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

Ponesimod / ACT-128800 / JNJ-67896153

Relapsing-remitting Multiple Sclerosis

Protocol AC-058B202

Multicenter, randomized, double-blind, parallel-group extension to study AC-058B201 to investigate the long-term safety, tolerability, and efficacy of 10, 20, and 40 mg/day ponesimod, an oral $S1P_1$ receptor agonist, in patients with relapsing -remitting multiple sclerosis.

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LIST OF ABBREVIATIONS

ACTH	Adrenocorticotropic hormone
AE	Adverse event
ALT	Alanine aminotransferase/serum glutamic pyruvic transaminase (SGPT)
ARR	Annualized relapse rate
AST	Aspartate aminotransferase/serum glutamic oxaloacetic transaminase (SGOT)
AV	Atrioventricular
BP	Blood pressure
bpm	Beats per minute
CL	Confidence limit
CNS	Central nervous system
CRF	Case report form
CRO	Contract research organization
CSF	Cerebrospinal fluid
CUALs	combined unique active lesions
DBP	Diastolic blood pressure
DMT	Disease modifying therapy
DTPA	Diethylenetriamine penta-acetic acid
DWI	Diffusion-weighted imaging
EAE	Experimental autoimmune encephalomyelitis
EC	Ethics Committee
eCRF	electronic Case report form
eDC	electronic Data Capture
EDSS	Expanded Disability Status Scale
ELISA	enzyme-linked immunosorbent assay
EOS	End-of-study
EOT	End-of-treatment

FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FLAIR	Fluid-attenuated inversion recovery
FS	Functional System
FU	Follow-up
FVC	Forced vital capacity
GCP	Good Clinical Practice
Gd+	Gadolinium-enhancing
HR	Heart rate
i.v.	Intravenous(ly)
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IFN	Interferon
IgG	Immunoglobulin G
INR	International Normalized Ratio
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
JCV	John Cunningham virus
MACE	Major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
MIAC	Medical Image Analysis Center
mITT	Modified intent-to-treat
MRI	Magnetic resonance imaging/image
MS	Multiple sclerosis
o.d.	Once daily
OCT	Optical coherence tomography
OSB	Ophthalmology safety board

PCR	Polymerase chain reaction
PD	Pharmacodynamic(s)
PFT	Pulmonary function test
PK	Pharmacokinetic(s)
PML	Progressive multifocal leukoencephalopathy
RMS	Relapsing multiple sclerosis
RNFL	Retinal nerve fiber layer
RRMS	Relapsing-remitting multiple sclerosis
S1P	Sphingosine-1-phosphate
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SOC	System organ class
SOP	Standard operating procedure
SPMS	Secondary progressive multiple sclerosis
SUSAR	Suspected unexpected serious adverse reaction
TdP	Torsades de pointes
TP	Treatment period
WBC	White blood cell
WHO	World Health Organization
WOCBP	Women of childbearing potential

GLOBAL AMENDMENT 11

Amendment rationale

This amendment applies to global protocol AC-058B202 Version 11, dated 04 May 2021, and the following local protocol version:

- Final Version 10.GBR.C dated 27 October 2020

The resulting amended global protocol is Version 12, dated 15 March 2022. The relevant local protocol versions have also been updated (ie, for the UK).

The reasons for this substantial amendment are:

- To allow any EDSS/FS tool which is used at the site as a standard instrument.
- To introduce immunogenicity analysis into the statistical section.
- To remove the bronchodilator test at the scheduled PFT due to the prolonged length of the study.
- To narrow the scope of vaccine-specific antibody titers from pre- to post vaccination to patients having received non-live vaccination against influenza or COVID-19 while on study treatment.
- To update the requirement for OCT to be performed only in the case of visual symptoms suggestive of macular edema or active uveitis, as consistent with the observed dynamic of this event on Sphingosine-1-phosphate (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 the OSB was disbanded for the ongoing long-term extension studies, its status has been clarified and where appropriate reference to the OSB has been removed.
- To confirm the disbandment of the IDMC.
- 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 Word comparison document, showing deletions and insertions in comparison to the previous protocol version.

Changes to the Patient information leaflet:

Where applicable, the same changes have also been made to the patient information leaflet.

Amended protocol sections

The following 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:

SPONSOR AND CRO CONTACT DETAILS

INVESTIGATOR SIGNATURE PAGE

PROTOCOL SYNOPSIS AC-058B202

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3.12.3.1	Visit P1 (Day 1)

Summary of previous amendments

Amendment	Date	Main reason(s)
1	14Apr10	• Adjustment of the AC-058B202 extension study protocol to reflect changes introduced in the AC-058B201 core study protocol.
2	16Feb12	• Ponesimod 40 mg treatment arm is stopped and patients from this treatment arm are re-randomized to either ponesimod 10 mg or 20 mg; • Introduction of treatment period 2; • Extension of ponesimod treatment by an additional 144 weeks (approximately 3 years) with 10 and 20 mg ponesimod in tablet formulation (i.e., new formulation); • Dose response relationship of ponesimod doses with lymphocyte counts, MRI-related endpoints and annualized relapse rates were introduced as additional objectives.
3	9Sep13	• Sponsor is now defined as unblinded - Investigators, patients and non-sponsor ancillary personnel are still blinded.
4	9Oct14	• Extension of ponesimod treatment by an additional 288 weeks (5.5 years) or until commercial availability of ponesimod for treatment of multiple sclerosis in the patient's country, whichever comes first.
5	6Nov14	• Modification of the requirements for contraceptive methods (i.e., a sperm immobilizing agent could be used in case no spermicide is commercially available).
6	29Oct15	• Amendment of the definition of a "confirmed relapse"; • Modification of the requirements for contraceptive methods (i.e., a contraceptive method from the Group 2 can be used without combining it with a spermicide or a sperm immobilizing agent); • Alignment with the information contained in the Investigator's Brochure on the risk of hypertension.

Amendment	Date	Main reason(s)
7	29Mar17	• To introduce treatment period (TP) 3, during which all patients will receive ponesimod 20 mg. This was based on a recommendation from the IDMC; results from an analysis comparing safety and efficacy outcomes of the two doses of ponesimod currently used in the study, 10 mg and 20 mg, suggested that the 20 mg dose had a better efficacy than the 10 mg dose, with a similar safety profile. • To allow women of childbearing potential (WOCBP) who wish to become pregnant to stay in the study, provided that the study drug had been interrupted prior to pregnancy and re-initiated only after delivery (and after breastfeeding had been stopped).
8	14May20	• To extend the duration of ponesimod treatment by up to an additional 108 weeks (2.1 years) in order to ensure treatment continuity until commercial availability in the patient's country. As a result, the combined duration of TP2 and TP3 is extended up to a maximum of 540 weeks. • To introduce the 2-week gradual uptitration regimen, to be used in case of re-initiation of study drug during TP3. • 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. • To provide guidance regarding conduct of the study during the COVID-19 (coronavirus) pandemic. • To introduce guidance for subject monitoring and discontinuation in case of liver enzyme abnormalities. • To align the cardiovascular criteria for discontinuation with that used in Phase 3 clinical studies with ponesimod.

Amendment	Date	Main reason(s)
9	19Oct20	• 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 drug 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. • To clarify procedures related to the reporting of multiple sclerosis (MS) relapses and align with the wording in the protocol for the ongoing Phase 3 study (AC-058B303/OPTIMUM-LT).
10	04May21	• To align instructions related to vaccination to those in the Investigator's Brochure. • To introduce the transition of paper Case Report Form (CRF) to electronic Case Report Form (eCRF). • To further clarify guidance regarding conduct of the study during the COVID-19 (coronavirus) pandemic and the deployment of COVID-19 vaccines. • To update sponsor contact information.

PROTOCOL SYNOPSIS AC-058B202

TITLE	Multicenter, randomized, double-blind, parallel-group extension to study AC-058B201 to investigate the long-term safety, tolerability, and efficacy of 10, 20, and 40 mg/day ponesimod, an oral $S1P_1$ receptor agonist, in patients with relapsing-remitting multiple sclerosis.
ACRONYM	None
OBJECTIVES	• To investigate the long-term safety and tolerability of ponesimod. • To investigate the long-term efficacy of ponesimod. • To explore the dose response relationship of 10, 20 and 40 mg ponesimod on lymphocyte count, MRI endpoints, annualized relapse rate (ARR), and safety endpoints.
DESIGN / PHASE	Prospective, multicenter, multinational, randomized, double-blind, multiple-dose, uncontrolled, parallel-group extension to Phase 2b study.
STUDY PLANNED DURATION	**First patient First visit** Q2 2010 **Last patient First visit** Q2 2011 **Last patient Last visit** Q4 2023
CENTERS / COUNTRIES	81 centers in 21 countries
PATIENTS / GROUPS	**Patients participating in the extension study** Patients who were randomized into study AC-058B201 (hereafter called "core study") and completed their regular Week 24 end-of-treatment (EOT) visit while on study treatment will qualify to enter this study (hereafter called "extension study"). Patients who received ponesimod during the core study will continue to receive their maintenance once daily (o.d.) doses of 10, 20, or 40 mg of ponesimod during treatment period (TP) 1. Patients who received placebo during the core study will be randomized in a 1:1:1 ratio to o.d. doses of 10, 20, or 40 mg of ponesimod during TP1. Patients receiving 40 mg ponesimod during TP1 will be re-randomized to 10 or 20 mg in a 1:1 ratio in TP2. Patients on

	10 and 20 mg ponesimod during TP1 will continue with these same doses throughout TP2. All patients will receive a maintenance dose of 20 mg ponesimod during TP3.
INCLUSION CRITERIA	1. Patients who completed study treatment at their regular Week 24 (EOT) visit within the core study. 2. Women of childbearing potential must: • Have a negative urine pregnancy test at their regular Week 24 visit within the core study. • Use reliable methods of contraception for up to at least 30 days after study drug discontinuation as described in Section 4.4.2. 3. Signed informed consent for participating in the extension study prior to administration of the first dose in the transition period (i.e., prior to continuation of dosing at Visit 11 (Week 24) of the core study).
EXCLUSION CRITERIA	1. Patients meeting at their regular Week 24 (EOT) visit, during the transition period, and/or at Visit E1 any of the study-specific criteria for permanent discontinuation of study drug as defined in Appendix 1, or patients receiving any of the prohibited concomitant medication as outlined in Section 3.4.4.3 and Appendix 8. 2. Any other clinically relevant medical or surgical condition, which, in the opinion of the investigator, would put the patient at risk by participating in the extension study.
CONCOMITANT MEDICATIONS	**Recommended** • Acute exacerbations of multiple sclerosis (MS) should be treated with methylprednisolone 1 g intravenously (i.v.) daily for 3 to 5 days. Oral taper with corticosteroids is not permitted. **Allowed** • Administration of i.v. atropine in the event of symptomatic bradycardia. • 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. • Glatiramer acetate and interferon (IFN) β-1a only during study drug interruptions for planned pregnancy. These treatments may be started 7 days after study drug interruption and must be stopped 7 days before re-initiation of study drug. • Low dose corticosteroid (up to 10 mg prednisone equivalent daily), given as short-term treatment (up to 2 weeks per treatment cycle with at least 8 weeks' interval between treatment cycles and no more than 4 weeks per year of the study duration on average). • Inhaled corticosteroids for pulmonary conditions. • Other treatments considered necessary for the patient's benefit and not categorized as prohibited concomitant medications. **Prohibited** • Systemic corticosteroids or adrenocorticotropic hormone, except for: the treatment of acute MS exacerbations (see Recommended concomitant medications above); short-term treatment with a low dose of corticosteroid; and inhaled corticosteroids for pulmonary conditions (see Allowed concomitant medications above). • Immunomodulating treatment (e.g., IFN β, glatiramer acetate, natalizumab or other monoclonal antibody therapy [except glatiramer acetate or IFN β-1a during study drug interruptions for planned pregnancy as described under "Allowed"]). • Immunosuppressive treatment (e.g., cladribine, mitoxantrone or other systemic immunosuppressive drugs such as azathioprine, cyclophosphamide, cyclosporine or methotrexate). • i.v. immunoglobulin. • 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 (HR) lowering systemic therapy [non-exhaustive list provided in Appendix 8]. • Medications with risk of torsades de pointes unless the benefit-risk is acceptable [non-exhaustive list provided in Appendix 9]. • Any investigational drug.
STUDY PERIODS	**Transition period (on core study medication)** • The transition period is defined as the time between study drug intake at Week 24 visit of the core study and the time of study drug intake at Visit E1. • Patients will have to continue using their core study medication every day until and including the day prior to Visit E1. **Treatment periods (on extension study medication)** • Starts with study drug intake at Visit E1. • The first visit of the extension study, Visit E1, will take place within three days after the regular Week 24 visit of the core study. • The AC-058B202 study treatment periods will comprise up to 636 weeks (12.3 years): – TP1: up to 96 weeks (from Visit E1 up to E13) of ponesimod treatment. The patients receive either 10, 20 or 40 mg ponesimod. – TP2 / TP3: up to 540 weeks (Visits P1 to EOT3) of ponesimod treatment. All patients on 40 mg ponesimod will be re-randomized to 10 or 20 mg ponesimod in a 1:1 ratio at Visit P1. Patients receiving 10 and 20 mg ponesimod will continue with these respective maintenance doses in the TP2.

	In TP3, all patients will receive a maintenance dose of 20 mg ponesimod until EOT3. Patients will be switched from TP1 to TP2 at Visit P1. Visit P1 must be scheduled as the next regular visit (12 weeks after the last visit of TP1) for patients who completed at least Visit E9 (Week 48) of TP1 (being still on treatment). Patients who have already completed treatment up to Visit E13 (EOT2) may still be enrolled into TP2, provided study drug was not discontinued for longer than 3 months. In this case, Visit P1 must be scheduled as soon as possible and **if applicable, patients must undergo a study drug re-initiation and/or uptitration.** During Visit P1 the following must be considered: • Patients must be switched from capsules to tablets • Patients receiving 40 mg ponesimod will be re-randomized to 10 or 20 mg ponesimod in a blinded fashion. When feasible, patients will be switched from TP2 to TP3 at the earliest scheduled visit following approval of protocol version 8 by Ethics Committees (ECs)/ Institutional Review Boards (IRBs) and health authorities and after having signed the revised Informed Consent Form. The day of the first open -label dose of ponesimod 20 mg will correspond to the start of TP3. Patients not enrolling into TP3 will have to perform the EOT3 visit. **End-of-treatment** • The EOT (EOT2 or EOT3) visit in the extension study, at an individual patient's level, should not be later than one day after the last dose of ponesimod. • Patients who prematurely discontinue study drug during the extension study must have their EOT2 or EOT3 visit as soon as possible but no later than 5 days after the last dose of study drug**.**

	• EOT2 visit must be performed by patients discontinuing study drug during/ at the end-of-TP1. • EOT3 visit must be performed by patients discontinuing study drug during/ at the end-of-treatment period 2 or TP3. • The EOT3 visit must also be performed by patients completing study treatment due to availability of commercially available ponesimod. Commercially available ponesimod may be initiated on the day after last intake of study drug. **Safety Follow-up period** • For TP1: 30 days after last dose of study drug. • For TP2 or TP3: 90 days after last dose of study drug. **End-of-study (EOS2/ EOS3)** Patients who completed ponesimod treatment or who discontinued study drug prematurely reach end-of-study (EOS) at an individual level: • 30 days after the last dose of study drug (EOS2) in TP1 • 90 days after the last dose of study drug (EOS3) in TP2 or TP3 The safety follow-up visits (including EOS3) will also be conducted for patients who have switched to commercially available ponesimod.
TRIAL DRUG	During TP1: One capsule of 10, 20 or 40 mg ponesimod, administered orally o.d. in the morning with or without breakfast (preferably always in the same way and at approximately the same time). During TP2: One tablet of 10 or 20 mg ponesimod, administered orally o.d. in the morning with or without breakfast (preferably always in the same way and at approximately the same time).

	During TP3: One tablet of 20 mg ponesimod, administered orally o.d. in the morning with or without breakfast (preferably always in the same way and at approximately the same time). All patients entering the extension study (no matter if they received placebo or ponesimod during the core study) will be required to perform the same uptitration or mock uptitration scheme as at the beginning of the core study. Patients who were on ponesimod in the core study will continue on the same dose in the transition period and have mock dose titrations on Day 1 (Visit E1), Day 8 (Visit E2), and Day 15 (Visit E3): • Group I: Group I in the core study (10 mg). 10 mg from Visit E1 (Day 1) until end of TP2. 20 mg during TP3 until EOT3. • Group II: Group II in the core study (20 mg). 20 mg from Visit E1 (Day 1) until EOT3. • Group III: Group III in the core study (40 mg). 40 mg from Visit E1 (Day 1) until at least Visit E9 or up to E13 (EOT2). 10 or 20 mg from Visit P1 until end of TP2. 20 mg during TP3 until EOT3. Patients who were on placebo (Group IV in the core study) will continue on placebo in the transition period and then be randomized 1:1:1 to: • Group IV: 10 mg from Day 1 (Visit E1) until end of TP2. Mock dose titrations on Day 8 (Visit E2) and Day 15 (Visit E3). 20 mg during TP3 until EOT3. • Group V: 10 mg from Day 1 (Visit E1) to Day 7. 20 mg from Day 8 (Visit E2) until EOT3. Mock dose titration on Day 15 (Visit E3).

	• Group VI: 10 mg from Day 1 (Visit E1) to Day 7. 20 mg from Day 8 (Visit E2) to Day 14. 40 mg from Day 15 (Visit E3) until at least Visit E9 or up to E13 (EOT2). 10 or 20 mg from Visit P1 until end of TP2. 20 mg during TP3 until EOT3.
REFERENCE DRUG	No active comparator or placebo will be used in this extension study.
EFFICACY ENDPOINTS	Exploratory efficacy endpoints will be analyzed over the combined treatment period with ponesimod within studies AC-058B201 and AC-058B202 (i.e., starting from the first administration of ponesimod and ending with the EOT2 or EOT3). For "changes from baseline to all assessments" as well as for all numerical endpoints all assessments available after initiation of ponesimod are considered in the combined treatment period. For time -to -event endpoints the start is defined as initiation of study treatment, and patients without events are censored at the end of the combined treatment period. The following exploratory endpoints will be analyzed: 1. Annualized confirmed relapse rate. 2. Time to first confirmed relapse. A relapse is defined as the occurrence of an acute episode of one or more new symptoms, or worsening of existing symptoms of MS, not associated with fever or infection, and lasting for at least 24 hours after a stable period of at least 30 days. A "confirmed relapse" is a relapse accompanied by an increase from the previous clinically stable assessment (i.e., performed at least 30 days after the onset of any previous relapse) of at least 0.5 point in the Expanded Disability Status Scale (EDSS) score, or one point in the score for at least one of the Functional System (FS) scores, excluding the bowel and bladder, and mental FS. The confirmatory EDSS must be performed within 7 days of the onset of a new symptom or worsening of an existing symptom of MS.

	Symptoms of transient neurological worsening that do not meet the criteria for "confirmed relapse" because unaccompanied by objective findings, but still judged to constitute a relapse by the treating neurologist, will be recorded as "unconfirmed relapse" and included in the number of total relapses. 3. Time to 24-week confirmed disability progression up to end of the study. Disability progression is defined as an increase of at least one full point in the EDSS score (or 1.5 points if the baseline EDSS was 0, or 0.5 points if the baseline EDSS was equal or greater than 5.5) with or without relapse, confirmed at the next scheduled EDSS assessment at least 24 weeks later (or if missing, at the next available scheduled EDSS assessment). The time to event is defined as the time from initiation of study treatment until the first EDSS assessment meeting the criteria for disability progression. 4. Other relapse-related endpoints: • Annualized total relapse rate. • Time to first (total) relapse. • Number of (confirmed and total) relapses. • Number of patients without any (confirmed and total) relapse. • Number of patients with a relapse requiring corticosteroid treatment. 5. MRI-related endpoints: • Number of gadolinium-enhancing (Gd+) lesions per patient recorded on T_1-weighted MRI scans at all assessments. • Number of patients with no Gd+ lesions on T_1-weighted MRI scans at all assessments. • Total volume of Gd+ lesions per patient on T_1-weighted MRI scans at all assessments. • Number of new or enlarging lesions per patient on T_2-weighted MRI scans at all assessments.

	• Change from baseline to all assessments in total lesion volume per patient on T_2-weighted MRI scans. • Number of combined unique active lesions (Gd+ lesions plus new or enlarging T_2 lesions without gadolinium-enhancement) per patient on MRI scans at all assessments. • Percentage change of brain volume from Visit 2 (from AC-058B201) up to the end of the study. • Percentage change of brain volume from Visit 11 (from AC-058B201) up to the end of the study. 6. Neurological endpoints: • Categorical change from baseline to all assessments in EDSS and FS scores. 7. Ophthalmological endpoints: • Change from baseline to all assessments of average retinal nerve fiber layer (RNFL) thickness, central foveal thickness and total macular volume as measured by optical coherence tomography (OCT) at selected centers. • Change from baseline to all assessments of average number of letters correctly read in a best corrected visual acuity test (recorded only at centers that also perform OCT). 8. Changes in vaccine-specific antibody titers from pre- to post vaccination will be explored at the end of the study, at the latest, for patients having received non-live vaccination against influenza or COVID-19 while in the study.
TOLERABILITY / SAFETY ENDPOINTS	The following safety and tolerability endpoints will be analyzed on treatment as described for the exploratory efficacy endpoints: • Change in electrocardiogram (ECG) parameters (HR, PR, QRS, QT, QTc) from baseline to all pre-dose assessments, and from pre-dose to post-dose at selected time points during the study. • Treatment-emergent clinically relevant abnormalities as assessed by 12-lead ECG (central reading).

	• Change in left ventricular ejection fraction as assessed by Standard 2D echocardiography (at selected centers) from baseline to all assessments. • Treatment-emergent clinically relevant abnormalities as assessed by Standard 2D/Doppler echocardiography (at selected centers). • Change in pulmonary function tests (PFTs: forced expiratory volume in 1 second [FEV_1], forced vital capacity [FVC], FEV_1/FVC ratio, and FEV_1 and FVC in percent of predicted value) from baseline to all assessments. • Change in ophthalmological exam (best corrected visual acuity, low contrast visual acuity, visual fields, dilated ophthalmoscopy), and at selected centers OCT from baseline to all assessments. • Change in systolic and diastolic blood pressure from baseline to all pre-dose assessments, and from pre-dose to post-dose at selected time points during the study. • Change in laboratory parameters (hematology, blood chemistry, and urinalysis) from baseline to all assessments. • Treatment-emergent laboratory abnormalities. • Change in body weight from baseline to all assessments. In addition, the following safety and tolerability parameters will be analyzed: • Treatment-emergent adverse events (AEs), until 15 days after study drug discontinuation. • Post-treatment AEs, from 16 days until up to 90 days after study drug discontinuation. • AEs leading to premature discontinuation of study drug. • Treatment-emergent serious adverse events (SAEs) until 15 days after study drug discontinuation. • Post-treatment SAEs from 16 days until up to 90 days after study drug discontinuation.
PHARMACOKINETIC / PHARMACODYNAMIC ENDPOINTS	**Pharmacokinetic (PK) analyses** • Plasma concentrations of ponesimod will be determined at trough (pre-dose): – on Days 8 and 15 (Visits E2 and E3) and

	– at Visits E4, E7, E9, E13 (EOT2), P2, P7, P14 and P22, as applicable **Pharmacodynamic (PD) analyses** • Absolute count and percent change in peripheral blood lymphocyte counts as a function of ponesimod dose and plasma concentrations at trough level (pre-dose) on Days 8 and 15 (Visits E2 and E3) and at Visits E4, E7, E9, E13 (EOT2), P2, P7, P14, P22, P30 and EOT3, as applicable. • Post-treatment lymphocyte recovery 8, 30, and 90 days (at 90 days for patients performing TP2 and TP3, if applicable) after study drug discontinuation. • Efficacy and safety parameters will be correlated with absolute lymphocyte counts and magnitude of reduction of lymphocyte counts on an exploratory basis. Additional PK and PD relationships to efficacy and safety parameters may be investigated.
STATISTICAL METHODOLOGY	ARRs and MRI-related endpoints (number of total T1 Gd+ lesions, number of combined unique active lesions, number of new or enlarging T2 lesions) will be analyzed by means of negative binomial regression models. Time to event data (e.g. time to first confirmed relapse, time to disability progression) will be analyzed using the log-rank test. The Kaplan-Meier estimates at different time points are provided together with the 95% two-sided confidence limits (CLs). The time to event will be displayed by a Kaplan-Meier plot. The dose response relationship will be explored for lymphocyte count, MRI-related endpoints (number of total T1 Gd+ lesions, number of combined unique active lesions, number of new or enlarging T2 lesions) and ARR using modeling techniques as described by Bretz et al. All statistical tests are of exploratory nature. Data from the core study AC-058B201 and extension study AC-058B202 will be combined and AC-058B202 will be analyzed alone where deemed appropriate. Baseline is defined as the last assessment performed prior to the first administration of study treatment in AC-058B201 for

	the analyses comparing treatment groups as randomized in AC-058B201 including the placebo treatment period, or first dose of ponesimod treatment in either AC-058B201 or AC-058B202 for the analyses which exclude the placebo treatment period. Full details of the treatment groups and how they are used in the analysis will be described in the SAP. AEs, SAEs, and AEs leading to premature discontinuation of study drug will be tabulated by system organ class (SOC) and individual preferred terms within each SOC.
STUDY COMMITTEES	**Independent Data Monitoring Committee** During the extension study the Independent Data Monitoring Committee (IDMC) continued to follow patients' data on a regular basis and had access to fully unblinded data to ensure patient safety. The IDMC was disbanded on 30th September 2021 following the planned unblinding of the studies. **Ophthalmology Safety Board** An OSB, composed of two independent ophthalmologists, reviewed and evaluated any new or suspected cases of macular edema in a blinded fashion. The OSB was decommissioned from the date of Global Protocol version 12. **MACE adjudication board** A MACE adjudication board will review and evaluate in a blinded fashion the MACE reported in the study. The composition and operations of MACE adjudication board are described in the MACE adjudication board charter.
ANCILLARY STUDIES	The following ancillary studies were implemented in the core study at selected sites and will be continued during the extension study. Details of these studies are described in this protocol. **Exploration of echocardiographic parameters** • Standard 2D/Doppler echocardiography will be performed to assess regional wall abnormalities, aortic valve morphology and function, mitral valve morphology and function, and left ventricular ejection fraction.

	Echocardiography assessments will only be conducted in patients who were assessed during the core study. **Exploration of ophthalmological parameters by optical coherence tomography (OCT)** • Average RNFL thickness, central foveal thickness, and total macular volume will be assessed by OCT as safety and efficacy parameters. From Global Protocol version 12 onwards the scope of this ancillary study will be limited to patients with suspicion of acute uveitis and macular edema.
META-ANALYSIS	Not applicable
PERIODIC ANALYSIS	• During the conduct of the study, data analyses may be performed periodically at specified timepoints (e.g., all patients who complete 12 months of treatment).

Table 1: Visit and assessment schedule (treatment period 1 – up to 96 weeks)

PERIODS	Name		Transition	Double-blind extension treatment period 1												
	Duration			Extended treatment with ponesimod for up to 96 weeks												
VISITS	Number	11	--	E 1	E 2	E 3	---	E 4	E 5	E 6	E 7	E 8	E 9	E 10	E 11	E 12	E 13
	Name	EOT[1]		Randomization			Phone call[2]										EOT2[3]
	Time	W 24	Day -3 to -1	Day 1	Day 8	Day 15	Day 22	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96
	Visit window			W 24 (EOT) + up to 3 days	±1 day	±1 day	±1 day	±2 days	±5 days	±5 days	±14 days	±14 days	±14 days	±14 days	±14 days	±14 days	±14 days
* Informed Consent[4]		X															
* Inclusion/Exclusion criteria		X	X	X													
EDSS / Functional Systems		X									X		X				X
* Chest X-ray		X															X
* MRI		X									X		X				X
Concomitant medications		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
* Physical Examination		X[5]			X	X		X	X	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]
Systolic/diastolic blood pressure		X		X[6]	X[6]	X[6]		X	X	X	X	X	X	X	X	X	X
* 12-lead ECG		X		X[6]	X[6]	X[6]		X	X	X	X	X	X	X	X	X	X
* Echocardiography[7]		X								X	X		X		X		X
Ophthalmologic examination[8]		X						X		X	X		X		X		X
Pulmonary function tests[9]		X			X	X		X	X	X	X		X		X		X
* Hematology/Blood chemistry		X			X	X		X	X	X	X	X	X	X	X	X	X
* Urinalysis		X			X	X		X	X	X	X	X	X	X	X	X	X
* Pregnancy Test		X						X	X	X	X	X	X	X	X	X	X
PK Sampling[10]		X			X	X		X			X		X				X
* Study Drug Dispensing/Return		X[11]		X	X[12]	X[12]		X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

See below for footnotes.
Note: The footnotes apply to Table 1, Table 2, Table 3 and Table 4.

Table 2: Visit and assessment schedule (Safety Follow-up for patients discontinuing during or at the end of treatment period 1 only)

PERIODS	Name	EXTENSION SAFETY FOLLOW-UP	
	Duration	30 days	
	Number	E14	E15
	Name	Follow-up E1	Follow-up E2 (EOS2)
	Time	W96 + 7 days	W96 + 30 days
	Visit Window	±1 day	±5 day
EDSS / Functional Systems			X
* MRI			X
Concomitant Medications		X	X
* Physical Examination		X	X[5]
Systolic/diastolic blood pressure		X	X
* 12-lead ECG		X	X
Ophthalmologic examination[8]			X
Pulmonary function tests		X	X
* Hematology/Blood chemistry		X	X
* Urinalysis		X	X
* Pregnancy Test			X
Adverse Events		X	X
Serious Adverse Events		X	X

See below for footnotes.
Note: The footnotes apply to Table 1, Table 2, Table 3 and Table 4.

Table 3: Visit and assessment schedule (treatment period 2 and treatment period 3 – up to 540 weeks and Safety Follow-up)

PERIODS	Name	Double-blind extension treatment period 2 / Open-label extension treatment period 3[17]			EXTENSION SAFETY FOLLOW-UP[14]		
	Duration	Extended treatment with ponesimod for up to 540 weeks			90 days		
VISITS	Number	P1-P3-P5-P7-P9-P11-P13-P15-P17-P19-P21-P23-P25-P27-P29-P31-P33-P35-P37-P39-P41-P43-P45	P2-P4-P6-P8-P10-12-P14-P16-P18-P20-P22-P24-P26-P28-P30-P32-P34-P36-P38-P40-P42-P44				
	Name			EOT3[13]	FU1	FU2	FU3 (EOS3)
	Time	Day 1-Week 24-48-72-96-120-144-168-192-216-240-264-288-312-336-360-384-408-432-456-480-504-528	Week 12-36-60-84-108-132-156-180-204-228-252-276-300-324-348-372-396-420-444-468-492-516	Week 540	8 days after the last dose of study drug	30 days after the last dose of study drug	90 days after the last dose of study drug
	Visit window	±14 days	±14 days	±14 days	±1 day	±5 days	±7 days
EDSS / Functional Systems[16]		X	X	X		X	X
* Chest X-ray		(X[15]) only at P1		X			
* MRI		(X) only at P1, P5, P9, P13, P17, P21, P25, P29, P33, P37, P41, P45		X		X	
Concomitant medications		X	X	X	X	X	X
* Physical Examination		(X[5]), at P37, P41, P45	(X[5]) until P36	X[5]	X	X[5]	X[5]
Systolic/diastolic blood pressure[6]		X	X	X	X	X	X
* 12-lead ECG[6]		(X[6]), at P37, P41, P45	(X[6]) until P36	X	X	X	
* Echocardiography[7]		(X[7]) at P37, P41, P45		X			
Ophthalmologic examination[8]		(X[8]), at P37, P41, P45		X		X	
Pulmonary function tests[9]		(X[9]), at P37, P41, P45		X	X	X	X
* Hematology/Blood chemistry		X	X	X	X	X	X
* Urinalysis		X	X	X	X	X	X
* Pregnancy Test[18]		X	X	X		X	
PK Sampling[10]		P7 only	(X) only at P2, P14, P22				
* Study Drug Dispensing/Return		X	X	X			
Adverse Events		X	X	X	X	X	X
Serious Adverse Events		X	X	X	X	X	X

See below for footnotes.
Note: The footnotes apply to Table 1, Table 2, Table 3 and Table 4.

