Actelion Pharmaceuticals Ltd
(a Janssen Pharmaceutical Company of Johnson & Johnson)*

Ponesimod / ACT-128800 / JNJ-67896153

Relapsing Multiple Sclerosis

Protocol AC-058B303

OPTIMUM-LT

Multicenter, non-comparative extension to study AC-058B301, to investigate the long-term safety, tolerability, and control of disease of ponesimod 20 mg in subjects with relapsing multiple sclerosis

Study Phase:	3
EudraCT Number:	2016-004719-10
Status and version:	Approved; Version 6
Date:	15 March 2022
EDMS No.:	EDMS-ERI-207656619; 7.0

* Actelion Pharmaceuticals Ltd ("Actelion") is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Actelion studies may vary, such as, but not limited to Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

SPONSOR CONTACT DETAILS

SPONSOR	Actelion Pharmaceuticals Ltd.* Gewerbestrasse 16 CH-4123 Allschwil Switzerland ☎ +41 61 565 65 65
Clinical Trial Physician	Contact details of the Clinical Trial Physician can be found in the Investigator Site File
MEDICAL HOTLINE	Site-specific toll telephone numbers and toll-free numbers for the Medical Hotline can be found in the Investigator Site File

ACTELION CONTRIBUTORS TO THE PROTOCOL

Clinical Leader	PPD
Study Responsible Physician	PPD
Principal Scientist	PPD
Trial Statistician	PPD
Medical Safety Officer	PPD

* Actelion Pharmaceuticals Ltd. is a Janssen pharmaceutical company of Johnson & Johnson and is hereafter referred to as the sponsor of the study.

CONTRACT RESEARCH ORGANIZATIONS INFORMATION

CENTRAL LABORATORY	PPD
CENTRAL ENROLLMENT	PPD
CENTRAL MRI READING	PPD
CENTRAL ECGs READING	PPD

A list of site-specific contact details for Contract Research Organizations (CROs) can be found in the Investigator Site File.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND ACRONYMS

9-HPT	9-Hole Peg Test
ACTH	Adrenocorticotropic hormone
Ad26.COV2.S	Janssen COVID-19 vaccine
AE	Adverse event
ALT	Alanine aminotransferase
ARR	Annualized Relapse Rate
AST	Aspartate aminotransferase
ATS	American Thoracic Society
AV	Atrioventricular
BP	Blood pressure
bpm	Beats per minute
CDA	Confirmed disability accumulation
CI	Confidence interval
CIS	Clinically isolated syndrome
CNS	Central nervous system
COVID-19	coronavirus disease-2019
CRO	Contract Research Organization
CSF	Cerebrospinal fluid
CTCAE	Common terminology criteria for adverse events
CUAL	Combined unique active lesion
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
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOS	End-of-Study
EOT	End-of-Treatment
ERS	European Respiratory Society
ETDRS	Early Treatment Diabetic Retinopathy Study
EUA	Emergency Use Authorization
EXTS	Extension Set
FA	Fluorescence angiography
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEF	Forced expiratory flow
FEV_1	Forced expiratory volume in 1 second
FS	Functional system
FU	Follow-up
FVC	Forced vital capacity
GCP	Good Clinical Practice
Gd	Gadolinium
Gd+	Gadolinium-enhancing
Hb	Hemoglobin
HIV	Human immunodeficiency virus
HR	Heart rate
I	Re-initiation visit
i.m.	Intramuscular
i.v.	Intravenous
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee

IEC	Independent Ethics Committee
IFN	Interferon
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive response technology
ISAC	Independent Statistical Analysis Center
ISF	Investigator site file
JCV	John Cunningham Virus
LT	Long Term
M13	ACT-338375 (ponesimod metabolite)
MACE	Major Adverse Cardiovascular Events
MedDRA	Medical Dictionary for Regulatory Activities
MIAC	Medical Image Analysis Center
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSFC	Multiple Sclerosis Functional Composite
NK	Natural killer
NMSS	US National Multiple Sclerosis Society
o.d.	Once a day
OCT	Optical coherence tomography
OSB	Ophthalmology Safety Board
P	Pregnancy visit
PASAT	Paced Auditory Serial Addition Test
PCBV	Percent Change in Brain Volume
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PFT	Pulmonary function test
PK	Pharmacokinetic
PML	Progressive multifocal leukoencephalopathy
PP	Primary progressive
PPMS	Primary progressive multiple sclerosis
PPS	Per-Protocol Set

PRMS	Progressive relapsing multiple sclerosis
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
R	Relapse visit
RMS	Relapsing multiple sclerosis
RR	Relapsing-remitting
RRMS	Relapsing-remitting multiple sclerosis
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
s.c.	Subcutaneous
S1P	Sphingosine-1-phosphate
SAE	Serious adverse event
SAF	Safety Set
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SDMT	Symbol Digit Modalities Test
SIV	Site initiation visit
SPMS	Secondary progressive multiple sclerosis
TTS	Thrombosis with Thrombocytopenia Syndrome
U	Unscheduled visit
ULN	Upper limit of the normal range
VNA	Virus neutralization assay
WOCBP	Women of childbearing potential
WHO	World Health Organization

GLOBAL AMENDMENT 5

Amendment rationale

This amendment applies to global protocol AC-058B303 Version 5, dated 19 October 2020. The resulting amended global protocol is Version 6, dated 15 March 2022, and all local protocol versions:

- Final Version 5.GBR.A dated 22 July 2021
- Final Version 5.ESP.A dated 22 July 2021

The reasons for this amendment are:

- To update the requirement for optical coherence tomography (OCT) assessments to be performed only in case presence of visual symptoms suggestive of macular edema or active uveitis as consistent with observed dynamic of this event on S1P treatment.
- To acknowledge the decommission of the Ophthalmology Safety Board (OSB). The number of cases of macular edema is expected to be low (most cases occur within the first 6 months of treatment) and no new patients will initiate treatment in the study. Therefore, an OSB review is no longer required and will be decommissioned for the ongoing long-term extension studies, its status has been clarified and where appropriate reference to the OSB has been removed.
- To correct a discrepancy in Section 8.5.2 to clarify that a sample for immunogenicity evaluations should not be taken at unscheduled visits.
- To add clarification and description of periodic analyses in addition to interim analyses in Section 11.5.
- Due to limited availability of COVID-19 vaccine-naïve MS patients, the COVID-19 vaccination sub-study is cancelled and removed from the protocol (Appendix 13 and Appendix 14).
- To provide a clarification that based on available evidence (and the fact that all patients in the study have already initiated treatment with ponesimod), additional ECG monitoring in specific cases (ie, treatment with QT prolonging drugs) is no longer required (Sections 7.5.1, Section 8.5.2, and Appendix 2).
- To introduce immunogenicity analyses into the statistical section (Section 11.4).
- To update the list of adverse events of special interest to include identified risks (Appendix 4).
- To confirm the disbandment of the IDMC.
- To clarify that the EXTS will also be used for efficacy analyses of the Combined Analysis Period in addition to the FAS (Section 11.2.6).
- Clarifications and minor corrections have been added to the protocol.

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:

ACTELION CONTRIBUTORS TO THE PROTOCOL

SIGNATURE PAGE FOR ACTELION PHARMACEUTICALS LTD.

Table 1	**Visit and assessment schedule**
Table 2	**Visit and assessment schedule (Part 2)**
3.2.5	**Sub-studies**
3.2.5.2	**Janssen COVID-19 vaccination sub-study**
3.4.8	**Opthalmologist**
3.5.1	**Independent Data Monitoring Committee**
3.5.2	**Ophthalmology Safety Board**
5.1.8	**Study treatment dose adjustments and interruptions**
5.1.12.7	**Ocular abnormalities**
5.1.12.7.1	**Guidance for monitoring and management of subjects with uveitis**
5.2.2.	**Allowed concomitant therapy**
6.	**Study endpoints**
7.	**Study assessments**
7.5.1	**12-lead electrocardiogram**
7.5.8	**Optical Coherence Tomography**
7.5.12.2	**Laboratory tests**
Table 10	**Minimum total blood volume to be drawn per subject**
8.	**Schedule of visits**
8.3.5	**Visit 4 - Week 12**

8.3.7 Visit 5 - Week 24

8.3.9 Visits 7, 11, 15, 19 - Weeks 48, 96, 144, 192

8.3.10 EOT Visit - Week 240

8.4.1 EOS Visit

8.5.2 Unscheduled visits (any other assessment; U1, U2, U3, etc.)

8.5.4 Additional unscheduled visit 30 days after study treatment interruption due to planned pregnancy with intention of study treatment re-initiation post partum

9.3 Premature termination or suspension of the study

10. Safety definitions and reporting requirements

10.4 Study safety monitoring

11. Statistical methods

11.2.6 Usage of the analysis sets

11.4.9 Immunogenicity Analysis

11.5.1 Additional periodic analyses

Appendix 4 Adverse events of special interest

Appendix 13 Protocol for the Janssen COVID-19 Vaccination (Ad26.COV2.S) Sub-study

Appendix 14 TTS Form

Summary of previous amendments

Amendment	Date	Main reason(s)
1	1 March 2018	The main reason for this amendment was to modify the pulmonary treatment discontinuation criteria based on changes in pulmonary function variables during the study treatment.
2	14 May 2020	The main reasons for this amendment were: • To allow the analysis of biomarkers in the serum sample taken at Visit 1 (Enrollment). • To amend the guidance for re-initiation of study treatment in the event of study treatment interruption in order to allow patients without the identified cardiovascular risk factors to re-initiate study drug at home. • The efficacy assessor role is no longer defined as "independent" and, depending on site setting, can now be assumed by the primary investigator / treating neurologist. • To provide guidance regarding conduct of the study during the COVID-19 (coronavirus) pandemic.
3	19 October 2020	The main reasons for this amendment were: • To inform study sites that the Independent Data Monitoring Committee (IDMC) will be disbanded after the clinical database closure of the last ponesimod double-blind study, in line with the disbandment date agreed per the IDMC Charter. • To provide further guidance on study conduct if/when ponesimod becomes commercially available during the study and patients are switched from study treatment to commercially available ponesimod. • To align the safety reporting procedures with Janssen Safety processes and standards following the integration of Actelion Safety into Janssen Safety.

Amendment	Date	Main reason(s)
4	20 July 2021	The main reasons for this amendment were: • To introduce vaccination sub-study for a sub-set of subjects to investigate the immune response induced by the Janssen COVID-19 vaccine (Ad26.COV2.S). • Inclusion of additional serum samples for all subjects at all scheduled visits for immunogenicity evaluations; eg, to measure anti-severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) antibody levels induced by vaccination with any COVID-19 vaccination or after recovery from COVID 19. • Addition of clarifications regarding conduct of the study during the COVID-19 pandemic and the administration of non-live and live vaccinations. • To make updates with regard to teriflunomide testing per the Aubagio® prescribing information.

PROTOCOL SYNOPSIS AC-058B303

TITLE	Multicenter, non-comparative extension of study AC-058B301, to investigate the long-term safety, tolerability, and control of disease of ponesimod 20 mg in subjects with relapsing multiple sclerosis
ACRONYM	OPTIMUM-LT
OBJECTIVES	**Safety objectives:** • To describe the long-term safety and tolerability of ponesimod 20 mg in subjects with relapsing multiple sclerosis (RMS). • To describe the effects of re-initiation of ponesimod treatment after interruption in subjects with RMS. **Efficacy objectives:** • To describe the long-term disease control in subjects with RMS receiving ponesimod 20 mg. • To describe the effect of a switch from teriflunomide to ponesimod 20 mg on disease control in subjects with RMS.
DESIGN	Multicenter, non-comparative, single-arm, Phase 3 study, as an extension of the AC-058B301 study
PERIODS	**Pre-treatment period:** The Pre-treatment period includes all pre-dose assessments of Visit 1 and starts when the subject completes the core study Follow-up (FU) visits FU1 or FU2 (whichever applies) and signs the informed consent. This should ideally occur on the day of core study FU1 or FU2 (whichever applies), but no later than 1 day after these visits. It continues until the first dosing of study treatment, which should occur at latest 7 days after signing the informed consent. **Treatment period:** The treatment period starts with the first dose of study treatment, which defines Day 1 (end of Visit 1) of the AC-058B303 study and post-dose assessments of Visit 1. The treatment period may last for 240 weeks or until ponesimod is commercially available for the treatment of MS in the subject's country. After Day 1, there will be visits at Day 15, Week 4, Week 12, and subsequently every 12 weeks until the End-of-Treatment (EOT). **EOT:** The EOT visit will take place at Week 240 or at the time ponesimod is commercially available for treatment of MS in the subject's country (whichever occurs first). The EOT visit should preferably take place 1 day after the last dose of study treatment but no later than 14 days after the last dose of study treatment.

	For those subjects completing study treatment due to the availability of commercially available ponesimod, an EOT visit should be conducted preferably within 7 days after stopping study treatment. Commercially available ponesimod may be initiated on the day after last intake of study treatment. **Safety follow-up / End-of-Study:** For an individual subject, End-of-Study (EOS) is reached when treatment and 30-day safety FU have been completed. The EOS Visit should be performed 30-44 days after the last dose of study treatment. The EOS visit should also be conducted for subjects who have switched to commercially available ponesimod.
PLANNED DURATION	Approximately 330 weeks from First subject-First visit to Last subject-Last visit.
SITE(S)/COUNTRY(IES)	Approximately 160 sites in 28 countries worldwide.
SUBJECTS / GROUPS	Subjects, having completed the double-blind treatment AC-058B301 study (core study) as scheduled and willing to participate in the AC-058B303 study (extension study), will be enrolled into one group treated with ponesimod 20 mg.
INCLUSION CRITERIA	1. Signed informed consent, prior to initiation of any study-mandated procedure. 2. Subjects with MS having completed the double-blind treatment in the core study as scheduled (i.e., who completed the double-blind treatment period until Week 108). 3. Compliance with teriflunomide elimination procedure assessed as sufficient by the investigator at visit FU1 or abbreviated visit FU2 of the core study, whichever occurred last. 4. For subjects of reproductive potential: • Women of childbearing potential (WOCBP): – must have a negative pre-treatment urine pregnancy test on Day 1; – must agree to undertake 4-weekly urine pregnancy tests during the study and until 6 weeks after the first of two consecutive tests showing teriflunomide plasma level <0.02 mg/L and until at least 30 days after study treatment discontinuation; – must have been using reliable methods of contraception uninterrupted since EOT in the core study and must agree to continue using reliable methods of contraception throughout the study until 6 weeks after the first of two consecutive tests showing teriflunomide plasma level <0.02 mg/L and until at least 30 days after discontinuation of study treatment. • Fertile male subjects participating in the study who are sexually active with WOCBP must agree to use a condom until 6 weeks after

	the first of two consecutive tests confirming plasma teriflunomide level <0.02 mg/L. Definition of WOCBP, fertile male subjects and the acceptable methods of contraception for this study are described in Section 4.4.
EXCLUSION CRITERIA	1. Any of the following cardiovascular conditions on Day 1 pre-dose: a. Resting heart rate <50 beats per minute as measured by the pre-dose 12-lead electrocardiogram (ECG); b. Presence of second degree atrioventricular (AV) block or third-degree AV block or a QT interval corrected for Fridericia's formula >470 ms (females), >450 ms (males) on pre-dose 12-lead ECG. 2. Any of the following alerts from central laboratory at Visit 14 of the core study (EOT) which was confirmed as an alert at repeated testing or not repeated prior to FU1 of the core study: a. Lymphocyte count: $<0.2 \times 10^9$/L (<200/mm^3 blinded results); b. Neutrophil count $<1.0 \times 10^9$/L(<1000 cells/mm^3); c. Platelet count $<50 \times 10^9$/L (<50 000 cells/mm^3); d. Creatinine clearance <30 mL/min (Cockroft-Gault). 3. At Visit 14 of the core study (EOT) >30% decrease from core study baseline forced expiratory volume in 1 second and/or forced vital capacity. 4. Clinically significant, persistent respiratory adverse events (AEs; e.g., dyspnea) not resolved prior to first dosing in the extension study. 5. Macular edema at any time between Visit 1 (Screening) in the core study and Day 1 of the extension study. 6. Presence of the following at core study Visit 14 (EOT, Week 108), FU1, or abbreviated visit FU2, or on Day 1 of the extension study pre-dose: a. Suspected opportunistic infection of the central nervous system or any other infection which, in the opinion of the investigator, contraindicates re-start of the study drug; b. Stevens-Johnson syndrome or toxic epidermal necrolysis or drug reaction with eosinophilia and systemic symptoms. 7. Need for and intention to administer forbidden study-treatment-concomitant therapy

<table>
<tr><td></td><td>8. Women who are pregnant or lactating.

9. Male subjects wishing to parent a child any time before the 6 week period following the first of two consecutive tests confirming plasma teriflunomide level <0.02 mg/L.

10. Treatment with any MS Disease Modifying Therapies (DMTs) between core study EOT and first dosing in extension study.

11. 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.

12. Subjects unlikely to comply with the extension study protocol based on investigator best judgment from the core study protocol, e.g., uncooperative attitude, inability to return for follow-up visits, or known likelihood of not completing the extension study.</td></tr>
<tr><td>STUDY TREATMENTS</td><td>Investigational treatment
From Day 1 to Day 14, ponesimod is gradually up-titrated until a maintenance dose of 20 mg is reached using a special kit consisting of tablets with the following doses:

<table><tr><th>Day</th><th>Dose strength</th></tr><tr><td>Days 1 and 2</td><td>2 mg</td></tr><tr><td>Days 3 and 4</td><td>3 mg</td></tr><tr><td>Days 5 and 6</td><td>4 mg</td></tr><tr><td>Day 7</td><td>5 mg</td></tr><tr><td>Day 8</td><td>6 mg</td></tr><tr><td>Day 9</td><td>7 mg</td></tr><tr><td>Day 10</td><td>8 mg</td></tr><tr><td>Day 11</td><td>9 mg</td></tr><tr><td>Days 12 to 14*</td><td>10 mg</td></tr><tr><td>Day 15 to EOT</td><td>20 mg</td></tr></table>* = Visit 2 is to take place at Day 15 (–1 day / +3 days). The titration kit will therefore include 3 additional tablets (to be used if applicable) for treatment on Day 15-17 (i.e., dose regimen = 20 mg).</td></tr>
<tr><td>CONCOMITANT THERAPY</td><td>Treatment of Relapses
• If a relapse requires treatment with corticosteroids, methylprednisolone 1 g intravenously (i.v.) daily for 3 to 5 days is recommended. Oral taper with corticosteroids is not permitted. 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.</td></tr>
</table>

- Treatment of relapses with plasma exchange (i.e., plasmapheresis, cytapheresis) is prohibited.

Allowed concomitant therapy

- Administration of i.v. atropine in the event of symptomatic bradycardia.
- Short-acting ß$_2$-agonists for respiratory symptoms and/or reduced pulmonary function during study 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 2).
- Glatiramer acetate and interferon (IFN) β-1a are allowed only during ponesimod interruptions for planned pregnancy. These treatments may be started 7 days after ponesimod cessation and must be stopped 7 days before ponesimod re-initiation).
- Other treatments considered necessary for the subject's well-being and not categorized as prohibited concomitant medications.
- Vaccination with non-live vaccines is allowed while on study treatment if the vaccination is advised by the primary investigator / treating neurologist, based on her/his clinical assessment of the risk/benefit for the individual patient, and if supported by guidelines for vaccination relevant to this patient population, as applicable.

Prohibited concomitant therapy

- Systemic corticosteroids and ACTH, except for the treatment of MS relapses (see Treatment of Relapses above) 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 4 weeks per year of the study duration on average) with low dose of corticosteroid (up to 10 mg of prednisone equivalent daily) or inhaled corticosteroids for pulmonary conditions.
- DMTs for MS (except glatiramer acetate or IFN β-1a during ponesimod interruptions for planned pregnancy as described under "Allowed").
- Immunosuppressive treatment (e.g., cladribine, lymphocyte-depleting biological agents such as rituximab or ocrelizumab, mitoxantrone, or other systemic immunosuppressive treatments such as azathioprine, cyclophosphamide, cyclosporine or methotrexate).
- Intravenous immunoglobulin (except in women who have interrupted study treatment for pregnancy; for these women i.v. immunoglobulin will be allowed after 30 days from interruption of the study treatment).
- Plasmapheresis, cytapheresis, or total lymphoid irradiation;
- Vaccination with live vaccines, except if performed during a temporary treatment interruption period. In this case it must be performed not earlier than 1 week after last dose of study treatment, and treatment can be re-initiated only after at least 4 weeks from completion of vaccination.
- β-blockers, diltiazem, verapamil, digoxin, or any other anti-arrhythmic or heart rate lowering systemic therapy (a non-exhaustive list of drugs is

	provided in Appendix 3) during the up-titration period (i.e., from Day 1 until Day 14 included and during the first 14 days after re-initiation of study treatment). Treatment with any of these therapies is also not recommended during the maintenance treatment period (from Day 15 until EOT) and should be considered with caution if an alternative medication cannot be used. • Any other investigational drug. • Any investigational therapeutic procedure for MS (e.g., stent placement or angioplasty for chronic cerebrospinal venous insufficiency, stem cell transplantation). Commercially available ponesimod may be initiated on the day following last intake of study treatment. The start date of commercially available ponesimod must be recorded on the Concomitant Medication page of the eCRF.
ENDPOINTS	**Main Efficacy endpoint(s)** In order to monitor disease activity in subjects after long-term treatment with ponesimod 20 mg, and to investigate the effect of switching from teriflunomide 14 mg to ponesimod 20 mg, the main analysis of efficacy will focus on the Combined Analysis Period, i.e., including data from both the core and extension studies. In addition, specific efficacy endpoints will also be analyzed over the Extension Analysis Period. The full list of efficacy endpoints together with details of which endpoints will be analyzed over which analysis periods is given in Section 6.1. Analysis over the Combined Analysis Period will use the core study baseline as a reference, while analysis over the Extension Analysis Period will use the extension study baseline as a reference. Baseline definitions for efficacy endpoints are provided in Section 11.1.3. The main clinical and magnetic resonance imaging-based endpoints are: • Annualized confirmed relapse rate (ARR; based on the number of confirmed relapses per subject-year). • Time from core study randomization to first confirmed relapse. • Time from core baseline to first 12-week confirmed disability accumulation (CDA). • Time from core baseline to first 24-week CDA. • Percent change from baseline in brain volume at all assessments. • Cumulative number of combined unique active lesions (CUAL, defined as new gadolinium-enhancing T1 lesions plus new or enlarging T2 lesions without double-counting the lesions) at all assessments. **Main Safety endpoints** In order to investigate the long-term safety of ponesimod and the changes in safety in subjects on teriflunomide switching to ponesimod 20 mg, analysis will be performed on all data in the core and extension studies combined, using the core baseline as a reference. In addition, safety data collected in the extension study

	will be analyzed independently, using the extension baseline as a reference. The full list of safety endpoints together with details of which endpoints will be analysed over which analysis periods is given in Section 6.2. The main safety endpoints are: • Treatment-emergent AEs, serious adverse events (SAEs), and AEs of special interest. • AEs leading to premature discontinuation of study treatment. Treatment-emergent period is defined as the time from first ponesimod administration in the analysis period up to 15 days (inclusive) after last study treatment administration. This definition applies regardless of whether the subject receives commercially available ponesimod after completing study treatment.
ASSESSMENTS	Refer to the schedule of assessments in Table 1 and Table 2.
STATISTICAL METHODOLOGY	**Analysis Strategy** In order to describe the disease activity in subjects after long-term treatment with ponesimod 20 mg, and to investigate the effect of switching from teriflunomide 14 mg to ponesimod 20 mg, the main analysis of efficacy will focus on integrating data from both the core and extension studies. Subjects will be analyzed according to the treatment they were randomized to in the core study. In addition, specific efficacy endpoints will be analyzed using data collected only from the extension study. Similarly, the long-term safety of ponesimod 20 mg and the changes in safety in teriflunomide 14 mg subjects switching to ponesimod 20 mg will be investigated by summarizing the integrated data from both the core and extension studies. In addition, specific safety endpoints will also be analyzed using data collected only from the extension study. No hypotheses are pre-specified. All analyses conducted will be descriptive and will be defined in detail in a Statistical Analysis Plan. **Sample Size** As the extension study is an extension of the confirmatory Phase 3 core study, there are no sample size considerations. The sample size will be determined by how many of the 1100 subjects planned to be enrolled in the core study enroll into the extension study. Based on anticipated discontinuation rates in the core study, approximately 800 subjects are expected to enter the extension study. **Analysis periods** **Extension Analysis Period:** This includes all available data collected on or after the start date of ponesimod treatment in the extension study, up to the EOS date

	for efficacy variables or up to the last treatment date + 15 days in the extension study for safety variables. **Combined Analysis Period:** For efficacy, this period includes all available data from randomization in the core up to the extension EOS date for subjects entering the extension, or up to the core EOS date for subjects not entering the extension. For safety this period includes all available data from the date of first study treatment administration in the core study up to the last treatment date + 15 days in the extension study for subjects entering the extension, or up to the last treatment date + 15 days in the core study for subjects not entering the extension. **Analysis Sets** Efficacy analysis described over the Combined Analysis Period will use the Full Analysis Set. Safety analysis described over the Combined Analysis Period will use the Safety Analysis Set. Efficacy and safety analysis described over the Extension Analysis Period will use the Extension Set. **Extension Set (EXTS):** The extension set includes all subjects who signed an informed consent to enter the extension study and who received at least one dose of ponesimod study treatment in the extension study. **Full Analysis Set (FAS):** Following the intention-to-treat principle, the FAS includes all subjects randomized in the core study. Subjects will be evaluated according to the treatment they have been randomized to in the core study, which may be different from the treatment they have received. **Safety Analysis Set (SAF):** The SAF includes all subjects who received at least one intake of core study treatment. Subjects will be evaluated according to the treatment they received during the core study. **Analysis of Efficacy Endpoints** The following baseline definitions will be used: • Core study baseline for efficacy is defined as the last non-missing assessment before randomization in the core study. • Extension study baseline is defined as the last non-missing assessment before first administration of ponesimod in the extension study. Analysis based on the Combined Analysis Period will use the core study baseline. Analysis based on the Extension Analysis Period will use the extension study baseline. All data will be listed and endpoints will be summarized by appropriate descriptive statistics.

	The main efficacy endpoints will be described by core study treatment for each period using the appropriate analysis set as follows: • ARR will be described using a negative binomial regression model with log of time as an offset variable. • Time to first relapse and time to 12 and 24-week CDA will be analyzed using Kaplan-Meier estimates. • CUAL will be described using a negative binomial regression model with the log of the number of scans used as an offset variable. • Percent Change in Brain Volume will be summarized descriptively over time. **Analysis of safety endpoints** Analysis over the Combined Analysis Period will be based on the SAF, and analysis over the Extension Analysis Period will be based on the EXTS. Cumulative data such as AEs and SAEs will only be summarized for subjects initially treated with ponesimod 20 mg in the core study. The analysis of the change from baseline for safety endpoints assessed by visit will be analyzed by core treatment group with the core baseline as the reference. In addition, safety data collected in the extension study will be analyzed for the Extension Analysis Period using the EXTS, and will be summarized both overall and split by the core treatment group. The analysis of the change from baseline for safety endpoints assessed by visit will be analyzed with the extension baseline as the reference. The following baseline definitions will be used: • The core baseline value for safety is defined as the last non-missing value recorded before the first administration of study treatment in the core study. • The extension baseline value for safety is defined as the last non-missing assessment before the first administration of ponesimod in the extension study. All data will be listed and endpoints will be summarized by appropriate descriptive statistics.
STUDY COMMITTEES	The Independent Data Monitoring Committee (IDMC) responsible for monitoring the core study has continued its duties for the extension study, until its disbandment which occurred on 30th September 2021. It was composed of physicians with relevant medical expertise. The composition and operation of the IDMC was described in the IDMC charter.

