assay by Idorsia PK analyses services. The lower limit of quantification is 1 ng/mL.

Concentrations will be calculated by interpolation from a calibration curve. Quality control samples will be analyzed throughout the study. Their measured concentrations will be used to determine between-run and overall precision and accuracy of the analyses.

If required, a selection of plasma PK samples may be analyzed by, or under the supervision of, the sponsor to assess the chiral inversion of ponesimod, and/or document the presence of circulating metabolites using a qualified research method.

The samples will be destroyed upon signature of the Clinical Study Report.

7.7.2 Pharmacodynamic assessments

The PD marker is total lymphocyte counts, which will be measured as part of the hematology tests [see Section 7.3.14].

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

Test	Number of tests	Volume per test	Total volume per test throughout the study
Viral serology at Screening[6]	1	5 mL	5 mL
Interferon gamma release assay for tuberculosis at Screening	1	3 x 1 mL	3 mL
Serum sample at Baseline[1]	1	5 mL	5 mL
Hematology[2]	18	3 mL	54 mL
Blood chemistry[3]	23	7.5 mL	172.5 mL
INR	23	3 mL	69 mL
Ponesimod PK	5	3 mL	15 mL
Teriflunomide plasma concentration	2	5 mL	10 mL
Vaccine specific Antibody titres[4]	2	5 mL	10 mL
Total blood volume drawn throughout the study: 343.5 mL[5, 6]			

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/µ L.
3. Includes serum pregnancy test at Screening, if needed.
4. Additional samples may be taken in the event of a vaccination with a non-live vaccine.
5. 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.
6. In the event of a positive Hepatitis C antibody test, site can draw an additional confirmatory blood sample (6 mL) for testing of Hepatitis 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 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 in account:

- The subject must come to the clinic in a fasted condition for all visits and, when applicable, 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 with an additional sample drawn 3 h post-dose at Visits 3 (Day 1) and 6 (Week 12). On these visits, post-dose 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 other discussion with the investigator or treating neurologist. Subjects will provide responses to the questionnaires while waiting for their appointment. Questionnaires should be completed in the following order:
  - PGI-S of Fatigue
  - WPAI:MS
  - SF-36v2™
  - eC-SSRS

To ensure compliance, at each visit the study personnel must remind WOCBP and fertile men 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. Subjects who were not eligible because of a negative test for varicella-zoster antibodies may also be re-screened once after having been vaccinated. All pre-randomization assessments should then be repeated at the time of re-screening (with the exception of CXR and dermatological examination if performed within 90 days prior to the date of re-screening).

Unscheduled visits may be performed at any time during the study. Depending on the reason for the unscheduled visit (e.g., relapse, AE, central laboratory re-test), appropriate assessments may be performed based on the judgment of the investigator and must be recorded in the eCRF. 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 the pre-dose assessments of Visit 3 (Day 1).

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

8.1.1 Visit 1 (Screening)

Visit 1 will be performed from 45 to 11 days prior to randomization. The Visit 1 date is defined as the date of start of pre-randomization period (i.e., signature of the ICF). 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 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].
- EDSS/FS (performed by the efficacy assessor)

- SBP/DBP
- Body weight and height
- Body temperature
- Physical examination
- Ophthalmological examination (under the responsibility of the ophthalmologist)
- OCT (under the responsibility of the ophthalmologist)
- Hematology, 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 and will be instructed to complete the symptoms domain of the FSIQ-RMS at home, provided no other assessment performed in the meantime excludes the subject). Once the results from the laboratory assessments confirm the subject's eligibility, the site coordinator will contact the subject to instruct him/her to start the completion of the FSIQ-RMS [see Section 7.2.7].
- Patient Preference Questionnaire (sub-study at selected site only; subjects who appear eligible based on the assessments made during this visit will be provided with the Patient Preference Questionnaire and will be instructed to complete the questionnaire at home, before coming to site for Visit 2).
- CXR (Any CXR performed within 90 days prior to 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 inclusion/exclusion criteria. The next visit (Visit 2) will only be scheduled if the subject meets all the eligibility criteria. 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 screen failure subjects).

8.1.2 Visit 2 (Baseline)

Visit 2 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, the following points should be considered:

- All Visit 1 assessments repeated at Visit 2 (Baseline; i.e., hematology, blood chemistry, 12-lead ECGs, physical examination, and SBP/DBP) must be performed at least 7 days after the Visit 1 assessments.
- 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).
- For WOCBP, the urine pregnancy test at Visit 2 must be performed at least 3 weeks after the serum pregnancy test performed at Visit 1.
- PGI-S of Fatigue (subject completes the questionnaire prior to any clinical assessments or interaction with health care providers, preferably while waiting for their appointment)
- WPAI:MS (subject completes the questionnaire after PGI-S of Fatigue, 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 PGI-S of Fatigue and 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 PGI-S of Fatigue, WPAI:MS, and SF-36v2^{TM} 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 [see Section 5.2]
- EDSS/FS (performed by the efficacy assessor)
- MS relapse
- SBP/DBP
- 12-lead ECG
- Physical examination
- Body temperature
- Skin examination (performed by the dermatologist). 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.
- Hematology, blood chemistry
- Urine pregnancy test for WOCBP
- Additional serum sample for potential retrospective analysis of viral serology titers
- Spirometry

- DL_{CO} (if applicable; under the responsibility of the pulmonologist)
- MRI
- MSFC and SDMT (second practice test)
- 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.
- Patient Preference Questionnaire (sub-study at selected site only; subjects who appear eligible based on the assessments made during this visit will be instructed to complete the questionnaire at home before coming to site for Visit 3).
- If the subject expresses any concern regarding her/his ability to swallow the medicine, she/he will be shown an example of a capsule to be used in the study and will be given the option to perform a swallowing test with a placebo capsule in order to test future compliance with study drug intake requirements. The test is to be done under the supervision of the site personnel.

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 screen failure subjects).

8.2 Treatment period

The treatment period consists of Visits 3 to 14 (Randomization Day 1, Week 2, 4, 12, and every 12 weeks thereafter until EOT/Week 108).

8.2.1 Visit 3 – Randomization Day 1

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 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 assessments during this visit will be divided into two parts: before (pre-dose) and after (post-dose) the administration of the study drug.

8.2.1.1 Visit 3 – Day 1 – pre-dose assessment

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 [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 and fertile men only)
- 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.

8.2.1.2 Visit 3 – Day 1 – Randomization and post-dose assessment

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 h post-dose. Starting at 4 h post-dose, the first-dose administrator must check whether the subject fulfills the discharge criteria from cardiac monitoring [see Section 5.1.11]. Subjects may be discharged from cardiac monitoring if they meet the discharge criteria before 12 h post-dose but no sooner than the (report of) 4 h post-dose ECG has been evaluated by the first-dose administrator [see Section 5.1.11].

Visit 3 randomization and 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 min) for up to 12 h post-dose with a minimum of 4 h post-dose (under the responsibility of the first-dose administrator)
- 12-lead ECG hourly (+/− 15 min) until the evaluation of the ECG performed at 4 h post-dose is available. For subjects not meeting the discharge criteria at 4 h post-dose, further ECGs will be performed every hour for up to 12 h post-dose until the discharge criteria are met (under the responsibility of the first-dose administrator)
- PK sampling at 3 (+/− 15 min) h post-dose
- Recording of AEs and SAEs (Note: 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 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 and fertile men 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 all blister packs (used, partially used and unused blister packs)
  - come fasted to the site
  - 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. To maintain the blinding of the study, subjects assigned to the teriflunomide arm will mock up-titrate. 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 Additional safety laboratory tests until Week 24 (Week 6, 8, 10, 14, 16, 18, 20, and 22)

The test window is ± 3 days. Under specific circumstances (e.g., subject lives far away from the site and cannot return every 2 weeks during the first 24 weeks), laboratory samples could be drawn in a local laboratory close to where the subject lives, and analyzed at central laboratory [see Section 7.3.14.1].

At Week 6, 10, 14, 18, and 22:

- Laboratory tests including AST, ALT, INR, AP and total bilirubin

At Week 8, 16, and 20:

- Laboratory tests including:
  - AST, ALT, INR, AP and total bilirubin
  - Total WBC counts
  - Total lymphocyte counts.

8.2.3 Visit 4 – Day 15

The visit window for this visit is ± 1 day. 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 3 days prior to or after this visit date. The visit includes:

- 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)
- MS relapse

- Health care resource utilization since the last visit
- Hematology, blood chemistry
- Urine pregnancy test for WOCBP
- Recording of AEs and SAEs
- Study medication accountability and compliance review
- IRT call and study drug dispensing
- Remind WOCBP and fertile men 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 all blister packs (used, partially used and unused blister packs)
  - come fasted to the site
  - 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 ± 3 days. The ECG 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:

- 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)
- Body temperature
- MS relapse
- Health care resource utilization since the last visit
- Physical examination
- Spirometry (pre-dose)
- DL_{CO} (if applicable; pre-dose, under the responsibility of the pulmonologist)
- Hematology, blood chemistry
- Urinalysis
- Urine pregnancy test for WOCBP
- Recording of AEs and SAEs
- Study medication accountability and compliance review

- Dispense one urine pregnancy test 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 and fertile men 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 all blister packs (used, partially used and unused blister packs)
  - come fasted to the site
  - 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 Visit 6 – Week 12 and Visit 7 – Week 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:

- PGI-S of Fatigue (subject completes the questionnaire prior to any clinical assessments or interaction with health care providers, preferably while waiting for their appointment)
- WPAI:MS (subject completes the questionnaire after PGI-S of Fatigue, 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 PGI-S of Fatigue and WPAI:MS, prior to any clinical assessments or interaction with health care providers, preferably while waiting for their appointment)
- 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 and 3 h (+/− 15 min) post-dose; Visit 6 only)
- MS relapse
- EDSS/FS (performed by the efficacy assessor)
- Health care resource utilization since the last visit
- MSFC/SDMT
- CGI-C
- Physical examination

- Body temperature
- Spirometry (pre-dose; Visit 6 only)
- DL_{CO} (if applicable; pre-dose; Visit 6 only; under the responsibility of the pulmonologist)
- OCT (under the responsibility of the ophthalmologist)
- Ophthalmological examination (under the responsibility of the ophthalmologist)
- Hematology, blood chemistry
- PK sampling (pre-dose and 3 h (+/− 15 min) post-dose; Visit 6 only)
- Urinalysis
- Urine pregnancy test for WOCBP
- Recording of AEs and SAEs
- Study medication accountability and compliance review
- IRT call and study drug 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 and fertile men 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 all blister packs (used, partially used and unused blister packs)
  - come fasted to the site
  - 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
- Give instructions for completion of FSIQ-RMS [see Section 7.2.7].

8.2.6 In-between-visit telephone calls until Weeks 108 (Weeks 18, 30, 42, 54, 66, 78, 90, and 102)

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, and 102 (+/− 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.

8.2.7 Visits 8, 9, 11, and 13 – Weeks 36, 48, 72, and 96

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:

- 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)
- Body temperature
- MS relapse
- EDSS/FS (performed by the efficacy assessor)
- Health care resource utilization since the last visit
- Hematology, blood chemistry
- Urine pregnancy test for WOCBP
- Recording of AEs and SAEs
- Study medication accountability and compliance review
- IRT call and study drug 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 and fertile men 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 all blister packs (used, partially used and unused blister packs)
  - come fasted to the site
  - 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 Visit 10 – Week 60

The visit window for this visit 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 visit includes:

- PGI-S of Fatigue (subject completes the questionnaire prior to any clinical assessments or interaction with health care providers, preferably while waiting for their appointment)

- WPAI:MS (subject completes the questionnaire after PGI-S of Fatigue, prior to any clinical assessments or interaction with health care providers, preferably while waiting for their appointment)
- SF-36v2™ (subject completes the questionnaire, after PGI-S of Fatigue and 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 PGI-S of Fatigue, WPAI:MS, and SF-36v2™ prior to any clinical assessments or interaction with health care providers, preferably while waiting for their appointment)
- 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
- EDSS/FS (performed by the efficacy assessor)
- MRI
- Health care resource utilization since the last visit
- MSFC/SDMT
- CGI-C
- Body weight
- Physical examination
- Body temperature
- Skin examination (skin examination performed by the dermatologist)
- Spirometry (pre-dose)
- DL_{CO} (if applicable; pre-dose; under the responsibility of the pulmonologist)
- OCT (under the responsibility of the ophthalmologist)
- Ophthalmological examination (under the responsibility of the ophthalmologist)
- Hematology, blood chemistry
- PK sampling (pre-dose)
- Urinalysis
- Urine pregnancy test for WOCBP
- Recording of AEs and SAEs
- Study medication accountability and compliance review
- IRT call and study drug 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 and fertile men 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 all blister packs (used, partially used and unused blister packs)
  - come fasted to the site
  - 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
- Give instructions for completion of FSIQ-RMS [see Section 7.2.7].

8.2.9 Visit 12 – Week 84

The visit window for this visit 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 visit includes:

- PGI-S of Fatigue (subject completes the questionnaire prior to any clinical assessments or interaction with health care providers, preferably while waiting for their appointment)
- WPAI:MS (subject completes the questionnaire after PGI-S of Fatigue, 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 PGI-S of Fatigue and WPAI:MS, prior to any clinical assessments or interaction with health care providers, preferably while waiting for their appointment)
- 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
- EDSS/FS (performed by the efficacy assessor)
- Health care resource utilization since the last visit
- MSFC/SDMT
- CGI-C
- Physical examination
- Body temperature
- Hematology, blood chemistry

- Urinalysis
- Urine pregnancy test for WOCBP
- Recording of AEs and SAEs
- Study medication accountability and compliance review
- IRT call and study drug 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 and fertile men 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 all blister packs (used, partially used and unused blister packs)
  - come fasted to the site
  - 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
- Give instruction for completion of FSIQ-RMS [see Section 7.2.7].

8.2.10 Visit 14 – EOT Visit

The EOT visit will take place at Week 108 (± 7 days) or earlier in case of premature discontinuation of study drug. In all cases, 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. Specific assessments (i.e., MRI, skin examination, CXR, spirometry, DL_{CO}, OCT / Ophthalmological examination, hematology, blood chemistry, PK) may be conducted up to 7 days prior to last intake of study drug. If a study treatment interruption is transformed into a 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. 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:

- PGI-S of Fatigue (subject completes the questionnaire prior to any clinical assessments or interaction with health care providers, preferably while waiting for their appointment)
- WPAI:MS (subject completes the questionnaire after PGI-S of Fatigue, prior to any clinical assessments or interaction with health care providers, preferably while waiting for their appointment)

- SF-36v2™ a second time (subject completes the questionnaire, after PGI-S of Fatigue and 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 PGI-S of Fatigue, WPAI:MS, and SF-36v2™ prior to any clinical assessments or interaction with health care providers, preferably while waiting for their appointment)
- Recording of changes in concomitant medications
- Assessment and recording in the eCRF of methods of contraception (for WOCBP only)
- SBP/DBP
- 12-lead ECG
- MS relapse
- EDSS/FS (performed by the efficacy assessor)
- MRI (in case of premature study treatment discontinuation, the MRI at EOT does not need to be performed if the EOT visit occurs within less than 4 weeks of the MRI assessment at Visit 10 [Week 60]; may be conducted up to 7 days before last intake of study drug)
- Health care resource utilization since the last visit
- MSFC/SDMT
- CGI-C
- Body weight
- Physical examination
- Body temperature
- Skin examination (performed by the dermatologist, may be conducted up to 7 days before last intake of study drug)
- CXR (in case of premature study treatment discontinuation, the CXR at EOT does not need to be performed if the EOT visit occurs within less than 24 weeks of the pre-randomization CXR) (may be conducted up to 7 days before last intake of study drug)
- Spirometry (may be conducted up to 7 days before last intake of study drug)
- DL_{CO} (if applicable; under the responsibility of the pulmonologist; may be conducted up to 7 days before last intake of study drug)
- OCT (under the responsibility of the ophthalmologist; may be conducted up to 7 days before last intake of study drug)
- Ophthalmological examination (under the responsibility of the ophthalmologist)
- Hematology, blood chemistry (may be conducted up to 7 days before last intake of study drug)
- PK sampling (pre-dose) (may be conducted up to 7 days before last intake of study drug)
- Urinalysis

- Urine pregnancy test for WOCBP
- Recording of AEs and SAEs
- Study medication accountability and compliance review
- IRT call
- Remind WOCBP and fertile men to use the methods of contraception defined for this study. The reminders must be documented in the hospital chart
- Dispense cholestyramine or activated charcoal
- Patient Preference Questionnaire (if applicable; subjects will be instructed to complete the questionnaire at home before coming to FU1 visit)
- Schedule an appointment for next visit and instruct subject to:
  - come fasted 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
- Give instruction for completion of FSIQ-RMS [see Section 7.2.7].

8.3 Post-treatment period

8.3.1 Post-treatment safety follow-up period

The safety FU period includes Visits 15 and 16 (FU1 and FU2).

- For subjects who enter the extension study, the safety FU period lasts for 14 to 37 days after the last dose of study drug and consists of a safety FU visit (FU1) at 15 days (−1 day, +7 days) after the last dose of study drug, and for subjects who need to repeat/complete the accelerated elimination procedure of teriflunomide after FU1, there is also an abbreviated safety FU2 visit (at 23–37 days after the last dose of study drug). For subjects who transition to the AC-058B303 study without FU2 visit, the FU1 visit corresponds to the EOS visit.
- For subjects who do not enter the extension study, the safety FU period lasts for 30 days after the last dose of study drug and includes two safety FU visits (FU1, FU2) at 14–22 and 30–37 days after the last dose of study drug, respectively. For these subjects, the EOS visit corresponds to the 30-day FU visit (FU2) or to the last visit of PTOP (i.e., Visit 14A [Week 108] of the PTOP), whichever is last.

8.3.1.1 Visit 15 – FU1

The FU1 visit will take place 14–22 days after the last dose of study drug. For subjects continuing in the AC-058B303 extension study, it is preferable to schedule the visit after the planned completion of the accelerated elimination procedure for teriflunomide. The visit includes:

- Recording of changes in concomitant medications
- Assessment and recording in the eCRF of methods of contraception (for WOCBP only)
- SBP/DBP
- 12-lead ECG
- Body temperature
- MS relapse
- Spirometry
- DL_{CO} (if applicable; under the responsibility of the pulmonologist)
- Hematology, blood chemistry
- Accelerated elimination procedure compliance review
  - If compliance is not confirmed: restart or complete missing intake for the accelerated elimination procedure
- Urinalysis
- Urine pregnancy test for WOCBP
- Recording of AEs and SAEs
- Remind WOCBP and fertile men to use the methods of contraception defined for this study. The reminders must be documented in the hospital chart
- If applicable, schedule an appointment for next visit and instruct subject to:
  - come fasted 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.

8.3.1.2 Visit 16 – FU 2

For subjects not continuing in the AC-058B303 extension study, the FU2 visit will take place between 30 and 37 days after the last dose of study drug.