Table 4: Visit and assessment schedule (unscheduled visits)

PERIODS	Name	UNSCHEDULED VISITS							
VISITS	Name	Relapse	Unscheduled	Re-initiation[20]		Interruption / planned pregnancy	Eligibility for re-initiation / pregnancy	Re-initiation D1 / pregnancy	Re-initiation D8 / 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 for re-initiation of study drug following study drug interruption for planned pregnancy	Unscheduled visit for re-initiation of study drug following study drug interruption for planned pregnancy
	Time	Any day between Day 1 and FU3 (EOS3)		Any day between Day 1 and EOT3		30 days after study drug interruption for planned pregnancy	30 days (±5 days) before study drug re-initiation		
	Visit window	+ 7 days	NA	NA	±1 day	±7 days	NA	NA	NA
EDSS / Functional Systems[16]		X	X			X	X		
* Chest X-ray									
* MRI			X			X	X		
Concomitant medications		X	X	X	X	X	X	X[19]	X
* Physical Examination		X	X[5]			X	X		
Systolic/diastolic blood pressure[6]		X	X	X	X	X	X	X	X
* 12-lead ECG[6]			X	X	X	X	X	X	X
Ophthalmologic examination[8]			X			X	X		
Pulmonary function tests[9]			X			X	X		
* Hematology/Blood chemistry			X			X	X		
* Urinalysis			X			X	X		
* Pregnancy Test[18]			X			X	X (first assessment)	X (first assessment)	
* Study Drug Dispensing/Return			X	X	X			X[19]	X
Adverse Events		X	X	X	X	X	X	X	X
Serious Adverse Events		X	X	X	X	X	X	X	X

See below for footnotes.
Note: The footnotes apply to Table 1, Table 2, Table 3 and Table 4.

*Data are not collected in the CRFs (unless a finding constitutes an AE or SAE), except for body weight (see footnote 5). For MRI and echocardiography only the date of assessment is collected in the CRFs.

1. All Week 24 (EOT) assessments of the core study (AC 058B201) must be completed prior to randomization in the extension study. If a patient is going to enter the extension study the Visit E1 should be scheduled within 3 days after the Week 24 (EOT) visit of the core study. Patients will have to continue using their core study medication every day until and including the day prior to Visit E1.
2. Phone call: The site will call the patient for information on health status / adverse events.
3. In the event of treatment discontinuation prior to Week 96 (whatever the reason), all assessments planned at Visit E13 (EOT2) must be performed as soon as possible, but no later than 5 days following the date of the last dose of study drug.
4. Informed Consent Form of the extension study must be signed by the patient prior to participating in any study related procedure of the extension study, and prior to continuing using their core study medication on the day of their Week 24 visit of the core study.
5. Physical examination must be performed at all study visits until P37, then yearly until P45, inclusive, and at EOT3, FU1, FU2, and FU3. Includes careful skin examination at each visit from E6 until P37, then at P41, P45, EOT3, and at FU2 and FU3. Body weight only at E7, E9, E11, E13, and yearly from P1 to EOT3.
6. Blood pressure must be performed pre dose at all visits. ECG must be performed pre dose at all study visits until P37, then yearly until Visit P45, inclusive. At the visit when the transition from treatment period 2 (TP2) to treatment period 3 (TP3) will occur, all patients must be monitored at the investigational site for at least 6 hours after dose administration [see Section 3.12.2]. In the event of re initiation of study drug, blood pressure and ECG must be performed pre dose (all patients) and hourly (±15 min) for at least 4 hours and up to 12 hours (only mandated for patients with cardiovascular risk factors and at the discretion of the investigator / treating neurologist for patients without cardiovascular risk factors) [see Appendix 5 and Section 3.12.5.3].
7. Standard 2D/Doppler echocardiography will assess regional wall abnormalities, aortic valve morphology and function, mitral valve morphology and function, and left ventricular ejection fraction. It will be performed at selected centers with adequate equipment and experience. During TP2 and TP3, echocardiography is performed at every other visit from P1 to P35, yearly from Visits P37 to P45, inclusive, and at EOT3.
8. Ophthalmological examination includes best corrected visual acuity, low contrast visual acuity, visual fields, dilated ophthalmoscopy, and optical coherence tomography (OCT) in case of suspicion of macular edema or active uveitis (OCT, only for subjects at risk). During TP2 and TP3, ophthalmologic examination is performed at every other visit from P1 to P35, yearly from Visits P37 to P45, inclusive, at EOT3 and FU2.
9. FEV_1 and FVC. Additional unscheduled pulmonary function tests (PFTs) will be conducted in the event of respiratory symptoms (e.g., dyspnea) or decreased lung function (FEV_1 and/or FVC <80% of baseline value) during the course of the study. During TP2 and TP3, PFTs are performed at every other visit from P1 to P35, yearly from Visits P37 to P45, inclusive, at EOT3 and FU visits.
10. Plasma sample at trough level (pre dose).
11. Patients will have to continue using their core study medication until and including the day prior to Visit E1.
12. Dose uptitration or mock uptitration will take place on Days 8 and 15 during TP1. Study drug re initiation during TP2 will require only one dose uptitration or mock uptitration on Day 8. Study drug re initiation during TP3 will require only one dose uptitration on Day 8.
13. EOT3 visit has to be performed 1 day after the last study drug intake. For premature discontinuations EOT3 should be performed as soon as possible, but no later than 5 days after the last dose of study drug. Additionally, EOT3 visit has to be performed as soon as possible, but no later than 5 days after the last dose of study drug for patients not enrolling into TP3, or for patients completing study treatment due to availability of commercially available ponesimod [see Section 3.12.3.5]. Commercially available ponesimod may be initiated on the day after last intake of study drug.
14. The three Safety Follow up visits must be performed:
    following premature treatment discontinuation
    following treatment discontinuation at EOT3
    following treatment discontinuation for switching to commercially available ponesimod

15. Patients completing the EOT2 (Visit E13) and having a chest X ray done at this visit must not repeat the chest X ray at Visit P1.
16. If the patient experiences a confirmed relapse she/he must be made aware by the primary investigator / treating neurologist of the possibility of withdrawal and of switching to standard treatments approved for RRMS. The patient's decision must be recorded in the medical records.
17. When feasible, patients will be transitioned from TP2 to TP3 at the earliest visit following approval of protocol version 8 by ECs/IRBs and health authorities and after having signed the revised Informed Consent Form. At this visit, all patients must be monitored at the investigational site for at least 6 hours after dose administration [see Section 3.12.2].
18. Women who interrupt the study drug because of planned pregnancy will be exempted from any protocol mandated pregnancy tests after the first positive pregnancy test and until 30 (±5) days before study drug re initiation.
19. Review and assess contraception methods and total duration of study drug interruption, which should not exceed 81 weeks.
20. As described in detail in Appendix 5, patients who miss taking the study drug for four or more consecutive days are required to re initiate ponesimod treatment using the gradual uptitration scheme. In such cases, there will be one or two visits; one visit on the day of re initiation (Day 1) for all patients. An additional visit 14 days (±1 day) after the day of re initiation (Day 15) only mandated for patients with cardiovascular risk factors [see Appendix 5], but may be scheduled for any patient at the discretion of the investigator / treating neurologist.

1 BACKGROUND AND RATIONALE

1.1 Multiple sclerosis

Multiple sclerosis (MS) is an inflammatory autoimmune disorder of the central nervous system (CNS) which is the most common cause of progressive neurological disability in young adults [Compston 2002, 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 major personal, social, and financial consequences for patients, their families, and health care systems.

1.1.1 Immune mediated disease

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

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

1.1.2 Clinical course

The large variety of symptoms and signs of MS results from axonal demyelination, which leads to the slowing or blockade of axonal conduction at diverse affected sites of the brain and spinal cord. Repeated episodes of disease activity may lead to progressive loss of neurological function.

The natural history of MS suggests that there are different patterns of disease activity [Lublin 1996, Compston 2008]. In relapsing-remitting MS (RRMS), patients have acute exacerbations with full or partial recovery and are otherwise stable between exacerbations (80 85% of the MS population). Some RRMS patients who have rare exacerbations and are minimally disabled 10 years after onset of MS, are retrospectively diagnosed benign MS (10% of the MS population).

Approximately 65 70% of RRMS patients later in their disease course experience gradual progression of disability, and are then described to have secondary progressive MS (SPMS) [Noseworthy 2000, Compston 2008].

Relapses are considered the clinical expression of acute, inflammatory, focal lesions, while progression is considered to reflect demyelination, axonal loss and gliosis. RRMS and SPMS are probably different stages of the same disease.

1.1.3 Epidemiology

There are around 2.5 million patients with MS throughout the world, of whom 250,000 to 350,000 are in the United States [Anderson 1992].

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 50 120 per 100,000 [Compston 2002]. The prevalence is highest in Northern Europe, Southern Australia, New Zealand and North America. The reason for this distribution proportional to distance from the equator in both hemispheres is unknown but may support the existence of environmental factors, in addition to genetic factors [Compston 2008]. In Asian populations MS is clearly less common, and appears to have a different natural history.

MS typically begins in young adults between 20 and 40 years of age (median age at onset: 31 years) but 5% of patients with MS present before the age of 16, and 2% before the age of 10 [Compston 2002]. Patients are mostly Caucasians of European ancestry, with a female predominance of approximately 2:1.

1.1.4 Treatment of MS

In RRMS, the major aims of treatment are to reduce relapse rate and prevent fixed disability attributable to relapse. Recently, new disease modifying drugs have been approved for RRMS. Currently there are several disease modifying therapies approved in at least one country for the treatment of MS.

Injectable disease modifying drugs:

- Interferon (IFN) β-1a 30 mcg intramuscularly once weekly (Avonex®)
- IFN β-1a 22 or 44 mcg subcutaneously 3 times weekly (Rebif®)
- IFN β-1b 250 mcg subcutaneously every other day (Betaferon®, Extavia®)
- Pegylated IFN β-1a 125 mcg subcutaneously every two weeks (Plegridy®)
- Glatiramer acetate 20 mg subcutaneously once daily (o.d.) or 40 mg subcutaneously 3 times weekly (Copaxone®)
- Glatiramer acetate 20 mg subcutaneously o.d. (Glatopa®)
- Natalizumab 300 mg intravenously every 4 weeks (Tysabri®)
- Mitoxantrone intravenously every 3 months (Novantrone®)
- Alemtuzumab concentrate for solution for infusion, 12 mg alemtuzumab in 1.2 mL (10 mg/mL) (Lemtrada®)
- Daclizumab 150 mg/mL solution in a single-dose prefilled syringe, 150 mg subcutaneously once monthly (Zinbryta®)
- Ocrelizumab 600 mg i.v. every 6 months (Ocrevus®)
- Ofatumumab 20 mg/0.4 mL Subcutaneous once monthly (Kesimpta®)

Orally administered disease modifying drugs:

- Fingolimod 0.5 mg orally o.d. (Gilenya®)
- Teriflunomide 7 mg, 14 mg (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®)

Additionally, there are drugs in late-stage development for the treatment of relapsing multiple sclerosis (RMS), including AIN457 (secukinumab).

1.2 Sphingosine-1-Phosphate receptors

The adaptive immune system relies on constant circulation of lymphocytes between lymphoid organs and other tissues. After maturation, lymphocytes leave the bone marrow or thymus, enter the circulation, and travel via the blood and the lymphatic system, surveying for cognate antigen [Tanaka 2004]. In the secondary lymphoid organs, which include lymph nodes, Peyer's patches, and the spleen, naïve lymphocytes encounter antigen-presenting cells and may become activated. Once activated, T cells must egress to reach target tissues, whereas antibody-producing B cells home to the bone marrow [Cyster 2003, Tanaka 2004]. Circulation of lymphocytes between blood, lymphatic system, and non-lymphoid tissues is tightly regulated, and it has been shown that the lysophospholipid S1P plays a central role in lymphocyte trafficking [Cyster 2005, Brinkmann 2007, 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]. The concentration of S1P is low within the lymph node parenchyma but very high in the adjacent efferent lymphatic circulation, two compartments separated by lymphatic endothelium. Lymphocytes are able to sense a concentration gradient of S1P and migrate towards higher S1P concentration. Lymphocyte egress from primary and secondary lymphoid organs is dependent on the $S1P_1$ receptor.

In the presence of an $S1P_1$ receptor agonist, lymphocytes lose their ability to sense S1P concentration gradients and cell-surface $S1P_1$ receptors are internalized by endocytosis. As a consequence, $S1P_1$ receptor agonists block lymphocyte migration out of lymphoid tissue into the lymphatic and vascular circulation, thereby reducing peripheral lymphocyte counts and preventing lymphocyte recruitment to sites of inflammation. Following withdrawal of an $S1P_1$ receptor agonist, the functional lymphocytes return to the circulation from their sites of sequestration. The concept of lymphocyte sequestration is, therefore, compatible with immunomodulation of rapid onset and reversibility.

This new strategy for therapeutic immunomodulation offers potential advantages over existing therapies. Sequestration of T cells in lymphoid organs will prevent the processes

that contribute to inflammatory diseases such as tissue invasion, local cytokine release, macrophage recruitment, and direct cell killing while sparing 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 [Pinschewer 2000].

S1P itself induces pleiotropic effects, which are mediated by a family of five G protein-coupled receptors, $S1P_1$-$S1P_5$, located on endothelial cells, vascular and cardiac smooth muscle cells, and cardiac myocytes [Alvarez 2007, Brinkmann 2007]. The first S1P receptor modulator, fingolimod (FTY720), which has been approved worldwide for the treatment of MS, is not selective for the $S1P_1$ receptor, but interacts also with $S1P_3$, $S1P_4$, and $S1P_5$ [Brinkmann 2007]. Two other S1P receptor modulators - siponimod (which binds to $S1P_1$ and $S1P_5$) and ozanimod (which binds to $S1P_1$) have also been approved for MS in some countries. It is expected that modulators with increased selectivity for the $S1P_1$ versus the $S1P_3$ receptor will reduce peripheral lymphocyte counts while causing fewer $S1P_3$ receptor-mediated side effects.

1.3 Ponesimod

Ponesimod an iminothiazolidinone derivative, is an $S1P_1$ receptor agonist that was selected for clinical development on the basis of its $S1P_1$ receptor selectivity. It also has high potency, a favorable pharmacokinetic (PK) profile after oral dosing, resulting in substantial and rapidly reversible sequestration of circulating lymphocytes. Ponesimod is a potential therapeutic agent for immune disorders in which activated T cells play a critical role, including, e.g., psoriasis, MS, Type I diabetes, rheumatoid arthritis, and Crohn's disease. It may also be effective in the prevention of transplant rejection and graft-versus-host disease. In these pathological situations, traditional immunosuppressants have high potential for toxicity, slow reversibility, and may increase the risk of infection or malignancy, while newer biologicals, such as IFNs and monoclonal antibodies, must be applied parenterally and may be associated with antibody induction and tolerance development [Shear 2006, Van Assche 2006, Wingerchuk 2008]. Thus, there is a clear medical need for safer and orally active drugs.

The clinical development program for ponesimod has to date assessed single- and multiple-dose safety and tolerability in humans, and initial insights have been gained into its PK and pharmacodynamic (PD) characteristics. Ponesimod will now be investigated primarily in patients suffering from T cell-mediated diseases.

1.3.1 Nonclinical studies

Studies have been conducted with ponesimod in animal models of T cell-mediated diseases, such as MS, rheumatoid arthritis, and skin hypersensitivity, and consistently indicate a therapeutic potential of ponesimod at oral doses that lower peripheral blood lymphocyte counts.

The main targets for ponesimod-related toxicity after treatment of up to 4 weeks were the lungs (mice, rats, and dogs), and the nervous system (clinical signs, dogs only). After 13, 26, and/or 52 weeks of treatment, the heart and skin were identified as additional toxicologically relevant targets in mice, rats, and dogs. Nonclinical safety testing of ponesimod indicates an embryotoxic and teratogenic potential.

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

1.3.2 Clinical studies

The clinical experience with ponesimod from studies concluded prior to initiation of the current extension study consisted of studies 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, and studies in patients with moderate -to -severe chronic plaque psoriasis treated for up to 28 weeks with doses up to 40 mg o.d. and in patients with RRMS treated for up to 24 weeks with doses up to 40 mg o.d.

One Phase 3 study that was ongoing at the start of this extension study (Study AC-058B301/OPTIMUM) was completed in May 2019 (last patient last visit) and the long-term extension study AC-058B303/OPTIMUM-LT is currently ongoing in RMS. Study AC-058B302/POINT was prematurely terminated (announcement 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 two-fold accumulation with repeated o.d. oral dosing, and steady-state is achieved within 4 5 days. There is a good correlation between the plasma concentration of ponesimod and the reduction of total lymphocyte count in peripheral blood. Food, age, race or sex do not appear to relevantly affect the PK or PD of ponesimod. The drug-drug interaction potential of ponesimod is judged to be low based on current nonclinical and clinical data.

More detailed information can be found in the Investigator's Brochure [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 at steady-state, at 40 mg o.d. The nadir in lymphocyte count is attained within 6 10 h following a single dose. There is no evidence of tachyphylaxis. Peripheral blood counts of both T and B cells are reduced by ponesimod, while Natural Killer (NK) cells and neutrophils are not reduced. 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 patients treated for up to 6 months and in psoriasis patients treated for up to 7 months was

consistent with observations made after short-term treatment in healthy subjects. In the MS Phase 2 study AC-058B201, at Week 24, the mean reduction from baseline in lymphocyte count was 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. In the psoriasis Phase 2 study AC-058A201, at Week 16, the mean reduction from baseline in lymphocyte count was 56.3% and 64.9% in the ponesimod 20 mg and 40 mg groups, compared to a mean decrease of 1.6% in the placebo group. Lymphocyte count remained stable on treatment and returned to baseline levels within 1 or 2 weeks following ponesimod treatment discontinuation.

More detailed information can be found in the Investigator's Brochure [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 patients with RRMS. A total of 464 patients 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 uptitration to 20 and 40 mg on Days 8 and 15, respectively. Of the 464 patients randomized in the study, all but two patients (ponesimod 20 mg) received treatment with study drug.

In the ponesimod groups, the mean cumulative number of new T1 gadolinium-enhancing (Gd+) lesions at Weeks 12 to 24 (primary efficacy endpoint) ranged from 1.1 3.5 compared to 6.2 on placebo. In the primary analysis (negative binomial regression analysis on the Per-protocol set with imputation for missing data), a statistically significant effect was demonstrated for each ponesimod dose group. The treatment effect (ratio) versus placebo with ponesimod 10 mg was 0.566 (95% confidence interval [CI]: 0.337, 0.952, p 0.0318), with ponesimod 20 mg 0.170 (95% CI: 0.100, 0.289, p 0.0001), and with ponesimod 40 mg 0.226 (95% CI: 0.133, 0.384, p 0.0001).

A mean reduction of 70% of the cumulative number of new T_1 Gd+ lesions from Week 12 to Week 24 was estimated with the 20 mg dose. Only a minor further increase in the effect was estimated for doses greater than 20 mg.

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 versus teriflunomide 14 mg in adult patients with relapsing MS over a treatment period of 108 weeks.

Results showed ponesimod 20 mg statistically significantly reduced ARR (confirmed relapses) up to EOS 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, an increase from baseline indicates worsening in fatigue symptoms).

Ponesimod 20 mg statistically significantly reduced by 56% the number of combined unique active lesions (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 patients 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 patients 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 Investigator's Brochure [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 5 mg or above resulted in dose-dependent sinus rate reductions in all treated patients; the changes were transient and resolved largely within 6 10 hours after dosing. In some patients, 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 uptitration regimen was successfully tested and is implemented in current clinical trials.

Difficulty in inspiration (dyspnea) and related pulmonary function test (PFT) changes have also been detected in humans. Mild transient dyspnea/cough was noted frequently 2 6 h

after an oral dose of 40 mg or higher, and was associated with a clinically relevant forced expiratory volume (FEV_1) decrease from baseline. Symptoms resolved spontaneously upon discontinuation of treatment with ponesimod, and PFTs returned to baseline upon drug discontinuation.

In the long-term clinical studies, an increased incidence of adverse events (AEs) of hypertension was observed in patients with hypertension at baseline, treated with ponesimod.

Elevations of aspartate transaminase (AST) and/or alanine aminotransferase (ALT), without any bilirubin increase have been noted with ponesimod; they were reversible upon discontinuation of dosing. The changes were asymptomatic.

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

Safety results from the completed AC-058B301/OPTIMUM study and the interim analysis of the ongoing AC-058B202 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 uptitration regimen.

- In the AC-058B301/OPTIMUM study, the proportion of patients who experienced at least one TEAE was similar in both treatment arms (88.8% and 88.2% of patients 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 reported bradyarrhythmia events were serious or leading to discontinuation of treatment; no second- or higher degree AV blocks were reported.
- In the interim analysis of AC-058B202 (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 two reliable methods of contraception and must not become pregnant while on study drug and for at least 30 days after study drug discontinuation. A hormonal contraceptive is allowed as one of the required methods of contraception, as the PK profile of hormonal contraceptives has been shown not to be substantially altered in the presence of ponesimod.

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

1.4 Study rationale

1.4.1 Medical background

Ponesimod, a potent, selective, and orally active $S1P_1$ receptor agonist, blocks the egress of lymphocytes from lymphoid organs and thus reduces the availability of circulating effector T cells that can invade target organs. Ponesimod is expected to leave intact immune functions that do not rely on lymphocyte trafficking, such as antibody generation by B cells, first-line defense by neutrophils and monocytes, and antigen-dependent T cell activation and expansion.

In mice with myelin oligodendrocyte glycoprotein peptide-induced experimental autoimmune encephalomyelitis (EAE), a model of MS, oral administration of ponesimod almost fully prevented onset and progression of EAE and significantly increased the survival of immunized mice. Histological analyses showed that ponesimod reduced inflammation, demyelination, and axonal loss in the brain, cerebellum, and spinal cord.

For more details see Section 1.3.1 and the ponesimod Investigator's Brochure [Ponesimod IB].

If this profile is confirmed in patients, ponesimod may offer a new type of selective immunomodulation for the treatment of RRMS.

In a Phase 2 study, the non-selective S1P receptor agonist fingolimod has established activity in MS, significantly reducing both the total number of gadolinium-enhanced lesions per patient recorded on T_1-weighted MRI scans at monthly intervals and the annualized relapse rate (ARR), during 6 months of treatment [Kappos 2006]. Results of a 24-month extension study of this Phase 2 trial demonstrated that patients who switched from placebo to fingolimod showed clear reductions in lesion counts and ARR compared to the placebo phase, and for patients who continued fingolimod treatment, lesion counts and ARR remained low [O'Connor 2009].

Later, efficacy of fingolimod in RRMS was reported in two Phase 3 studies. In the TRANSFORMS study, fingolimod as compared to IFN β-1a intramuscularly showed significant reductions in both the ARR (52% for the 0.5 mg dose, 38% for the 1.25 mg

dose), and the number of new MRI lesions [Cohen 2010]. In the FREEDOMS study, fingolimod as compared to placebo showed significant reductions in both ARR (54% for the 0.5 mg dose, 60% for the 1.25 mg dose), disability progression, and new MRI lesions [Kappos 2010].

The Phase 2b study AC-058B201, hereafter referred to as the "core study", was initiated as the first clinical study of ponesimod in patients with RRMS. The core study was designed to find the best potentially clinically effective dose of ponesimod based on the reduction in the number of new Gd+ lesions on 4-weekly T_1-weighted MRI scans. Tolerability and safety of ponesimod were assessed closely throughout the core study, including the monitoring for events potentially related to immunosuppression (e.g., infections, malignancies).

This study, AC-058B202, hereafter referred to as the "extension study", is designed to provide further treatment to patients who completed the core study, and to investigate the long-term safety, tolerability and efficacy of ponesimod for up to 636 weeks.

1.4.2 Patient population

For the core study RRMS patients with predictors of high clinical activity in terms of MRI activity or clinical relapses were selected in order to maximize potential treatment effect. Patients who were randomized into the core study and completed their regular Week 24 (end-of-treatment [EOT]) Visit while on study treatment will qualify to enter this extension study. Patients participating in the extension study need to sign a new Informed Consent Form. Prior to being enrolled into the treatment period (TP) 2, patients have to sign another Informed Consent Form. Similarly, prior to being enrolled into TP3, patients will have to sign a revised Informed Consent Form. The maximum number of patients in this extension study equals the number of randomized patients in the core study.

1.4.3 Study design

This is a prospective, multicenter, multinational, randomized, double-blind, multiple-dose, uncontrolled, parallel-group extension study in patients with RRMS who have completed their regular Week 24 (EOT) Visit of the core study while on study treatment.

1.4.4 Placebo

No placebo will be used as comparator in this extension study. All patients who have been on placebo during the core study will be randomized 1:1:1 to 10, 20, or 40 mg ponesimod during TP1 in the extension study.

1.4.5 Dose selection

- During TP1 of this extension study:

Patients who received ponesimod during the core study will continue treatment with their originally assigned dose. Patients who have been on placebo during the core study will be randomized 1:1:1 to 10, 20, or 40 mg ponesimod. Therefore, the maintenance doses of ponesimod during the extension study will be 10, 20, or 40 mg o.d. for up to 96 weeks during TP1. All patients (no matter if they received placebo or ponesimod during the core study) will be required to perform the same uptitration or mock uptitration scheme as at the beginning of the core study.

Uptitration of dose: Transient dose-dependent effects of ponesimod on sinus node automaticity and AV conduction with attenuation and disappearance after repeated dosing from Day 2 onwards were observed in the Phase 1 studies. In order to minimize the first-dose effects on HR and AV conduction at doses of 20 mg and above, the same uptitration scheme will be applied in this extension study as in the core study.

- During TP2 of this extension study:

Patients who have completed at least Visit E9 (Week 48) of TP1 (being still on treatment), will be enrolled into TP2.

Based on the AC-058B201 core study results, ponesimod at doses of 10 and 20 mg was well tolerated. The 40 mg dose was associated with an increased incidence of AEs of dyspnea, peripheral edema, cough and, possibly, infection-related AEs while no significant efficacy benefit was achieved with this dose as compared to 20 mg. For this reason, patients in the 40 mg ponesimod treatment arm will be re-randomized to 10 or 20 mg ponesimod in a 1:1 ratio for the TP2. Patients on 10 and 20 mg ponesimod will continue with these maintenance doses.

Patients who have already completed treatment up to Visit E13 (EOT2) may still be enrolled into TP2, provided study drug was not discontinued for longer than 3 months. In this case, Visit P1 must be scheduled as soon as possible and, **if applicable, patients must undergo a study drug re-initiation and/or uptitration.**

- During TP3 of this extension study:

The Independent Data Monitoring Committee (IDMC) required an analysis comparing safety and efficacy outcomes of the two doses of ponesimod currently used in the study, 10 mg and 20 mg. The analysis show that the dose of 20 mg has a better efficacy than the dose of 10 mg, with a similar safety profile. Based on these results, the IDMC has subsequently recommended stopping the ponesimod 10 mg treatment arm and switching all patients to ponesimod 20 mg.

For this reason, patients receiving 10 mg ponesimod during the TP2 will receive a maintenance dose of 20 mg ponesimod in TP3. Patients on 20 mg ponesimod will continue with the same maintenance dose. When feasible, the transition from TP2 to TP3 will occur at the earliest visit following approval of protocol version 8 by Ethics Committees (ECs)/Institutional Review Boards (IRBs) and health authorities and after patients have signed the revised Informed Consent Form. The day of the open-label dose of ponesimod 20 mg will correspond to the start of TP3. At this visit, all patients must be monitored at the investigational site for at least 6 hours after dose administration [see Section 3.12.2].

Re-initiation of study drug: A gradual uptitration of ponesimod from a 2 mg starting dose to a 20 mg maintenance dose over a period of 14 days, as outlined in Table 6, was found to successfully mitigate first-dose effects on HR and AV conduction in the Phase 3 study AC-058B301/OPTIMUM. This 2 week uptitration regimen will be implemented in the study on days of re-initiation of treatment following treatment interruption of 4 days or more [see Appendix 5].

Patients not enrolling into TP3 will have to perform the EOT3 visit [see Section 3.12.3.5].

1.4.6 Treatment duration

In view of the AC-058B201 results, it was decided to prolong this extension study of ponesimod treatment with two selected doses, which both showed a statistically significant therapeutic effect on the primary endpoint and were well tolerated. Furthermore, this extension of ponesimod treatment allows assessing not only long-term safety and tolerability of the two selected doses, but also the effect of long-term (up to 12 years) ponesimod treatment on medically relevant clinical endpoints, relapse rate and sustained disability progression.

Treatment with ponesimod will be extended up to 636 weeks (12.3 years): up to 96 weeks during TP1 and up to 540 weeks during TP2 and TP3. For patients who have been treated with ponesimod during the core study, this will lead to maximum treatment duration with ponesimod of up to 660 weeks (12.8 years): 24 weeks during the core study, plus up to 636 weeks during the extension study.

Study treatment for each patient lasts until the end of the 636 weeks in the extension or until whichever of the following occurs first:

- Ponesimod is commercially available for the treatment of MS in the patient's country;
- The sponsor decides to stop study AC-058B202;
- The patient or the investigator decides to discontinue study drug.

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-058B202 study can continue to receive ponesimod until ponesimod is available in

their local country, or for a maximum of 636 weeks. Patients will get access to the study drug for a maximum of 636 weeks. If ponesimod becomes available locally before the end of the 636 weeks in the AC-058B202 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 EOT3 visit and the EOT3 and FU visits will be conducted as described in Table 3.

1.4.7 Study endpoints

The study endpoints focus on long-term safety, tolerability, and efficacy. Only exploratory endpoints will be investigated. These are described in more detail in Section 3.10.

1.4.8 Statistical hypotheses and sample size

No statistical hypothesis has been set for this study. The sample size will depend solely on the number of patients who complete their regular Week-24 (EOT) visit in the core study while on study treatment and who decide to participate in this extension study.

2 STUDY OBJECTIVES

The objective of this study is to investigate the long-term effects of ponesimod, orally administered o.d. at doses of 10, 20, or 40 mg, on safety, tolerability, and efficacy. Only exploratory analyses will be performed.