	An independent statistical analysis center (not otherwise involved with study conduct or statistical analysis) will generate reports, exclusively for review by the IDMC. An Ophthalmology Safety Board (OSB) composed of two independent ophthalmologists reviewed and evaluated any reported case of macular edema. The OSB was decommissioned from the date of Protocol Version 6. The composition and operation of the OSB was described in the OSB charter. A Major Adverse Cardiovascular Events (MACE) adjudication board will review and evaluate 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 or not the event belongs 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 the diffusing capacity of the lungs, measured using carbon monoxide (DL_{CO}), will be continued in these subjects who participated in the sub-study in the core study.**

Table 1 Visit and assessment schedule

Periods	Name	AC-058B301 (core study)		AC-058B303 (extension study) TREATMENT PERIOD							
	Duration	NA		Treatment may continue until 240 weeks or until ponesimod is commercially available (whichever occurs first)							
Visits	Number	NA		1	2	3	4	5	6, 8-10, 12-14, 16-18, 20-22	7, 11, 15, 19	23
	Name	FU1 Core Study	Abbreviated FU2 Core Study (1)	Enrollment	W2	W4	W12	W24	W36, W60, W72, W84, W108, W120, W132, W156, W168, W180, W204, W216, W228	W48, W96, W144, W192	EOT
	Time	NA	NA	Day 1(2)	Day 15	Week 4	Week 12	Week 24	Every 12 weeks	Every 48 weeks	W240 or earlier (14)
	Visit window	NA	NA	NA	−1 to +3 days	±7 days	±7 days	±14 days	±14 days	±14 days	14 days
Informed consent*				X							
Inclusion/exclusion criteria*				X							
Demographics				X							
Medical History*				X							
EDSS/FS*				X			X	X	X	X	X
Relapse*		X	X	←				X (3)			→
SDMT*							X	X		X	X
MSFC*										X	X
SF-36**								X		X	X
eC-SSRS**										X	X
MRI**(15)										X	X
Concomitant medications*		X	X	X	X	X	X	X	X	X	X
Physical examination*				X				X		X	X
Dermatological examination* (4)										X	X
Body weight*										X	X
Body temperature*		X		X	X	X	X	X	X	X	X
Systolic/diastolic blood pressure*(5)		X		X(5)	X	X	X	X	X	X	X
12 Lead ECG**(6)		X		X						X	X
Pulse rate*					X	X	X	X	X		
Ophthalmological examination/OCT* (7)							X	X		X	X
Pulmonary function tests* (8)		X				X				X	X
Hematology/Chemistry**		X			X	←	(9)	→	X	X	X
Urinalysis*		X						X	X	X	X

Periods	Name	**AC-058B301 (core study)**		**AC-058B303 (extension study) TREATMENT PERIOD**							
	Duration	NA		Treatment may continue until 240 weeks or until ponesimod is commercially available (whichever occurs first)							
Visits	Number	NA		1	2	3	4	5	6, 8-10, 12-14, 16-18, 20-22	7, 11, 15, 19	23
	Name	FU1 Core Study	Abbreviated FU2 Core Study (1)	Enrollment	W2	W4	W12	W24	W36, W60, W72, W84, W108, W120, W132, W156, W168, W180, W204, W216, W228	W48, W96, W144, W192	EOT
	Time	NA	NA	Day 1(2)	Day 15	Week 4	Week 12	Week 24	Every 12 weeks	Every 48 weeks	W240 or earlier (14)
	Visit window	NA	NA	NA	−1 to +3 days	±7 days	±7 days	±14 days	±14 days	±14 days	14 days
Pregnancy test*/** (10)		X		X		X	X	X	X	X serum	X serum
Elimination procedure compliance		X	X								
Teriflunomide plasma concentration				X (11)							
Serum sample for immunogenicity evaluations** (16)									X	X	X
Additional serum sample for viral serology/biomarkers*				X							
Study treatment dispensing & accountability (12)*				X	X	X	X	X	X	X	X
AEs* / SAEs*(13)		X	X	X	X	X	X	X	X	X	X

* Data collected in the eCRF
** Electronically transferred to the sponsor
Day 1 (date of treatment start) is to be used as the reference date for the purpose of calculating the subsequent visit dates (and time windows).

1) This visit will only take place if the compliance with the teriflunomide elimination procedure in the core study was not sufficient and has to be re-assessed prior to the study drug administration on Day 1.
2) Visit 1 includes a pre-treatment period which lasts from signing of the informed consent until first dosing of study treatment. Ideally, all assessments and procedures of Visit 1 (e.g., signing of the informed consent, first study treatment dosing and post-dose cardiac monitoring) should occur on the same day as the core study FU1 or abbreviated FU2 (whichever applies). In all cases, informed consent should be signed no later than one day after FU1 or FU2 visit (whichever applies) and all assessments and procedures of Visit 1 must be completed (i.e., study treatment start) no longer than 7 days after signing of the informed consent. The date of Day 1 corresponds to the date of the first dose of study treatment in the extension study. The investigator should make every effort to minimize the duration between EOT of the core study and Day 1 of the extension study. Ideally the treatment interruption should last no longer than 15 days.
3) 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 visit starting with Visit 4 (Week 12) 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 10].
4) Dermatological examination to be performed by a dermatologist.
5) Systolic / diastolic blood pressure: Only pre-dose except Day 1. On Day 1 pre-dose and hourly (+/− 15 min) for at least 4 hours post-dose and up to 12 hours.
6) ECGs: Only pre-dose except Day 1. On Day 1 pre-dose and hourly (+/− 15 min) for at least 4 hours post-dose and up to 12 hours.

7) OCT and/or ophthalmological examination to be performed at any visit in the presence of visual symptoms suggestive of macular edema or active uveitis. From Protocol Version 6, scheduled OCT examinations at visits 4, 5, 7, 11, 15, 19, and 23 will not be required.
8) PFTs including spirometry to be performed in all subjects; DL_{CO} to be performed in a subset of subjects at selected sites only.
9) Monitoring of hematology/chemistry every 4 weeks for the first 24 weeks after enrollment (±7 days).
10) Between visits, urine pregnancy tests are done every 4 weeks (±7 days) at home. At all visits, the methods of contraception will be reviewed and the contraceptive method form entered in the eCRF must be updated as applicable.
11) Blood sample for a teriflunomide test (results to be communicated to site only if needed, e.g., in the case of AEs where the measurement of exposure to teriflunomide is of relevance).
12) Scheduled study medication dispensing/return procedures may be adapted according to the site practice. No medication dispensed at EOT.
13) All AEs and SAEs that occur after signing the informed consent and up to 30 days after study treatment discontinuation (i.e., EOS) must be reported.
14) The EOT Visit will take place at Week 240 or earlier if ponesimod becomes commercially available in the subject's country or the subject prematurely discontinues from the study. In all cases, the EOT visit should take place 1 day after the last dose of study treatment but no later than 14 days after the last dose of study treatment. Commercially available ponesimod may be initiated on the day following last intake of study treatment.
15) In case of premature study treatment discontinuation, the MRI assessment at EOT does not need to be performed if the EOT visit occurs within 4 weeks of the MRI assessment at Visits 7, 11, 15, or 19 (Weeks 48, 96, 144, or 196).
16) To be collected for all subjects at all scheduled visits after approval of protocol version 5.

AE = adverse event; DL_{CO} = diffusing capacity of the lungs, measured using carbon monoxide; 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; EOS = End-of-Study; EOT = End-of-Treatment; FS = Functional System; FU = follow-up; MRI = magnetic resonance imaging; MSFC = Multiple Sclerosis Functional Composite; NA = not applicable; OCT = optical coherence tomography; PFT = pulmonary function test; SAE = serious adverse event; W = week.

Table 2 Visit and assessment schedule (Part 2)

Periods	Name	**FOLLOW-UP**	**UNSCHEDULED**							
	Duration	30 Days								
Visits	Number	24	R1, R2, …	U1, U2, …	I1, I2, …(13)		P1, P2, …(9)			
					D1	D15				
	Name	EOS	Relapse	Unscheduled (8)	Re-initiation D1	Re-initiation D15	Interruption / planned pregnancy	Eligibility for re-initiation / planned pregnancy	Re-initiation D1 / pregnancy	Re-initiation D15 / pregnancy
					Day 1 of re-initiation	Day 15 of re-initiation	Unscheduled visit after drug interruption for planned pregnancy	Unscheduled visit prior to study drug re-initiation after interruption for planned pregnancy	Unscheduled visit following study drug interruption for planned pregnancy for re-start	Unscheduled visit following study drug interruption for planned pregnancy for re-start
	Time	Last study treatment intake + 30 days	Any day between Day 1 and EOS	Any day between Day 1 and EOS	Any day between Day 1 and EOS	Any day between Day 1 and EOS	Earliest after Visit 5 (Week 24) and until 6 weeks after the first of two consecutive tests showing teriflunomide plasma level <0.02 mg/L and at least 30 days after study treatment discontinuation	30 days (±5 days) before study drug re-initiation		
	Visit window	+14 days	+7 days	NA	NA	± 1 day	± 7 days	NA	NA	NA
EDSS/FS*		X	X	X			X	X		
Relapse*		X	X	X(11)	X(11)	X(11)	X(11)	X	X	X(11)
MRI**				X			X	X		
Concomitant medications*		X	X	X	X		X	X	X	
Physical examination*			X	X			X	X		
Dermatological examination*				X			X			
Body weight*				X			X	X	X	
Body temperature*		X	X	X	X	X	X	X	X	X
Systolic/diastolic blood pressure*		X	X	X	X(1)	X	X	X	X(1)	X
12 Lead ECG**		X		X	X(2)	X	X	X	X(2)	X
Pulse rate*			X	X(12)			X(12)			

Periods	Name	**FOLLOW-UP**	**UNSCHEDULED**							
	Duration	30 Days								
Visits	Number	24	R1, R2, …	U1, U2, …	I1, I2, …(13)		P1, P2, …(9)			
					D1	D15				
	Name	EOS	Relapse	Unscheduled (8)	Re-initiation D1	Re-initiation D15	Interruption / planned pregnancy	Eligibility for re-initiation / planned pregnancy	Re-initiation D1 / pregnancy	Re-initiation D15 / pregnancy
					Day 1 of re-initiation	Day 15 of re-initiation	Unscheduled visit after drug interruption for planned pregnancy	Unscheduled visit prior to study drug re-initiation after interruption for planned pregnancy	Unscheduled visit following study drug interruption for planned pregnancy for re-start	Unscheduled visit following study drug interruption for planned pregnancy for re-start
	Time	Last study treatment intake + 30 days	Any day between Day 1 and EOS	Any day between Day 1 and EOS	Any day between Day 1 and EOS	Any day between Day 1 and EOS	Earliest after Visit 5 (Week 24) and until 6 weeks after the first of two consecutive tests showing teriflunomide plasma level <0.02 mg/L and at least 30 days after study treatment discontinuation	30 days (±5 days) before study drug re-initiation		
	Visit window	+14 days	+7 days	NA	NA	± 1 day	± 7 days	NA	NA	NA
Ophthalmological examination/OCT* (3)		X		X			X	X		
Pulmonary function tests* (4)		X		X			X	X		
Hematology/Chemistry**		X		X			X	X		
Serum sample for immunogenicity evaluations**(14)		X								
Urinalysis*		X		X			X	X		
Teriflunomide plasma concentration (5) **				X						
Viral serology				X						
Pregnancy test*/**		X serum		X			X serum	X urine (first assessment)	X (first assessment; 10)	

Periods	Name	**FOLLOW-UP**	**UNSCHEDULED**							
	Duration	30 Days								
Visits	Number	24	R1, R2, …	U1, U2, …	I1, I2, …(13)		P1, P2, …(9)			
					D1	D15				
	Name	EOS	Relapse	Unscheduled (8)	Re-initiation D1	Re-initiation D15	Interruption / planned pregnancy	Eligibility for re-initiation / planned pregnancy	Re-initiation D1 / pregnancy	Re-initiation D15 / pregnancy
					Day 1 of re-initiation	Day 15 of re-initiation	Unscheduled visit after drug interruption for planned pregnancy	Unscheduled visit prior to study drug re-initiation after interruption for planned pregnancy	Unscheduled visit following study drug interruption for planned pregnancy for re-start	Unscheduled visit following study drug interruption for planned pregnancy for re-start
	Time	Last study treatment intake + 30 days	Any day between Day 1 and EOS	Any day between Day 1 and EOS	Any day between Day 1 and EOS	Any day between Day 1 and EOS	Earliest after Visit 5 (Week 24) and until 6 weeks after the first of two consecutive tests showing teriflunomide plasma level <0.02 mg/L and at least 30 days after study treatment discontinuation	30 days (±5 days) before study drug re-initiation		
	Visit window	+14 days	+7 days	NA	NA	± 1 day	± 7 days	NA	NA	NA
Study treatment dispensing & accountability (6)*				X	X	X			X	X
AEs*/ SAEs* (7)		X	X	X	X	X	X	X	X	X

* Data collected in the eCRF.
** Electronically transferred to the sponsor
Day 1 (date of enrollment visit) is to be used as the reference date for the purpose of calculating the subsequent visit dates (and time windows).

1) SBP/DBP: Pre-dose (all subjects) and hourly (+/− 15 min) for at least 4 hours post-dose and up to 12 hours (only mandated for subjects with cardiovascular risk factors and at the discretion of the investigator / treating neurologist for subjects without cardiovascular risk factors [see Section 5.1.9]).
2) ECGs: Pre-dose (all subjects) and hourly (+/− 15 min) for at least 4 hours post-dose and up to 12 hours (only for subjects with cardiovascular risk factors (only mandated for subjects with cardiovascular risk factors and at the discretion of the investigator / treating neurologist for subjects without cardiovascular risk factors [see Section 5.1.9]).
3) OCT and/or ophthalmological examination to be performed at any visit in the presence of visual symptoms suggestive of macular edema or active uveitis. From Protocol Version 6 scheduled OCT examinations at visit 24, visits for Interruption / planned pregnancy, visits for Eligibility for re-initiation / planned pregnancy, and at unscheduled visits will not be required.
4) PFTs include spirometry to be performed in all subjects; DL_{CO} to be performed in a subset of subjects at selected sites only.
5) Teriflunomide testing no longer required with approval of protocol version 5. Under protocol versions 1 to 4, teriflunomide plasma concentration may be assessed at Week 19 ± 7 days and at Week 21 ± 7 days and may be repeated at Visit 5 (Week 24) and at following visits if necessary until two consecutive test results confirming plasma concentration of teriflunomide <0.02 mg/L are available.

6) Scheduled study medication dispensing/return procedures may be adapted according to the site practice.
7) All AEs and SAEs up to 30 days after study treatment discontinuation must be reported.
8) Unscheduled visits may be performed at any time during the study and the indicated assessments are optional, based on the judgment of the investigator.
9) The wish to become pregnant and stay in the study must be communicated by the female subject to the principal investigator / treating neurologist during a scheduled visit. Interruption of contraception for planned pregnancy may only take place after Visit 5 (Week 24) and at earliest 6 weeks after the first of two consecutive tests confirming plasma teriflunomide level <0.02 mg/L and at least 30 days after ponesimod interruption. Please note: teriflunomide testing is no longer required with the approval of protocol version 5.
10) Review and assess contraception methods and total duration of study treatment interruption, which should not exceed 81 weeks.
11) Only if the subject is meeting the principal investigator / treating neurologist at unscheduled visits.
12) Only if no 12-lead ECG is performed at this visit.
13) As described in detail in Section 5.1.9, subjects who miss taking the study drug for four or more consecutive days are required to re-initiate ponesimod using the original up-titration scheme. In such cases, there will be one or two visits; one visit on the day of re-initiation (Day 1) for all subjects. An additional visit 14 days (±1 day) after the day of re-initiation (Day 15) only mandated for subjects with cardiovascular risk factors (see Section 5.1.9), but may be scheduled for any subject at the discretion of the investigator / treating neurologist.
14) To be collected for all subjects at all scheduled visits after approval of protocol version 5.

AE = adverse event; DBP = diastolic blood pressure; DL_{CO} = diffusing capacity of the lungs, measured using carbon monoxide; ECG = electrocardiogram; EDSS = expanded disability status scale; EOS = End-of-Study; FS = Functional System; I = re-initiation visit; HR = heart rate; MRI = Magnetic resonance imaging; OCT = Optical coherence tomography; P = pregnancy visit; PFT = pulmonary function test; R = relapse visit; SAE = serious adverse event; SDMT = Symbol Digit Modalities Test; SBP = systolic blood pressure; U = unscheduled visit.

PROTOCOL

1 BACKGROUND

1.1 Multiple sclerosis

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

1.1.1 Pathogenesis

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

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

1.1.2 Clinical course

The two main clinical features of MS are exacerbations (also called attacks or relapses) and progressive loss of neurological function. Relapses are considered the clinical expression of acute, inflammatory, focal lesions of the brain or spinal cord, corresponding to axonal demyelination, which leads to the slowing or blockade of axonal conduction at diverse affected sites of the brain and spinal cord. This inflammatory disease activity may translate to a large variety of clinical symptoms and signs and/or acute lesions visualized on magnetic resonance imaging (MRI). 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 [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 defining 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 2011].

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

1.1.3 Epidemiology

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

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

MS is the most common chronic neurologic disease in adults between 20 and 50 years of age with a peak onset of MS in the early thirties. Women are affected approximately twice as often as men. 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 must 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 several 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 s.c. 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®)

- Ocrelizumab 600 mg i.v. every 6 months (Ocrevus®)
- Ofatumumab 20 mg/0.4 mL Subcutaneous once monthly (Kesimpta®)

Additional injectable drug currently in late-stage development for the treatment of RMS include AIN457 (secukinumab).

1.1.4.2 Orally administered disease-modifying therapies

Several oral drugs have been approved for MS:

- Fingolimod 0.5 mg 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 3.5 mg/kg body weight over 2 years (Mavenclad®)
- Siponimod 0.25 and 2 mg orally o.d. (Mayzent®)
- Ozanimod 0.92 mg orally o.d. (Zeposia®)
- Diroximel fumarate 231 mg twice daily (Vumerity®)
- Monomethyl fumarate 95 mg capsules (Bafiertam™)

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 S1P1 receptor. S1P1 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 S1P1 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, S1P1–S1P5, 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 S1P1 receptor but interacts with S1P3, S1P4, and S1P5 [Brinkmann 2007, Brinkmann 2010]. Two other S1P receptor modulators - siponimod and ozanimod (which bind to $S1P_1$ and $S1P_5$) have also been approved for MS in some countries.

1.3 Ponesimod

Ponesimod, an iminothiazolidinone derivative, is an orally active, selective modulator of the S1P1 that induces a rapid, dose-dependent, and reversible reduction in peripheral blood lymphocyte count by blocking the egress of lymphocytes from lymphoid organs. T and B cells are most sensitive to ponesimod-mediated sequestration. In contrast, monocyte, natural killer (NK) cell and neutrophil counts are not reduced by ponesimod. The effect of ponesimod on circulating effector T cells represents a promising therapeutic approach for diseases in which activated T cells play a critical role.

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

1.3.1 Nonclinical studies

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

- Ponesimod causes a rapid and substantial reduction in circulating lymphocytes in rats and dogs, which is also rapidly and fully reversible. The effect correlates well with the plasma concentration of ponesimod.
- Studies with ponesimod in animal models of T-cell-mediated diseases, such as MS, rheumatoid arthritis, type 1 diabetes and skin hypersensitivity, consistently indicated a therapeutic potential of ponesimod at oral doses that lower peripheral blood lymphocyte counts.
- Ponesimod shows an oral bioavailability of 35−74%, low clearance, and a tissue distribution greater than total body water in rats and dogs. Plasma protein binding is high (≥98.9%) in rats, dogs, and humans.
- The metabolism of ponesimod is comparable in rats, dogs, and humans. The main metabolite, ACT-338375 (M13), is present in plasma of mice, rats, and dogs at levels similar to or higher than steady-state exposures in humans at 40 mg/day.
- Based on available nonclinical data, the potential for drug-drug interactions (DDIs) is limited. The metabolite M13 has no liability for causing DDIs via inhibition of cytochrome P450 (CYP) enzymes or transport proteins. M13 is not a time-dependent inhibitor of CYP3A4, CYP2D6 or CYP2C9. Neither ponesimod nor the M13 metabolite approach plasma concentrations expected to inhibit CYP2C9 or CYP2C19 after daily doses of 20 mg at steady state.
- The 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 7 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]. Study AC-058B301/OPTIMUM was completed (last patient last visit) in May 2019 and Study AC-058B302/POINT was prematurely terminated (announcement made in November 2019) due to failure to meet recruitment targets.

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 2–2.5 fold accumulation of the drug with repeated daily oral dosing, and steady state is achieved within 4−5 days. There is a good correlation between the plasma concentration of ponesimod and the peripheral blood total lymphocyte count. Food, age, race or sex do not appear to relevantly affect the PK and PD of ponesimod. The PK DDI potential of ponesimod is judged to be low based on current nonclinical and clinical data.

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

1.3.2.2 Pharmacodynamics in humans

Oral administration of ponesimod dose-dependently reduces the circulating lymphocyte count in humans. The maximum reduction from baseline of approximately 65–80% is achieved after a single dose of ≥50 mg, or 40 mg o.d. at steady state. The nadir in lymphocyte count is attained within 6–10 hours following a given single dose. There is no evidence of tachyphylaxis on lymphocyte count. Peripheral blood counts of both T and B cells are reduced by ponesimod, while NK cells and neutrophils are not reduced. Food, race and 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 [Olsson 2014] 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 40, 20, and 10 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%, 83%, and 43% in the 40, 20, and 10 mg groups, respectively vs placebo ($p < 0.0001$).

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 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 10 mg and 40 mg dose levels were subsequently discontinued during the extension study and all subjects were transitioned to the 20 mg dose level.

The results from an interim analysis of study AC-058B201/B202 with cut-off date of 31 March 2019 have shown sustained low rates of MRI and clinical disease activity as well as low rates of relapse and disability accumulation during long-term treatment with ponesimod for up to 9 years. The model--adjusted ARR estimated with ponesimod 20 mg was approximately 0.15.

Study AC-058B301/OPTIMUM was a prospective, multicenter, randomized, double-blind, active controlled, parallel group, Phase 3, superiority study. The study was designed to compare the efficacy, safety, and tolerability of ponesimod 20 mg vs teriflunomide 14 mg in adult subjects with relapsing MS over a treatment period of 108 weeks.

Results showed that ponesimod 20 mg statistically significantly reduced ARR (confirmed relapses) by 30.5% compared to teriflunomide 14 mg (ARR = 0.202 for ponesimod 20 mg vs. 0.290 for teriflunomide 14 mg, rate ratio: 0.695 [99% CL: 0.536: 0.902], p = 0.0003).

In addition, the change from baseline to Week 108 in fatigue (based on the Fatigue Symptom and Impact Questionnaire-Relapsing Multiple Sclerosis [FSIQ-RMS] weekly symptoms score) was statistically significantly lower in the ponesimod 20 mg arm compared with the teriflunomide 14 mg arm (mean = -0.01 for ponesimod 20 mg vs 3.56 for teriflunomide 14 mg, mean difference: -3.57 [95% CL: -5.83: -1.32], p = 0.0019, where an increase from baseline indicates worsening in fatigue symptoms).

Ponesimod 20 mg also statistically significantly reduced by 56% the number of CUALs between baseline and Week 108 compared to teriflunomide 14 mg (mean CUALs per year = 1.405 for ponesimod 20 mg vs. 3.164 for teriflunomide 14 mg, rate ratio: 0.44 [95% CL: 0.36: 0.54], p <0.0001).

A 12-week CDA was observed in 10.1%, and 12.4% of subjects up to EOS in the ponesimod 20 mg and teriflunomide 14 mg arms, respectively (hazard ratio: 0.83 [95% CL, 0.58 to 1.18]; log-rank p = 0.2939). A 24-week CDA was observed in 8.1%, and 9.9% of subjects up to EOS in the ponesimod 20 mg and teriflunomide 14 mg arms, respectively. Exploratory analysis (not formally tested as per testing procedure) showed that the hazard ratio: 0.84 (95% CL, 0.57 to 1.24]; log-rank p = 0.3720).

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

1.3.2.4 Safety and tolerability

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

desensitization. To minimize the first-dose effects on HR and AV conduction, a dose up-titration regimen was successfully tested and has been 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 hours after an oral dose of 40 mg or higher, and was associated with a clinically relevant forced expiratory volume in 1 second (FEV_1) decrease from baseline. Symptoms resolved spontaneously upon discontinuation of treatment with ponesimod, and PFTs returned to baseline upon drug discontinuation.

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.

Safety results from the completed OPTIMUM study and the interim analysis of the ongoing AC-058B201/B202 study were consistent with previous studies and provide support for the long-term safety of ponesimod. Results of the AC-058B301/OPTIMUM study also support the safety and tolerability of the gradual ponesimod up-titration regimen.

- In the OPTIMUM study, the proportion of subjects who experienced at least one TEAE was similar in both treatment arms (88.8% and 88.2% of subjects in the ponesimod 20 mg and the teriflunomide 14 mg arms, respectively). The most common TEAEs in the ponesimod 20 mg arm were ALT increased (19.5%), nasopharyngitis (19.3%), headache (11.5%) and upper respiratory tract infections (10.6%). Initiation of ponesimod using the gradual uptitration regimen (starting with ponesimod 2 mg) was not associated with clinically significant bradyarrhythmia events; none of the reported bradyarrhythmia events was serious or leading to discontinuation of treatment; no second- or higher degree AV blocks were reported.

- In the interim analysis of AC-058B201/B202 (cut-off date of 31 March 2019), long-term treatment with ponesimod was not associated with new safety or tolerability concerns. Study AC-058B202 is ongoing. The results of the interim analysis support the long-term benefit/risk profile of the 20 mg dose as the most optimal dose of ponesimod. Ponesimod 20 mg was shown to be safe and well tolerated in adults with RRMS over long-term treatment of up to 9 years (median exposure to ponesimod in the 20 mg dose group of 8.02 years, corresponding to a total of 817 subject-years).

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 exposure to the study treatment and for at least 30 days after study treatment 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].

1.4 Purpose and rationale of the study

The AC-058B303 study (extension study) is the long-term extension for the AC-058B301 study (core study). The core study has been designed to investigate the efficacy, safety and tolerability of ponesimod in subjects with RMS. The subjects are treated with either ponesimod or the active comparator, teriflunomide. The purpose of this long-term extension of the core study is to characterize the long-term safety and control of disease of ponesimod in subjects with RMS. In particular, the study will allow to observe potential adverse events which may only occur after long-term treatment with ponesimod. The study will also investigate the effect of re-initiation of ponesimod after a brief interruption in a relatively large population (all subjects treated with ponesimod in the core study and eligible for the extension study) on disease activity in terms of relapses and MS-related MRI lesions. There is currently limited guidance on when a new MS treatment should be started after discontinuation of teriflunomide and the study will contribute with data on safety and efficacy of switching from teriflunomide to ponesimod after an interruption as mandated by the protocol. The study will also allow confirmation of sustained efficacy of ponesimod in terms of relapses, MRI lesions and reduction of disability accumulation during long-term treatment. In addition, combined data from the core study together with the results of the current extension study will allow comparison of MS activity in subjects who were switched from teriflunomide to ponesimod versus those who were treated with ponesimod in both studies.

Published data from Phase 2 dose finding study AC-058B201 and preliminary data from its extension study (AC-058B202) indicate that ponesimod at the dose used in this study (20 mg once daily) has adequate efficacy in reducing disease activity in RMS patients.

Study AC-058B201 showed that ponesimod had clinically important and statistically significant effects on the primary endpoint, which was the cumulative number of new MRI T1 Gd+ lesions per patient recorded every 4 weeks from Weeks 12 to 24 after study treatment initiation as compared to placebo. T1 Gd+ lesions are a well-recognized marker of MS disease activity and prognostic marker of relapses.

In addition, preliminary data (with treatment up to 6.25 years with median exposure of approximately 5.3 years) from extension study AC-058B202 demonstrated sustained effect on MRI lesions and sustained low relapse rate. The observed reduction in circulating lymphocyte

count associated with ponesimod treatment provides the biological plausibility for the observed efficacy results.

The magnitude of effect of this dose of ponesimod on MRI lesions and relapse rates observed in the Phase 2 studies, viewed in the context of published results from Phase 3 studies with teriflunomide, supports the hypothesis that ponesimod may be superior to teriflunomide in terms of frequency of relapses. The core study (AC-058B301) will formally test this hypothesis.

Therefore it seems justified to switch subjects who were treated with teriflunomide in the core study to open-label ponesimod in the extension study and to continue treatment for 240 weeks or until ponesimod is commercially available in the respective countries (see Section 3.2.3.1), unless the overall data that will be submitted to Health Authorities do not support the approval of ponesimod in the intended indication.

2 STUDY OBJECTIVES

2.1 Safety objectives

- To describe the long-term safety and tolerability of ponesimod 20 mg in subjects with RMS.
- To describe the effects of re-initiation of ponesimod treatment after interruption in subjects with RMS.

2.2 Efficacy objectives

- To describe the long-term disease control in subjects with RMS receiving ponesimod 20 mg.
- To describe the effect of a switch from teriflunomide to ponesimod 20 mg on disease control in subjects with RMS.

3 OVERALL STUDY DESIGN AND PLAN

3.1 Study design

This study is a prospective, multicenter, open-label, non-comparative, long-term extension of the Phase 3 confirmatory core study.

Subjects who have completed the 108-week treatment period in the core study will be enrolled into one group treated with ponesimod 20 mg o.d. Based on anticipated discontinuation rates in the core study, approximately 800 subjects are expected to enter the extension study.

The study will be conducted in approximately 160 sites in 28 countries.

3.2 Study periods

The extension study consists of a pre-treatment period, a treatment period, and a safety follow-up.

3.2.1 Core study follow up period and transition into the extension study

Eligible subjects may enter the extension study following the safety follow-up (FU) period of the core study. For subjects transitioning into the extension study, the core study safety FU period

concludes with a safety Follow-up Visit 1 (FU1) or with an abbreviated Follow-up Visit 2 (FU2) at 14–22 and 23–37 days, respectively, after the last dose of the study drug in the core study (End-of-Treatment; EOT). The abbreviated FU2 visit will take place only if the compliance with teriflunomide elimination procedure was deemed not sufficient by the investigator at FU1 visit but transition to the extension study is still planned.