- Recording of changes in concomitant medications
- Assessment and recording in the eCRF of methods of contraception (for WOCBP only)
- SBP/DBP
- 12-lead ECG
- Body temperature
- MS relapse
- EDSS/FS (performed by the efficacy assessor)
- Spirometry
- DL_{CO} (if applicable; under the responsibility of the pulmonologist)
- Hematology, blood chemistry
- Accelerated elimination procedure compliance review (if applicable)

  - If compliance is not confirmed: decide whether to restart or complete the accelerated elimination procedure
- Serum pregnancy test for WOCBP
- Recording of AEs and SAEs
- Dispense urine pregnancy tests for WOCBP, remind to test for pregnancy on a 4-weekly basis (+/−4 days – until the first of two tests showing teriflunomide plasma level < 0.02 mg/L [see Section 5.1.14]) and to communicate the results to the principal investigator / treating neurologist [by phone])
- Remind WOCBP and fertile men to use the methods of contraception defined for this study (until the first of two tests showing teriflunomide plasma level < 0.02 mg/L [see Section 5.1.14]. The reminders must be documented in the hospital chart
- If applicable, schedule an appointment for next visit and instruct subject to:
  - come fasted to the site at the next visit
  - 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

For subjects continuing in the AC-058B303 extension study and in whom compliance with teriflunomide elimination procedure was assessed as not sufficient at FU1 visit, an abbreviated FU2 will take place between 23 and 37 days after the last dose of study drug. The abbreviated FU2 visit includes:

- Accelerated elimination procedure compliance review
- Recording of AEs/SAEs,
- MS relapse
- Recording of changes in concomitant medications

If the teriflunomide accelerated procedure is still assessed as not sufficient at abbreviated FU2 visit, the subject will be not eligible to enter the extension study and will need to perform the remaining assessments scheduled for a full FU2 visit.

8.3.2 Post-treatment observation period

Subjects who prematurely discontinue study treatment will perform the EOT and safety FU visits (FU1, FU2) and will enter the PTOP which lasts until 108 weeks after randomization (i.e., planned 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 3.1.3.2 and Table 3]. After FU2 has been performed, the study visits must continue according to the original visit and assessment schedule. If the first PTOP visit window overlaps with FU1 or FU2 visits, visits and assessments can be combined.

The PTOP consists of visits 6A, 7A, 8A, 9A, 10A, 11A, 12A, 13A and 14A conducted at Weeks 12, 24, 36, 48, 60, 72, 84, 96, and 108. 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:

- Recording of changes in concomitant medications
- Assessment and recording in the eCRF of methods of contraception (for males and WOCB; until 6 weeks after the first of two tests showing teriflunomide plasma level < 0.02 mg/L)
- SBP/DBP
- 12-lead ECG (Visits 10A and 14A only)
- Body temperature
- MS relapse
- Physical examination (Visits 10A, and 14A only)
- Skin examination (Visits 10A and 14A only; performed by the dermatologist)
- EDSS/FS (performed by the efficacy assessor)
- MRI (Visits 10A and 14A only)
- Spirometry (Visit 14A only)
- DL_{CO} (if applicable; under the responsibility of the pulmonologist; Visit 14A only)
- Hematology, blood chemistry (Visit 7A, 10A, 12A, and 14A only)
- Urinalysis (Visits 7A, 10A, 12A, and 14A only)
- Recording of AEs and SAEs
- Dispense two urine pregnancy tests for WOCBP, remind to test for pregnancy on a 4-weekly basis (+/−4 days – until the first of two tests showing teriflunomide plasma level < 0.02 mg/L [see Section 5.1.14]) and to communicate the results to the principal investigator / treating neurologist [by telephone])
- Remind WOCBP and fertile men to use the methods of contraception defined for this study (until 6 weeks after the first of two tests showing teriflunomide plasma level < 0.02 mg/L [see Section 5.1.14]). The reminders must be documented in the hospital chart
- Give instruction for completion of FSIQ-RMS at Visit 6A–Week 12, Visit 7A–Week 24, Visit 10A–Week 60, Visit 12A–Week 84, and Visit 14A–Week 108 only). At Visit 14A (Week 108), the FSIQ-RMS will be completed prior to the visit, ideally, during the 7 consecutive days preceding the visit
- PGI-S of Fatigue (at Visit 6A–Week 12, Visit 7A–Week 24, Visit 10A–Week 60, Visit 12A–Week 84, and Visit 14A–Week 108 only; subject completes the questionnaire prior to any clinical assessments or interaction with health care providers, preferably while waiting for their appointment).

- If applicable, schedule an appointment for the next visit and instruct subject to:
  - come fasted 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.

8.4 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 drug (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 17] and the relapse symptoms form [see Appendix 18] 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 from the 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., and increase 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 AEs 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 AEs on the AE page of the eCRF and, if applicable, on the SAE form).

Additionally, the following assessments must be done during those visits:

- PGI-S of Fatigue (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 PGI-S of Fatigue, prior to any clinical assessments or interaction with health care providers, preferably while waiting for their appointment)
- Recording of changes in concomitant medications
- MS relapse
- EDSS/FS (performed by the efficacy assessor)
- CGI-C
- Health care resource utilization since the last visit
- Recording of AEs and SAEs
- Schedule an appointment for next visit and instruct subject to:
  - come fasted 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
- Give instruction for completion of FSIQ-RMS [see Section 7.2.7].

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 5.1.10, 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):

- 12-lead ECG pre-dose and hourly (+/− 15 min) for up to 12 h post-dose (under the responsibility of the first-dose administrator)
- SBP/DBP pre-dose and hourly (+/− 15 min) for up to 12 h 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 h post-dose but no sooner than 4 h post-dose [see Section 5.1.11].

The following assessments need to be done during the visit 14 days after the day of re-initiation:

- 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 performed in addition.

8.5 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:

- PGI-S of Fatigue (subject completes the questionnaire prior to any clinical assessments or interaction with health care providers, preferably while waiting for their appointment)
- Assessment of concomitant medications
- Assessment of methods of contraception (for WOCBP only)
- PFTs
- SBP/DBP
- 12-lead ECGs (e.g., in case of need of concomitant treatment with a QT-prolonging drug with known risk of Torsades de Pointes [see Appendix 3])
- Ophthalmological examination (e.g., presence of visual symptoms suggestive of active uveitis [see Section 5.1.13.7])
- OCT (e.g., presence of visual symptoms suggestive of macular edema or active uveitis [see Section 5.1.13.7])
- MRI
- EDSS/FS
- FSIQ-RMS
- CGI-C
- Physical examination
- Body temperature
- Pulse rate (to be assessed only if no 12-lead ECG is performed)
- Skin examination
- Measurement of vital signs and/or body weight
- Complete laboratory tests including: hematology, blood chemistry, viral serology, urinalysis, or serum pregnancy test (for WOCBP only)
- Assessment of AEs and SAEs
- 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, 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. Administration of inhaled

short-acting β2 agonist (e.g., albuterol/salbutamol) for symptom relief may be performed at the discretion of the investigator. Administration of short-acting β2 agonist will be collected in the eCRF.

If any of the laboratory variables listed in Section 7.3.14.2 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 7.3.14].

8.6 Four-weekly pregnancy tests after EOS

WOCBP [see Section 4.5.1] must have additional urine pregnancy tests on a 4-weekly basis until 6 weeks after the first of two tests showing teriflunomide plasma level < 0.02 mg/L [see Section 5.1.14]. The visit window for these tests is +/– 4 days.

These tests can be done by the subject at home. The principal investigator / treating neurologist must be informed about the results of this test via phone, and must report it in the source data.

9 STUDY COMPLETION AND POST-STUDY TREATMENT / MEDICAL CARE

9.1 Study completion

For an individual subject, EOS is reached when treatment, safety FU and, if applicable, PTOP periods have been completed:

- For subjects who completed the 108-week treatment period and enter the extension study, the EOS visit corresponds to the FU visit (FU1) conducted 14–22 days after the last dose of study drug, or to the abbreviated FU2 visit conducted 23–37 days after the last study drug.
- For all the other subjects, the EOS visit corresponds to the FU visit (FU2) 30–37 days after the last dose of study drug or to the last visit of PTOP (i.e., Visit 14A (Week 108) of the PTOP), whichever is latest.

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 EOS visits, 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, 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 assessment, 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, including undergoing the accelerated elimination procedure for teriflunomide. Data obtained during this last appointment / telephone call will be recorded in the subjects' medical records but it will not be collected in the eCRF. 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 a 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 a 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 a 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.

An extension study with ponesimod treatment, conducted under a separate protocol, will be considered for subjects who complete the 108-week treatment as scheduled.

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 15 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 10.3.1]. 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 initiation of study treatment in the extension study or up to the last visit of PTOP (i.e., Week 108 visit of the PTOP) (whichever is latest; extension study conducted under a separate protocol) 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 3.3.4] must ensure that blinded study personnel at the study site, such as the treating neurologists, 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 assessment or ECG interpretation reports, or to AEs with onset on Day 1 or on the first day of re-initiation of study drug which have an onset after study drug intake and are resolved at the time of discharge from cardiac monitoring.

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 AEs 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 AEs 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

10.2.2.1 During pre-randomization period

All SAEs that occur after study start (i.e., signing of informed consent) must be reported (whether considered associated or not associated with study design or study-mandated procedures).

These SAEs must be reported on an SAE form and also in the eCRF.

10.2.2.2 During treatment period

All SAEs, regardless of investigator-attributed causal relationship, must be reported.

These SAEs must be reported on an SAE form and also on the AE pages in the eCRF.

10.2.2.3 During 30-day follow-up period

All SAEs, regardless of investigator-attributed causal relationship, that occur up to 30 days after study treatment discontinuation, must be reported on AE pages in the eCRF and on an SAE form.

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 an SAE form.

10.2.4.2 After the PTOP period

New SAEs occurring after the 30-day FU period, or after the last visit of PTOP (whichever applies and is last) must be reported to the Actelion drug safety department within 24 h 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 h of the investigator's first knowledge of the event.

MS relapses and associated symptoms are exempted 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 h 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 documents to assess expectedness of a suspect serious adverse reaction and reported by the sponsor to health authorities, IRBs/IECs and investigators are the reference safety information section of the IB [Ponesimod IB] and reference safety information of the Aubagio® Summary of Product Characteristics.

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. If the woman wishes to continue pregnancy, Actelion Global Drug Safety will request the unblinding of the treatment assignment and only the subject allocated to teriflunomide will have to perform an accelerated elimination procedure.

10.3.1 Reporting of pregnancy

Irrespective of the treatment received by the subject, any pregnancy occurring during the study including during the 30 days following study treatment discontinuation and the entire duration for continued contraception after EOT, as mandated by the protocol [see Section 5.1.14], must be reported within 24 h 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.

Any pregnancy diagnosed in the female partner of a male subject during treatment with the investigational product must be reported to Actelion within 24 h of the investigator's

knowledge of the event. A Pregnant partner information release form will be provided to the pregnant partner prior to collecting any information on the pregnancy and its outcome.

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 3.4].

11 STATISTICAL METHODS

All statistical analyses will be conducted by Actelion or by designated CROs supervised by Actelion.

The SAP(s) for the final analyses will be approved prior to database lock. The SAP for the clinical study report will provide the full details of all analyses, data displays, and algorithms to be used for data derivations. Separate SAPs and reports are planned for the final analyses of PK data, the MRI sub-study, and the Patient Preference sub-study.

A separate SAP for the blinded interim analysis to determine the FSIQ-RMS response thresholds will be finalized shortly after the first subject is enrolled into the study.

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, minimum, median, Q1, Q3, 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 changes from baseline are 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 equal 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 unless stated otherwise in the SAP.

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.

All primary statistical analyses of efficacy endpoints will be based on the FAS. In order to adhere to the intention-to-treat principle as much as possible:

- 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 Interactive Voice Response System (which may be different to the information available on the eCRF after data validation);
- Unless otherwise stated, all available efficacy data up to the EOS date will be included, irrespective of whether a subject has stopped study treatment earlier or has received any MS treatment other than that to which the subject was randomized to.

11.1.3 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 accrued

after occurence of a major protocol deviation will be excluded for the PPS analysis for a given subject.

All reportable protocol deviations will be evaluated before unblinding and classified into the four 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 received the wrong study treatment or incorrect dose;
- Subject took an unauthorized concomitant medication;
- Occurrence of major protocol deviation that could confound the interpretation of analysis conducted on the FAS.

Additional details regarding the definition of the reasons for subject/data exclusion from the PPS will be defined in the final SAP.

11.1.4 Safety Set

The safety set (SAF) includes all randomized subjects who received at least one dose of study treatment. Subjects will be analyzed based on actual treatment taken.

11.1.5 FSIQ-RMS Measurement Set

An FSIQ-RMS measurement set (FMS) includes the first 291 randomized subjects who received at least one dose of study treatment [see Section 11.5.5 for sample size justification].

11.1.6 Other analysis sets

Other analysis datasets are defined in the corresponding SAPs, e.g., PK populations, sub-study populations, and subgroups of (special) interest.

11.1.7 Usage of the analysis sets

The FAS 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 will supplement those based on the FAS and assess the robustness of treatment effects.

MRI, clinical exploratory endpoints and other clinical exploratory endpoints will be analyzed using the FAS.

The FMS will be used for the confirmation of the threshold values for the minimal level of change required to identify FSIQ-RMS responders.

All safety data will be analyzed using the SAF.

11.2 Variables

11.2.1 Primary efficacy variable

The primary endpoint is the ARR defined as the number of confirmed relapses per subject-year. All relapses up to EOS (including the FU period and PTOP) 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 relapse and confirmed relapse, see Section 6.1.1.

11.2.2 Secondary efficacy variables

There are four secondary efficacy endpoints, which will be analyzed as per the statistical testing strategy outlines in Section 11.3.1:

- Change from baseline to Week 108 in fatigue-related symptoms as measured by the symptoms domain of the FSIQ-RMS;
- Cumulative number of CUAL from baseline to Week 108;
- Time to 12-week CDA from baseline to EOS;
- Time to 24-week CDA from baseline to EOS.

11.2.2.1 Fatigue Symptoms and Impact Questionnaire (FSIQ-RMS)

The endpoint is defined as the absolute change in the FSIQ–RMS (weekly) symptoms score from baseline to Week 108. Additional details will be provided in the SAP.

11.2.2.2 Cumulative number of CUAL from baseline to Week 108

Cumulative number of CUAL [defined in Section 6.1.2] from baseline to Week 108 is calculated as the sum of lesions at all post-baseline MRI visits up to Week 108.

11.2.2.3 Time to 12-week CDA

Time to 12-week CDA from baseline to EOS is defined as:

- Increase of at least 1.5 in EDSS for subjects with a baseline EDSS score of 0;
- Increase of at least 1.0 in EDSS for subjects with a baseline EDSS score of 1.0 to 5.0;
- Increase of at least 0.5 in EDSS for subjects with a baseline EDSS score $\geq$ 5.5;

confirmed after 12 weeks, see detailed definition in Section 6.1.2.

Time to first 12-week CDA is defined as 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 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.

11.2.2.4 Time to 24-week CDA

Time to 24-week CDA from baseline to EOS is defined as EDSS increase described in Section 6.1.2 confirmed after 24 weeks.

Time to first 24-week CDA is defined as start date of the first 24-week CDA minus date of randomization +1 in days.

For a subject without a 24-week CDA, the censored time to 24-week CDA is defined as:

- [date of last EDSS assessment without an EDSS increase (as defined above)] 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.

11.2.3 Other efficacy variables

11.2.3.1 Exploratory efficacy variables

MRI-based exploratory variables:

- Percent change in brain volume from baseline to Week 108;
- Number of Gd+ T1 lesions at Week 60 and Week 108;
- Cumulative number of new or enlarging T2 lesions from baseline to Week 108, calculated as the sum of lesions at all post-baseline MRI visits up to Week 108;
- Change from baseline to Week 60 in the volume of T2 lesions, calculated as the value at Week 60 minus the value at Baseline;
- Change from baseline to Week 108 in the volume of T2 lesions, calculated as the value at Week 108 minus the value at Baseline;
- Change from baseline to Week 60 in the volume of T1 hypointense lesions, calculated as the value at Week 60 minus the value at Baseline;
- Change from baseline to Week 108 in the volume of T1 hypointense lesions, calculated as the value at Week 108 minus the value at Baseline;
- Absence of Gd+ T1 lesions at Week 60 and Week 108;

- Absence of new or enlarging T2 lesions at Week 60 and Week 108;
- Proportion of Gd+ lesions at Baseline evolving to PBHs by Week 108 (axonal loss);
- Change of CCI [redacted];
- Change in CCI [redacted];
- Cumulative number of CCI [redacted].

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

- Time to first confirmed relapse up to EOS;
  Defined as: Date of first confirmed relapse minus date of randomization date + 1 in days. Subjects without any relapse will be censored at the EOS date, and the time is defined as EOS date minus date of randomization + 1 in days.
- Absence of confirmed relapses from baseline to Weeks 60 and 108;
- Time to 24-week CDA from baseline to EOS defined similarly to 12-week CDA;
- Change in EDSS from baseline up to Week 108, by visit;
- NEDA status up to EOS (defined by the absence of confirmed relapse, Gd+ T1 lesions, new or enlarging T2 lesions, 12-week CDA, and annual brain volume decrease ≥ 0.4% from baseline to EOS). If at least one of the four criteria is not fulfilled or the subject discontinues treatment prematurely, the subject is not considered to have achieved NEDA.

Other exploratory variables:

- Change from baseline up to Week 108 in MSFC Z-score;
- Change from baseline up to Week 108 in the SDMT score;
- FSIQ-RMS Patient Improvement Response (minimally important difference) is defined as a reduction in the FSIQ-RMS weekly symptom score ≥ a threshold value anchored on the PGI-S of Fatigue scale, which will be determined by a blinded analysis of the data as described in Section 11.4.
- FSIQ-RMS Clinical Improvement Response (clinically important difference) is defined as a reduction in the FSIQ-RMS weekly symptom score ≥ a threshold value anchored on the CGI-C scale, which will be determined by a blinded analysis of the data as described in Section 11.4.
- Change from baseline up to Week 108 in fatigue-related impact sub-domain scores (Physical, Cognitive / Emotional, Coping) as measured by FSIQ-RMS.
- Change from baseline in PGI-S of Fatigue by visit up to Week 108;
- Change from baseline in CGI-C by visit up to Week 108;

Detailed information on the analyses of these endpoints will be provided in the SAP. Additional exploratory endpoints and/or analyses may be defined in the SAP.

11.2.4 Safety variables

The following safety endpoints/variables will be analyzed. The SAP will summarize these variables in more detail.

- Treatment-emergent AEs, SAEs, AEs of special interest, and MACE;
- 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, QTcB, 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 drug;
- Notable abnormalities for selected 12-lead ECG variables (HR, PR, QT, QTc) at 3 h post-dose assessment on Day 1 and Week 12 and at the re-initiation of study drug when post-dose monitoring is required;
- Treatment-emergent decrease of FEV_1 or FVC > 20% from baseline values;
- Treatment-emergent 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 vs 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 FU visit;
- Change in lung diffusion capacity as assessed by DL_{CO} expressed in absolute change and % of predicted value from baseline to all timepoints up to EOS;
- Change from baseline to EOS vs change from baseline to EOT in DL_{CO} (absolute and % of predicted);
- Treatment-emergent notable BP abnormalities;
- Treatment-emergent notable laboratory abnormalities;
- Change in body weight from baseline to EOS;
- Treatment-emergent eC-SSRS suicidal ideation score of 4 or above, or a "yes" response on the eC-SSRS suicidal behavior item.