The exploratory objectives are:

- To investigate the long-term safety and tolerability of ponesimod.
- To investigate the long-term efficacy of ponesimod.
- To explore the dose response relationship of 10, 20, and 40 mg ponesimod on lymphocyte count, MRI endpoints, ARR, and safety endpoints.

3 INVESTIGATIONAL PLAN

3.1 Overall study design and plan

3.1.1 Study design

This is a prospective, multicenter, multinational, randomized, double-blind, multiple -dose, uncontrolled, parallel-group extension study in patients with RRMS having completed their regular Week 24 (EOT) Visit of the core study while on study treatment. Investigators, contract research organizations (CROs), and patients were blinded to study treatment assignment during TP1 and TP2. During TP3, open-label ponesimod 20 mg is dispensed to all patients. Blinding is discussed in Section 3.8.2.

The study is designed to investigate the long-term safety, tolerability, and efficacy of three doses of ponesimod.

This extension study comprises three treatment periods: TP1 (up to 96 weeks), TP2 and TP3 (up to 540 weeks).

After a transition period of up to 3 days from the AC-058B201 to the AC-058B202 study, patients having received treatment with ponesimod (10, 20, or 40 mg) during the core study will continue their treatment on the same dose during TP1 of this extension study. Patients having received placebo in the core study will be randomized 1:1:1 to 10, 20, or 40 mg ponesimod during TP1.

Patients who completed at least Visit E9 (Week 48) of TP1 (being still on treatment) will be enrolled into TP2 starting with Visit P1. At Visit P1 all patients receiving 40 mg ponesimod will be re-randomized to 10 or 20 mg ponesimod in a 1:1 ratio. Patients on 10 and 20 mg ponesimod will continue with these doses.

Patients who have already completed treatment up to Visit E13 (EOT2) may still be enrolled into TP2, provided study drug was not discontinued for longer than 3 months. In this case, Visit P1 must be scheduled as soon as possible and if applicable, patients must undergo a study drug re-initiation and/or uptitration.

Patients receiving 10 mg ponesimod during TP2 will be switched to 20 mg ponesimod in TP3. Patients on 20 mg ponesimod in TP2 will continue with the same dose in TP3. When feasible, the transition from TP2 to TP3 will occur at the earliest visit following approval of protocol version 8 by ECs/IRBs and health authorities and after the patient has signed the revised Informed Consent Form. At this visit, all patients must be monitored at the investigational site for at least 6 hours after dose administration [see Section 3.12.2]. The day of the first open-label dose of 20 mg will correspond to the start of TP3.

Patients not enrolling into TP3 will have to perform the EOT3 visit [see Section 3.12.3.5].

The study consists of the following study periods:

Transition period (on core study medication)

- The transition period is defined as the time between study drug intake at the Week 24 visit of the core study and the time of study drug intake at Visit E1.
- Patients will have to continue using their core study medication every day until and including the day prior to Visit E1.

Treatment periods (on extension study medication)

- Study treatment period is subdivided into TP1 (up to 96 weeks), TP2 and TP3 (up to 540 weeks).
- Study treatment will be extended to up to a maximum of 636 weeks in total.

TP1 (up to 96 weeks):

- The first visit of the extension study in TP1, Visit E1, will take place within 3 days after the regular Week-24 visit of the core study.
- On Visit E1 (Day 1 of the extension study), patients who have been on placebo during the core study will be randomized 1:1:1 to either ponesimod 10, 20, or 40 mg, and start their treatment with 10 mg ponesimod. Patients who have received ponesimod during the core study will continue treatment on the same dose. For all patients, the treatment on Visit E1 will be administered in the clinical setting. All patients must be monitored at the investigational site for at least 6 hours after dose administration [see Section 3.12.2].
- On Visit E2 (Day 8 of the extension study; day of first (mock) uptitration), the study drug will be administered in the clinical setting and either uptitrated to the dose of 20 mg ponesimod, or a mock dose titration will take place. The patient must be monitored at the investigational site for at least 6 hours after dose administration on Day 8 [see Section 3.12.2].
- On Visit E3 (Day 15 of the extension study; day of second (mock) uptitration), the study drug will be administered in the clinical setting and either up-titrated to the dose of 40 mg ponesimod, or a mock dose titration will take place. The patient must be monitored at the investigational site for at least 6 hours after dose administration on Day 15 [see Section 3.12.2].
- On Day 22 of the extension study the site will call the patient to obtain information on health status / AEs.
- From Visit E4 (Week 4, Day 29 of the extension study) visits will be performed every four weeks until Visit E6 (Week 12).
- From Visit E6 (Week 12) until the end of the treatment period of up to 96 weeks (Visits E6 to E13; Weeks 12, 24, 36, 48, 60, 72, 84 and 96) or until study drug discontinuation, visits will be performed every 12 weeks.

TP2 and TP3 (up to 540 weeks):

- Patients will be switched from TP1 to TP2 at Visit P1. As soon as a patient has completed at least Visit E9 (Week 48) of TP1 (being still on treatment) following approval of global protocol version 3, Visit P1 can be scheduled as the next regular visit (12 weeks after Visit E9 or E10 or E11 or E12). After completing Visit E13 (EOT2), Visit P1 must be scheduled as soon as possible, provided study drug was not discontinued for longer than 3 months and a re-initiation / uptitration must be performed, if applicable.
- All patients will be switched from capsules to tablets at Visit P1.

- All patients receiving 40 mg ponesimod during TP1 will be re-randomized to 10 or 20 mg ponesimod in a 1:1 ratio. Patients receiving 10 mg and 20 mg ponesimod will continue with these respective maintenance doses.
- When feasible, patients will be switched from TP2 to TP3 at the earliest scheduled visit, following approval of protocol version 8 by ECs/IRBs and health authorities, and after having signed the revised Informed Consent Form. The day of the first open-label dose of ponesimod 20 mg will correspond to the start of TP3. Patients not enrolling into TP3 will have to perform the EOT3 visit.
- All patients receiving 10 mg ponesimod during TP2 will receive a maintenance dose of 20 mg ponesimod during TP3, if they agree to continue in TP3. Patients receiving 20 mg ponesimod will continue with 20 mg ponesimod. Treatment allocation during TP1 and TP2 will not be revealed. All patients must be monitored at the investigational site for at least 6 hours after the first dose administration in TP3 [see Section 3.12.2].
- All visits will be performed every 12 weeks.

End-of-treatment

- The EOT visit (EOT2 or EOT3) in the extension study, at an individual patient's level, should not be later than one day after the last dose of ponesimod.
- Patients who prematurely discontinue study drug during the TP1, TP2, or TP3 of the extension study must have their EOT2 or EOT3 visit as soon as possible but no later than 5 days after the last dose of study drug.
- EOT2 visit must be performed by patients discontinuing study drug during / at the end-of-treatment period 1.
- EOT3 visit must be performed by patients discontinuing study drug during / at the end-of-treatment period 2 or TP3.
- The EOT3 visit must also be performed by patients completing study treatment due to availability of commercially available ponesimod. Commercially available ponesimod may be initiated on the day after last intake of study drug.

Safety Follow-up period

For TP1:

In the case of discontinuation from study drug before Visit P1, safety will be followed up for 30 days after last dose of study drug. There are two Safety Follow-up visits:

- Visit E14 (Follow-up Visit E1):
  8 days after the last study drug intake.
- Visit E15 (Follow-up visit E2):
  30 days after the last study drug intake.

For TP2 and TP3:

In the case of discontinuation from study drug after Visit P1, safety will be followed up for 90 days after last dose of study drug. There are three Safety Follow-up visits:

- Visit FU1 (Follow-up visit 1):
  8 days after the last study drug intake.
- Visit FU2 (Follow-up visit 2):
  30 days after the last study drug intake.
- Visit FU3 (Follow-up visit 3):
  90 days after the last study drug intake.

Patients who discontinue study drug prematurely must have the corresponding Safety Follow-up visits after their last study drug intake.

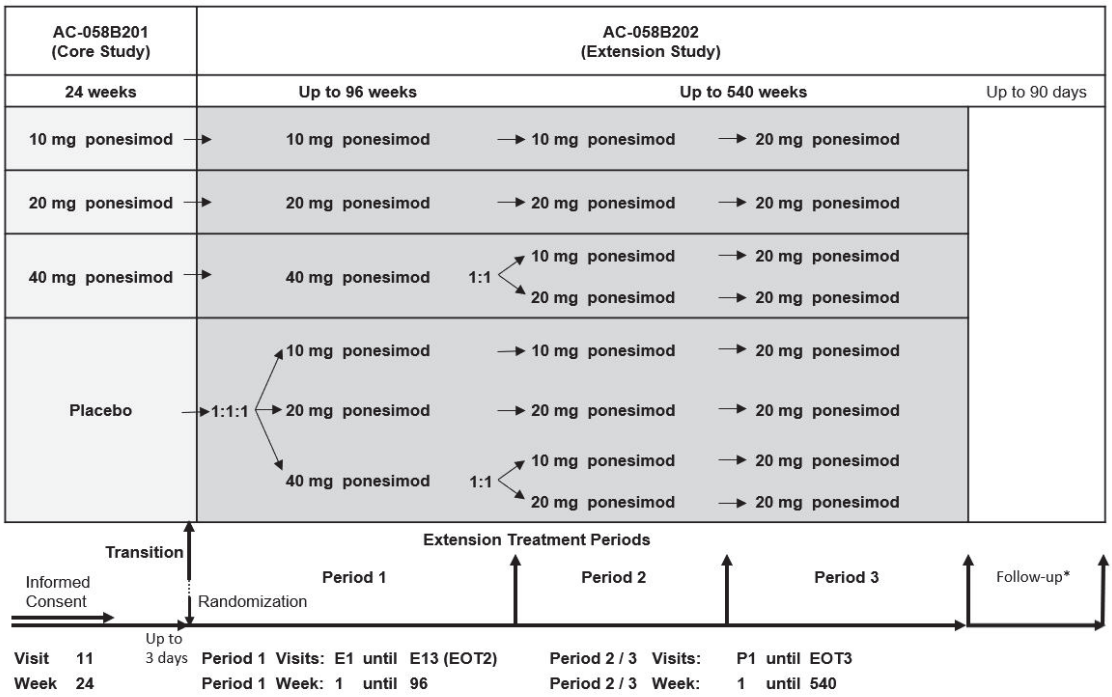
These visits and assessments will also be conducted for patients who have switched to commercially available ponesimod.

End-of-study (EOS2/EOS3)

- End-of-study (EOS) visit 2 (EOS2) for an individual patient is reached 30 days after the last dose of study drug in TP1.
- Patients not enrolling into TP2 have to perform EOS2.
- EOS3 for an individual patient is reached 90 days after the last dose of study drug for patients that have enrolled into TP2 and TP3, if applicable.
- Patients not enrolling into TP3 have to perform EOS3.
- The maximum duration of this extension study for an individual patient is up to 649 weeks (636 weeks of treatment extension, and 90 days of follow-up).

Patients will follow the standard of care after completing the study.

Figure 1: Study design



*Safety follow-up visits:
After treatment period 1: at 8 and 30 days after last dose of study drug
After treatment period 2 and treatment period 3: at 8, 30 and 90 days after last dose of study drug

3.2 Study committees

3.2.1 Independent Data Monitoring Committee

The IDMC implemented for the core study continued to monitor patients' data on a regular basis, and had access to fully unblinded data to ensure patient safety. The IDMC was disbanded on 30th September 2021 following the planned unblinding of the studies.

3.2.2 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. As of the implementation of Global Protocol version 12, the OSB will be decommissioned as macular edema is considered a well characterized risk associated with ponesimod treatment.

3.2.3 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 predefined 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 are described in the MACE adjudication board charter.

3.3 Role of key site personnel throughout the study

In order to maintain the blind during TP1 and TP2 [see Section 3.8.2] and to facilitate the performance of efficacy and safety assessments required by the protocol throughout all treatment periods of the study, it is essential that:

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

It is recommended that the designated personnel remain unchanged throughout the entire course of the extension study and, preferably, the same personnel with the same roles as in the core study be maintained.

At each center, the study staff will consist of:

- A primary investigator
- A treating neurologist (who may be the primary investigator)
- A clinical coordinator / study nurse
- An evaluating neurologist*
- A physician evaluating cardiac safety assessments*
- MRI staff
- An ophthalmologist
- A pulmonary function laboratory technician or expert

* During TP3, the roles of the evaluating neurologist and/or the physician evaluating cardiac safety assessment can be performed by the primary investigator or treating neurologist, provided they have the required training/qualifications.

3.3.1 Primary investigator / treating neurologist

The primary investigator / treating neurologist must be a qualified neurologist, or must name a sub-investigator who is a qualified neurologist. The primary 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.

It is the responsibility of the primary investigator / treating neurologist to explain the study in all its aspects to the patient and obtain her/his informed consent. Neurological examination for obtaining the Expanded Disability Status Scale (EDSS) and Functional Systems (FS) scores throughout the trial will be conducted by an evaluating neurologist. During the open-label phase of the study (TP3), the role of evaluating neurologist can be performed by the primary investigator / treating neurologist [see Section 3.3.3].

The primary investigator / treating neurologist will be responsible for patient clinical care and management, e.g., eligibility evaluation, supervision of study drug administration, confirming relapses, monitoring of safety (including recording and treating of AEs physical examination, and routine laboratory results), and concomitant medications.

The primary investigator / treating neurologist will have access to the patient's MRI images and/or reports from the local radiologist 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.

If cardiac events of potential clinical concern occur at any time during the study treatment and have not already been evaluated by the physician evaluating cardiac safety assessments, the treating neurologist may consult with the physician evaluating cardiac safety assessments in order to determine the need for medical management, evaluate seriousness and decide on actions to be taken on study treatment, if any.

Preferably, the same physician should maintain the role of the treating neurologist for a given patient throughout the study. A back-up treating neurologist may conduct a patient study visit only if the primary treating neurologist is not available.

3.3.2 Clinical coordinator / study nurse

The clinical coordinator / study nurse will assist the primary investigator / treating neurologist in all aspects of patient management. She/he will be responsible for scheduling visits and assessments as planned in the study protocol, recording concomitant medications, maintaining source documentation, and entering data into the electronic case report form (eCRF). She/he will instruct the patients on study drug administration, and collect, process, and send all blood and urine samples to the central laboratory. Additionally, she/he may be responsible for coordinating the conduct of MRI, PFTs, ophthalmological and cardiac examination.

3.3.3 Evaluating neurologist

The evaluating neurologist will perform the detailed neurological examination for obtaining the EDSS/FS scores according to protocol schedule, as well as EDSS/FS scores at every unscheduled visit for confirmation of relapse. To ensure consistency across sites, the evaluating neurologist must be well trained on EDSS/FS scoring prior to enrollment of the first patient at the study site. Preferably, the same physician should maintain the role of evaluating neurologist for a given patient throughout the study. A back-up evaluating neurologist may conduct neurological examination, and EDSS/FS scoring if the primary evaluating neurologist is not available. This back-up evaluating neurologist must be well trained in EDSS/FS scoring and capable to ensure homogeneity in EDSS/FS scoring with the primary evaluating neurologist. If a change is required during the study, the new evaluating neurologist will be trained on EDSS/FS scoring prior to the performance of any EDSS/FS assessment.

During the blinded phases of the extension study (TP1 and TP2), the evaluating neurologist must be independent and not otherwise involved in the clinical care of the study patient. During the open-label phase (TP3), the role of the evaluating neurologist may be performed by the principal investigator / treating neurologist (depending on the site setting, and provided that she/he is well trained on EDSS/FS scoring).

3.3.4 Physician evaluating cardiac safety assessments

The physician evaluating cardiac safety assessments must be a physician adequately trained and experienced in cardiology. She/he must be qualified and equipped to provide emergency treatment in cases of acute cardiac events. 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.

During the blinded phases of the extension study (TP1 and TP2), the physician evaluating cardiac safety assessments must be independent and not otherwise involved in the clinical care of the study patient [see Section 3.8.2]. During the open-label phase (TP3), the primary investigator / treating neurologist may perform this role if qualified.

She/he is responsible for oversight of all BP and ECG assessments requested by the protocol during:

- TP1 (Visits E1 to EOT2 and Follow-up visits E1 and E2 as applicable), and
- TP2 and TP3: at P1, at the visit during which the transition from TP2 to TP3 takes place (i.e., the day of the first open-label dose of 20 mg), re-initiation, and re-uptitration visits.

Additionally, she/he is responsible for the close post-dose monitoring of the patient following study drug intake on Visit E1 (Day 1), Visit E2 (Day 8), Visit E3 (Day 15), P1,

the visit during which the transition from TP2 to TP3 takes place (i.e., the day of the first open-label dose of 20 mg), re-initiation, and re-uptitration visits. She/he will assess eligibility for discharge or continued patient management on Visits E1, E2, E3, P1 re-initiation, and re-uptitration visits.

She/he will support the primary investigator in making a decision on eligibility of the patients (based on cardiac results) prior to randomization in the extension study by alerting the primary investigator to any significant cardiac abnormalities, and providing adequate treatment in cases of cardiac events.

Significant findings (e.g., new ECG abnormalities, bradycardia), which in the view of the physician evaluating cardiac safety meet the definition of an AE, must be reported to the primary investigator / treating neurologist and recorded on the Adverse Event form of the eCRF.

Any cardiac events of potential clinical concern at any time during the study, including AV blocks, must be assessed for seriousness by the physician evaluating cardiac safety and reported accordingly. In addition, the physician evaluating cardiac safety assessments should determine the need for medical management, and assist the treating neurologist in deciding what actions should be taken on study treatment, if any.

Treatment for bradycardia, if any, will be reported to the primary investigator / treating neurologist and recorded as concomitant medication on the appropriate eCRF form.

3.3.5 MRI staff

The MRI staff will be responsible for performing the scheduled and unscheduled MRI investigations according to the study MRI Technology Manual (separate document). They will export the original data to the MIAC, c/o University Hospital Basel, Switzerland, and ensure storage of the primary data at the study site.

3.3.6 Ophthalmologist

The ophthalmologist will perform the ophthalmological examinations as scheduled in the study protocol.

3.3.7 Pulmonary function laboratory technician or expert

The PFTs must be performed by qualified staff, such as a pulmonary function technician or expert according to the American Thoracic Society/European Respiratory Society guidelines and study protocol schedule.

3.4 Study population

3.4.1 Patient population

Patients who were randomized into the core study and completed their regular Week-24 (EOT) Visit while on study treatment will qualify to enter this extension study. The

maximum number of patients in the extension study equals the number of randomized patients in the core study.

3.4.2 Inclusion criteria

Eligible patients must meet all of the following inclusion criteria:

1. Patients who completed study treatment at their regular Week 24 (EOT) Visit within the core study.
2. Women of childbearing potential must:
   - Have a negative urine pregnancy test at their regular Week 24 visit within the core study.
   - Use reliable methods of contraception for up to at least 30 days after study drug discontinuation as described in Section 4.4.2.
3. Signed informed consent for participating in the extension study prior to administration of the first dose in the transition period (i.e., prior to continuation of dosing at Visit 11 (Week 24) of the core study).

3.4.3 Exclusion criteria

Eligible patients must meet none of the following exclusion criteria:

1. Patients meeting at their regular Week 24 (EOT) Visit, during the transition period, and/or at Visit E1 any of the study-specific criteria for permanent discontinuation of study drug as defined in Appendix 1, or patients receiving any of the prohibited concomitant medication as outlined in Section 3.4.4.3 and Appendix 8.
2. Any other clinically relevant medical or surgical condition, which, in the opinion of the investigator, would put the patient at risk by participating in the extension study.

3.4.4 Concomitant medications

3.4.4.1 Recommended concomitant medications

Acute exacerbations of MS should be treated with methylprednisolone 1 g intravenously daily for 3 to 5 days. Oral taper with corticosteroids is not permitted.

3.4.4.2 Allowed concomitant medications

Administration of intravenous (i.v.) atropine in the event of symptomatic bradycardia.

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.

Patients receiving non-live vaccination against influenza or COVID-19 while on study treatment will have 5 mL of blood drawn prior to and at least 3 weeks after vaccination in order to explore changes in vaccine-specific antibody titers from pre- to post vaccination. Samples will be analyzed at the end of the study at the latest. In case of a vaccine requiring the administration of multiple doses, the post-vaccination sample should be collected at least 3 weeks after the administration of the last dose.

Glatiramer acetate and IFN β-1a are allowed only during study drug interruptions for planned pregnancy. These treatments may be started 7 days after study drug interruption and must be stopped 7 days before study drug re-initiation.

Low dose of corticosteroids (up to 10 mg of prednisone equivalent daily), given as short-term treatment (up to 2 weeks per treatment cycle with at least 8 weeks' interval between treatment cycles and no more than 4 weeks per year of the study duration on average), and inhaled corticosteroids for pulmonary conditions.

Other treatments considered necessary for the patient's benefit and not categorized as prohibited concomitant medications.

3.4.4.3 Prohibited concomitant medications

- Systemic corticosteroids or adrenocorticotropic hormone (ACTH), except for: the treatment of acute MS exacerbations [see Section 3.4.4.1]; short-term treatment with a low dose of corticosteroid; and inhaled corticosteroids for pulmonary conditions [see Section 3.4.4.2].
- Immunomodulating treatment (e.g., IFN β, glatiramer acetate, natalizumab or other monoclonal antibody therapy [except glatiramer acetate or IFN β-1a during study drug interruptions for planned pregnancy as described under "Allowed"]).
- Immunosuppressive treatment (e.g., cladribine, mitoxantrone or other systemic immunosuppressive drugs such as azathioprine, cyclophosphamide, cyclosporine or methotrexate).
- i.v. immunoglobulin.
- 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 the 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 HR -lowering systemic therapy [non-exhaustive list provided in Appendix 8] during the titration (i.e., during the first 14 days after re-initiation of study treatment). 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.

- Medications with risk of torsades de pointes (TdP) should not be administered as ponesimod may potentially enhance their effect on QT interval unless the benefit-risk is acceptable, as judged by the investigator [non-exhaustive list provided in Appendix 9].
- Any investigational drug.

3.5 Study drugs

Study drug is ponesimod.

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

3.5.1 Ponesimod

During TP1:

Ponesimod was supplied as its free base in hard gelatin capsules formulated at strengths of 10, 20, and 40 mg.

During TP2:

Ponesimod was supplied as oral film-coated tablets formulated at strengths of 10 and 20 mg.

During TP3:

Ponesimod is supplied as oral film-coated tablets formulated at strength of 2, 3, 4, 5, 6, 7, 8, 9, 10, and 20 mg.

3.5.2 Study drug storage and dispensing

The investigator is responsible for safe and proper handling and storage of the study drug at the investigational site and for ensuring that the study drug is administered only to patients enrolled in the study and in accordance with the protocol.

Study drug must be kept in a locked room, which can be accessed only by the pharmacist, the investigator, or another duly designated person. The study drug must be stored according to the conditions specified on the medication labels. The study centers will be supplied with study drug according to the centers' needs depending on the number of patients entering the extension study. Each center will have an individual stock of study drug, which will be re-supplied continuously as soon as a predefined minimum level of study drug has been reached.

3.5.3 Study drug dosing scheme

One capsule (during TP1) or one tablet (during TP2 and TP3) of study drug will be administered orally o.d. in the morning, with or without breakfast (preferably always in the

same way and at approximately the same time). On each day of the study visits, the administration of the study drug will only be done once PK trough level sampling and the following safety assessments are completed: BP, ECG, PFTs, laboratory tests, and urine pregnancy test.

Since this study was initially performed in a double-blind fashion during TP1 and TP2, all patients, notwithstanding whether they have been on placebo or ponesimod during the core study, needed to perform an uptitration scheme. For patients treated with ponesimod during the core study this was a mock uptitration. The treatment groups in the extension study will be as follows:

Patients who were on ponesimod in the core study continued on the same dose in the transition period and had mock dose titrations on Day 1 (Visit E1), Day 8 (Visit E2), and Day 15 (Visit E3):

- Group I: Group I in the core study (10 mg).
  10 mg from Visit E1 (Day 1) until end of TP2.
  20 mg during TP3 until EOT3.

- Group II: Group II in the core study (20 mg).
  20 mg from Visit E1 (Day 1) until EOT3.

- Group III: Group III in the core study (40 mg).
  40 mg from Visit E1 (Day 1) until at least Visit E9 or up to E13 (EOT2).
  10 or 20 mg from Visit P1 until end of TP2.
  20 mg during TP3 until EOT3.

Patients who were on placebo (Group IV in the core study) continued on placebo in the transition period and then be randomized 1:1:1 to:

- Group IV: 10 mg from Day 1 (Visit E1) until end of TP2.
  Mock dose titrations on Day 8 (Visit E2) and Day 15 (Visit E3).
  20 mg during TP3 until EOT3.

- Group V: 10 mg from Day 1 (Visit E1) to Day 7.
  20 mg from Day 8 (Visit E2) until EOT3.
  Mock dose titration on Day 15 (Visit E3).

- Group VI: 10 mg from Day 1 (Visit E1) to Day 7.
  20 mg from Day 8 (Visit E2) to Day 14.
  40 mg from Day 15 (Visit E3) until at least Visit E9 or up to E13 (EOT2).
  10 or 20 mg from Visit P1 until end of TP2.
  20 mg during TP3 until EOT3.

An overview of the titration scheme by treatment arm is provided in Table 5.

Table 5: Ponesimod dose levels and uptitration scheme

		Treatment groups					
					Ponesimod		
	Core study:	Placebo			10 mg	20 mg	40 mg
		↙	↓	↘	↓	↓	↓
	Extension study:	10 mg	20 mg	40 mg	10 mg	20 mg	40 mg
Transition [1]	Day –3 to Day –1	0 mg	0 mg	0 mg	10 mg	20 mg	40 mg
Dose level 1 [4]	Day 1 to Day 7	10 mg	10 mg	10 mg	10 mg[2,3]	20 mg[2,3]	40 mg[2,3]
Dose level 2 [4]	Day 8 to Day 14	10 mg[2]	20 mg	20 mg	10 mg[2,3]	20 mg[2,3]	40 mg[2,3]
Dose level 3 [4]	Day 15 up to W96	10 mg[2,3]	20 mg[2,3]	40 mg[3]	10 mg[2,3]	20 mg[2,3]	40 mg[2,3]
Dose level 4 [5]	Day 1 up to W540	10 mg[3]	20 mg[3]	10/20 mg[3]	10 mg[3]	20 mg[3]	10/20 mg[3]
Dose level 5 [6]		20 mg[3]	20 mg[3]	20 mg[3]	20 mg[3]	20 mg[3]	20 mg[3]

[1] Transition dose core study maintenance dose.[2] Mock uptitrations. [3] Maintenance dose. [4] Treatment period 1.
[5] Treatment period 2. [6] Treatment period 3.

3.5.4 Study drug up- and down-titration

Study drug up-titration other than described in this protocol is not allowed. Down-titration of study drug is not allowed.

3.6 Study drug discontinuation and study withdrawal

3.6.1 Study drug discontinuation

The investigator must permanently discontinue the study drug if continued administration of the study drug is believed to be contrary to the best interests of the patient.

The premature discontinuation of study drug might be triggered by an AE, a diagnostic or therapeutic procedure, an abnormal assessment (e.g., ECG, PFTs or laboratory abnormalities), or for administrative reasons, in particular withdrawal of the patient's consent.

In addition, study drug must be discontinued if any of the specific discontinuation criteria listed in Appendix 1 is met, including cardiac and pulmonary parameters, arterial hypertension, lymphocyte counts, infection, macular edema and pregnancy.

Heightened vigilance is required for opportunistic infections, particularly viral infections with neurological symptoms such as reactivation of human herpes viruses (herpes simplex

viruses, varicella-zoster virus, Epstein-Barr virus, cytomegalovirus) and reactivation of John Cunningham virus (JCV) causing progressive multifocal leukoencephalopathy (PML). The patient must be instructed to contact the investigator immediately if symptoms of infection occur. In the event of an opportunistic infection, the study drug must be permanently discontinued [Appendix 3].

If for any reason a patient has to be treated with immunomodulators, immunosuppressants, immunoglobulins or investigational drugs, or has to undergo plasmapheresis, cytapheresis or total lymphoid irradiation, the study drug must be permanently discontinued.

Please refer to Section 3.6.2 and Appendix 5 for further guidance on re-initiation of the ponesimod in case of an interruption of the study drug.

3.6.2 Study drug interruption

Study drug interruption should be avoided.

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

Study drug may be temporarily interrupted in response to an AE, a diagnostic or therapeutic procedure, a laboratory abnormality, a planned pregnancy, or for administrative reasons. The permitted maximum duration of the study drug interruption is 81 weeks for planned pregnancies and 12 weeks for other reasons (if exceeded, the patient will then be prematurely discontinued from the study).

In the event of a re-initiation of study drug, one tablet of ponesimod 2, 3, 4, 5, 6, 7, 8, 9, or 10 mg will be taken orally o.d. during the uptitration period (Day 1 to 14). During the maintenance period, patients will continue to take one tablet of ponesimod 20 mg orally o.d. [Table 6]. If a blister kit with the starting dose of 2 mg is not available at the site, re-initiation should be delayed until it becomes available (temporary treatment interruption).

Detailed guidance on how to re-initiate study drug in the event of drug interruption is provided in Appendix 5.

Table 6: 2-week gradual uptitration regimen

Treatment period	*Duration*	*Dose regimen*
Titration	Day 1 and 2	2 mg
Titration	Day 3 and 4	3 mg
Titration	Day 5 and 6	4 mg
Titration	Day 7	5 mg
Titration	Day 8	6 mg
Titration	Day 9	7 mg
Titration	Day 10	8 mg
Titration	Day 11	9 mg
Titration	Day 12 to 14*	10 mg
Maintenance	Day 15 until EOT3	20 mg

* An additional visit 14 days (±1 day) after the day of re initiation (Re initiation Day 15) is mandated for patients with cardiovascular risk factors [see Appendix 5], but may be scheduled for any patient at the discretion of the investigator / treating neurologist. 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).
EOT3 End of Treatment

3.6.3 Patients' follow-up after study drug discontinuation

All randomized patients who received the study drug (for any length of time) must perform all protocol-mandated assessments of the corresponding EOT visit at the time of premature study drug discontinuation, i.e., as soon as possible but no later than 5 days after the last dose of study drug. In addition, the corresponding Safety Follow-up visits must be performed.

- For TP1:

The corresponding EOT visit is EOT2.

In case of study drug discontinuation during or after completion of TP1, Follow-up Visit E1 and Follow-up visit E2 should be done 8 and 30 days respectively after the day of the last dose of study drug, regardless of the timing of the EOT2 visit.

- For TP2 and TP3:

The corresponding EOT visit is EOT3.

Follow-up visits 1, 2 and 3 should be done 8, 30, and 90 days, respectively, after the day of the last dose of study drug, regardless of the timing of the EOT3 visit.

Patients will follow the standard of care after completing the study.

3.6.4 Study withdrawal

A patient will be considered as withdrawn from the study if, and only if, she/he is lost to follow-up after all means of contact have been exhausted.

The potential follow-up of patients after their withdrawal of consent will be subject to local regulations.

3.6.5 Replacement policy

3.6.5.1 Patients

Randomized patients discontinued from the study drug for any reason will not be replaced.

3.6.5.2 Centers

All centers with patients who are on study drug at their regular Week 24 (EOT) visit of the core study can participate in the extension study.