The core study FU period ends when all assessments of FU1 or FU2 (whichever applies) have been completed. At FU1 or FU2 (whichever applies) the subject's compliance with teriflunomide elimination procedure needs to be assessed as sufficient by the investigator in order to confirm eligibility for the extension study.

3.2.2 Pre-treatment period

The pre-treatment period includes all pre-dose assessments of Visit 1 and starts when the subject completes the core study FU visits FU1 or FU2 (whichever applies) and signs the informed consent. This will be considered as the enrollment into the extension study.

Ideally, signing of informed consent will occur on the day of FU1 or FU2 visit (whichever applies). In all cases, informed consent should be signed no later than one day after FU1 or FU2 visit (whichever applies). Ideally, the assessment results of all inclusion and exclusion criteria will be available when the informed consent is signed. In all cases, the assessment results of all inclusion and exclusion criteria must be available prior to first dosing of study treatment.

The pre-treatment period ends with the first dose of study treatment (i.e., Day 1). The pre-treatment period must not last longer than 7 days (i.e., signing of the informed consent until study treatment initiation $\leq$ 7 days).

3.2.3 Treatment period

The treatment period starts with the first dose of study treatment, which defines Day 1 of the extension study. All post-dose assessments of Visit 1 will be conducted during the treatment period.

Ideally, all assessments and procedures of Visit 1, including first study treatment dosing and post-dose cardiac monitoring, should occur on the same day as the core study FU1 or abbreviated FU2 (whichever applies). In all cases, all assessments and procedures of Visit 1 must be completed (i.e., study treatment start) no longer than 7 days after signing of the informed consent (start of Visit 1).

The time from last dose of study treatment in the OPTIMUM study to the first dose of ponesimod in this study will last at least 14 days, but can last up to 44 days. The investigator should make every effort to minimize the duration of the treatment interruption between EOT of the core study and Day 1 of the extension study. Ideally, the treatment interruption should not last longer than 15 days.

The treatment period consists of 240 weeks of treatment with ponesimod including a 14-day gradual up-titration beginning on Day 1, followed by daily treatment with 20 mg ponesimod.

Treatment will stop before 240 weeks if ponesimod becomes commercially available for the treatment of multiple sclerosis in the subject's country.

The visits during the treatment period will consist of an enrollment visit; three visits at 2 (i.e., 15 days), 4, and 12 weeks after enrollment; and visits every 12 weeks thereafter until the EOT.

The treatment period may include a study treatment interruption period of variable duration [see Section 5.1.12]. The permitted maximum duration of the study treatment interruption is 81 weeks for planned pregnancies and 12 weeks for other reasons (if exceeded, then the subject will be prematurely discontinued from the study). During the treatment interruption the subject will follow the planned visit schedule off-treatment with the corresponding assessments with exceptions of assessments that are contra-indicated due to the subject's condition (e.g., in the event of pregnancy, scheduled MRI assessments will not be performed).

3.2.3.1 End-of-treatment

The EOT visit will take place at Week 240 or at the time ponesimod is commercially available for treatment of MS in the subject's country (whichever occurs first). The EOT visit should preferably take place 1 day after the last dose of study treatment but no later than 14 days after the last dose of study treatment. The EOT may take place in case:

- of premature discontinuation of study treatment for subjects meeting the study specific criteria for permanent discontinuation of study treatment described in Section 5.1.12;
- the sponsor decides to stop the extension study;
- the subject or the investigator decides to discontinue the study treatment;
- ponesimod is commercially available for the treatment of MS in the subject's country.

In some countries, additional reimbursement negotiations and central formulary approvals will be needed before ponesimod becomes available. In this case, patients participating in the AC-058B303 study can continue to receive ponesimod until ponesimod is available in their local country, or for a maximum of 240 weeks. Patients will get access to the study drug for a maximum of 240 weeks. If ponesimod becomes available locally before the end of the 240 weeks in the AC-058B303 extension study, then patients will be considered as having completed the extension study and will be switched to commercially available supply if they wish to continue ponesimod treatment. For these patients, the switch to commercially available ponesimod should occur at the EOT visit, and commercially available ponesimod may be initiated on the day following last intake of study treatment.

3.2.4 Safety follow-up

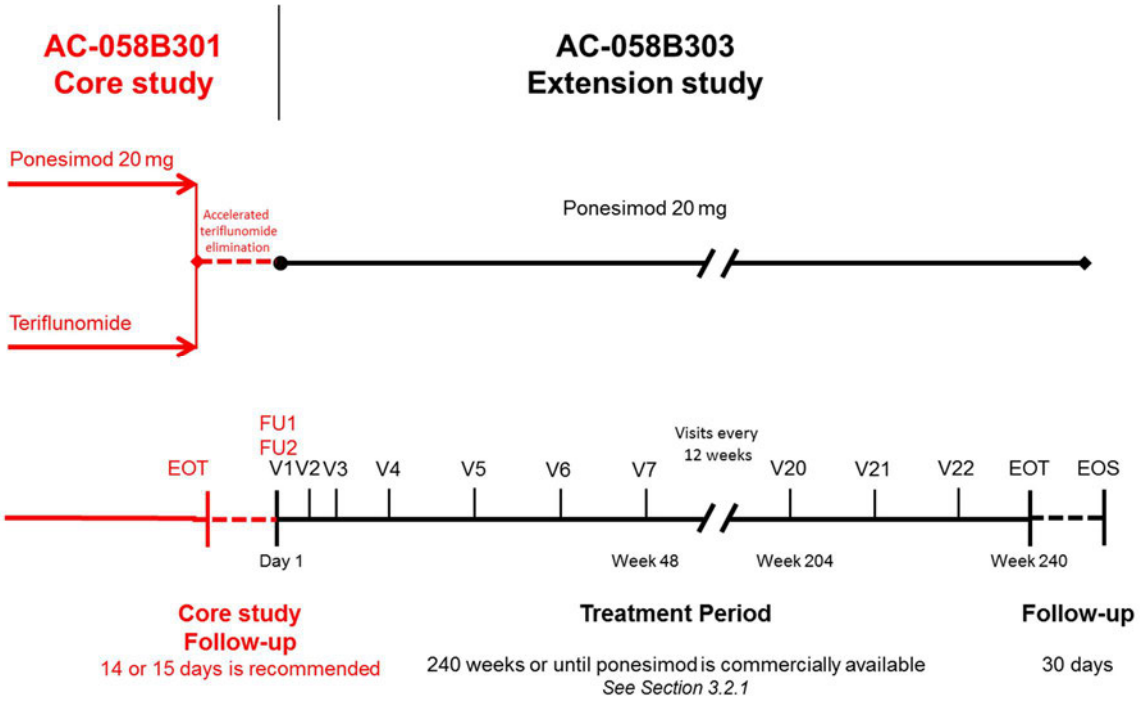
For an individual subject, End-of-Study (EOS) is reached when treatment and safety FU have been completed. The EOS Visit should be performed 30–44 days after the permanent discontinuation of study treatment. If during study treatment interruption, the subject fulfills the criteria for

premature discontinuation, the EOS visit should be scheduled as soon as possible after the decision to prematurely discontinue has been taken.

The EOS visit and all assessments will also be conducted for subjects who have switched to commercially available ponesimod.

The overall study design is depicted in Figure 1.

Figure 1 Study design



EOT = End-of-Treatment; EOS = End-of-Study; V = Visit; FU = Follow-up; - - - = no study treatment.

3.2.5 Sub-studies

One of the four sub-studies performed during the core study will continue during the extension study (i.e., the DL_{CO} sub-study).

3.2.5.1 Pulmonary function monitoring

A sub-study assessing the diffusing capacity of the lungs, measured using carbon monoxide (DL_{CO}), will be continued in these subjects who participated in the sub-study in the core study. Eligible subjects choosing to continue participation will provide consent under a separate informed consent.

3.2.5.2 Janssen COVID-19 vaccination sub-study

A sub-study using the Janssen COVID-19 vaccine (Ad26.COV2.S) was cancelled from Protocol Version 6 onwards.

3.3 Study design rationale

This study is an open-label long-term extension of the core study. The purpose of this extension study is to collect long-term safety and efficacy data and to provide ponesimod treatment to subjects who completed the core study. Eligible subjects who have completed the core study treatment may be enrolled to receive ponesimod 20 mg for a period of 240 weeks or until ponesimod is commercially available. The study will be open-label since all the subjects will receive ponesimod 20 mg o.d., in order to maximize the safety population exposed to ponesimod. Although this is an open-label, non-comparative study, until introduction of Protocol Amendment 2, EDSS / Functional system (FS) assessments were performed with the efficacy assessor being blinded to safety, efficacy and other data as described in Section 3.4.3 to limit bias.

Switching from double-blind setting in the core study will require a wash out period between the end of treatment in the core study and the first dose of ponesimod in the extension study. In order to keep the blind until the database lock in the core study, all the subjects will need to undergo the accelerated elimination procedure of teriflunomide after EOT in the core study. The compliance with the accelerated elimination procedure of teriflunomide will be assessed by the investigator after the completed elimination procedure at FU1 Visit of the core study and, if deemed not sufficient by the investigator also at the abbreviated FU2. The recommended compliance should include intake of 33 doses of cholestyramine (8 g or 4 g) or 22 doses of activated charcoal (50 g). The elimination procedure may take approximately 3 weeks to be completed and may be initiated up to 7 days after the last day of study drug intake in the core study. The maximum interval between the last dose of study drug in core study and the first dose of ponesimod in the extension study might be up to 44 days (considering a maximum of 37 days from EOT to FU2 and a maximum of 7 days from FU2 to first dosing in the extension study). Ideally, the treatment interruption should last no longer than 15 days, and Visit 1 should be completed the same day as or a day after core study FU1 or abbreviated FU2 visits, whichever applies, and no longer than 7 days after these visits. During this time the subjects will not receive any DMT for MS. Given the short duration of interruption, no clinically important impact of this treatment interruption on the course of MS is expected.

3.4 Site staff and their roles

In order 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 the event of absence of any of the staff listed below.

For each site, the preferred study staff will consist of:

- A principal investigator
- A treating neurologist (who may be the principal investigator)
- An efficacy assessor (who may be the principal investigator or treating neurologist)
- First dose administrator
- A clinical coordinator/study nurse (if required)
- MRI staff
- A radiologist/neuroradiologist or neurologist with MRI expertise
- An ophthalmologist
- A pulmonary function laboratory technician or expert
- A pulmonologist (only at sites participating in the DL_{CO} sub-study)
- A dermatologist

3.4.1 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.

3.4.2 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 treatment administration, reporting MS relapses on the specific MS relapses pages of the electronic case report form (eCRF) [see Section 7.4.2 and Section 10.1.6], monitoring of safety including recording and treating of adverse events (AEs), physical examination (including neurological examination), routine laboratory results, concomitant medications, blood pressure (BP), and ECGs. The treating neurologist may perform the role of the efficacy assessor if qualified (see Section 3.4.3). The treating neurologist will have access to the subject's MRI images and/or reports from the local neurologist/radiologist or neurologist with MRI expertise but not to the results of the central reading from the Medical Image Analysis Center (MIAC). The exception is incidental findings with safety concerns discovered during central MRI reading. In this event, the central MRI reading will send an incidental finding report to the site.

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 4.4].

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.

3.4.3 Efficacy assessor

The efficacy assessor is a physician or a qualified health care provider 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/FS scores using the "Neurostatus" scoring documents [see Appendix 1] according to the protocol schedule, as well as EDSS/FS scores at every unscheduled visit for confirmation of relapse. The treating neurologist may perform the role of the efficacy assessor if qualified.

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 two years thereafter. Training and certification achieved during the core study are acceptable.

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 Multiple Sclerosis Functional Composite (MSFC) test.

3.4.4 First-dose administrator

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

He/she must be qualified and equipped to provide emergency treatment in cases of acute cardiac events. In case of the occurrence of such events, and if 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 treatment. The principal investigator / treating neurologist may perform this role if qualified. The first-dose administrator is not required to dispense ponesimod to the subject.

She/he is responsible for oversight of all BP and ECG assessments requested by the protocol at Visit 1 (Day 1) and at visits for re-initiation of study treatment. This includes the close monitoring of the subject during the first 4 hours and up to 12 hours following study treatment intake [see Sections 5.1.9 and 5.1.10]. She/he will independently assess eligibility for discharge or continued subject management on Visit 1 and on visits for re-initiation of study treatment where post-dose monitoring is required. 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. 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.

If applicable, he/she will support the principal investigator in making a decision on eligibility of the subject prior to enrollment, and on providing adequate treatment in cases of cardiac events.

Significant findings, which in the view of the first-dose administrator meet the definition of an AE, must be reported to the principal investigator and recorded on the Adverse Event page of the eCRF.

Any cardiac events of potential clinical concern on Day 1 and on the first day of re-initiation of study drug must be assessed by the first-dose administrator for seriousness, reported to the principal investigator, and recorded on the AE page of the eCRF. 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.

3.4.5 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 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 treatment administration, and collect, process, and send all blood samples to the central laboratory. Additionally, she/he may be responsible for coordinating the conduct of:

- MRI
- PFTs
- Ophthalmological and cardiac examination [see Section 3.4.4]
- MSFC score
- Symbol Digit Modalities Test (SDMT)

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

3.4.6 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 MIAC, c/o University Hospital Basel, Switzerland, and primary data will be stored at the study site.

3.4.7 Local neurologist/radiologist or neurologist with MRI expertise

The local neuroradiologist or a neurologist with MRI expertise will review the MRI images for safety purposes and provide access to the subject's MRI images and/or reports to the principal investigator / treating neurologist. 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. This also applies to incidental findings with safety concerns that have been detected during central MRI reading at MIAC and communicated to the local radiologist.

3.4.8 Ophthalmologist

The ophthalmologist will review and interpret the ophthalmological examinations and optical coherence tomography (OCT)[1] assessments as scheduled in the study protocol [see Section 7.5.7 and 7.5.8]. In the event of suspected clinically significant findings (e.g., macular edema or active uveitis), an unscheduled OCT examination should be performed by the ophthalmologist, and the principal investigator / treating neurologist will be notified for reporting of an AE on the AE page of the eCRF. In the event of findings observed at any visit during the study, the ophthalmologist

[1] Scheduled OCT assessments are only applicable to Global Protocol version 1 to 5. The requirement for scheduled OCT assessments was removed from Protocol Version 6 onwards.

will conduct further examination, as per local standard practice, to rule out or confirm the diagnosis.

3.4.9 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 / European Respiratory Society (ATS/ERS) guidelines [Miller 2005a].

3.4.10 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 treatment 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.

3.4.11 Dermatologist

A dermatologist will perform a complete skin examination as indicated in Table 1 and Table 2.

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 examinations, as per local standard practice, to rule out or confirm the diagnosis.

3.5 Study committees

3.5.1 Independent Data Monitoring Committee

The Independent Data Monitoring Committee (IDMC) responsible for monitoring the core study has continued its duties for the extension study, until its disbandment which occurred on 30th September 2021. It was composed of physicians with relevant medical expertise. The composition and operation of the IDMC was described in the IDMC charter.

3.5.1.1 Independent Statistical Analysis Center

An independent Statistical Analysis Center (ISAC, Frontier Science), not otherwise involved in study conduct or statistical analysis, will generate all analysis reports required throughout the trial period, exclusively for review by the IDMC (including if required unblinded analysis by treatment allocation in the core study). The reports will be generated from efficacy and safety data periodically transferred by the sponsor to the ISAC.

3.5.2 Ophthalmology Safety Board

An Ophthalmology Safety Board (OSB) composed of two independent ophthalmologists will review and evaluate any new or suspected cases of macular edema. The composition and operation of the OSB is described in the OSB charter. From Protocol Version 6 onwards, the OSB will be decommissioned as macular edema is considered a well characterized identified risk with treatment with ponesimod.

3.5.3 Major adverse cardiovascular events adjudication board

A major adverse cardiovascular events (MACE) adjudication board will review and evaluate 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 does not belong to one of the pre-specified categories, including cardiovascular death, myocardial infarction, or 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 who have completed the 108-week treatment period in the core study. These subjects were determined to have an 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).

4.2 Inclusion criteria

1. Signed informed consent, prior to initiation of any study-mandated procedure.
2. Subjects with MS having completed the double-blind treatment in the core study as scheduled (i.e., who completed the double-blind treatment period until Week 108).
3. Compliance with the teriflunomide elimination procedure assessed as sufficient by the investigator at visit FU1 or abbreviated visit FU2 of the core study, whichever occurred last (the recommended compliance should include intake of 33 doses of cholestyramine (8 g or 4 g) or 22 doses of activated charcoal (50 g).
4. For subjects of reproductive potential: [#]
   - Women of childbearing potential (WOCBP):
     - Must have a negative pre-treatment urine pregnancy test on Day 1;
     - Must agree to undertake 4-weekly urine pregnancy tests during the study and until 6 weeks after the first of two consecutive tests showing teriflunomide plasma level <0.02 mg/L and until at least 30 days after study treatment discontinuation;
     - Must have been using reliable methods of contraception uninterrupted since EOT in the core study and must agree to continue using reliable methods of contraception

throughout the study until 6 weeks after the first of two consecutive tests showing teriflunomide plasma level <0.02 mg/L and until at least 30 days after discontinuation of study treatment.

- Fertile male subjects participating in the study who are sexually active with WOCBP must agree to use a condom until 6 weeks after the first of two consecutive tests confirming plasma teriflunomide level <0.02 mg/L.

Definition of WOCBP, fertile male subjects and the acceptable methods of contraception for this study are described in Section 4.4.

Women who interrupt the study treatment because of planned pregnancy will be exempt from any protocol-mandated pregnancy tests after the first positive urine pregnancy test and until 30 days before study drug re-initiation. These women will also interrupt contraception 30 days after the study treatment interruption and until after delivery [see Section 5.1.12.4].

The inclusion criterion 4 was valid for all subjects throughout the recruitment period. Following approval of protocol version 5 (by which time all subjects had been off teriflunomide for over 2 years), teriflunomide plasma testing is no longer required.

4.3 Exclusion criteria

1. Any of the following cardiovascular conditions on Day 1 pre-dose:
   a. Resting heart rate (HR) <50 beats per minute (bpm) as measured by the pre-dose 12-lead ECG;
   b. Presence of second or third degree atrioventricular (AV) block or a QT interval corrected for heart rate on the basis of Fridericia's formula (QTcF) >470 ms (females), >450 ms (males) on pre-dose 12-lead ECG.
2. Any of the following alerts from central laboratory at Visit 14 of the core study (EOT) which was confirmed as an alert at repeated testing or not repeated prior to FU1 of the core study:
   a. Lymphocyte count: $<0.2 \times 10^9$/L (<200/mm^3 blinded results);
   b. Neutrophil count $<1.0 \times 10^9$/L (<1000 cells/mm^3);
   c. Platelet count $<50 \times 10^9$/L (<50 000 cells/mm^3);
   d. Creatinine clearance <30 mL/min (Cockroft-Gault).
3. At Visit 14 of the core study (EOT) >30% decrease from core study baseline FEV_1 and/or forced vital capacity (FVC);
4. Clinically significant, persistent respiratory AEs (e.g., dyspnea) not resolved prior to first dosing in the extension study.
5. Macular edema at any time between Visit 1 (Screening) in the core study and Day 1 of extension study.
6. Presence of the following at core study Visit 14 (EOT, Week 108), FU1, or abbreviated visit FU2, or on Day 1 (pre-dose) of the extension study:

a. Suspected opportunistic infection of the CNS or any other infection which, in the opinion of the investigator, contraindicates re-start of the study drug;
b. Stevens-Johnson syndrome or toxic epidermal necrolysis or drug reaction with eosinophilia and systemic symptoms.

7. Need for and intention to administer forbidden study-treatment-concomitant therapy;
8. Women who are pregnant or lactating;
9. Male subjects wishing to father a child any time before the 6 week period following the first of two consecutive tests confirming plasma teriflunomide level <0.02 mg/L;
10. Treatment with any MS DMTs between core study EOT and first dosing in extension study;
11. 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;
12. Subjects unlikely to comply with protocol, e.g., uncooperative attitude, inability to return for follow-up visits, or known likelihood of not completing the study including mental condition rendering the subject unable to understand the nature, scope, and possible consequences of the study.

4.4 Subjects of reproductive potential

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

4.4.1 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 have been using one of the following reliable methods of contraception uninterrupted since EOT in the core study, and must agree to continue using these methods of contraception treatment until 6 weeks after the first of two consecutive tests showing teriflunomide plasma level <0.02 mg/L and until at least 30 days after discontinuation of study treatment:

- 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 enrollment.
  - 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 enrollment).

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.

4.4.2 Fertile male subject

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

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

Important note: Teriflunomide testing is no longer required with the approval of protocol version 5. In consequence, there are no longer any restrictions with regards to male subjects who intend to have a child.

4.5 Medical history

4.5.1 Ongoing medical history from the core study

Clinically significant past or concomitant disease or diagnosis ongoing from the core study and ongoing at enrollment of the extension study is collected in the extension study eCRF prior to enrollment.

4.5.2 Additional medical history not reported in the core study

Any new or additional clinically significant past or concomitant disease or diagnosis that cannot be reported in the core study database is collected in the extension study eCRF prior to enrollment.

4.5.3 MS disease history

Complications or symptoms associated with MS present within 24 months prior to the core study and ongoing at enrollment of the extension study are collected in the extension study eCRF prior to enrollment.

4.5.4 MS disease changes

Any MS disease (e.g., RRMS or SPMS with superimposed relapses) changes since the subject entered the core study are collected in the extension study eCRF prior to enrollment.

5 TREATMENTS

5.1 Study treatment

The study treatment is the investigational drug ponesimod. The treatment period consists of an up-titration period (from Day 1 to 14) and a maintenance period (Day 15 until EOT). Ponesimod dose is increased over 15 days until a maintenance dose of 20 mg is reached.

Note that the term "study treatment" or "study drug" refers to study medication provided by the sponsor, as opposed to "commercially available ponesimod" that may be started after discontinuation of study treatment.

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. One tablet of ponesimod 2, 3, 4, 5, 6, 7, 8, 9, or 10 mg will be taken orally o.d. during the up-titration period (Day 1 to 14). During the maintenance period, one tablet of ponesimod 20 mg will be taken orally o.d.

5.1.2 Study treatment administration

5.1.2.1 Up-titration (performed by IVRS)

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 4 days or more [see Section 5.1.9].

Table 3 Dosing scheme

Treatment period	*Duration*	*Dose regimen*	*Dose level*
Up-titration	Day 1 and 2	2 mg	1 and 2
Up-titration	Day 3 and 4	3 mg	3 and 4
Up-titration	Day 5 and 6	4 mg	5 and 6
Up-titration	Day 7	5 mg	7
Up-titration	Day 8	6 mg	8
Up-titration	Day 9	7 mg	9
Up-titration	Day 10	8 mg	10
Up-titration	Day 11	9 mg	11
Up-titration	Day 12 to 14*	10 mg	12 to 14
Maintenance	Day 15 until EOT	20 mg	15 to 17*

* = Visit 2 is to take place at Day 15 (1 / +3 day). The titration kit will therefore include 3 additional tablets (to be used if applicable) for treatment on Day 15-17 (i.e., dose regimen = 20 mg).
EOT = End-of-Treatment.

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

One tablet will be taken orally o.d., preferably in the morning, either with breakfast or before or after breakfast, at approximately the same time each day. The tablet will be swallowed as a whole. The last administration date and time of study treatment prior to the study visits and the administration date and time of study treatment on the days of visits will be recorded in the eCRF.

5.1.2.2 Maintenance

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

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

5.1.3 Treatment assignment

After the subject has signed the informed consent form and eligibility has been confirmed, the investigator/delegate contacts the Interactive Response Technology system (IRT) at Visit 1 to enroll the subject.

5.1.4 Blinding

The treatment groups in the core study remained blinded until the randomization list was revealed for the core study.

5.1.5 Study treatment supply

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

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

5.1.5.1 Study treatment packaging and labeling

5.1.5.1.1 Study treatment packaging

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

5.1.5.1.2 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.

5.1.5.2 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.

5.1.5.3 Study treatment dispensing

The subjects will receive sufficient study treatment to cover the period up to the next scheduled visit. Alternatively, scheduled study medication dispensing/return procedures may be adapted according to the site practice (i.e., if the subject comes to the investigational site more frequently than the scheduled visits, it is then possible to dispense medication in smaller quantities). Subjects are asked to return all used, partially used and unused study treatment blister packs/bottles 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 tablets from the remaining study treatment, and to bring the remaining study treatment to 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.

5.1.5.4 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. The return to the sponsor of unused study drug, or used returned study drug for destruction, will be documented on the investigational product destruction form. When the study

site is an authorized destruction unit and study intervention supplies are destroyed on-site, this must also be documented on the investigational product destruction form.

5.1.6 Study treatment accountability and compliance with study treatment

5.1.6.1 *Study treatment accountability*

The inventory of study treatment dispensed and returned (i.e., study treatment accountability) must be performed by the study staff on the day of the subject visit and before providing further study treatment. It is recorded on the IMP dispensing and accountability log as well as in the eCRF, and checked by the Clinical Research Associate (CRA) during site visits and at the end of the study. The study treatment accountability log in the eCRF will include at least the following information for each study treatment unit dispensed to the subject:

- Dispensed kit number
- Date dispensed / Number of tablets dispensed.
- Date returned / Number of tablets returned.

All study treatment supplies, including partially used or empty blisters/bottles must be retained at the site for review by the CRA.

If the subject forgets to bring the remaining study treatment to a study visit, he/she must be instructed to not take any tablet from the remaining study treatment and to bring it at the next visit.

5.1.6.2 Study treatment compliance

Study treatment compliance is based on study treatment accountability. Study treatment compliance will be calculated at each visit using the formula defined below:

Compliance =
[(number of tablets dispensed − number of tablets returned) / total number of tablets that should have been taken during the period*] × 100

* The period is defined as the number of days between visits and is equal to the number of tablets that should have been taken.

5.1.7 Accelerated elimination of teriflunomide and duration of continued contraception

Approximately half of the subjects in the core study received teriflunomide as their study treatment, but due to blinding, all subjects will undergo an accelerated elimination procedure followed by an assessment of compliance to the elimination procedure prior to administration of the first dose of ponesimod in the extension study.

During the early stages of the study (protocol versions 1 through 4), additional plasma teriflunomide tests may have been required to confirm that teriflunomide plasma levels were sufficiently low (<0.02 mg/L) before fertile male participants could stop contraceptive requirements and in the case of planned pregnancies (see Section 5.1.12.5). Following approval of

protocol version 5, these tests are no longer required now that all ongoing subjects have been off teriflunomide for over 2 years (last subject entered this extension study on 20-May-2019) [Aubagio® USPI, Aubagio® SmPC].

5.1.8 Study treatment dose adjustments and interruptions

Study treatment up-titration, other than described in Section 5.1.2, is prohibited. Study treatment down-titration is not foreseen in any situation and is prohibited.

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

Study treatment may be temporarily interrupted in response to an AE, a diagnostic or therapeutic procedure, a laboratory abnormality, vaccination (see Section 5.2.3), or for administrative reasons. Study-specific criteria for interruption of study treatment are described in Section 5.1.12. The permitted maximum duration of the study treatment interruption is 81 weeks for planned pregnancies and 12 weeks for other reasons (if exceeded, the subject will then be prematurely discontinued from the study).

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

Study treatment dose interruptions must be recorded in the eCRF.

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

If study treatment intake (up-titration or maintenance phases) 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 treatment after study treatment interruptions.

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

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

- If the subject missed taking the dose in the morning:
  - The dose should be taken at any time on the same day.
  - Regular dosing should be resumed with the morning dose on the following day.
- If the subject missed taking the dose for up to three consecutive days:
  - Dosing should be resumed in the morning, with the same dose taken prior to study treatment interruption.
  - Study treatment 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 of ponesimod for four or more consecutive days, then the original up-titration scheme for the investigational study treatment needs to be re-applied.

1. Subjects with cardiovascular risk factors (i.e., meeting any of the below-listed Criteria for Cardiac Monitoring at Site) will require cardiac monitoring and therefore must have their re-initiation of study drug performed at the site. On the day of the re-initiation of ponesimod, the subject must be monitored for at least 4 hours post-dose, following the cardiac assessment schedule and applying the discharge criteria as described in Section 5.1.10.