11.2.5 Other variables

- Change from baseline by visit up to Week 108 in SF-36v2™ Health Survey domain and component scores;
- Change from baseline by visit up to Week 108 in WPAI:MS scores;

- Health care resource utilization from baseline by visit up to Week 108 (number of hospitalizations, length of stay, number of ICU admissions for MS relapse and visits to an emergency medical services facility for MS);
- Plasma concentrations of ponesimod pre-dose at Day 15; Weeks 12, 60, and 108; and 3 h post-dose on Day 1 and Week 12;
- Peripheral blood lymphocyte counts pre-dose by visit (absolute count and change from baseline) up to Week 108;
- Change from baseline to EOS vs change from baseline to EOT in lymphocyte counts (absolute and % change);
- Post-treatment lymphocyte recovery at 15 days and 30 days after study drug discontinuation.

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 the investigational treatment (ponesimod 20 mg) with the comparator (teriflunomide 14 mg) at full alpha.

If the primary endpoint null hypothesis is rejected, the alpha will be split evenly (1/3 of alpha) between the following three secondary endpoints using the fallback procedure, allowing for passing on alpha within the fallback procedure as per the following sequence:

- Change from baseline to Week 108 in fatigue-related symptoms as measured by the symptoms domain of the FSIQ–RMS [Fatigue]
- Cumulative number of CUAL from baseline to Week 108 [CUALs]
- Time to 12-week CDA from baseline to EOS [12-week CDA]

If a secondary endpoint listed as part of the fallback procedure above is successful, the preserved alpha in the sequence is passed along to the next secondary endpoint in the sequence and the summed alpha is used for testing that endpoint. Thus, as sequential tests are successful, the alpha accumulates for the endpoints later in the sequence; these endpoints are then potentially tested with a progressively larger alpha, but always with at least 1/3 of the alpha.

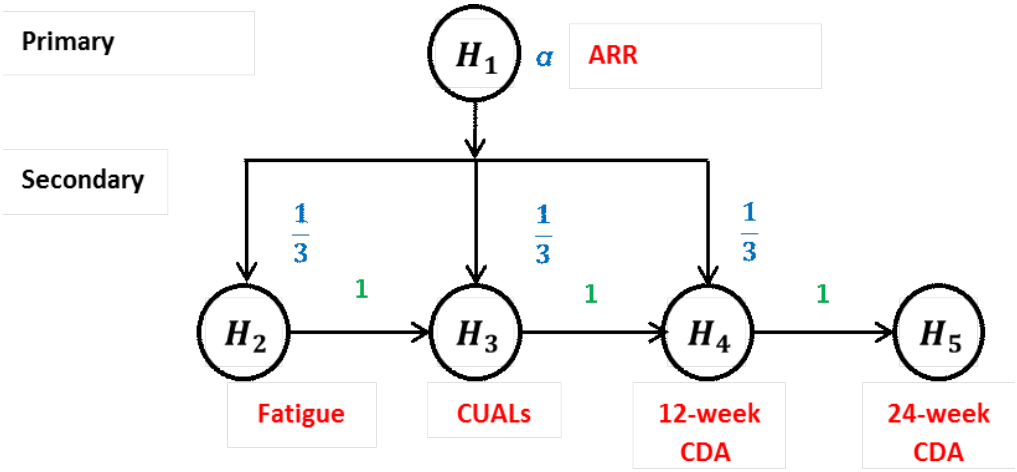
In a last step, the secondary endpoint

- Time to 24-week CDA from baseline to EOS [24-week CDA]

is tested in a subsequent stage following Time to 12-week CDA with the remaining alpha.

A graphical description of this testing strategy for the primary and secondary endpoints following the approach of Bretz, et al. [Bretz 2009] is provided in Figure 8.

Figure 8 Overall testing strategy



The primary null hypothesis will be tested at a two-sided 1% alpha level, and if this is rejected the study will be declared to show conclusive evidence of efficacy. If the primary null hypothesis can only be rejected at the two-sided 5% alpha level, the study will be declared positive.

Analyses for secondary endpoints will be conducted at an overall two-sided 5% alpha level, with multiplicity adjustment as per the testing strategy outlined in Figure 8.

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:

$$\log\left(\mu_j / t_j\right) = \mathbf{x}'_j\boldsymbol{\theta}, \text{ i.e., } \log\left(\mu_j\right) = \mathbf{x}'_j\boldsymbol{\theta} + \log\left(t_j\right), \text{ where}$$

$\mathbf{x}_j$ 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 μ_{P20mg} and μ_{T14mg}. The primary null hypothesis is that the ARR (μ) does not differ between ponesimod 20 mg and teriflunomide 14 mg. The alternative hypothesis is that the ARR differs between ponesimod 20 mg and Teriflunomide 14 mg.

$$H_{0,\,ARR}: \mu_{P20mg} - \mu_{T14mg} = 0$$

vs

$$H_{1,\,ARR}: \mu_{P20mg} - \mu_{T14mg} \neq 0$$

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 0.01 for conclusive evidence and 0.05 for a positive study. Two-sided 95% and 99% Wald CIs will be calculated for the relative reduction in mean ARR for ponesimod 20 mg compared to teriflunomide 14 mg.

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.

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. No other missing data imputation is used for the main analysis of the primary endpoint.

11.3.2.2.2 Sensitivity analyses 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 times a decision must be taken by the treating neurologist to refer the subject to the efficacy assessor. Once referred to the efficacy assessor the symptom is considered a relapse and is assessed for confirmation. To ensure there is 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 Week 108 (+ FU period) 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:

$$1 - \frac{\text{Cumulative time between randomization and EOS}}{\text{Cumulative time between randomization and theoretical Week 108}}$$

A worst case imputation will impute the observed ARR for ponesimod subjects up to EOS during the period EOS up to Week 108 and impute zero relapses for the teriflunomide subjects during this period. A second approach will impute the observed teriflunomide ARR up to EOS for the period EOS up to Week 108 for both treatments, using simulations and bootstrapping techniques to calculate the 95% and 99% CIs. A third and more conservative approach will impute the observed individual treatment ARR up to EOS for the period EOS up to Week 108.

11.3.2.3 Main analysis

The primary statistical analysis will be performed on the FAS population using the model described in Section 11.3.2.1 for confirmed relapses, with the stratification variables (prior use of DMTs and EDSS category), as well as the number of relapses in the year prior to study entry and the logarithm of time on treatment up to EOS as an offset variable, included in the model.

11.3.2.4 Supportive/sensitivity analyses

The following supportive analyses (based on the FAS, if not otherwise stated) are planned using the model described in Section 11.3.2.1:

- ARR only counting confirmed relapses occurring up to EOT + 7 days;
- Analysis with treatment as the only covariate in the model for all confirmed relapses up to EOS;
- Analysis adjusting for the stratification covariate using the actual EDSS at baseline and prior use of DMTs as recorded on the eCRF for all confirmed relapses up to EOS and up to EOT + 7 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 + 7 days and EOS (PTOP) to further assess the impact of treatment discontinuation and/or switching to alternative MS treatments;

- Analyses based on the PPS population counting confirmed relapses up to EOS;
- Analysis using all relapses (confirmed or unconfirmed) up to EOS;
- A descriptive summary of the amount of data collected under protocol version 3 or earlier versions, compared to protocol version 4 will be considered in the SAP. Further additional inferential analysis will be described if deemed necessary.

Further 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 factors) are:

- Baseline EDSS (≤ 3.5, > 3.5);
- Geographical region (North America, Latin America, Western Europe, Eastern Europe, Rest of the World);
- Gender (male, female);
- Age (< 40, ≥ 40);
- MS subtype (relapsing remitting, secondary progressive with superimposed relapses);
- Prior MS treatment (yes, no);
- Relapse in the year prior to study entry (≤ 1, ≥ 2);
- Gd+ T1 lesions at Baseline (absent, present);
- Highly active disease (yes, no). A subject is considered to have highly active disease if one or both of the following conditions are met:
    - Any MS disease modifying therapy received in the 12 months prior to study and one or both of the following conditions are met:
        - ≥ 1 relapse within the last 12 months prior to study and baseline MRI shows either ≥ 1 Gd+ T1 lesion and/or ≥ 9 T2lesions
        - ≥ 1 relapse within the last 24 months prior to study and number of relapses in the 12 months prior to study $\geq$ number of relapses between 24 and 12 months prior to study.
    - ≥ 2 relapses within the last 12 months prior to study and baseline EDSS > 2 and ≥ 1 Gd+ T1 lesion on baseline MRI.

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 as outlined in Section 11.3.1 if the primary analysis on ARR has led to the rejection of the null hypothesis in favor of ponesimod 20 mg.

The endpoints will be analyzed using the FAS. All secondary endpoints will also be analyzed using the PPS.

11.3.3.1 Absolute change in FSIQ-RMS from baseline to Week 108

11.3.3.1.1 Hypothesis

The FSIQ-RMS weekly symptoms score ranges from 0 to 90 with a higher score indicating more pronounced fatigue. A repeated measurement ANCOVA will be used to compare the change from baseline to Week 108 across both treatment groups. The underlying hypotheses are expressed as two means, assuming the outcomes of the endpoint for both treatments are normally distributed:

$H_{0,\,FSIQ}$: $\mu_{P20mg} - \mu_{T14mg} = 0$

vs

$H_{1,\,FSIQ}$: $\mu_{P20mg} - \mu_{T14mg} \neq 0$

Each null hypothesis will be tested by an F-test by comparing the resulting p-value to the local alpha as per the overall testing strategy, see Section 11.3.1.

11.3.3.1.2 Main Analysis

The main analysis for this variable will be performed on the FAS comparing ponesimod 20 mg to teriflunomide 14 mg using a repeated measurements ANCOVA model with baseline, prior use of DMTs, EDSS category and the FSIQ symptoms score at baseline as covariates.

11.3.3.1.3 Supportive analyses

The following supportive analyses (based on the FAS if not otherwise stated) are planned:

- Analysis with treatment as the only factor within subgroups levels;
- Analysis based on the PPS.

11.3.3.2 Cumulative number of combined unique active lesions

11.3.3.2.1 Hypothesis

Two-sided hypotheses are expressed in terms of the model parameters μ_{P20mg} and μ_{T14mg}. The primary null hypothesis is that the CUAL (μ) does not differ between ponesimod

20 mg and teriflunomide 14 mg. The alternative hypothesis is that the CUAL differs between ponesimod 20 mg and teriflunomide 14 mg.

$H_{0,\,CUAL}$: $\mu_{P20mg} - \mu_{T14mg} = 0$

vs

$H_{1,\,CUAL}$: $\mu_{P20mg} - \mu_{T14mg} \neq 0$

The null hypothesis will be tested by a two-sided Wald test within the negative binomial regression model [see Section 11.3.1], by comparing the resulting p-value to the local alpha as per the overall testing strategy, see Section 11.3.1. Two-sided 95% Wald CIs will be calculated for the relative reduction in mean CUAL for ponesimod 20 mg compared to teriflunomide 14 mg.

11.3.3.2.2 Main Analysis

The main statistical analysis will be performed on the FAS using a similar model as described in Section 11.3.2.1 for confirmed relapses, with the stratification variables, prior use of DMTs and EDSS category, as well as the presence of T1 Gd+ lesions at baseline, included in the model.

11.3.3.2.3 Supportive analyses

The following supportive analyses (based on the FAS if not otherwise stated) are planned using the same type of model, but:

- based on the PPS;
- subgroup analyses with subgroups defined by baseline characteristics.

11.3.3.3 Time to 12-week CDA

11.3.3.3.1 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 $S_{P20mg}(t)$ and $S_{T14mg}(t)$.

$H_{0,CDA}$: $S_{P20mg}(t) = S_{T14mg}(t)$ for all $t \geq 0$

vs

$H_{1,CDA}$: $S_{P20mg}(t) \neq S_{T14mg}(t)$ for all $t \geq 0$

The null hypothesis will be tested using a two-sided stratified log-rank test by comparing the resulting p-value to the local alpha as per the overall testing strategy, see Section 11.3.1.

11.3.3.3.2 Main Analysis

The main analysis will be performed on the FAS by a two-sided stratified log-rank test with stratification factors (prior use of DMTs and EDSS category). Kaplan-Meier estimates for the survival functions will be provided.

11.3.3.3.3 Supportive analyses

The following supportive analyses (based on the FAS if not otherwise stated) are planned:

- Unstratified log-rank test;
- Adjusted (for same variables as primary analysis) and unadjusted Cox's proportional hazards model;
- Unadjusted Cox's proportional hazards model within subgroups levels;
- Stratified and unstratified log-rank test based on the PPS;
- Adjusted and unadjusted Cox's proportional hazards model based on the PPS;
- Worst case analysis where all unconfirmed disability accumulations at Week 108 (these events cannot be confirmed due to Week 108 being the last scheduled on-treatment visit) are considered as confirmed.

11.3.3.4 Time to 24-week CDA

11.3.3.4.1 Hypothesis

Hypotheses are formulated in terms of "survival" functions S(t), i.e., the probability that time to 24-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 $S_{P20mg}(t)$ and $S_{T14mg}(t)$.

$$H_{0,CDA24}: S_{P20mg}(t) = S_{T14mg}(t) \text{ for all } t \geq 0$$

vs

$$H_{1,CDA24}: S_{P20mg}(t) \neq S_{T14mg}(t) \text{ for all } t \geq 0$$

The null hypothesis will be tested using a two-sided stratified log-rank test by comparing the resulting p-value to the local alpha as per the overall testing strategy, see Section 11.3.1.

11.3.3.4.2 Main Analysis

The main analysis will be performed on the FAS by a two-sided stratified log-rank test with stratification factors (prior use of DMTs and EDSS category). Kaplan-Meier estimates for the survival functions will be provided.

11.3.3.4.3 Supportive analyses

Supportive analyses as described in Section 11.3.3.3.3 for the Time to 12-week CDA endpoint are planned.

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 or by other baseline variables. Details will be provided in the SAP. All statistical models used will be stratified by prior use of DMTs and EDSS category. Adjustment for further covariates, e.g., baseline value when modeling change from baseline variables, will be detailed in the SAP. All subjects will be included in the analysis even if subjects are off study treatment. Missing data imputation rules will be described in the SAP.

11.3.4.1 Percent change in brain volume from baseline to Week 108

The percent change in brain volume from baseline to Week 108 will be performed on the FAS using an ANCOVA with treatment as a factor and the randomization stratification factors (prior use of DMTs and EDSS category), as well as brain volume at baseline as covariates.

11.3.4.2 Number of Gd+ T1 lesions at Week 60 and Week 108

The number of Gd+ T1 lesions at each visit will be analyzed using a negative binomial regression model similar to that described in Section 11.3.2.1.

11.3.4.3 Change in volume of T2 lesions, T1 hypointense lesions, EDSS, CCI [redacted] from baseline to Week 60 and Week 108

All variables related to change in lesion volume, change in EDSS, change in CCI [redacted] at Week 60 and Week 108 will be analyzed using an ANCOVA with treatment, including stratification variablesand baseline values as covariates. Changes to other visits will be summarized descriptively.

11.3.4.4 Absence of Gd+ T1 lesions, and new or enlarging T2 lesions and subjects relapse-free at Week 60 and Week 108

Absence of Gd+ T1 lesions, and new or enlarging T2 lesions, and subjects that are relapse-free at Weeks 60 and 108 will be analyzed using a logistic regression with treatment as a factor, including stratification variables and baseline value as covariates.

11.3.4.5 Other MRI endpoints

Cumulative number of new or enlarging T2 lesions from baseline to Week 108 and cumulative number of CCI [redacted] will be analyzed in a similar manner to cumulative CUAL. Proportion of Gd+ lesions at Baseline evolving to PBHs by Week 108 (axonal loss) will be summarized descriptively.

11.3.4.6 Time to first confirmed relapse

The analysis for this variable will be performed on the FAS using a two-sided stratified log-rank test with stratification variables (prior use of DMTs, EDSS category) and number of relapses in the year prior to study entry. Kaplan-Meier estimates for the survival functions will be plotted using Kaplan-Meier curves and will be tabulated by 12-week intervals.

11.3.4.7 NEDA status up to EOS

NEDA is analyzed using a logistic regression model with treatment as a factor and stratification variables and number of relapses in the year prior to study entry included in the model.

11.3.4.8 Change of MSFC Z-score and SDMT score from baseline to Week 108

The changes from baseline to the Week 108 assessment of both scores are analyzed using an ANCOVA, similar to the analyses described for brain volume changes in Section 11.3.4.1.

11.3.4.9 Change of FSIQ-RMS and sub-scores from baseline to each visit (total score and impact score)

The absolute change from baseline FSIQ-RMS weekly symptoms score and impact sub-domain scores is analyzed over time using a repeated measurement ANCOVA, as for the analysis for change in FSIQ-RMS symptoms score to Week 108. Estimates and two-sided 95% CI will be calculated for the effects of ponesimod relative to teriflunomide at each visit.

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 15 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 20 mg or teriflunomide 14 mg.

For each specific safety event of interest, the number and percentage of subjects with at least one event will be reported. Point estimates and 95% CIs for safety event incidences and the relative risk ratio relative to teriflunomide 14 mg will be provided without adjustment for multiplicity.

Time to first onset of safety events of interest may be displayed by Kaplan-Meier estimates. Subjects not experiencing the safety event will be censored at the minimum of the EOS date and 15 days after last dose of study drug. Where applicable, study treatment will be compared by 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 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 20 mg or teriflunomide 14 mg.

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. The definition of the AEs of special interest is provided in Appendix 5.

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 15 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

11.3.5.2.1 12-lead ECG assessments

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, QTcF) will be summarized for all data of the 3-h 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 (using data from the ECG provider).

11.3.5.2.2 Cardiac safety events

Cardiac safety events will include:

- Treatment-emergent QTc > 450 ms, > 480 ms, > 500 ms
- Treatment-emergent QTc increase from baseline > 30 ms, > 60 ms
- Other treatment-emergent abnormalities observed by 12-lead ECG
- Treatment-emergent (serious) cardiac AEs of special interest.

11.3.5.3 Pulmonary safety

11.3.5.3.1 Pulmonary functional testing

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, FVC and FEV_1/FVC ratio (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 percentage points from baseline at any time up to EOT will be summarized by treatment.

The trend effect of treatment on the percent predicted FEV_1 over time will be analyzed by treatment using a regression analysis with time as the independent variable and FEV_1 adjusted for 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 from baseline to EOS and from baseline to EOT in FEV_1 or FVC (absolute and % predicted) will be plotted by treatment. A scatter plot will display

the change from baseline to EOS vs 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.

11.3.5.3.2 Lung diffusion capacity

Descriptive summary statistics and changes from baseline by visit and study treatment will be provided for observed treatment-emergent values and changes from baseline (expressed in absolute change and % of predicted value) in DL_{CO}.

11.3.5.3.3 Pulmonary safety events

Pulmonary safety events will include:

- Treatment-emergent decrease of FEV_1 or FVC to < 80% of baseline values
- (Serious) pulmonary AEs of special interest
- Withdrawal due to pulmonary reasons / AE

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. 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 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.

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; see Appendix 6]
- Treatment-emergent laboratory test abnormalities based on FDA guidance for DILI [FDA 2009b] (for ALT / AST / total bilirubin)

- Lymphocyte count reversibility after EOT, expressed in absolute change and percent change from baseline

The definition for notable abnormalities is provided in Appendix 6.

11.3.5.6 Ocular safety

Ocular safety events will include:

- Treatment-emergent ocular AEs of specific interest

11.3.5.7 Vaccine-specific antibody titers

For subjects receiving non-live vaccination while on study treatment, descriptive summary statistics by study treatment will be provided for observed values and absolute changes in vaccine-specific antibody titers from pre- to post-vaccination.

11.3.5.8 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.