3.7 Treatment exposure and compliance

Records of study drug dispensed, used, dosages administered, returned, and intervals between visits will be kept during the study. Study drug accountability (i.e., capsule [during TP1] or tablet [during TP2 and TP3] counts) will be performed on a regular basis by the study staff and will be checked by the monitor during site visits and at the completion of the study. Patients will be asked to return all unused study drug (or empty bottle[s]) at each visit.

3.8 Treatment assignment and blinding

3.8.1 Treatment assignment

During TP1:

Patients who received ponesimod during the core study will continue to receive their maintenance doses of 10, 20, or 40 mg of ponesimod, respectively.

Patients who received placebo during the core study will be randomized in a 1:1:1 ratio to 10, 20, or 40 mg of ponesimod.

During TP2:

All patients on 10 and 20 mg ponesimod will continue with these maintenance doses. Patients on 40 mg ponesimod will be re-randomized to 10 or 20 mg ponesimod centrally via Interactive Voice Response System (IVRS). Each of the study sites will keep the unique site number assigned for the core study.

- Every patient will keep the patient number assigned during the core study, which will identify the patient throughout the extension study.

- After entering the transition period and continuing administration of core study treatment, a CRF is assigned to each patient. The unique CRF number is preprinted on each CRF page.
- Randomization will be performed by IVRS or Interactive Web Response System (IWRS) at Visit E1 (Day 1) for TP1. Patients who received one of the three active doses (10, 20, or 40 mg ponesimod) within the core study will be assigned to their current dose. Patients who received placebo within the core study will be randomized in a 1:1:1 ratio to receive 10, 20, or 40 mg ponesimod. Randomization via IVRS will be performed also for TP2 starting at Visit P1. Patients on 40 mg ponesimod will be then re-randomized to 10 or 20 mg ponesimod in a 1:1 ratio. Patients on 10 and 20 mg ponesimod will continue to receive their current dose. The dispensed study drug is labeled with a preprinted medication bottle number, also assigned by the IVRS/IWRS.
- The IVRS/IWRS will allocate medication bottles containing medication that corresponds to the treatment designated. Each patient will receive one bottle with 10 capsules at Visit E1 (Day 1) and Visit E2 (Day 8), and a bottle with 36 capsules at Visit E3 (Day 15), and at Visits E4 and E5 (Weeks 4 and 8). At Visits E6 through E12 (Weeks 12, 24, 36, 48, 60, 72, and 84 respectively) each patient will receive three bottles with 36 capsules each. At Visits P1 through P36 each patient will receive three bottles with 36 tablets each. All tear-off labels of dispensed study drug bottles will be attached to the appropriate drug label dispensing log.
- If drug packages are damaged, the center must immediately contact the monitor upon receipt of the shipment. The damage will be discussed and it will be mutually agreed if these bottles can be used or not. A written confirmation from the sponsor will be required. In addition, the receipt of damaged drug packages needs to be confirmed via IVRS/IWRS.
- The randomization code will be kept strictly confidential. Actelion Quality Management will keep a sealed randomization code in a secure location. A second set was provided to the statistician of the IDMC by Actelion Quality Management. See Section 3.8.2 for further details on blinding.
- The randomization code was revealed to the sponsor at the time of the AC-058B202 study interim analyses.

During TP3:

Patients receiving 20 mg ponesimod will continue with 20 mg ponesimod as maintenance dose. Patients on 10 mg ponesimod during TP2 will be re-allocated to 20 mg ponesimod centrally via an IVRS. Each of the study sites will keep the unique site number assigned for the core study.

- Every patient will keep the patient number assigned during the core study, which will identify the patient throughout the extension study.

- When feasible, re-allocation will be performed by IVRS or IWRS at the earliest visit following approval of protocol version 8 by ECs/IRBs and health authorities and after the patient has signed the revised Informed Consent Form. Patients on 20 mg ponesimod will continue to receive their current dose. The dispensed study drug is labeled with a preprinted medication bottle number, also assigned by the IVRS/IWRS.
- At this visit, patient will receive three bottles with 36 tablets of ponesimod 20 mg each. All tear-off labels of dispensed study drug bottles will be attached to the appropriate drug label dispensing log.
- If drug packages are damaged, the site must immediately contact the monitor upon receipt of the shipment. The damage will be discussed and it will be mutually agreed if these bottles can be used or not. A written confirmation from the sponsor will be required. In addition, the receipt of damaged drug packages needs to be confirmed via the IVRS/IWRS.

3.8.2 Blinding

The study was initially conducted in a double-blind fashion during TP1 and TP2. The primary investigator/ treating neurologist, evaluating neurologist, clinical coordinator/ study nurse, physician evaluating cardiac safety assessments, PFT and MRI staff, patients, and CRO staff remained blinded to the previous treatment allocation during TP1 and TP2. The different doses of ponesimod were indistinguishable and were packaged in the same way. During TP3, blinding rules are not applicable because only one dose of ponesimod (i.e., 20 mg) will be dispensed to all patients until the end of the study.

The IDMC was unblinded (the IDMC Charter is a stand-alone document separate from the study protocol).

During TP1 and TP2, the following measures were taken to ensure that the efficacy assessments (i.e., EDSS/FS) were done independently and that cardiac safety assessments were performed without the potential to reveal the treatment assignment, in order to avoid potential bias:

- An independent evaluating neurologist, not involved in any other aspects of patient care and management, was responsible for performing the neurological assessments for obtaining the EDSS/FS scores throughout the study.
- The patient was instructed not to discuss AEs (other than those required for EDSS assessments), HR, pulmonary function and/or concomitant medications with the independent evaluating neurologist.
- During TP1, the primary investigator / treating neurologist and independent physician evaluating cardiac safety assessments were not to discuss any issues related to patient care and management unless mandated for reasons of patient safety.
- Potentially unblinding information was not be shared with the independent evaluating neurologist under any circumstances.

Data analyses of the ongoing extension study have been performed periodically for strategic planning of the future development of ponesimod. For such analyses, it was necessary to unblind the TP1 treatment assignment of patients who received placebo in the core study, AC-058B201.

Patients who were randomized to 10, 20 or 40 mg ponesimod in the core study received the same dose in TP1 of this extension study. Therefore, these patients' treatment assignments were unblinded when the core study data were analyzed and the clinical study report published.

The potential for this sponsor's unblinding to introduce bias in the conduct of the extension study was evaluated. This potential bias was considered minimal and without consequences for the scientific validity of the trial for the following reasons:

- AC-058B202 study is an exploratory study.
- Individual treatment allocation in the extension study was unblinded by the sponsor when performing interim analyses, but remained blinded to investigators (including the independent evaluating neurologist and the physician evaluating the cardiac safety assessments), CROs and patients during TP1 and TP2.
- Data monitoring of the study was performed independently by the IDMC until its disbandment on 30th September 2021.
- The analysis of the MRI scans performed by a central reading facility showed results consistent with the clinical parameters (ARR and confirmed disability accumulation).

3.8.3 Emergency procedure for unblinding

The investigator and the study staff must remain blinded to the dose of ponesimod assigned to the patient during TP1 and TP2, even if the patient refuses to participate in any study procedures, or prematurely discontinues the study drug or experiences an AE, or if the patient dies.

The dose of ponesimod may be revealed only if the patient experiences a medical emergency the management of which would be improved by knowledge of the assigned dose of ponesimod.

The IVRS/IWRS will be set up to allow the primary investigator / treating neurologist to receive the dose assignment of ponesimod of her/his study patients at any time. The occurrence of any code break during the study must be clearly justified and explained by the primary investigator / treating neurologist. Before breaking the code, every attempt must be made by the investigator to discuss the intended code break with the sponsor. In all cases, the sponsor must be informed as soon as possible before or after the code break.

Any code break must be documented in a detailed report with the date and time of the code break, and signed by the primary investigator. This report is to be attached to the CRF. At

the end of the study, the monitor will collect all code break reports and will return them to the sponsor for filing.

3.9 Study drug packaging and labeling

3.9.1 Study drug packaging

The study drug ponesimod is provided as capsules during TP1 and as tablets during TP2 and TP3, and is supplied in bottles. The 2-week gradual uptitration used for re-initiation of study drug during TP3 is supplied as blister packs.

During the transition period patients will continue using their core study medication. On Visit E1 each patient must bring back the remaining core study medication and will receive the following medication bottles after drug assignment by IVRS:

- **Dose level 1 (TP1):** One bottle on Day 1 (Visit E1) for the 7-day titration period from Day 1 to Day 7 (end of first step) with 10 capsules of:
  Ponesimod 10 mg for former placebo patients
  Core study maintenance dose for patients continuing on active treatment.

- **Dose level 2 (TP1):** One bottle on Day 8 (Visit E2) for the 7-day titration period from Day 8 to Day 14 (end of second step) with 10 capsules of:
  Ponesimod 10 or 20 mg for former placebo patients
  Core study maintenance dose for patients continuing on active treatment.

- **Dose level 3 (TP1):**
  One bottle on Day 15 (Visit E3) for the 14-day maintenance period from Day 15 to Day 28 with 36 capsules of ponesimod 10, 20, or 40 mg.
  One bottle each at Weeks 4 (Day 29) and 8 (Visits E4 and E5) for the maintenance period from Week 4 to Week 12 with 36 capsules of ponesimod 10, 20, or 40 mg.
  Three bottles each at Weeks 12, 24, 36, 48, 60, 72, and 84 (Visits E6 through E12) for the maintenance period from Week 12 to Week 96. One bottle contains 36 capsules of either 10, 20, or 40 mg ponesimod.

- **Dose level 4 (TP2):**
  Three bottles each at Visits P1 to P36 or until the earliest visit following approval of protocol version 8 by ECs/IRBs and health authorities and signature of the revised Informed Consent Form by the patients and when the switch to TP3 is feasible. One bottle contains 36 tablets of either 10 or 20 mg ponesimod.

- **Dose level 5 (TP3):**
  Three bottles each at all visits from the earliest visit following approval of protocol version 8 by ECs/IRBs and health authorities and signature of the revised Informed

Consent Form by the patients and when the switch to TP3 is feasible. One bottle contains 36 tablets of 20 mg ponesimod.

3.9.2 Study drug labeling

The labeling will comply with the applicable laws and regulations of each country.

3.10 Study endpoints

3.10.1 Efficacy endpoints

Only exploratory efficacy endpoints will be investigated.

Exploratory efficacy endpoints will be analyzed over the combined treatment period with ponesimod within studies AC-058B201 and AC-058B202 (i.e., starting from the first administration of ponesimod and ending with the EOT visit 2 or 3, as applicable). For "changes from baseline to all assessments" as well as for all numerical endpoints, all assessments available after initiation of ponesimod are considered in the combined treatment period. For time to event endpoints, the start is defined as initiation of study treatment, and patients without events are censored at the end of the combined treatment period.

The following exploratory endpoints will be analyzed:

1. Annualized confirmed relapse rate.
2. Time to first confirmed relapse.

Definition of relapse

A relapse is defined as the occurrence of an acute episode of one or more new symptoms, or worsening of existing symptoms of MS, not associated with fever or infection, and lasting for at least 24 hours after a stable period of at least 30 days.

A "confirmed relapse" is a relapse accompanied by an increase from the previous clinically stable assessment (i.e., performed at least 30 days after the onset of any previous relapse) of at least 0.5 point in the EDSS score, or one point in the score for at least one of the FS scores, excluding the bowel and bladder, and mental FS. The confirmatory EDSS must be performed within 7 days of the onset of a new symptom or worsening of an existing symptom of MS.

Symptoms of transient neurological worsening that do not meet the criteria for "confirmed relapse" because unaccompanied by objective findings, but still judged to constitute a relapse by the treating neurologist, will be recorded as "unconfirmed relapse" and included in the number of total relapses.

Confirmed and unconfirmed relapse will be recorded in the CRF. Start/end date and dose of corticosteroid treatment will also be recorded in the CRF.

For exploratory efficacy endpoints both confirmed and total relapses are analyzed.

The severity of relapse will be calculated for each relapse according to the algorithm defined in Table 7.

Table 7: Severity of relapse

Mild relapse	Moderate relapse	Severe relapse
EDSS increase of 0.5 point ***or*** 1-point increase in 1 to 3 FS*	EDSS increase of 1 or 2 points ***or*** 2-point increase in 1 or 2 FS* ***or*** 1-point increase in 4 or more FS*	Exceeding moderate relapse criteria: EDSS increase of 2.5 points ***or*** 2-point increase in 3 FS* ***or*** 3-point increase in 1 FS* ***or*** 2-point increase in more than 2 FS*

* excluding the bowel and bladder, and mental FS.
Note: The EDSS increase is the increase observed at the EDSS assessment associated with the relapse, as compared the preceding EDSS assessment (performed prior to the relapse).

3. Time to 24-week confirmed disability progression up to end of the study.

   Disability progression is defined as an increase of at least one full point in the EDSS score (or 1.5 points if the baseline EDSS was 0, or 0.5 points if the baseline EDSS was equal or greater than 5.5) with or without relapse, confirmed at the next scheduled EDSS assessment at least 24 weeks later (or if missing, at the next available scheduled EDSS assessment). The time to event is defined as the time from initiation of study treatment until the first EDSS assessment meeting the criteria for disability progression.

4. Other relapse-related endpoints:

   - Annualized total relapse rate.
   - Time to first (total) relapse.
   - Number of (confirmed and total) relapses.
   - Number of patients without any (confirmed and total) relapse.
   - Number of patients with a relapse requiring corticosteroid treatment.

5. MRI-related endpoints:

- Number of Gd+ lesions per patient recorded on T_1-weighted MRI scans at all assessments.
- Number of patients with no Gd+ lesions on T_1-weighted MRI scans at all assessments.
- Total volume of Gd+ lesions per patient on T_1-weighted MRI scans at all assessments.
- Number of new or enlarging lesions per patient on T_2-weighted MRI scans at all assessments.
- Change from baseline to all assessments in total lesion volume per patient on T_2-weighted MRI scans.
- Number of combined unique active lesions (Gd+ lesions plus new or enlarging T_2 lesions without gadolinium-enhancement) per patient on MRI scans at all assessments.
- Percentage change of brain volume from Visit 2 (from AC-058B201) up to the end of the study.
- Percentage change of brain volume from Visit 11 (from AC-058B201) up to the end of the study.

6. Neurological endpoints:
   - Categorical change from baseline to all assessments in EDSS and FS scores.
7. Ophthalmological endpoints:
   - Change from baseline to all assessments of average retinal nerve fiber layer (RNFL) thickness, central foveal thickness and total macular volume as measured by optical coherence tomography (OCT) at selected centers.
   - Change from baseline to all assessments of average number of letters correctly read in a best corrected visual acuity test (recorded only at the centers that also perform OCT).
8. Changes in vaccine-specific antibody titers from pre- to post vaccination will be explored at the end of the study, at the latest, for patients having received non-live vaccination against influenza or COVID-19 while in the study.

3.10.2 Safety and tolerability endpoints

The following safety and tolerability endpoints will be analyzed on treatment as described for the exploratory efficacy endpoints:

- Change in ECG parameters (HR, PR, QRS, QT, QTc) from baseline to all pre-dose assessments, and from pre-dose to post-dose at selected time points during the study.
- Treatment-emergent clinically relevant abnormalities as assessed by 12-lead ECG (central reading).
- Change in left ventricular ejection fraction as assessed by Standard 2D echocardiography (at selected centers) from baseline to all assessments.
- Treatment-emergent clinically relevant abnormalities as assessed by Standard 2D/Doppler echocardiography (at selected centers).
- Change in PFTs (FEV_1, forced vital capacity [FVC], FEV_1/FVC ratio, and FEV_1 and FVC in percent of predicted value) from baseline to all assessments.
- Change in ophthalmological exam (best corrected visual acuity, low contrast visual acuity, visual fields, dilated ophthalmoscopy, and at selected centers, OCT) from baseline to all assessments.
- Change in systolic blood pressure (SBP) and diastolic blood pressure (DBP) from baseline to all pre-dose assessments and from pre-dose to post-dose at selected time points during the study.
- Change in laboratory parameters (hematology, blood chemistry, and urinalysis) from baseline to all assessments.
- Treatment-emergent laboratory abnormalities.
- Change in body weight from baseline to all assessments.

In addition, the following safety and tolerability parameters will be analyzed:

- Treatment-emergent AEs, until 15 days after study drug discontinuation.
- Post-treatment AEs, from 16 days until up to 90 days after study drug discontinuation.
- AEs leading to premature discontinuation of study drug.
- Treatment-emergent serious adverse events (SAEs) until 15 days after study drug discontinuation.
- Post-treatment SAEs from 16 days until up to 90 days after study drug discontinuation.

3.10.3 Pharmacokinetic and pharmacodynamic analyses

3.10.3.1 Pharmacokinetic analyses

- Plasma concentrations of ponesimod will be determined at trough (pre-dose):
  TP1: on Days 8 and 15 (Visits E2 and E3) and at Visits E4, E7, E9, and E13 (EOT2),
  TP2 and TP3: P2, P7, P14 and P22, as applicable.

3.10.3.2 Pharmacodynamic analyses

- Absolute count and percent change in peripheral blood lymphocyte counts as a function of ponesimod dose and plasma concentrations at trough level (pre-dose) on Days 8 and 15 (Visits E2 and E3) and at Visits E4, E7, E9, E13 (EOT2), P2, P7, P14, P22, P30 and EOT3, as applicable.
- Post-treatment lymphocyte recovery 8, 30, and 90 days (at 90 days for patients performing TP2 and TP3, if applicable) after study drug discontinuation.
- Efficacy and safety parameters will be correlated with absolute lymphocyte counts and magnitude of reduction of lymphocyte counts on an exploratory basis.

Additional PK and PD relationships to efficacy and safety parameters may be investigated.

3.11 Study assessments

3.11.1 Efficacy assessments

The efficacy assessments will be performed according to Table 1, Table 2, Table 3, and Table 4.

3.11.1.1 Brain magnetic resonance imaging parameters

MRI parameters include the number and volume of Gd+ lesions on T_1-weighted MRI scans, number of new and enlarging lesions and lesion volume on T_2-weighted MRI, and global measures of loss of brain tissue.

T_1-weighted imaging before and after i.v. administration of 0.1 mmol/kg body weight (0.2 mL/kg) of gadolinium-DTPA as well as T_2-weighted imaging will be performed. Gadolinium-DTPA may cause nausea and vomiting, and in very rare cases allergic reactions which could require immediate anti-anaphylactic therapy (such as steroids, epinephrine, etc.). It is recommended to use macrocyclic gadolinium-based contrast agents (e.g., gadobutrol, gadoterate, gadoteridol) as described in the MRI manual.

All MRI data will be analyzed by the MIAC, c/o University Hospital Basel, Switzerland. MRI scans which are of unacceptable quality for central reading evaluation will be repeated.

Detailed instructions on procedures, standardization, qualification, recording, and transfer of data, etc., will be provided in the study MRI Technology Manual (separate document). In addition to study-specific requirements, the MRI equipment needs to be maintained and calibrated according to the manufacturer's recommendations and local standard operating procedures (SOPs). A calibration log must be maintained.

Incidental, non-MS-related findings identified by the central reading facility will be communicated to the primary investigator / treating neurologist. Furthermore, all MRI scans performed for the study must be analyzed by the local radiologist, neuroradiologist

or neurologist with MRI expertise. The primary investigator / treating neurologist must have access to the MRI images and/or reports, and be informed of any findings of concern for the patient's safety, including non-MS-related findings detected on the MRI scan.

Incidental clinically relevant findings on MRI will be reported in the Medical History or as AE, as applicable.

MRI will be performed at the following time points during the study:

- TP1: Visit E7, Visit E9 and Visit E13
- TP2 and TP3: Yearly (from Visit P1 to EOT3, inclusive)
- At the Follow-up visit E2 or FU2, as applicable.

3.11.1.2 Relapses

The clinical parameter "Relapse" includes confirmed and unconfirmed relapses [as defined in Section 3.10.1].

Patients will be instructed to contact their primary investigator / treating neurologist at the clinical site immediately in the event of the appearance of any symptoms suggestive of an MS exacerbation. An unscheduled visit will be organized as soon as possible after onset or worsening of the symptom(s) as follows:

The primary investigator / treating neurologist will examine the patient and decide whether the patient has to be referred to the evaluating neurologist.

In the event of a patient's referral to the evaluating neurologist, the evaluating neurologist will perform the EDSS/FS within 7 days after onset or worsening of the symptom(s).

The decision regarding whether the neurological change is considered as confirmed or unconfirmed relapse will be made by the primary investigator / treating neurologist based on the EDSS/FS scores assessed by the evaluating neurologist.

3.11.1.3 Expanded Disability Status Scale and Functional System scores

EDSS and FS scores [Kurtzke 1983] are based on a standard neurological examination for assessing neurologic impairment in MS. Among the eight FS, seven are ordinal clinical rating scales ranging from 0 to 5 or 6, assessing Visual, Brain Stem, Pyramidal, Cerebellar, Sensory, Bowel & Bladder, and Cerebral functions. The ratings of the individual FS scores are then used to rate the EDSS in conjunction with observations and information concerning gait and use of assistance. 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 (Appendix 7) will be performed at the following time points during the study:

- Visit E7, Visit E9, Visit E13 and at all following visits during TP2 and TP3 until EOT3.

- At Follow-up visit E2 or at FU2 and FU3, as applicable.
- At any unscheduled visit in the event of suspected relapse.

As of the implementation of Global Protocol version 12, EDSS and FS assessments can be performed using the EDSS scale set up at the site as a standard. If Neurostatus is used, the neurologist using the scale must be trained and certified.

3.11.1.4 Ancillary study: Ophthalmological assessments

As of the implementation of Global Protocol version 12, regular OCT is no longer required and the scope of this ancillary study will be limited.

Unscheduled OCT will only be performed for subjects at risk (with findings suggestive of macular edema, or if active uveitis is diagnosed during the study) at the ophthalmologist's discretion.

At centers performing OCT, the assessment of best corrected visual acuity will be standardized and the number of correctly read letters recorded in the CRF. Details are provided in Appendix 11.

The OCT equipment needs to be maintained and calibrated according to the manufacturer's recommendations and local SOPs. A calibration log must be maintained.

3.11.2 Safety and tolerability assessments

The definitions, reporting, and follow-up of AEs, SAEs, and potential pregnancies are described in Section 4. For time points of the below-mentioned assessments, see Table 1, Table 2, Table 3, and Table 4.

3.11.2.1 12-lead electrocardiogram (ECG)

A standard 12-lead ECG will be recorded with the patient in a fully rested supine position at all study visits until Visit P37, then yearly until Visit P45, inclusive, and at Visits EOT2 or EOT3, Follow-up visits E1 and E2 or FU1 and FU2, as applicable. The ECG equipment is supplied by the ECG central reader. Please refer to the manual provided by central reader for maintenance and operation of the equipment.

The 12-lead ECG assessment during TP1 must be performed by the physician evaluating cardiac safety. During TP2 and TP3, the physician evaluating cardiac safety is responsible for performing the 12-lead ECG assessments at P1, at the visit during which the transition from TP2 to TP3 takes place, re-initiation, and re-uptitration visits. At all other scheduled visits for TP2 and TP3 the 12-lead ECG assessment may be done by the physician evaluating cardiac safety or the primary investigator / treating neurologist.

The following parameters will be evaluated: HR (bpm), PR (ms), QRS (ms), QT (ms), QTc (ms), and any ECG findings.

- At Visit E1 (Day 1) the pre-dose ECG must be performed prior to randomization and it must be checked if the patient fulfills any of the study-specific cardiovascular criteria for permanent discontinuation of study drug as defined in Appendix 1. The patient must not be randomized if any of these criteria is met.
- During the treatment period ECGs must be performed at pre-dose.
- At Visits E1, E2, E3 (Days 1, 8, and 15 respectively), P1, on re-initiation and re-uptitration days, the visit during which the transition from TP2 to TP3 takes place, ECGs must be performed at pre-dose and hourly for up to 12 hours post-dose, if applicable. ECG monitoring will be performed with the patient in a fully resting supine position.
- In the event of a clinically relevant change from baseline in HR or other ECG parameters persisting after the post-dose monitoring, the patient will be carefully monitored for an additional period and 12-lead ECG will be performed as described in Appendix 2.
- If the patient does not meet the discharge criteria at 12 hours post-dose, the patient will be kept in the hospital for observation and additional ECGs will be performed until changes in HR and/or other ECG parameters are no longer clinically relevant.
- Significant findings observed after study drug initiation, which in view of the physician evaluating cardiac safety meet the definition of an AE, must be recorded on the Adverse Event form of the eCRF.
- Treatment for bradycardia, if any, will be recorded as concomitant medication on the appropriate eCRF form.
- 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 patients according to the study protocol schedule. ECGs will be assessed by the physician evaluating cardiac safety and ECG print-outs must be filed with the source documentation. The data records will be sent to the evaluation center for central reading. Details will be provided in the ECG manual.

3.11.2.2 Ancillary study: Doppler echocardiography

Standard 2D/Doppler echocardiography will assess regional wall abnormalities, aortic valve morphology and function, mitral valve morphology and function, and left ventricular ejection fraction. It will be performed at selected centers with adequate equipment and experience. During TP2 and TP3, echocardiography is performed at every other visit from P1 to P35, yearly from Visits P37 to P45, inclusive, and at EOT3 [see Table 1 and Table 3]. The echocardiography equipment needs to be maintained and calibrated according to the manufacturer's recommendations and local SOPs. A calibration log must be maintained.

Echocardiography assessments will only be conducted in patients who were assessed during the core study.

The physician conducting Standard 2D/Doppler echocardiography must have at least Level 2 training as defined in the American College of Cardiology Board/American Heart Association clinical competence statement on echocardiography [Quiñones 2003].

An echocardiography monitoring plan was developed for the study in close cooperation with cardiac experts. The evaluation of the echocardiography will be done centrally at a Core Imaging Lab. Detailed instructions on procedures, standardization, qualification, recording, and transfer of data, etc., will be provided in a separate manual.

3.11.2.3 Blood pressure

BP measurements include SBP and DBP. The sphygmomanometer needs to be maintained and calibrated according to the manufacturer's recommendations and local SOPs. A calibration log must be maintained.

Automated BP monitoring will be performed using the same type of device throughout the study on the same arm. The BP should preferably be measured with the patient in a fully rested supine position. It is strongly recommended that BP is measured in the same position throughout the study.

BP measurements will be performed throughout the study at each visit from Visit E1 to EOT2 or EOT3, at the Safety Follow-up visits E1 and E2 or FU1, FU2 and FU3 (as applicable), and at any unscheduled relapse visit. At Visits E1, E2, and E3 (Days 1, 8, and 15, respectively), P1, on re-initiation and re-uptitration days, the visit during which the transition from TP2 to TP3 takes place, SBP and DBP will be measured at pre-dose, and hourly for up to 12 hours post-dose, if applicable.

If SBP is not >90 mmHg after the post-dose monitoring, the patient will be carefully monitored for an additional period, and BP measurements will be performed as described in Appendix 2.

If the patient does not meet the discharge criteria at 12 hours post-dose, she/he will be kept in the hospital for observation, and additional BP measurements will be performed until SBP is >90 mmHg.

3.11.2.4 Pulmonary function test

PFTs will assess FEV_1 and FVC, and must be conducted by a PFT technician or expert. The PFT equipment needs to be maintained and calibrated according to the manufacturer's recommendations and the recommendations for range and accuracy for forced expiratory maneuvers from the ATS/ERS guidelines [Miller 2005]. A calibration log must be maintained.

PFTs will be conducted according to the American Thoracic Society/European Respiratory Society guidelines [Miller 2005]. Three well-performed test breaths will be measured; the highest FEV_1 and FVC values from these 3 breath tests will be recorded in the CRF. For

data analysis FEV_1 and FVC as percent of predicted value and the ratio FEV_1/FVC will be derived from above-mentioned values (as provided in the CRF).

Details on PFT performance and the training of the responsible site personnel prior to enrollment of the first patient at the site are described in Appendix 12. It is highly recommended to use the same device as used during the core study for the extension study.

PFTs will be performed pre-dose:

- TP1: at Visits E2 and E3 (Days 8 and 15), Visits E4 to E7, E9, E11 and E13
- TP2 and TP3: at every other visit from P1 to P35, yearly from Visit P37 to P45, inclusive, and at EOT3.
- Follow-up: at Visits E1 and E2 or FU1, FU2 and FU3.

During the visits requiring bronchodilator assessment (yearly from visit P1 to EOT3) two pre-dose PFT assessments will be performed:

- One PFT assessment prior to administration of the bronchodilator
- A second PFT assessment 30 minutes (± 15 minutes) after administration of the bronchodilator.

In addition, unscheduled PFTs will be conducted in the event of respiratory symptoms (e.g., dyspnea) or decreased lung function (FEV_1 and/or FVC <80% of baseline value) during the course of the study. See Appendix 1.

3.11.2.5 Bronchodilator assessment

As of the implementation of Global Protocol version 12, the bronchodilator assessment is no longer required.

3.11.2.6 Ophthalmological assessments

As of the implementation of Global Protocol version 12, regular OCT is no longer required.

Unscheduled OCT will only be performed for subjects at risk according to the ophthalmologist's decision (with findings suggestive of macular edema, or if active uveitis is diagnosed during the study; see Section 3.11.1.4).

Clinically relevant findings meeting the definition of an AE [see Section 4.2.1] must be recorded on an AE form of the eCRF.

Ancillary study

Measurement of average RNFL thickness, central foveal thickness, and total macular volume will be explored as safety and efficacy outcomes by OCT and will be measured and recorded at selected centers with adequate equipment and experience.

An ophthalmological assessment will be performed by an ophthalmologist at the following visits:

- TP1: at Visit E4, Visit E6, Visit E7, Visit E9, Visit E11 and Visit E13;
- TP2 and TP3: at every other visit from Visit P1 to P35, yearly from P37 to P45, inclusive, and at EOT3;
- Follow-up: at Visit E2 or FU2, as applicable.

In addition, an unscheduled ophthalmological assessment will be performed during the study in the event of any new visual symptoms or decrease in visual acuity.

From Global Protocol version 12 onwards the scope of this ancillary study will be limited to patients with suspicious of acute uveitis and macular edema.

In case of suspected clinically significant findings (e.g., macular edema) during the study, it is highly recommended to perform an OCT assessment in addition to the safety ophthalmological assessments [see Appendix 1, section E].

3.11.2.7 Weight

Body weight will be measured using the same scales:

- TP1: at Visit E7, Visit E9, Visit E11 and Visit E13
- TP2 and TP3: yearly (from Visit P1 to EOT3).

3.11.2.8 Physical examination

Physical examination (i.e., inspection, percussion, palpation and auscultation) will be performed during the course of the study at each scheduled visit, except Visit E1 (Day 1), until Visit P37, then yearly until Visit P45, inclusive. Physical examination will also be performed at EOT2 or EOT3 and at the Follow-up visits E1 or FU1, E2 or FU2, and FU3, as applicable. In addition, physical examination will be performed at any unscheduled relapse visit. Clinically relevant findings meeting the definition of an AE [see Section 4.2.1] must be recorded on an AE form of the eCRF.