   Criteria for Cardiac Monitoring at Site (cardiovascular risk factors):

   - Sinus bradycardia HR <55 bpm
   - History or presence during the study of first or second-degree Mobitz type I AV block
   - History or presence during the study of myocardial infarction or heart failure

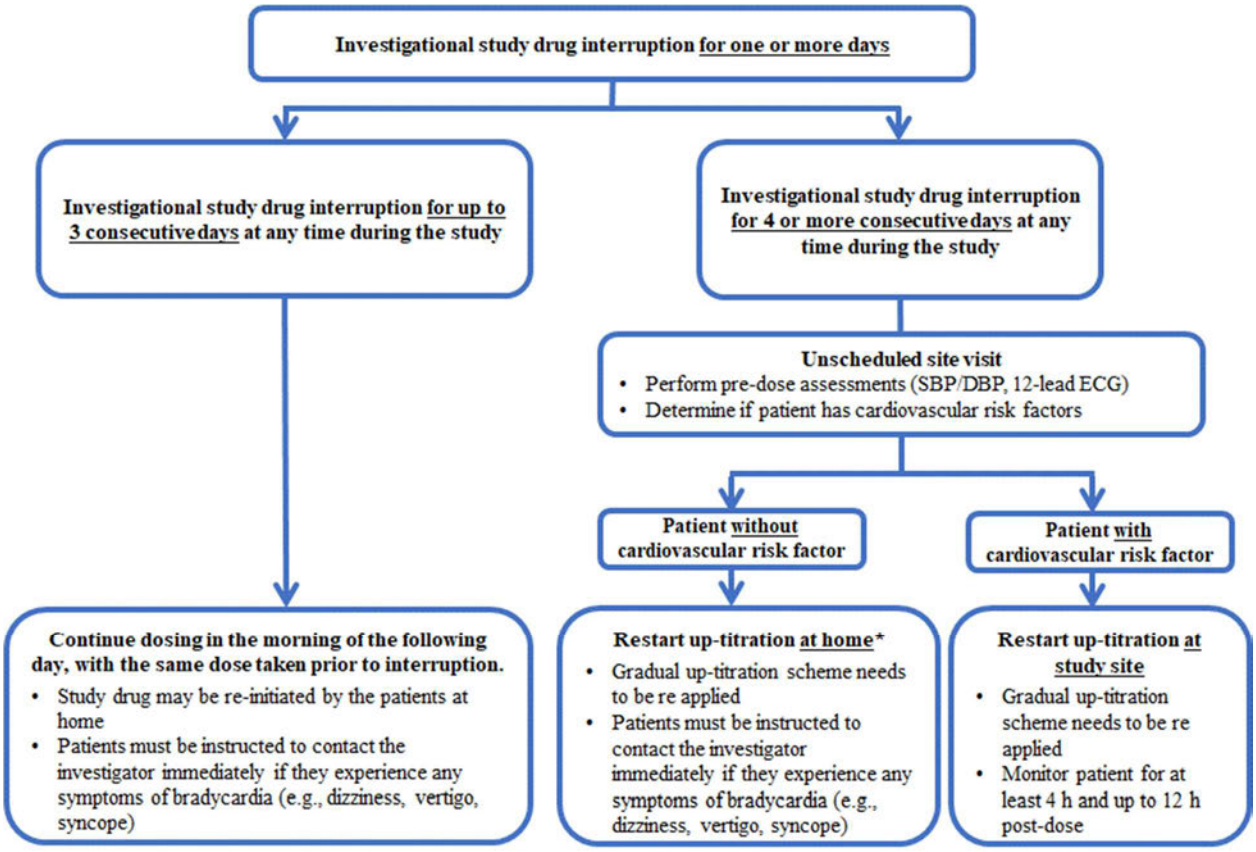
   In the event of a re-initiation, the treating neurologist may consult with the first-dose administrator and/or a cardiologist to determine the most appropriate monitoring strategy. Cardiology advice should be sought in case of history or presence during the study of the following conditions or abnormalities:

   - Atrial flutter, fibrillation or any other arrhythmias treated with anti-arrhythmic drugs;
   - Unstable ischemic heart disease or cardiac decompensated failure;
   - Cardiac arrest or cerebrovascular disease (e.g., transient ischemic attack, stroke);
   - Mobitz Type II second-degree heart block, sick sinus syndrome or sino-atrial heart block;
   - Subjects receiving concomitant therapy with drugs that decrease HR (e.g., beta-blockers, calcium channel blockers and other drugs that may decrease HR).

2. Subjects who do not meet any of the Criteria for Cardiac Monitoring at Site (as confirmed at pre-dose ECG assessment) may either re-initiate the study drug at home after receiving up-titration kit from the site or re-initiate study drug at site and be monitored for at least 4 hours post-dose at the discretion of the investigator / treating neurologist (see Section 8.5.3). Subjects re-initiating study drug at home must be instructed to contact the investigator or local

emergency facilities immediately if they experience any cardiac adverse effects including symptoms of potential bradycardia (e.g., dizziness, vertigo, syncope). The additional visit 14 days (±1 day) after the day of re-initiation (Day 15) (see Section 8.5.3) may be scheduled at the discretion of the investigator / treating neurologist.

Figure 2 Algorithm for management of treatment interruptions



*Patients without cardiovascular risk factors may either re-initiate study drug at home, or at site and be monitored for at least 4 hours post-dose at the discretion of the investigator / treating neurologist.

Whenever the investigator / treating neurologist becomes aware that the subject did not report having missed the study treatment 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, needs to re-initiate treatment, or should permanently discontinue treatment.

5.1.10 Criteria for discharge from cardiac monitoring on Day 1, and on the first day of re-initiation of the investigational study treatment 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 hours post-dose have been obtained) on Day 1, and on the first day of re-initiation of study treatment 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 <60 ms;
- 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 hours post-dose, the subject should be carefully monitored for an additional period, and a 12-lead ECG and BP measurement must be performed every hour. The subject can be discharged from cardiac monitoring as soon as the above criteria are met.

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

5.1.11 Premature discontinuation of study treatment

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 240 weeks or ponesimod is commercially available. The decision to prematurely discontinue study treatment may be made by the subject, the investigator, or the sponsor.

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 the event 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 the sponsor, e.g., in the event of premature termination or suspension of the study [see Section 9.3].

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

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 premature discontinuation from study treatment 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.

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

5.1.12.1 Cardiovascular

Subjects must be prematurely discontinued from study treatment if:

- The following change in HR is observed at any time throughout the study, as documented by 12-lead ECG:
  - HR <30 bpm, or
  - HR <40 bpm is sustained for at least 1 hour and is associated with symptoms of bradycardia (e.g., syncope, dizziness, or vertigo), or
- QTcF >500 ms is observed at any time throughout the study, as documented by 12-lead ECG, or
- The subject does not meet the criteria for discharge from cardiac monitoring on Day 1, or on the first day of re-initiation of study treatment following drug interruptions, if applicable, after 12 hours post dose monitoring.

FU monitoring must be provided until the event leading to study treatment discontinuation 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 treatment 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 in the extension study 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 eCRF.

In the event of any clinical signs or 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. If a cardiac origin is suspected, premature discontinuation of study treatment should be considered.

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

5.1.12.2 Hematological abnormalities

Subjects must be prematurely discontinued from study treatment at any time throughout the study in the event of:

- Confirmed total lymphocyte count $<0.2 \times 10^9$/L (<200 cells/mm^3)

Confirmation will be carried out as follows:

Whenever 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 preferably within 48 hours but no later than within 1 week to repeat the test at trough level (pre-dose) with the central laboratory (unless the clinical situation mandates immediate local testing). If the repeat test confirms a total lymphocyte count $<0.2 \times 10^9$/L the study treatment must be discontinued. Lymphocyte counts must be monitored at least once a week by the central laboratory until the lymphocyte count has returned to $\geq 0.8 \times 10^9$/L or $\geq 80\%$ of the baseline value in the extension study. Any clinically relevant finding meeting the definition of an AE will be recorded accordingly in the eCRF.

In the event of a clinically relevant infection (e.g., opportunistic infection, serious infection), the study treatment may be interrupted and the subject referred to an expert in infectious diseases for further examination and treatment at the discretion of the investigator. In the event of study treatment 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 treatment may be re-initiated at the discretion of the investigator.

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

A guidance for screening and monitoring of subjects for opportunistic infection is provided in Sections 5.1.12.2.1 and 5.1.12.2.2. Subjects must 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.

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

5.1.12.2.1 Guidance for 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., ciclosporin, tacrolimus, sirolimus, and mycophenolate), therapeutic monoclonal antibodies (e.g., rituximab, infliximab, etanercept, basiliximab, daclizumab, efalizumab, alemtuzumab, and muromonab-CD3) [Kappos 2011] and, in rare instances in subjects treated with fingolimod or dimethyl fumarate.

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.

For subjects with prior exposure to natalizumab or other immunosuppressive agents who have been enrolled in the core 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 and, in the event of clinical features indicative of these conditions, the following diagnostic procedures are recommended:

- Perform MRI including T1 sequences with Gd (and additional sequences if needed), and include comparison with the previous MRI images in the interpretation of the MRI results;
- Interrupt study treatment 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.

If 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 the study treatment 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 treatment should be permanently discontinued, and the subject should be managed according to the local standard of care.

The PML cases should be reported to the sponsor as serious adverse events (SAEs).

If at the scheduled visit the MRI 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 treatment should be interrupted and should not be re-introduced until this suspicion has been ruled out.

5.1.12.2.2 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 treatment must be permanently discontinued in case of opportunistic CNS infections. For any other opportunistic infections, the study treatment 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 primarily with neurological symptoms. The neurotropic herpes viruses (herpes simplex and varicella-zoster) are frequent human pathogens and their reactivation can cause serious infections of the CNS such as encephalitis and meningitis. The most frequent characteristics of these infections are an acute onset, associated with fever, headache, confusion, personality changes, and disorientation. Any suspicion of these infections must lead to immediate discontinuation of study 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].

5.1.12.3 Respiratory system

In the event of abnormal spirometry results or persistent respiratory symptoms (e.g., dyspnea), the subject will be closely observed, spirometry will be repeated, and study treatment discontinuation should be considered, according to the guidance provided in Table 4.

Table 4 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 treatment 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.

Baseline = assessment done at Visit 2 (Baseline) of the core study; AE = adverse event; FEV_1 = forced expiratory volume in 1 second; FU = follow-up; FVC = forced vital capacity; PFT = pulmonary function test.

If clinically significant, persistent respiratory AEs (e.g., dyspnea) are reported, PFTs must be performed and study treatment may be interrupted at the discretion of the investigator. In the event of study treatment 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 treatment interruption, if PFTs normalize and lung toxicity is unlikely, study treatment may be re-initiated at the discretion of the investigator.

The decision to permanently discontinue study treatment will be made after evaluation of all available information concerning concomitant medication, 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 treatment may be prescribed short-acting β2 agonist (to be used on an 'as needed' basis' 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 treatment discontinuation should be considered at the discretion of the investigator.

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

5.1.12.4 Pregnancy

If a subject becomes pregnant while on study drug, study treatment 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. All initial reports of pregnancy in female participants must be reported to the sponsor by the study site personnel within 24 hours of their knowledge of the event (see Section 10.3.1).

5.1.12.5 Planned pregnancy

Female subjects participating in the study and wishing to become pregnant during the study may stay in the study and will have the study treatment interrupted prior to pregnancy and re-started after delivery.

Before becoming pregnant the following protocol requirements must be met:

- The wish to become pregnant and stay in the study must be communicated by the female subject to the principal investigator / treating neurologist during a scheduled visit.
- Prior to interrupting contraception, the subject must have 2 negative urine pregnancy tests: one at the scheduled visit on the day of study treatment interruption and one 30 days after study treatment interruption.
- The total duration of the study treatment interruption due to planned pregnancy must not exceed 81 weeks, otherwise the study treatment will be discontinued.
- The interruption of contraception must take place after Visit 5 (Week 24) and at earliest 6 weeks after the first of two consecutive tests confirming plasma teriflunomide level <0.02 mg/L[#] and at least 30 days after ponesimod interruption.
- The subject must agree to be followed by an appropriate health care professional (e.g., gynecologist, obstetrician and/or midwife) during pregnancy according to local practice, to have the reports from pregnancy assessments communicated to the principal investigator / treating neurologist and to have the information on the subject's MS status communicated by the principal investigator / treating neurologist to that health care professional.

Important note: Teriflunomide testing is no longer required with the approval of protocol version 5

In addition to the protocol requirements above, the principal investigator / treating neurologist must explain the following to the subject:

- The potential impact of pregnancy and the post-partum period on the subject's MS and potential medical treatments that would be available for the subject while the study treatment is interrupted.
- Re-initiation of study treatment can only take place after delivery and breastfeeding has ended, if applicable, and will require a medical evaluation of subject's eligibility for study treatment re-initiation.
- Timing of the interruption and possible re-initiation of study treatment and of contraception, related urine pregnancy tests and unscheduled visits.
- The need for re-uptitration at the study treatment re-initiation.
- Breastfeeding must be completely stopped prior to the re-initiation of the study treatment.
- The need to follow the visit schedule as per protocol during pregnancy, including all scheduled assessments and procedures except MRI, PFTs, and without study treatment dispensing.

The re-start of study treatment after delivery requires the following eligibility criteria to be met:

- The subject has completely stopped breastfeeding prior to re-start of the study treatment.
- The subject must have been using the reliable methods of contraception as described in Section 4.4.1 for at least 30 days prior to re-start of study treatment.
- The subject must have had 2 negative urine pregnancy tests performed 30 days apart; the second one must be during the re-start visit.
- The subject did/does not fulfill any protocol criteria for permanent study treatment discontinuation [see Section 5.1.12] at any of the previous visits or at the unscheduled visit for re-start of the study treatment, except the planned pregnancy.
- If the subject received another DMT (IFN β or glatiramer acetate) during pregnancy and post-partum, this treatment must be discontinued at least 7 days before study treatment re-start.

If the subject agrees to all of the above, the study treatment will be interrupted at the scheduled visit once the subject, after having received the above explanation from the principal investigator / treating neurologist, has confirmed the wish to become pregnant and interrupt and potentially re-start the study treatment. The sponsor must be contacted in each particular case in order to confirm that the subject who wishes to become pregnant can continue in the study.

The above requirements for re-initiation of study drug after delivery apply to all cases of study treatment interruption for planned pregnancy irrespective of the duration of pregnancy, and also

to all cases where planned pregnancy did not occur but where contraception was interrupted for any duration, and the subject thereafter wishes to re-start study treatment.

5.1.12.6 Liver abnormalities

In the event 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 treatment discontinuation should be considered according to the guidance provided in Table 5.

Note: All events of ALT or AST ≥3xULN and total bilirubin ≥2xULN (>35% direct bilirubin) or ALT or AST ≥3xULN and INR >1.5 may indicate severe liver injury (possible 'Hy's Law') and must be reported to sponsor in an expedited manner and as an SAE if SAE criteria are met. The INR stated threshold value will not apply to participants receiving anticoagulants.

Table 5 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[a] OR ALT or AST ≥3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%) and retest cannot be done within 72 hours, permanently discontinue study treatment, 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 treatment, 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 [a] • 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 treatment, and perform FU.

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

[a] Note: All events of ALT or AST ≥3xULN **and** total bilirubin ≥2xULN (>35% direct bilirubin) or ALT or AST ≥3xULN **and** INR >1.5 may indicate severe liver injury **(possible 'Hy's Law') and must be reported to sponsor in an expedited manner and as an SAE if SAE criteria are met**. The INR stated threshold value will not apply to participants receiving anticoagulants.

Whenever AST or ALT ≥3 × the upper limit of normal range (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 5. Further diagnostic work-up (including hepatitis serological testing by the central lab) 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 the event of study treatment interruption, the subject will be closely observed and FU liver tests will be performed. Following study treatment interruption, if liver tests normalize and drug-related hepatotoxicity is unlikely, study treatment may be re-initiated at the discretion of the investigator. The decision to permanently discontinue study treatment 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 treatment should be permanently discontinued according to Table 5. In all cases of permanent study treatment discontinuation, FU monitoring must be provided until signs and symptoms have resolved and changes in liver function are no longer regarded as clinically relevant or until medically indicated.

5.1.12.7 Ocular abnormalities

In the event of suspected clinically significant findings (e.g., macular edema or active uveitis), 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 treatment and will be managed and followed up until resolution. Any clinically relevant finding meeting the definition of an AE will be recorded accordingly in the eCRF.

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

5.1.12.7.1 Guidance for monitoring and management of subjects with uveitis

If active uveitis (ocular pain, floaters, blurred vision, increased intraocular pressure) is suspected at EOT or FU1 visit in the core study, or during a scheduled ophthalmological assessment, or at an unscheduled assessment due to ophthalmological symptoms in the extension study, fluorescence angiography (FA) should be performed (unless contra-indicated according to the ophthalmologist) in addition to the scheduled ophthalmological assessment 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 contra-indicated) and OCT 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 treatment. Such subjects will need to be controlled by the ophthalmologist 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 tonometry (Goldmann applanation tonometry is recommended, 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 must be discontinued. If uveitis is progressing in spite of treatment, the investigator may consider interrupting or permanently discontinuing the study treatment.

5.2 Concomitant therapy

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. All study treatment concomitant therapies will be recorded on the Concomitant Medications page of the eCRF. In addition, all medication taken by the subject at EOS of the core study, i.e., all medication ongoing or started at this time, will be recorded on the Concomitant Medications page of the eCRF.

5.2.1 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 adrenocorticotropic hormone (ACTH) is not recommended unless deemed absolutely necessary, and must be documented in the subject charts by the investigator. Oral taper with corticosteroids is not permitted.
- Treatment of relapses with plasma exchange (i.e., plasmapheresis, cytapheresis) is prohibited.

5.2.2 Allowed concomitant therapy

- 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 treatment;
- QT-prolonging drugs with known risk of Torsades de Pointes should be used with caution as ponesimod may potentially enhance their effect on QT interval [guidance is provided in Appendix 2];

- Glatiramer acetate and INF β-1a are allowed only during ponesimod interruptions for planned pregnancy. These treatments may be started 7 days after ponesimod cessation and must be stopped 7 days before ponesimod re-initiation;
- Other treatments considered necessary for the subject's wellbeing and not categorized as prohibited concomitant medications.
- Vaccination with non-live vaccines is allowed while on study treatment if the vaccination is advised by the primary investigator / treating neurologist, based on her/his clinical assessment of the risk/benefit for the individual patient, and if supported by guidelines for vaccination relevant to this patient population, as applicable.

5.2.3 Forbidden study-treatment-concomitant therapy

- Systemic corticosteroids and ACTH, except for the treatment of MS relapses [see Section 5.2.1] 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 4 weeks per year of the study duration on average) 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 (except glatiramer acetate or INF β-1a during ponesimod interruptions for planned pregnancy as described under "Allowed").
- Immunosuppressive treatment (e.g., cladribine, lymphocyte-depleting biological agents such as rituximab or ocrelizumab, mitoxantrone, or other systemic immunosuppressive treatments such as azathioprine, cyclophosphamide, cyclosporine or methotrexate);
- i.v. immunoglobulin (except in women who have interrupted study treatment for pregnancy; for these women i.v. immunoglobulin will be allowed after 30 days from interruption of the study treatment);
- Plasmapheresis, cytapheresis, or total lymphoid irradiation;
- Vaccination with live vaccines, except if performed during a temporary treatment interruption period. In this case it must be performed not earlier than 1 week after last dose of study treatment, and treatment can be re-initiated only after at least 4 weeks from completion of vaccination;
- β-blockers, diltiazem, verapamil, digoxin, digitoxin or any other anti-arrhythmic or HR lowering systemic therapy (a non-exhaustive list of drugs provided in Appendix 3) during the up-titration period (i.e., from Day 1 until Day 14 included, and during the first 14 days after re-initiation of study treatment). Treatment with any of these therapies is also not recommended during the maintenance treatment period (from Day 15 until EOT) and should be considered with caution if an alternative medication cannot be used;

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

Commercially available ponesimod may be initiated on the day following last intake of study treatment. The start date of commercially available ponesimod must be recorded on the Concomitant Medication page of the eCRF.

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

Endpoints for the main part of this study are summarized below.

6.1 Efficacy endpoints

In order to monitor disease activity with long-term treatment with ponesimod, and to investigate the effect of switching from teriflunomide to ponesimod, the main analysis of efficacy will focus on the Combined Analysis Period, i.e., including data from both the core and extension studies. In addition, specific efficacy endpoints will also be analysed over the Extension Analysis Period, i.e., only including data from the extension study. Analysis over the Combined Analysis Period will use the core study baseline as a reference, while analysis over the Extension Analysis Period will use the extension study baseline as a reference. Baseline definitions for efficacy endpoints are provided in Section 11.1.3.

The tables below detail which endpoints will be analyzed for the Extension Analysis Period, and which for the Combined Analysis Period. See Section 11.1 for further details regarding the analysis strategy.

6.1.1 Main clinical endpoints

The main clinical endpoints are those relating to disease activity (relapses, disability accumulation, and composite of the latter including MRI).

Table 6 Main clinical endpoints

Endpoints	Combined Analysis Period	Extension Analysis Period
• ARR (based on the number of confirmed relapses* per subject-year)	Y	Y
• Time from core study randomization to first confirmed relapse*	Y	N
• Time from core baseline to 12-week CDA	Y	N
• Absence of relapses*	Y	Y
• Time from core baseline to 24-week CDA	Y	N
• Change from baseline in EDSS at all assessments	Y	Y
• NEDA status at EOS according to NEDA 3 (defined by the absence of confirmed relapse, Gd+ T1 lesions, new or enlarging T2 lesions and 12-week CDA)	Y	N
• NEDA status at EOS according to NEDA 4 (defined by the absence of confirmed relapse, Gd+ T1 lesions, new or enlarging T2 lesions, 12-week CDA, and annual brain volume change ≥–0.4% from baseline to all assessments)	Y	N

*Definition of relapse

- A relapse is defined as new, worsening or recurrent neurological symptoms that occur at least 30 days after the onset of a preceding relapse, and that last at least 24 hours, in the absence of fever or infection.
- The new, worsening or recurrent neurological symptoms are to be evaluated by the treating neurologist and, if all the elements of the above definition have been verified, and in the absence of another, better explanation of the subject's symptoms, the event is considered as a relapse [see Section 7.4.2]. 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).

ARR = annualized relapse rate; CDA = confirmed disability accumulation; EDSS = Expanded Disability Status Scale; EOS = End-of-Study; FS = functional system; NEDA = no evidence of disease activity.

6.1.2 MRI-based endpoints

Table 7 MRI-based endpoints

Endpoints	Combined Analysis Period	Extension Analysis Period
• PCBV at all assessments	Y	Y
• CUAL, defined as new Gd+ T1 lesions plus new or enlarging T2 lesions without double-counting the lesions) at all assessments	Y	Y
• Number of Gd+ T1 lesions at all assessments	Y	Y
• Cumulative number of new or enlarging T2 lesions (relative to baseline) at all assessments	Y	Y
• Volume of MRI lesions (T2 lesions, T1 hypointense lesions) at all assessments	Y	Y
• Absence of MRI lesions (Gd+ T1 lesions, new or enlarging T2 lesions) at all assessments	Y	Y
• Proportion of Gd+ lesions at baseline evolving to PBHs at all assessments	Y	Y

CUAL = cumulative number of combined unique active lesions; MRI = magnetic resonance imaging PBH = persistent black holes; PCBV = percent change from baseline in brain volume.

6.1.3 Other endpoints

Table 8 Other endpoints

Endpoints	Combined Analysis Period	Extension Analysis Period
• Change from baseline in MSFC Z-score at all assessments	Y	Y
• Change in the SDMT score at all assessments	Y	Y
• Change from baseline in SF-36v2™ Health Survey domain and component scores	Y	Y

MSFC = Multiple Sclerosis Functional Composite; SDMT = Symbol Digit Modalities Test.

6.2 Safety endpoints

In order to investigate the long-term safety of ponesimod and the changes in safety in teriflunomide subjects switching to ponesimod 20 mg, analysis will be performed on all data in the core and extension studies combined, using the core baseline as a reference. In addition, safety data

collected in the extension study will be analyzed independently, using the extension baseline as a reference.

Table 9 details which endpoints will be analyzed for the Extension Analysis Period, and which for the Combined Analysis Period.

Table 9 Analysis of safety endpoints

Endpoints	Combined Analysis Period	Extension Analysis Period
Adverse events		
• Treatment-emergent AEs, SAEs, and AEs of special interest[#]	Y*	Y
• AEs leading to premature discontinuation of study treatment	Y	Y
Cardiac safety		
• Treatment-emergent morphological ECG abnormalities (as defined by the ECG provider)	Y*	Y
• Absolute values by visit for 12-lead ECG parameters (HR, PR, QRS, QT, QTcB, QTcF)	Y	Y
• Change from baseline values by visit for ECG parameters (HR, PR, QRS, QT, QT QTcB, QTcF)	Y	Y
• Change in ECG parameters (HR, PR, QRS, QT, 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 treatment	N	Y
Pulmonary safety		
• Absolute values and percent change from baseline in FEV_1 and FVC at all assessments	Y	Y
• Treatment-emergent decrease from baseline >20% and >30% in FEV_1 or FVC	Y	Y
• Treatment-emergent decrease from baseline >20 percentage points in % of predicted FEV_1 and FVC	Y	Y
• 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 EOS**	Y	N

Table 9 Analysis of safety endpoints

Endpoints	Combined Analysis Period	Extension Analysis Period
• Absolute change from baseline to EOS versus change from baseline to EOT in FEV_1 and FVC (absolute and % of predicted)**	Y	N
• Change in lung diffusion capacity as assessed by DL_{CO} (at selected sites only) expressed in absolute change (mL) and % of predicted value from baseline at all assessments	Y	Y
• Change from baseline to EOS versus change from baseline to EOT in DL_{CO} (absolute and % of predicted) (at selected sites only)**	Y	N
Other endpoints		
• Absolute values and change from baseline for HR, SBP, DBP and body weight at all assessments	Y	Y
• Treatment-emergent notable blood pressure abnormalities[##]	Y	Y
• Absolute values and change from baseline for laboratory tests (hematology, blood chemistry, urinalysis) at all assessments	Y	Y
• Treatment-emergent notable laboratory abnormalities[##]	Y	Y
• Change from baseline to EOS versus change from baseline to EOT in lymphocyte counts (absolute and percent change)**	Y	N
• Treatment-emergent eC-SSRS suicidal ideation score of 4 or above, or a "yes" response on the eC-SSRS suicidal behavior item	Y	N

* Cumulative safety data, i.e., AEs for the combined analysis period will only be presented for subjects who received 20 mg ponesimod in the core study.

[#] The selection of AEs of special interest [see Appendix 4] is based on the anticipated risks of treatment with ponesimod; the final list of AEs of special interest will be defined in the SAP.

[##] The selection of notable abnormalities considered for the analyses is based on standard definitions and the anticipated risks of treatment with ponesimod; the final list of abnormalities will be defined in the SAP.

** Only for subjects who have no exposure to commercially available ponesimod prior to the EOS visit.

AE = adverse event; DBP = diastolic blood pressure; 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; EOS = End-of-Study; EOT = End-of-Treatment; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HR = heart rate; 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; SAE = serious adverse event; SAP = statistical analysis plan; SBP = systolic blood pressure.

The treatment-emergent period is defined as the time from first ponesimod administration in the applicable Analysis Period up to 15 days (inclusive) after last study treatment administration. This definition applies regardless of whether the subject receives commercially available ponesimod after completing study treatment.

7 STUDY ASSESSMENTS

The assessments pertaining to a visit may be performed within the allowed time window.

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 the sponsor of the delegation. The set up and oversight will be agreed upon with the sponsor. The supervision of any external facilities remains under the responsibility of the principal investigator.

Any incidental finding of an abnormality discovered by an external facility must be shared with the principal investigator, who is responsible for reporting the event (e.g., AE) in the eCRF as appropriate. Clinically relevant incidental findings will be followed up per local medical practice.

Calibration certificates for the following devices used to perform study assessments must be available prior to enrolling 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 7.5.5].
- 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 7.5.6].
- ECGs.
- BP monitoring device.

7.1 Informed consent

Prior to performing any study-specific procedures or assessments, the subject must provide written informed consent to participate in the extension study.

It is recommended to hand out the informed consent form to the subject at core study EOT (or earlier) in order to allow ample time for reading and discussion prior to core study FU1 visit. Ideally, signing of informed consent will occur on the day of FU1 or FU2 visit (whichever applies). In all cases, informed consent should be signed no later than one day after FU1 or FU2 visit (whichever applies) and 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 assessment or as part of the core study, and the results are available prior to the subject's signing of informed consent, such procedures or assessments may be used to assess eligibility, and do not have to be repeated. In such cases, it must be clear from the source document when and for which reason the assessment was done prior to the signing of the informed consent. It is the responsibility of the principal investigator / treating neurologist to explain the study in all its aspects to the subject and obtain her/his informed consent. The informed consent process will be documented in the investigator site file. The language used in the oral and written information about the trial, and including the Informed Consent Form (ICF), must be provided in a language that is fully understandable to the subject.

Additional informed consents must be obtained from those subjects continuing participation in the DL_{CO} sub-study.

7.2 Demographics and medical history

Demographics (age, gender and childbearing potential) and medical history [see Section 4.5] are to be recorded in the eCRF at Visit 1.