11.3.5.9 Analysis of other variable(s)

11.3.5.9.1 PK

Trough level (pre-dose) plasma concentrations of ponesimod at Weeks 12, 60 and 108 and plasma concentrations of ponesimod at 3 h post-dose at Day 1 and Week 12 will be analyzed by descriptive statistics, including arithmetic mean, standard deviation, minimum, maximum, and median.

11.3.5.9.2 PD

Total lymphocyte counts at each visit assessment will be analyzed by descriptive statistics, including arithmetic mean, standard deviation, minimum, maximum, and median.

The relationship between ponesimod concentration and total lymphocyte counts will be investigated by modeling and simulation.

11.3.5.9.3 Quality of Life Questionnaire (SF36v2™)

Data in the health survey domain and component scores will be summarized descriptively by visit and study treatment up to Week 108 in the FAS.

11.3.5.9.4 WPAI:MS Questionnaire

Data in the pharmacoeconomic WPAI:MS Questionnaire will be summarized descriptively by visit and study treatment, up to Week 108 in the FAS.

11.3.5.9.5 Health care resource utilization

Data on health care resource utilization will be summarized descriptively by visit and study treatment, up to Week 108 in the FAS.

11.3.5.9.6 Patient preferences

Data on patient preferences will be summarized descriptively by visit and study treatment, up to 15 days after last dose of study drug in the FAS (sub-study).

11.4 Interim analyses

No unblinded interim analysis is planned for the study; however, a blinded interim analysis based on the first 291 randomized subjects will be performed in order to confirm the definition of FSIQ responders.

In order to understand and interpret change in the FSIQ-RMS Fatigue Symptoms endpoint within this clinical population, it is important to anchor this change to a meaningful threshold of change from the clinician and patient perceptions. The first threshold, the Minimally Important Differences (MID), is computed as the smallest difference in scores between groups in the domain of interest that patients perceive as beneficial. Similarly, the Clinically Important Differences (CID) is computed as another threshold in which the clinician perceives the change as beneficial. There are multiple methods to compute Minimally Clinically Important Differences, which include: patient perspective, clinician perspective, and data-driven approaches (anchor- and distribution-based). Comparison of these methods allows for the approximation of MID and CID responder thresholds.

Within this study, two anchors have been selected for evaluating change on the FSIQ-RMS Fatigue Symptom score: the PGI-S of Fatigue for patient-reported change in fatigue severity and the CGI-C for the clinician's global impression of the patient's MS severity. Each will be collected simultaneously to the FSIQ-RMS measures.

For the blinded FSIQ responder definition analysis, the MID as assessed by subjects will be measured using a common distribution-based method: ½ standard deviation change from baseline of the FSIQ-RMS Fatigue Symptom score based on the FMS. Anchor-based estimates for the MID will group subjects based on change on the PGI-S of Fatigue from baseline to each subsequent visit. Anchor-based methods for the CID calculation as assessed by clinician's grouped improvement categories on the CGI-C from weekly baseline and subsequent visit scores. Effect size estimates for each group of subjects will be calculated as the mean score difference between weekly baseline and subsequent visit scores, divided by the pooled baseline standard deviation. Cohen's thresholds for interpreting the magnitude of an effect size suggests the following: 0.2 (small), 0.5 (moderate), and 0.8 (large). As such, the expectation for interpreting the MID and CID are effect-size estimates greater than 0.2, which is considered the minimal amount of change necessary for detecting meaningful improvement.

11.5 Sample size

The sample size is calculated based on the primary endpoint, and the power is calculated for the secondary endpoints. For the secondary endpoint FSIQ-RMS, no sample size calculations were carried out as valid assumptions are difficult to make due to the recent release of the 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 1100 subjects (550 per treatment group) will provide a power of approximately 90% for a significance level of 0.01, under the assumption that ARR is 0.320 for teriflunomide 14 mg and 0.215 for ponesimod 20 mg (which corresponds to a risk reduction of 33%), and using a dispersion = 0.9. An annual dropout rate of approximately 15% has been assumed for the first year and 7.5% for the second year.

The adjusted risk reduction for teriflunomide 14 mg vs placebo in the fixed two-year duration TEMSO study was 31.5%, and 36% in the variable duration TOWER study. An integrated analysis showed a pooled 34% reduction compared to placebo. A 33% reduction for ponesimod 20 mg compared to teriflunomide 14 mg gives a relative 55% reduction compared to placebo, similar to that observed in the fingolimod Phase 3 trials. The dispersion from the ponesimod Phase 2 study was 1.0; the calculated dispersion from the TEMSO study is 0.8, so the chosen dispersion is the mean of the two.

11.5.2 Secondary endpoints

Keeping the sample size fixed at 550 subjects per treatment group, the power to detect clinically meaningful treatment effects for the secondary endpoints is shown below. No power was calculated for FSIQ-RMS or Time to 24-week CDA.

11.5.2.1 Cumulative number of CUAL

Assuming 1.5 CUAL per year for teriflunomide, a reduction of 33% for ponesimod and a dispersion of 3.65 will give an approximate power of 80% for a two-sided local significance level of 0.05/3. If, within the fallback procedure, alpha can be passed on to the hypothesis on CUAL a local two-sided significance level of 0.05/3*2, results in a power of 86%. Dropout rates as for the primary endpoint have been assumed.

11.5.2.2 Time to 12-week CDA

Assuming a 12-week CDA rate at 2 years for teriflunomide 14 mg of 16% and a hazard ratio of 0.67 (i.e., 2-year progression of 11% for ponesimod 20 mg), this gives with a sample size of 1100 an approximate power of 45% for a two-sided local significance level of 0.05/3. If, within the fallback procedure, alpha can be passed on to Time to 12-week CDA a local two-sided significance level of 0.05/3*2 (~0.033) or 0.05 can be used resulting

in a power of approximately 56% or 62%, respectively. Dropout rates as for the primary endpoint have been assumed.

11.5.3 Sample size sensitivity

Increasing the ARR for ponesimod to 0.223 (which corresponds to a risk reduction of 30%) decreases the power to approximately 80%. If the ARR is 10% lower than assumed in both ponesimod 20 mg (ARR = 0.194) and teriflunomide 14 mg (ARR = 0.288), the power reduces to approximately 87%.

11.5.4 Sample size re-estimation

There is no sample-size re-estimation planned.

11.5.5 Other sample size considerations

The sample size necessary for the confirmation of minimal change thresholds for identifying responders on the FSIQ-RMS symptom scale is based on psychometric analyses, which will be performed using data from the FMS.

For confirmation, as a preliminary analysis, these thresholds will be evaluated using blinded data collected within the Phase 3 clinical trial (AC-058B301) on a subset of subjects with available data on the FSIQ-RMS, the PGI-S of Fatigue and the CGI-C (in MS) between baseline and Week 108.

Using data collected within a non-interventional observational study, preliminary thresholds were calculated using two anchors: 1) patient-reported severity of fatigue as measured by the PGI-S of Fatigue with a mean improvement level of 6.19 and 2) clinician-reported severity of MS as measured by the CGI-C with a mean improvement level of 11.68. Given the consideration of these thresholds, it is necessary to identify the number of subjects required to detect the same level of change within the confirmatory Phase 3 clinical trial. As the data will be blinded for this psychometric confirmatory analysis, power calculation based upon a paired t-test for mean difference between baseline and Week 108 was conducted.

Results from a statistical power analysis suggest that, in order to detect a −6.19 change from baseline in FSIQ-RMS Symptoms score (assumed baseline standard deviation = 24.1), an N of approximately 98 subjects demonstrating change would be necessary to obtain statistical power at a recommended 0.90 level. For the −11.68 change from baseline in FSIQ-RMS Symptoms score (assumed baseline standard deviation = 24.1), an N of approximately 29 subjects demonstrating change would be necessary to obtain statistical power at a recommended 0.90 level.

In an observational study with MS patients over 13 weeks where the FSIQ-RMS was administered, 27% of the patients indicated no change in their fatigue level, 43% improved in a meaningful way on the PGI-S of Fatigue, and the remaining 30% worsened. If this

information is applied to the power calculation for the blinded analysis set, the sample size needs to be increased to 228 subjects (98 would demonstrate an improvement, 130 subjects would not change or deteriorate and could therefore not be used for the analysis).

Furthermore, adjusting for a drop-out rate of 15% and 7.5% for Year 1 and Year 2, respectively, leads to a sample size of 291 subjects for the blinded responder threshold analysis.

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.

eCRF data will be captured via electronic data capture (EDC 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 5.1.5.2 and 10.1.5].

Entries recorded by the subject in the electronic device (FSIQ-RMS, PGI-S of Fatigue, SF-36v2™, MS Patient Preference Questionnaire, 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, an 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, spirometry, eDiary, PGI-S of Fatigue, MS Patient Preference Questionnaire, 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 data 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 local language(s).

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 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.

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).

Separate reports are planned for the final analyses of PK data, the MRI sub-study, and the Patient Preference sub-study.

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 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.

14 REFERENCES

[Alvarez 2007] Alvarez SE, Milstien S, Spiegel S. Autocrine and paracrine roles of sphingosine-1-phosphate. Trends Endocrinol Metab 2007;18:300–7.

[Aubagio® USPI] Aubagio® (teriflunomide) oral tablets – Full prescribing information; http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202992s000lbl.pdf

[Aubagio® SmPC] Aubagio® (teriflunomide) oral tablets – Summary of Product Characteristics; http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002514/WC500148682.pdf

[Bana E Costa 1999] Bana E Costa C, Vansnick JC. The MACBETH approach: basic ideas, software and an application. In: Meskens N, Roubens M, editors. Advances in Decision Analysis. Dordrecht: Kluwer Academic Publishers; 1999. p. 131–157.

[Benedict 2006] Benedict R H, Cookfair D, et al. Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). J Int Neuropsychol Soc 12(4):549–58.

[Bowling 2001] Bowling A, Ebrahim S. Measuring patients' preferences for treatment and perceptions of risk. Quality in Health Care 2001;10 (Supplement 1):i2–i8.

[Bretz 2009] Bretz F, Maurer W, Brannath W, et al. A graphical approach to sequentially rejective multiple test procedures. Statist. Med 2009; 28(4), 586-604.

[Brinkmann 2007] Brinkmann V. Sphingosine 1-phosphate receptors in health and disease: Mechanistic insights from gene deletion studies and reverse pharmacology. Pharmacol Ther 2007;9 (11):883–897.

[Brinkmann 2010] Brinkmann V, Billich A, Baumruker T, et al. Fingolimod (FTY720): discovery and development of an oral drug to treat multiple sclerosis. Nat Rev Drug Discov 2010;115:84–105.

[Cohen 2018] Cohen J, Comi G, Selmaj K, et al. Clinical and Magnetic Resonance Imaging Results From RADIANCE Part B, a Multicenter, Randomized, Double-Blind, Phase 3 Trial of Ozanimod Versus Intramuscular Interferon β-1a in Relapsing Multiple Sclerosis (RMS) (P3.410). Neurology. Apr 2018;90(15 Supplement):P3.410.

[Comi 2012] Comi G, Jeffery D, Kappos L, et al; ALLEGRO Study Group. Placebo-controlled trial of oral laquinimod for multiple sclerosis. N Engl J Med 2012;366(11):1000–9.

[Comi 2018] Comi G, Arnold D, Cree B, et al. Ozanimod Demonstrates Efficacy and Safety in a Multicenter, Randomized, Double-Blind, Double-Dummy, Active-Controlled Phase 3 Trial of Relapsing Multiple Sclerosis (SUNBEAM) (P3.396). Neurology. Apr 2018;90(15 Supplement):P3.396.

[Compston 2002] Compston A, Coles A. Multiple sclerosis. Lancet 2002;359:1221–31.

[Compston 2008] Compston A, Coles A. Multiple sclerosis. Lancet 2008;372:1502–18.

[Confavreux 2014a] Confavreux C, Vukusic S. The clinical course of multiple sclerosis. Handb Clin Neurol 2014;122:343–69.

[Confavreux 2014b] Confavreux C, O'Connor P, Comi G, et al. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol 2014;13(3):247–56.

[Coyle 2001] Coyle D, Wells G, Graham I, et al. The impact of risk on preference values: Implications for evaluations of postmenopausal osteoporosis therapy. Value in Health. 2001;4(5):385–91.

[CTCAE 2010] Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 Published: May 28, 2009 (v4.03: June 14, 2010); U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES; National Institutes of Health; National Cancer Institute; http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

[Cyster 2005] Cyster JG. Chemokines, sphingosine-1-phosphate, and cell migration in secondary lymphoid organs. Annu Rev Immunol 2005;23:127–59.

[EMA 2006] EMEA CHMP Guideline on clinical investigational or medicinal products for the treatment of multiple sclerosis adopted on 16 November 2006 accessed on 24.01.2011 at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003485.pdf

[EMA 2012] EMA CHMP Guideline on clinical investigational or medicinal products for the treatment of multiple sclerosis. DRAFT adopted by CHMP for public consultation. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/10/WC500133438.pdf

[EMA 2015] Guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/03/WC500185161.pdf

[Fasolo 2014] Fasolo B, Bana E Costa C. Tailoring value elicitation to decision makers' numeracy and fluency: Expressing value judgments in numbers or words. Omega 2014;44:83–90.

[FDA 2009a] Final Guidance to the Industry on Patient Reported Outcomes: Use in Medical Product Development to Support Label Claims http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf

[FDA 2009b] Guidance for Industry. Drug-induced liver injury: premarketing clinical evaluation. FDA CDER July 2009.

[Gilenya® SmPC] Gilenya® Summary of Product Characteristics; http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002202/WC500104528.pdf

[Gold 2012] Gold R, Kappos L, Arnold DL, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med 2012;367:1098–107.

[ICH E1A 1995] Guideline for Industry. The Extent of Population Exposure to Assess Clinical Safety: for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions. ICH 1995.

[Izquierdo 2013] Izquierdo G, O'Connor P, Montalban X, et al. Five-year results from a Phase 2 study of oral fingolimod in relapsing multiple sclerosis. Mult Scler 2013 Nov [Epub ahead of print].

[Kappos 2007] Kappos L, Bates D, Hartung HP, et al. Natalizumab treatment for multiple sclerosis: recommendations for subject selection and monitoring. Lancet Neurol 2007;6:431–41.

[Kappos 2011] Kappos L, Bates D, Edan G, et al. Natalizumab treatment for multiple sclerosis: updated recommendations for patient selection and monitoring. Lancet Neurol 2011;10:745–58.

[Kurtzke 1983] Kurtzke J F. Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). Neurology 1983;33:1444–1452.

[Lublin 1996] Lublin FD, Reingold SC, et al. Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. Neurology 1996;46(4):907–11.

[Lublin 2003] Lublin FD, Baier M, Cutter G. Effect of relapses on development of residual deficit in multiple sclerosis. Neurology 2003;61:1528–32.

[Lublin 2014] Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: The 2013 revisions. Neurology 2014 [Epub ahead of print].

[Macintyre 2005] Macintyre N, Crapo RO, Viegi G, et al. ATS/ERS Task Force. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J 2005;26(4):720–35.

[Maruish 2011] Maruish ME (Ed.). User's manual for the SF-36v2 Health Survey (3rd ed.). Lincoln, RI: QualityMetric Incorporated; 2011.

[Miller 2005a] Miller MR, Crapo R, Hankinson J, et al,; ATS/ERS Task Force. General considerations for lung function testing. Eur Respir J. 2005 Jul;26(1):153–61. Review.

[Miller 2005b] Miller MR, Hankinson J, Brusasco V, et al; ATS/ERS Task Force. Standardisation of spirometry. Eur Respir J. 2005 Aug;26(2):319–38.

[Milo 2010] Milo R, Kahana E. Multiple sclerosis: geoepidemiology, genetics and the environment. Autoimmun Rev 2010;9(5):A387–394.

[Noseworthy 2000] Noseworthy JH, Lucchinetti CF, Rodriguez M, et al. Multiple sclerosis. N Engl J Med 2000;343:938–52.

[O'Connor 2011] O'Connor P, Wolinsky JS, Confavreux C, et al. Randomized Trial of Oral Teriflunomide for Relapsing Multiple Sclerosis. N Engl J Med 2011;365:1293–303.

[Pinschewer 2000] Pinschewer DD, Ochsenbein AF, Odermatt B, et al. FTY720 immunosuppression impairs effector T cell peripheral homing without affecting induction, expansion, and memory. J Immunol 2000;164:5761–70.

[Polman 2005] Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria." Ann Neurol 2005;58:840–846.

[Polman 2011] Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol. 2011;69(2):292–302.

[Ponesimod IB] Investigator's Brochure for ponesimod S1P1 receptor agonist, version 13. Actelion Pharmaceuticals Ltd, July 2018.

[Pugliatti 2002] Pugliatti M, Sotgiu S, Rosati G. The worldwide prevalence of multiple sclerosis. Clin Neurol Neurosurg 2002;104(3):182–91.

[Quanjer 1993] Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party

Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J Suppl 1993;16:5–40.

[Renoux 2007] Renoux C, Vukusic S, et al. Natural history of multiple sclerosis with childhood onset. N Engl J Med 2007 Jun 21;356(25):2603–13.

[Schwab 2007] Schwab JM, Cyster JG. Finding a way out: lymphocyte egress from lymphoid organs. Nat Immunol 2007;8:1295–301.

[Smith 1982] Smith, A. Symbol digit modalities test: Manual, (Western Psychological Services, Los Angeles, 1982).

[Smith 2001] S.M. Smith, N. De Stefano, M. Jenkinson, et al. Normalised accurate measurement of longitudinal brain change. J Comput Assist Tomogr 2001 25(3):466–475.

[Smith 2002] S.M. Smith, Y. Zhang, M. Jenkinson, et al. Accurate, robust and automated longitudinal and cross-sectional brain change analysis. Neuroimage 2002;17(1):479–489.

[Sobhani 2010] Sobhani K, Garrett DA, Liu DP, Rainey PM. A rapid and simple high-performance liquid chromatography assay for the leflunomide metabolite, teriflunomide (A77 1726), in renal transplant recipients. Am J Clin Pathol 2010;133(3):454–7.

[Steiner 2007] Steiner I, Kennedy PG, Pachner AR. The neurotropic herpes viruses: herpes simplex and varicella-zoster. Lancet Neurol 2007;6:1015–28.

[WHO 2008] Thompson AJ, Rompani P, Dua T, et al. WHO/MSIF: Atlas of MS: multiple sclerosis resources across the world. Mult Scler 2008; S153.

Appendix 1 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 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.