Skin examination

A complete skin examination will be performed as part of the physical examination at all visits from Visit E6 (Week 12) through EOT2 or EOT3 and at the Follow-up visits E2 or FU2 and FU3, as applicable. The skin examination can be done by a dermatologist or by the primary investigator / treating neurologist. In the event of findings of suspicious or pre-cancerous or cancerous skin disorders observed at any visit during the study, the primary investigator / treating neurologist will refer the patient to a dermatologist for further examination. A biopsy may be required to rule out or confirm diagnosis. Any new findings during the study must be recorded on the AE form of the eCRF.

Detailed guidance on the skin examination is provided in Appendix 4.

3.11.2.9 Laboratory assessments

3.11.2.9.1 Type of laboratory

At all scheduled visits, except Visit E1 (Day 1), blood chemistry, hematology and urinalysis tests will be performed. The analysis of the blood samples will be carried out at the central laboratory. The contact details of the central laboratory as well as sampling, storage, and shipment procedures for completion of laboratory tests are described in the central laboratory manual. During TP1 and TP2, the central laboratory will provide all laboratory results to the site with the exception of the results of the total white blood cell (WBC) count and total lymphocyte count. During TP3, the central laboratory will provide all laboratory results to the site, including the total WBC count and total lymphocyte count. In the event of a clinically significant abnormality of total WBC count and/or total lymphocyte count, an alert will be communicated to the primary investigator.

Whenever a total lymphocyte count < 200 cells/µL is recorded by the central laboratory, an alert will be sent to the primary investigator and the sponsor [see Appendix 1]. The primary investigator will immediately contact the patient 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) by the central laboratory (unless the clinical situation mandates immediate local testing). If a local laboratory test was performed, the test results have to be captured in the CRF.

If the repeat test confirms a lymphocyte count < 200 cells/µL, the study drug must be discontinued and lymphocyte count needs to be monitored at least once a week by the central laboratory (unless the clinical situation mandates immediate local testing) until the lymphocyte count has returned to ≥ 1000 cells/µL or ≥ 80% of the baseline value. If a local laboratory test was performed, the follow-up test results have to be captured in the CRF.

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 patient, and ask the patient about any potential symptoms. The patient 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 8 [see Appendix 1].

Patients receiving non-live vaccination against influenza or COVID-19 while on study treatment will have 5 mL of blood drawn prior to and at least 3 weeks after vaccination to explore changes in vaccine -specific antibody titers from pre- to post vaccination. Samples will be analyzed at the end of the study at the latest.

For WOCBP, urine pregnancy tests will be performed at the site at all visits from Visit E4 (Week 4) until EOT2 or EOT3 and at Follow-up visit E2 or FU2 using the kits provided by the central laboratory. All laboratory reports (central and local) must be signed and dated by the primary investigator or other qualified study personnel at the study site within 5 calendar days of receipt and filed with the source documentation. Any clinically significant marked laboratory abnormality must be reported as an AE and/or SAE as appropriate and must be followed until it returns to within the normal range or stabilization, or until the change is no longer clinically relevant.

If a blood sample is lost or deteriorated and could not be analyzed, the sample may need to be repeated at the investigator's discretion.

3.11.2.9.2 Laboratory parameters

- Hematology
  - Red blood cell count
  - Total and differential WBC counts (basophils, eosinophils, lymphocytes, monocytes, neutrophils, band forms)
  - Platelet count
  - Hemoglobin
  - Hematocrit
  - Mean corpuscular hemoglobin
  - Mean corpuscular volume
- Blood chemistry
  - Glucose (preferably under fasting conditions)
  - ALT, AST, alkaline phosphatase, total bilirubin, lactate dehydrogenase, International Normalized Ratio (INR)
  - Creatinine
  - Urea
  - Cholesterol
  - Triglycerides
  - Sodium, potassium, chloride, calcium
  - Total Protein, albumin
  - C-reactive protein
- Urinalysis
  - pH
  - Glucose
  - Proteins
  - Blood
  - Leukocytes
  - Bilirubin, urobilinogen
- Pregnancy test

- Urine pregnancy tests will be performed at all Visits E4 to EOT2 or EOT3 and at Follow-up visit E2 or FU2, as applicable.

Female patients who interrupt the study drug because of planned pregnancy will be exempted from any protocol-mandated pregnancy tests after the first positive pregnancy test and until 30 (±5) days before study drug re-initiation.

Results will not be recorded in the CRF. In the event of pregnancy, the appropriate pregnancy notification form must be completed [see Section 4.4.3].

- Additional analyses in the event of infections
  - The storage period of the serum sample, which was collected at Visit 2 (Baseline) of the core study and stored at the central laboratory for potential retrospective analyses of viral serology titers in the event of infections (e.g., suspected opportunistic infections) during the study, will be extended until completion of the extension study.

- Analyses in case of vaccination against influenza or COVID-19 non-live vaccines
  Two serum samples will be taken prior to and at least 3 weeks after vaccination to be analyzed by the specialized laboratory for vaccine-specific antibody titers.

3.11.3 Pharmacokinetic and pharmacodynamic assessments

3.11.3.1 Pharmacokinetic assessments

PK samples will be collected during this study for all patients, in order to provide information about study drug exposure in the target population.

To prevent degradation of ponesimod in the plasma samples, exposure to light must be minimized. After centrifugation, plasma samples must be kept in the dark. Samples are to be stored under controlled temperature on site between 80 °C and 20 °C.

- Plasma concentrations of ponesimod will be determined at trough level (pre-dose):
  TP1: on Days 8 and 15 (Visits E2 and E3) and at Visits E4, E7, E9 and E13
  TP2 and TP3: P2, P7, P14 and P22, as applicable.

3.11.3.2 Pharmacodynamic assessments

The PD marker is total lymphocyte counts, which will be measured as part of the hematology tests [see Section 3.11.2.9].

3.11.4 Total blood volume

The maximum total blood volume to be drawn per patient during the entire course of the study will be as follows:

Treatment period	Blood volume
Hematology[1]	Up to 58 × 3 mL = Up to 174 mL
Blood chemistry	Up to 58 × 8 mL = Up to 464 mL
Ponesimod PK	Up to 10 × 5 mL = Up to 50 mL
Vaccine-specific antibody titer[2]	2 × 5 mL = 10 mL
INR	Up to 17 × 3 mL = Up to 51 mL
Total blood volume[3]	Up to 739 mL or Up to 749 mL [2]

1. Additional samples may be needed in the event of lymphocytes <200 cells/µL.
2. Patients receiving non-live vaccination against influenza or COVID-19 while on study treatment will have 5 mL of blood drawn prior to and at least 3 weeks after vaccination. Thus, the total blood volume for these patients will be 10 mL higher than for other patients.
3. If a sample is lost or not evaluable, a new sample may need to be taken if deemed necessary by the investigator.

Safety Follow-up period	Blood volume
Hematology	3 × 3 mL = 9 mL
Blood chemistry	3 × 8 mL = 24 mL
INR	3 × 3 mL = 9 mL
Total blood volume[1]	42 mL

1. If a sample is lost or not evaluable, a new sample may need to be taken if deemed necessary by the investigator.

3.11.5 Baseline parameters and concomitant medications

3.11.5.1 Informed consent

Prior to continued administration of core study medication at core study Visit 11 (Week 24) the patient must provide written informed consent to participate in the extension study.

If the signing of informed consent and continued administration of core study medication at core study Visit 11 (Week 24) take place on the same day, it must be clearly stated in the source documents that the patient has given full informed consent prior to continued administration of core study medication at core study Visit 11 (Week 24). It is the responsibility of the primary investigator / treating neurologist to explain the study in all its aspects to the patient and obtain her/his informed consent. For patients who provide informed consent but are subsequently not enrolled into the extension study, the reasons for not being enrolled will be recorded and provided to the sponsor.

Prior to starting TP2 patients have to sign a new Informed Consent Form.

Prior to continuing with the extended period (additional 288 weeks) of TP2, which starts with visit P13, patients have to sign a new Informed Consent Form.

Following approval of protocol version 8 by ECs/IRBs and Health Authorities and prior to starting TP3, patients have to sign a revised Informed Consent Form at the earliest scheduled visit.

3.11.5.2 Demographics and disease characteristics

The following information will be documented in the CRF.

The patient number assigned in the core study will be maintained and will identify patients in the extension study.

Baseline demographics including gender, date of birth, race, and height are recorded in the core study only.

Body weight is recorded both in the core and the extension study.

Clinically relevant medical history / concomitant illnesses are recorded in the core study. A medical history eCRF form is created to collect medical history reported during the extension study. The medical history reported during study AC-058B201 must not be repeated on this eCRF form.

MS-specific disease history and characteristics are recorded in the core study.

3.11.5.3 Concomitant medications

All medications taken by the patient from the beginning of the transition period until EOS2 or EOS3, i.e., all medications ongoing, started or stopped during this period, will be recorded on the Concomitant Medications form of the extension eCRF.

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 form of the eCRF.

3.12 Visit and assessment schedule

Table 1, Table 2, Table 3, and Table 4 provide an overview of the assessment schedule.

During the extension study, patients will visit the study center up to a total of 63 times in the morning preferably under fasting conditions.

1. Transition period (on core study medication)
   - The first visit of the extension study, Visit E1, will take place within three days after the Week 24 visit of the core study.
   - Patients will have to continue using their core study medication every day until and including the day prior to Visit E1.
   - The transition period is defined as the time of study drug intake at the Week 24 visit and the end as the time of study drug intake at Visit E1.

2. Treatment periods (on extension study medication)
   - Randomization

   TP1:
   - Study drug administration: Visit E1 (Day 1)
   - Study treatment visits: Visits E2 to E13 (EOT2) on Days 8 and 15, and at Weeks 4, 8, 12, 24, 36, 48, 60, 72, 84 and 96
   - Phone call with the patient on Day 22
   - Unscheduled visit(s) for relapse assessment
   - Unscheduled visit(s) for ophthalmological assessments or PFT in the event of clinical symptoms

   TP2 and TP3:
   - Study drug administration: Visit P1
   - Study treatment visits: Visits P1 to EOT3
   - Unscheduled visit(s) for relapse assessment
   - Unscheduled visit(s) for ophthalmological assessments or PFT in the event of clinical symptoms

3. Safety Follow-up period

TP1:

In the case of discontinuation from study drug before Visit P1 the study follow-up visits E1 (Visit E14) and E2 (Visit E15) at 8 and 30 days after the last study drug administration have to be performed.

TP2 and TP3:

In the case of discontinuation from study drug after Visit P1 the study follow-up visits FU1, FU2 and FU3 at 8, 30 and 90 days after the last study drug administration have to be performed.

3.12.1 Transition period

It is the responsibility of the primary investigator / treating neurologist to obtain written informed consent prior to continued administration of core study medication from each patient after adequate explanation of the aims, methods, objectives, and potential hazards of the study.

3.12.2 Extension treatment period 1

3.12.2.1 Visit E1 (Day 1) / Randomization and study drug administration

The patient should arrive at the clinic early in the morning and must bring back all remaining core study medication.

Visit E1 is the visit when patients who were on placebo in the core study will receive their first dose of ponesimod (10 mg). Patients who were on active treatment in the core study will continue treatment on their maintenance dose from the core study. Start of the treatment period is defined as the time point when patients take their dose of ponesimod from the bottle assigned on Visit E1.

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

3.12.2.1.1 Visit E1 (Day 1) / pre-dose

The following assessments must be performed:

- Concomitant medications since the Week 24 (EOS) visit of the core study, if any;
- 12-lead ECG and SBP/DBP (under the responsibility of the physician evaluating cardiac safety assessments);
- Recording of AEs/SAEs since the Week 24 (EOS) visit of the core study;
- Recording of ongoing AEs from core study.

The results of these assessments must be provided to the primary investigator, who must make the final decision on randomization (based on inclusion/exclusion criteria) and the administration of the study drug.

If eligible, patients will be enrolled in the extension study. Core study placebo patients will be randomized to ponesimod 10, 20, or 40 mg, and take their first dose (10 mg) of ponesimod. Patients on active treatment during the core study continue treatment with their maintenance dose from the core study.

3.12.2.1.2 Visit E1 (Day 1) / post-dose

After dispensing the study drug (ponesimod 10, 20, or 40 mg), the physician evaluating cardiac safety assessments (or trained personnel working under her/his responsibility) will perform the following assessments:

- 12-lead ECG and SBP/DBP every hour for 6-hours post-dose

The primary investigator / treating neurologist must record the following:
- Change to concomitant medication, if any;
- AEs and SAEs.

At the end of this visit, i.e., 6 hours post-dose, the physician evaluating cardiac safety assessments must check the hospital discharge criteria [Appendix 2]. If the patient meets these criteria and has completed all scheduled assessments, she/he will receive one study drug bottle for the period until the next visit. The patient will be instructed to take the study drug every morning, with or without breakfast (preferably always in the same way and at approximately the same time). However, on the morning of the next visit no study drug is to be taken prior to the visit. The dose for that day will be taken from the new drug bottle (allocated to the patient on that day) after all pre-dose assessments for that visit have been completed.

The patient will receive a patient's card containing contact details, and will be instructed to contact the site if she/he has any questions or problems.

The next visit, Visit E2 (Day 8), will be scheduled, and the patient will be reminded to bring back all unused study drug (or empty bottle).

Thereafter, the patient will be discharged under the responsibility of the primary investigator / treating neurologist, or the physician evaluating cardiac safety assessments.

3.12.2.2 Visit E2 (Day 8) / first uptitration

The visit window for this visit is ±1 day.

Visit E2 is the visit of the first uptitration for patients who were on placebo in the core study and were randomized to receive ponesimod at 20 or 40 mg in the extension study. For all other patients this will be a mock uptitration and they will continue to take their maintenance dose. The patient will arrive at the clinic early in the morning and receive the study drug.

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

3.12.2.2.1 Visit E2 (Day 8) / pre-dose

The following assessments must be performed:

- Changes in concomitant medications since Visit E1 (Day 1), if any;
- Physical examination;
- PFTs (FEV_1, FVC);
- 12-lead ECG and SBP/DBP (under the responsibility of the physician evaluating cardiac safety assessments);
- Recording of AEs and SAEs.

The primary investigator / treating neurologist must make the final decision on treatment continuation.

If the patient can be continued, the following assessments will be performed under the responsibility of the primary investigator / treating neurologist:

- Laboratory tests (central laboratory) in fasting condition:
  - Hematology, blood chemistry, urinalysis
- PK assessments:
  - A blood sample will be taken prior to study drug intake

3.12.2.2.2 Visit E2 (Day 8) / post-dose

After dispensing the study drug, the physician evaluating cardiac safety assessments (or trained personnel working under her/his responsibility) will perform the following assessments:

- 12-lead ECG and SBP/DBP every hour for 6-hours post-dose

The primary investigator / treating neurologist must record the following:

- Change to concomitant medication, if any;
- AEs and SAEs.

At the end of this visit, i.e., 6 hours post-dose, the physician evaluating cardiac safety assessments must check the hospital discharge criteria [Appendix 2]. If the patient meets these criteria and has completed all scheduled assessments, she/he will receive one study drug bottle for the period until the next visit. The patient must be instructed to take the study drug every morning, with or without breakfast (preferably always in the same way and at approximately the same time). However, on the morning of the next visit no study drug is to be taken prior to the visit. The dose for that day will be taken from the new drug bottle (allocated to the patient on that day) after all pre-dose assessments for that visit have been completed.

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

The next visit, Visit E3 (Day 15), will be scheduled and the patient will be reminded to bring back all unused study drug (or empty bottle).

Thereafter, the patient will be discharged under the responsibility of the primary investigator / treating neurologist or the physician evaluating cardiac safety assessments.

3.12.2.3 Visit E3 (Day 15) / second uptitration

The visit window for this visit is ±1 day.

Visit E3 is the visit of the second uptitration for patients who were on placebo in the core study and were randomized to receive ponesimod at 40 mg in the extension study. For all other patients this will be a mock uptitration and they will continue to take their maintenance dose. The patient will arrive at the clinic early in the morning and receive the study drug.

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

3.12.2.3.1 Visit E3 (Day 15) / pre-dose

The following assessments must be performed:

- Changes in concomitant medications since Visit E2 (Day 8), if any;
- Physical examination;
- PFTs (FEV_1, FVC);
- 12-lead ECG and SBP/DBP (under the responsibility of the physician evaluating cardiac safety assessments);
- Recording of AEs and SAEs.

The primary investigator / treating neurologist must make the final decision on treatment continuation.

If the patient can be continued, the following assessments will be performed under the responsibility of the primary investigator / treating neurologist:

- Laboratory tests (central laboratory) in fasting condition:
  - Hematology, blood chemistry, urinalysis
- PK assessments:
  - A blood sample will be taken prior to study drug intake

3.12.2.3.2 Visit E3 (Day 15) / post-dose

After dispensing the study drug, the physician evaluating cardiac safety assessments (or trained personnel working under her/his responsibility) will perform the following assessments:

- 12-lead ECG and SBP/DBP every hour for 6-hours post-dose

The primary investigator / treating neurologist must record the following:

- Change to concomitant medication, if any;
- AEs and SAEs.

At the end of this visit, i.e., 6 hours post-dose, the physician evaluating cardiac safety assessments will check the hospital discharge criteria [Appendix 2]. If the patient meets these criteria and has completed all scheduled assessments, she/he will receive one study drug bottle for the period until the next visit. The patient will be instructed to take the study drug every morning, with or without breakfast (preferably always in the same way and at approximately the same time). However, in the morning of the next visit no study drug is to be taken prior to the visit. The dose for that day will be taken from the new drug bottle (allocated to the patient on that day) after all pre-dose assessments for that visit have been completed.

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

A phone call will be scheduled with the patient for Day 22 to obtain information on health status and AEs between Visit E3 and Visit E4.

The next visit, Visit E4 (Week 4 Day 29), will be scheduled and the patient will be reminded to bring back all unused study drug (or empty bottle).

Thereafter, the patient will be discharged under the responsibility of the primary investigator / treating neurologist or the physician evaluating cardiac safety assessments.

3.12.2.4 Phone call on Day 22

The window for the phone call is ±1 day.

The patient will be called and asked to report on any change or unusual observation in health status.

The phone call will be recorded in the patient's records and AEs will be reported in the CRF as appropriate.

The patient will be reminded of the scheduled Visit E4 (Week 4).

3.12.2.5 Visits E4, E5 and E6 (Weeks 4, 8 and 12)

The visit window for Visit E4 (Week 4/Day 29) is ±2 days, the visit window for Visit E5 and E6 (Weeks 8 and 12) is ±5 days.

At Visits E4, E5 and E6, the following assessments must be performed before study drug administration:

- PFTs (FEV_1, FVC)
- 12-lead ECG and SBP/DBP (under the responsibility of the physician evaluating cardiac safety assessments)
- Laboratory tests (central laboratory) in fasting condition:
  Hematology, blood chemistry, urinalysis
  Pregnancy test
- Only at Week 4: A blood sample for PK assessments will be taken prior to study drug intake

The following assessments can be performed after study drug administration:

- Change in concomitant medication, if any;
- Physical examination (only at Week 12: including careful skin examination);
- Recording of AEs and SAEs;
- Only at Weeks 4 and 12: Ophthalmological examination (best corrected visual acuity, low contrast visual acuity, visual fields, and dilated ophthalmoscopy;
- Only at Week 12: Standard 2D/Doppler echocardiography (at selected centers).

When the patient has completed all scheduled pre-dose assessments, she/he will receive one (Visits E4 and E5) or three (Visit E6) study drug bottle(s) for the period until the next visit and will take one capsule. The patient will be instructed to take the study drug every morning, with or without breakfast (preferably always in the same way and at approximately the same time). However, in the morning of the next visit no study drug is to be taken prior to the visit. The dose for that day will be taken from the new drug bottle (allocated to the patient on that day) after all pre-dose assessments for that visit have been completed.

The next visit will be scheduled and the patient will be reminded to bring back all unused study drug (or empty bottle).

3.12.2.6 Visits E7, E9 and E11 (Weeks 24, 48 and 72)

The visit window for these visits is ±14 days.

At Visits E7, E9, and E11, the following assessments must be performed before study drug administration:

- PFTs (FEV_1, FVC)
- 12-lead ECG and SBP/DBP (under the responsibility of the physician evaluating cardiac safety assessments)
- Laboratory tests (central laboratory) in fasting condition:
  Hematology, blood chemistry, urinalysis
  Pregnancy test
- Only at Weeks 24 and 48: A blood sample for PK assessments will be taken prior to study drug intake

The following assessments can be performed after study drug administration:

- Change in concomitant medication, if any;
- Physical examination (including careful skin examination);
- Standard 2D/Doppler echocardiography (at selected centers);
- Ophthalmological examination (best corrected visual acuity, low contrast visual acuity testing, visual fields, and dilated ophthalmoscopy;
- Recording of AEs and SAEs;
- Only at Weeks 24 and 48:
  EDSS and FS scores (assessed by the independent evaluating neurologist);
  MRI examination.

When the patient has completed all scheduled pre-dose assessments, she/he will receive three study drug bottles for the period until the next visit and will take one capsule. The patient will be instructed to take the study drug every morning, with or without breakfast (preferably always in the same way and at approximately the same time). However, in the morning of the next visit no study drug is to be taken prior to the visit. The dose for that day will be taken from the new drug bottle (allocated to the patient on that day) after all pre-dose assessments for that visit have been completed.

The next visit will be scheduled and the patient will be reminded to bring back all unused study drug (or empty bottle).

3.12.2.7 Visits E8, E10 and E12 (Weeks 36, 60 and 84)

The visit window for these visits is ±14 days.

At Visits E8, E10, and E12, the following assessments must be performed before study drug administration:

- 12-lead ECG and SBP/DBP (under the responsibility of the physician evaluating cardiac safety assessments)
- Laboratory tests (central laboratory) in fasting condition:
  - Hematology, blood chemistry, urinalysis
  - Pregnancy test

The following assessments can be performed after study drug administration:

- Change in concomitant medication, if any;
- Physical examination (including careful skin examination);
- Recording of AEs and SAEs.

When the patient has completed all scheduled pre-dose assessments, she/he will receive three study drug bottles for the period until the next visit and will take one capsule. The patient will be instructed to take the study drug every morning, with or without breakfast (preferably always in the same way and at approximately the same time). However, in the morning of the next visit no study drug is to be taken prior to the visit. The dose for that day will be taken from the new drug bottle (allocated to the patient on that day) after all pre-dose assessments for that visit have been completed.

The next visit will be scheduled and the patient will be reminded to bring back all unused study drug (or empty bottle).

3.12.2.8 Visit E13 (Week 96) – EOT2

The visit window for this visit is ±14 days.

A Visit E13 (EOT2 visit) will be performed:

- For patients completing Week 96 according to the protocol and who did not sign yet the informed consent for the protocol version 3 in order to enter into TP2:
  - One day after the last dose of study drug
- For patients who discontinue study drug prematurely:
  - As soon as possible but no later than 5 days after the last dose of study drug

At Visit E13 (EOT2) the following assessments must be performed:

- Change in concomitant medication, if any;
- Physical examination (including careful skin examination);
- PFTs (FEV_1, FVC);
- Ophthalmological examination (best corrected visual acuity, low contrast visual acuity, visual fields, and dilated ophthalmoscopy);
- 12-lead ECG and SBP/DBP (under the responsibility of the physician evaluating cardiac safety assessments);
- Standard 2D/Doppler echocardiography (at selected centers);
- Laboratory tests (central laboratory) in fasting condition:
  - Hematology, blood chemistry, urinalysis;
  - Pregnancy test;
- A blood sample for PK assessments will be taken;
- EDSS and FS scores (assessed by the independent evaluating neurologist);

- MRI examination;
- Chest X-ray;
- Recording of AEs and SAEs.

When the patient has completed all scheduled assessments, Visit E14 (Follow-up Visit E1) will be scheduled 8 days after the last dose of study drug.

3.12.3 Extension treatment periods 2 and 3

Patients who completed at least Visit E9 from TP1 are allowed to enroll into TP2 starting with Visit P1. Patients who have already completed treatment up to Visit E13 (EOT2) may still be enrolled into TP2, provided study drug was not discontinued for longer than 3 months. In this case, Visit P1 must be scheduled as soon as possible and, if applicable, patients must undergo a study drug re-initiation and/or uptitration.

The TP2 and TP3 consist of the visits and assessments described in Sections 3.12.3.2 and 3.12.3.3.

Patients will be transitioned from TP2 to TP3 at the earliest scheduled visit following approval of protocol version 8 by ECs/IRBs and health authorities, signature of the revised Informed Consent Form, and when it is feasible. The day of the first open-label dose of ponesimod 20 mg will correspond to the start of TP3. After this transition, patients will continue with their regular schedule of assessments [see Section 3.12.3.4].

Patients not enrolling into TP3 will have to perform the EOT3 visit [see Section 3.12.3.5].

3.12.3.1 Visit P1 (Day 1)

This visit must be scheduled 12 weeks after the last visit in TP1. The visit window for this visit is ±14 days.

Patients who have already completed treatment up to Visit E13 (EOT2) of TP1 may still be enrolled into TP2, provided study drug was not discontinued for longer than 3 months. In this case, Visit P1 must be scheduled as soon as possible and if applicable, patients must undergo a study drug re-initiation and/or uptitration.

At Visit P1 the following assessments must be performed before study drug administration:

- 12-lead ECG and SBP/DBP (under the responsibility of the physician evaluating cardiac safety assessments)
- PFTs (FEV_1, FVC)
- Laboratory tests (central laboratory) preferably under fasting conditions:
  - Hematology, blood chemistry, urinalysis
  - Pregnancy test

The following assessments can be performed after study drug administration:

- Change in concomitant medication, if any;
- Physical examination (including careful skin examination);
- Ophthalmological examination (best corrected visual acuity, low contrast visual acuity, visual fields, and dilated ophthalmoscopy);
- Standard 2D/Doppler echocardiography (at selected centers);
- EDSS and FS scores (assessed by the independent evaluating neurologist);
- MRI examination;
- Chest X-ray;
- Recording of AEs and SAEs.

When the patient has completed all scheduled pre-dose assessments, she/he will receive three study drug bottles for the period until the next visit and will take one tablet. The patient will be instructed to take the study drug every morning, with or without breakfast (preferably always in the same way and at approximately the same time). However, in the morning of the next visit no study drug is to be taken prior to the visit. The dose for that day will be taken from the new drug bottle (allocated to the patient on that day) after all pre-dose assessments for that visit have been completed.

The next visit will be scheduled and the patient will be reminded to bring back all unused study drug (or empty bottles).

3.12.3.2 Visits P2, P4, P6, P8, P10, P12, P14, P16, P18, P20, P22, P24, P26, P28, P30, P32, P34, P36, P38, P40, P42 and P44 (respectively, Weeks 12, 36, 60, 84, 108, 132, 156, 180, 204, 228, 252, 276, 300, 324, 348, 372, 396, 420, 444, 468, 492 and 516)

The visit window for these visits is ±14 days.

At every other visit, starting with Visit P2, the following assessments must be performed before study drug administration:

- 12-lead ECG and SBP/DBP (under the responsibility of the physician evaluating cardiac safety assessments or primary investigator / treating neurologist)
  - Blood pressure must be performed pre-dose at all visits;
  - ECG must be performed pre-dose at each of these visits up to and including P36.
- Laboratory tests (central laboratory) preferably under fasting conditions:
  - Hematology, blood chemistry, urinalysis
  - Pregnancy test (NB: Female patients who interrupt the study drug because of planned pregnancy will be exempted from any protocol-mandated pregnancy tests

after the first positive pregnancy test and until 30 (±5) days before study drug re-initiation).

- Only at Visits P2, P14 and P22: A blood sample for PK assessments will be taken prior to study drug intake.

The following assessments can be performed after study drug administration:

- Change in concomitant medication, if any;
- Physical examination (including careful skin examination) until P36;
- Recording of AEs and SAEs;
- EDSS and FS scores (assessed by the evaluating neurologist).

When the patient has completed all scheduled pre-dose assessments, she/he will receive three study drug bottles for the period until the next visit and will take one tablet. The patient will be instructed to take the study drug every morning, with or without breakfast (preferably always in the same way and at approximately the same time). However, in the morning of the next visit no study drug is to be taken prior to the visit. The dose for that day will be taken from the new drug bottle (allocated to the patient on that day) after all pre-dose assessments for that visit have been completed.

The next visit will be scheduled and the patient will be reminded to bring back all unused study drug (or empty bottles).

3.12.3.3 Visits P3, P5, P7, P9, P11, P13, P15, P17, P19, P21, P23, P25, P27, P29, P31, P33, P35, P37, P39, P41, P43 and P45 (respectively, Weeks 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360, 384, 408, 432, 456, 480, 504 and 528)

The visit window for these visits is ±14 days.

At every other visit, starting with Visit P3, the following assessments must be performed before study drug administration:

- 12-lead ECG and SBP/DBP (under the responsibility of the physician evaluating cardiac safety assessments or primary investigator / treating neurologist)
  - Blood pressure must be performed pre-dose at all visits;
  - ECG must be performed pre-dose at all study visits up to and including P37, then yearly thereafter (at P41 and P45).
- PFTs (FEV_1 and FVC) to be performed at each of these visits up to and including P37, then yearly thereafter (at P41 and P45).
- Laboratory tests (central laboratory) preferably under fasting conditions:
  - Hematology, blood chemistry, urinalysis

- Pregnancy test (NB: Female patients who interrupt the study drug because of planned pregnancy will be exempted from any protocol-mandated pregnancy tests after the first positive pregnancy test and until 30 (±5) days before study drug re-initiation).

- Only at Visit P7: A blood sample for PK assessments will be taken prior to study drug intake.

The following assessments can be performed after study drug administration; these assessments are to be performed at each visit (unless otherwise noted):

- Change in concomitant medication, if any;
- Physical examination (including careful skin examination) up to and including P37, then yearly thereafter (at P41 and P45);
- Standard 2D/Doppler echocardiography (at selected centers) up to and including P37, then yearly thereafter (at P41 and P45);
- Ophthalmological examination (best corrected visual acuity, low contrast visual acuity testing, visual fields, and dilated ophthalmoscopy) up to and including P37, then yearly thereafter (at P41 and P45);
- Recording of AEs and SAEs;
- EDSS and FS scores (assessed by the evaluating neurologist);
- MRI examination will be performed yearly at Visits P5, P9, P13, P17, P21, P25, P29, P33, P37, P41 and P45.

When the patient has completed all scheduled pre-dose assessments, she/he will receive three study drug bottles for the period until the next visit and will take one tablet. The patient will be instructed to take the study drug every morning, with or without breakfast (preferably always in the same way and at approximately the same time). However, in the morning of the next visit no study drug is to be taken prior to the visit. The dose for that day will be taken from the new drug bottle (allocated to the patient on that day) after all pre-dose assessments for this visit have been completed.

The next visit will be scheduled and the patient will be reminded to bring back all unused study drug (or empty bottles).

3.12.3.4 Transition from treatment period 2 to treatment period 3

When feasible, patients are switched from TP2 to TP3 at the earliest scheduled visit following approval of protocol version 8 by ECs/IRBs and health authorities and after having signed the revised Informed Consent Form.

At this visit, all patients must be monitored at the investigational site for at least 6 hours after dose administration [see Appendix 2]. The day of the first open-label dose of ponesimod 20 mg will correspond to the start of TP3.

Patients will then continue to come to the site every 12 weeks and will continue to perform the visits and assessments scheduled as detailed in Sections 3.12.3.2 and 3.12.3.3.

Patients not enrolling into TP3 will have to perform the EOT3 visit [see Section 3.12.3.5].