7.3 Study-concomitant therapies

All study-concomitant therapy (including contraceptives and traditional and alternative medicines, i.e., plant-, animal-, or mineral-based medicines, vaccinations) taken by the subject from the EOS of the core study 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.

7.4 Efficacy assessments

7.4.1 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 only be performed at visits indicated in Table 1 and by the efficacy assessor who should preferably maintain this role for a given subject throughout the study [see Section 3.4.3]. The efficacy assessor must not consult prior EDSS/FS scores when performing the current EDSS/FS assessment. In no case will the treating neurologist alter the EDSS/FS score obtained by the efficacy assessor. The examination will be based on the modified neurological examination 'Neurostatus' [Appendix 1] using the corresponding scoring documents. The EDSS/FS scoring will be recorded in the eCRF. NB: Fatigue, which is an optional part of the 'Neurostatus' assessment, will not contribute to the Cerebral FS score.

7.4.2 Detection and evaluation of relapses

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

Step 1: At every study visit, subjects are reminded to contact their principal investigator / treating neurologist immediately in the event of the appearance of any new or worsening neurological symptoms. In addition, the site will contact the subject 6 weeks (±7 days) after each of the visits following Visit 4 (Week 12) in order to proactively inquire about any new or worsened neurological symptoms. If applicable, this 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 10].

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 visit (including unscheduled visits at which the subject is attended by the principal investigator / treating neurologist), the principal investigator / treating neurologist will interview and examine the subject to determine whether or not a relapse may have occurred since last visit using a dedicated relapse assessment questionnaire [see Appendix 10] and the relapse symptom form [see Appendix 11]. NB: Visits for laboratory re-test (due to a non-evaluable assessment, e.g., a non-analyzable blood sample, MRI rejected by MIAC for quality reasons), or repeated test (e.g., repeated test of serum leucocyte level or repeated PFT as required per protocol) are not considered scheduled or unscheduled visits. Unscheduled visits for safety reasons such as unscheduled ophthalmology assessments, unscheduled PFTs or unscheduled MRIs do not require relapse assessments unless in connection with or as a consequence of these assessment the subject is seen at the site by the principal investigator / treating neurologist.

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 have been verified, 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 (NB: at scheduled visits the EDSS assessment planned for this visit will be used). The completed questionnaire and the outcome of the examination will be collected in the eCRF.

Step 3: The efficacy assessor will perform the EDSS/FS assessment within 7 days of the onset of new or worsening neurological symptom(s) [see Section 7.4.1]. **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 5.2.1], treatment should be initiated as early as recommended by local clinical practice. The neurological examination by the efficacy assessor must always be performed prior to the treatment start.

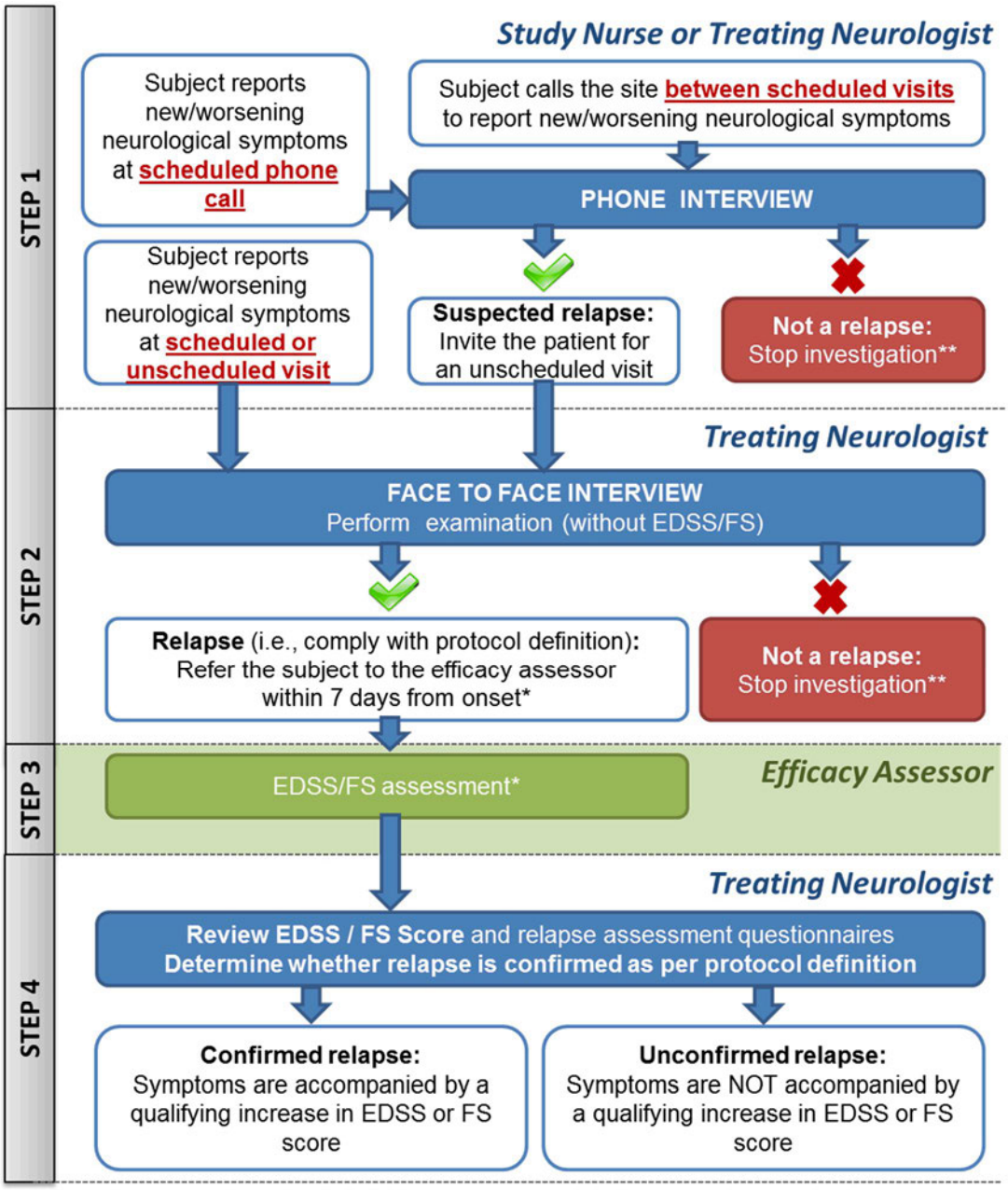
Step 4: The treating neurologist will review the EDSS/FS score obtained by the efficacy assessor and determine presence or absence of qualifying increase in EDSS/FS (i.e., of the magnitude described in Section 6.1 from a previously clinically stable EDSS/FS score and consistent with the subject's new 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].

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

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

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

Figure 3 Flow diagram for the detection and evaluation of relapses



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

7.4.3 MRI evaluations

MRI scans will be performed at Visits indicated in Table 1 and Table 2. In case of premature study treatment discontinuation, the MRI assessment at EOT does not need to be performed if the EOT visit occurs within 4 weeks of the MRI assessment at Visits 7, 11, 15, or 19 (Weeks 48, 96, 144, or 196). All MRI data will be analyzed by the MIAC, c/o University Hospital Basel, Switzerland for MRI efficacy outcomes.

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.

T1-weighted imaging before and after i.v. administration of 0.1 mmol/kg body weight (= 0.2 mL/kg) of Gd as well as T2-weighted imaging will be performed. Gd may cause nausea and vomiting, and in very rare cases allergic reactions that could require immediate anti-anaphylactic therapy (such as steroids, epinephrine/adrenaline, etc.). It is recommended to use macrocyclic gadolinium-based contrast agents (e.g., gadobutrol, gadoterate, gadoteridol) as described in the MRI manual.

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

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 have access to the MRI images and/or reports, and be informed of any findings of concern for the subject's safety including non-MS-related findings detected on the MRI scan. 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 as an AE.

7.4.4 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 at visits indicated in Table 1 and Table 2.

MSFC will be administered in combination with SDMT [see Section 7.4.5] in the following sequence:

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

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

A more comprehensive description of the test and its administration is provided in Appendix 6.

7.4.5 Symbol Digit Modalities Test

The SDMT [Smith 1982, Benedict 2006] measures attention and processing speed much like the PASAT. It will be administered at visits indicated in Table 1 and Table 2.

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.

Study personnel will be trained to administer and score the SDMT.

A sample of the SDMT is provided as Appendix 7. The rater will record the subject's responses on a validated paper form that will be collected and transcribed in the eCRF.

The sponsor 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 translation.

7.5 Safety assessments

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

7.5.1 12-lead electrocardiogram

A standard 12-lead ECG will be recorded at visits indicated in Table 1 and Table 2, with the subject in a fully rested supine position after the subject has been allowed to rest for a minimum of 5 minutes prior to the measurement. Pre-dose ECG may also be performed at unscheduled visits.

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. Details will be provided in the ECG laboratory manual.

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

During the treatment period ECGs must be performed at pre-dose.

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

#Subjects who do not meet any of the Criteria for Cardiac Monitoring at Site (See protocol Section 5.1.9) may re-initiate the study drug at home without post-dose cardiac monitoring.

7.5.2 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 preferably in a fully rested supine position after the subject has been allowed to rest for a minimum of 5 minutes prior to the measurement. It is highly recommended to use the same position (supine or sitting) at all BP measurements. At each pre-dose assessment, SBP and DBP will be measured twice (i.e., two SBP measurements and two DBP measurements). The two obtained measurements (i.e., two SBP measurements and two DBP measurements) and the position and arm used are to be recorded in the eCRF. The means of the two obtained measurements will be calculated by the eCRF. Post-dose assessments at Visit 1 (Day 1) and at visits for re-initiation of study treatment 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 treatment.

BP measurements will be performed at all scheduled study visits. In addition, unscheduled BP measurements may be performed at any time during the study. At Visit 1 (Day 1) and on days of re-initiation of study treatment, [see Section 5.1.10], SBP and DBP will be measured at pre-dose and hourly (+/− 15 min) thereafter for a minimum of 4 hours and up to 12 hours post-dose.[#]

#Subjects who do not meet any of the Criteria for Cardiac Monitoring at Site (See protocol Section 5.1.9) may re-initiate the study drug at home without post-dose cardiac monitoring

Subjects may be discharged from cardiac monitoring if they meet the discharge criteria before 12 hours post-dose but no sooner than 4 hours post-dose [see Section 5.1.10]. If the subject does not meet the defined discharge criteria at 12 hours post-dose, the subject will be permanently discontinued from the study treatment, but will continue the cardiac monitoring. Additional BP measurements will be performed until changes are no longer clinically relevant (i.e., discharge criteria are met; see Section 5.1.10), or until medically indicated.

7.5.3 Body temperature

Body temperature will be assessed at all scheduled study visits. Body temperature will also be assessed at unscheduled visits for relapses. In addition, body temperature measurements may be performed at any time during the study, as part of unscheduled visits.

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.

7.5.4 Pulse rate

Pulse rate will be assessed at visits where no 12-lead ECG is performed as indicated in Table 1 and Table 2. Pulse rate may also be assessed at any time during the study, as part of unscheduled visits 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.

7.5.5 Spirometry

Spirometry tests will be performed at visits indicated in Table 1 and Table 2. In addition, unscheduled spirometry must be conducted in the event of persistent respiratory symptoms (e.g., dyspnea).

It is highly recommended that all spirometry assessments are performed in the morning, and prior to study treatment intake. Subjects must refrain from taking short-acting-beta-agonists (e.g.,

salbutamol) for 6 hours and long-acting-beta-agonists for 24 hours prior to spirometry testing. If taken, the test should be rescheduled. To perform the spirometry test, subjects will be rested for a minimum of 5 minutes prior to start.

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 (FEF25%, FEF50%, FEF75%, respectively); the mean FEF between 25% and 75% of the FVC (FEF25–75%); and the peak exploratory flow.

Spirometry tests will be conducted according to the ATS/ERS guidelines [Miller 2005a, 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.

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.

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.

7.5.6 DL_{CO} sub-study

Subjects who participated in the DL_{CO} sub-study during the core study will be asked to continue their participation in the DL_{CO} sub-study during the extension study. The subjects may choose to continue participation by providing consent under a separate informed consent for the DL_{CO} sub-study. The assessment will be conducted at visits indicated in Table 1 and Table 2. In addition, unscheduled DL_{CO} tests may be performed at any time during the study.

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.

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). There must be a minimal interval of at least 4 minutes between each effort performed. Data from all DL_{CO} efforts collected during a session will be captured in the eCRF.

The mean of two best within session DL_{CO} efforts 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 hemoglobin (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.

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 treatment 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 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.

7.5.7 Ophthalmologic assessments

Ophthalmologic assessments will be performed at visits indicated in Table 1. In addition, unscheduled ophthalmological examination will be done in the event of visual symptoms or findings suggestive of active uveitis [see Section 5.1.12.7.1].

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 if there is a suspicion of active uveitis during the study (unless contra-indicated according to the ophthalmologist) [see Section 5.1.12.7]. While the visual acuity and ocular pressure measurement themselves may be performed by a delegate

(e.g., technician, optometrician), the review and interpretation must be performed by the ophthalmologist. Conduct, review, and interpretation of all other ophthalmological exams must be performed by the ophthalmologist. 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.

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.

7.5.8 Optical Coherence Tomography

OCT was assessed at visits indicated in Table 1 and Table 2 in Protocol Versions 1 to 5. The requirement for scheduled OCT assessments was removed from Protocol Version 6 onwards. 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 if active uveitis is diagnosed during the study [see Section 5.1.12.7]. While the OCT exam may be performed by a delegate (e.g., technician, optometrician), the review and interpretation must be performed by the ophthalmologist.

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.

7.5.9 Weight

Body weight will be measured at visits indicated in Table 1. In addition, unscheduled body weight measurement may be performed at any time during the study. Data will be collected in the eCRF.

7.5.10 Physical examination

Physical examination is performed by the principal investigator or treating neurologist at visit indicated in Table 1 and Table 2. In addition, unscheduled physical examination may be performed at any time during the study.

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 7.4.1] does not obviate the requirement for the examination of the neurological function as part of the physical examination by the treating neurologist.

7.5.11 Dermatological examination

A complete skin examination will be performed by a dermatologist at visits indicated in Table 1 and Table 2. In addition, unscheduled complete skin examination may be performed by the dermatologist at any time during the study, if indicated.

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.

7.5.12 Laboratory assessments

7.5.12.1 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 the sponsor's clinical database.

Under specific circumstances, 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.

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

The central laboratory will provide all laboratory results by fax or normal mail to the site. Any alerts will be indicated on the report [see Section 5.1.12].

- Teriflunomide plasma concentration: A plasma sample will be taken on Day 1 for a teriflunomide test (results to be communicated to site only if needed, e.g., in the case of AEs where the measurement of exposure to teriflunomide is of relevance).

- **Important note:** Additional teriflunomide testing is no longer required with the approval of protocol version 5. Under protocol versions 1 to 4, teriflunomide plasma concentration may be assessed at Week 19 ± 7 days and at Week 21 ± 7 days and may be repeated at Visit 5 (Week 24) and at following visits if necessary until two consecutive test results confirming plasma concentration of teriflunomide <0.02 mg/L are available.

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.

7.5.12.2 Laboratory tests

Blood samples will be drawn when applicable, before the morning administration of study medication visits indicated in Table 1. Fasting conditions are recommended but not required. Unscheduled laboratory tests may be performed at any time during the study.

Urinalysis will be assessed using dipsticks at visits indicated in Table 1 and Table 2. In addition, unscheduled urinalysis may be performed at any time during the study.

Hematology

- Red blood cell count
- Total and differential white blood cell counts (basophils, eosinophils, lymphocytes, monocytes, neutrophils, band forms)

- Platelet count
- Hb
- Hematocrit

Clinical chemistry

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

Biomarkers and additional analyses in the event of infections

- A serum sample will be taken at Visit 1 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 and for analysis of biomarkers.

Immunogenicity evaluations

- At every scheduled visit after approval of protocol version 5, a 5 mL serum sample will be taken for immunogenicity evaluations (e.g., anti-SARS-CoV-2 antibody titers, SARS-CoV-2 neutralization assays).

Pregnancy test

A serum and urine pregnancy tests for WOCBP and will be performed at visits indicated in Table 1 and Table 2 and if pregnancy is suspected during the study. Additionally, urine pregnancy tests will be performed at home every 4 weeks (±7 days) between the visits. Subjects will communicate the result (telephone call) of the tests to the principal investigator / treating neurologist.

Female subjects who interrupt the study treatment because of planned pregnancy will be exempted from any protocol-mandated pregnancy tests after the first positive pregnancy test and until 30 days before study drug re-initiation.

Serum pregnancy testing results will be automatically transferred from the central laboratory database to the sponsor's clinical database. Urine pregnancy testing results will be recorded in the eCRF. In the event 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.

Teriflunomide plasma level tests:

The results of the teriflunomide test conducted with the plasma sample taken on Day 1 will be communicated to site only if needed, e.g., in the case of AEs where the measurement of exposure to teriflunomide is of relevance.

During the early stages of the study (protocol versions 1 through 4), additional plasma teriflunomide tests may have been required to confirm that teriflunomide plasma levels were sufficiently low (<0.02 mg/L) before fertile male participants could stop contraceptive requirements and in the case of planned pregnancies (see Section 5.1.12.5). Following approval of protocol version 5, these tests are no longer required now that all ongoing subjects have been off teriflunomide for over 2 years (last subject entered this extension study on 20-May-2019) [Aubagio® USPI, Aubagio® SmPC].

The plasma teriflunomide concentration will be determined by using a high-performance liquid chromatography method [Sobhani 2010].

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

The electronic self-rated version of the Columbia-Suicide Severity Rating Scale (eC-SSRS) is used to reliably and consistently monitor subjects for suicidal ideation and behavior during the study. It will be completed at visits indicated in Table 1 and Table 2.

The eC-SSRS assesses lifetime suicidality during an initial baseline evaluation, and then prospectively monitors ideations and behaviors at subsequent follow-up assessments. At each visit the eC-SSRS is completed, the treating neurologist will review the responses provided by the subject and assess the findings. The eC-SSRS is a fully structured clinical interview designed and developed for electronic administration. Subjects will be asked to respond to standardized clinical questions aimed at measuring the severity of suicidal ideation (rated on a 5-point ordinal scale), the levels of suicidal behavior, and the category self-injurious behavior without suicidal intent. Any 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, and after the SF-36v2™ has been completed. Preferably, subjects would complete the eC-SSRS while waiting for their appointment before any interaction with health care providers.

The clinical site will provide either a telephone, tablet, or computer for the subject to complete the eC-SSRS. A sample of the telephone administered eC-SSRS (in English) is provided as Appendix 8. The data will be collected by a vendor who will send the results to the sponsor.

In exceptional cases only (e.g., problem with the server), a clinician administered C-SSRS (paper version) may be administered by an adequately qualified and trained clinician. The clinician administered C-SSRS (paper version) does not need to be recorded in the eCRF. However, any subject who reaches a C-SSRS suicidal ideation score of 4 or above, or who responds "yes" on the C-SSRS suicidal behavior item must be referred to an appropriate health professional, as described above. Furthermore, an eC-SSRS should be completed at the next applicable visit (provided the reason for conducting a paper C-SSRS is no longer applicable).

The sponsor has been granted a license agreement for the use of the eC-SSRS and the clinician administered C-SSRS (paper version).

7.7 Quality of life assessments

7.7.1 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 visits indicated in Table 1 and Table 2.

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. 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 9.

The sponsor 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.

7.8 Total blood volume

The total blood volume to be drawn per subject during the entire course of the study is described in Table 10.

Table 10 Minimum total blood volume to be drawn per subject

Test	Number of tests	Volume per test	Total volume per test throughout the study
Hematology[1,2]	26	3 mL	78 mL
Blood chemistry[3]	26	7.5 mL	195 mL
INR	26	3 mL	78 mL
Teriflunomide plasma concentration[4]	1	5 mL	5 mL
Serum sample for immunogenicity evaluations [5]	10	5 mL	50 mL
Total blood volume drawn throughout the study: approximately 406 mL*			

1. Additional sample may be needed for viral serology in the event of infection
2. Additional samples may be needed in the event of lymphocytes < 200 cells/µL or unscheduled visits.
3. Includes serum pregnancy tests at select visits for WOCBP [see Table 1].
4. Additional teriflunomide plasma concentration tests may be necessary in order to obtain two consecutive test results confirming plasma concentration of teriflunomide <0.02 mg/L are available. NB: teriflunomide plasma concentration tests are optional and no longer required following approval of protocol version 5.
5. To be collected in all subjects at all visits following approval of protocol version 5. Note: the number of visits remaining per subject was calculated during preparation of protocol version 5. As of 3 June 2021, the mean number of visits remaining in the study (in those subjects with >1 visit remaining) was 10 (range: 2 to 25).

* Note:

- More tests may occur as the subject may remain in the study until ponesimod becomes available on the market.
- If a sample is lost or not evaluable, a new sample may need to be taken if deemed necessary by the investigator

INR = International Normalized Ratio; WOCBP = women of childbearing potential.

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 and Table 2.

The schedule of visit dates should be established at the time of enrollment (Visit 1). To the extent possible, subjects will be expected to adhere to the established visit schedule. The assessments pertaining to a visit may be performed within the allowed time window.

- The timepoint for every visit refers to Day 1 (first dosing of study treatment).
- When scheduling the different assessments for a subject visit, the following should be taken into account:
  - At Day 1 (first dosing of study treatment) and on the days of re-initiation of study treatment 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 treatment, 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.
- Recommended 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.

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.

Unscheduled visits may be performed at any time during the study. Depending on the reason for the unscheduled visit (e.g., AE), 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 Core study follow up period and transition into the extension study

8.1.1 Core study – FU1

Subjects eligible for this study will have completed the FU1 visit of the core study (14–22 days after the last dose of the study drug in the core study). Day 1 (Visit 1) of the extension may occur on the same day as the core study FU1 visit provided the results from assessments required for eligibility [see Section 4.3] are available and based on investigator judgment, the accelerated elimination procedure has been successfully completed prior to the first dose administration in the extension

study. The investigator should make every effort to minimize the duration between EOT of the core study and Day 1 of the extension study. Ideally the treatment interruption should last no longer than 15 days.

The core study FU1 visit includes the following assessments:

- MS relapse
- Recording of changes in concomitant medications
- Assessment and recording in the eCRF of methods of contraception (for WOCBP only)
- Body temperature
- SBP/DBP
- 12-lead ECG
- Spirometry
- DL_{CO} (if applicable; under the responsibility of the pulmonologist)
- Hematology, blood chemistry
- Urinalysis
- Accelerated elimination procedure compliance assessment
- Urine pregnancy test for WOCBP
- Recording of AEs and SAEs.

8.1.2 Core study – abbreviated FU2

For subjects transitioning to the extension study, an abbreviated FU2 visit will take place only if the compliance with teriflunomide elimination procedure was deemed not sufficient by the investigator at the core study FU1. The core study abbreviated FU2 visit should occur 23–37 days after last drug intake and includes the following assessments:

- Recording of changes in concomitant medications
- Accelerated elimination procedure compliance assessment
- Recording of AEs and SAEs
- MS relapse assessment.

8.2 Pre-treatment period

The pre-treatment period is included within Visit 1 and begins with the subject signing the informed consent at Visit 1. It continues until the administration of study treatment on Day 1. Visit 1 would ideally start on the day of the core study FU1 or abbreviated FU2 visits (whichever applies), but no later than 1 day after these visits.

8.2.1 Visit 1 – pre-dose

Enrollment and Visit 1 starts with the signing of the informed consent, which would ideally occur on the day of FU1 or FU2 visit (whichever applies). In all cases, informed consent should be signed no later than one day after FU1 or FU2 visit (whichever applies).

The following assessment must be performed pre-dose at Visit 1: inclusion/exclusion criteria concomitant medications, MS relapse, body temperature, ECG, SBP/SDP and pregnancy test. The remaining assessments (i.e., medical history, EDSS/FS and physical examination) can be performed up to 7 days after the subject has signed informed consent and before the first dose of study treatment.

The following assessments must be performed pre-dose:

- Informed consent
- Inclusion/exclusion criteria
- Demographics
- Medical History
- EDSS/FS
- MS relapse (pre-dose Day 1)[*/**]
- Recording of concomitant medications[*/**]
- Assessment and recording in the eCRF of methods of contraception (for WOCBP only)
- Physical examination
- 12-lead ECG (pre-dose Day 1)
- Body temperature (pre-dose Day 1)[*]
- SBP/DBP (pre-dose Day 1)[*]
- Urine pregnancy test (pre-dose Day 1)[*/**]
- Recording of AEs/SAEs

[*]These assessments do not need to be repeated if Day 1 occurs the same day as the core study FU1 visit.
[**]These assessments do not need to be repeated if Day 1 occurs the same day as the core study abbreviated FU2 visit.

8.3 Treatment period

The treatment period consists of Visit 1 to the EOT visit.

8.3.1 Visit 1 – post-dose (includes first dosing)

The treatment period starts with the first dosing of study treatment, which defines Day 1 of the extension study. Visit 1 transitions into the treatment period with the administration of study treatment on Day 1.

Ideally, all assessments and procedures of Visit 1 including first dosing of study treatment and post-dose cardiac monitoring would occur on the same day as the core study FU1 or abbreviated FU2 (whichever applies). In all cases, all assessments and procedures of Visit 1 must be completed (i.e., study treatment start) no later than 7 days after signing the informed consent.

The following assessments are performed:

- Enroll via IRT to obtain study treatment kit number;
  - Dispensing of study treatment;

- SBP/DBP hourly (+/− 15 min) for up to 12 hours post-dose with a minimum of 4 hours post-dose;
- 12-lead ECG hourly (+/− 15 min) until the evaluation of the ECG performed at 4 hours post-dose is available. For subjects not meeting the discharge criteria at 4 hours post-dose, further ECGs will be performed every hour for up to 12 hours post-dose until the discharge criteria are met;
- Recording of AEs/SAEs;
- Blood sample for teriflunomide test (results to be communicated to site only if needed, e.g., in the case of AEs where the measurement of exposure to teriflunomide is of relevance);
- Blood sample for virology (to be analyzed in case of a viral infection and the virus can be identified);
- Remind WOCBP and fertile men to use the methods of contraception defined for this study (for WOCBP throughout the study until at least 30 days after study treatment discontinuation and until 6 weeks after the first of two consecutive tests confirming plasma teriflunomide level <0.02 mg/L[#], and for fertile men, until 6 weeks after the first of two consecutive tests confirming plasma teriflunomide level <0.02 mg/L[#]). The reminders must be documented in the hospital chart;
- Schedule an appointment for next visit and instruct subject to:
  - come fasted to the site (recommended)
  - bring back all blister packs (used, partially used and unused blister packs)
  - 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 will need to gradually up-titrate from 2 mg to 10 mg during Day 1 to 14. As there is no site visit planned until Day 15, subjects will be instructed during Visit 1 on how to perform the gradual up-titration. The subject will be instructed to contact the site if she/he has any questions or problems.

Important note: Teriflunomide testing is no longer required with the approval of protocol version 5

8.3.2 Visit 2 – Day 15

The visit window for this visit is −1 / +3 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 3 days prior to or after this visit date. The visit includes:

- MS relapse
- 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)

- Pulse rate (pre-dose)
- Hematology, blood chemistry
- Study medication accountability and compliance review
- IRT call and study treatment dispensing
- Recording of AEs and SAEs
- Remind WOCBP and fertile men to use the methods of contraception defined for this study (for WOCBP throughout the study until at least 30 days after study treatment discontinuation and until 6 weeks after the first of two consecutive tests confirming plasma teriflunomide level <0.02 mg/L[#], and for fertile men, until 6 weeks after the first of two consecutive tests confirming plasma teriflunomide level <0.02 mg/L[#]). The reminders must be documented in the hospital chart.
- Schedule an appointment for next visit and instruct subject to:
  - Come fasted to the site (recommended)
  - Bring back all bottles
  - 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.

Important note: Teriflunomide testing is no longer required with the approval of protocol version 5

8.3.3 Visit 3 – Week 4

The visit window for these visits is ± 7 days. Measurement of SBP/DBP (pre-dose) defines the date of the visit. All other assessments may be performed up to 7 days prior to or after this visit date. The visits include:

- MS relapse
- 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)
- Pulse rate (pre-dose)
- Spirometry (pre-dose)
- DL_{CO} (if applicable; pre-dose, under the responsibility of the pulmonologist)
- Hematology, blood chemistry
- Urine pregnancy test for WOCBP
- Study medication accountability and compliance review
- Recording of AEs and SAEs
- Remind WOCBP and fertile men to use the methods of contraception defined for this study (for WOCBP throughout the study until at least 30 days after study treatment discontinuation and until 6 weeks after the first of two consecutive tests confirming plasma teriflunomide level <0.02 mg/L[#] and for fertile men, until 6 weeks after the first of two consecutive tests

confirming plasma teriflunomide level <0.02 mg/L[#]). The reminders must be documented in the hospital chart.