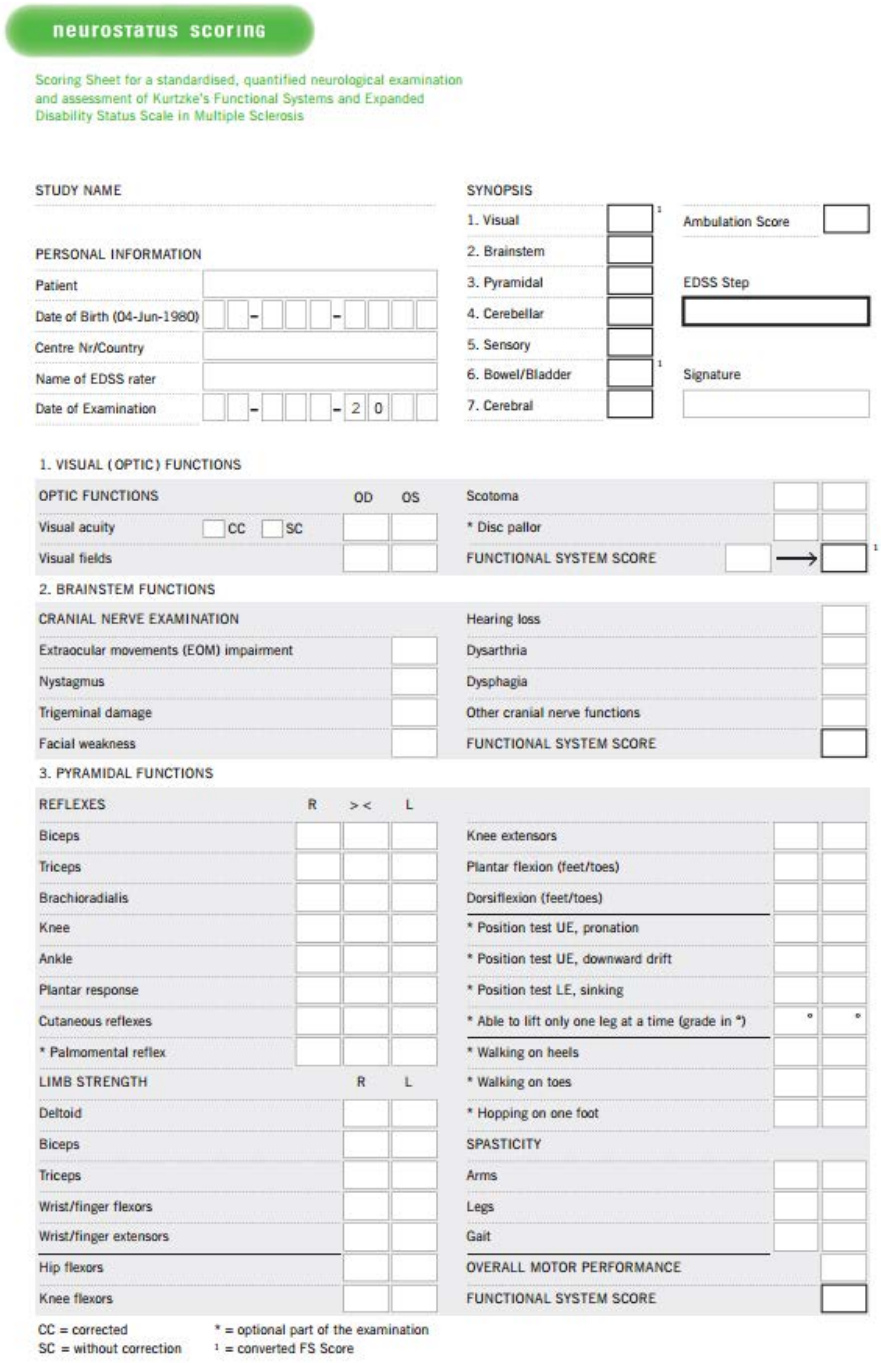
[c]No additional tests are required. However, it is desirable that any diagnosis of MS be made with access to imaging based on these criteria. If imaging or other tests (for instance, CSF) are undertaken and are negative, extreme caution needs to be taken before making a diagnosis of MS, and alternative 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 2 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

SYNOPSIS

1. Visual [ ]¹ Ambulation Score [ ]
2. Brainstem [ ]
3. Pyramidal [ ] EDSS Step [ ]
4. Cerebellar [ ]
5. Sensory [ ]
6. Bowel/Bladder [ ]¹ Signature
7. Cerebral [ ]

PERSONAL INFORMATION

Patient
Date of Birth (04-Jun-1980) __-__-__
Centre Nr/Country
Name of EDSS rater
Date of Examination __-__-20__

1. VISUAL (OPTIC) FUNCTIONS

OPTIC FUNCTIONS	OD	OS
Visual acuity ☐ CC ☐ SC		
Visual fields		

Scotoma
* Disc pallor
FUNCTIONAL SYSTEM SCORE → [ ]¹

2. BRAINSTEM FUNCTIONS

CRANIAL NERVE EXAMINATION
Extraocular movements (EOM) impairment
Nystagmus
Trigeminal damage
Facial weakness

Hearing loss
Dysarthria
Dysphagia
Other cranial nerve functions
FUNCTIONAL SYSTEM SCORE

3. PYRAMIDAL FUNCTIONS

REFLEXES	R	><	L
Biceps			
Triceps			
Brachioradialis			
Knee			
Ankle			
Plantar response			
Cutaneous reflexes			
* Palmomental reflex			

LIMB STRENGTH	R	L
Deltoid		
Biceps		
Triceps		
Wrist/finger flexors		
Wrist/finger extensors		
Hip flexors		
Knee flexors		

Knee extensors
Plantar flexion (feet/toes)
Dorsiflexion (feet/toes)
* Position test UE, pronation
* Position test UE, downward drift
* Position test LE, sinking
* Able to lift only one leg at a time (grade in *) ° °
* Walking on heels
* Walking on toes
* Hopping on one foot

SPASTICITY
Arms
Legs
Gait
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

Appendix 3 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 hypokalaemia 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 5.1.10] 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 steadystate [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 4 Prohibited anti-arrhythmic and HR-lowering drugs

The following anti-arrhythmic and HR-lowering drugs (systemic administration) are prohibited during the study [see Section 5.2.5]:

- 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
- Morcizine
- 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 5 Adverse events of special interest

AEs of special interest will include the anticipated risks of treatment with ponesimod, teriflunomide (e.g., liver enzyme abnormalities) and the events that may be related to MS comorbitities (e.g., seizures or stroke), and will address the following safety areas:

- Effect on HR and rhythm related AEs
- Hepatobiliary disorders / Liver enzyme abnormality related AEs
- Pulmonary related AEs
- Eye disorders related AEs
- Infection related AEs
- Skin malignancy related AEs
- Non-skin malignancy related AEs
- Cardiovascular related AEs
- Hypertension related AEs
- Stroke related AEs
- Seizure related AEs

A list of AEs of special interest (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 or teriflunomide 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 Table 8 below may be defined in the central laboratory manual.

Table 8 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 **ALERT:** **< 50**	> 600	> 999
RBC count (10^{12} /L)	ND	ND	ND	ND
WBC count (10^9 /L)	NA	< 1.9	> 20.0	> 100.0
Lymphocyte (10^9 /L)	ND	< 0.2 **ALERT:** **< 0.2**	> 4.0	> 8.0
Neutrophils (10^9 /L)	< 1.5	< 1.0 **ALERT:** **< 1.0**	ND	ND
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**

Parameter (SI unit)	**LL**	**LLL**	**HH**	**HHH**
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 **ALERT:** **> 150**
Creatinine clearance (mL/min)	< 60	< 30 **ALERT:** **< 30**	ND	ND
Urea (mmol/L)	ND	ND	> 2.5 ULN	> 5 ULN
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

Parameter (SI unit)	LL	LLL	HH	HHH
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**
Teriflunomide (ng/mL)	ND	ND	ND	> 20 **ALERT:** **> 20**

* HH and HHH based on CTCAE 2010 v4.03 [CTCAE 2010]. An ALERT will 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 Sections 5.1.13 and 5.1.14]; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ND = not defined; may be complemented by definitions provided by the central laboratory (see central laboratory manual); ULN = upper limit of normal.

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 either 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

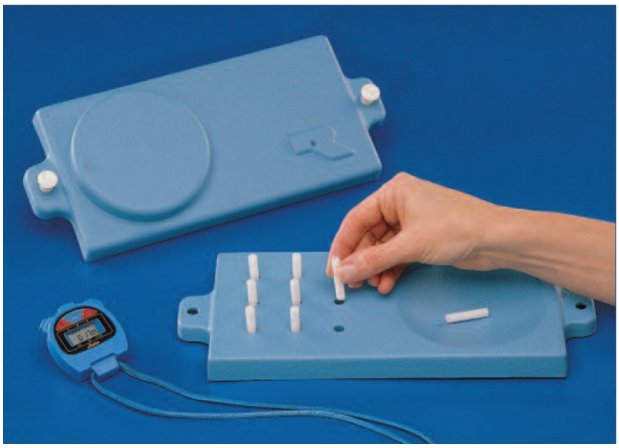
Time to complete the test in seconds:

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 10__	3 4 __	5 8 __	2 7 __	6 8 __	4 10__	9 13__	7 16__	1 8 __	4 5 __
RATE #1 (3″)	1+4 5 __	8 12__	1 9 __	5 6 __	1 6 __	3 4 __	7 10__	2 9 __	6 8 __	9 15__
	4 13__	7 11__	3 10__	5 8 __	3 8 __	6 9 __	8 14__	2 10__	5 7 __	1 6 __
	5 6 __	4 9 __	6 10__	3 9 __	8 11__	1 9 __	7 8 __	4 11__	9 13__	3 12__
	7 10__	2 9 __	6 8 __	9 15__	5 14__	2 7 __	4 6 __	8 12__	3 11__	1 4 __
	8 9 __	5 13__	7 12__	1 8 __	8 9 __	2 10__	4 6 __	9 13__	7 16__	9 16__
	3 12__	1 4 __	5 6 __	7 12__	4 11__	8 12__	1 9 __	3 4 __	8 11__	2 10__

Total Correct (raw) = _____ Percent Correct = _____

PASAT - Form B

Name_____ Date_____

PRACTICE	9+1 10__	3 4 __	5 8 __	2 7 __	6 8 __	4 10__	9 13__	7 16__	1 8 __	4 5 __
RATE #1 (3″)	2+7 9 __	5 12__	8 13__	2 10__	9 11__	6 15__	4 10__	1 5 __	3 4 __	6 9 __
	3 9 __	6 9 __	2 8 __	8 10__	4 12__	9 13__	1 10__	6 7 __	7 13__	2 9 __
	4 6 __	1 5 __	5 6 __	7 12__	3 10__	9 12__	7 16__	2 9 __	6 8 __	8 14__
	4 12__	2 6 __	5 7 __	8 13__	5 13__	9 14__	3 12__	7 10__	1 8 __	4 5 __
	2 6 __	4 6 __	3 7 __	6 9 __	1 7 __	7 8 __	3 10__	8 11__	3 11__	9 12__
	1 10__	3 4 __	5 8 __	2 7 __	6 8 __	4 10__	9 13__	7 16__	1 8 __	4 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 (FSIQ-RMS)

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**.

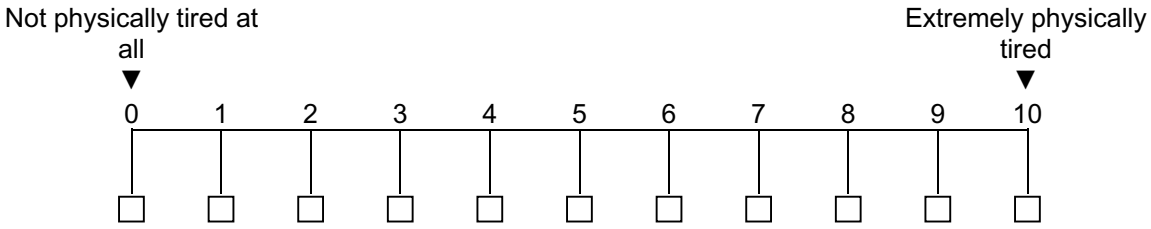
Please select the response that best describes your experience. Please answer all of the questions and do not skip any. There are no right or wrong answers to any of the questions.

Section 1

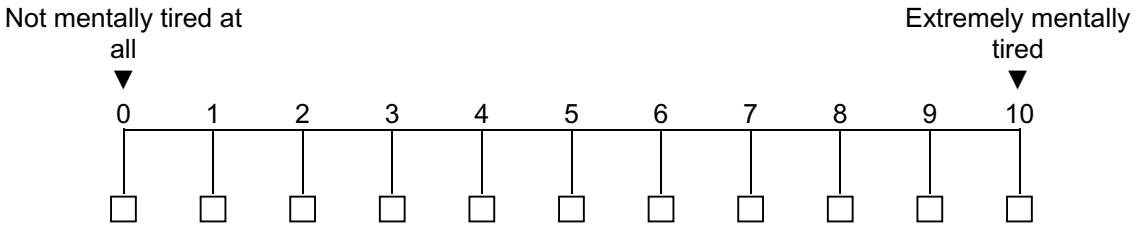
Instructions:

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).

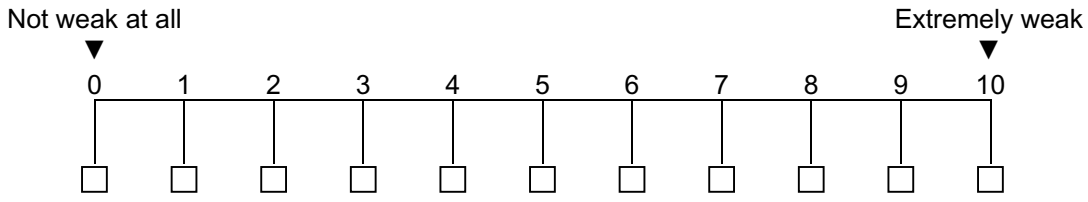
1. In the past 24 hours, while doing routine daily activities, how **physically tired did you feel**?



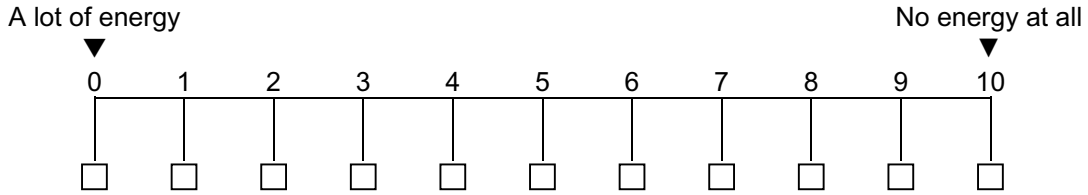
2. In the past 24 hours, while doing routine daily activities, how **mentally tired did you feel**?



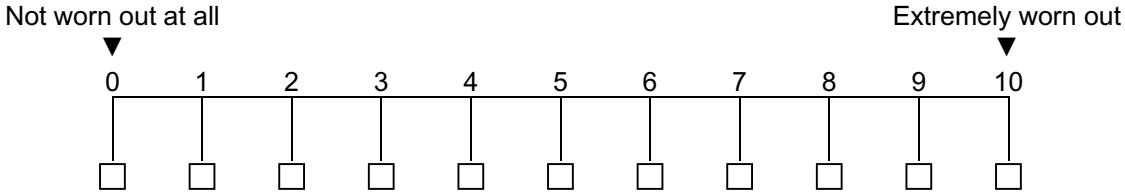
3. In the past 24 hours, while doing routine daily activities, how **physically weak did you feel**?



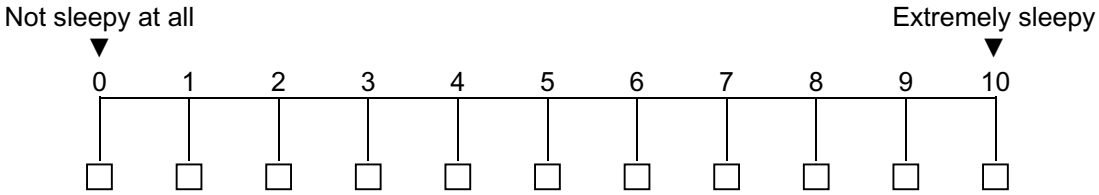
4. In the past 24 hours, how would you rate your **energy** while doing routine daily activities?



5. In the past 24 hours, while doing routine daily activities, how **worn out did you feel**?



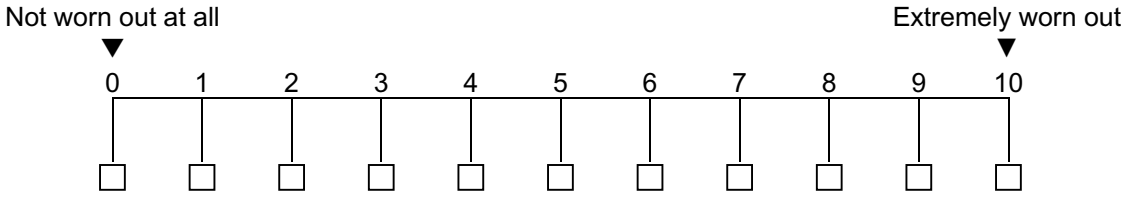
6. In the past 24 hours, while doing routine daily activities, how **sleepy did you feel**?



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 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 11 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 box 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 question is about activities you might do during a typical day.

Does your health now limit you in vigorous activities, 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

The following question is about activities you might do during a typical day.

Does your health now limit you in moderate activities, 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

The following question is about activities you might do during a typical day. 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
The following question is about activities you might do during a typical day. 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
The following question is about activities you might do during a typical day. 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

The following question is about activities you might do during a typical day. Does <u>your health now limit you</u> in bending, kneeling, or stooping? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
The following question is about activities you might do during a typical day. Does <u>your health now limit you</u> in walking <u>more than a mile</u>? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
The following question is about activities you might do during a typical day. Does <u>your health now limit you</u> in walking <u>several hundred yards</u>? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all

The following question is about activities you might do during a typical day. Does <u>your health now limit you</u> in walking <u>one hundred yards</u>? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
The following question is about activities you might do during a typical day. Does <u>your health now limit you</u> in bathing or dressing yourself? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities? Cut down on the <u>amount of time</u> you spent on work or other activities <u>as a result of your physical health</u> 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? 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 have you had any of the following problems with your work or other regular daily activities? Were 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 any of the following problems with your work or other regular daily activities? 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?

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 had any of the following problems with your work or other regular daily activities?

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 had any of the following problems with your work or other regular daily activities?

Did 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

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks 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

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks 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

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks 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

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks 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

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

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

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

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

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

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

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

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

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

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 past 4 weeks, how much of the time has your physical health or emotional problems 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 the following statement for you? I seem to get sick a little easier than other people. Definitely true Mostly true Don't know Mostly false Definitely false
How TRUE or FALSE is the following statement for you? I am as healthy as anybody I know. Definitely true Mostly true Don't know Mostly false Definitely false

How TRUE or FALSE is the following statement for you?

I expect my health to get worse.

Definitely true
Mostly true
Don't know
Mostly false
Definitely false

How TRUE or FALSE is the following statement for you?

My health is excellent.

Definitely true
Mostly true
Don't know
Mostly false
Definitely false

Appendix 12 Patient's Global Impression of Severity (PGI-S) of Fatigue

Patient's Global Impression of Severity of Fatigue

Please select the response which best describes the severity of your fatigue **today**

1. Overall, how severe is your fatigue today?	Not severe at all ▼ 0 1 2 3 4 5 6 7 8 9 10 ▼ Very severe

Appendix 13 Clinician's Global Impression of Change (CGI-C)

CLINICIAN GLOBAL IMPRESSION OF CHANGE

1. Check the one number that best describes the severity of the patient's relapsing Multiple Sclerosis compared to **Visit 2 (baseline)**.

- ☐1 Very much improved
- ☐2 Much improved
- ☐3 Minimally improved
- ☐4 No change
- ☐5 Minimally worse
- ☐6 Much worse
- ☐7 Very much worse

Appendix 14 MS Patient Preference Questionnaire

Questionnaire

[Benefits of MS treatments]

Patients with multiple sclerosis are prescribed medication to prevent new relapses, to increase the time until their MS gets worse, and to reduce the chance of disability due to disease progression. The following sections focus on your preferences for the benefits associated with some MS treatments.