3.12.3.5 EOT3 (Week 540)

The visit window for this visit is ±14 days.

An EOT3 visit will be performed:

- For patients who complete Week 540 of TP3 according to the protocol:
  One day after the last dose of study drug
- For patients who complete TP2 according to the protocol but do not enroll into TP3:
  As soon as possible but no later than 5 days after the last dose of study drug
- For patients who discontinue study drug prematurely during TP2 or TP3:
  As soon as possible but no later than 5 days after the last dose of study drug

For patients completing study treatment due to availability of commercially available ponesimod, an EOT3 visit should be conducted as soon as possible, but no later than 5 days after the last dose of study drug. Commercially available ponesimod may be initiated on the day after last intake of study drug.

At EOT3 visit the following assessments must be performed:

- PFTs (FEV_1, FVC);
- Change in concomitant medication, if any;
- Physical examination (including careful skin examination);
- Ophthalmological examination (best corrected visual acuity, low contrast visual acuity, visual fields, and dilated ophthalmoscopy);
- 12-lead ECG and SBP/DBP (under the responsibility of the physician evaluating cardiac safety assessments or primary investigator / treating neurologist);
- Standard 2D/Doppler echocardiography (at selected centers);
- Laboratory tests (central laboratory) preferably under fasting conditions:
  - Hematology, blood chemistry, urinalysis;
  - Pregnancy test;
- EDSS and FS scores (assessed by the evaluating neurologist);
- MRI examination;
- Chest X-ray;
- Recording of AEs and SAEs.

When the patient has completed all scheduled assessments, Follow-up visit 1 will be scheduled 8 days after the last dose of study drug.

3.12.4 Safety Follow-up period

All patients, whether they performed the EOT2 or EOT3 visit or prematurely discontinued from study drug, will have to perform the corresponding Safety Follow-up visits:

TP1:

In the case of discontinuation from study drug before Visit P1, safety will be followed up for 30 days after last dose of study drug. There are two Safety Follow-up visits:

- Follow-up Visit E1 (Visit E14):
  - 8 days after the last study drug administration (EOT2 + 7 days)
- Follow-up visit E2 (Visit E15):
  - 30 days after the last study drug administration

TP2 and TP3:

In the case of discontinuation from study drug after Visit P1 safety will be followed up for 90 days after last dose of study drug. There are three Safety Follow-up visits:

- Follow-up visit 1 (FU1):
  - 8 days after the last study drug administration
- Follow-up visit 2 (FU2):
  - 30 days after the last study drug administration
- Follow-up visit 3 (FU3):
  - 90 days after the last study drug administration

These visits and assessments will also be conducted for patients who have switched to commercially available ponesimod. Note that for these patients, the timing of each Safety Follow-up visit refers to the time since the last **study drug** administration, independent of any administration of commercially available ponesimod.

3.12.4.1 Visit E14: EOT2 + 7 days (Follow-up Visit E1)

The visit window for this visit is ±1 day.

Eight days after the last study drug administration, the following assessments must be performed:

- Change in concomitant medication, if any;
- Physical examination;
- PFTs (FEV_1, FVC);
- Laboratory tests (central laboratory) in fasting condition:
  - Hematology, blood chemistry, urinalysis;
- 12-lead ECG and SBP/DBP (under the responsibility of the physician evaluating cardiac safety assessments);

- Recording of AEs and SAEs.

When the patient has completed all scheduled assessments, Visit E15 (Follow-up visit E2) will be scheduled 30 days after the last dose of study drug.

3.12.4.2 Visit E15: EOT2 + 30 days (Follow-up visit E2)

The visit window for this visit is ±5 days.

Thirty days after the last study drug administration, the following assessments must be performed:

- Change in concomitant medication, if any;
- Physical examination (including careful skin examination);
- PFTs (FEV_1, FVC);
- Ophthalmological examination (best corrected visual acuity, low contrast visual acuity, visual fields, and dilated ophthalmoscopy);
- Laboratory tests (central laboratory) in fasting condition:
  - Hematology, blood chemistry, urinalysis;
  - Pregnancy test;
- 12-lead ECG and SBP/DBP (under the responsibility of the physician evaluating cardiac safety assessments);
- EDSS and FS scores (assessed by the independent evaluating neurologist);
- MRI examination;
- Recording of AEs and SAEs.

Before discharge, WOCBP must be reminded that they must use the chosen methods of contraception until 30 days after the last study drug administration.

3.12.4.3 Follow-up visit 1 (FU1): 8 days after the last dose of study drug

The visit window for this visit is ±1 day.

At this visit the following assessments must be performed:

- Change in concomitant medication, if any;
- Physical examination;
- PFTs (FEV_1, FVC);
- Laboratory tests (central laboratory) preferably under fasting conditions:
  - Hematology, blood chemistry, urinalysis;
- 12-lead ECG and SBP/DBP (under the responsibility of the physician evaluating cardiac safety assessments or primary investigator / treating neurologist);
- Recording of AEs and SAEs.

When the patient has completed all scheduled assessments, Follow-up visit 2 (FU2) will be scheduled 30 days after the last dose of study drug.

3.12.4.4 Follow-up visit 2 (FU2): 30 days after the last dose of study drug

The visit window for this visit is ±5 days.

Thirty days after the last study drug administration, the following assessments must be performed:

- Change in concomitant medication, if any;
- Physical examination (including careful skin examination);
- PFTs (FEV_1, FVC);
- Ophthalmological examination (best corrected visual acuity, low contrast visual acuity, visual fields, and dilated ophthalmoscopy);
- Laboratory tests (central laboratory) preferably under fasting conditions:
  - Hematology, blood chemistry, urinalysis;
  - Pregnancy test;
- 12-lead ECG and SBP/DBP (under the responsibility of the physician evaluating cardiac safety assessments or primary investigator / treating neurologist);
- EDSS and FS scores (assessed by the evaluating neurologist);
- MRI examination;
- Recording of AEs and SAEs.

When the patient has completed all scheduled assessments, Follow-up visit 3 will be scheduled 90 days after the last dose of study drug.

Before discharge, WOCBP must be reminded that they must use the chosen methods of contraception until 30 days after the last study drug administration.

3.12.4.5 Follow-up visit 3 (FU3): 90 days after the last dose of study drug

The visit window for this visit is ±7 days.

Ninety days after the last study drug administration, the following assessments must be performed:

- Change in concomitant medication, if any;
- Physical examination (including careful skin examination);
- PFTs (FEV_1, FVC);
- Laboratory tests (central laboratory) preferably under fasting conditions:
  - Hematology, blood chemistry, urinalysis;
- SBP/DBP (under the responsibility of the physician evaluating cardiac safety assessments or primary investigator / treating neurologist);
- EDSS and FS scores (assessed by the evaluating neurologist);

- Recording of AEs and SAEs.

3.12.5 Unscheduled visits

3.12.5.1 Unscheduled relapse visit

Patients will be instructed to contact their treating neurologist at the clinical site immediately in the event of appearance of any symptoms suggestive of an MS exacerbation. An unscheduled visit will be organized as soon as possible after onset or worsening of the symptom(s) as follows:

The primary investigator / treating neurologist will examine the patient and decide whether the patient has to be referred to the evaluating neurologist.

In the event of the patient's referral to the evaluating neurologist, the evaluating neurologist will perform the EDSS and FS within 7 days after onset or worsening of the symptom(s).

In order to exclude potential other reasons for the symptom(s) observed, the primary investigator / treating neurologist will need to perform the following assessments:

- Physical examination;
- Vital signs: SBP/DBP, pulse rate, body temperature.

Results must be documented in the patient's records, but should not be recorded in the CRF, unless a finding constitutes an AE.

The decision regarding whether the neurological change is considered as confirmed or unconfirmed relapse will be made by the primary investigator / treating neurologist based on the EDSS/FS scores assessed by the evaluating neurologist.

A Specific Relapse eCRF form must be completed for confirmed and unconfirmed relapses. MS relapses and associated symptoms are not to be entered on the AE form of the eCRF with the following exceptions:

- MS relapses with fatal outcome (these must always be recorded as an AE on the AE form 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 form of the eCRF and, if applicable, on the SAE form).

If a relapse visit is within 5 days prior to the date of a regular MRI visit, efforts should be made to perform the MRI assessments prior to the start of treatment with i.v. corticosteroids.

In the event of a confirmed MS relapse, the primary investigator / treating neurologist should re-counsel the patient to ensure she/he is reminded of alternative treatment options available for RRMS. The patient's attention must be drawn to the possibility of

withdrawing from the study and switching to standard treatment approved for RRMS. The patient's decision must be recorded in the medical records.

3.12.5.2 Unscheduled visits (any other assessment)

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 CRF. During such visits, any of the following assessments may be performed at the investigator's discretion:

- Change in concomitant medication, if any;
- Physical examination (including careful skin examination);
- PFTs (FEV_1, FVC);
- Ophthalmological examination (best corrected visual acuity, low contrast visual acuity, visual fields, and dilated ophthalmoscopy; OCT in case of suspected clinically significant findings [e.g., macular edema]);
- Laboratory tests (central laboratory) preferably under fasting conditions:
  - Hematology, blood chemistry, urinalysis;
  - Pregnancy test;
- 12-lead ECG and SBP/DBP (under the responsibility of the physician evaluating cardiac safety assessments or primary investigator / treating neurologist);
- EDSS and FS scores (assessed by the evaluating neurologist);
- MRI examination;
- Recording of AEs and SAEs.

3.12.5.3 Additional visits for re-initiation or re-uptitration of study drug

As described in detail in Appendix 5, patients who miss taking the dose of study drug for 4 or more consecutive days will need to re-initiate study drug using the gradual uptitration scheme outlined in Table 6.

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

- One visit on the day of re-initiation (Day 1) for all patients;
- An additional visit 14 days (±1 day) after the day of re-initiation (Day 15) only mandated for patients with cardiovascular risk factors [see Appendix 5] but may be scheduled for any patient at the discretion of the investigator / treating neurologist.

The following assessments need to be done during the visits on Day 1 of re-initiation:

- SBP/DBP pre-dose and hourly (±15 min) for at least 4 hours and up to 12 hours post-dose (under the responsibility of the physician evaluating the cardiac safety assessments)[1];
- 12-lead ECG pre-dose and hourly (±15 min) for at least 4 hours and up to 12 hours post-dose (under the responsibility of the physician evaluating the cardiac safety assessments)[1];
- IVRS call and study drug dispensing[2];
- Recording of changes in concomitant medication, if any;
- Recording of AEs and SAEs;
- The discharge criteria will be applied for patients undergoing cardiac monitoring. Patients 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 Appendix 2].

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

- SBP/DBP (pre-dose);
- 12-lead ECG (pre-dose);
- IVRS call return of study drug blisters/bottles and unused medication, and dispensing of new blisters/bottles, if appropriate;
- Recording of AEs and SAEs.

These visits for when re-initiating and/or up-titrating the dose are additional unscheduled visits. The regular scheduled study visits must continue according to the original visit and assessment schedule.

[1] All patients must have a pre-dose assessment. Only patients with cardiovascular risk factors [see Appendix 5] 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 [see Appendix 2]. Patients 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.

[2] Patients with cardiovascular risk factors [see Appendix 2] will receive only the uptitration kit. Patients without cardiovascular risk factors [see Appendix 2] and who re-initiated at home will receive both the uptitration kit and blisters/bottles for maintenance.

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

As described in Appendix 1 section D, female patients who wish to become pregnant must have a negative pregnancy test at an unscheduled visit 30 days after they interrupt the study drug before they can interrupt the contraception.

During this visit, the following assessments will be performed:

- Urine or serum pregnancy test;
- EDSS and FS assessment (performed by the evaluating neurologist);
- MRI examination;
- Assessment of methods of contraception;
- Recording of changes in concomitant medication, if any;
- Body temperature;
- Body weight;
- Physical examination;
- PFTs (FEV_1, FVC);
- 12-lead ECG and SBP/DBP (under the responsibility of the physician evaluating cardiac safety assessments or primary investigator / treating neurologist);
- Ophthalmological examination (best corrected visual acuity, low contrast visual acuity testing, visual fields, and dilated ophthalmoscopy; OCT in case of suspected clinically significant findings [e.g., macular edema]);
- Laboratory tests (central laboratory) preferably under fasting conditions: Hematology, blood chemistry, urinalysis;
- Recording of AEs and SAEs.

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

3.12.5.5 Additional unscheduled visit for eligibility assessment for re-initiation of study drug for female subjects who interrupted the study drug for planned pregnancy and who wish to re-initiate the study drug after delivery

As described in Appendix 1 section D, female patients who interrupted the study drug for planned pregnancy and who wish to re-initiate the study drug after delivery will need to be assessed for eligibility for study drug re-initiation. Unless the patient has been treated with a disease modifying therapy (DMT; IFN β-1a 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:

- PFTs (FEV_1 and FVC);
- Laboratory tests (central laboratory) preferably under fasting conditions:
  Hematology, blood chemistry, urinalysis;
- Assessment of methods of contraception;
- Recording of changes in concomitant medication, if any;
- Body temperature;
- Body weight;
- Physical examination;
- 12-lead ECG and SBP/DBP (under the responsibility of the physician evaluating cardiac safety assessments or primary investigator / treating neurologist);
- EDSS and FS assessment (performed by the evaluating neurologist);
- MRI examination;
- Ophthalmological examination (best corrected visual acuity, low contrast visual acuity testing, visual fields, and dilated ophthalmoscopy; OCT in case of suspected clinically significant findings [e.g., macular edema]);
- Recording of AEs and SAEs;
- Remind the patient to use the methods of contraception defined for this study. The reminders must be documented in the hospital chart;
- Confirm that the patient did/does not fulfill any protocol criteria for permanent study drug discontinuation [see Appendix 1] at any of the previous visits or at the unscheduled visit for re-initiation of study drug except the wish to become pregnant;
- If the patient has been treated with a DMT (IFN β-1a or glatiramer acetate) during and after pregnancy, the patient must be instructed to interrupt the treatment 7 days before study drug re-initiation and this instruction must be documented in the hospital records.

If all eligibility criteria for study drug re-initiation at this visit are fulfilled, an appointment should be scheduled for the next visit (i.e., additional unscheduled visit for re-initiation of study drug) 25 35 days later. The patient is instructed to contact their primary investigator / treating neurologist at the clinical site immediately in the event of the appearance of any symptoms suggestive of an MS exacerbation.

The patient must be instructed/reminded that the breastfeeding has to be completely stopped before study drug re-initiation.

If the urine pregnancy test is positive, the patient is not eligible for study drug re-initiation.

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 patient wishes to re-initiate the study drug.

3.12.5.6 Unscheduled visits for re-initiation of the study drug after delivery

The following assessments/procedures must be performed during these visits:

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

- Assessment of methods of contraception and confirmation that the patient has been using reliable methods of contraception, as described in Section 4.4.2, for at least 30 days;
- Assessment of total duration of study drug interruption (which should not exceed 81 weeks);
- Confirmation that breastfeeding has been completely stopped;
- If the patient has been treated with a DMT (IFN β-1a or glatiramer acetate) during and after pregnancy, confirmation that this treatment has been discontinued no 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 up to 12 hours post-dose;
- Change in concomitant medication, if any;
- Recording of AEs and SAEs;
- Study drug dispensing/returning;
- The discharge criteria will be applied as described in Appendix 2, as applicable.

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

4 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

4.1 Summary table

Periods	Treatment (including transition and study drug interruption)	Follow-up[2]	After Follow-up
Time frame	During study drug administration until 15 days after study drug discontinuation and during study drug interruption	Treatment period 1: From 16 until 30 days after study drug discontinuation Treatment periods 2 and 3: From 16 until 90 days after study drug discontinuation	Treatment period 1: After 30 days Treatment periods 2 and 3: After 90 days
AE/SAE reporting on eCRF AE form	All AEs/SAEs	All AEs/SAEs	None
SAE reporting on SAE form	All SAEs	All SAEs	If felt appropriate by investigator
Reconciliation [1]	Yes	Yes	Not applicable

1. Reconciliation between clinical and drug safety databases.
2. AEs/SAEs occurring between treatment periods 1, 2 and 3 must be reported in the AE eCRF form.

AE adverse event; eCRF electronic case report form; SAE serious adverse event.

4.2 Adverse events

4.2.1 Definitions of adverse events

An AE is any adverse change from the patient's baseline condition, i.e., any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease that occurs during the course of the study, whether or not considered related to the study drug.

A treatment-emergent AE is any AE temporally associated with the use of a study drug, i.e., occurring during study drug administration until 15 days after study drug discontinuation, whether or not considered related to the study drug. This definition applies

regardless of whether the patient receives commercially available ponesimod after completing study drug treatment.

AEs include:

- Exacerbation of a pre-existing disease;
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition;
- Disease or medical condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study;
- Continuous persistent disease or symptoms present at baseline that worsen following the start of the study;
- Lack of efficacy in the acute treatment of a life-threatening disease;
- Events considered by the investigator to be related to study-mandated procedures;
- Abnormal assessments, e.g., change on physical examination, ECG findings, if they represent a clinically significant finding that was not present at baseline 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 baseline or worsened during the course of the study or led to dose reduction, interruption or permanent discontinuation of study drug.

AEs do not include:

- Medical or surgical procedure, e.g., surgery, endoscopy, tooth extraction, transfusion. However, the event leading to the procedure is an AE. If this event is serious, the procedure must be described in the SAE narrative;
- Pre-existing disease or medical condition that does not worsen;
- Situations in which an adverse change did not occur, e.g., hospitalizations for cosmetic elective surgery or for social and/or convenience reasons.

Special reporting situations are described in Section 4.5.

Cardiac events

Significant findings (e.g., new ECG abnormalities, bradycardia), which meet the definition of an AE, must be recorded on the AE form of the eCRF.

Any cardiac events of clinical concern, including AV blocks, must be assessed by the physician evaluating cardiac safety assessments for seriousness, and reported accordingly.

Relapse

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

- MS relapses with fatal outcome (these must always be recorded as an AE on the AE form 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 form of the eCRF and, if applicable, on the SAE form).

4.2.2 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 form of the eCRF.

If the intensity of an AE worsens during study drug administration, only the worst intensity must be reported on the AE form. If the AE lessens in intensity, no change in the intensity is required.

The three categories of intensity are defined as follows:

- **Mild**

The event may be noticeable to the patient. It does not influence daily activities and usually does not require intervention.

- **Moderate**

The event may make the patient uncomfortable; performance of daily activities may be influenced; intervention may be needed.

- **Severe**

The event may cause noticeable discomfort and usually interferes with daily activities. The patient 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 4.3.1]. These terms are used to describe the intensity of a specific event (as in mild, moderate, or severe myocardial infarction). However, a severe event (such as severe headache) may be of relatively minor medical significance and is not necessarily serious. For example, nausea lasting several hours may be rated as severe, but may not be clinically serious. Fever of 39 °C that is not considered severe may become serious if it prolongs hospital discharge

by a day [see Section 4.3.1.2]. Seriousness rather than severity serves as a guide for defining regulatory reporting obligations.

These definitions do not apply to clinically significant and asymptomatic laboratory test abnormalities or abnormal assessments (e.g., ECG findings) considered as AEs. The investigator must select "non-applicable" on the AE form of the eCRF to qualify the intensity of the AE.

4.2.3 Relationship to study drug

Each AE must be assessed by the investigator as to whether or not there is a reasonable possibility of causal relationship to the study drug and reported as either related or unrelated.

- **Related to study drug**

This category applies to any AE (whether serious or not) that appears to have a reasonable possibility of causal relationship to the use of the study drug (i.e., a relationship cannot be ruled out). Guidelines to determine whether an event might be considered related include (but are not limited to) the following:

- The event occurred in close temporal relationship to study drug administration.
- The event abated (diminished) or disappeared when treatment with the study drug was down-titrated, interrupted, or discontinued.
- The event reoccurred when treatment was reintroduced.
- Environmental factors such as clinical state and other treatments could equally have caused the event.

- **Unrelated to study drug**

This category applies to any AE (whether serious or not) that does not appear to have a reasonable relationship to the use of study drug (see above guidelines).

4.2.4 Reporting of adverse events

4.2.4.1 Treatment period (including transition period and study drug interruption)

The end date and outcome of all AEs that occurred during the core study and that are still ongoing when the patient is entering the transition period must be recorded on a separate page of the extension study CRF. In the event that the AE is worsening or becoming serious, it must be recorded as a new AE on the specific AE form of the extension study CRF. The sponsor may contact the investigator to obtain further information.

All AEs that occur from the start of the transition period of the extension study until 15 days after study drug discontinuation must be recorded on specific AE form of the extension study eCRF.

Treatment-emergent AEs are defined as all AEs with onset date from the date of first study drug intake (date of Visit E1 for patients who received placebo in the core study, date of core study Visit 1 for patients who received active treatment in the core study) until 15 days after study drug discontinuation. This definition applies regardless of whether the patient receives commercially available ponesimod after completing study drug treatment.

All AEs occurring during TP1, TP2, and TP3 must be reported on an AE form of the eCRF, regardless of causal relationship. This applies also to AEs occurring during the study drug interruption (e.g., due to planned pregnancy), i.e., all AEs during study drug interruption must be reported on an AE form in the eCRF.

4.2.4.2 Follow-up period

All AEs regardless of causal relationship occurring from 16 days after study drug discontinuation until 30 or 90 days (as applicable) after study drug discontinuation must be recorded on specific AE form of the extension study eCRF.

4.2.5 Follow-up of adverse events

AEs still ongoing after study drug discontinuation for a given patient must be followed up to 30 or 90 days (as applicable) after study drug discontinuation, or until resolution, stabilization or until the event is no longer clinically relevant or until the event is otherwise explained.

4.3 Serious adverse events

4.3.1 Definitions

4.3.1.1 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
- Requiring hospitalization as an inpatient 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, or requires intervention to prevent at least one of the outcomes listed above

Life-threatening refers to an event in which the patient 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.

Important medical events that may not immediately result in death, be life-threatening, or require hospitalization may be considered to be SAEs when, based upon appropriate medical judgment, they may jeopardize the patient, and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.

The reference safety document to assess whether or not an SAE must be reported by the sponsor to health authorities, ECs/IRBs and investigators in an expedited fashion is the Investigator's Brochure [Ponesimod IB].

4.3.1.2 Hospitalization - Prolongation of existing hospitalization

Hospitalization is defined as an admission to a hospital or a prolongation of existing hospitalization due to an AE.

If on Days 1, 8, or 15 a patient needs to stay at the hospital more than 12 hours post-dose due to an AE, this constitutes an SAE.

The following reasons for hospitalizations are not considered AEs, and therefore not SAEs:

- Hospitalizations for cosmetic elective surgery, social and/or convenience reasons.
- Standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for coronary angiography in a patient with stable angina pectoris.
- Elective treatment of a pre-existing disease or medical condition that did not worsen, e.g., elective hip replacement for arthritis. Complications that occur during hospitalization are AEs or SAEs (for example if a complication prolongs hospitalization).

4.3.1.3 Serious adverse events related to study-mandated procedures

Such SAEs are defined as SAEs that appear to have a reasonable possibility of causal relationship (i.e., a relationship cannot be ruled out) to study-mandated procedures (excluding administration of study drug) such as complication of a mandated invasive procedure (e.g., blood sampling, heart catheterization), or car accident on the way to the hospital for a study visit, etc.

4.3.2 Reporting of serious adverse events

4.3.2.1 Treatment period (including transition period and study drug interruption)

All SAEs regardless of causal relationship that occur from the start of the transition period until 15 days after study drug discontinuation must be recorded.

Treatment-emergent SAEs are defined as all SAEs with onset date from the date of first study drug intake (date of Visit E1 for patients who received placebo in the core study, date of core study Visit 1 for patients who received active treatment in the core study) until 15 days after study drug discontinuation.

These SAEs are reported on SAE forms and also on the AE form in the extension study eCRF. Therefore, they are entered both in the drug safety and clinical databases, and must be reconciled before study closure.

All SAEs occurring during TP1, TP2, and TP3 must be reported on an AE page of the CRF, regardless of causal relationship. This applies also to SAEs occurring during study drug interruption (e.g., due to planned pregnancy), i.e., all SAEs during study drug interruption must be reported on SAE forms and also on the AE form of the eCRF.

4.3.2.2 Follow-up period

All SAEs regardless of causal relationship occurring from 16 days after study drug discontinuation until 30 or 90 days (as applicable) after study drug discontinuation must be reported.

These SAEs are reported on SAE forms and also on the AE form in the eCRF. Therefore, they are entered both in the drug safety and clinical databases, and must be reconciled before study closure.

4.3.2.3 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.

All SAEs must be recorded on SAE forms, irrespective of the study drug received by the patient, whether or not this event is considered by the investigator to be related to study drug.

These SAE forms must be completed and signed by a physician from the study site and sent to the sponsor within 24 hours using the contact details provided on the form. The investigator must complete the SAE form in English (unless otherwise specified) and assess the relationship to study drug.

Such preliminary reports will be followed by detailed descriptions that should include copies of hospital case reports, autopsy reports, hospital discharge summaries and other documents when requested and applicable. Follow-up 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.

Suspected (considered related to the study drug) and unexpected (not previously described in the reference safety document) serious adverse reactions (SUSARs) will be expedited by the sponsor to health authorities, ECs/IRBs and investigators, as appropriate. Unblinding of SUSARs will be performed as appropriate.

MS relapses and associated symptoms are exempt from being reported on an SAE form by the investigator to the sponsor, with the following exceptions:

- MS relapses with fatal outcome.
- 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 form of the eCRF and, if applicable, on the SAE form).

4.3.3 Follow-up of serious adverse events

SAEs still ongoing at the EOS2 or EOS3 must be followed until resolution or stabilization or until the event is otherwise explained.

New SAEs occurring at any time after the EOS / after the 30-day follow-up period may be reported to the sponsor within 24 hours of the investigator's knowledge of the event, if felt appropriate by the investigator. Therefore, these SAEs are entered only into the drug safety database and hence will not affect study closure.

4.4 Pregnancy

In embryo-fetal studies in rats and rabbits ponesimod shows teratogenic potential. Therefore, appropriate precautions must be taken by WOCBP. Women must not become pregnant while on the study drug and until 30 days after study drug discontinuation.

If a woman becomes pregnant when on study drug, study drug MUST be discontinued immediately. The investigator must counsel the patient 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 Appendix 1, section D, are fulfilled.

4.4.1 Definition of childbearing potential

The assessment of a woman's childbearing potential can be done at any time during the study. 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 gynecologist.
- Postmenopausal, defined as 12 consecutive months with no menses without an alternative medical cause.

4.4.2 Acceptable methods of contraception

The investigator must explain and stress the importance of using acceptable methods of contraception during the study, and for at least 30 days after study drug discontinuation.

During TP1 and TP2, WOCBP must follow the below contraception scheme:

- Two methods of contraception (one from Group 1 and one from Group 2 below) during the study, and for at least 30 days after study drug discontinuation, as follows:
  - Group 1: Oral, implantable, transdermal or injectable hormonal contraceptives, intrauterine devices, female sterilization (tubal ligation), or partner's sterilization (vasectomy).
  - Group 2: Condoms, diaphragm or cervical cap.

Abstention and rhythm methods were not acceptable methods of contraception during TP1 and TP2.

During TP3, WOCBP must follow the below contraception scheme:

- Two methods of contraception, one must be from Group 1 and one must be from Group 2, defined as follows:
  - Group 1: Oral, implantable, transdermal or injectable hormonal contraceptives, intrauterine devices.
  - Group 2: Condoms, diaphragm or cervical cap.
- Female sterilization (tubal ligation).
- Sterilization of the male partner (vasectomy).
- True abstinence from intercourse with a male partner only when this is in line with the preferred lifestyle of the patient.

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

If during the study a switch to a hormonal contraceptive from Group 1 is considered, it must be taken for at least 1 month in parallel to previous forms of contraception from Group 1, and contraception from Group 2 must remain in use throughout the study period.

If there is any doubt on what contraceptive advice should be given to an individual patient, consultation with a gynecologist is recommended.

4.4.3 Reporting of pregnancy

Irrespective of the treatment received by the patient, any pregnancy (irrespective whether it was planned or not) occurring during the entire study including during the 30 days following permanent study drug 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 must be sent to the sponsor, and on an AE form of the eCRF, as applicable.

4.4.4 Follow-up of pregnancy

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

Any AE associated with the pregnancy occurring during the follow-up period after study drug discontinuation or during study drug interruption for planned pregnancy must be reported on the separate AE form in the eCRF. 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. Any SAE occurring during the pregnancy must also be reported on an SAE form as described in Section 4.3.2.

4.5 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 pill 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 form of the eCRF. Any special reporting situation that meets the criteria of an SAE should be recorded as an SAE.

4.6 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.

5 STATISTICAL METHODOLOGY AND ANALYSES

5.1 Statistical analysis plan

Statistical analysis plans (SAPs) will be followed for any periodic analysis performed during the study. The SAPs will provide full details of the analyses, imputation rules and the algorithms to be used for data derivations.

Full details of the treatment groups and how they are used in the analysis will be described in the SAP.

The SAP will include the definition of major protocol deviations and the exclusion of patients from the analysis sets.

5.2 Analysis sets

Data from the core study AC-058B201 and extension study AC-058B202 will be combined.

Baseline is defined as the last assessment performed prior to the first administration of study treatment in AC-058B201 for the analyses comparing treatment groups as randomized in AC-058B201 including the placebo treatment period, or first dose of ponesimod treatment in either AC-058B201 or AC-058B202 for the analyses which exclude the placebo treatment period.

The following analysis populations are defined:

- **All-randomized population:**

  This set includes all randomized patients in AC-058B201.

- **All-treated – extension population:**

  The 'All-treated - extension population' includes all randomized patients who received at least one ponesimod dose in the extension AC-058B202.

  Additional analysis sets will be defined in the SAP as needed.

5.3 Efficacy endpoints

All statistical tests are of exploratory nature. No adjustment for multiple comparisons will be made.

Annualized relapse rate:

ARRs will be explored by means of negative binomial regression models.

Time to event data:

The time to event (e.g., first confirmed relapse) will be analyzed using the log-rank test. The Kaplan-Meier estimates at different time points will be provided together with the 95% two-sided confidence limits (CLs) calculated using Greenwood's formula for the estimate of the standard error. The time to event will be displayed by a Kaplan-Meier plot.

Patients free of relapse

The proportion of relapse free patients will be estimated by means of Kaplan-Meier method (time to first confirmed relapse).

MRI-related endpoints

Number of total T1 Gd+ lesions, number of combined unique active lesions, and number of new or enlarging T2 lesions will be analyzed by means of negative binomial regression models.

Methods for handling of missing data will be defined in the SAP for the individual endpoints as applicable.

5.4 Dose response assessment

The dose response relationship will be explored for lymphocyte count, MRI-related endpoints (number of total T1 Gd+ lesions, number of combined unique active lesions,

number of new or enlarging T2 lesions) and ARR using modeling techniques as described by Bretz et al [Bretz 2005].

5.5 Sample size

Sample size is determined by the number of patients completing the core study and deciding to enter the extension study.

5.6 Safety and tolerability endpoints

All AEs and SAEs are coded using the MedDRA dictionary.

AEs will be analyzed by treatment groups.

The treatment-emergent AEs will be tabulated by system organ class (SOC) and individual preferred terms within each SOC. AEs will also be tabulated by severity and by relationship to ponesimod. Summary tables will be accompanied by individual patient listings.