- Schedule an appointment for next visits, including hematology, blood chemistry to be collected at Week 8, and instruct subject to:
  - Come fasted to the site (recommended)
  - Bring back all study treatment bottles
  - 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.

Important note: Teriflunomide testing is no longer required with the approval of protocol version 5

8.3.4 Additional safety laboratory tests until Week 24 (Weeks 8, 16 and 20)

The test window is ± 7 days. Under specific circumstances (e.g., subject lives far away from the site and cannot return every 4 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 [see Section 7.5.12.1].

8.3.5 Visit 4 – Week 12

The visit window for these visits is ± 7 days. The IRT call defines the date of the visit. All other assessments may be performed up to 7 days prior to or after this visit date. The visits include:

- EDSS/FS
- MS relapse
- SDMT
- 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)
- Pulse rate (pre-dose)
- Ophthalmological examination (under the responsibility of the ophthalmologist)
- OCT (under the responsibility of the ophthalmologist)[2]
- Hematology, blood chemistry
- Urine pregnancy test for WOCBP
- Study medication accountability and compliance review
- IRT call and study treatment dispensing
- Recording of AEs and SAEs

[2] Scheduled OCT assessments are only applicable to Global Protocol Version 1 to 5. The requirement for OCT assessments was removed from Global Protocol Version 6 onwards.

- Remind WOCBP and fertile men to use the methods of contraception defined for this study (for WOCBP throughout the study until at least 30 days after study treatment discontinuation and until 6 weeks after the first of two consecutive tests confirming plasma teriflunomide level <0.02 mg/L[#] and for fertile men, until 6 weeks after the first of two consecutive tests confirming plasma teriflunomide level <0.02 mg/L[#]). Schedule an appointment for next visits, including hematology, blood chemistry to be collected at Weeks 16 and 20, and instruct subject to:
  - Come fasted to the site (recommended)
  - Bring back all study treatment bottles
  - 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.

Important note: Teriflunomide testing is no longer required with the approval of protocol version 5

8.3.6 In-between-visit telephone calls until Week 240 (every 6 weeks)

The site will contact the subject in between 12-weekly visits (e.g., Visit 5-Week 24, Visit 6-Week 36). These telephone calls will be conducted either at Weeks 18, 30, 42, and up to Week 234 (+/− 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.

8.3.7 Visit 5 – Week 24

The visit window for these visits is ± 14 days. The IRT call defines the date of the visit. All other assessments may be performed within the visit window of this visit date. The visits include:

- EDSS/FS
- MS relapse
- SDMT
- SF-36 v2
- Recording of changes in concomitant medications
- Assessment and recording in the eCRF of methods of contraception (for WOCBP only)
- Physical examination
- Body temperature
- SBP/DBP (pre-dose)
- Pulse rate (pre-dose)
- Ophthalmological examination (under the responsibility of the ophthalmologist)
- OCT (under the responsibility of the ophthalmologist)[3]
- Hematology, blood chemistry

[3] Scheduled OCT assessments are only applicable to Global Protocol version 1 to 5. The requirement for OCT assessments was removed from Protocol Version 6 onwards.

- Urinalysis
- Urine pregnancy test for WOCBP
- Study medication accountability and compliance review
- IRT call and study treatment dispensing
- Recording of AEs and SAEs
- Remind WOCBP and fertile men to use the methods of contraception defined for this study (for WOCBP throughout the study until at least 30 days after study treatment discontinuation and until 6 weeks after the first of two consecutive tests confirming plasma teriflunomide level <0.02 mg/L[#] and for fertile men, until 6 weeks after the first of two consecutive tests confirming plasma teriflunomide level <0.02 mg/L[#], if applicable). Schedule an appointment for next visit and instruct subject to:
  - Come fasted to the site (recommended)
  - Bring back all study treatment bottles
  - 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.

Important note: Teriflunomide testing is no longer required with the approval of protocol version 5

8.3.8 Visits 6, 8, 9, 10, 12, 13, 14, 16, 17, 18, 20, 21, 22; Weeks 36, 60, 72, 84, 108, 120, 132, 156, 168, 180, 204, 216, 228

The visit window for these visits is ± 14 days. The IRT call defines the date of the visit. All other assessments may be performed within the window of this visit date. The visits include:

- EDSS/FS
- MS relapse
- 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)
- Pulse rate (pre-dose)
- Hematology, blood chemistry, and (following approval of protocol version 5) a serum sample for immunogenicity evaluations (e.g., anti SARS-CoV-2 antibody testing) will be collected for all subjects
- Urinalysis
- Urine pregnancy test for WOCBP (NB: female subjects who interrupt the study treatment because of planned pregnancy will be exempted from any protocol-mandated pregnancy tests after the first positive pregnancy test and until 30 days before study drug re-initiation. Study medication accountability and compliance review
- IRT call and study treatment dispensing
- Recording of AEs and SAEs

- Remind WOCBP and fertile men to use the methods of contraception defined for this study (for WOCBP throughout the study until at least 30 days after study treatment discontinuation and until 6 weeks after the first of two consecutive tests confirming plasma teriflunomide level <0.02 mg/L[#] and for fertile men, until 6 weeks after the first of two consecutive tests confirming plasma teriflunomide level <0.02 mg/L[#], if applicable). Schedule an appointment for next visit and instruct subject to:
  - Come fasted to the site (recommended)
  - Bring back all study treatment bottles
  - 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.

Important note: Teriflunomide testing is no longer required with the approval of protocol version 5

8.3.9 Visits 7, 11, 15, 19 - Weeks 48, 96, 144, 192

The visit window for these visits is ± 14 days. The IRT call defines the date of the visit. All other assessments may be performed within the window of this visit date. The visits include:

- EDSS/FS
- MS relapse
- MSFC
- SDMT
- SF-36 v2
- eC-SSRS
- MRI
- Recording of changes in concomitant medications
- Assessment and recording in the eCRF of methods of contraception (for WOCBP only)
- Physical examination
- Dermatological examination
- Body weight
- Body temperature
- SBP/DBP (pre-dose)
- 12-lead ECG (pre-dose)
- Ophthalmological examination (under the responsibility of the ophthalmologist)
- OCT (under the responsibility of the ophthalmologist)[4]
- Spirometry (pre-dose)
- DL_{CO} (if applicable; pre-dose, under the responsibility of the pulmonologist)

[4] Scheduled OCT assessments are only applicable to Global Protocol version 1 to 5. The requirement for OCT assessments was removed from Protocol Version 6 onwards.

- Hematology, blood chemistry, and (following approval of protocol version 5) a serum sample for immunogenicity evaluations (e.g., anti SARS-CoV-2 antibody testing) will be collected for all subjects
- Urinalysis
- Serum pregnancy test for WOCBP (NB: female subjects who interrupt the study treatment because of planned pregnancy will be exempted from any protocol-mandated pregnancy tests after the first positive pregnancy test and until 30 days before study drug re-initiation. Study medication accountability and compliance review
- IRT call and study treatment dispensing
- Recording of AEs and SAEs
- Remind WOCBP and fertile men to use the methods of contraception defined for this study (for WOCBP throughout the study until at least 30 days after study treatment discontinuation and until 6 weeks after the first of two consecutive tests confirming plasma teriflunomide level <0.02 mg/L[#] and for fertile men, until 6 weeks after the first of two consecutive tests confirming plasma teriflunomide level <0.02 mg/L[#], if applicable). Schedule an appointment for next visit and instruct subject to:
  - Come fasted to the site (recommended)
  - Bring back all study treatment bottles
  - 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.

Important note: Teriflunomide testing is no longer required with the approval of protocol version 5

8.3.10 EOT Visit – Week 240

The visit window for this visit is ± 14 days. The ECG assessment defines the date of the visit. All other assessments may be performed within the window of this visit date. If a study treatment interruption is transformed into a permanent premature discontinuation, the EOT visit should be done as soon as possible, preferably 7 days after the decision to discontinue was made.

For those subjects completing study treatment due to the availability of commercially available ponesimod, an EOT visit should be conducted preferably within 7 days after stopping study treatment. Commercially available ponesimod may be initiated on the day after last intake of study treatment.

The visits include:

- EDSS/FS
- MS relapse
- MSFC
- SDMT

- SF-36 v2
- eC-SSRS
- MRI (in case of premature study treatment discontinuation, the MRI assessment at EOT does not need to be performed if the EOT visit occurs within 4 weeks of the MRI assessment at Visits 7, 11, 15, or 19 (Weeks 48, 96, 144, or 196)
- Recording of changes in concomitant medications
- Assessment and recording in the eCRF of methods of contraception (for WOCBP only)
- Physical examination
- Dermatological examination
- Body weight
- Body temperature
- SBP/DBP
- 12-lead ECG
- Ophthalmological examination (under the responsibility of the ophthalmologist)
- OCT (under the responsibility of the ophthalmologist)[5]
- Spirometry
- DL_{CO} (if applicable; pre-dose, under the responsibility of the pulmonologist)
- Hematology, blood chemistry, and (following approval of protocol version 5) a serum sample for immunogenicity evaluations (e.g., anti SARS-CoV-2 antibody testing) will be collected for all subjects
- Urinalysis
- Serum pregnancy test for WOCBP (NB: female subjects who interrupt the study treatment because of planned pregnancy will be exempted from any protocol-mandated pregnancy tests after the first positive pregnancy test and until 30 days before study drug re-initiation. Study medication accountability and compliance review
- Recording of AEs and SAEs
- Remind WOCBP and fertile men to use the methods of contraception defined for this study (for WOCBP throughout the study until at least 30 days after study treatment discontinuation and until 6 weeks after the first of two consecutive tests confirming plasma teriflunomide level <0.02 mg/L[#] and for fertile men, until 6 weeks after the first of two consecutive tests confirming plasma teriflunomide level <0.02 mg/L[#], if applicable). Schedule an appointment for next visit and instruct subject to:
  - Come fasted to the site (recommended)
  - Bring back all study treatment bottles
  - 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.

[5] Scheduled OCT assessments are only applicable to Global Protocol version 1 to 5. The requirement for OCT assessments was removed from Protocol Version 6 onwards.

Important note: Teriflunomide testing is no longer required with the approval of protocol version 5

8.4 Follow-up period

The follow-up period includes the EOS visit 30 days after the last day of study treatment intake.

8.4.1 EOS Visit

This visit will be conducted 30–44 days after the permanent discontinuation of study treatment. All assessments should be conducted within the visit window. The last assessment conducted for the study will define the visit date.

The EOS visit should also be conducted for subjects who have switched to commercially available ponesimod.

The visits include:

- EDSS/FS
- MS relapse
- Recording of changes in concomitant medications
- Assessment and recording in the eCRF of methods of contraception (for WOCBP only)
- Body temperature
- SBP/DBP
- 12-lead ECG
- Ophthalmological examination (under the responsibility of the ophthalmologist)
- OCT (under the responsibility of the ophthalmologist)[6]
- Spirometry
- DL_{CO} (if applicable; under the responsibility of the pulmonologist)
- Hematology, blood chemistry, and (following approval of protocol version 5) a serum sample for immunogenicity evaluations (e.g., anti SARS-CoV-2 antibody testing) will be collected for all subjects
- Urinalysis
- Serum pregnancy test for WOCBP
- Recording of AEs and SAEs
- Remind WOCBP and fertile men to use the methods of contraception defined for this study until 6 weeks after the first of two consecutive tests confirming plasma teriflunomide level <0.02 mg/L[#] if such test results have not been obtained prior to EOS visit.

Important note: Teriflunomide testing is no longer required with the approval of protocol version 5

[6] Scheduled OCT assessments are only applicable to Global Protocol version 1 to 5. The requirement for OCT assessments was removed from Protocol Version 6 onwards.

8.5 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, or may be required such as in the case of a planned pregnancy. These visits include (but are not limited to) those performed due to safety (e.g., occurrence of an AE, laboratory abnormalities, planned study treatment interruption), administration of study treatment (e.g., re-initiation, return of unused study medication, need to initiate treatment with a QT-prolonging drug), and/or MS related issues (e.g., relapses).

The date of the visit and the reason for such visits as well as any data related to study assessments performed at unscheduled visits will be recorded in the eCRF.

8.5.1 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 10] and the relapse symptoms form [see Appendix 11] 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: SBP/DBP, 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 subject 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 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:

- Recording of changes in concomitant medications
- Recording of AEs and SAEs
- Schedule an appointment for next visit, unless already done and instruct subject to:
  - Preferably come fasted to the site and 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.

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 count as the ones of this regular visit.

8.5.2 Unscheduled visits (any other assessment; U1, U2, U3, etc.)

An unscheduled site visit may be performed at any time during the study (between scheduled visits), as necessary, at the investigator's discretion. The date of the visit and the reason for such visits as well as any data related to study assessments performed at unscheduled visits will be recorded in the eCRF. During such visits, any of the following assessments may be performed at the investigator's discretion:

- EDSS/FS
- MS Relapse (if the subject is meeting the principal investigator / treating neurologist)
- MRI
- Assessment of concomitant medications
- Assessment of methods of contraception (for WOCBP only)
- Physical examination
- Dermatological examination
- Body temperature
- Body weight
- SBP/DBP

- Teriflunomide plasma concentration[#]
- Pulse rate (to be assessed only if no 12-lead ECG is performed)
- Ophthalmological examination (e.g., presence of visual symptoms suggestive of active uveitis [see Section 5.1.12.7])
- OCT (e.g., presence of visual symptoms suggestive of macular edema or active uveitis [see Section 5.1.12.7])
- Complete laboratory tests including: hematology, blood chemistry, viral serology, urinalysis, urine or serum pregnancy test (for WOCBP only).
- IRT call – return of study treatment bottles and unused medication, and dispensing of new bottles, if appropriate.
- Assessment of AEs and SAEs.

Important note: Teriflunomide testing is no longer required with the approval of protocol version 5

Additional unscheduled spirometry will have to be conducted in the event of respiratory symptoms (e.g., dyspnea) and in the event of FEV_1 or FVC at a scheduled visit showing decrease from extension study baseline by >30% 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 7.5.12.2 need 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 7.5.12].

8.5.3 Additional unscheduled visits for re-initiation of study treatment (I1, I2, etc.)

As described in detail in Section 5.1.9, subjects who miss taking the dose of study drug for 4 or more consecutive days will need to re-initiate study drug using the original up-titration scheme.

In such cases, there will be one or two visits:

- One visit on the day of re-initiation (D1) for all subjects;
- An additional visit 14 days (±1 day) after the day of re-initiation (D15) only mandated for subjects with cardiovascular risk factors (see Section 5.1.9) but may be scheduled for any subject at the discretion of the investigator / treating neurologist.

The following assessments/procedures must be done during the visit on the day of re-initiation (D1):

- MS relapse (if the subject is meeting the principal investigator / treating neurologist)
- Body temperature;
- SBP/DBP pre-dose and hourly (+/− 15 min) for up to 12 hours post-dose (under the responsibility of the first-dose administrator)*;

- 12-lead ECG pre-dose and hourly (+/− 15 min) for up to 12 hours post-dose (under the responsibility of the first-dose administrator)*;
- IRT call and study treatment dispensing§;
- Recording of AEs and SAEs;
- Recording of changes in concomitant medications;
- The discharge criteria will be applied as described for Day 1. Subjects may be discharged from cardiac monitoring if they meet the discharge criteria before 12 hours post-dose but no sooner than 4 hours post-dose [see Section 5.1.10].

* All subjects are required to have a pre-dose assessment. Only subjects with cardiovascular risk factors [see Section 5.1.9] are required to be monitored for at least 4 hours and up to 12 hours post-dose at the study site. In this case, discharge criteria will be applied as described for Day 1 [see Section 5.1.10]. Subjects without cardiovascular risk factors may re-initiate study drug at home or at site and be monitored for at least 4 hours post-dose at the discretion of the investigator / treating neurologist.

§ Subjects with cardiovascular risk factors [see Section 5.1.9] will receive only the up-titration kit. Subjects without cardiovascular risk factors [see Section 5.1.9] and who re-initiated at home will receive both the up-titration kit and blisters/bottles for maintenance.

For subjects attending the visit 14 days after the day of re-initiation (if applicable), the following assessments need to be done:

- MS relapse (if the subject is meeting the principal investigator / treating neurologist);
- Body temperature;
- SBP/DBP (pre-dose);
- 12-lead ECG (pre-dose);
- IRT call – return of study treatment blisters/bottles and unused medication, and dispensing of new blisters/bottles, if appropriate;
- Recording of AEs and SAEs.

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 treatment.

These visits for re-initiating study treatment 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 must be performed in addition.

8.5.4 Additional unscheduled visit 30 days after study treatment interruption due to planned pregnancy with intention of study treatment re-initiation post-partum

As described in Section 5.1.12.4, female participants who wish to become pregnant must have a negative pregnancy test at an unscheduled visit 30 days after they interrupt study treatment before they can interrupt the contraception. In addition, interruption of contraception should take place

after Visit 5 (Week 24) and at earliest 6 weeks after the first of two consecutive tests confirming plasma teriflunomide level <0.02 mg/L[#] and at least 30 days after study treatment discontinuation.

During this visit, the following assessment will be performed:

- EDSS/FS
- MS Relapse (if the subject is meeting the principal investigator / treating neurologist)
- MRI
- Assessment of concomitant medications
- Assessment of methods of contraception (for WOCBP only)
- Physical examination
- Dermatological examination
- Body temperature
- Body weight
- SBP/DBP
- Spirometry
- Pulse rate (to be assessed only if no 12-lead ECG is performed)
- Ophthalmological examination (e.g., presence of visual symptoms suggestive of active uveitis [see Section 5.1.12.7])
- OCT (e.g., presence of visual symptoms suggestive of macular edema or active uveitis [see Section 5.1.12.7])
- Complete laboratory tests including: hematology, blood chemistry, viral serology, urinalysis and serum pregnancy test.
- Recording of AEs and SAEs.

The principal investigator / treating neurologist or the study nurse must instruct/remind the subject to interrupt the contraception until after delivery and to follow all the visits scheduled as per protocol during the drug interruption period and until the study treatment has been re-started or permanently discontinued

Important note: Teriflunomide testing is no longer required with the approval of protocol version 5

8.5.5 Additional unscheduled visits for eligibility assessment for re-initiation of study treatment for female subjects who interrupted the study treatment for planned pregnancy and who wish to re-start the study treatment after delivery

As described in Section 5.1.12.4, female subjects who interrupted the study treatment for planned pregnancy and who wish to re-start the study treatment after delivery will need to be assessed for the eligibility for the study treatment restart. Unless the subject has been treated with a DMT (interferon β or glatiramer acetate) during the pregnancy and post-partum, this visit should take place as soon as possible after delivery in order to minimize the post-partum period without MS treatment. In addition, this visit should take place 30 (± 5) days before the study drug re-initiation.

During this visit, the following assessments must be performed before study drug administration:

Urine pregnancy test first and, if urine pregnancy test is negative:

- EDSS/FS assessment
- MS relapse
- MRI examination
- Recording of changes in concomitant medications, if any
- Assessment and recording in the eCRF of methods of contraception
- Physical examination
- Body temperature
- Body weight
- SBP/DBP
- Ophthalmological examination (under the responsibility of the ophthalmologist)
- OCT (e.g., presence of visual symptoms suggestive of macular edema or active uveitis [see Section 5.1.12.7])
- Spirometry, DL_{CO} (if applicable; under the responsibility of the pulmonologist)
- Hematology, blood chemistry
- 12-lead ECG
- Urinalysis
- Recording of AEs and SAEs
- Remind the subject to use the methods of contraception defined for this study. The reminders must be documented in the hospital chart.
- Confirmation that the subject did/does not fulfill any protocol criteria for permanent study treatment discontinuation [see Section 5.1.12] at any of the previous visits or at the unscheduled visit for re-start of the study medication except the planned pregnancy.
- If the subject has been treated with a DMT (interferon β or glatiramer acetate) during and after pregnancy, the subject must be instructed to interrupt the treatment 7 days before re-start of ponesimod and this instruction must be documented in the hospital records.

If all the eligibility criteria for study treatment restart which are assessable at this visit are fulfilled, schedule an appointment for next visit (i.e., additional unscheduled visits for re-initiation of study treatment) 25–35 days later and instruct the subject to 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.

The subject must be instructed/reminded that that breastfeeding must be completely stopped before study drug re-initiation.

If the urine pregnancy test is positive, the subject is not eligible for ponesimod re-start.

This visit must be performed in all cases of study drug interruption for planned pregnancy, irrespective of the duration of pregnancy, and also in all cases where planned pregnancy did not

occur but where the contraception was interrupted for any duration and the subject wishes to re-start study treatment.

8.5.6 Unscheduled visit for re-start of the study treatment after delivery

The following assessments/procedures must be performed during the visit:

Urine pregnancy test first, and, if negative:

- Assessment and recording in the eCRF of methods of contraception and confirmation that that the subject has been using reliable methods of contraception as described in Section 4.4.1 for at least 30 days;
- Assessment of total duration of study treatment interruption (which should not exceed 81 weeks);
- Confirmation that breastfeeding has been completely stopped;
- If the subject has been treated with a DMT (interferon β or glatiramer acetate) during and after pregnancy, confirmation that this treatment has been discontinued not less than 7 days prior to study drug re-initiation;
- 12-lead ECG and SBP/DBP (under the responsibility of the physician evaluating cardiac safety assessments) at pre-dose and every hour (+/− 15 min) for 4-hours post-dose*;
- The discharge criteria will be applied as described for first day of re-initiation [see Section 5.1.10]*;
- Body temperature;
- Body weight;
- Recording of AEs and SAEs;
- Recording of changes in concomitant medications;
- MS relapse;
- Dispensing of study treatment.

If the urine pregnancy test is positive, the subject is not eligible for ponesimod re-start. The regular scheduled study visits must continue according to the original visit and assessment schedule.

* All subjects are required to have a pre-dose assessment. Only subjects with cardiovascular risk factors [see Section 5.1.9] are required to be monitored for at least 4 hours and up to 12 hours post-dose at the study site. In this case, discharge criteria will be applied as described for Day 1 [see Section 5.1.10]. Subjects without cardiovascular risk factors may re-initiate study drug at home.

9 STUDY COMPLETION AND POST-STUDY TREATMENT/MEDICAL CARE

9.1 Study completion

For an individual subject, EOS is reached when treatment and FU periods have been completed.

The reason(s) for discontinuing the study along with who made the decision, if applicable, (i.e., subject, investigator or the sponsor) 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 the sponsor for any reason, including premature termination or suspension of the study [see Section 9.3].

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 if 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 the sponsor), 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 treatment and discuss (FU) post-study medical care. 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

The sponsor reserves the right to terminate the study at any time globally or locally. Investigators can terminate the participation of their site in the study at any time.

If the study is suspended or prematurely terminated, the sponsor will promptly inform the investigators, the Institutional Review Boards (IRBs) / Independent Ethics Committees (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 the sponsor must promptly inform all enrolled subjects and ensure their appropriate treatment and FU, as described in Section 9.2. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subjects' interests.

In addition, if the investigator suspends or terminates the study without prior agreement from the sponsor, the investigator must promptly inform the sponsor and the IRB/IEC, and provide both with a detailed written explanation of the termination or suspension.

If the IRB/IEC suspends or terminates its approval/favorable opinion of the study, the investigator must promptly notify the sponsor and provide a detailed written explanation of the termination or suspension.

Any suspension or premature termination of the study was to be discussed with the IDMC until its disbandment which occurred on 30th September 2021.

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.

10 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

Safety definitions and reporting requirements for all subjects participating in this study are summarized below.

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. This definition applies regardless of whether the subject receives commercially available ponesimod after completing study treatment. Treatment-emergence is considered with respect to the relevant Analysis Period, i.e., relative to the first dose of ponesimod in the core study for the Combined Analysis Period, and relative to the first dose of ponesimod in the extension study for the Extension Analysis Period.

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 (i.e., signing of informed consent).
- 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, which 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.

Special reporting situations are described in Section 10.5.

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 prior to start of extension study treatment and which is ongoing at the start of treatment worsens after the start of study treatment, a new AE must be recorded in the eCRF. 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 usually does not 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 subsequently reported as either related or unrelated. The determination of the likelihood that the study treatment 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 treatment start (Day 1) and up to 30 days after permanent study treatment discontinuation (i.e., EOS) must be recorded on specific AE pages of the eCRF. This also applies to AEs occurring during the treatment interruption (e.g., due to planned pregnancy), for example, all AEs during study treatment interruption should be reported in the eCRF. If, during study treatment interruption which lasted >30 days the subject fulfills the criteria for permanent study treatment discontinuation, the reporting of AEs should continue until the EOS visit, which should be scheduled as soon as possible after the decision for permanent study treatment discontinuation has been taken. The sponsor may contact the investigator to obtain further information concerning AEs.

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 permanent study treatment discontinuation must be followed up until they are no longer considered clinically relevant.

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 International Council for Harmonisation (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 in-patient hospitalization, or prolongation of existing hospitalization.
- Resulting in persistent or significant disability or incapacity.
- Congenital anomaly or birth defect.
- Is a suspected transmission of any infectious agent via a medicinal product
- 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 (for example, if a complication prolongs hospitalization).

10.2.2 Reporting of serious adverse events

All SAEs occurring after study treatment start (Day 1) and up to 30 days after permanent study treatment discontinuation must be reported on AE pages in the eCRF and on SAE forms, regardless

of the investigator-attributed causal relationship with study treatment or study-mandated procedures.

10.2.3 Follow-up of serious adverse events

Serious adverse events 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

New SAEs occurring after the 30-day FU period must be reported to the sponsor within 24 hours of the investigator's knowledge of the event, **only** if considered by the investigator to be causally related to previous exposure to the study treatment.

10.2.5 Reporting procedures

All SAEs, as well as product quality complaints (PQCs), occurring during the study must be reported to the appropriate sponsor contact person by study site personnel within 24 hours of their knowledge of the event.

MS relapses and associated symptoms are exempt from being reported on an SAE form by the investigator to the sponsor with the exceptions described in Section 10.1.6.

All SAEs must be recorded on an SAE form by the investigator, and whether or not this event is considered by the investigator to be related to study treatment. The SAE forms must be completed and signed by a physician from the study site and transmitted to the sponsor (contact details are provided on the SAE form) within 24 hours. The investigator must complete the SAE form in English, and must assess the causal relationship of the event to study treatment.

FU information about a previously reported SAE must also be reported within 24 hours of receiving it. The sponsor 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 safety information section of the IB [Ponesimod IB] is the reference safety document to assess expectedness of a suspect serious adverse reaction and reporting by the sponsor to health authorities, IRBs/IECs and investigators.

10.3 Pregnancy

If a woman becomes pregnant while on study treatment, study treatment 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.

Women who wish to interrupt the study treatment because of planned pregnancy and restart the study treatment after delivery and lactation, if applicable, will be allowed to stay in the study provided the conditions mentioned in the Section 5.1.12.5 are fulfilled.

10.3.1 Reporting of pregnancy

Any pregnancy (irrespective if planned or not) occurring during the entire study including during 30 days following permanent study treatment discontinuation, must be reported to the sponsor by study site personnel within 24 hours of their knowledge of the event. Pregnancies must be reported on the appropriate pregnancy notification form, which is transmitted to the sponsor, and on the AE page in the eCRF.

10.3.2 Follow-up of pregnancy

Any pregnancy must be followed to its conclusion and its outcome reported to the sponsor.

Any AE associated with the pregnancy occurring during the FU period after study treatment discontinuation or during study treatment interruption for planned pregnancy must be reported on separate AE pages in the eCRF. Any SAE occurring during the pregnancy must be reported using an SAE form as described in Section 10.2.2. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using an SAE form.

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 sponsor's 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 monitored safety data until its disbandment which occurred on 30th September 2021 [see Section 3.5.1]. The sponsor may request additional data pertaining to the diagnostic work-up of an AE or SAE (e.g., medical imaging, local laboratory values) for the purpose of safety monitoring. Such additional data may be shared with external experts.

10.5 Special reporting situations

Safety events of interest on a sponsor study drug in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug (defined as the intake of >1 pills on the same calendar day)
- Suspected abuse/misuse of a sponsor study drug
- Accidental or occupational exposure to a sponsor study drug
- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without patient exposure to the Johnson & Johnson medicinal product, e.g., product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Exposure to a sponsor study drug from breastfeeding

Special reporting situations should be recorded on the AE pages of the eCRF, and study treatment errors must be documented in the study treatment log of the eCRF. Any special reporting situation that meets the criteria of an SAE should be recorded as an SAE.

10.6 Product quality complaint handling

Definition

A PQC is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, i.e., any dissatisfaction relative to the identity, quality, durability, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system.

Procedures

All initial PQCs must be reported to the sponsor by the study site personnel within 24 hours after being made aware of the event.

A sample of the suspected product should be maintained under the correct storage conditions until a shipment request is received from the sponsor.

11 STATISTICAL METHODS

All statistical analyses will be conducted by the sponsor or by designated Contract Research Organizations supervised by the sponsor.