[Screen 1 - Number of Relapses]

Relapsing MS (RMS), is the most common type of MS. Relapses are signs or symptoms from the central nervous system, (which consists of the brain, spinal cord and optic nerves) such as muscle weakness, tingling, double vision or dizziness, and are due to changes in the central nervous system due to inflammation which occurs in MS.

Please use the 'i' button to see more information on relapses in MS.

[Screen 2]

Imagine a treatment where patients could experience:

0	**or**	**4**
relapses in the next 2 years		

[Screen 3]

For you, how much more preferable is:

0	compared to	**4**
relapses in the next 2 years		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

[Screen 4]
Imagine a treatment where patients could experience:

1	**or**	**4**
relapses in the next 2 years		

[Screen 5]
For you, how much more preferable is:

1	compared to	**4**
relapses in the next 2 years		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

[Screen 6]
Imagine a treatment where patients could experience:

0	**or**	**1**
relapses in the next 2 years		

[Screen 7]
For you, how much more preferable is:

0	compared to	**1**
relapses in the next 2 years		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

[Screen 8]
Imagine a treatment where patients could experience:

2	**or**	**4**
relapses in the next 2 years		

[Screen 9]
For you, how much more preferable is:

2	compared to	**4**
relapses in the next 2 years		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

[Screen 10]
Imagine a treatment where patients could experience:

1	**or**	**2**
relapses in the next 2 years		

[Screen 11]
For you, how much more preferable is:

1	compared to	**2**
relapses in the next 2 years		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

[Screen 12]
Imagine a treatment where patients could experience:

3	**or**	**4**
relapses in the next 2 years		

[Screen 13]
For you, how much more preferable is:

3	compared to	**4**
relapses in the next 2 years		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

[Screen 14]
Imagine a treatment where patients could experience:

2	**or**	**3**
relapses in the next 2 years		

[Screen 15]
For you, how much more preferable is:

2	compared to	**3**
relapses in the next 2 years		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

Thank you. You have provided all the required responses. You can check and change your responses by selecting Back. Select OK and then Next when ready to save your responses.

Time until your MS gets worse

[Screen 1]
In patients with MS, the disease usually gets worse although it cannot be predicted in an individual case how much worse MS will become and how long it will take for MS to become worse.

[Screen 2]

Please select the situation that is closest to your current functioning level related to MS.

Before answering, please use the 'i' button to see the descriptions of the levels of disability used in this questionnaire.

☐ Situation 1: You have **no disability** or **mild disability.** If your MS gets worse, you will move to a stage of **moderate disability.**

☐ Situation 2: **You have moderate disability**. If your MS gets worse, you will move to a stage of **relatively severe disability**

☐ Situation 3: **You have relatively severe disability**. If your MS gets worse, you will move to a stage of **severe disability.**

☐ Situation 4: **You have severe disability**. If your MS gets worse, you will move to a stage of **very severe disability**

[Screen 3]

Imagine a treatment where patients could experience:

8	**or**	**2**
years until MS got worse		

[Screen 4]

For you, how much more preferable is:

8	compared to	**2**
years until your MS gets worse		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

[Screen 5]
Imagine a treatment where patients could experience:

6	**or**	**2**
years until MS got worse		

[Screen 6]
For you, how much more preferable is:

6	compared to	**2**
years until your MS gets worse		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

[Screen 7]
Imagine a treatment where patients could experience:

8	**or**	**6**
years until MS got worse		

[Screen 8]
For you, how much more preferable is:

8	compared to	**6**
years until your MS gets worse		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

[Screen 9]
Imagine a treatment where patients could experience:

4	**or**	**2**
years until MS got worse		

[Screen 10]
For you, how much more preferable is:

4	compared to	**2**
years until your MS gets worse		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

[Screen 11]
Imagine a treatment where patients could experience:

6	**or**	**4**
years until MS got worse		

[Screen 12]
For you, how much more preferable is:

6	compared to	**4**
years until your MS gets worse		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

Thank you. You have provided all the required responses. You can check and change your responses by selecting Back. Select OK and then Next when ready to save your responses.

[Screen 0 - Disability due to disease progression]
The treatments in MS aim to reduce the progression from your current level of functioning to the next level of disability. The questions in this section relate to preventing a transition from one MS-related disability level to the next level ("worsening of MS"). Please tell us your preferences, independent of your current MS functioning level.

Before answering, please use the 'i' button to see the descriptions of the levels of disability used in this questionnaire.

[Screen 1]
Imagine a treatment where patients could experience:

No or Mild	**or**	**Very Severe**
disability		

[Screen 2]
For you, how much more preferable is:

No or Mild	compared to	**Very Severe**
disability		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

[Screen 3]
Imagine a treatment where patients could experience:

Moderate	**or**	**Very Severe**
disability		

[Screen 4]
For you, how much more preferable is:

Moderate	compared to	**Very Severe**
disability		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

[Screen 5]

Imagine a treatment where patients could experience:

No or Mild	**or**	**Moderate**
disability		

[Screen 6]

For you, how much more preferable is:

No or Mild	compared to	**Moderate**
disability		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

[Screen 7]

Imagine a treatment where patients could experience:

Relatively Severe	**or**	**Very Severe**
disability		

[Screen 8]

For you, how much more preferable is:

Relatively Severe	compared to	**Very Severe**
disability		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable

Weakly preferable
Very weakly preferable

[Screen 9]

Imagine a treatment where patients could experience:

Moderate	**or**	**Relatively Severe**
disability		

[Screen 10]

For you, how much more preferable is:

Moderate	compared to	**Relatively Severe**
disability		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

[Screen 11]

Imagine a treatment where patients could experience:

Severe	**or**	**Very Severe**
disability		

[Screen 12]

For you, how much more preferable is:

Severe	compared to	**Very Severe**
disability		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

[Screen 13]

Imagine a treatment where patients could experience:

Relatively Severe	**or**	**Severe**
disability		

[Screen 14]

For you, how much more preferable is:

Relatively Severe	compared to	**Severe**
disability		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

Thank you. You have provided all the required responses. You can check and change your responses by selecting Back. Select OK and then Next when ready to save your responses.

[Risks of MS treatments]

Patients with multiple sclerosis are treated with drugs that may be associated with liver failure, serious infections or increased risk for cancer. For some of the MS drugs, increased monitoring in the hospital may be necessary after the first dose of the drug to ensure that quick medical help is available in case of important side effects. The following sections focus on your preferences for the risks associated with some MS treatments.

[Screen 1 - Liver Failure]

Drugs for MS may interfere with the functioning of your liver and in rare cases lead to liver failure. The next section will ask you about the chance of liver failure (serious enough to require hospitalization or interruption of the MS treatment) within 10 years of treatment.

Please use the 'i' button to see more information on liver failure related to MS treatment.

[Screen 2]

Imagine a treatment where:

0	**or**	**8**
out of 100 patients could experience liver failure within 10 years of treatment		

[Screen 3]

For you, how much more preferable is:

0	compared to	**8**
out of 100 patients having liver failure within 10 years of treatment		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

[Screen 4]

Imagine a treatment where:

2	**or**	**8**
out of 100 patients could experience liver failure within 10 years of treatment		

[Screen 5]

For you, how much more preferable is:

2	compared to	**8**
out of 100 patients having liver failure within 10 years of treatment		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

[Screen 6]

Imagine a treatment where:

0	**or**	**2**
out of 100 patients could experience liver failure within 10 years of treatment		

[Screen 7]

For you, how much more preferable is:

0	compared to	**2**
out of 100 patients having liver failure within 10 years of treatment		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

[Screen 8]

Imagine a treatment where:

4	**or**	**8**
out of 100 patients could experience liver failure within 10 years of treatment		

[Screen 9]

For you, how much more preferable is:

4	compared to	**8**
out of 100 patients having liver failure within 10 years of treatment		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

[Screen 10]

Imagine a treatment where:

2	**or**	**4**
out of 100 patients could experience liver failure within 10 years of treatment		

[Screen 11]
For you, how much more preferable is:

2	compared to	**4**
out of 100 patients having liver failure within 10 years of treatment		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

[Screen 12]
Imagine a treatment where:

6	**or**	**8**
out of 100 patients could experience liver failure within 10 years of treatment		

[Screen 13]
For you, how much more preferable is:

6	compared to	**8**
out of 100 patients having liver failure within 10 years of treatment		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

[Screen 14]
Imagine a treatment where:

4	**or**	**6**
out of 100 patients could experience liver failure within 10 years of treatment		

[Screen 15]
For you, how much more preferable is:

4	compared to	**6**
out of 100 patients having liver failure within 10 years of treatment		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

Thank you. You have provided all the required responses. You can check and change your responses by selecting Back. Select OK and then Next when ready to save your responses.

[Screen 1 - Serious Infection leading to disability]

Some of the treatments for MS may lead to a weakened immune system and some patients may develop serious infections. The following questions are related to the chance (probability) of developing a severe infection leading to a disability within 10 years of treatment.

Please use the 'i' button to see more information on serious infection leading to disability.

[Screen 2]

Imagine a treatment where:

5 out of 100,000	**or**	**5 out of 100**
patients could experience a serious infection leading to disability within 10 years of treatment		

[Screen 3]

For you, how much more preferable is:

5 out of 100,000	compared to	**5 out of 100**
patients having a serious infection leading to disability within 10 years of treatment		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

[Screen 4]

Imagine a treatment where:

5 out of 10,000	or	**5 out of 100**
patients could experience a serious infection leading to disability within 10 years of treatment		

[Screen 5]
For you, how much more preferable is:

5 out of 10,000	compared to	**5 out of 100**
patients having a serious infection leading to disability within 10 years of treatment		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

[Screen 6]
Imagine a treatment where:

5 out of 100,000	or	**5 out of 10,000**
patients could experience a serious infection leading to disability within 10 years of treatment		

[Screen 7]
For you, how much more preferable is:

5 out of 100,000	compared to	**5 out of 10,000**
patients having a serious infection leading to disability within 10 years of treatment		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

[Screen 8]
Imagine a treatment where:

5 out of 1,000	or	**5 out of 100**
patients could experience a serious infection leading to disability within 10 years of treatment		

[Screen 9]
For you, how much more preferable is:

5 out of 1,000	compared to	**5 out of 100**
patients having a serious infection leading to disability within 10 years of treatment		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

[Screen 10]
Imagine a treatment where:

5 out of 10,000	or	**5 out of 100**
patients could experience a serious infection leading to disability within 10 years of treatment		

[Screen 11]
For you, how much more preferable is:

5 out of 10,000	compared to	**5 out of 100**
patients having a serious infection leading to disability within 10 years of treatment		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

Thank you. You have provided all the required responses. You can check and change your responses by selecting Back. Select OK and then Next when ready to save your responses.

[Screen 1 - Cancer]

Some MS drugs acting through the immune system may increase the risk of getting a malignant tumor (cancer). This can be a skin cancer, blood cancer or any other type of cancer. There is currently no evidence supporting such risk for the MS drugs used in this study but patients are being observed for development of cancer.

Please use the 'i' button for more information on the risk of cancer in MS.

[Screen 2]

Imagine a treatment where:

0	**or**	**150**
out of 1,000 patients could develop cancer within 10 years of treatment		

[Screen 3]

For you, how much more preferable is:

0	compared to	**150**
out of 1,000 patients developing cancer within 10 years of treatment		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

[Screen 4]
Imagine a treatment:

50	**or**	**150**
out of 1,000 patients could develop cancer within 10 years of treatment		

[Screen 5]
For you, how much more preferable is:

50	compared to	**150**
out of 1,000 patients developing cancer within 10 years of treatment		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

[Screen 6]
Imagine a treatment:

0	**or**	**50**
out of 1,000 patients could develop cancer within 10 years of treatment		

[Screen 7]
For you, how much more preferable is:

0	compared to	**50**
out of 1,000 patients developing cancer within 10 years of treatment		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

[Screen 8]
Imagine a treatment where:

100	**or**	**150**
out of 1,000 patients could develop cancer within 10 years of treatment		

[Screen 9]
For you, how much more preferable is:

100	compared to	**150**
out of 1,000 patients developing cancer within 10 years of treatment		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

[Screen 10]
Imagine a treatment where:

50	**or**	**100**
out of 1,000 patients could develop cancer within 10 years of treatment		

[Screen 11]
For you, how much more preferable is:

50	compared to	**100**
out of 1,000 patients developing cancer within 10 years of treatment		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

Thank you. You have provided all the required responses. You can check and change your responses by selecting Back. Select OK and then Next when ready to save your responses.

[Screen 1 - Monitoring of the heart]
With some treatments for MS it is necessary to monitor the heart on the day of the first dose of the drug or when re-starting the drug after an interruption of more than 3 days.

Please use the 'i' button to see more information on monitoring of the heart in MS.

[Screen 2]
Imagine a treatment where patients could experience:

0	**or**	**24**

hours spent in the hospital for monitoring of the heart

[Screen 3]

For you, how much more preferable is:

0	compared to	**24**
hours spent in the hospital for monitoring of the heart		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

[Screen 4]

Imagine a treatment where patients could experience:

6	**or**	**24**
hours spent in the hospital for monitoring of the heart		

[Screen 5]
For you, how much more preferable is:

6	compared to	**24**
hours spent in the hospital for monitoring of the heart		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

[Screen 6]
Imagine a treatment where patients could experience:

0	**or**	**6**
hours spent in the hospital for monitoring of the heart		

[Screen 7]
For you, how much more preferable is:

0	compared to	**6**
hours spent in the hospital for monitoring of the heart		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

[Screen 8]

Imagine a treatment where patients could experience:

12	**or**	**24**
Hours spent in the hospital for monitoring of the heart		

[Screen 9]

For you, how much more preferable is:

12	compared to	**24**
hours spent in the hospital for monitoring of the heart		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

[Screen 10]

Imagine a treatment where patients could experience:

6	**or**	**12**
hours spent in the hospital for monitoring of the heart		

[Screen 11]

For you, how much more preferable is:

6	compared to	**12**
hours spent in the hospital for monitoring of the heart		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

[Screen 12]

Imagine a treatment where patients could experience:

18	**or**	**24**
hours spent in the hospital for monitoring of the heart		

[Screen 13]

For you, how much more preferable is:

18	compared to	**24**
hours spent in the hospital for monitoring of the heart		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

[Screen 14]

Imagine a treatment where patients could experience:

12	**or**	**18**
hours spent in the hospital for monitoring of the heart		

[Screen 15]
For you, how much more preferable is:

12	compared to	**18**
hours spent in the hospital for monitoring of the heart		

Extremely preferable
Very strongly preferable
Strongly preferable
Moderately preferable
Weakly preferable
Very weakly preferable

Thank you. You have provided all the required responses. You can check and change your responses by selecting Back. Select OK and then Next when ready to save your responses.

[Screen 1 - Weights]
The following section will show you all the treatment outcomes you have previously seen and we will ask you several questions about which treatment outcome is the most important (for you) and how you judge moving from the worst possible outcome to the best outcome. Once you have identified the most important outcome it will be removed from the list and then you will be asked to indicate your **next** most important outcome until all questions are completed.

Please use the 'i' button to see more information on the weighting questions.

[Screen 2]
Which of the following improvements is most important? (Please select one)

	Worse		Best
Number of relapses	4 relapses	→	0 relapses
Time until your MS gets worse	2 years	→	8 years
Disease progression	Very severe disability	→	No or Mild disability
Liver Failure	8 out of 100 patients	→	No patients
Serious infection leading to disability	5 out of 100 patients	→	5 out of 100,000 patients
Cancer	150 out of 1,000 patients	→	No patients
Monitoring of the heart	24 hours in hospital	→	No time spent in hospital

[Screen 3]
How important is this improvement?

	Worse		Best
Treatment outcome 1 selected	*outcome level*	→	*outcome level*

- Extremely important
- Very strongly important
- Strongly important
- Moderately important
- Weakly important
- Very weakly important

[Screen 4]
Which of the following improvements is the next most important? (Please select one)

	Worse		Best
Treatment outcome 1	outcome level	⇒	outcome level
Treatment outcome 2	outcome level	⇒	outcome level
Treatment outcome 3	outcome level	⇒	outcome level
Treatment outcome 4	outcome level	⇒	outcome level
Treatment outcome 5	outcome level	⇒	outcome level
Treatment outcome 6	outcome level	⇒	outcome level
Treatment outcome 7	outcome level	⇒	outcome level

[Screen 5]
How important is this improvement?

	Worse		Best
Treatment outcome 2 selected	*outcome level*	⇒	*outcome level*

- Extremely important
- Very strongly important
- Strongly important
- Moderately important
- Weakly important
- Very weakly important

[Screen 6]

How much more important is the improvement at the top compared to the improvement at the bottom?

	Worse		Best
Treatment outcome 1 selected	*outcome level*	⟹	*outcome level*

	Worse		Best
Treatment outcome 2 selected	*outcome level*	⟹	*outcome level*

- Extremely important
- Very strongly important
- Strongly important
- Moderately important
- Weakly important
- Very weakly important
- Indifferent

[Screen 7]
Which of the following improvements is the next most important? (Please select one)

	Worse		Best
Treatment outcome 1	outcome level	⇒	outcome level
Treatment outcome 2	outcome level	⇒	outcome level
Treatment outcome 3	outcome level	⇒	outcome level
Treatment outcome 4	outcome level	⇒	outcome level
Treatment outcome 5	outcome level	⇒	outcome level
Treatment outcome 6	outcome level	⇒	outcome level
Treatment outcome 7	outcome level	⇒	outcome level

[Screen 8]
How important is this improvement?

	Worse		Best
Treatment outcome 3 selected	*outcome level*	⇒	*outcome level*

- Extremely important
- Very strongly important
- Strongly important
- Moderately important
- Weakly important
- Very weakly important

[Screen 9]

How much more important is the improvement at the top compared to the improvement at the bottom?

	Worse		Best
Treatment outcome 2 selected	*outcome level*	⟹	*outcome level*

	Worse		Best
Treatment outcome 3 selected	*outcome level*	⟹	*outcome level*

- Extremely important
- Very strongly important
- Strongly important
- Moderately important
- Weakly important
- Very weakly important
- Indifferent

[Screen 10]

Which of the following improvements is the next most important? (Please select one)

	Worse		Best
Treatment outcome 1	outcome level	⇒	outcome level
Treatment outcome 2	outcome level	⇒	outcome level
Treatment outcome 3	outcome level	⇒	outcome level
Treatment outcome 4	outcome level	⇒	outcome level
Treatment outcome 5	outcome level	⇒	outcome level
Treatment outcome 6	outcome level	⇒	outcome level
Treatment outcome 7	outcome level	⇒	outcome level

[Screen 11]

How important is this improvement?

	Worse		Best
Treatment outcome 4 selected	*outcome level*	⇒	*outcome level*

- Extremely important
- Very strongly important
- Strongly important
- Moderately important
- Weakly important
- Very weakly important

[Screen 12]

How much more important is the improvement at the top compared to the improvement at the bottom?

	Worse		Best
Treatment outcome 3 selected	*outcome level*	⟹	*outcome level*

	Worse		Best
Treatment outcome 4 selected	*outcome level*	⟹	*outcome level*

- Extremely important
- Very strongly important
- Strongly important
- Moderately important
- Weakly important
- Very weakly important
- Indifferent

[Screen 13]

Which of the following improvements is the next most important? (Please select one)

	Worse		Best
Treatment outcome 1	outcome level	⇒	outcome level
Treatment outcome 2	outcome level	⇒	outcome level
Treatment outcome 3	outcome level	⇒	outcome level
Treatment outcome 4	outcome level	⇒	outcome level
Treatment outcome 5	outcome level	⇒	outcome level
Treatment outcome 6	outcome level	⇒	outcome level
Treatment outcome 7	outcome level	⇒	outcome level

[Screen 14]
How important is this improvement?