Treatment-emergent SAEs will be listed and summarized similarly to AEs.

AEs leading to premature discontinuation of study drug will be listed and summarized by crude incidence rates.

Post-treatment AEs, SAEs, and abnormalities (i.e. occurring from 16 until 30 or 90 days after study drug discontinuation) will be tabulated and/or listed dependent on the observed events.

AEs ongoing at the end of the core study and reported separately on the extension CRF will be listed.

Reasons for premature discontinuation of ponesimod will be listed and summarized by frequency tables.

Reasons for death will be listed and summarized similarly to AEs leading to premature discontinuation.

PFTs and BPs will be summarized by descriptive statistics by timepoint both for the absolute values and for the change from baseline.

The proportion of patients with treatment-emergent ECG abnormalities will be displayed. Absolute values and changes during the course of the study of ECG numeric parameters will be summarized by descriptive statistics.

Treatment-emergent abnormalities as assessed by Standard 2D/Doppler echocardiography will be summarized by treatment group and presented similarly to the AEs. Absolute percentage and change of left ventricular ejection fraction during the course of the study will be summarized by descriptive statistics. Individual patient listings will be provided.

Treatment-emergent laboratory abnormalities will be summarized for each laboratory parameter providing their incidence and frequency. Standard numeric laboratory parameters are transformed to standard units. Absolute values and changes during the course of the study of laboratory parameters values converted to standardized units will be summarized descriptively at the relevant time points.

AEs, SAEs, and abnormalities are defined as treatment-emergent when occurring during study drug administration until 15 days after study drug discontinuation.

All safety and tolerability data will be presented in patient listings.

5.7 Pharmacokinetic and pharmacodynamic endpoints

Trough level (pre-dose) plasma concentrations of ponesimod at each time point of measurement and by treatment will be analyzed by descriptive statistics, including arithmetic mean, standard deviation, minimum, maximum, and median.

Relationship between ponesimod concentration and total lymphocytes counts will be explored, as well as the relationship of ponesimod concentration and other possible PD variables (e.g., safety parameters).

Efficacy and safety parameters will be correlated with absolute lymphocyte counts and magnitude of reduction of lymphocyte counts on an exploratory basis.

5.8 Exposure to study drug

Exposure to study drug will be described in terms of duration and dose by treatment groups. The duration of exposure is defined as the time elapsing between the study drug initiation and discontinuation, inclusive. The exposure time will be tabulated descriptively. The cumulative distribution of exposure time by different class intervals (e.g., <3 months, at least 3 months, at least 6 months, etc.) will be tabulated to show the number and percentage of patients in each class interval.

5.9 Baseline parameters and concomitant medications

Continuous demographic variables (e.g., age, height, weight, etc.) and disease characteristics (e.g., onset date, severity, etc.) will be derived from the core study AC-058B201 and summarized descriptively.

Previous and concomitant medications will be coded according to the WHO drug code and the Anatomical Therapeutic Chemical Classification System. They will be summarized by type (e.g., previous, concomitant, for AE) by tabulating the number and percentages of patients having received each treatment.

5.10 Additional periodic analyses

During the conduct of the study, data analyses might be performed periodically at specified timepoints (e.g., all patients who complete 12 months of treatment).

Until its disbandment on 30th September 2021, the IDMC was empowered to recommend modifications of the protocol (to enhance patient safety), or to recommend early termination of the study or of a selected dose group of the study if major concerns arose about the patients' safety at any time during the course of this study or during any other study with the same investigational drug. There are no limitations to the number and timing of interim analyses aimed at guaranteeing the safety of the patients.

5.11 Immunogenicity Analysis

The following humoral immune responses are measured, based on the COVID-19 immunogenicity samples, including S- and N-ELISA (enzyme-linked immunosorbent assay) 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.

6 PROCEDURES AND GOOD CLINICAL PRACTICE

6.1 Procedures

6.1.1 Protocol amendments

Any change to a protocol must be considered to be an amendment if the documents have already been submitted to ECs/IRBs or health authorities. An amendment could therefore occur before or after the approval of these documents by ECs/IRBs or health authorities. Each amendment must be documented in writing and approved by the sponsor. It must be reviewed by the Coordinating/Principal Investigator.

Changes to the Core Patient Information and Informed Consent requested by ECs/IRBs are not considered to be formal amendments, as long as they do not significantly change the core document or affect the protocol.

- **Non-substantial amendment**

Purely administrative or minor logistical changes require only a non-substantial amendment. Such changes include but are not limited to changes in study staff or contact details (e.g., the sponsor instead of CRO monitors) or minor changes in the packaging or labeling of study drug.

The implementation of a non-substantial amendment may be undertaken with or without notification to the appropriate ECs/IRBs and health authorities (subject to national regulations).

- **Substantial amendment**

A substantial amendment is required for significant changes. These include but are not limited to: new data affecting the safety of patients, and changes to the objectives or endpoints of the study, eligibility criteria, dose regimen, study assessments/procedures, or treatment or study duration, with or without the need to modify the Core Patient Information and Informed Consent.

Substantial amendments must be approved by the appropriate ECs/IRBs and in some jurisdictions by the health authorities. The implementation of a substantial amendment may only occur after formal approval by the appropriate ECs/IRBs and/or health authorities and must be signed by the investigators.

- **Urgent amendment**

An urgent amendment might become necessary to ensure the safety of the patients included in the study. The requirements for approval must not prevent any immediate action being taken by the investigators or the sponsor in the best interests of the patients. If deemed necessary, an investigator may therefore implement an immediate change to the protocol for safety reasons, and in such exceptional cases the implementation of urgent amendments will occur before submission to and approval by ECs/IRBs and health authorities.

In such cases, the investigator must notify the sponsor within 24 hours. A related substantial amendment will be prepared and submitted by the sponsor to the appropriate ECs/IRBs and health authorities within 10 working days of receiving the notification.

6.1.2 Monitoring

The monitor will contact and visit the investigator regularly and on request must be permitted to have access to all source documents needed to verify the entries on the CRF and other protocol-related documents, provided that patient confidentiality is maintained in accordance with local regulations. It will be the monitor's responsibility to inspect the CRFs at regular intervals throughout the study, to verify adherence to the protocol and the completeness, consistency and accuracy of the data being entered on the CRFs. The sponsor's monitoring standards require full verification that informed consent has been

provided, and verification of adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of the main efficacy, safety and tolerability endpoints. Additional checks of the consistency of the source data with the CRFs will be performed according to the study-specific monitoring plan.

The investigator must ensure that patient anonymity is maintained. On CRFs or other documents submitted to the sponsor, patients must be identified only by number, and never by name. The investigator must keep a patient identification code list showing the randomization number, the patient's name, date of birth and address or any other locally accepted identifiers. Documents identifying the patients (e.g., signed Informed Consent Forms) should not be sent to the sponsor, and must be kept in strict confidence by the investigator.

The investigator and co-investigators agree to cooperate with the monitor(s) to ensure that any issues detected in the course of these monitoring visits are resolved. If the patient is hospitalized or dies in a hospital other than the study center, the investigator is responsible for contacting that hospital in order to document the SAE.

The investigator 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 special problems and/or government queries, it is also necessary to have access to the complete study records, provided that patient confidentiality is protected.

An initiation visit will be performed before the first patient is included in the study. Monitoring visits and contacts will occur at regular intervals thereafter, according to a frequency defined in the study-specific monitoring plan. As a rule, the close-out visit will be performed after study closure, however the close-out visit may occur prematurely upon site or sponsor's request.

6.1.3 Data management

6.1.3.1 Data collection

As used in this protocol, the term CRF/ eCRF should be understood to refer to the electronic Data Capture (eDC) system post-migration to eDC. Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in the CRF. All CRF entries, corrections, and alterations must be made by the investigator or authorized study site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

The study data will be transcribed by study site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor. A copy of these files will also be kept at the clinical site. All data recorded on source documents will be kept at the clinical site.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the participant's source documents. Data must be entered into the CRF in English. The CRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

All participative measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study site personnel.

6.1.3.2 Database management and quality control

Laboratory samples will be processed centrally through a global central laboratory and the results will be sent electronically to the sponsor.

Electronic data from the ECG central evaluation will be transferred to the sponsor.

After the database has been declared complete and accurate, the database will be locked. Any changes to the database after that time may only be made by joint written agreement between the Science Project Leader and the Trial Statistician.

6.1.4 Recording of data and retention of documents

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents are to be classified into two different categories: investigator's file, and patient clinical source documents.

The investigator's file will contain the protocol and all protocol amendments, the FDA form 1572 for studies conducted under a US Investigational New Drug, a financial disclosure form, the CRFs and data clarification and query forms, EC/IRB and health authority approval with correspondence, informed consent, drug records, staff curricula vitae and authorization forms and other appropriate documents/correspondence in accordance with ICH Good Clinical Practice (GCP) and local regulations.

Patient clinical source documents include, but are not limited to hospital/clinic records, physicians' and nurses' notes, appointment book, original laboratory reports, ECG, X -ray, MRI, pathology and special assessment reports, consultant letters, etc.

These two categories of documents must be kept on file by the investigator for as long as is necessary to comply with national and international regulations (generally 2 years after either discontinuation of clinical development, or the last marketing approval of the investigational drug). No study document may 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.

When source documents are required for the continued care of the patient, appropriate copies must be made for storing off site.

6.1.5 Audit

Representatives of the sponsor's clinical quality assurance department may conduct audits of clinical research activities in accordance with internal SOPs to evaluate compliance with the principles of GCP and ICH related guidelines.

Health authorities may also wish to conduct an inspection (during the study or after its completion). Should an inspection be requested by a health authority, the investigator must inform the sponsor immediately that such a request has been made.

The investigator must permit such audits by the sponsor or health authorities and must facilitate them by providing access to the relevant source documents.

6.1.6 Handling of study drug(s)

The sponsor will supply all study drug(s) to the site according to local regulations. Drug supplies must be kept in an appropriate, secure area and stored according to the conditions specified on the drug labels. The site must maintain an accurate record of the shipment and dispensing of study drug(s) on an accountability form, which must be given to the monitor at the end of the study. An accurate record of the date and amount of study drug(s) dispensed to each patient must be available for inspection at any time.

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

6.1.7 Publication and reporting of study results

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.

6.1.8 Disclosure and confidentiality

By signing this protocol, the investigator agrees to keep all information provided by the sponsor in strict confidence and to request similar confidentiality from his or her staff and the EC/IRB. Study documents provided by the sponsor (including Investigator's Brochures, protocols, CRFs and other protocol-related documents) will be stored appropriately to ensure their confidentiality. The information provided by the sponsor to the investigator may not be disclosed to others without direct written authorization from the sponsor, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

6.1.9 Premature termination or suspension of the study

Both the sponsor and the investigator reserve the right to terminate the study at any time.

If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators, the ECs/IRBs and health authorities, as appropriate, and provide the reasons for the termination or suspension.

If the study is prematurely terminated or suspended for any reason, the investigator in agreement with the sponsor must promptly inform all enrolled patients and ensure their appropriate treatment and follow-up.

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

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

Premature termination or suspension of the study was to be discussed between the IDMC (until it was disbanded) and the sponsor.

6.2 Good Clinical Practice

6.2.1 Ethics and Good Clinical Practice

The investigator will ensure that this study is conducted in full compliance with the principles of the "Declaration of Helsinki" (as amended in Tokyo, Venice, Hong Kong, Somerset-West, Edinburgh, and Seoul), and with the laws and regulations of the country in which the clinical research is conducted. A copy of the Declaration of Helsinki will be provided to each investigational site.

All studies must follow ICH GCP Guidelines and, if applicable, the US Code of Federal Regulations. In other jurisdictions in which GCP Guidelines exist, the investigators must strictly ensure adherence to the stated provisions.

6.2.2 Ethics Committee / Institutional Review Board

The investigator will submit this protocol and any related document provided to the patient (such as patient information used to obtain informed consent) to an EC or IRB. 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 trial, the documents reviewed and the date of approval. A list of members participating in the meeting must be provided, including the functions of these members. If study staff were present, it must be clear that none of these persons voted.

Modifications made to the protocol after receipt of the EC/IRB approval must also be submitted as amendments by the investigator to the EC/IRB in accordance with local procedures and regulations [see Section 6.1.1].

6.2.3 Informed consent

It is the responsibility of the investigator to obtain informed consent according to GCP and local regulations from each individual participating in this study after adequate explanation of the aims, methods, objectives and potential hazards of the study. The investigator must also explain to patients that they are completely free to refuse to enter the study or to withdraw from it at any time for any reason. Appropriate forms for documenting informed consent will be provided to the sites prior to the study.

The Informed Consent and Patient Information will be provided in the local language.

6.2.4 Compensation to patients and investigators

The sponsor provides insurance in order to indemnify (with both legal and financial coverage) the investigator/center against claims arising from the study, except for claims that arise from malpractice and/or negligence.

The compensation of the patient in the event of study-related injuries will comply with applicable regulations.

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8 APPENDICES

Appendix 1: Study-specific criteria for permanent discontinuation of study drug

A) Cardiovascular

Patients must be permanently discontinued from study drug, if:

- the following change in HR is observed at any time throughout the study, as documented by 12-lead ECG:
  - HR <30 bpm, or
  - HR <40 bpm is sustained for at least 1 hour and is associated with symptoms of bradycardia (e.g., syncope, dizziness, or vertigo), or
- QTcF >500 ms is observed at any time throughout the study, as documented by 12 lead ECG, or
- pharmacological intervention or cardiac pacing for any rhythm disorders is required at any time throughout the study, or
- the patient does not meet the criteria for discharge [Appendix 2] from hospital on Days 1, 8, or 15 (or on days of re-initiation or re-uptitration following dose interruptions, if applicable) after 12-hour post-dose monitoring.

The above-mentioned conditions require immediate assessment by the physician evaluating cardiac safety assessments. Follow-up monitoring must be provided until the event resolves or the change is regarded no longer clinically relevant.

In the event of any signs or symptoms of bradycardia or other arrhythmia (e.g., syncope, palpitations), at any time during study treatment, the physician evaluating cardiac safety assessments should be consulted. If a cardiac origin is suspected, permanent discontinuation of study drug should be considered**.**

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

B) Immune system

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

- A clinically relevant infection requiring discontinuation of treatment in the view of the primary investigator, and/or
- Total lymphocyte count <200 cells/µL

Whenever a total lymphocyte count <200 cells/µL is recorded by the central laboratory, an alert will be sent to the primary investigator and sponsor. The primary investigator will immediately contact the patient and ask her/him to return to the site preferably within 48 hours but no later than within 1 week to repeat the test by the central laboratory (unless the clinical situation mandates immediate local testing). If the repeat test confirms a lymphocyte count <200 cells/µL, the study drug must be discontinued and lymphocyte count must be monitored at least once a week by the central laboratory (unless the clinical situation mandates immediate local testing) until the lymphocyte count has returned to ≥ 1,000 cells/µL or ≥ 80% of the baseline value. If a local laboratory test was performed, the test results must be captured in the CRF.

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

More details on opportunistic infections are provided in Appendix 3.

C) Respiratory system

Patients must be* or may be# permanently discontinued from study drug at any time throughout the study, if the following changes in pulmonary function are observed:

- If an FEV_1 and/or FVC <80% of the study baseline value is observed the patient should have a repeat test done on a different day, preferably within 1 week but not more than 2 weeks later.
    - *If the FEV_1 and/or FVC is <70% of study baseline at the repeat test and the opinion of the investigator is that this change is clinically significant, the patient is to be discontinued.
    - #If the FEV_1 and/or FVC is <80% (but ≥ 70%) of study baseline at the repeat test accompanied by persistent respiratory symptoms discontinuation of the patient may be considered at the discretion of the investigator.
- #A respiratory AE requiring discontinuation of treatment in the view of the investigator.

Follow-up monitoring needs to be provided until respiratory AEs have resolved and changes in pulmonary function are no longer regarded as clinically relevant according to internationally accepted guidelines [Pellegrino 2005], i.e., change from baseline of FEV_1 and FVC is <12% and <200 mL.

D) Pregnancy

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

Planned pregnancy:

Female patients participating in the study and wishing to become pregnant during the study may stay in the study and will have the study drug interrupted prior to pregnancy and re-initiated after delivery.

Before becoming pregnant, the following protocol requirements must be met:

- The wish to become pregnant and stay in the study has to be communicated by the female patient to the primary investigator / treating neurologist during a scheduled visit occurring no later than at Visit P28 (Week 324). If the wish to become pregnant is communicated after Visit P28 (Week 324), the study drug interruption for a planned pregnancy would not be allowed.
- Prior to interrupting contraception, the patient must have 2 negative urine pregnancy tests: one at the scheduled visit on the day of study drug interruption and one 30 days after study drug interruption.
- The total duration of the study drug interruption due to planned pregnancy must not exceed 81 weeks, otherwise the study drug will be discontinued.
- The patient 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 primary investigator / treating neurologist and to have the information on the patient's MS status communicated by the primary investigator / treating neurologist to that health care professional.

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

- The potential impact of pregnancy and post-partum period on the patient's MS and potential medical treatments that would be available for the patient while the study drug is interrupted;
- Re-initiation of study drug can only take place after delivery and after breastfeeding has been stopped, if applicable, and will require a medical evaluation of patient's eligibility for study drug re-initiation;
- Timing of the interruption and possible re-initiation of study drug and of contraception, related pregnancy tests and unscheduled visits;
- The need for re-uptitration at the study drug re-initiation;

- The need to follow the visit schedule as per protocol during pregnancy including all the scheduled assessments and procedures except MRI, PFTs and without study drug dispensing.

The re-initiation of study drug after delivery requires the following eligibility criteria:

- The patient has completely stopped breastfeeding prior to re-initiation of the study drug;
- The patient must have been using the reliable methods of contraception as described in Section 4.4 for at least 30 days prior to re-initiation of study drug;
- The patient must have had 2 negative urine pregnancy tests performed 30 days apart; the second one must be during the re-initiation visit;
- The patient did/does not fulfill any protocol criteria for permanent study treatment discontinuation per Appendix 1 at any of the previous visits or at the unscheduled visit for re-initiation of the study drug except the planned pregnancy;
- In case the patient received another DMT (IFN β-1a or glatiramer acetate) during pregnancy and post-partum, this treatment must be discontinued at least 7 days before study drug re-initiation.

If the patient agrees to all of the above, the study drug will be interrupted at the scheduled visit once the patient, after having received the above explanation from the primary investigator / treating neurologist, has confirmed the wish to become pregnant and interrupt and potentially re-initiate the study drug. The sponsor has to be contacted in each particular case to confirm that the patient 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 drug interruption for planned pregnancy, irrespective of the duration of pregnancy and also to all cases where planned pregnancy did not occur but where the contraception was interrupted for any duration and the patient wishes to re-initiate the study drug.

E) Ocular abnormalities

In the event of suspected clinically significant findings (e.g., macular edema), an unscheduled ophthalmological assessment with OCT should be performed. In case of macular edema confirmed by the local ophthalmologist, the subject must permanently discontinue study treatment. Macular edema is to be managed and followed up until resolution. Any clinically relevant finding meeting the definition of an AE will be recorded accordingly in the eCRF.

F) Liver abnormalities

In the event of abnormal liver tests or signs and symptoms suggestive of drug induced liver injury (DILI), the patient will be closely observed, liver tests will be repeated, and study treatment discontinuation should be considered according to the guidance provided in Table 8.

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 patients receiving anticoagulants.

Table 8: Guidance for patient 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 patients 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 patient, and ask the patient about any potential symptoms. The patient 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 8. Further diagnostic work-up and consultation with a hepatologist or other specialist should be considered, and adequate medical management should be provided according to local practice and the clinical situation. Any clinically relevant finding meeting the definition of an AE will be recorded accordingly in the CRF.

In the event of study treatment interruption, the patient 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 patient. Note: The re-initiation is not permitted for situations where the study treatment should be permanently discontinued according to Table 8. 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.

Reference for Appendix 1

[Pellegrino 2005] Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. Eur Respir J 2005;26:948-68.

Appendix 2: Criteria for discharge from hospital

Discharge Criteria Applied on Days 1, 8 and 15

On Days 1, 8 and 15, at Visit P1 and at the visit during which the transition from TP2 to TP3 took place, ECG and SBP/DBP were monitored for up to 6 hours post-dose. At the time of discharge (i.e., 6-hour post-dose) must have been met:

- HR >50 bpm, and SBP >90 mmHg
- No ECG abnormality or AE requiring continued hospitalization or prohibiting study continuation as an out-patient

If a patient did not meet the discharge criteria (as described above) at 6 hours post-dose, the patient was carefully monitored for an additional period, and a 12-lead ECG and a BP measurement was performed every 2 hours. The patient was kept in hospital for observation until changes in ECG/BP parameters were regarded as no longer being clinically relevant.

Study drug was permanently discontinued if the patient did not meet the criteria for discharge at 12 hours post-dose.

Discharge Criteria Applied for Study Drug Re-initiation

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

- ECG-derived resting HR >45 bpm, and if HR <50 bpm it must not be the lowest value post-dose;
- SBP >90 mmHg;
- QT corrected for HR on the basis of Fridericia's formula (QTcF) <500 ms and QTcF increase from pre-dose <60 ms;
- No persisting significant ECG abnormality (e.g., AV block second or third degree) or ongoing AE requiring continued hospitalization or prohibiting study continuation as an out-patient.

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

Should the patient not meet the criteria for discharge from post-dose monitoring at 12-hour post-dose, she/he must be permanently discontinued from study drug. Patients who are permanently discontinued should not be discharged from post-dose monitoring before vital signs return to near baseline values or until there is no persisting ECG abnormality

(e.g., AV block second degree or higher), ongoing AE requiring continued cardiac monitoring, or until medically indicated.

Appendix 3: Guidance on monitoring of patients for opportunistic infections

A) Guidance for screening, exclusion and on-treatment monitoring of subjects for Progressive multifocal leukoencephalopathy (PML):

PML is an opportunistic infection of the CNS that can lead to death or severe disability. Active replication of the human polyoma JCV in glial cells of the brain, causing lytic death in oligodendrocytes, is the underlying pathobiology of PML. The infection typically arises in severely immunocompromised patients - 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 patients treated with natalizumab are at increased risk of developing PML. In addition to natalizumab, cases of PML have been reported in patients treated with various drugs, usually in combination with corticosteroids, including alkylating agents (e.g., cyclophosphamide, carmustine, and dacarbazine), purine analogues (e.g., fludarabine, cladribine, and azathioprine), immunosuppressants (e.g., cyclosporin, tacrolimus, sirolimus, and mycophenolate), and therapeutic monoclonal antibodies (e.g., rituximab, infliximab, etanercept, basiliximab, daclizumab, efalizumab, alemtuzumab, and muromonab-CD3) [Kappos 2011].

The great majority of natalizumab-associated PML cases have occurred while on treatment. However, there are reports of natalizumab-associated PML occurring respectively 2 and 3 months after discontinuation of natalizumab. In one patient, who had started fingolimod treatment 6 weeks after stopping natalizumab, a confirmed PML diagnosis was made 3 months after starting fingolimod with symptoms suggestive of PML reported one month after starting fingolimod.

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

- Perform MRI including T1 sequences with gadolinium and include comparison with the previous MRI images in the interpretation of the MRI results. NB: In addition, fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted imaging (DWI) sequences may be performed and sent to MIAC. MIAC will only analyze the additional sequences selected by the local radiologist, neuroradiologist, or neurologist with MRI expertise, upon notification for review of the investigational site. In that instance, MIAC will communicate the results of the review to the site.
- Interrupt study drug until PML or other opportunistic CNS infections 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 patient 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 patient 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 JCV 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,

other causes of the atypical neurological signs or symptoms or MRI findings need to be considered. Re-starting of the study drug should be considered if the benefit risk is still favorable, according to the investigator.

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

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

Cases of PML must be reported to the sponsor as an SAE.

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

B) General guidance for monitoring of subjects with opportunistic infection 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 patients should also be alert to potential systemic infections caused by fungi and bacteria. In the event of opportunistic infection, the patient must discontinue the study drug and must be referred to an expert in infectious diseases for further examination and treatment.

It is important to recognize that opportunistic infections caused by the reactivation of human herpes viruses (herpes simplex viruses, varicella-zoster virus, Epstein-Barr virus, cytomegalovirus) may be associated with neurological symptoms primarily. The neurotropic herpes viruses (herpes simplex and varicella-zoster) are frequent human pathogens and their reactivation can cause serious infections of the CNS such as encephalitis and meningitis. The most frequent characteristics of these infections are of acute onset, associated with fever, headache, confusion, personality changes, and disorientation. Any suspicion of these infections must lead to immediate discontinuation of study drug treatment and to early initiation of antiviral treatment [Steiner 2007]. In the event of a suspected opportunistic infection of the CNS, FLAIR and DWI sequences may be performed and sent to MIAC. MIAC will only analyze the additional sequences selected by the site local radiologist, neuroradiologist, or neurologist with MRI expertise, upon notification for review of the investigational site. In that instance, MIAC will communicate the results of the review to the site.

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 signs of skin, mucosal surfaces, gastrointestinal tract, liver, hematological or other abnormality or organ dysfunction suggesting a potential opportunistic infection.

Patients should be advised to be pro-active 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].

References for Appendix 3

[Kappos 2007] Kappos L, Bates D, Hartung HP, et al. Natalizumab treatment for multiple sclerosis: recommendations for patient 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

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

Appendix 4: Guidance for skin examination

Since the skin might be the first organ for manifestation of immunosuppression, a complete skin examination must be performed in order to distinguish normal, abnormal, and suspicious skin lesions. The skin examinations can be done by a dermatologist or by the primary investigator / treating neurologist. In the event of abnormal or suspicious findings the primary investigator / treating neurologist must refer the patient to a dermatologist for further examination, including the taking of skin biopsies if required.

In the initial examination, it is important that the patient be disrobed as completely as possible. This will minimize chances of missing important individual skin lesions. The patient should first be viewed from a distance of about 1.5 to 2 m so that the general character of the skin and the distribution of lesions can be evaluated. The presence or absence of lesions on mucosal surfaces should also be determined.

Four basic features of any skin lesion must be noted and considered in the examination of skin: the localization and distribution of lesions, the type of lesion, the shape of the individual lesion, and the arrangement of the lesion.

Special attention should be paid to nevi (moles), especially those that have recently changed, bleed, or itch. When looking at nevi, four features are essential for detection of skin cancer: Asymmetry, border irregularity, color variability, diameter >6 mm. These features or rapidly changing lesions are associated with an increased risk of malignancy.

The following descriptions of skin lesions and common dermatologic terms are provided to facilitate documentation of skin examination.

Descriptions of primary skin lesions

Macule	A flat, colored lesion, <2 cm in diameter, not raised above the surface of the surrounding skin. A "freckle," or ephelid, is a prototype pigmented macule.
Patch	A large (>2 cm), flat lesion with a color different from the surrounding skin. This differs from a macule only in size.
Papule	A small, solid lesion, <0.5 cm in diameter, raised above the surface of the surrounding skin and hence palpable (e.g., a closed comedone, or whitehead, in acne).
Nodule	A larger (0.5 5.0 cm), firm lesion raised above the surface of the surrounding skin. This differs from a papule only in size (e.g., dermal nevus).
Tumor	A solid, raised growth >5 cm in diameter.
Plaque	A large (>1 cm), flat-topped, raised lesion; edges may either be distinct (e.g., in psoriasis) or gradually blend with surrounding skin (e.g., in eczematous dermatitis).
Vesicle	A small, fluid-filled lesion, <0.5 cm in diameter, raised above the plane of surrounding skin. Fluid is often visible, and the lesions are often translucent.
Pustule	A vesicle filled with leukocytes. Note: The presence of pustules does not necessarily signify the existence of an infection.
Bulla	A fluid-filled, raised, often translucent lesion >0.5 cm in diameter.
Cyst	A soft, raised, encapsulated lesion filled with semisolid or liquid contents.
Wheal	A raised, erythematous papule or plaque, usually representing short-lived dermal edema.
Telangiectasia	Dilated, superficial blood vessels.

Common dermatological terms

Lichenification	A distinctive thickening of the skin that is characterized by accentuated skin-fold markings and that feels thick on palpation.
Crust	Dried exudate of body fluids that may be either yellow (serous exudate) or red (hemorrhagic exudate).
Milia	Small, firm, white papules that are filled with keratin (and may in part resemble pustules).
Erosion	Loss of epidermis without an associated loss of dermis.
Ulcer	Loss of epidermis and at least a portion of the underlying dermis.
Excoriations	Linear, angular erosions that may be covered by crust and are caused by scratching.
Atrophy	An acquired loss of substance. In the skin, this may appear as a depression with intact epidermis (i.e., loss of dermal or subcutaneous tissue) or as sites of shiny, delicate, wrinkled lesions (i.e., epidermal atrophy).
Scar	A change in the skin secondary to trauma or inflammation. Sites may be erythematous, hypopigmented, or hypertrophic depending on their age of character. Sites on hair-bearing areas may be characterized by destruction of hair follicles.
Pruritus	A sensation that elicits the desire to scratch. Pruritus is often the predominant symptom of inflammatory skin diseases (e.g., atopic dermatitis, allergic contact dermatitis); it is also commonly associated with xerosis and aged skin.

Appendix 5: Guidance for re-initiation of study drug in the event of drug interruption

If study drug intake (during uptitration or maintenance phase) is interrupted by the patient for any reason, she/he must immediately inform the primary investigator / treating neurologist.

Note that under no circumstances should a patient take more than one capsule per day during TP1 or more than one tablet per day during TP2 and TP3.

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

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

A) If the patient 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.

B) If the patient 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 drug interruption.
- Study drug intake may be re-initiated by the patient at home.
- Patients must be instructed to contact the investigator immediately if they experience any symptoms of bradycardia (e.g., dizziness, vertigo, syncope).

C) If the patient missed taking the dose for four or more consecutive days, then the gradual uptitration scheme outlined in Table 6 (blister kit with starting dose of 2 mg) must be used:

1. Patients 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 patient must be monitored for at least 4 hours post-dose, following the cardiac assessment schedule and applying the discharge criteria as described in Appendix 2.

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.

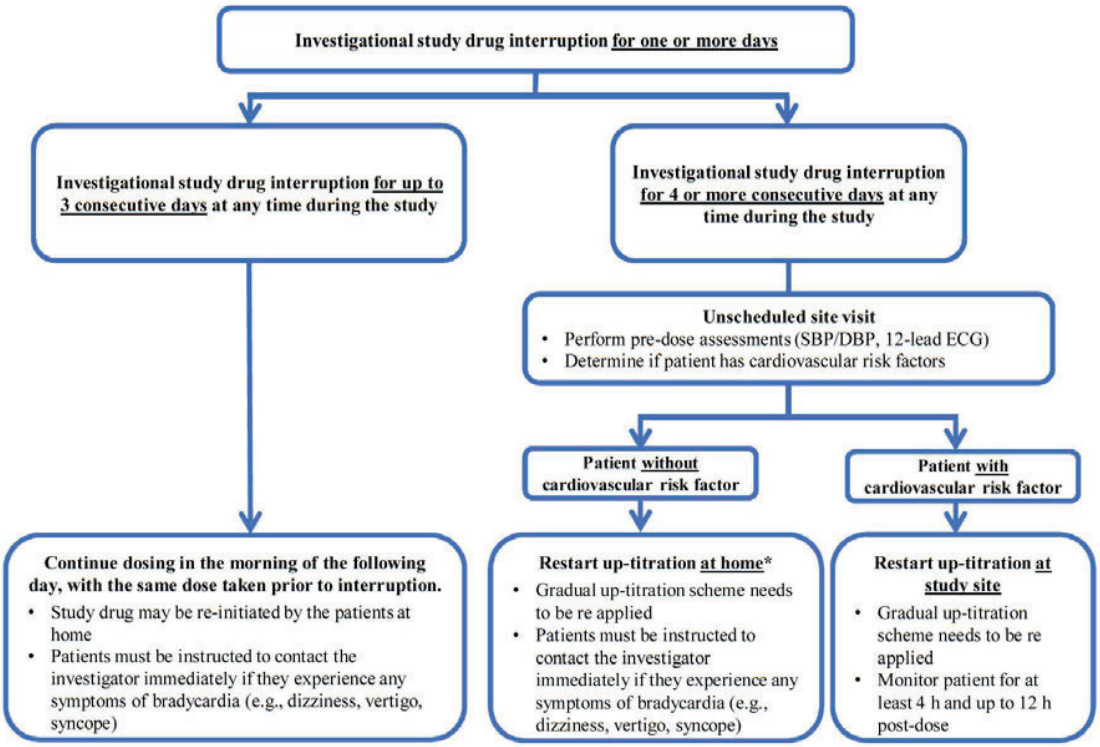
In the event of a re-initiation, the treating neurologist may consult with the physician evaluating cardiac safety assessments and/or a cardiologist to determine the most appropriate monitoring strategy. Cardiologist advice should be sought in case of history or presence during the study of the following 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;
- Patients receiving concomitant therapy with drugs that decrease HR (e.g., beta-blockers, calcium channel blockers and other drugs that may decrease HR).

2. Patients 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 a gradual uptitration blister kit with a starting dose of 2 mg from the site or re-initiate study drug at site using the blister kit with the starting dose of 2 mg and be monitored for at least 4 hours post-dose at the discretion of the investigator / treating neurologist [see Section 3.12.5.3]. Patients 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 3.12.5.3] may be scheduled at the discretion of the investigator / treating neurologist.

If a blister kit with the starting dose of 2 mg is not available at the site, re-initiation should be delayed until it becomes available (temporary treatment interruption).

Figure 2: Algorithm for management of treatment



*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.

Appendix 6: Diagnostic criteria for MS (2005 revision of McDonald Criteria)

Clinical presentation	Additional data needed for MS diagnosis
• ≥ 2 attacks • Objective clinical evidence of 2 or more lesions	• None
• ≥ 2 attacks • Objective clinical evidence of 1 lesion	• Dissemination in space[1], demonstrated by: - MRI - ≥ 2 MRI lesions consistent with MS + positive CSF - or await further clinical attack implicating a different site
• 1 attack • Objective clinical evidence of ≥ 2 lesions	• Dissemination in time[2], demonstrated by: - MRI - or second clinical attack
• 1 attack • Objective clinical evidence of 1 lesion (monosymptomatic presentation; clinically isolated syndrome)	• Dissemination in space[1], demonstrated by: - MRI - or ≥ 2 MRI lesions consistent with MS + positive CSF • and Dissemination in time[2], demonstrated by: - MRI - or second clinical attack
• Insidious neurological progression suggestive of MS	• One year of disease progression and dissemination in space[1], demonstrated by two of the following: - Positive brain MRI (≥ 9 T_2 lesions in brain), or ≥ 4 T_2 lesions in brain with positive visual evoked potentials, - Positive spinal cord MRI (≥ 2 focal T_2 lesions), - Positive CSF (oligoclonal IgG bands or increased IgG index).

[1] For MRI lesions disseminated in space, at least 3 of the following criteria must be met: one Gd+ lesion or 9 T_2-hyperintense lesions in the brain and spine, at least one infratentorial or spine lesion, at least one juxtacortical lesion, and at least 3 periventricular lesions.

[2] For MRI lesions disseminated in time, either of the following criteria must be met: Gd+ lesion ≥ 3 months after initial presentation, but in different location from initial event; and new T_2 lesion, compared with reference MRI done ≥ 30 days after onset of initial event.

Appendix 7: Kurtzke Expanded Disability Status Scale (EDSS)

Neurological examination / Functional Systems (1)
• **Pyramidal functions** ☐ grade 0 = Normal. ☐ grade 1 = Abnormal signs without disability. ☐ grade 2 = Minimal disability (e.g., fatigability in motor tasks). ☐ grade 3 = Mild or moderate paraparesis or hemiparesis; Or severe monoparesis. ☐ grade 4 = Marked paraparesis or hemiparesis; Or moderate quadriparesis; Or monoplegia. ☐ grade 5 = Paraplegia, hemiplegia, or marked quadriparesis. ☐ grade 6 = Quadriplegia.
• **Cerebellar functions** ☐ grade 0 = Normal. ☐ grade 1 = Abnormal signs without disability. ☐ grade 2 = Mild ataxia. ☐ grade 3 = Moderate truncal or limb ataxia. ☐ grade 4 = Severe ataxia, all limbs. ☐ grade 5 = Unable to perform coordinated movements due to ataxia.
• **Brainstem functions** ☐ grade 0 = Normal. ☐ grade 1 = Signs only. ☐ grade 2 = Moderate nystagmus or other mild disability. ☐ grade 3 = Severe nystagmus, marked extraocular weakness, or moderate disability of other cranial nerves. ☐ grade 4 = Marked dysarthria or other marked disability. ☐ grade 5 = Inability to swallow or speak.

Neurological examination / Functional Systems (2)

- **Sensory functions**

☐ grade 0 = Normal.

☐ grade 1 = Vibration or figure-writing decrease only, in one or two limbs.

☐ grade 2 = Mild decrease in touch or pain or position sense, and/or moderate decrease in vibration in one or two limbs;
Or vibratory (c/s figure-writing) decrease alone in three or four limbs.

☐ grade 3 = Moderate decrease in touch or pain or position sense, and/or essentially lost vibration in one or two limbs;
Or mild decrease in touch or pain and/or moderate decrease in all proprioceptive tests in three or four limbs.

☐ grade 4 = Marked decrease in touch or pain or loss of proprioception, alone or combined, in one or two limbs;
Or moderate decrease in touch or pain and/or severe proprioceptive decrease in more than two limbs.

☐ grade 5 = Loss (essentially) of sensation in one or two limbs;
Or moderate decrease in touch or pain and/or loss of proprioception for most of the body below the head.

☐ grade 6 = Sensation essentially lost below the head.

- **Bowel/bladder functions**

☐ grade 0 = Normal.

☐ grade 1 = Mild urinary hesitancy, urgency, or retention, and/or constipation.

☐ grade 2 = Moderate urinary hesitancy, urgency, retention, or rare incontinence, and/or severe constipation.

☐ grade 3 = Frequent urinary incontinence or intermittent self-catheterization, and/or severe bowel dysfunction.

☐ grade 4 = In need of almost constant catheterization.

☐ grade 5 = Loss of bladder function, external or indwelling catheter.

☐ grade 6 = Loss of bowel and bladder function

Neurological examination / Functional Systems (3)

- **Visual (optic) functions**

  ☐ grade 0 = Normal.

  ☐ grade 1 = Mild scotoma and/or visual acuity of worse eye (corrected) better than 20/30 (0.67).

  ☐ grade 2 = Worse eye with large scotoma and/or maximal visual acuity (corrected) of 20/30 to 20/59 (0.67-0.34).

  ☐ grade 3 = Worse eye with large scotoma, or moderate decrease in fields, and/or maximal visual acuity (corrected) of 20/60 to 20/99 (0.33-0.2).

  ☐ grade 4 = Worse eye with marked decrease of fields and/or maximal visual acuity (corrected) of 20/100 to 20/200 (0.1-0.2);
  Or grade 3 plus maximal acuity of better eye of 20/60 (0.3) or less.

  ☐ grade 5 = Worse eye with maximal visual acuity (corrected) less than 20/200 (0.1);
  Or grade 4 plus maximal acuity of better eye of 20/60 (0.3) or less.

  ☐ grade 6 = Grade 5 plus maximal acuity of better eye of 20/60 (0.3) or less.

- **Cerebral (or mental) functions**

  ☐ grade 0 = Normal.

  ☐ grade 1 = Mood alteration only (does not affect EDSS score).

  ☐ grade 2 = Mild decrease in mentation.

  ☐ grade 3 = Moderate decrease in mentation.

  ☐ grade 4 = Marked decrease in mentation.

  ☐ grade 5 = Dementia.

- **Other function**

  ☐ None.

  ☐ Any other neurological findings attributed to MS

  Please specify:

  •

  •

EDSS score	
0	Normal neurological exam [all Grade 0 in Functional Systems (FS)].
1.0	No disability, minimal signs in one FS (i.e., grade 1).
1.5	No disability, minimal signs in more than one FS (more than one grade 1).
2.0	Minimal disability in one FS (one FS grade 2, others 0 or 1).
2.5	Minimal disability in two FS (two FS grade 2, others 0 or 1).
3.0	Moderate disability in one FS (one FS grade 3, others 0 or 1), or mild disability in three or four FS (three/four FS grade 2, others 0 or 1) though fully ambulatory.
3.5	Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3; or five FS grade 2 (others 0 or 1).
4.0	Ambulatory without aid or rest for >500 m, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combination of lesser grades exceeding limits of previous steps.
4.5	Ambulatory without aid or rest for >300 m, up and about much of the day; characterized by relatively severe disability usually consisting of one FS grade 4 or combination of lesser grades exceeding limits of previous steps.
5.0	Ambulatory without aid or rest for >200 m (usual FS equivalents are one grade 5 alone, others 0 or 1, or combination of lesser grades usually exceeding specifications for step 4.5).
5.5	Ambulatory without aid or rest for >100 m.
6.0	Unilateral assistance (cane or crutch) required to walk at least 100 m with or without resting.
6.5	Constant bilateral assistance (canes or crutches) required to walk at least 20 m without resting.
7.0	Unable to walk 5 m even with aid, essentially restricted to wheelchair; wheels self and transfers alone; up and about in wheelchair some 12 hours a day.
7.5	Unable to take more than a few steps; restricted to wheelchair; may need some help in transfer.
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but out of the bed most of the day; retains many self-care functions; generally has effective use of arms.
8.5	Essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions.
9.0	Helpless bed patient; can communicate and eat.
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow.
10.0	Death due to MS.

Appendix 8: Prohibited anti-arrhythmic and HR-lowering therapy

The following anti-arrhythmic drugs are prohibited during the titration (i.e., during the first 14 days after re-initiation of study treatment). [See Section 3.4.4.3 *Prohibited concomitant medications.*]

- Adenosine
- Acetobulol
- Ajmaline
- Amiodarone
- Aprinidine
- Atenolol
- Azimilide
- Bepridil
- Betaxolol
- Bisiprolol
- Bretylium
- Bunaftine
- Carvidiol
- 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 with the sponsor the use of any potential anti-arrhythmic or HR-lowering drug.

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 9: List of medications with risk of torsades de pointes (TdP)

The use of the following QT-prolonging medications with risk of TdP is prohibited during the study unless the benefit-risk is acceptable, as judged by the investigator.

- Amiodarone
- Anagrelide
- Arsenic trioxide
- Astemizole
- Azithromycin
- Bepridil
- Chloroquine
- Chlorpromazine
- Cilostazol
- Ciprofloxacin
- Cisapride
- Citalopram
- Clarithromycin
- Cocaine
- Disopyramide
- Dofetilide
- Domperidone
- Donepezil
- Dronedarone
- Droperidol
- Erythromycin
- Escitalopram
- Flecainide
- Fluconazole
- Gatifloxacin
- Grepafloxacin
- Halofantrine
- Haloperidol
- Ibutilide
- Levofloxacin
- Levomethadyl
- Mesoridazine
- Methadone
- Moxifloxacin
- Ondansetron
- Pentamidine
- Pimozide
- Probucol
- Procainamide
- Propofol
- Quinidine
- Sevoflurane
- Sotalol
- Sparfloxacin
- Sulpiride
- Terfenadine
- Thioridazine
- Vandetanib

The above list is based on the one published by AZCERT (October 2015) [AZCERT]. Any marketed drugs with new reported TdP or new marketed drugs with risk of TdP in their labels should not be administered unless the benefit-risk is acceptable, as judged by the investigator.

Reference for Appendix 9

[AZCERT] University of Arizona CERT. List of QT-prolonging medications with risk of TdP. Available under: www.AZCERT.org; www.QTdrugs.org [Accessed October 2015]

Appendix 10: 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 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 and Assessments

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.

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 patient'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 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.

Study Drug Dispensation

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 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 patient 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. Patients 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 patient'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 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 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 3.4.4.2, 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 patients.

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 re-initiated only after at least 4 weeks from completion of vaccination (see Section 3.4.4.3).
- Patients receiving non-live vaccination against influenza or COVID-19 while on study treatment will have 5 mL of blood drawn prior to and at least 3 weeks after vaccination to explore changes in vaccine-specific antibody titers from pre- to post vaccination. Samples will be analyzed at the end of the study at the latest (see Section 3.11.2.9).
    - In case of a vaccine requiring the administration of multiple doses, the post-vaccination sample should be collected at least 3 weeks after the administration of the last dose.
    - Every effort should be made to collect these samples for further analysis.
- 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 4.

References:

1. https://www.multiplesclerosisnewstoday.com/columns/2021/01/12/covid-19-vaccine-recommendations-ms-society/
2. https://www.nationalmssociety.org/coronavirus-covid-19-information/multiple-sclerosis-and-coronavirus/covid-19-vaccine-guidance#section-1
3. https://www.nationalmssociety.org/coronavirus-covid-19-information/multiple-sclerosis-and-coronavirus/ms-treatment-guidelines-during-coronavirus
4. Zheng, I. Kar, C.K. Chen et al. Multiple Sclerosis Disease-Modifying Therapy and the COVID-19 Pandemic: Implications on the Risk of Infection and Future Vaccination. *CNS Drugs* (2020) 34:879–896
5. https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

Appendix 11: Considerations for Optical Coherence Tomography assessments

As of the implementation of Global Protocol version 12, regular Optical Coherence Tomography (OCT) is no longer required.

Unscheduled OCT will only be performed for subjects at risk according to the ophthalmologist's decision (with findings suggestive of macular edema, or if active uveitis is diagnosed during the study).

Unscheduled OCT will be performed for subjects at risk according to the ophthalmologist's discretion as described in Sections 3.11.1.4 and 3.11.2.6 at selected centers with adequate equipment and experience the average retinal nerve fiber layer (RNFL) thickness, central foveal thickness, and total macular volume will be measured by OCT. If a center was selected to perform OCT, all efforts should be taken to perform OCT in all eligible subjects at this center.

In case OCT will be performed, both OCT and the assessment of best corrected visual acuity will be standardized as described below, and the results of both assessments will be recorded in the CRF.

Site requirements

Technicians performing OCT must either have been certified in earlier studies or have at least one year experience in using OCT in subjects.

There is no special storage of the computer files required. Scanning results must be printed out and filed as source data in the subject's records.

Scanning Parameters

If a center was selected to perform OCT, the following scans will be performed for subjects at risk and for both eyes as suggested by the investigator under point W1:

- Fast retinal nerve fiber layer (FRNFL) scan
- Fast macular thickness (FMT) scan

In order to ensure an adequate quality of the scan the signal strength must be ≥ 6.

Fixation

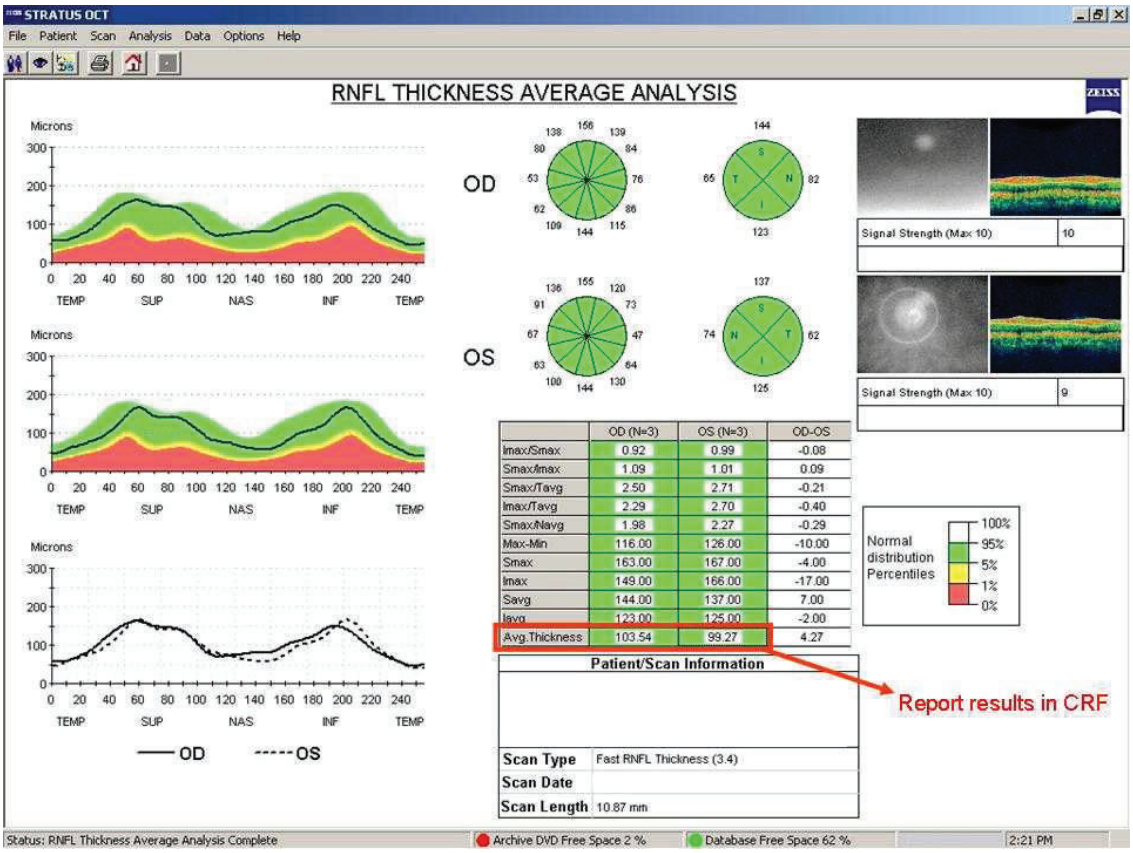
The subject needs to be instructed to look at the green fixation target during the assessment. This target will be located centrally for the FMT scan, and off center nasally for the FRNFL scan. If a subject with poor central vision, unable to fixate on the internal fixation target, is enrolled in the study this subject should not perform the OCT assessment.

Fast retinal nerve fiber layer thickness scan protocol

The FRNFL thickness scan protocol will be performed using default settings that obtain three circle scans of 3.4 mm around the optic disc. The scans will be obtained following the temporal, superior, nasal, inferior, temporal (TSNIT) pattern. Care should be taken to evenly center the circular scans on the optic nerve. The analysis used on these scans is the RNFL thickness average analysis. The FRNFL thickness scans must be well centered on the optic nerve. Off center scans must be repeated.

The following protocol will be applied:

1. Select scan acquisition protocol (FRNFL thickness scan).
2. Move fixation target to move the optic nerve towards the center of the screen.
3. Select “move scan and landmark”.
4. Move the scan and landmark until the scan is exactly encircling the optic nerve.
5. If needed, use the focus knob in order to obtain the highest quality OCT image.
6. Once a high quality circle scan with good signal strength and no blink artefact is obtained, freeze with flash and save.
7. The scan should be reviewed using the RNFL thickness single eye analysis for each eye with:
   - Very well centered optic nerve.
   - Well-defined RNFL and retinal pigment epithelium (RPE).
   - Signal strength ≥ 6.
   - No blink artefacts or fishtails.
   - No algorithm errors.



Once scans are acceptable, the RNFL thickness (single eye) analysis report will be printed for documentation, and the treating Neurologist needs to be provided with the results of the average RNFL thickness from both eyes for recording in the CRF. In addition, a printout of the results needs to be filed as source data in the subject's records.

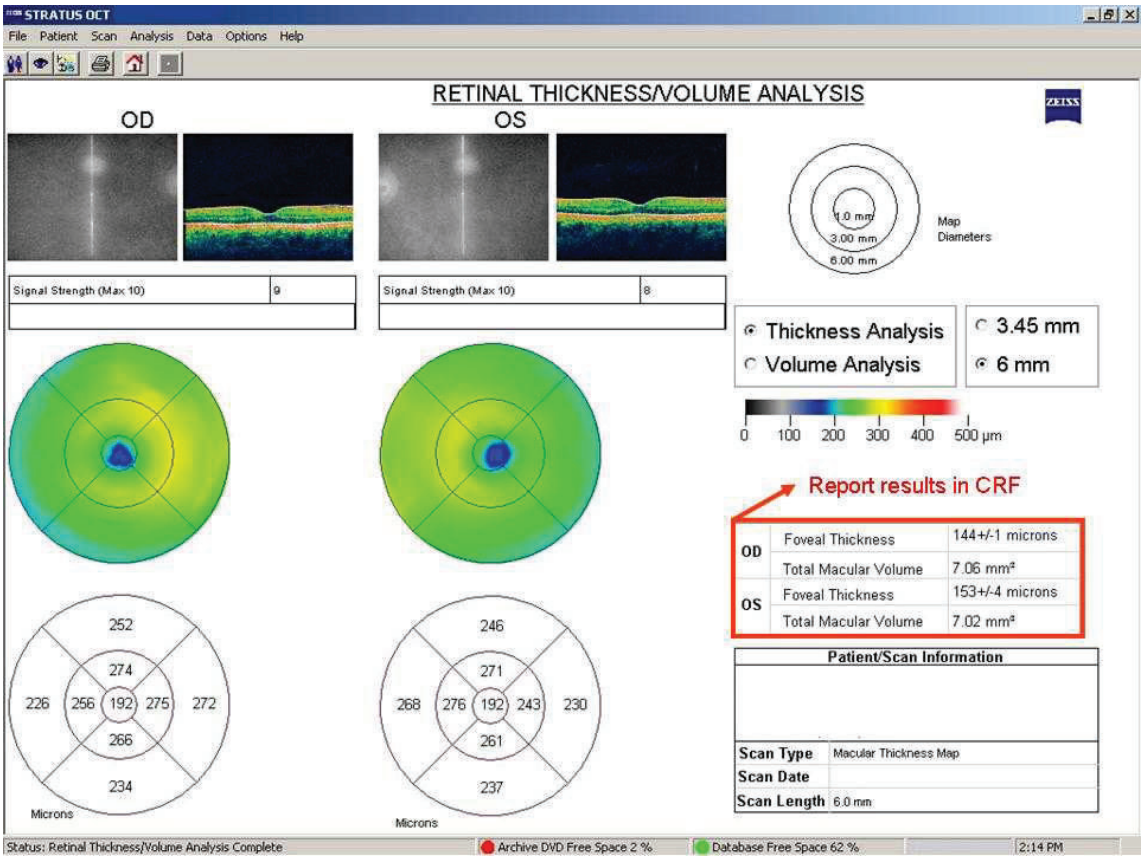
Fast macular thickness scan protocol

The fast macular thickness (FMT) scan protocol will be performed using default settings. The retinal thickness / volume tabular analysis will be used for the study printouts. Each assessment will be performed on both eyes. FMT scans will be centered on the fovea.

The following protocol will be applied:

1. Select scan acquisition protocol (FMT Scan).
2. Instruct subject to fixate on the target and perform OCT with fovea centered.
3. With the scan centered on the fovea, select Z-offset optimization setting to show scan on OCT screen.
4. Select optimize polarization to increase the signal strength.

5. Use the focus knob to obtain a highest quality OCT image, focusing for a strong RNFL.
6. Review scans using retinal map (single eye) analysis with:
   - Well centered fovea in the topographical map.
   - Well-defined RNFL and RPE.
   - Signal strength ≥ 6.
   - No blink artefacts or fishtails.
   - No algorithm errors.



Once a scan is acceptable, the retinal map (single eye) analysis report will be printed for documentation, and the treating Neurologist needs to be provided with the results of central foveal thickness and total macular volume for recording in the CRF. In addition, a printout of the results needs to be filed as source data in the subject's records.

Best corrected visual acuity

At centers where unscheduled OCT is performed for subjects with findings suggestive of macular edema or active uveitis, the assessment of best corrected visual acuity will be

standardized, and the number of correctly identified letters recorded in the CRF for each eye.

Best corrected visual acuity should be tested with perfect glasses, which provides the ability of doing a refraction if required. It will be measured by using the early treatment diabetic retinopathy study (ETDRS) acuity testing. In order to achieve best standardization, it is recommended to use a device providing self-calibrated test lighting. Calibration must be done according to the manufacturer's recommendation, as well as the selection of the testing distance. If no device providing self-calibrated test lighting is available a half-dimmed light of the room with good illumination of the chart is recommended in order to enhance contrast and optimize the reading. If this is not feasible the testing should be performed according to local routine practice and the best possible lighted conditions to obtain visual acuity data should be chosen in order to avoid any memory effect, different versions of the ETDRS test chart should be used for each eye if available.

The number of letters correctly identified should be counted as follows (based on the visual logMAR chart): the subject will be instructed to start on the last row where s/he can read all of the letters, and then read down until reaching a row where a minimum of three letters cannot be read. The number of letters can be calculated by assuming that the subject could have read all of the letters above where s/he started the test. That number of letters should then be added on to the number of letters actually read by the subject. For each eye the number of correctly identified letters will be recorded in the subject's records as source data and in the CRF. Only the number of letters correctly identified by the subject should be recorded in the CRF, **please do not modify the number** (e.g. by adding 30 if at 4 m the total is ≥ 20) to obtain visual score.

Appendix 12: Considerations for pulmonary function tests

Pulmonary function tests (PFTs) must be conducted according to the American Thoracic Society/European Respiratory Society guidelines [Miller 2005a, Miller 2005b].

Patient considerations

The subject should be instructed before and during the test course, and a demonstration provided if necessary.

Prior to performing the test, the subject needs to avoid the following:

- Eating a large meal (for at least 2 hours)
- Smoking (for at least 1 hour)
- Consuming alcohol (for at least 4 hours)
- Performing vigorous exercise (for 30 minutes)
- Wearing restricting clothes

The connection mouth-mouthpiece must be checked to avoid any leak.

The equipment must be adjusted so that the subject can sit comfortably and reach the mouthpiece without having to flex or extend the neck.

The test is started after the subject has been seated for at least 10 minutes and is as relaxed as possible. The subject should remain seated throughout the entire testing period.

The same test position has to be used throughout the study, and preferably the test is done always at approximately the same time and under the same conditions.

Tester considerations

PFTs in this study must be conducted by a PFT technician or expert. The personnel conducting the PFTs must be well trained according to the requirements outlined in the American Thoracic Society/European Respiratory Society guidelines.

The level and training of the personnel conducting PFTs must be homogeneous. Ideally, the person conducting PFTs should remain the same for each subject during the entire course of the study.

Equipment and quality considerations

Both flow measuring devices and volumic spirometers are accepted. It is highly recommended to use the same equipment for each subject during the entire course of the study.

The spirometer must be capable of accumulating volume for ≥ 15 seconds (longer times are recommended) and measuring volumes of ≥ 8 L (Body temperature and pressure

saturated, BTPS) with an accuracy of at least ± 3 % of reading or ± 0.005 L, whichever is greater, with flows between 0 and 14 L·s-1. Total resistance to airflow at 14.0 L·s ^{1} must be < 1.5cm H2O L ^{1}·s ^{1} (0.15 kPa·L ^{1}·s ^{1}).

Flow measuring devices have to demonstrate their linearity in measuring volume in 3 different ranges of flow. Calibration checks with regards to volume accuracy must be undertaken at least daily using a 3-L or 2-L syringe. Calibration checks must be undertaken at least weekly, using a 3-L syringe discharged at least 3 times to give a range of flows varying between 0.5 and 12 L·s ^{1}.

The volume accuracy and leaks of volume measuring devices must be checked daily.

The equipment needs to be maintained and calibrated according to the manufacturer's recommendations and local standard operating procedures (SOPs). A calibration log must be maintained.

Measuring and reporting

Three well-performed test breaths will be measured; the highest FEV_1 and FVC values from these 3 breath tests will be recorded in the subject's records as source data and in the CRF (even if they do not come from the same curve).

An individual test breath is considered as well-performed if it meets the following criteria:

- Is free from artifacts (e.g., cough during the first second of exhalation, glottis closure, early termination of cut off, effort that is not maximal, leaks, obstructed mouthpiece).
- Have a “good start” with an extrapolated volume <5% of FVC or 0.15 L.
- Have a satisfactory exhalation with a duration of >6 s (or a plateau in the volume-time curve if the subject cannot or should not continue to exhale).
- For FEV_1, start of test is determined by “back extrapolation method”.
- For FEV_1 and FVC, three “acceptable” spirograms must be obtained. The two largest values (among the three acceptable) must be within 0.150 L of each other for FVC and for FEV_1.
- Result must be reported at BTPS conditions and adjusted for altitude (by any method measuring temperature and barometric pressure proven effective by the manufacturer).

Calculations

Calculate FEV_1 % predicted and FVC % predicted according to following formula.

Predicted normal value for FEV_1 (liters):

Gender	Equation
Male	4.30 H 0.029 A 2.49
Female	3.95 H 0.025 A 2.60
Between 18 and 25 years, substitute 25 years in the equation H: standing height (m); A: age (yr).	

Predicted normal value for FVC (liters):

Gender	Equation
Male	5.76 H 0.026 A 4.34
Female	4.43 H 0.026 A 2.89
Between 18 and 25 years, substitute 25 years in the equation H: standing height (m); A: age (yr).	

age (pfdt - brthdtn)/365.25

Ethnic group adjustment:

For patients of ethnic groups other than White/Caucasian the predicted normal value must be adjusted by a conversion factor of 0.9 prior to calculation of FVC and FEV_1 percent of predicted, i.e.:

> FVC predicted normal for patient of ethnic group other than white/Caucasian
> FVC predicted normal x 0.9
>
> FEV_1 predicted normal for patient of ethnic group other than white/Caucasian
> FEV_1 predicted normal x 0.9

Percent of the predicted normal values for FEV_1 and FVC:

For each FEV1 and FVC measured values a percent of the predicted normal value will be calculated as follows:

> Percent of the predicted value (%) [measured value] x 100 / [predicted normal value]

The results of these PFTs will be recorded in the subject's records as source data and in the case report form (CRF).

For these calculations one decimal place must be used (e.g. 79.8 will not be rounded up to 80).

Hygiene and infection control considerations

Attention must be paid for preventing the transmission of infection to subjects during PFTs. Particular attention should be paid when using reusable mouthpieces, spacer devices and/or volume based spirometers with a closed circuit technique.

References

[Miller 2005a] Miller MR, Crapo R, Hankinson J, et al. General considerations for lung function testing. Eur Respir J 2005a; 26: 153-161.

[Miller 2005b] Miller MR, Crapo R, Hankinson J, et al. Standardization of spirometry. Eur Respir J 2005b; 26: 319-338.

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: _____

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_____

_____

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 19:59:27 (GMT)	Document Approval