The Statistical Analysis Plan (SAP) will provide the full details of all analyses, data displays, and algorithms to be used for data derivations. The extension study database will be combined with the core study database, with indicator variables in the database to distinguish between the two studies. Statistical analyses will be descriptive and no inferential statistics are planned in the protocol.

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.

11.1 Analysis strategy

11.1.1 Analysis strategy for efficacy

In order to describe the disease activity in subjects after long-term treatment with ponesimod 20 mg, and to investigate the effect of switching from teriflunomide 14 mg to ponesimod 20 mg, the main analysis of efficacy will focus on combined data from both the core and extension studies. Subjects will be analyzed according to the treatment they were randomized to in the core study. This will allow the assessment of the effect of early long-term treatment with ponesimod 20 mg compared with delaying the treatment with ponesimod 20 mg for 2 years.

Following 108 weeks of treatment with either ponesimod 20 mg or teriflunomide 14 mg in the core study, it must be assumed that the two populations will not be similar in terms of baseline characteristics at the start of the extension study, split by core study randomized treatment and overall. With this limitation acknowledged, specific efficacy endpoints will be analysed only for the extension study. Section 6.1 details which efficacy endpoints will be analysed for the combined core and extension studies, and which additionally will be analyzed for the extension study.

11.1.2 Analysis strategy for safety

The long-term safety of ponesimod and the changes in safety in teriflunomide 14 mg subjects switching to ponesimod 20 mg will be investigated by summarizing the combined data from both the core and extension studies. Cumulative data such as AEs and SAEs will only be summarized for subjects initially treated with ponesimod 20 mg in the core study to allow a long-term assessment of up to 6 years. To assess trends over time and to assess the switch from teriflunomide 14 mg to ponesimod 20 mg, the analysis of the change from baseline for safety endpoints will be assessed by visit from core baseline up to last treatment + 15 days, and will be analyzed by core treatment group.

In addition, all safety data collected in the extension study will be analyzed for the extension study only, and will be summarized both overall and split by the core treatment group. For this analysis, the extension study baseline is used as the reference.

Section 6.2 details which safety endpoints will be analyzed for the combined core and extension studies, and which will be analyzed for the extension study.

11.1.3 Baseline definitions

The following baseline definitions will be used:

- The core baseline value for efficacy is defined as the last non-missing value recorded before randomization in the core study for each endpoint and each subject individually.
- The core baseline value for safety is defined as the last non-missing value recorded before the first study treatment administration in the core study for each endpoint and each subject individually.

- The extension baseline value for efficacy and safety is defined as the last non-missing value recorded in either the core or extension studies before the first administration of ponesimod in the extension study (unless otherwise specified in the SAP).

Analysis over the Extension Analysis Period will use the extension study baseline, whilst analysis over the Combined Analysis Period will use the core study baseline.

11.1.4 Analysis periods

11.1.4.1 Extension analysis period

This period includes all available data collected on or after the first date of ponesimod treatment in the extension study, up to the extension EOS date for efficacy variables or up to the last study treatment date + 15 days in the extension study for safety variables. This definition applies regardless of whether the subject receives commercially available ponesimod after completing study treatment.

11.1.4.2 Combined analysis period

For efficacy this period includes all available data from randomization in the core study up to the extension EOS date for subjects entering the extension, or up to the core EOS date for subjects not entering the extension. For safety this period includes all available data from the date of first treatment administration up to the last treatment date + 15 days in the extension study for subjects entering the extension, or up to the last treatment date + 15 days in the core study for subjects not entering the extension.

11.2 Analysis sets

11.2.1 Extension Set

The Extension Set (EXTS) includes all subjects who signed an informed consent to enter the extension study and who received at least one dose of ponesimod study medication in the extension study.

11.2.2 Full Analysis Set

Following the intention-to-treat (ITT) principle, the Full Analysis Set (FAS) includes all subjects randomized in the core study. Subjects will be evaluated according to the treatment they have been randomized to in the core study, which may be different from the treatment they have received.

11.2.3 Safety Set

The Safety Set (SAF) includes all subjects who received at least one administration of core study treatment. Subjects will be analyzed according to the treatment they received during the core study.

11.2.4 Per-Protocol Set

The Per-Protocol Set (PPS) comprises all subjects included in the FAS without any major protocol deviations, that impact the assessment of the main efficacy endpoints, occurring prior to or at randomization in the core study. Only the data for a subject collected after a major protocol

deviation for subjects developing protocol deviations during either study will be excluded for the PPS analysis.

All reportable protocol deviations will be defined in the SAP.

11.2.5 Other analysis sets

Other analysis sets will be described in the study SAP.

11.2.6 Usage of the analysis sets

The EXTS will be used for efficacy and safety analyses of the Extension Analysis Period. The FAS and EXTS will be used for efficacy analyses of the Combined Analysis Period. The SAF will be used for the safety analysis of the Combined Analysis Period in an as-treated approach.

11.3 Variables

11.3.1 Main efficacy variables

11.3.1.1 Annualized relapse rate (confirmed relapses)

ARR for each period is defined using the following variables:

- The number of confirmed relapses per subject between the start and end of the period.
- The subject's length of observation in the period in years, defined as: [end of period date minus start of period date + 1] divided by 365.25.

The ARR will be calculated for the following periods:

- Combined Analysis Period;
- Extension Analysis Period.

11.3.1.2 Time to first confirmed relapse

The time to first confirmed relapse is defined as:

- Date of first confirmed relapse (in either the core or extension study) minus date of randomization in the core + 1 in days.

Time to first confirmed relapse is calculated over the Combined Analysis Period. Subjects who entered the extension study and remained free of relapses will be censored at the extension EOS date, subjects who did not enter the extension and ended the core study free of relapses will be censored at the core study EOS date. For censored subjects the time is defined as EOS date minus date of randomization + 1 in days.

11.3.1.3 Time to first 12 or 24-week CDA

Time to 12 or 24-week CDA from core baseline to EOS (extension EOS for subjects entering the extension study or core EOS for subjects not entering the extension) 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 ≥5.5;

confirmed after 12 or 24 weeks.

Time to first 12 or 24-week CDA is defined as start date of the first 12 or 24-week CDA minus date of randomization in the core study + 1 in days. For a subject without a 12 or 24-week CDA, the censored time to 12 or 24-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 in the core study + 1.

Further details of the derivation of this variable will be provided in the SAP.

11.3.1.4 Cumulative number of combined unique active lesions

Cumulative number of combined unique active lesions (CUAL) [defined in Section 6.1.2] will be calculated for the following periods:

- Combined Analysis Period;
- Extension Analysis Period.

Cumulative number of CUAL is calculated as the sum of lesions at all post baseline MRI visits up to the end of each analysis period.

11.3.1.5 Longitudinal percent change over time in brain volume from baseline

Percent change in brain volume (PCBV) will be calculated at each visit using the skull as scaling constraint by performing halfway registration between images from the MRI assessments from baseline to the end of both the Combined Analysis Period and the Extension Analysis Period:

- Percent change from the mean brain surface displacement between the MRI scans (SIENA method).

Further details of the derivation of this variable will be provided in the SAP.

11.3.2 Other efficacy variables

All other efficacy variables will be described in the SAP.

11.3.3 Safety variables

All safety variables will be defined in detail in the SAP. See Section 6.2 for the safety endpoint definitions.

11.4 Description of statistical analyses

11.4.1 Overall testing strategy

This extension study is exploratory in nature and no hypotheses are pre-specified. No multiplicity adjustments will be made for the efficacy endpoints.

11.4.2 Analysis of the main efficacy variable

11.4.2.1 Statistical model

A generalized linear model with negative binomial distribution for the number of confirmed relapses will be assumed.

T_j denotes the length of observation for subject j
Y_j denotes the number of relapses for subject j during t_j
μ_j denotes the mean of the negative binomial distribution of Y_j.

The mean for the distribution of the ARR for subject j, denoted by μ_j / t_j, will be modeled by the following equation:

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

$\mathbf{x}_j$ is the vector denoting study treatments and covariates for subject j
$\boldsymbol{\theta}$ is the vector of unknown fixed model parameters.

A negative binomial regression model will be used to calculate the ARRs by the core study treatment for the appropriate analysis set and period. Two-sided 95% Wald CIs will be calculated for the ARRs.

11.4.2.2 Handling of missing data

All confirmed relapses from randomization in the core study up to the EOS visit in either core or extension studies for all subjects in the full analysis set (FAS) will be used in the main analysis of the ARR endpoint regardless of study treatment compliance; therefore, no data will be excluded from the analysis.

Every effort will be made to collect relapse information as completely 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 efficacy analysis, unless it is clear that they have occurred prior to the start of the analysis period.

No missing data imputation is defined for the analysis of ARR variable.

11.4.2.3 Main analysis of ARR

The main statistical analysis will be performed on the FAS using all data in the Combined Analysis Period. The model described in Section 11.4.2.1 for confirmed relapses will be used, with core

study treatment as a factor and the logarithm of time on study up to the end of the Combined Analysis Period as an offset variable. Sensitivity analysis will be described in the SAP.

11.4.2.4 Additional analyses of ARR

The same analysis as described in Section 11.4.2.3 will also be performed using all data in the Extension Analysis Period based on the EXTS with the logarithm of time on study during the Extension Analysis Period as an offset variable. The SAP will describe in more detail extension baseline covariates that will be considered in case of extension baseline imbalances.

No follow-up relapse data will be available in the extension study for subjects who discontinue study early in the core study or for subjects who complete the core study and choose not to enter the extension study, which could lead to biases in any treatment effect estimates. The SAP will describe imputation methods including a worst case, best case and most plausible case to address this.

11.4.2.5 Subgroup analyses

All subgroup analysis will be defined in the SAP.

11.4.3 Time to first confirmed relapse

The analysis of time from randomization in the core study to first relapse during the Combined Analysis Period will be performed on the FAS using Kaplan-Meier methods; estimates for the survival functions will be plotted using KM curves and will be tabulated by 12-week intervals.

11.4.4 Time to 12 and 24-week CDA

The analysis of time from core study baseline to first 12- and 24-week CDA will be summarized in a similar manner to the time to first relapse variable.

11.4.5 Cumulative number of combined unique active lesions

The statistical analysis of CUAL will be performed for each analysis period based on the associated analysis set using a similar model as described in Section 11.4.2.1 for the main analysis of the confirmed relapses with core study treatment as a factor and the log of the number of scans in the period used as an offset variable. The SAP will describe in more detail extension baseline covariates that will be considered in case of extension baseline imbalances.

11.4.6 Percent change from baseline in brain volume

PCBV will be summarized descriptively by core treatment group for the Combined Analysis Period using the FAS and for the Extension Analysis Period for the EXTS.

11.4.7 Analysis of the other efficacy variables

The analysis of all other efficacy variables will be detailed in the SAP.

11.4.8 Analysis of the safety variables

If not otherwise stated, only safety data considered treatment-emergent (up to 15 days after the last treatment administration) in the respective analysis period [as defined in Section 11.1.4] will be included in tables and figures. All safety data will be included in listings, with flags for safety data not considered to be treatment-emergent to a specific analysis period.

Generally, safety data is presented as follows:

Safety data collected in the extension study will be analyzed based on the **Extension Analysis Period** using the EXTS and will be summarized for all subjects overall and split by core study treatment group. The analysis of change from baseline for safety endpoints assessed by visit will use the extension baseline as reference.

Furthermore, the long-term safety of ponesimod 20 mg and the changes in safety for teriflunomide 14 mg subjects switching to ponesimod 20 mg will be assessed by summarizing all data in the **Combined Analysis Period** using the SAF. Cumulative data such as AEs and SAEs will only be summarized for subjects initially treated with ponesimod 20 mg in the core study. Safety endpoints assessed by visit will be summarized by core study treatment group. Analysis of change from baseline for safety endpoints assessed by visit will use the core baseline as reference.

11.4.8.1 Adverse events

All AEs will be coded using the latest version of MedDRA available at the time of database closure.

11.4.8.1.1 Treatment-emergent AEs and SAEs

Treatment-emergent AEs and SAEs will be tabulated by 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 study treatment.

AEs and SAEs will be summarized over the:

- Extension Analysis Period by core study treatment and overall, using the EXTS;
- Combined Analysis Period for subjects who received ponesimod 20 mg in the core study only, using the SAF.

11.4.8.1.2 AEs of special interest and MACE

AEs of special interest and MACE will be summarized in the same way as described in Section 11.4.8.1.1. The list of AEs of special interest is provided in Appendix 4.

11.4.8.1.3 AEs leading to premature discontinuation of study treatment

(S)AEs leading to premature discontinuation of study treatment will be summarized by core study treatment and overall for the Extension Analysis Period based only on the EXTS, in a similar manner as that described in Section 11.4.8.1.1.

11.4.8.1.4 Post-treatment AEs and SAEs

Post-treatment (S)AEs occurring after the last treatment administration + 15 days up to EOS will be summarized based on the EXTS in a similar manner as described in Section 11.4.8.1.1.

11.4.8.1.5 Deaths

Fatal SAEs occurring any time after the start of treatment in the extension study will be summarized by core study treatment and overall, based on the EXTS in a similar manner as described in Section 11.4.8.1.1.

11.4.8.2 Cardiac safety

11.4.8.2.1 Treatment-emergent abnormalities

Treatment-emergent morphological ECG abnormalities will be summarized in a similar manner to AEs, and will include the cardiac safety events:

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

11.4.8.2.2 Absolute values and change from baseline by visit

Descriptive summary statistics for observed treatment-emergent absolute values and absolute change from core baseline in numeric 12-lead ECG values for the parameters HR, PR, QRS, QT, QTcB and QTcF by visit will be provided for the Combined Analysis Period by core study treatment using the SAF.

In addition, descriptive summary statistics by core study treatment and overall for absolute change from extension baseline for pre-dose parameters by visit will be provided for the Extension Analysis Period using the EXTS.

11.4.8.2.3 Change from pre-dose to post-dose

The change from pre-dose to post-dose assessments at 1 h, 2 h, 3 h, and 4 h on the day of initiation of ponesimod in the extension study will be summarized by core study treatment and overall for the following parameters: HR, PR, QT, QTcB, QTcF. This analysis will be based on the Extension Analysis Period using the EXTS.

11.4.8.3 Pulmonary safety

11.4.8.3.1 Absolute values and change from baseline

Descriptive summary statistics by visit for the Combined Analysis Period using the SAF will be provided for observed (absolute and percent of predicted) treatment-emergent values and changes from core baseline for FEV_1, FVC and FEV_1/FVC ratio (all expressed in absolute change, % change).

The mean (and 95% CIs) for change from core baseline to EOS and from core baseline to EOT for FEV_1 and FVC (absolute change, percent change and absolute change in % predicted)** will be plotted by core study treatment for the Combined Analysis Period using the SAF.

** applies only to subjects who have no exposure to commercially available ponesimod prior to the EOS visit.

11.4.8.3.2 Treatment-emergent decreases in FEV_1 and FVC

The number and proportion of treatment-emergent decreases of % of predicted FEV_1 or FVC >20 percentage points from core baseline at any time during the Combined Analysis Period for subjects who received ponesimod 20 mg in the core study based only on the SAF will be summarized in a similar manner to the AEs as described in Section 11.4.8.1.1.

11.4.8.3.3 Reversibility of treatment-emergent decreases in FEV_1 and FVC

For the subset of subjects with a decrease of ≥200 mL or ≥12% in FEV1 or FVC from core baseline at EOT, the number and percentage of subjects with a decrease of <200 mL and <12% from core baseline to EOS** in FEV1 or FVC will be summarized for subjects who received ponesimod 20 mg in the core study only for the Combined Analysis Period using the SAF.

** applies only to subjects who have no exposure to commercially available ponesimod prior to the EOS visit.

11.4.8.3.4 Lung diffusion capacity

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

11.4.8.3.5 Pulmonary safety events

Treatment-emergent pulmonary safety events over the Combined Analysis Period for subjects who received ponesimod 20 mg in the core study only, will be summarized in a similar manner to AEs and will include the events:

- Pulmonary AEs or SAEs of special interest;
- Withdrawal due to pulmonary reasons/AE.

The analysis of other pulmonary variables will be described in the SAP.

11.4.8.4 Vital signs

Descriptive summary statistics by visit will be provided for observed treatment-emergent values and absolute change from core baseline for HR, sBP, dBP and body weight by core study treatment for the Combined Analysis Period using the SAF. These parameters will also be summarized descriptively for the Extension Analysis Period by core study treatment, and overall using the EXTS.

Treatment-emergent notable BP abnormalities will also be summarized for both analysis periods. The definition for notable abnormalities is provided in Appendix 5.

11.4.8.5 Laboratory endpoints

Descriptive summary statistics by visit will be provided for observed treatment-emergent values and absolute change from core baseline for laboratory tests (hematology, blood chemistry, urinalysis) by core study treatment for the Combined Analysis Period using the SAF. These parameters will also be summarized descriptively for the Extension Analysis Period by core study treatment and overall using the EXTS.

Treatment-emergent laboratory notable abnormalities will be summarized for subjects who received ponesimod 20 mg in the core study only for the Combined Analysis Period using the SAF.

The definition for notable abnormalities is provided in Appendix 5 and 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 5]
- Treatment-emergent laboratory test abnormalities based on FDA guidance for DILI [FDA 2009b] (for ALT / AST / total bilirubin).

Lymphocyte count reversibility after EOT will be summarized descriptively by comparing the mean (and 95% CIs) for absolute change in lymphocyte counts from core baseline to EOS, and from core baseline to EOT.** This analysis will be performed for the Combined Analysis Period by core study treatment using the SAF.

** applies only to subjects who have no exposure to commercially available ponesimod prior to the EOS visit.

11.4.8.6 eC-SSRS

The number and percentage of subjects 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 core study treatment for the Combined Analysis Period.

11.4.8.7 Other Safety Variables

The analysis of all other safety variables will be described in detail in the SAP.

11.4.9 Immunogenicity Analysis

The following humoral immune responses are measured, based on the COVID-19 immunogenicity samples, including S- and N-ELISA assays and titers of neutralizing antibodies in a subset of samples.

- SARS-CoV-2 binding antibodies to S protein (ELISA): Analysis of antibodies binding to SARS-CoV-2 S protein
- SARS-CoV-2 seroconversion based on antibodies to N protein (ELISA): Analysis of antibodies binding to SARS-CoV-2 N protein
- SARS-CoV-2 neutralization (wtVNA): Analysis of neutralizing antibodies to the wild-type virus

Descriptive statistics of assays will be presented overall, by vaccination type, and by COVID-19 AE status as applicable.

11.5 Interim analyses

An unblinded interim analysis will be performed after the randomization list unblinding of the core study. Further interim analyses may be performed subsequent to this date.

11.5.1 Additional periodic analyses

During the conduct of the study, data analyses might be performed at specified intervals of time (eg, all patients who complete 12 months of treatment).

11.6 Sample size

As the extension study is an extension of the confirmatory Phase 3 core study, there are no sample size statistical considerations. The sample size will be pragmatically determined by how many of the 1100 subjects planned in the core phase enroll into the extension study. Based on anticipated discontinuation rates in the core study, approximately 800 subjects are expected to enter the extension study.

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 (ref. to 21 CFR Part 11).

Subject pre-treatment and treatment data will be completed for all subjects (i.e., eligible and non-eligible) through the eCRF.

For each subject enrolled (i.e., from whom an informed consent has been obtained), 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 eCRFs or other documents (e.g., documents attached to SAE reports) submitted to the sponsor and any external service providers, 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 enrollment number, the subject's name, date of birth, and address or any other locally accepted identifiers. Documents identifying the subjects (e.g., signed informed consent forms) must not be sent to the sponsor, 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 the sponsor 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 the sponsor 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, SF-36v2™,eC-SSRS assessments will be processed through a central laboratory/provider and the results will be sent electronically to the sponsor. Any data received from central laboratory or central ECG facility generated in relation to follow up on adverse events which are ongoing at end of study should be entered in the database even if obtained after the EOS visit.

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 eCRFs 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

The sponsor 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 Institutional Review Board (IRB) or Independent Ethics Committee (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 or subject information leaflet 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 to the consent process and/or to obtain consent from the subject and/or legal representative will be listed on the Actelion Delegation of Authority form and the Janssen Delegation Log. 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/Janssen Delegation Log.

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. This must include the study reference, the subject number, the date and, if applicable, time when the subject was first introduced to the clinical study, the date and, if applicable, time 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), a copy of the signed ICF given to the subject / legal representative.

13.4 Compensation to subjects and investigators

The sponsor 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 the sponsor or its representative, in a timely manner. The investigator/delegate must document and explain any deviation from the approved protocol. Deviations considered to be a violation of GCP must be reported to the IRB/IEC and regulatory authorities according to the sponsor or (overruling) local requirements.

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 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 site file (ISF) and subject clinical source documents.

These records must be kept by the investigator for as long as is necessary to comply with the sponsor's requirements (i.e., 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 site for any or all of the documents, special arrangements, respecting the data confidentiality, must be made between the investigator and the sponsor to store these documents outside the site, so that they can be retrieved in the event of a regulatory inspection. No study document should be destroyed without prior written approval from the sponsor. Should the investigator wish to assign the study records to another party, or move them to another location, the sponsor 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 coversheet, signed and dated by the investigator/delegate to confirm that these certified copies are exact copies containing 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 the sponsor'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.

13.8 Monitoring

Prior to study start, a site initiation visit (SIV) will be performed after the required essential study documents are approved by the sponsor. 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 are present during the SIV and will dedicate enough time to it. Site Information Technology (IT) 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 follow-up letter will be provided to the principal investigator and filed in the ISF.

During the study, the monitor will contact and visit the site regularly and must be permitted, on request, to have access to study 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 eCRFs and other protocol-related documents. The sponsor monitoring standards require full verification that informed consent has been provided, 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 eCRFs 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 must ensure that the eCRF is completed after a subject's visit (site visit or phone call), 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 when there are no more active subjects and all FU issues have been resolved. If a site does not enroll any subjects, the close-out visit may be performed prior to study database closure at the discretion of the sponsor.

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 E6 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 the sponsor. If the site needs to transfer the ISF to another location and/or if site facility can no longer store the ISF, the principal investigator must inform the sponsor immediately.

If the principal investigator changes, or if the site relocates, the monitor must be notified as soon as possible.

13.10 Audit

Representatives of the sponsor's clinical quality assurance department 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 the sponsor's requirements (e.g., SOPs) will also be verified. Prior to initiating this audit, the investigator will be contacted by the sponsor 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 IRB/IEC may also conduct an inspection of the sponsor's clinical study (during the study or after its completion).

Should an inspection be announced by a health authority and/or IRB/IEC, the investigator must inform the sponsor 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

All information, including but not limited to information regarding ponesimod or the sponsor's operations (e.g., patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including exploratory research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of ponesimod, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of exploratory analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and sub-study approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed 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.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law. The disclosure of the final study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

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® SmPC] http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002514/WC500148682.pdf

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

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

[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.

[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.

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

[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.

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

[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.

[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 JF. 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.

[Olsson 2014] Olsson T, Boster A, Fernandez O, Freedman O, Freedman MS, Pozzilli C, Bach D, Berkani O, Mueller MS, Sidorenko T, Radue EW, Melanson M. Oral ponesimod in relapsing-remitting multiple sclerosis: a randomised phase II trial. J Neurol Neurosurg Psychiatry 2014;85(11):1198-208.

[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, Actelion Pharmaceuticals Ltd., a Janssen Pharmaceutical Company of Johnson & Johnson (current version on file).

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

[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).

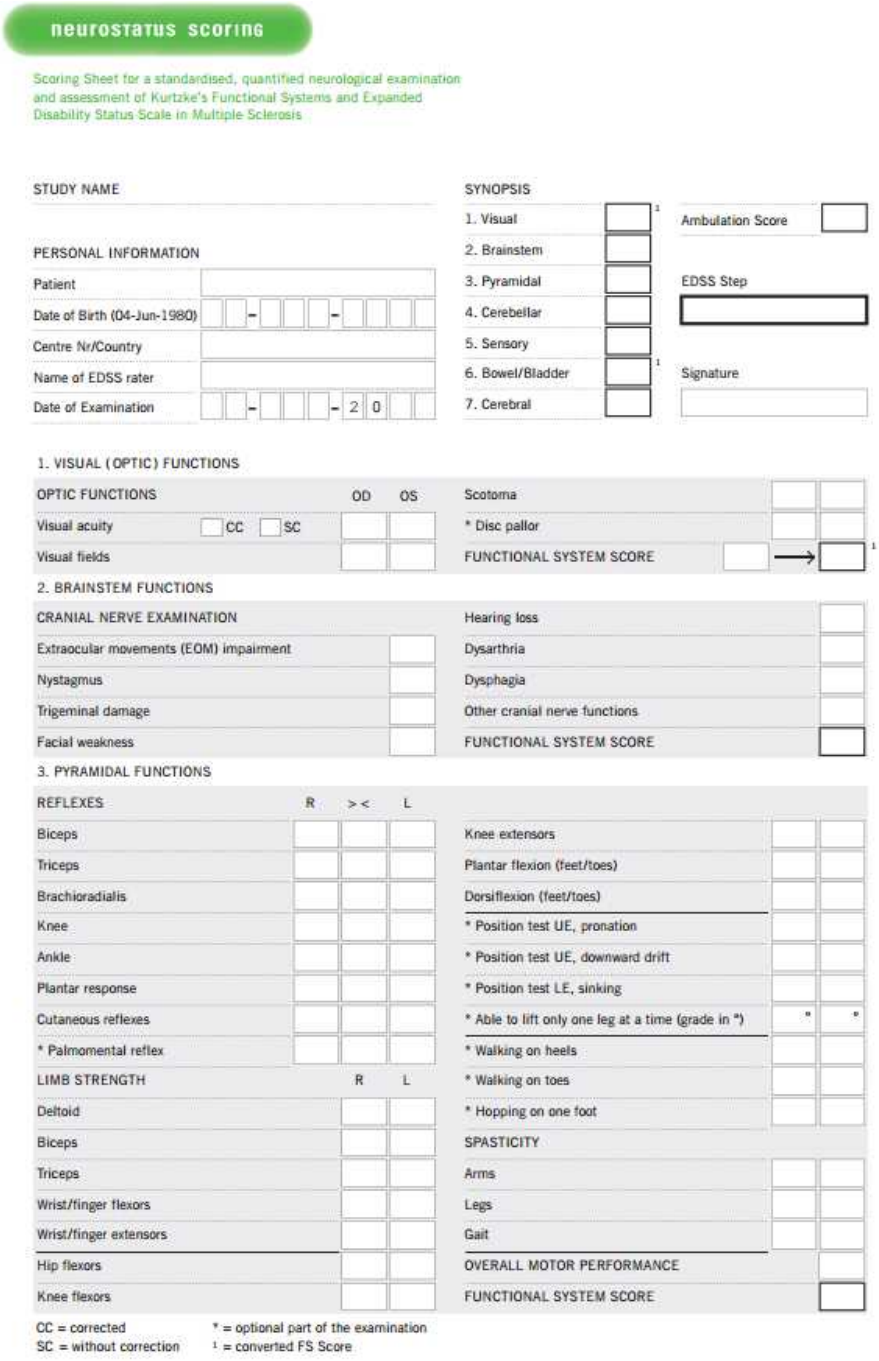
[Sobhani 2010] Sobhani K, Garrett DA, Liu DP, Rainey PM. A rapid and simple high-performance liquid chromatography assay for the leflunomide metabolite, teriflunomide (A77 1726), in renal transplant recipients. Am J Clin Pathol 2010;133(3):454–7.

[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.

15 APPENDICES

Appendix 1 Neurostatus® scoring sheet



neurostatus scoring

Scoring Sheet for a standardised, quantified neurological examination and assessment of Kurtzke's Functional Systems and Expanded Disability Status Scale in Multiple Sclerosis

STUDY NAME

PERSONAL INFORMATION

Patient	
Date of Birth (04-Jun-1980)	- -
Centre Nr/Country	
Name of EDSS rater	
Date of Examination	- - 2 0

SYNOPSIS

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

1. VISUAL (OPTIC) FUNCTIONS

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

Scotoma			
* Disc pallor			
FUNCTIONAL SYSTEM SCORE		→	[1]

2. BRAINSTEM FUNCTIONS

CRANIAL NERVE EXAMINATION			
Extraocular movements (EOM) impairment		Hearing loss	
Nystagmus		Dysarthria	
Trigeminal damage		Dysphagia	
Facial weakness		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 2 Guidance for concomitant treatment with QT-prolonging drugs with known risk of Torsades de Pointes

QT-prolonging medications with known risk of Torsades de Pointes (e.g., azithromycin, citalopram, clarithromycin, erythromycin, escitalopram, moxifloxacin, etc.) should be administered with caution since ponesimod may potentially enhance their effect on QT interval. A list of QT-prolonging medications with known risk of TdP is published by AZCERT [University of Arizona CERT http://crediblemeds.org/]. The investigator should also take into account other relevant risk factors such as hypokalemia, bradycardia or QTc interval prolongation when considering treatment with a QT-prolonging drug. Based on the available evidence, the additional ECG monitoring will no longer be required for re-initiating or increasing the dose of a QT-prolonging drugs with known risk of Torsades de Pointes from Protocol Version 6 onwards.