	Worse		Best
Treatment outcome 5 selected	*outcome level*	⟹	*outcome level*

- Extremely important
- Very strongly important
- Strongly important
- Moderately important
- Weakly important
- Very weakly important

[Screen 15]
How much more important is the improvement at the top compared to the improvement at the bottom?

	Worse		Best
Treatment outcome 4 selected	*outcome level*	⟹	*outcome level*

	Worse		Best
Treatment outcome 5 selected	*outcome level*	⟹	*outcome level*

- Extremely important
- Very strongly important
- Strongly important
- Moderately important
- Weakly important
- Very weakly important
- Indifferent

[Screen 16]
Which of the following improvements is the next most important? (Please select one)

	Worse		Best
Treatment outcome 1	outcome level	⇒	outcome level
Treatment outcome 2	outcome level	⇒	outcome level
Treatment outcome 3	outcome level	⇒	outcome level
Treatment outcome 4	outcome level	⇒	outcome level
Treatment outcome 5	outcome level	⇒	outcome level
Treatment outcome 6	outcome level	⇒	outcome level
Treatment outcome 7	outcome level	⇒	outcome level

[Screen 17]
How important is this improvement?

	Worse		Best
Treatment outcome 6 selected	*outcome level*	⇒	*outcome level*

- Extremely important
- Very strongly important
- Strongly important
- Moderately important
- Weakly important
- Very weakly important

[Screen 18]

How much more important is the improvement at the top compared to the improvement at the bottom?

	Worse		Best
Treatment outcome 5 selected	*outcome level*	⟹	*outcome level*

	Worse		Best
Treatment outcome 6 selected	*outcome level*	⟹	*outcome level*

- Extremely important
- Very strongly important
- Strongly important
- Moderately important
- Weakly important
- Very weakly important
- Indifferent

[Screen 19]
Which of the following improvements is the next most important? (Please select one)

	Worse		Best
Treatment outcome 1	outcome level	⇒	outcome level
Treatment outcome 2	outcome level	⇒	outcome level
Treatment outcome 3	outcome level	⇒	outcome level
Treatment outcome 4	outcome level	⇒	outcome level
Treatment outcome 5	outcome level	⇒	outcome level
Treatment outcome 6	outcome level	⇒	outcome level
Treatment outcome 7	outcome level	⇒	outcome level

[Screen 20]
How important is this improvement?

	Worse		Best
Treatment outcome 7 selected	*outcome level*	⇒	*outcome level*

- Extremely important
- Very strongly important
- Strongly important
- Moderately important
- Weakly important
- Very weakly important

[Screen 21]
How much more important is the improvement at the top compared to the improvement at the bottom?

	Worse		Best
Treatment outcome 6 selected	*outcome level*	⟹	*outcome level*

	Worse		Best
Treatment outcome 7 selected	*outcome level*	⟹	*outcome level*

- Extremely important
- Very strongly important
- Strongly important
- Moderately important
- Weakly important
- Very weakly important
- Indifferent

Thank you. You have provided all the required responses. You can check and change your responses by selecting Back. Select OK and then Next when ready to save your responses.

[Screen 1 - Numeracy]
The questions in the next section are about your numeracy. Please read the questions carefully and try to give the correct answer.

Please use the 'i' button to see more information on numeracy.

[Screen 2]
Imagine that we roll a fair, six-sided die 1,000 times. Out of 1,000 rolls, how many times do you think the die would come up with even (2, 4, or 6)?

_____

[Screen 3]

In the BIG BUCKS LOTTERY, the chance of winning a £10,000 prize is 1%. What is your best guess about how many people would win a £10,000 prize if 1,000 people each buy a single ticket to BIG BUCKS?

_____

[Screen 4]
In the ACME PUBLISHING SWEEPSTAKES, the chance of winning a car is 1 in 1,000. What percent of tickets of ACME PUBLISHING SWEEPSTAKES win a car?

__.__%

Thank you. You have provided all the required responses. You can check and change your responses by selecting Back. Select OK and then Next when ready to save your responses.

[Screen 1 - Comprehension/Ease of use]

Thank you for participating in this study. In the next screens please tell us about your experience with completing the questionnaire.

[Screen 2]

On a scale of 1 to 7, where 1 = not at all easy and 7 = very easy, how easy was it to understand the questions in the questionnaire?

_____

[Screen 3]

Was enough information provided to help you understand the purpose of the questionnaire?

- ☐ Yes
- ☐ No
    - If yes, where did you receive the best information to help with this questionnaire?
        - From the clinic
        - From the help pages in the questionnaire
        - Other

200 characters

Please state other

[Screen 4]

- If no, what additional information would have been helpful?

200 characters

[Screen 5]
What was the most challenging aspect of completing this questionnaire?

400 characters

[Screen 6]
Please use the box below to provide any other general comments on your experience with this questionnaire.

400 characters

Thank you. You have provided all the required responses. You can check and change your responses by selecting Back. Select OK and then Next when ready to save your responses.

Appendix 15 Child Pugh Classification

Parameter	Points scored for observed findings		
	1	2	3
Ascites	Absent	Slight	Moderate
Hepatic encephalopathy grade*	None	1 or 2	3 or 4
Bilirubin micromol/L (mg/dL)	< 34.2 < 2	34.2 – 51.3 2 – 3	> 51.3 > 3
Albumin g/L (g/dL)	> 3.5	2.8 – 3.5	< 2.8
INR	< 1.7	1.7 – 2.3	> 2.3
Child Pugh classification: A: score 5–6 B: score 7–9 C: score 10–15			

*Hepatic encephalopathy classification:
Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2–3 cps delta activity

Sources:
Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling. **FDA,** May 2003 http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072123.pdf (Accessed 13 March 2015)

BMJ Best practice website, http://bestpractice.bmj.com/best-practice/monograph/278/diagnosis/criteria.html (Accessed 13 March 2015)

Appendix 16 Electronic self-rated version of the Columbia-Suicide Severity Rating Scale (eC-SSRS)

eC-SSRS 2.0 Call Script – Lifetime (Corresponding to Visit 2 - baseline assessment)

Core Language: US English
Introduction
NRT01
In this interview, I am 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 I will ask about thoughts regarding wanting to be dead or killing yourself that you have not actually acted on. Later I will ask about any actions you may have actually done or preparations you have made. I 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?
If Yes, press 1 If No, press 2
Ideation Level = 1
Active Suicide Ideation
Q02
Have you actually had any thoughts of killing yourself, at any time?
If Yes, press 1 If No, press 2
Ideation Level = 2
Q03
Have you thought about how you might do this?

If Yes, press 1 If No, press 2
Ideation Level = 3
Q03.1
What way of killing yourself did you think of most often?
If with medication, press 1 If by hanging, press 2 If by jumping, press 3 If with a gun, press 4 If by some other method, press 5
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?
If Yes, press 1 If No, press 2
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?
If Yes, press 1 If No, press 2
Q05q
Did you actually intend to carry out the details of your plan?

If Yes, press 1 If No, press 2
Ideation Level = 5
Q05r
How did you intend to kill yourself?
If with medication, press 1 If by hanging, press 2 If by jumping, press 3 If with a gun, press 4 If by some other method, press 5
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. I want to ask you a few more questions about that. When responding to these questions, I 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?
If these thoughts occurred less than once a week, press 1 If about once a week, press 2 If these thoughts occurred 2 to 5 times a week, press 3 If daily or almost daily, press 4 If these thoughts occurred many times a day, press 5
Q01b
How long did the thoughts last?

If these thoughts were fleeting, lasting seconds to minutes, press 1 If less than an hour, press 2 If these thoughts lasted between 1 and 4 hours, press 3 If between 4 and 8 hours, press 4 If these thoughts lasted more than 8 hours, press 5
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?
If Yes, press 1 If No, press 2
Q01d
How easily could you control or stop these thoughts?
If you could easily control these thoughts, press 1 If with a little difficulty, press 2 If you could control these thoughts, but with some difficulty, press 3 If with a lot of difficulty, press 4 If you were unable to control these thoughts, press 5
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?
If Yes, press 1 If No, press 2
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.

If something definitely stopped you from wishing you were dead or that you could fall asleep and not wake up, press 1 If something probably stopped you, press 2 If you are uncertain whether something stopped you from wishing you were dead or that you could fall asleep and not wake up, press 3 If something most likely did not stop you, press 4 If something definitely did not stop you from wishing you were dead or that you could fall asleep and not wake up, press 5
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?
If Yes, press 1 If No, press 2
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?
If it was completely to get attention, revenge or a reaction from others, press 1 If it was mostly to get attention, revenge or a reaction from others, press 2 If equally to get attention, revenge or a reaction from others and to end or stop the pain, press 3 If mostly to end or stop the pain (that is, you could not go on living with the pain or how you were feeling), press 4 If completely to end or stop the pain, press 5
Q02aNRT
You indicated before that you had thought of killing yourself. I want to ask you a few more questions about that. When responding to these questions, I 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?
If these thoughts occurred less than once a week, press 1 If about once a week, press 2 If these thoughts occurred 2 to 5 times a week, press 3 If daily or almost daily, press 4 If these thoughts occurred many times a day, press 5
Q02b
How long did these thoughts of killing yourself last?
If these thoughts were fleeting, lasting seconds to minutes, press 1 If less than an hour, press 2 If these thoughts lasted between 1 and 4 hours, press 3 If between 4 and 8 hours, press 4 If these thoughts lasted more than 8 hours, press 5
Q02c
Did you make any attempt to try to control or stop these thoughts, whether you were successful in controlling them or not?
If Yes, press 1 If No, press 2
Q02d
How easily could you control or stop thinking about killing yourself?
If you could easily control these thoughts, press 1 If with a little difficulty, press 2 If you could control these thoughts, but with some difficulty, press 3 If with a lot of difficulty, press 4 If you were unable to control these thoughts, press 5

Q02e.1
Did you think about things like family, religion, or fear of pain or death that might affect your decision about killing yourself?
If Yes, press 1 If No, press 2
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.
If something definitely stopped you from attempting suicide, press 1 If something probably stopped you, press 2 If you are uncertain whether something stopped you from attempting suicide, press 3 If something most likely did not stop you, press 4 If something definitely did not stop you from attempting suicide, press 5
Q02f.1
When you thought about killing yourself, did you have a reason in mind like ending your pain or getting attention or revenge?
If Yes, press 1 If No, press 2
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?

If it was completely to get attention, revenge or a reaction from others, press 1 If it was mostly to get attention, revenge or a reaction from others, press 2 If equally to get attention, revenge or a reaction from others and to end or stop the pain, press 3 If mostly to end or stop the pain (that is, you could not go on living with the pain or how you were feeling), press 4 If completely to end or stop the pain, press 5
Q03aNRT
You indicated before that you had thought about how you might kill yourself. I want to ask you a few more questions about that. When responding to these questions, I 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?
If these thoughts occurred less than once a week, press 1 If about once a week, press 2 If these thoughts occurred 2 to 5 times a week, press 3 If daily or almost daily, press 4 If these thoughts occurred many times a day, press 5
Q03b
When you had these thoughts, how long did they last?
If these thoughts were fleeting, lasting seconds to minutes, press 1 If less than an hour, press 2 If these thoughts lasted between 1 and 4 hours, press 3 If between 4 and 8 hours, press 4 If these thoughts lasted more than 8 hours, press 5
Q03c
Did you make any attempt to try to control or stop these thoughts, whether you were successful in controlling them or not?

If Yes, press 1 If No, press 2
Q03d
How easily could you control or stop thinking about how you might kill yourself?
If you could easily control these thoughts, press 1 If with a little difficulty, press 2 If you could control these thoughts, but with some difficulty, press 3 If with a lot of difficulty, press 4 If you were unable to control these thoughts, press 5
Q03e.1
Did you think about things like family, religion, or fear of pain or death that might affect your decision about killing yourself?
If Yes, press 1 If No, press 2
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.
If something definitely stopped you from attempting suicide, press 1 If something probably stopped you, press 2 If you are uncertain whether something stopped you from attempting suicide, press 3 If something most likely did not stop you, press 4 If something definitely did not stop you from attempting suicide, press 5
Q03f.1
When you thought about killing yourself, did you have a reason in mind like ending your pain or getting attention or revenge?
If Yes, press 1 If No, press 2

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?
If it was completely to get attention, revenge or a reaction from others, press 1 If it was mostly to get attention, revenge or a reaction from others, press 2 If equally to get attention, revenge or a reaction from others and to end or stop the pain, press 3 If mostly to end or stop the pain (that is, you could not go on living with the pain or how you were feeling), press 4 If completely to end or stop the pain, press 5
Q04aNRT
You indicated before that you had thought about killing yourself and that you had some intention of acting on these thoughts. I want to ask you a few more questions about that. When responding to these questions, I 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?
If these thoughts occurred less than once a week, press 1 If about once a week, press 2 If these thoughts occurred 2 to 5 times a week, press 3 If daily or almost daily, press 4 If these thoughts occurred many times a day, press 5
Q04b
How long did the thoughts last?

If these thoughts were fleeting, lasting seconds to minutes, press 1 If less than an hour, press 2 If these thoughts lasted between 1 and 4 hours, press 3 If between 4 and 8 hours, press 4 If these thoughts lasted more than 8 hours, press 5
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?
If Yes, press 1 If No, press 2
Q04d
How easily could you control or stop thinking about killing yourself?
If you could easily control these thoughts, press 1 If with a little difficulty, press 2 If you could control these thoughts, but with some difficulty, press 3 If with a lot of difficulty, press 4 If you were unable to control these thoughts, press 5
Q04e.1
Did you think about things like family, religion, or fear of pain or death that might affect your decision about killing yourself?
If Yes, press 1 If No, press 2
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.

If something definitely stopped you from attempting suicide, press 1 If something probably stopped you, press 2 If you are uncertain whether something stopped you from attempting suicide, press 3 If something most likely did not stop you, press 4 If something definitely did not stop you from attempting suicide, press 5
Q04f.1
When you thought about killing yourself, did you have a reason in mind like ending your pain or getting attention or revenge?
If Yes, press 1 If No, press 2
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?
If it was completely to get attention, revenge or a reaction from others, press 1 If it was mostly to get attention, revenge or a reaction from others, press 2 If equally to get attention, revenge or a reaction from others and to end or stop the pain, press 3 If mostly to end or stop the pain (that is, you could not go on living with the pain or how you were feeling), press 4 If completely to end or stop the pain, press 5
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. I want to ask you a few more questions about that. When responding to these questions, I 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?

If these thoughts occurred less than once a week, press 1 If about once a week, press 2 If these thoughts occurred 2 to 5 times a week, press 3 If daily or almost daily, press 4 If these thoughts occurred many times a day, press 5
Q05b
How long did the thoughts last?
If these thoughts were fleeting, lasting seconds to minutes, press 1 If less than an hour, press 2 If these thoughts lasted between 1 and 4 hours, press 3 If between 4 and 8 hours, press 4 If these thoughts lasted more than 8 hours, press 5
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?
If Yes, press 1 If No, press 2
Q05d
How easily could you control or stop thinking about killing yourself?
If you could easily control these thoughts, press 1 If with a little difficulty, press 2 If you could control these thoughts, but with some difficulty, press 3 If with a lot of difficulty, press 4 If you were unable to control these thoughts, press 5
Q05e.1
Did you think about things like family, religion, or fear of pain or death that might affect your decision about killing yourself?

If Yes, press 1 If No, press 2
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.
If something definitely stopped you from attempting suicide, press 1 If something probably stopped you, press 2 If you are uncertain whether something stopped you from attempting suicide, press 3 If something most likely did not stop you, press 4 If something definitely did not stop you from attempting suicide, press 5
Q05f.1
When you thought about killing yourself, did you have a reason in mind like ending your pain or getting attention or revenge?
If Yes, press 1 If No, press 2
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?
If it was completely to get attention, revenge or a reaction from others, press 1 If it was mostly to get attention, revenge or a reaction from others, press 2 If equally to get attention, revenge or a reaction from others and to end or stop the pain, press 3 If mostly to end or stop the pain (that is, you could not go on living with the pain or how you were feeling), press 4 If completely to end or stop the pain, press 5

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?
If Yes, press 1 If No, press 2
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?
If Yes, press 1 If No, press 2
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 didn't intend to act on the thoughts?
If Yes, press 1 If No, press 2

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?
If Yes, press 1 If No, press 2
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?
If Yes, press 1 If No, press 2
Midpoint Transition
We are almost finished. So far I have been asking about thoughts and feelings you may have had. Now I 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?
If Yes, press 1 If No, press 2
Q06b
Use the number keys on your telephone 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?
If Yes, press 1 If No, press 2
If loop = 2
When you made your first attempt, were you trying to end your life?
If Yes, press 1 If No, press 2
If loop = 3
When you made your most serious attempt, were you trying to end your life?
If Yes, press 1 If No, press 2
Q06e
Did you think it was possible that you could have died from what you did?
If Yes, press 1 If No, press 2

Q06d
So then, if you wanted to die, even a little, when you did this, Press 1. If 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, Press 2.
Q07a
Have you ever done anything to intentionally hurt or harm yourself?
If Yes, press 1 If No, press 2
Q07b
Use the number keys on your telephone 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?
If Yes, press 1 If No, press 2
Q07e
Did you think it was possible that you could have died from what you did?

If Yes, press 1 If No, press 2
Q07d
So then, if you wanted to die, even a little, when you did this, Press 1. If 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, Press 2.
Q08a
Have you done anything dangerous where you could have died?
If Yes, press 1 If No, press 2
Q08b
Use the number keys on your telephone 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?

If Yes, press 1 If No, press 2
Q08c
Were you trying to end your life?
If Yes, press 1 If No, press 2
Q08d
So then, if you wanted to die, even a little, when you did this, Press 1. If 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, Press 2.
Lethality
Q09
If Q06a = YES
As a result of your most serious attempt, were you injured more seriously than surface scratches or mild nausea?
If Yes, press 1 If No, press 2
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?
If Yes, press 1 If No, press 2
Q09RB
Did this occur within the past: I months?

If Yes, press 1 If No, press 2
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.
If Yes, press 1 If No, press 2
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?
If Yes, press 1 If No, press 2
Q09c
Did your injury cause you to be extremely drowsy, or result in broken bones, or severe bleeding?
If Yes, press 1 If No, press 2
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. I 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?
If Yes, press 1 If No, press 2
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?
If Yes, press 1 If No, press 2
Q09.1RB
Did this occur within the past: I months?
If Yes, press 1 If No, press 2
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.
If Yes, press 1 If No, press 2
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?

If Yes, press 1 If No, press 2
Q09.1c
Did your injury cause you to be extremely drowsy, or result in broken bones, or severe bleeding?
If Yes, press 1 If No, press 2
Q09.2
If Q06a = YES
As a result of your first attempt, were you injured more seriously than surface scratches or mild nausea?
If Yes, press 1 If No, press 2
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?
If Yes, press 1 If No, press 2
Q09.2RB
Did this occur within the past: I months?
If Yes, press 1 If No, press 2
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.
If Yes, press 1 If No, press 2
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?
If Yes, press 1 If No, press 2
Q09.2c
Did your injury cause you to be extremely drowsy, or result in broken bones, or severe bleeding?
If Yes, press 1 If No, press 2
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 I 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?
If Yes, press 1 If No, press 2

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?
If Yes, press 1 If No, press 2
Q09.4RB
Did this occur within the past: I months?
If Yes, press 1 If No, press 2
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.
If Yes, press 1 If No, press 2
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?
If Yes, press 1 If No, press 2
Q09.4c
Did your injury cause you to be extremely drowsy, or result in broken bones, or severe bleeding?