Appendix 3 Prohibited anti-arrhythmic and HR-lowering drugs

The following anti-arrhythmic and HR-lowering drugs (systemic administration) are prohibited during the up-titration period (i.e., from Day 1 until Day 14 included and during the first 14 days after re-initiation of study treatment) [see Section 5.2.3]:

- Adenosine
- Acebutolol
- Ajmaline
- Amiodarone
- Aprinidine
- Atenolol
- Azimilide
- Bepridil
- Betaxolol
- Bisprolol
- 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

This list is not exhaustive; other anti-arrhythmic or HR-lowering drugs are also prohibited during uptitration. In case of doubt, please discuss the use of any potential anti-arrhythmic or HR-lowering drug with the sponsor.

Treatment with any of these therapies is also not recommended during maintenance treatment with ponesimod (i.e., 20 mg) and should be considered with caution if an alternative medication cannot be used.

Appendix 4 Adverse events of special interest

AEs of special interest will include the anticipated risks of treatment with ponesimod, and the events that may be related to MS comorbidities (e.g., seizures or stroke). The following safety areas were updated from Protocol version 6 onwards to include identified risks:

- Bradyarrhythmia occurring post-first dose
- Macular edema
- Bronchoconstriction
- Severe liver injury
- Serious opportunistic infections including PML
- Skin cancer
- Convulsions
- Unexpected neurological or psychiatric symptoms/signs (PRES, ADEM, atypical MS relapses)

A list of AEs of special interest (MedDRA preferred terms) will be defined in the SAP.

Appendix 5 Abnormalities for ECG, BP and laboratory variables

Notable abnormalities for ECG and BP that are related to the potential effects of ponesimod will address the following variables:

- Morphological ECG findings (defined as any abnormal finding not present prior to start of treatment).
- HR outliers (bpm), based on ECG
- PR interval (ms)
- QT/QTc interval (ms), QTcB or QTcF
- BP (mmHg)

The definition of the abnormal values to be reported will be described in the SAP.

Laboratory abnormalities

Laboratory values below or above the normal range will be graded at three levels (H, HH, HHH for values above normal range and L, LL, LLL for values below the normal range) where L stands for “low”, H for “high”.

The term “marked abnormality” describes laboratory values above or below the thresholds, with grading of abnormalities at two levels: LL/HH and LLL/HHH. These thresholds have been defined by the sponsor in order to flag and/or communicate abnormal laboratory results from the central laboratory to the investigators, and for the purpose of standardized data analysis and reporting by the sponsor. The definitions of marked abnormal values are based mainly on the Common Terminology Criteria for Adverse Events (CTCAE) [CTCAE 2010] grading system and, in specific cases (e.g., lymphocyte levels), are adjusted based on the known PD effect of the study treatments (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 treatment) 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 11 below may be defined in the central laboratory manual.

Table 11 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 (for pre-treatment assessments, and post-treatment assessments when baseline ≤ ULN) or increase from baseline >20 g/L (for post-treatment assessments when baseline is >ULN)	Increase in >40 g/L above ULN (for pre- treatment assessments, and post-treatment assessments when baseline ≤ ULN) or increase from baseline >40 g/L (for post-treatment assessments when baseline is >ULN)
MCH (pg/Cell)	ND	ND	ND	ND
MCV (fL)	ND	ND	ND	ND
Hematocrit (L/L)	<0.28 (female) <0.32 (male)	<0.20	>0.55 (female) >0.60 (male)	>0.65
Platelet count (10^9 /L)	<75	<50	>600	>999
RBC count (10^{12} /L)	ND	ND	ND	ND
WBC count (10^9 /L)	NA	<1.9	>20.0	>100.0
Lymphocyte (10^9 /L)	ND	<0.2 **ALERT:** **<0.2**	>4.0	≥8.0
Neutrophils (10^9 /L)	<1.5	<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 **ALERT:** **≥1.5 combined with ALT or AST ≥3 ULN**	≥2.5 ULN
Lactate dehydrogenase	ND	ND	ND	ND
Creatinine (umol/L)*	ND	ND	>1.5 ULN or >1.5 × baseline	>3 ULN or >3 × baseline
Creatinine clearance (mL/min)	<60	<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
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:**

Parameter (SI unit)	LL	LLL	HH	HHH
				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]. Note: All events of ALT or AST ≥3xULN **and** total bilirubin ≥2xULN (>35% direct bilirubin) or ALT or AST ≥3xULN **and** INR >1.5 may indicate severe liver injury **(possible 'Hy's Law') and must be reported to sponsor in an expedited manner and as an SAE if SAE criteria are met**. The INR stated threshold value will not apply to participants receiving anticoagulants.
ALERT = study-specific alerts that trigger specific actions by the investigator [see Sections 5.1.12]; 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 6 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 score) that can be used to detect change over time in a group of MS subjects. This is done by creating Z-scores for each component of the MSFC.

MSFC Score = {Zarm, average + Zleg, average + Zcognitive} / 3.0

Where Zxxx =Z-score

Nine Hole Peg Test

Name:_____

Dominant Hand (circle one): Right Left

Time to complete the test in seconds:

Date: _____ Dominant Hand: _____ Non-Dominant Hand: _____

Date: _____ Dominant Hand: _____ Non-Dominant Hand: _____

Date: _____ Dominant Hand: _____ Non-Dominant Hand: _____

Date: _____ Dominant Hand: _____ Non-Dominant Hand: _____

PASAT - Form A

Name_____ Date_____

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

Total Correct (raw) = _____ Percent Correct = _____

PASAT - Form B

Name_____ Date_____

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

Total Correct (raw) = _____ Percent Correct = _____

Appendix 7 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 8 Electronic self-rated version of the Columbia-Suicide Severity rating Scale (eC-SSRS)

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
Assess prior responses and present introduction:

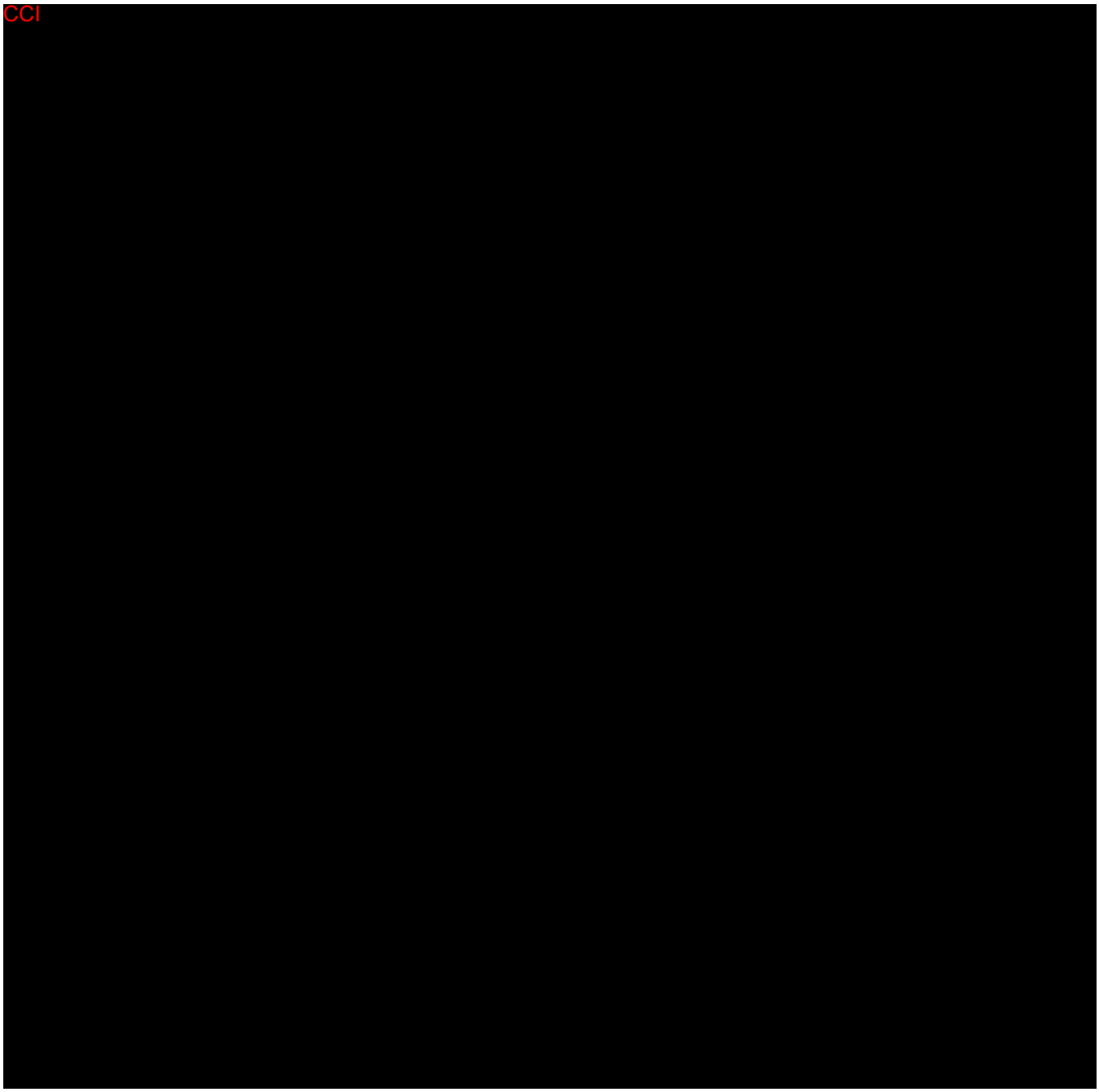
Other than the times you have already told me about since your last call when you did things intending to kill yourself or thought you might have died, when you started to do something to end your life but someone or something stopped you, and when you started to do something to end your life but stopped 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 9 SF-36v2™

CCI

[redacted]


CCI

CCI

[redacted]

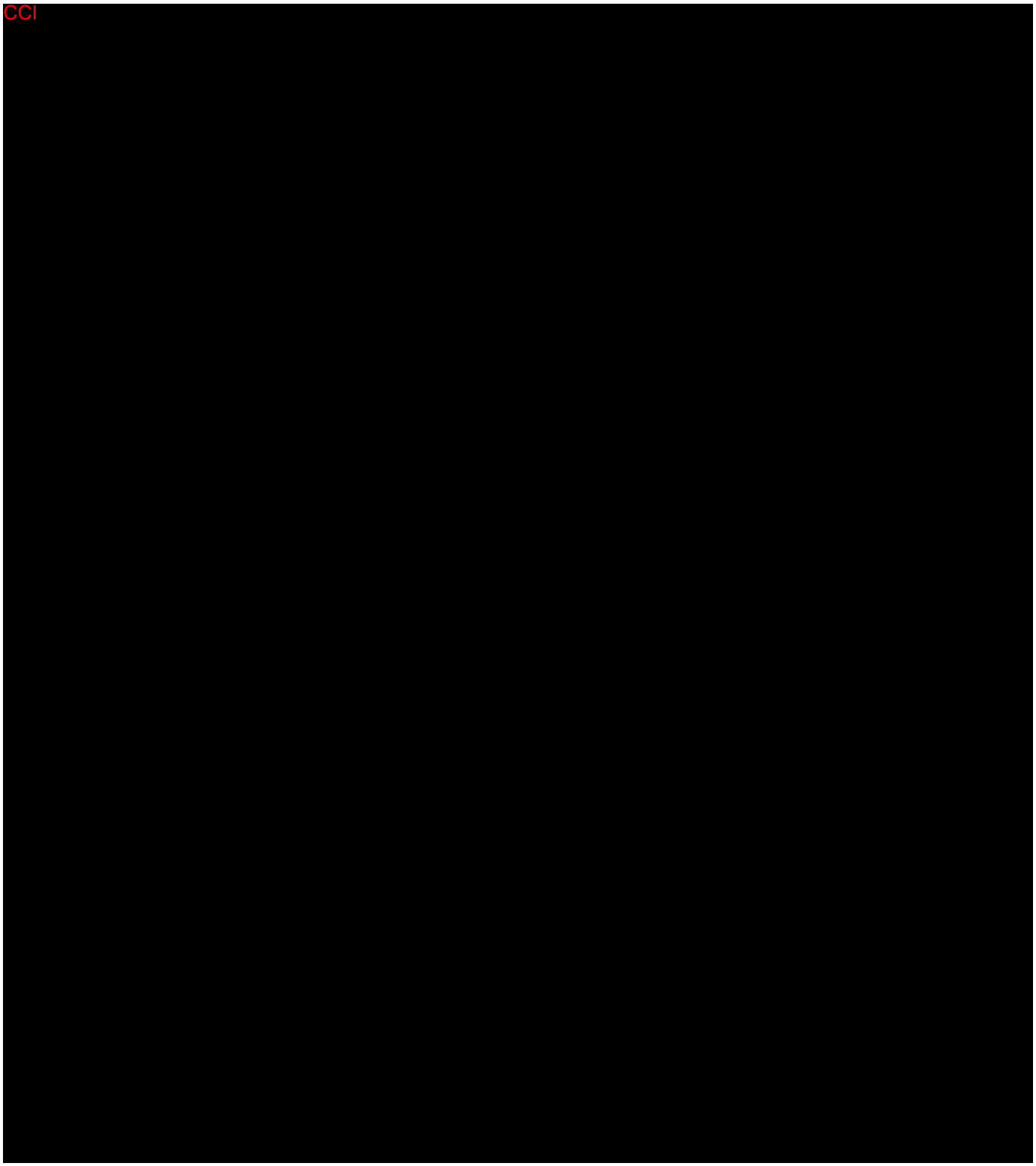
CCI

[redacted]

CCI

[redacted]

CCI



CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

Appendix 10 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 11 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:		

Appendix 12 Guidance on study conduct during the COVID-19 (coronavirus) pandemic

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study-related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgment of the investigator to protect the health and well-being of participants and site staff. If at any time a participant's safety is considered to be at risk, study intervention will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation with the participant, investigator, and the sponsor. Missed assessments/visits will be captured in the clinical trial management / EDC system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the case report form (CRF).

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a participant has tested positive for COVID-19, the investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

GUIDANCE SPECIFIC TO THIS PROTOCOL:

- **Patient Visits & Assessments**

Assessments that may be completed over the phone include assessment of relapse, eC-SSRS, review of adverse events and concomitant medications. Vital signs can be collected in a remote

setting by the subject, caregiver, delegated site staff/in-home nurse, or general practitioner, as feasible. Please ensure the remote method you choose is allowable per local regulations and fully documented in the subject source files.

It is important for safety monitoring of laboratory parameters to continue according to the protocol schedule. If access to the study site (and therefore the central lab) is not possible, local laboratories may be used to monitor laboratory parameters. An alternative, if allowed per local regulations, is to use delegated site staff/in-home nursing to collect blood samples at the subject's home and ship to either the central laboratory or an accredited local laboratory for testing. Where local laboratories are used, it's important to ensure appropriate documentation of laboratory reference ranges. If abnormal laboratory values requiring follow-up in the protocol, or any other abnormality deemed critical by the investigator, are unable to be followed-up, it is recommended to temporarily interrupt (for a maximum of 12 weeks) until the abnormality can be considered resolved or permanently discontinue study treatment.

Other protocol-required examinations and assessments not conducive to remote administration can be conducted as soon as it is feasible for the subject to come to the site for a visit. As clinically indicated, other local resources such as the subject's general practitioner or delegated site staff/in-home nursing can be considered.

- **Study Drug Dispensation**

If a subject is unable to travel to the site for a scheduled visit where study drug would be dispensed, the following alternate measures should be discussed with the sponsor and may be considered to ensure continuity of treatment:

- A caregiver or family member may pick up study drug on behalf of the subject if first discussed and agreed by the subject. The conversation with the subject must be documented in the source files. The subject must name the individual who will pick up study drug on their behalf. This is necessary for site staff to confirm the study drug is provided to the appropriate individual, ensure proper chain of custody of study drug, and to maintain subject privacy. This must be confirmed and documented in the subject source file.
- Investigative site staff may deliver study drug directly to the subject's home. The chain of custody and transit conditions must be clearly documented within the subject source file.
- If no other alternative is feasible, direct-to-patient shipment of study drug from the site may be considered with prior approval from the sponsor and relevant health authority, as applicable.
- It is important to remind subjects that in case of treatment interruption of 4 or more consecutive days, they should inform the investigator and/or site staff immediately. Ponesimod treatment can only be restarted with uptitration and on-site cardiac monitoring, as applicable, as described in the protocol.

- **COVID-19 Infection in MS Patients:**

There is currently no available data suggesting that patients treated with ponesimod should have treatment interrupted during the COVID-19 pandemic. In general, patients receiving immunomodulators should continue treatment and continue to exercise precautionary measures to minimize the risk of infection. If a subject develops symptoms associated with coronavirus infection, it is recommended to confirm the diagnosis using locally approved laboratory kits and reported to the local health authorities, as required. Subjects with positive test results for coronavirus should have this recorded as an AE, and if hospitalized, this should be reported as an SAE. It is important to notify the treating physician of the subject's participation in this clinical study and details of the study treatment. It is also recommended to follow local MS Society recommendations.

- **On-site Monitoring Visits:**

In case on-site monitoring visits are not possible, your monitor may arrange remote site monitoring activities with you until the point at which regular on-site monitoring visits may resume.

All of the above measures are recommended for consideration on a temporary basis during the COVID-19 pandemic to enable continuity of treatment and to ensure that subject assessments, particularly those assessing relapse and safety, continue as outlined in the protocol without imposing health risk to subjects, their families, and site staff. Every effort should be made to complete all protocol-required assessments. Investigators should use their clinical judgment and benefit risk assessment in determining if a subject can continue study treatment in the absence of on-site clinic visits. If remote visits are not possible, or if in the investigator's judgment, appropriate safety monitoring is not feasible in a remote setting, the investigator should consider temporarily interrupting study treatment (for a maximum of 12 weeks per protocol) or discontinuing study treatment and initiating treatment with another available disease modifying treatment (DMT).

STUDY CONDUCT RELATED TO COVID-19 VACCINE DEPLOYMENT FOR NONCOVID-19 CLINICAL TRIALS

Current guidelines from global MS societies recommended that people with MS should be vaccinated against COVID-19.[1,2,3] Having MS does not increase the risk of COVID-19 virus infection or the risk to develop severe forms of the infection more than the general population and it is important that DMT in MS patients is continued and maintained.[4] It is therefore recommended that people with MS currently taking a DMT, including ponesimod, continue with their treatment unless advised to stop by their treating physicians (e.g., MS patients on DMT with risk factors for severe COVID-19 infections).

No clinical data are available on the efficacy and safety of vaccinations in patients taking ponesimod.

Based on preclinical data, vaccinations may be less effective if administered during treatment.

There are 4 main types of COVID-19 vaccines (all non-live) that are currently available (see below). For a complete overview of the COVID-19 vaccine landscape, please refer to the WHO website.[5]

- **mRNA vaccines** are based on the SARS-CoV-2 spike glycoprotein antigen encoded by RNA and formulated in lipid nanoparticles;
- **Protein subunit vaccines** based on full-length spike protein (S), receptor-binding domain (RBD), non-RBD S protein fragments, and non-S structural proteins;
- **Vector vaccines** consisting of a recombinant adenovirus carrying the gene for SARS-CoV-2 virus spike glycoprotein;
- **Inactivated vaccines** use viruses whose genetic material has been destroyed so they cannot replicate, but can still trigger an immune response.

As stated in Section 5.2.2, vaccination with non-live vaccines is allowed while on study treatment if the vaccination is advised by the primary investigator / treating neurologist, based on her/his clinical assessment of the risk/benefit for the individual patient, and if supported by guidelines for vaccination relevant to this patient population, as applicable.

Therefore, all above mentioned COVID-19 vaccines may be administered to study subjects.

Important notes and reminders:

- Vaccination with live vaccines is prohibited, except if performed during a temporary treatment interruption period. In this case it must be performed not earlier than 1 week after the last dose of study treatment, and treatment can be reinitiated only after at least 4 weeks from completion of vaccination (see Section 5.2.3).
- Please report any administered vaccines on a Concomitant Medication page in the CRF.

If a patient is eligible for COVID-19 vaccination in accordance with their local regulations their participation in the study should be modified as required.

The reporting of any AEs (including SARS-CoV-2 infection or those associated with COVID-19 vaccination) should be reported as described in Section 10.

References:

1. MS International Federation 2021. MS, the coronavirus and vaccines – updated global advice. Available from: https://www.msif.org/news/2020/02/10/the-coronavirus-and-ms-what-you-need-to-know/ews today 2021. Accessed 19 July 2021.
2. National MS Society 2021. COVID-19 vaccine guidance for people living with MS. https://www.nationalmssociety.org/coronavirus-covid-19-information/multiple-sclerosis-and-coronavirus/covid-19-vaccine-guidance#section-1. Accessed 19 July 2021.

3. National MS Society 2021. MS treatment guidelines during coronavirus. Available from: https://www.nationalmssociety.org/coronavirus-covid-19-information/multiple-sclerosis-and-coronavirus/ms-treatment-guidelines-during-coronavirus. Accessed 19 July 2021.
4. Zheng C, Kar I, Chen CK, et al. Multiple Sclerosis Disease-Modifying Therapy and the COVID-19 Pandemic: Implications on the Risk of Infection and Future Vaccination. CNS Drugs. 2020;34(9):879-896.
5. WHO 2021. COVID-19 vaccine tracker and landscape. Available from: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines. Accessed 19 July 2021.

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Actelion Pharmaceuticals Ltd

Signature: [electronic signature appended at the end of the protocol] Date: _____
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Signature

User	Date	Reason
PPD	17-Mar-2022 20:00:35 (GMT)	Document Approval

Janssen Research & Development *

Clinical Protocol

GUIDANCE ON STUDY CONDUCT DURING MAJOR DISRUPTION

Multicenter, Non-Comparative Extension to Study AC-058B301, to Investigate the Long-Term Safety, Tolerability, and Control of Disease of Ponesimod 20 mg in Subjects With Relapsing Multiple Sclerosis

Protocol AC-058B303; Phase 3

ACT-128800 / JNJ-67896153 ponesimod

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; Janssen Sciences Ireland UC; Janssen Biopharma Inc.; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

United States (US) sites of this study will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).

EudraCT NUMBER: 2009-011470-15

Status: Approved
Date: 12 May 2022
Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-RIM-736230, 2.0

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

Study Conduct During Major Disruption Due to the Regional Crisis

It is recognized that the regional crisis may have an impact on the conduct of this clinical study due to, for example, travel restrictions/limited access to public places, including hospitals; study site personnel being unavailable, or reassigned to critical tasks.

The sponsor is providing options for study related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. In case it is not possible to obtain initial informed consent of potential participant or updated written informed consent of study participant due to movement restrictions, study participant may provide consent verbally in the presence of an impartial witness. If, at any time, a participant's travel to the study site is considered to be dangerous, study participation may be interrupted, and study follow-up conducted. If it becomes necessary to discontinue participation in the study, the procedures outlined in the protocol for discontinuing study intervention will be followed.

If, as a result of the regional crisis scheduled visits cannot be conducted in person at the study site, they will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow-up. Modifications to protocol-required assessments may be permitted after consultation with the participant, investigator, and the sponsor. All protocol deviations related to the regional crisis should be documented with the prefix "Regional Crisis" in the CRF. Missed/remote assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "Regional Crisis" in the CRF.

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. Modifications made to the study conduct as a result of the regional crisis should be summarized in the clinical study report.

All of the described measures are recommended for consideration on a temporary basis during the regional crisis to enable continuity of treatment and to ensure that patient assessments, particularly those assessing relapse and safety, continue as outlined in the protocol without imposing health risk to patients, their families, and site staff. Every effort should be made to complete all protocol-required assessments. Investigators should use their clinical judgment and benefit risk assessment in determining if a patient can continue study treatment in the absence of on-site clinic visits. If remote visits are not possible, or if in the investigator's judgment, appropriate safety monitoring is not feasible in a remote setting, the investigator should consider transferring the patient to

another clinical trial site, temporarily interrupting study treatment (for a maximum of 12 weeks per protocol) or discontinuing study treatment and initiating treatment with another available disease modifying treatment (DMT). Alternatively, the patient may be shared with another site, especially if a return to the original site is feasible. If study treatment is interrupted or a patient discontinues from the study the investigator must check the availability of subsequent standard of care.

Patient Visits and Assessments

The investigator should assess the feasibility and risk of maintaining scheduled treatment visits on a case-by-case basis, depending on local conditions and guidance by local authorities, and should not hesitate to contact the study sponsor for additional guidance. Assessments that may be completed over the phone include assessment of relapse, review of adverse events and concomitant medications. Vital signs can be collected in a remote setting by the patient, caregiver, delegated site staff/in-home nurse, or general practitioner, as feasible. Please ensure the remote method you choose is allowable per local regulations and fully documented in the patient source files.

Other protocol-required examinations and assessments not conducive to remote administration can be conducted as soon as it is feasible for the patient to come to the site for a visit. As clinically indicated, other local resources such as the patient's general practitioner or delegated site staff/in-home- nursing can be considered.

Specific Laboratory Instructions

It is important for safety monitoring of laboratory parameters to continue according to the protocol schedule. If access to the study site (and therefore the central laboratory) is not possible, local laboratories may be used to monitor laboratory parameters. An alternative, if allowed per local regulations, is to use delegated site staff/in-home nursing to collect blood samples at the patient's home and ship to either the central laboratory or an accredited local laboratory for testing. Where local laboratories are used, it is important to ensure appropriate documentation of laboratory reference ranges. If abnormal laboratory values requiring follow-up in the protocol, or any other abnormality deemed critical by the investigator, are unable to be followed up, it is recommended to temporarily interrupt (for a maximum of 12 weeks) until the abnormality can be considered resolved or permanently discontinue study treatment.

At times when courier support is not available to move samples to the central laboratory, then laboratory assessments should focus on the following order of priority:

1. Utilize local laboratory assessments required to ensure participant safety. Generally, this includes CBC (complete blood count) and serum chemistry assessments, as per protocol assessment schedule and investigator clinical judgement.
2. All samples such as biopsy tissue which have long-term stability should continue to be collected and stored at the study site. Other labs considered investigational, such as immunogenicity samples, can be collected and stored as per the protocol until a time where transportation services are restored.

3. Should local laboratories be used, please refer to the study protocol on what is to be collected in terms of local laboratory documentation, ie, laboratory ranges.

Study Drug Dispensation and Other Trial Supplies

Study drug supply is monitored via IWRS. It is imperative for ongoing management, any study medications dispensed is recorded in IWRS. Any interruptions of patient treatment due to supply availability, should be alerted to the Site Manager. Damaged supplies should be reported as soon as possible so managing re-supply can be prioritized. Trial related supplies such as laboratory kits may be interrupted. Local laboratory supplies may be utilized as outlined in the Study Laboratory Manual. For other supplies, consult with the Site Manager to discuss feasible options.

To ensure uninterrupted treatment, consider performing an early (unscheduled) study drug dispensation for your patients as soon as possible at your discretion ensuring that the material will not expire before the next scheduled visit. This is important since an interruption of ponesimod treatment may be associated with return of MS disease activity. Also, due to the known risk of bradyarrhythmia upon treatment re-initiation after an interruption of 4 days or longer, treatment must be restarted using the up-titration kit. If a patient is unable to travel to the site for a scheduled visit where study drug would be dispensed, the following alternate measures should be discussed with the sponsor and may be considered to ensure continuity of treatment:

- A caregiver or family member may pick up study drug on behalf of the patient if first discussed and agreed by the patient. The conversation with the patient must be documented in the source files. The patient must name the individual who will pick up study drug on their behalf. This is necessary for site staff to confirm the study drug is provided to the appropriate individual, ensure proper chain of custody of study drug, and to maintain patient privacy. This must be confirmed and documented in the patient source file.
- Investigative site staff may deliver study drug directly to the patient's home. The chain of custody and transit conditions must be clearly documented within the patient source file.
- If no other alternative is feasible, direct-to-patient shipment of study drug from the site may be considered with prior approval from the sponsor and relevant health authority, as applicable.
- It is important to remind patients that in case of treatment interruption of 4 or more consecutive days, they should inform the investigator and/or site staff immediately. Ponesimod treatment can only be restarted with up-titration and on-site cardiac monitoring, as applicable, as described in the protocol.

On-site Monitoring Visits:

In case on-site monitoring visits are not possible, your Site Manager may arrange remote site monitoring activities with you until the point at which regular on-site monitoring visits may resume.

SAE reporting should continue as usual until further notification through any of the following methods:

- Secure! email
- If secure email is not possible, please call your Site Manager or Local Trial Manager

For sites not impacted, please continue to adhere to all protocol and contractual agreements (protocol compliance to treatment, safety and efficacy evaluations, safety reporting and data entry timelines).

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Actelion Pharmaceuticals Ltd

Signature: [electronic signature appended at the end of the protocol] Date: _____
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Signature

User	Date	Reason
PPD	12-May-2022 20:48:52 (GMT)	Document Approval