If Yes, press 1 If No, press 2
Q09.5
If Q06a = YES
As a result of your first attempt, were you injured more seriously than surface scratches or mild nausea?
If Yes, press 1 If No, press 2
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?
If Yes, press 1 If No, press 2
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.
If Yes, press 1 If No, press 2
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?

If Yes, press 1 If No, press 2
Q09.5c
Did your injury cause you to be extremely drowsy, or result in broken bones, or severe bleeding?
If Yes, press 1 If No, press 2
Q09.6
If Q06a = YES
As a result of your most serious attempt, were you injured more seriously than surface scratches or mild nausea?
If Yes, press 1 If No, press 2
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?
If Yes, press 1 If No, press 2
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.
If Yes, press 1 If No, press 2

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?
If Yes, press 1 If No, press 2
Q09.6c
Did your injury cause you to be extremely drowsy, or result in broken bones, or severe bleeding?
If Yes, press 1 If No, press 2
Q09.8RB
Did this occur within the past: I months?
If Yes, press 1 If No, press 2
Q09.8
Although you were not injured most recently, how serious could your injuries have been?
If what you did was not likely to cause injury, Press 1 If what you did was likely to cause physical injury, but probably not death, Press 2 If 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, Press 3
Q09.9
Although you were not injured the first time, how serious could your injuries have been?

If what you did was not likely to cause injury, Press 1 If what you did was likely to cause physical injury, but probably not death, Press 2 If 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, Press 3
Q09.10RB
Did this occur within the past: I months?
If Yes, press 1 If No, press 2
Q09.10
Although you were not injured during the most serious time, how serious could your injuries have been?
If what you did was not likely to cause injury, Press 1 If what you did was likely to cause physical injury, but probably not death, Press 2 If 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, Press 3
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?
If Yes, press 1 If No, press 2
Q10a
About how many times have you been stopped from ending your life by someone or something?
Please enter the number using your touch tone phone.
Q10RB

Was the last time you were stopped from trying to end your life by someone or something in the past: I months?
If Yes, press 1 If No, press 2
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?
If Yes, press 1 If No, press 2
Q11a
About how many times have you stopped yourself from ending your life?
Please enter the number using your touch tone phone.
Q11RB
Was the last time you stopped yourself from trying to end your life in the past: I months?
If Yes, press 1 If No, press 2
Preparatory Acts or Behaviors
Q12NRT
Asses prior responses and present introduction:
Other than the times you have already told me 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 me 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 me 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 me 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 me about when you did things intending to kill yourself or thought you might have died,
Other than the times you have already told me 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 me 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?
If Yes, press 1 If No, press 2
Q12a
About how many times?
Please enter the number using your touch tone phone.
Q12RB

Was the last time you took steps toward making a suicide attempt or preparing to kill yourself in the past: I months?
If Yes, press 1 If No, press 2
Exit
Thank you and Good bye.

eC-SSRS 2.0 Call Script – Since Last Call (Corresponding to Week 60 and Week 108 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
Introduction
NRT01
The last time you called this telephone system to answer questions about thoughts or actions related to wanting to be dead or killing yourself was [date]. That was [num] days ago. During this call I want you to only consider thoughts or actions that have occurred since that call. In answering the following questions, only report your thoughts and actions over the past [num] days or since [date].
If days SLC > 120
The last time you called this telephone system to answer questions about thoughts or actions related to wanting to be dead or killing yourself was [date]. During this call I want you to only consider thoughts or actions that have occurred since that call. In answering the following questions, only report your thoughts and actions since [date].
Passive Suicide Ideation
Q01
Since your last call, have you wished you were dead or wished you could go to sleep and not wake up?
If Yes, press 1 If No, press 2
Ideation Level = 1
Active Suicide Ideation
Q02

Since your last call on [date], [num] days ago have you actually had any thoughts of killing yourself?
If days SLC > 120
Since your last call on [date], have you actually had any thoughts of killing yourself?
If Yes, press 1 If No, press 2
Ideation Level = 2
Q03
Have you thought about how you might do this?
If Yes, press 1 If No, press 2
Ideation Level = 3
Q03.1
What way of killing yourself did you think of most often?
If with medication, press 1 If by hanging, press 2 If by jumping, press 3 If with a gun, press 4 If by some other method, press 5
Q04
Since your last call, 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?
If Yes, press 1 If No, press 2

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 call?
If Yes, press 1 If No, press 2
Q05q
Did you actually intend to carry out the details of your plan?
If Yes, press 1 If No, press 2
Ideation Level = 5
Q05r
How did you intend to kill yourself?
If with medication, press 1 If by hanging, press 2 If by jumping, press 3 If with a gun, press 4 If by some other method, press 5
Ideation Probing
Q01aNRT
You just indicated that since your last call, you had wished you were dead or wished that you could go to sleep and not wake up. I want to ask you a few more questions about that. When responding to these questions, I 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 call, you had wished you were dead or wished that you could go to sleep and not wake up. I want to ask you a few more questions about that. When responding to these questions, I want you to think about the time when these thoughts were most severe since your last call.
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?
If these thoughts occurred less than once a week, press 1 If about once a week, press 2 If these thoughts occurred 2 to 5 times a week, press 3 If daily or almost daily, press 4 If these thoughts occurred many times a day, press 5
Q01b
How long did the thoughts last?
If these thoughts were fleeting, lasting seconds to minutes, press 1 If less than an hour, press 2 If these thoughts lasted between 1 and 4 hours, press 3 If between 4 and 8 hours, press 4 If these thoughts lasted more than 8 hours, press 5
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?
If Yes, press 1 If No, press 2
Q01d
How easily could you control or stop these thoughts?

If you could easily control these thoughts, press 1 If with a little difficulty, press 2 If you could control these thoughts, but with some difficulty, press 3 If with a lot of difficulty, press 4 If you were unable to control these thoughts, press 5
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?
If Yes, press 1 If No, press 2
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.
If something definitely stopped you from wishing you were dead or that you could fall asleep and not wake up, press 1 If something probably stopped you, press 2 If you are uncertain whether something stopped you from wishing you were dead or that you could fall asleep and not wake up, press 3 If something most likely did not stop you, press 4 If something definitely did not stop you from wishing you were dead or that you could fall asleep and not wake up, press 5
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?
If Yes, press 1 If No, press 2

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?
If it was completely to get attention, revenge or a reaction from others, press 1 If it was mostly to get attention, revenge or a reaction from others, press 2 If equally to get attention, revenge or a reaction from others and to end or stop the pain, press 3 If mostly to end or stop the pain (that is, you could not go on living with the pain or how you were feeling), press 4 If completely to end or stop the pain, press 5
Q02aNRT
You indicated before that since your last call you had thought of killing yourself. I want to ask you a few more questions about that. When responding to these questions, I 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 call you had thought of killing yourself. I want to ask you a few more questions about that. When responding to these questions, I want you to think about the time you were feeling most suicidal since your last call.
Q02a
When you were feeling most suicidal, how often did you think of killing yourself?
If these thoughts occurred less than once a week, press 1 If about once a week, press 2 If these thoughts occurred 2 to 5 times a week, press 3 If daily or almost daily, press 4 If these thoughts occurred many times a day, press 5
Q02b
How long did these thoughts of killing yourself last?

If these thoughts were fleeting, lasting seconds to minutes, press 1 If less than an hour, press 2 If these thoughts lasted between 1 and 4 hours, press 3 If between 4 and 8 hours, press 4 If these thoughts lasted more than 8 hours, press 5
Q02c
Did you make any attempt to try to control or stop these thoughts, whether you were successful in controlling them or not?
If Yes, press 1 If No, press 2
Q02d
How easily could you control or stop thinking about killing yourself?
If you could easily control these thoughts, press 1 If with a little difficulty, press 2 If you could control these thoughts, but with some difficulty, press 3 If with a lot of difficulty, press 4 If you were unable to control these thoughts, press 5
Q02e.1
Did you think about things like family, religion, or fear of pain or death that might affect your decision about killing yourself?
If Yes, press 1 If No, press 2
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.

If something definitely stopped you from attempting suicide, press 1 If something probably stopped you, press 2 If you are uncertain whether something stopped you from attempting suicide, press 3 If something most likely did not stop you, press 4 If something definitely did not stop you from attempting suicide, press 5
Q02f.1
When you thought about killing yourself, did you have a reason in mind like ending your pain or getting attention or revenge?
If Yes, press 1 If No, press 2
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?
If it was completely to get attention, revenge or a reaction from others, press 1 If it was mostly to get attention, revenge or a reaction from others, press 2 If equally to get attention, revenge or a reaction from others and to end or stop the pain, press 3 If mostly to end or stop the pain (that is, you could not go on living with the pain or how you were feeling), press 4 If completely to end or stop the pain, press 5
Q03aNRT
You indicated before that since your last call you had thought about how you might kill yourself. I want to ask you a few more questions about that. When responding to these questions, I 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 call you had thought about how you might kill yourself. I want to ask you a few more questions about that. When responding to these

questions, I want you to think about the time you were feeling the most suicidal since your last call.
Q03a
When you were feeling most suicidal, how often did you think about how you might kill yourself?
If these thoughts occurred less than once a week, press 1 If about once a week, press 2 If these thoughts occurred 2 to 5 times a week, press 3 If daily or almost daily, press 4 If these thoughts occurred many times a day, press 5
Q03b
When you had these thoughts, how long did they last?
If these thoughts were fleeting, lasting seconds to minutes, press 1 If less than an hour, press 2 If these thoughts lasted between 1 and 4 hours, press 3 If between 4 and 8 hours, press 4 If these thoughts lasted more than 8 hours, press 5
Q03c
Did you make any attempt to try to control or stop these thoughts, whether you were successful in controlling them or not?
If Yes, press 1 If No, press 2
Q03d
How easily could you control or stop thinking about how you might kill yourself?

If you could easily control these thoughts, press 1 If with a little difficulty, press 2 If you could control these thoughts, but with some difficulty, press 3 If with a lot of difficulty, press 4 If you were unable to control these thoughts, press 5
Q03e.1
Did you think about things like family, religion, or fear of pain or death that might affect your decision about killing yourself?
If Yes, press 1 If No, press 2
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.
If something definitely stopped you from attempting suicide, press 1 If something probably stopped you, press 2 If you are uncertain whether something stopped you from attempting suicide, press 3 If something most likely did not stop you, press 4 If something definitely did not stop you from attempting suicide, press 5
Q03f.1
When you thought about killing yourself, did you have a reason in mind like ending your pain or getting attention or revenge?
If Yes, press 1 If No, press 2
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?

If it was completely to get attention, revenge or a reaction from others, press 1 If it was mostly to get attention, revenge or a reaction from others, press 2 If equally to get attention, revenge or a reaction from others and to end or stop the pain, press 3 If mostly to end or stop the pain (that is, you could not go on living with the pain or how you were feeling), press 4 If completely to end or stop the pain, press 5
Q04aNRT
You indicated before that since your last call you thought about killing yourself and that you had some intention of acting on these thoughts. I want to ask you a few more questions about that. When responding to these questions, I 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 call you thought about killing yourself and that you had some intention of acting on these thoughts. I want to ask you a few more questions about that. When responding to these questions, I want you to think about the time you were feeling the most suicidal since your last call.
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?
If these thoughts occurred less than once a week, press 1 If about once a week, press 2 If these thoughts occurred 2 to 5 times a week, press 3 If daily or almost daily, press 4 If these thoughts occurred many times a day, press 5
Q04b
How long did the thoughts last?

If these thoughts were fleeting, lasting seconds to minutes, press 1 If less than an hour, press 2 If these thoughts lasted between 1 and 4 hours, press 3 If between 4 and 8 hours, press 4 If these thoughts lasted more than 8 hours, press 5
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?
If Yes, press 1 If No, press 2
Q04d
How easily could you control or stop thinking about killing yourself?
If you could easily control these thoughts, press 1 If with a little difficulty, press 2 If you could control these thoughts, but with some difficulty, press 3 If with a lot of difficulty, press 4 If you were unable to control these thoughts, press 5
Q04e.1
Did you think about things like family, religion, or fear of pain or death that might affect your decision about killing yourself?
If Yes, press 1 If No, press 2
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.

If something definitely stopped you from attempting suicide, press 1 If something probably stopped you, press 2 If you are uncertain whether something stopped you from attempting suicide, press 3 If something most likely did not stop you, press 4 If something definitely did not stop you from attempting suicide, press 5
Q04f.1
When you thought about killing yourself, did you have a reason in mind like ending your pain or getting attention or revenge?
If Yes, press 1 If No, press 2
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?
If it was completely to get attention, revenge or a reaction from others, press 1 If it was mostly to get attention, revenge or a reaction from others, press 2 If equally to get attention, revenge or a reaction from others and to end or stop the pain, press 3 If mostly to end or stop the pain (that is, you could not go on living with the pain or how you were feeling), press 4 If completely to end or stop the pain, press 5
Q05aNRT
You indicated before that since your last call 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. I want to ask you a few more questions about that. When responding to these questions, I 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 call 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. I want to ask you a few more questions about that. When responding to these questions, I want you to think about the time you were feeling the most suicidal since your last call.
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?
If these thoughts occurred less than once a week, press 1 If about once a week, press 2 If these thoughts occurred 2 to 5 times a week, press 3 If daily or almost daily, press 4 If these thoughts occurred many times a day, press 5
Q05b
How long did the thoughts last?
If these thoughts were fleeting, lasting seconds to minutes, press 1 If less than an hour, press 2 If these thoughts lasted between 1 and 4 hours, press 3 If between 4 and 8 hours, press 4 If these thoughts lasted more than 8 hours, press 5
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?
If Yes, press 1 If No, press 2
Q05d
How easily could you control or stop thinking about killing yourself?

If you could easily control these thoughts, press 1 If with a little difficulty, press 2 If you could control these thoughts, but with some difficulty, press 3 If with a lot of difficulty, press 4 If you were unable to control these thoughts, press 5
Q05e.1
Did you think about things like family, religion, or fear of pain or death that might affect your decision about killing yourself?
If Yes, press 1 If No, press 2
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.
If something definitely stopped you from attempting suicide, press 1 If something probably stopped you, press 2 If you are uncertain whether something stopped you from attempting suicide, press 3 If something most likely did not stop you, press 4 If something definitely did not stop you from attempting suicide, press 5
Q05f.1
When you thought about killing yourself, did you have a reason in mind like ending your pain or getting attention or revenge?
If Yes, press 1 If No, press 2
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?
If it was completely to get attention, revenge or a reaction from others, press 1 If it was mostly to get attention, revenge or a reaction from others, press 2 If equally to get attention, revenge or a reaction from others and to end or stop the pain, press 3 If mostly to end or stop the pain (that is, you could not go on living with the pain or how you were feeling), press 4 If completely to end or stop the pain, press 5
Midpoint Transition
We are almost finished. So far I have been asking about thoughts and feelings you may have had. Now I would like to know about things you may have done to try to hurt yourself since your last call.
Suicidal Behavior
Q06a
Since your last call on [date] have you made a suicide attempt?
If Yes, press 1 If No, press 2
Q06b
Use the number keys on your telephone to enter the number of suicide attempts you have made since your last call.
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?
If Yes, press 1 If No, press 2
If loop = 2
When you made your first attempt, were you trying to end your life?
If Yes, press 1 If No, press 2
If loop = 3
When you made your most serious attempt, were you trying to end your life?
If Yes, press 1 If No, press 2
Q06e
Did you think it was possible that you could have died from what you did?
If Yes, press 1 If No, press 2
Q06d
So then, if you wanted to die, even a little, when you did this, Press 1. If 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, Press 2.
Q07a
Since your last call, have you done anything to intentionally hurt or harm yourself?

If Yes, press 1 If No, press 2
Q07b
Use the number keys on your telephone to enter the number of times you have intentionally hurt or harmed yourself since your last call. 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?
If Yes, press 1 If No, press 2
Q07e
Did you think it was possible that you could have died from what you did?
If Yes, press 1 If No, press 2
Q07d
So then, if you wanted to die, even a little, when you did this, Press 1. If 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, Press 2.

Q08a
Since your last call, have you done anything dangerous where you could have died?
If Yes, press 1 If No, press 2
Q08b
Use the number keys on your telephone to enter the number of times you have done dangerous activities where you could have died in the past [num] days.
Use the number keys on your telephone to enter the number of times you have done dangerous activities where you could have died since your last call.
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?
If Yes, press 1 If No, press 2
Q08c
Were you trying to end your life?

If Yes, press 1 If No, press 2
Q08d
So then, if you wanted to die, even a little, when you did this, Press 1. If 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, Press 2.
Lethality
Q09
If Q06a = YES
As a result of your most serious attempt since your last call, were you injured more seriously than surface scratches or mild nausea?
If Yes, press 1 If No, press 2
If Q06a = NO
As a result of the most serious time you tried to hurt yourself since your last call, were you injured more seriously than surface scratches or mild nausea?
If Yes, press 1 If No, press 2
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.
If Yes, press 1 If No, press 2

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?
If Yes, press 1 If No, press 2
Q09c
Did your injury cause you to be extremely drowsy, or result in broken bones, or severe bleeding?
If Yes, press 1 If No, press 2
Q09.10
Although you were not injured during the most serious time, how serious could your injuries have been?
If what you did was not likely to cause injury, Press 1 If what you did was likely to cause physical injury, but probably not death, Press 2 If 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, Press 3
Interrupted Attempts
Q10
Since your last call, 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?
If Yes, press 1 If No, press 2
Q10a
About how many times have you been stopped from ending your life by someone or something since your last call?

Please enter the number using your touch tone phone.
Aborted Attempts
Q11
Since your last call, 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?
If Yes, press 1 If No, press 2
Q11a
About how many times have you stopped yourself from ending your life in the last [num] days, since your last call?
If days SLC > 120
About how many times have you stopped yourself from ending your life since your last call?
Please enter the number using your touch tone phone.
Preparatory Acts or Behaviors
Q12NRT
Asses prior responses and present introduction:
Other than the times you have already told me about since your last call 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 me about since your last call 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 me about since your last call 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 me about since your last call 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 me about since your last call when you did things intending to kill yourself or thought you might have died,
Other than the times you have already told me about since your last call when you started to do something to end your life but someone or something stopped you,
Other than the times you have already told me about since your last call 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?
If Yes, press 1 If No, press 2
Q12a
About how many times?
Please enter the number using your touch tone phone.
Exit
Thank you and Good bye.

Appendix 17 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 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 visit as soon as possible but at least 24 hours after the onset of symptom(s)* *→ Go to Question 7, but if question 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 1 below option*
- ❑ 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 another and better explanation for the subject's current symptoms than an MS relapse?

- ❑ Yes → *STOP Relapse investigation and enter subject'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 18 Relapse symptom form

TO BE FILLED OUT BY THE TREATING NEUROLOGIST

Relapse symptom Form		
Visual (optic) functions		
Did the subject 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 subject 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 subject 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 subject 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 subject 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 subject 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 subject 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 subject 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 subject report any other symptoms attributable to a relapse?	❑ Yes	❑ No

- If yes, please specify: