Janssen Research & Development

Statistical Analysis Plan

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

Short Title

Long-term Safety and Efficacy Study of ponesimod 20 mg in subjects with relapsing multiple sclerosis

Protocol AC-058B303; Phase 3

JNJ-67896153 (ponesimod)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

TABLE OF CONTENTS

VERSION HISTORY

Table 1 SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	04-March-2024	Not Applicable	Initial release

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis populations, derived variables, and statistical methods for the analysis of efficacy and safety for the extension study 67896153AC-058B303, following the unblinding of the core study AC-058B301 (OPTIMUM), as planned in the AC-058B303 protocol.

The SAP consists of selected efficacy and safety analyses. Data from the extension study are pooled with that of the corresponding core study AC 058B301 (OPTIMUM). Statistical analysis will be descriptive unless otherwise stated. A database lock for final analysis will occur after all enrolled subjects in the extension study have completed the end of study visit or prematurely discontinue the study.

This document is based on the AC-058B303 protocol Final Version 6, dated 15 March 2022, and Version 6.UKR.A dated 04 August 2022.

1.1. Objectives and Endpoints

The study has the following objectives:

1.1.1. Safety objectives and endpoints

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

Table 2 details the endpoints that will be analyzed for the Extension Analysis Period and for the Combined Analysis Period. See Section 5.1.5 for further details regarding the analysis strategy for safety.

Table 2: Safety endpoints

Endpoints	Combined Analysis Period	Extension Analysis Period
Adverse events		
• Treatment-emergent AEs, SAEs, and AESIs [#]	Y*	Y
• AEs leading to premature discontinuation of study treatment	Y	Y
Cardiac safety		
• Treatment-emergent morphological ECG abnormalities (as defined by the ECG provider)	Y*	Y
• Absolute values by visit for 12-lead ECG parameters (HR, PR, QRS, QT, QTcB, QTcF)	Y	Y
• Change from baseline values by visit for ECG parameters (HR, PR, QRS, QT, QT QTcB, QTcF)	Y	Y
• Change in ECG parameters (HR, PR, QRS, QT, QT QTcB, QTcF) from pre-dose to selected post-dose assessments (1 h, 2 h, 3 h, 4 h) on day of re-initiation of study treatment	N	Y
Pulmonary safety		

Table 2: Safety endpoints

Endpoints	Combined Analysis Period	Extension Analysis Period
• Absolute values and percent change from baseline in FEV_1 and FVC at all assessments	Y	Y
• Treatment-emergent decrease from baseline > 20% and >30% in FEV_1 or FVC	Y*	Y
• Treatment-emergent decrease from baseline > 20 percentage points in % of predicted FEV_1 and FVC	Y*	Y
• Change in lung diffusion capacity as assessed by DL_{CO} (at selected sites only) expressed in absolute change (mL) and % of predicted value from baseline at all assessments	Y	Y
Other endpoints		
• Absolute values and change from baseline for HR, SBP, DBP, and body weight at all assessments	Y	Y
• Treatment-emergent notable blood pressure abnormalities	Y*	Y
• Absolute values and change from baseline for laboratory tests (hematology, blood chemistry) at all assessments	Y	Y
• Treatment-emergent notable laboratory abnormalities	Y*	Y

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

The selection of AEs of special interest is based on the anticipated risks of treatment with ponesimod

AE = adverse event; AESI-adverse event of special interest; DBP = diastolic blood pressure; ECG = electrocardiogram; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HR = heart rate; QTcB = QT corrected for heart rate on the basis of Bazett's formula; QTcF = QT corrected for heart rate on the basis of Fridericia's formula; SAE = serious adverse event; SAP = statistical analysis plan; SBP = systolic blood pressure.

Analyses on the Combined Analysis Period use the core baseline as a reference, while analyses on the Extension Analysis Period use the extension baseline as a refence.

1.1.2. Efficacy objectives and endpoints

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

The tables below detail which endpoints will be analyzed for the Extension Analysis Period and for the Combined Analysis Period. See Section 5.1.1 for definitions of the Analysis Periods, and Section 5.1.5 for further details regarding the analysis strategy.

1.1.2.1. Main clinical endpoints

The main clinical endpoints are those relating to disease activity, i.e., relapses and disability accumulation.

Table 3: Main clinical endpoints

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

ARR = Annualized Relapse Rate; CDA = confirmed disability accumulation; EDSS = Expanded Disability Status Scale.
Analyses on the Combined Analysis Period use the core baseline as a reference, while analyses on the Extension Analysis Period use the extension baseline as a reference.

1.1.2.2. MRI-based endpoints

Table 4: MRI-based endpoints

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

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

1.1.2.3. Other endpoints

Table 5: Other endpoints

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

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

1.2. Study Design and treatment period

Study AC-058B303 (the "extension study") is a prospective, multi-center, open-label, non-comparative, long-term extension of the Phase 3 confirmatory AC-058B301 (the "core study"). Details of the AC 058B301 study can be found in the study Protocol Final Version 7, dated 5 December 2018.

Subjects who have completed the 108-week treatment period in the core study will be enrolled as one group treated with ponesimod 20 mg once daily in the extension study, independent of previous treatment allocation.

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

1.2.1. Core study follow up period and transition into the extension study

Eligible subjects may enter the extension study following the safety follow-up (FU) period of the core study. For subjects transitioning into the extension study, the core study safety FU period concludes with a safety Follow-up Visit 1 (FU1) or with an abbreviated Follow-up Visit 2 (FU2) at 14-22 and 23-37 days, respectively, after the last dose of the study drug in the core study (End of-Treatment; EOT). The abbreviated FU2 visit will take place only if the compliance with teriflunomide elimination procedure was deemed not sufficient by the investigator at FU1 visit but transition to the extension study is still planned. The core study FU period ends when all assessments of FU1 or FU2 (whichever applies) have been completed. At FU1 or FU2 (whichever applies) the subject's compliance with teriflunomide elimination procedure needs to be assessed as sufficient by the investigator in order to confirm eligibility for the extension study.

1.2.2. Pre-treatment period

The pre-treatment period includes all pre-dose assessments of Visit 1 and starts when the subject completes the core study FU visits FU1 or FU2 (whichever applies) and signs the informed consent. This will be considered as the enrollment into the extension study. The pre-treatment period ends with the first dose of study treatment (i.e., Day 1). The pre-treatment period must not last longer than 7 days (i.e., signing of the informed consent until study treatment initiation $\leqslant$ 7 days).

1.2.3. Treatment period

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

The treatment period consists of 240 weeks of treatment with ponesimod including a 14-day gradual up-titration beginning on Day 1, followed by daily treatment with 20 mg ponesimod. Treatment will stop before 240 weeks if ponesimod becomes commercially available for the treatment of multiple sclerosis in the subject's country (Treatment may also stop before 240 weeks for subjects prematurely discontinued study treatment due to efficacy or safety or other reasons). The visits during the treatment period will consist of an enrollment visit; three visits at 2 (i.e., 15 days), 4, and 12 weeks after enrollment; and visits every 12 weeks thereafter until the EOT visit. The treatment period may include a study treatment interruption period of variable duration. The permitted maximum duration of the study treatment interruption is 81 weeks for planned pregnancies and 12 weeks for other reasons (if exceeded, then the subject will be prematurely discontinued from the study). During the treatment interruption the subject may follow the planned visit schedule off-treatment with the corresponding assessments with exceptions of assessments that are contra-

indicated due to the subject's condition (e.g., in the event of pregnancy, scheduled MRI assessments will not be performed).

1.2.3.1. End-of-treatment visit

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

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

In some countries, additional reimbursement negotiations and central formulary approvals will be needed before ponesimod becomes available. In this case, subjects participating in the AC-058B303 study can continue to receive ponesimod until ponesimod is available in their respective country, or for a maximum of 240 weeks. Subjects will get access to the study drug for a maximum of 240 weeks*. If ponesimod becomes available locally before the end of the 240 weeks in the AC-058B303 extension study, then subjects 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 subjects, the switch to commercially available ponesimod should occur at the EOT visit, and commercially available ponesimod may be initiated on the day following last intake of study treatment.

*except for subjects in Ukraine where the maximum treatment duration will be 288 weeks (or not later than preplanned global Last Subject Last End of Treatment in Q4 2023)

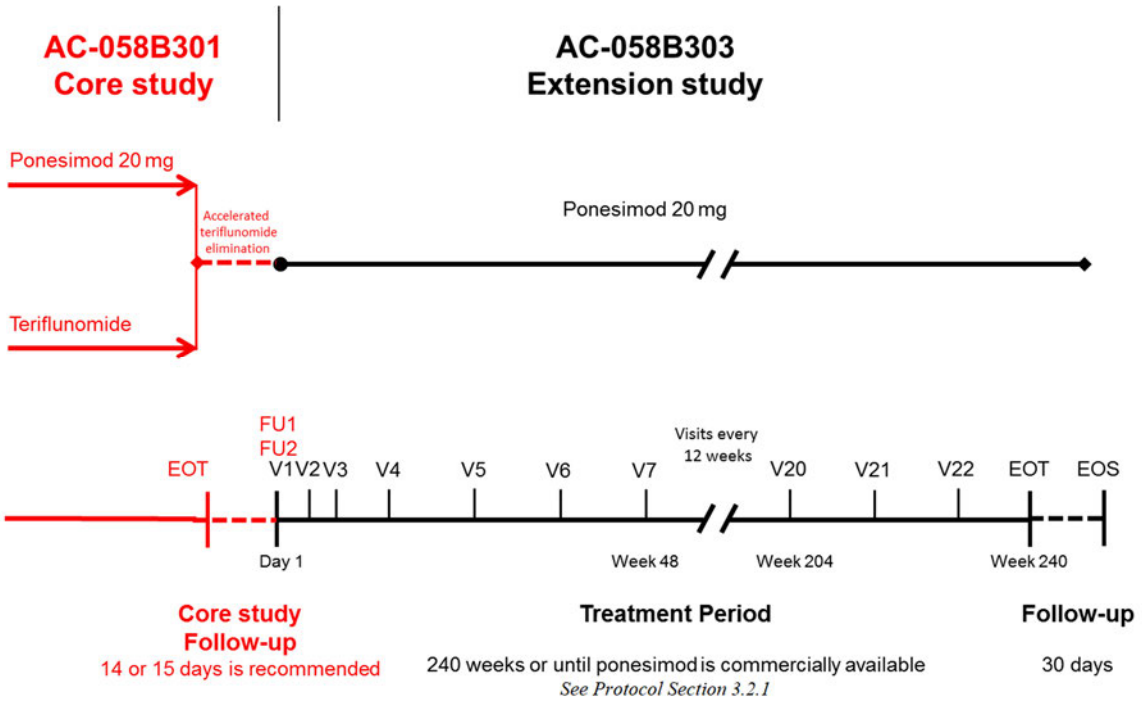
1.2.4. Safety follow-up

For an individual subject, End-of-Study (EOS) is reached when treatment and safety FU have been completed. The EOS Visit should be performed 30-44 days after the permanent discontinuation of study treatment. If during study treatment interruption, the subject fulfills the criteria for premature discontinuation, the EOS visit should be scheduled as soon as possible after the decision to prematurely discontinue has been taken.

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

The overall AC-058B303 study design is depicted in Figure 1.

Figure 1: Study Design



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

1.3. Procedures for Randomization and Stratification

This extension study is open-label, and all subjects receive ponesimod 20 mg. No randomization or stratification procedures were performed.

1.4. Blinding

This extension study is open-label, and all subjects receive ponesimod 20 mg. The study treatment groups in the core study will remain blinded until the randomization list is revealed for the core study after core database lock.

2. STATISTICAL HYPOTHESES

As the present study is an open label long-term extension of the confirmatory Phase 3 core study, no hypotheses are pre-specified. All analyses conducted will be exploratory. No multiplicity adjustments will be made for the efficacy endpoints.

3. SAMPLE SIZE DETERMINATION

As the extension study is an extension of the confirmatory Phase 3 core study, there are no sample size statistical considerations. The sample size is pragmatically determined by how many of the 1133 subjects randomized in the core study enroll into the extension study. Based on anticipated discontinuation rates in the core study, the sample size was estimated to be approximately 875 subjects. At this final analysis, there are in total 877 subjects enrolled in the extension study.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

4.1. Definitions of analysis sets

4.1.1. Extension set (EXTS)

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

4.1.2. DL_{CO} sub-study extension set (DLCO EXTS)

The DL_{CO} sub-study extension set includes all subjects in the extension set who have consented to participate in the DL_{CO} sub-study during the extension study ('DLco sub-study' ticked on 'Informed Consent' extension study eCRF). Subjects are summarized in the same study treatment group as in the extension set.

4.1.3. Full analysis set (FAS)

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

4.1.4. Safety set (SAF)

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

4.1.5. DL_{CO} sub-study safety set (DLCO SAF)

The DLCO safety set includes all subjects in the safety set who have consented to participate in the DL_{CO} sub-study during the core study ('DL_{CO} sub-study' ticked on 'Informed Consent' core study eCRF). Subjects are summarized in the same study treatment group as in the safety set.

4.2. Usage of the analysis sets

The EXTS will be used for efficacy and safety analyses of the Extension Analysis Period. The FAS and EXTS will be used for efficacy analyses of the Combined Analysis Period. The SAF will be used for the safety analysis of the Combined Analysis Period in an as-treated approach. The DLCO SAF and the DLCO EXTS will be used for analyses of the DL_{CO} sub-study endpoints on the Combined Analysis Period and in the Extension Analysis Period respectively. Table 6 below provides an overview of analysis set in use for efficacy and safety endpoints. More details are depicted in the respective section.

Table 6: Use of analysis set

Endpoint category	Endpoint	Combine period				Extension period	
		FAS	EXTS	SAF	DLCO SAF	EXTS	DLCO EXTS
Efficacy	ARR	Y	Y			Y	
	Time from core study randomization to first confirmed relapse	Y	Y				
	Duration of relapse		Y			Y	
	Absence of relapse		Y			Y	
	Time from core baseline to 12-week CDA	Y	Y				
	Time from core baseline to 24-week CDA	Y	Y				
	Change from baseline in EDSS		Y			Y	
	Gd+ T1 lesions by visit		Y			Y	
	New or enlarging T2 lesions by visit		Y			Y	
	Cumulative new or enlarging T2		Y			Y	
	CUAL by visit		Y			Y	
	Cumulative CUAL	Y	Y			Y	
	Total Volume of T1 hypointense lesions and the change from baseline		Y			Y	
	Total volume of T2 lesions and the change from baseline		Y			Y	
	Proportion of T1 Gd+ lesions at baseline evolving to PBHs (persistent black holes) at all assessments		Y			Y	
	Percentage change in Brain volume from baseline	Y	Y			Y	
	NEDA status at EOS according to NEDA 3		Y				
	NEDA status at EOS according to NEDA 4		Y				
	Change from baseline in MSFC Z-score		Y			Y	
	Change from baseline in the SDMT score		Y			Y	
	Change from baseline in SF-36v2™ Health Survey		Y			Y	

Table 6: Use of analysis set

Endpoint category	Endpoint	Combine period				Extension period	
		FAS	EXTS	SAF	DLCO SAF	EXTS	DLCO EXTS
	domain and component scores						
Safety	Exposure			Y		Y	
	Adverse Event			Y		Y	
	Laboratory test and the associated abnormal findings			Y		Y	
	Vital signs and the associated abnormal findings			Y		Y	
	ECG and the abnormal findings			Y		Y	
	Pulmonary safety and the associated abnormal findings (except lung diffusing capacity)			Y		Y	
	Diffusing capacity				Y		Y
	eC-SSRS			Y			
Demographic	Demographic		Y				
Disposition	Disposition	Y	Y				

5. STATISTICAL ANALYSES

5.1. General Considerations

5.1.1. Analysis Periods

5.1.1.1. Extension Analysis Period

This period includes all available data collected on or after the date of first intake of ponesimod treatment in the extension study, through the extension EOS for efficacy variables, or the last treatment date in the extension study + 15 days for safety variables.

5.1.1.2. Combined Analysis Period

For efficacy, this period includes all available data from randomization in the core study up to extension EOS for subjects entering the extension, or until the core EOS date for subjects not entering the extension.

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

5.1.1.3. Core Analysis Period

This period is defined for efficacy only. It includes all available data from randomization in the core study up to the core EOS date.

5.1.1.4. Post-treatment analysis Period

This period is defined for post-treatment analyses for certain safety variables. It includes all available data from extension EOT date (defined in Section 5.1.9.3) + 16 days (inclusive) in the extension study up to the extension EOS.

5.1.2. Labels for treatment group

The following labels are used to indicate the subject's core / extension treatment allocations:

- Ponesimod 20 mg / Ponesimod 20 mg
- Teriflunomide 14 mg / Ponesimod 20 mg
- Total

If not otherwise specified, disposition demographic and efficacy analyses will be presented by treatment groups and total using labels “Ponesimod 20 mg / Ponesimod 20 mg”, “Teriflunomide 14 mg / Ponesimod 20 mg” and “Total”. Safety analyses will be presented by treatment groups and total using labels “Ponesimod 20 mg / Ponesimod 20 mg”, “Teriflunomide 14 mg / Ponesimod 20 mg” and “Total”, except the analyses for exposure, treatment-emergent event incidence and adverse events during combined period, that is only presented by “Ponesimod 20 mg / Ponesimod 20 mg” on SAF.

5.1.3. Baseline and change-from-baseline

5.1.3.1. Extension Baseline

The **extension baseline value** for efficacy and safety is the last valid non-missing assessment that is taken on or after EOT visit in the core study, and prior to first study drug intake in the extension study. Records meeting these criteria in both core or the extension database are considered for extension baseline. Consequently, the extension baseline value may be the pre-dose assessment on Day 1 of the extension study, but it may also be the value at any visit from EOT visit of the core study (EOT/FU1/FU2 or unscheduled visits). In particular, laboratory parameters are not scheduled to be assessed on Day 1 of the extension study, and so (unless there is an eligible unscheduled assessment) the extension baseline for laboratory parameters will be the last value as above observed in the core study.

Specifically, for MRI and PFT variables only, in case of available assessments on extension Day 1, these should be considered as valid assessments for the extension baseline derivation, even if taken after first dose of treatment on Day 1.

In case of multiple ECG or vital signs assessments (for the same subject, visit, parameter) in the core study visits (EOT/FU1/FU2 or unscheduled visits) that should be considered for the purpose of the baseline value derivation, the average of the results should be taken for use as baseline record.

The derived "extension baseline" value is considered a visit and is displayed in the Combined Analysis Period by visit tables, with corresponding change from core baseline to "extension baseline".

5.1.3.2. Core Baseline

The **core baseline value** for efficacy is defined as the last non-missing value recorded before or on randomization in the core study for each endpoint and each subject individually.

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

These variables are used as derived in the core study and are not re-derived for the extension analysis.

On days where study drug is initiated or re-initiated, the pre-dose assessment for that day is defined as the last non-missing assessment prior to the study drug intake on that day. The pre-dose assessment on Day 1 of the Analysis Period (if available) is identical to the corresponding baseline for that Analysis Period. In case of (partially) missing assessment dates/times, or for assessments reported on Day 1 (or day of re-initiation) with recorded assessment time contradicting the time point label (e.g., pre-dose, 2 hours post-dose), the nominal visit and time point labels will be used to determine whether an assessment is considered for baseline (e.g., a blood pressure measurement with an assessment date on Day 1 but with a missing assessment time or an assessment time prior to the reported time of first study drug intake will not be considered for baseline if reported under the time point "2 hours post-dose" in the eCRF; however, it will be considered if reported as "Pre-dose" in the eCRF).

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

Absolute change from baseline is defined as post-baseline value minus baseline value, i.e., a positive sign indicates an increase compared to baseline. A percentage change from baseline is defined as the absolute change from baseline divided by the baseline value (if the baseline value is > 0) and then multiplied by 100. Absolute and percent change from both core and extension baseline is calculated and stored for all continuous safety data.

5.1.4. Visit Windows

For the extension visits, visit based assessments are generally summarized according to the nominal visit, except for subjects prematurely discontinuing study treatment, which are re-assigned following the visit windowing described in Section 5.1.10. Scheduled nominal visits, e.g., Week XX, are identified based on the eCRF recorded nominal visit label. Note that the eCRF allows for considering a visit under multiple visit labels, e.g., a Follow-up 1 or a Relapse visit can be considered in addition a Week XX visit. This second visit label is collected on the Visit Summary eCRF under 'Corresponding visit'. In selecting results for a nominal scheduled visit both visit labels are considered. Priority is given to the first visit label, then to the second visit label. If no result is available at a scheduled nominal visit, premature EOT remapping is applied [Section 5.1.10].

In addition, to incorporate the extended 288-week treatment period for Ukraine subjects impacted by regional crisis, additional visits (Extension Visit 24, Visit 25, Visit 26, Visit 27) will be added. The Extension Visit 23-Week 240 contains data from regional crisis-impacted Ukraine subjects who attend this visit, as well as the Extension EOT visit data of other non-impacted subjects who complete study treatment until week 240. The Extension EOT visit contains Visit 27- Week 288 visit data from regional crisis-impacted Ukraine subjects, as well as the Extension EOT visit data of other non-impacted subjects (including subjects who completed study treatment at Week 240 and subjects who switched to commercial ponesimod at early weeks and subjects who discontinued study treatment prematurely at earlier weeks).

Extension Analysis Period

Summaries by visit are presented by extension baseline (derived), and further scheduled nominal visits up to Week 240 (or up to Week 288 for Ukraine subjects). Generally, by-visit tables tabulate the extension baseline and nominal and derived visits as follows:

- Extension baseline (Note: This is not a nominal visit but the derived baseline [see Section 5.1.3.1])
- Extension Visit 2 - Week 2
- Extension Visit 3 - Week 4
- Extension Visit 4 - Week 12
- Extension Visit 5 - Week 24
- Extension Visit 6 - Week 36
- Extension Visit 7 - Week 48
- Extension Visit 8 - Week 60
- Extension Visit 9 - Week 72
- Extension Visit 10 - Week 84
- Extension Visit 11 - Week 96
- Extension Visit 12 - Week 108
- Extension Visit 13 - Week 120
- Extension Visit 14 - Week 132
- Extension Visit 15 - Week 144
- Extension Visit 16 - Week 156
- Extension Visit 17 - Week 168
- Extension Visit 18 - Week 180
- Extension Visit 19 - Week 192
- Extension Visit 20 - Week 204
- Extension Visit 21 - Week 216
- Extension Visit 22 - Week 228
- Extension Visit 23 - Week 240
- Extension Visit 24 – Week 252 (This is applicable for Ukraine subjects only)
- Extension Visit 25 – Week 264 (This is applicable for Ukraine subjects only)
- Extension Visit 26 – Week 276 (This is applicable for Ukraine subjects only)
- Extension Visit 27 – Week 288 (This is applicable for Ukraine subjects only)
- Extension EOT Visit
- Extension EOS Visit

Premature EOT visits and EOT visits from subjects who switched to commercial ponesimod are mapped to and summarized within a scheduled visit, following the window approach described in Section 5.1.10; they will not be summarized as "Visit 23 - Week 240" (or "Visit 27 – Week 288, for impacted Ukraine subjects) unless they are mapped to this visit using the approach described in Section 5.1.10.

Combined Analysis Period

Summaries by visit are presented by Core Baseline (derived), and further scheduled nominal core visits up to Core Week 108, derived Follow-up visits (FU1, FU2), Extension Baseline and further scheduled nominal extension visits up to Extension Week 240 (or Extension Week 288, for impacted Ukraine subjects). Generally, by visit tables tabulate the baselines and nominal and derived visits as follows:

- Core Baseline (Note: This is not a nominal visit but the derived baseline, see Section 5.5.1 of the core CSR SAP)
- Core Visit 4 - Week 2
- Core Visit 5 - Week 4
- Core Visit 6 - Week 12
- Core Visit 7 - Week 24
- Core Visit 8 - Week 36
- Core Visit 9 - Week 48
- Core Visit 10 - Week 60
- Core Visit 11 - Week 72
- Core Visit 12 - Week 84
- Core Visit 13 - Week 96
- Core Visit 14 - Week 108
- Core Day-15 follow-up (derived)
- Core Day-30 follow-up (derived)
- Extension baseline (Note: This is not a nominal visit but the derived baseline for the extension study [see Section 5.1.3.1])
- Extension Visit 2 - Week 2
- Extension Visit 3 - Week 4
- Extension Visit 4 - Week 12
- Extension Visit 5 - Week 24
- Extension Visit 6 - Week 36
- Extension Visit 7 - Week 48
- Extension Visit 8 - Week 60
- Extension Visit 9 - Week 72
- Extension Visit 10 - Week 84
- Extension Visit 11 - Week 96
- Extension Visit 12 - Week 108
- Extension Visit 13 - Week 120
- Extension Visit 14 - Week 132
- Extension Visit 15 - Week 144
- Extension Visit 16 - Week 156
- Extension Visit 17 - Week 168

- Extension Visit 18 - Week 180
- Extension Visit 19 - Week 192
- Extension Visit 20 - Week 204
- Extension Visit 21 - Week 216
- Extension Visit 22 - Week 228
- Extension Visit 23 - Week 240
- Extension Visit 24 – Week 252 (This is applicable for Ukraine subjects only)
- Extension Visit 25 – Week 264 (This is applicable for Ukraine subjects only)
- Extension Visit 26 – Week 276 (This is applicable for Ukraine subjects only)
- Extension Visit 27 – Week 288 (This is applicable for Ukraine subjects only)
- Extension EOT Visit
- Extension EOS Visit.

5.1.5. Analysis Strategy

5.1.5.1. Analysis strategy for efficacy

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

Following 108 weeks of treatment with either ponesimod 20 mg or teriflunomide 14 mg in the core study, it must be assumed that the two populations will not be similar in terms of baseline characteristics at the start of the extension study. With this limitation acknowledged, specific efficacy endpoints will be analyzed only for the extension study, split by core study randomized treatment and overall. Section 4.2 details which efficacy endpoints will be analyzed for the combined core and extension studies, which additionally will be analyzed for the extension study, and which will be analyzed for the core study.

5.1.5.2. Analysis strategy for safety

The long-term safety of ponesimod and the changes in safety in teriflunomide 14 mg subjects switching to ponesimod 20 mg will be investigated by summarizing the combined data from both the core and extension studies. Subjects will be analyzed according to the actual treatment they received in the core study (as derived in the core study ADaMs and not re-derived for the extension study analysis). Cumulative data such as AEs and SAEs will only be summarized for subjects initially treated with ponesimod 20 mg in the core study to allow a long-term assessment of up to 6 years. To assess trends over time and to assess the switch from teriflunomide 14 mg to ponesimod 20 mg, the analysis of the change from baseline for safety endpoints will be assessed by core study treatment group and by visit from core baseline up to last treatment + 15 days plus the EOS visit.

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

5.1.6. Definition of treatment-emergent

A safety assessment (ECG, vital signs, laboratory, etc.) is considered treatment-emergent relative to the Analysis Period, and a safety event (AE, serious adverse event [SAE], Death, etc.) is considered treatment-emergent relative to the Analysis Period, if the assessment date is on or after the study treatment start date in the Analysis Period and prior to or on the study treatment end date + 15 days (inclusive). In case of planned pregnancy interruption, a safety assessment is considered treatment emergent relative to the Analysis Period if one of the following conditions is met:

- the assessment date is on or after the study treatment start date in the Analysis Period and prior to or on the last study drug intake date prior to pregnancy interruption + 15 days (inclusive)
- the assessment date is on or after the re-initiation date of study treatment after planned pregnancy and prior to or on the End of Treatment (EOT) date + 15 days (inclusive).

In case of multiple planned pregnancies interruptions, the above definition will be adapted, that any assessment in the following interval is not considered as treatment emergent: date between the last study drug intake date prior to each pregnancy interruption + 15 days (inclusive) and the re-initiation date of study treatment after each planned pregnancy (excluded).

If both the assessment date/time and the date/time of study treatment start (or of re initiation after planned pregnancy) are available, only events with date/time on or after the date/time of study treatment start (or of re initiation after planned pregnancy) are considered to be treatment emergent. In case of (partially) missing assessment dates/times, or for assessments on treatment Day 1 with reported assessment time contradicting the time point label, the nominal visit and time point labels will be used to determine whether an assessment is considered as treatment-emergent or not. For example, a blood pressure measurement with an assessment date on Day 1 but a missing assessment time or an assessment time after the time of first study drug intake, will not be considered treatment emergent if reported under the time point "Pre-dose" in the eCRF, however it will be considered treatment-emergent if reported as "2 hours post-dose" in the eCRF.

Missing or partially missing onset or occurrence dates are imputed as described in Section 6.13. If both the onset/occurrence date/time and the date/time of study treatment start are available, only events with date/time on or after the date/time of study treatment start are considered to be treatment emergent.

For subjects who are currently on an interruption for planned pregnancy on the database lock date, study treatment end date for the above definitions is taken as the date associated with the study drug record on the "Maintenance" eCRF page of the extension study, where reason for treatment end = "Temporarily interrupted due to planned pregnancy as defined in the protocol".

5.1.7. Study Day

5.1.7.1. Extension Study Day

For all data analyses on the Extension Analysis Period described in this SAP, the first day of study drug intake in the extension study is defined as Extension study Day 1. The day prior to study drug start date in the extension study is defined as Extension study Day minus1; therefore there is no study Day 0. Study days of dates prior to Extension Day 1 are calculated as 'date minus extension

study drug start date', and study days of date after Extension Day 1 are calculated as 'date minus extension study drug start date + 1'.

5.1.7.2. Combined Study Day

For all data analyses on the Combined Analysis Period Study, **Day** refers to the number of days elapsed since randomization date plus 1 (e.g., Combined Study Day 1 is the day of randomization). For dates prior to randomization, the combined study day is the negative number of days elapsed between the date under consideration and the day of randomization. Therefore, there is no study Day 0.

5.1.8. Coding

The following coding dictionaries will be used:

- AEs will be coded using MedDRA version 26.0;
- Medications (previous and concomitant) will be coded using the WHO-Drug Dictionary version March 2023 B3G .

5.1.9. Dates

The following variables for the core study are used as derived in the core study, and are not re-derived for the extension analysis:

- Core study treatment start date;
- Core EOT / study treatment end date;
- Core EOS date;
- Core screening date;
- Core Study Day;
- Core Treatment Day.

5.1.9.1. Extension enrollment date

The extension enrollment date is the date when the subject signed the Informed Consent Form and is taken directly from RAVE.

5.1.9.2. First study drug intake date/time in extension study

The first study drug intake date/time in the extension study is taken as the earliest intake documented in any of the following eCRF sections: 'Study Drug Administration - Day 1 / Re-Initiation', 'Study Drug Administration', Study drug administration - Re-initiation after planned pregnancy', 'Up-titration Summary', 'Up-titration Ponesimod', or 'Maintenance Ponesimod'. This is derived in the SDTM.DM dataset as the 'Date/Time of first study treatment' (RFXSTDTC).

5.1.9.3. Extension End-of-Treatment (EOT) date

If a subject is considered to have prematurely discontinued treatment in the extension study, the date of last study drug intake in the extension study corresponds the end of treatment date, derived as:

- The maximum of [End date up-titration on eCRF page 'Up-titration Summary', Treatment end date on eCRF page 'Up-titration Ponesimod'; Treatment end date on eCRF page 'Maintenance

Ponesimod']; this is derived in the SDTM.DM dataset as the 'Date/Time of last study treatment' (RFXENDTC);
- If missing based on the above, then the treatment termination date as recorded on the RAVE primary form is taken. This is derived in the SDTM.DS dataset as 'Start Date/Time of Disposition Event' (DSSTDTC) where the 'Subcategory for Disposition Event' (DSSCAT) is 'TREATMENT TERMINATION' and the 'Standardized Disposition Term' (DSDECOD) is not 'COMPLETED'.

If a subject is considered to have completed treatment as per protocol, the date of last extension study drug intake corresponds to the minimum of:

- Treatment end date on extension study eCRF page 'Maintenance Ponesimod' corresponding to the record "Completed as per protocol"; this is derived in the SDTM.DM dataset as the 'Date/Time of last study treatment' (RFXENDTC);
- If missing based on the above, then the treatment termination date as recorded on the RAVE primary form is taken. This is derived in the SDTM.DS dataset as 'Start Date/Time of Disposition Event' (DSSTDTC) where the 'Subcategory for Disposition Event' (DSSCAT) is 'TREATMENT TERMINATION' and the 'Standardized Disposition Term' (DSDECOD) is 'COMPLETED';

5.1.9.4. Extension End-of-Study (EOS) date

If a subject is considered to have completed the extension study per protocol, the extension End-of-Study (EOS) date is defined as the date on the end of extension study eCRF page. This is derived in the SDTM.DM dataset as the 'Subject Reference End Date/Time' (RFENDTC). If this date is missing, the last recorded visit on the eCRF is considered as the extension EOS date. If this date is also missing, the date of last contact during the extension study is taken, derived in the SDTM.DS dataset as 'Start Date/Time of Disposition Event' (DSSTDTC) where the 'Standardized Disposition Term' (DSDECOD) is not 'LOST TO FOLLOW-UP'.

5.1.10. Re-assignment of EOT visits / visit windowing

For core study, analysis visits are used as derived in the core study and are not re-derived for the extension analysis.

Extension study

If a subject discontinued study drug prematurely, as defined in Section 5.4.1.1.5, the EOT visit will be considered as the premature EOT visit. This rule also applies to subjects who are treatment completers but switched to commercial ponesimod prior to Week 240.

For all parameters unless stated below: For subjects who discontinued study drug prematurely with available premature EOT visit and subjects who switched to commercial ponesimod, the visit may be re-assigned to a scheduled visit as follows:

- If a result is missing for a scheduled visit, it can be replaced with a result from a premature EOT visit available in the respective visit window [see Table 7].

Table 7: Premature End-of-Treatment remapping

Visit window	Nominal value Day	Lower limit for Day	Upper limit for Day
Week 2	15	2	22
Week 4 (Except LB)	29	23	70
Week 12 (Except LB)	85	71	126
Week 4* (For LB only)	29	23	42
Week 8* (For LB only)	57	43	70
Week 12* (For LB only)	85	71	98
Week 16* (For LB only)	113	99	126
Week 20* (For LB only)	141	127	154
Week 24* (For LB only)	169	155	210
Week 24 (Except LB)	169	127	210
Week 36	253	211	294
Week 48	337	295	378
Week 60	421	379	462
Week 72	505	463	546
Week 84	589	547	630
Week 96	673	631	714
Week 108	757	715	798
Week 120	841	799	882
Week 132	925	883	966
Week 144	1009	967	1050
Week 156	1093	1051	1134
Week 168	1177	1135	1218
Week 180	1261	1219	1302
Week 192	1345	1303	1386
Week 204	1429	1387	1470
Week 216	1513	1471	1554
Week 228	1597	1555	1638
Week 240	1681	1639	Open end** / 1722***
Week 252***	1765	1723	1806
Week 264***	1849	1807	1890
Week 276***	1933	1891	1974
Week 288***	2017	1975	Open end

Day refers to treatment day, i.e., days from extension study treatment start.
* These analysis windows applied for Laboratory (LB) assessments only, as described
** This applied for subjects not impacted by regional crisis
*** This applied for Ukraine subjects with extended treatment period and additional visits

MRI and C-SSRS: For MRI and C-SSRS measurements visit windowing of premature EOT visits is conducted using ± 3 months around the target day (Week 48: Day 246 to Day 428; Week 96: Day 582 to Day 764; Week 144: Day 918 to Day 1100; Week 192: Day 1254 to Day 1436; Week 240: ≥ Day 1590 for subjects who are not impacted by extended study duration, or Day 1590 to 1772 for Ukraine subjects with extended study duration; Week 288: ≥ Day 1926 (this applies for Ukraine subjects with extended study duration due to regional crisis) Note: as planned pregnancy visits are considered scheduled MRIs for analysis, they are also re-mapped using the same rules.

MSFC and SDMT: For premature EOT visits which occurred before day 245, the remapping rules follow the same in Table 7. For premature EOT visits and the EOT visits from patients who switched to commercial ponesimod, the remapping of EOT visits follows the same rule as in MRI and C-SSRS.

SF-36: For SF-36 questionnaires collected via an electronic device visit windowing is applied as a general process. To ensure a more precise visit labels, questionnaires based on dates will be assigned to the visits as following. If multiple questionnaires are available, the one closest to target is selected. The visit windowing will also be applied to premature EOT assessments.

Week 24 -- Target: Day 169; Range: Day 1 to Day 252;
Week 48 -- Target: Day 337, Range: Day 253 to Day 504;
Week 96 -- Target: Day 673, Range: Day 505 to Day 840;
Week 144 -- Target: Day 1009, Range: Day 841 to Day 1176;
Week 192 -- Target: Day 1345, Range: Day 1177 to Day 1512;
Week 240 -- Target: Day 1681, Range: ≥ Day 1513 for subjects who are not impacted by extended study duration, or Day 1513 to 1848 for Ukraine subjects with extended study duration;
Week 288 -- Target: Day 2017, Range: ≥ Day 1849 (this applies for Ukraine subjects with extended study duration due to regional crisis).

5.2. Subject Dispositions

All disposition summaries will be in a n (%) format, i.e. a frequency count with accompanying percentage.

5.2.1. Definition of disposition variables

For all disposition variable definitions for the core study (such as subjects randomized, subjects treated, subjects discontinued treatment/study, etc.), refer to the core study SAP. These variables will be used as derived in the core.

5.2.1.1. Enrolled subjects in the extension study

Subjects enrolled are those subjects who have signed the Informed Consent Form for the extension study (per the 'Informed Consent' eCRF module).

5.2.1.2. Treated subjects in the extension study

A subject is considered treated if they received at least one dose of ponesimod in the extension study and signed the informed consent form for the extension study.

5.2.1.3. Subjects completing the core treatment and study as per protocol and not entering the extension

A subject is considered to meet these criteria if they completed treatment and study in the core per protocol (according to the corresponding definition included in the core study SAP) and did not subsequently enter the extension study.

5.2.1.4. Subjects prematurely discontinued from treatment in the extension

See definition in Section 5.4.1.1.

5.2.1.5. Subjects completed study in the extension as per protocol

See definition in Section 5.4.1.1.

5.2.1.6. Subjects prematurely discontinued from study in the extension

A subject is considered to have prematurely discontinued from study in the extension if a reason for study stopped and a date of discontinuation ('Date of last successful contact') is reported in the eCRF page "Study Discontinuation". See also Section 5.4.1.1.8 for more details.

5.2.1.7. Subjects prematurely discontinued from treatment or study in the extension

Subjects are considered to have prematurely discontinued from treatment or study in the extension if they prematurely discontinued from treatment in the extension, or they prematurely discontinued from study in the extension , or both.

5.2.1.8. Subjects interrupted treatment for planned pregnancy in the extension

Subjects who interrupted treatment for planned pregnancy in the extension have a record in the extension eCRF labeled 'Maintenance Ponesimod' form with reason for treatment end given as 'Temporarily interrupted due to planned pregnancy as defined in the protocol' and without first study drug intake date in the extension eCRF 'Study drug administration- Re-initiation after planned Pregnancy' form. The duration of treatment interruption due to planned pregnancy is defined as [min (EOS date, end date of pregnancy interruption) – Start date of pregnancy interruption + 1]. Duration of treatment interruption due to planned pregnancy is excluded from all definitions of exposure durations and compliance with study treatment.

5.2.1.9. Last study drug intake date prior to pregnancy interruption date

The last study drug intake date prior to pregnancy interruption is taken as the date associated with the study drug record on the 'Maintenance Ponesimod' eCRF page of the extension study, where reason for treatment end = 'Temporarily interrupted due to planned pregnancy as defined in the protocol'.

5.2.1.10. Time in study

The following variables are defined for time in study during the **Extension Analysis Period**:

Time in extension study (months) is defined as the time elapsed between (extension enrollment date and the date of extension EOS visit +1) × 12 / 365.25.

In addition, the duration of time in the extension study for each subject is categorized as follows:

- ≤ 6 months;
- > 6 months and ≤ 12 months;
- > 12 months and ≤ 18 months;

- > 18 months and ≤ 24 months;
- > 24 months and ≤ 30 months;
- > 30 months and ≤ 36 months;
- > 36 months and ≤ 42 months;
- > 42 months and ≤ 48 months;
- > 48 months and ≤ 54 months;
- > 54 months and ≤ 60 months;
- > 60 months

The following variables are defined for time in the combined studies during the **Combined Analysis Period**:

Time in combined core/extension studies (months) is defined as the time elapsed between date of randomization in the core study and the core EOS visit (for subjects who did not enter the extension study) or extension EOS visit date (for subjects who entered the extension study) + 1) × 12 / 365.25.

The potential interruption between the core study and the extension study is ignored for the duration on combined studies variable derivation.

In addition, the time in combined core/extension studies for each subject is categorized as follows:

- ≤ 6 months;
- > 6 months and ≤ 12 months;
- > 12 months and ≤ 18 months;
- > 18 months and ≤ 24 months;
- > 24 months and ≤ 30 months;
- > 30 months and ≤ 36 months;
- > 36 months and ≤ 42 months;
- > 42 months and ≤ 48 months;
- > 48 months and ≤ 54 months;
- > 54 months and ≤ 60 months;
- > 60 months and ≤ 66 months;
- > 66 months and ≤ 72 months;
- > 72 months and ≤ 78 months;
- > 78 months and ≤ 84 months;
- > 84 months

5.2.2. Analysis of subject disposition

5.2.2.1. Subject disposition

Frequency counts and percentages for all the following variables will be presented in a summary table by core treatment group and overall based on the FAS:

Core study:

- Subjects randomized in the core study;
- Subjects treated in the core study;
- Subjects prematurely discontinued treatment in the core study;

- Subjects completed treatment in the core study;
- Subjects prematurely discontinued from the core study;
- Subjects completed the core study per protocol;
- Subjects completed the core treatment and study per protocol;
- Subjects completed the core treatment and study as protocol and did not enroll in the extension study.

Extension study:

- Subjects enrolled in the extension study;
- Subjects treated in the extension study;
- Subjects prematurely discontinued treatment in the extension study;
- Subjects interrupted treatment for planned pregnancy;
- Subjects completed treatment in extension study (further split into: "Completed as per protocol" or "Approved Drug Available For Indication");
- Subjects prematurely discontinued from the extension study;
- Subjects completed the extension study;
- Subjects completed the extension treatment and study per protocol;
- Subjects prematurely discontinued from treatment or study in the extension study.

The denominator for percentages for core study variables above will be based on the number of randomized subjects in the core study. The denominator for percentages for the extension study variables above will be based on the number of enrolled subjects in the extension study (except for the percentage of 'enrolled in the extension study', which will be based on the number of randomized subjects in the core study).

A subject disposition flow-chart will be produced including all the disposition information listed above.

The number and percent of subjects in the EXTS are summarized by country and site, by core study treatment group, and overall.

All subject disposition variables will be presented in a dedicated listing.

5.2.2.2. Study treatment and study discontinuation

Frequency counts and percentages for all subjects who discontinued treatment, all subjects who discontinued study, reasons for discontinuation of treatment, and reasons for discontinuation of study, will be presented in a summary table which will be stratified by core study treatment and overall, for the Extension Analysis Period using the EXTS.

A KM plot for time to premature treatment discontinuation will be produced for the Extension Analysis Period on the EXTS. Subjects that complete the study treatment will be censored at the date of study treatment completion.

Reasons for treatment discontinuation in the extension and reasons for extension study discontinuation will be presented in separate listings.

5.2.3. Analysis sets

The number and percentage of subjects in each analysis set are summarized in a table, by core treatment group, and overall. Percentages are based on the FAS.

A listing of subject membership in the different analysis sets will be created.

5.2.4. Time in study

Time in study will be analyzed, by core treatment group and overall, separately for each of the following Analysis Periods:

- Extension Analysis Period (using EXTS);
- Combined Analysis Period (using EXTS).

Time on study will be summarized descriptively, separately for Combined and Extension Analysis Period as follows:

- Time in study (months): descriptive statistics;
- Time in study (months) by category (cumulative): frequency counts and percentages.

A KM plot for time to end of extension study will be produced for the Extension Analysis Period on the EXTS. Subjects complete study will be censored at the date of study completion.

Time on study information will be included in subject disposition listing(s).

5.3. Analysis of efficacy variables

5.3.1. Definition of Endpoint(s)

5.3.1.1. Relapse-related variables

5.3.1.1.1. Annualized Relapse Rate (ARR)

The ARR is defined as the number of relapses per subject-year.

The ARR will be calculated for both confirmed relapses and for all relapses, for both the Combined and the Extension Analysis Periods.

To evaluate the ARR for both the Combined and the Extension Analysis Periods, the following variables will be derived per subject and Analysis Period:

- Number of all relapses (confirmed and unconfirmed) from start date of the Analysis Period up to the end of Analysis Period;
- Number of confirmed relapses from start date of the Analysis Period up to end of analysis;
- Length of observation expressed in years, defined as: (Analysis Period end date − Analysis Period start date of + 1) in days, divided by 365.25.
- Logarithm of the length of observation during Analysis Period as derived above.

Additionally, for the Core Analysis Period, the following ARR related variables from the core study will be included in the ADaM dataset as derived in the core study:

- Number of confirmed relapses from date of randomization in the core up to core EOS;
- Length of observation during the core study expressed in years, defined as: [core EOS date − date of randomization in the core + 1] in days, divided by 365.25;

Additionally, the number of confirmed relapses and length of observation time will be derived per 24-week time period, separately for the Core and the Extension Analysis Periods, for the following time periods:

Core Analysis Period

- Core Week 0-24: ≥ Core Day 1 ≤ Core Day 168;
- Core Week 24-48: > Core Day 168 ≤ Core Day 336;
- Core Week 48-72: > Core Day 336 ≤ Core Day 504;
- Core Week 72-96: > Core Day 504 ≤ Core Day 672;
- Core Week 96-EOS: > Core Day 672 ≤ Core EOS;

Extension Analysis Period

- Extension Week 0-24: ≥ Extension Day 1 ≤ Extension Day 168;
- Extension Week 24-48: > Extension Day 168 ≤ Extension Day 336;
- Extension Week 48-72: > Extension Day 336 ≤ Extension Day 504;
- Extension Week 72-96: > Extension Day 504 ≤ Extension Day 672;
-
- Extension Week 96-120: > Extension Day 672 ≤ Extension Day 840;
- Extension Week 120-144: > Extension Day 840 ≤ Extension Day 1008;
- Extension Week 144-168: > Extension Day 1008 ≤ Extension Day 1176;
-
- Extension Week 168-192: > Extension Day 1176 ≤ Extension Day 1344;
- Extension Week 192-216: > Extension Day 1344 ≤ Extension Day 1512;
- Extension Week 216-Extension EOS: > Extension Day 1512 ≤ Extension EOS;

Core Day 1 is the date of randomization in the core study. Extension Day 1 is the date of first ponesimod administration in the extension study. In the event that a subject has their core EOS visit date recorded after their extension treatment start date, the extension treatment start date will be considered to be Extension Day 1 and the core EOS will be considered to be the extension treatment start date minus 1 day.

For both the core and extension studies, the number of relapses is derived according to the number of relapses entered on the eCRF module ‘Relapse Summary’. Whether a relapse is confirmed is according to the treating neurologist / principal investigator, i.e., according to the question ‘Relapse meeting the criteria for a confirmed relapse?’ on eCRF module ‘Relapse Summary’.

Also based on the eCRF module ‘Relapse Summary’, each reported relapse episode is assessed as being treated with corticosteroids (as per eCRF question ‘Treatment of relapse with corticosteroids?’) and as leading to hospitalization (as per eCRF question ‘Did the MS relapse require hospitalization for reasons other than administration of IV corticosteroids?’). These relapse

qualifiers are solely derived from eCRF module 'Relapse Summary', i.e., irrespective of corresponding documentation in eCRF module 'Corticosteroids for Treatment of Relapse'.

5.3.1.1.2. Time to first (confirmed) relapse

The time to first (confirmed) relapse is defined as:

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

Time to first (confirmed) relapse is calculated over the Combined Analysis Period only. The following censoring rules are applied:

- Subjects who entered the extension study and remained free of relapses will be censored at the extension EOS date;
- Subjects who prematurely discontinued from extension study and remained free of relapses will be censored at the date of last contact.
- Subjects who did not enter the extension and ended the core study free of relapses will be censored at the core study EOS date;
- Subjects who prematurely discontinued from core study and remained free of relapses will be censored at the date of last contact.

For censored subjects, the time is defined as EOS − date of randomization + 1 in days.

5.3.1.1.3. Duration of (confirmed) relapse

Duration of (confirmed) relapse (days) is derived as (confirmed) relapse end date − relapse start date + 1 day. Duration of (confirmed) relapse will be set to be missing if either start date or end date is missing or incomplete.

5.3.1.2. MRI-related variables

MRI data are read centrally by Medical Image Analysis Center (MIAC) and provided to the sponsor. The derivation of the MRI endpoints is according to the visit identification in the MIAC database.

In the core study, MRI scans are scheduled at Baseline, at the Week 60 Visit, and the Week 108 (EOT) Visit. For subjects prematurely discontinuing treatment, an additional premature EOT visit MRI is scheduled. In addition, unscheduled MRI scans may be conducted any time. MRI scans are used as mapped in the core study, as described in the core study SAP.

In the extension study, MRI scans are scheduled at Week 48, Week 96, Week 144, and Week 192 Visits, and at the Week 240 EOT (for Ukraine subjects in addition at Week 288 EOT) Visit. In addition, unscheduled MRI scans may be conducted any time including at planned pregnancy interruption and re-initiation visits.

MRI variables are based on the result from the corresponding nominal visit (or from a re-mapped premature EOT or pre-planned pregnancy visit.

5.3.1.2.1. T1 Gd+ lesions

The following variables are derived at each scheduled visit during the Combined Analysis Period:

- **Total number of T1 Gd+ lesions**, derived as:
  Number of new T1 Gd+ lesions (T1GdNewR) + number of persisting T1 Gd+ lesions (T1GdR);
- **Total number of T1 Gd+ lesions**, categorized (0, 1, 2, 3, 4, 5, 6-10, 11+).

In addition, the following analyses will be conducted:

- The **cumulative number of Gd+ T1 lesions from core baseline to extension EOS** and corresponding number of scans included will be used as derived.
- **Absence of Gd+ T1 lesions at each visit:** 'Gd+ T1 lesions at each visit' are considered 'absent', if the number of Gd+ T1 lesions at each visit is zero. If > 0 they are considered 'present'. This applies to nominal visit collected in the CRF.
- **Absence of Gd+ T1 lesions from Core baseline until extension EOS:** Absence of new Gd+ T1 lesions from Core baseline to extension EOT (including all unscheduled scans) is defined 'absent' if the 'number of new Gd+ T1 lesions' at all post-baseline MRI scans up to the extension EOS is zero. This includes all scheduled and all unscheduled visits. If > 0 at any visit it is considered 'present'. The corresponding 'Number of MRI scans' and time to last MRI scan are derived. If no MRI result at the visit is available (based on visit window), the information is considered missing (for lesion free subjects).
- **Total volume of T1 hypointense lesions and the change from baseline**: Total volume of T1 hypointense lesions (mm3) (variable T1BHVOL) is recorded by the central reader at each visit. The change from Core baseline is derived as the change from total volume of T1 hypointense lesions at Core study Visit 2-Baseline. The change from Extension baseline is derived as the change from last available record of total of T1 hypointense lesions prior to Extension Baseline.
- **Proportion of Gd+ T1 lesions at Core Baseline evolving to persistent black holes (PBHs):** It is the proportion (%) of 'Number of T1 hypointense lesions (persistent black holes) evolved from T1 Gad.-enhancing lesion at V2 - Baseline core study' (variable T1BHV2C) at each scan visit out of the 'Number of Gd+ T1 lesions at Core baseline'.

Note: Gd+ T1 lesions are assumed to not enhance for more than 12 weeks. This requires handling of data as follows:

- *If at a visit, number of persisting T1 Gd+ lesions are not recorded, the number of Gd+T1 lesions is the number of new T1 Gd+ lesions. Rationale: As per central reader processes persisting T1 Gd+ lesions are not assessed for subjects with scheduled MRIs scheduled more than 12 weeks apart.*
- *If at an MRI scan which is >12 weeks (84 days) since the last previous scheduled MRI scan a persisting lesion count > 0 is recorded, these persisting lesions are considered implausible and therefore not to be considered in derivations of total Gd+ T1 counts.*

5.3.1.2.2. New or enlarging T2 lesions

The following variables will be evaluated at each visit:

- **Total number of new or enlarging T2 lesions (relative to previous visit)**, derived as:
  Number of new or enlarging T2 lesions without gadolinium-enhancement (T2new_R) + new or enlarging T2 lesions with gadolinium-enhancement (T2newGd_R);
- **Total number of new or enlarging T2 lesions (relative to previous visit) categorized** (0, 1–5, 6–10, 11+);
- **Cumulative new or enlarging T2 lesions from core baseline** up to each visit up to extension EOS. Cumulative new or enlarging T2 lesions will not be derived if any post-baseline record is missing with a reason of "Dependent evaluation missing: Reference required for evaluation is not available (missing or rejected)" in the SDTM variable MO.MOREASND.

Where "new" refers to last prior available scheduled visit (note: planned pregnancy visits are considered scheduled MRIs for analysis), and specifically for evaluations at extension study Visit 7, results are compared to Visit 14 EOT from the core study.

In addition, the follow cumulative variables are derived:

The **cumulative number of new or enlarging T2 lesions from core baseline to extension EOS** is derived as the sum of number of the sum of total number of new or enlarging T2 lesions (as derived above) at all post-baseline MRI at all post-core baseline MRI scans up to the extension EOT MRI visit. This includes premature EOT scans if available, and unscheduled scans only if it is the last available scan for the subject.

The time up to the last MRI (years) included in the above is derived as = Date of last MRI considered in derivation − core randomization date + 1 divided by 365.25 days.

Similarly, the **cumulative number of new or enlarging T2 lesions from extension baseline to extension EOS** is derived as described above, together with the time, where time is relative to enrollment in the extension study.

If the baseline MRI is missing, new or enlarging T2 lesions as compared to baseline cannot be assessed and consequently the endpoint is considered missing. The baseline MRI is considered missing if presence of T1 Gd+ lesions at baseline is missing. The following analyses will be conducted as well:

- **Absence of new or enlarging T2 lesions at each visit:** 'New or enlarging T2 lesions' are considered 'absent', if the number of New or enlarging T2 lesions at each visit is zero. If > 0 they are considered 'present'. This applies to nominal visit collected in the CRF.
- **Absence of new or enlarging T2 lesions from Core baseline until extension EOS:** Absence of new or enlarging T2 lesions from Core baseline to extension EOT (including all unscheduled scans) is defined 'absent' if the 'number of new or enlarging T2 lesions' at all post-baseline MRI scans up to the extension EOS is zero. This includes all scheduled and all unscheduled visits. If > 0 at any visit it is considered 'present'. The corresponding 'Number of MRI scans' and time to last MRI scan are derived. If no MRI result at the visit is available (based on visit window), the information is considered missing (for lesion free subjects).

- **Total volume of T2 lesions and the change from baseline**: Total volume of T2 lesions (mm3) (variable T2VOL) is recorded by the central reader at each visit. The change from Core baseline is derived as the change from total volume of T2 lesions at Core study Visit 2-Baseline. The change from Extension baseline is derived as the change from last available record of total volume of T2 lesions prior to Extension Baseline.

5.3.1.2.3. Combined unique active lesions (CUAL) and cumulative CUAL

The number of combined unique active lesions (CUAL) at each scan visit is defined as the sum of new T1 Gd+ lesions (T1GdNew_R) and new or enlarging T2 lesions without gadolinium-enhancement (T2New_R) at each scan visit. Categorization of CUAL at each visit is (0, 1–5, 6–10, 11-15, 16-20, 21-25, 26+).

The cumulative number of CUAL from core baseline to extension EOS is defined as the sum of new T1 Gd+ lesions (T1GdNew_R) and new or enlarging T2 lesions without gadolinium-enhancement (T2New_R) (i.e., without double-counting the lesions) at all post-baseline MRI visits up to the extension EOS. This includes premature EOT scans, if available, and unscheduled scans only if it is the last available scan for the subject. Categorization of cumulative CUAL at each visit is (0, 1–5, 6–10, 11-15, 16-20, 21-25, 26-30, 31-35, 36-40, 41+).

The cumulative number of CUAL from extension baseline to extension EOS is also derived as described above.

The time up to the last MRI (years) included in the above is derived as = Date of last MRI considered in derivation – core randomization date / extension enrollment date + 1 divided by 365.25 days.

Note that CUAL will be calculated at each visit only if baseline Gd+ T1 lesions is available and "New or enlarging T2 lesions" is not missing at that visit. Otherwise the CUAL is set to be missing.

5.3.1.2.4. Percent Change of Brain Volume from Baseline

Brain volume is recorded by the central reader as normalized brain volume at the baseline visit and at subsequent visits as a percent change relative to the value at the baseline visit. Percent change of brain volume from baseline to subsequent visits is not manually derived but taken directly from the central reader variable at the corresponding scheduled visit.

The following types of percent change of brain volume are assessed in the extension study:

- Percentage change of Brain Volume from Core Baseline
- Percentage change of Brain Volume from Extension Baseline, i.e. from Core study EOT
- Annual percentage change of Brain Volume from Core Baseline to Core study week 108, defined as: percentage change of MRI brain volume assessment at core study week 108 relative to Core baseline / years-of-follow-up. Here the years-of-follow-up is: (Date of MRI brain volume assessment at core study week 108 – randomization date in core study +1) / 365.25
- Annual percentage change of Brain Volume from Core Baseline to extension EOS, defined as: percentage change of last MRI brain volume assessment relative to Core baseline / years-of-follow-up. Here the years-of-follow-up is: (Date of last MRI brain volume assessment in extension study – randomization date in core study +1) / 365.25.

- Annual percentage change of Brain Volume at any assessment by visit from Core Baseline to extension EOS, defined as: percentage change of last MRI brain volume assessment by visit relative to Core baseline / years-of-follow-up. Here the years-of-follow-up is: (Date of last MRI brain volume assessment of the visit in extension study – randomization date in core study +1) / 365.25.

5.3.1.3. Neurological variables

5.3.1.3.1. CDA: 12/24-week confirmed disability accumulation

A 12/24-week confirmed disability accumulation (CDA) is defined as a 12/24-week sustained increase from the core baseline EDSS score, according to the definitions described below, which is confirmed at a scheduled visit after 12/24 weeks. 12/24-week CDA is defined for the Combined Analysis Period only.

Every EDSS score obtained (scheduled or unscheduled) within a 12/24-week window after the first progression should also meet the progression criteria, in order to count a subject as having 12/24-week CDA. The 12/24-Week CDA progression starts on the day of the first sustained increase of EDSS after core baseline.

Core baseline EDSS is defined as the last available EDSS score prior to or on the date of randomization.

In the core study, disability as measured by EDSS is assessed in all subjects at Screening, Baseline, and thereafter at scheduled visits every 12 weeks until the end of study. Additional EDSS assessments for individual subjects may have been conducted between scheduled visits (i.e., during an MS relapse).

In the extension study, disability as measured by EDSS is assessed in all subjects at enrollment and thereafter at scheduled visits every 12 weeks until the end of study, as well as at unscheduled visits (during an MS relapse or at any time during the study based on the judgment of the investigator).

CDA is defined as:

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

confirmed after 12 or 24 weeks.

Disability progression can only be confirmed at a scheduled visit, where the EOT and EOS visits count as scheduled visits and can only be confirmed in the absence of a relapse.

Steps to determine 12/24-week CDA

1. All valid post-baseline EDSS assessments (scheduled or unscheduled) will be compared to baseline to assess if the absolute change from baseline meets the CDA criteria, described above. Take the first absolute change from core baseline that meets the criteria for EDSS increase. Onset date of the corresponding potential 12/24-week CDA is the EDSS assessment date.

2. Confirmation of the 12/24-week CDA:

a. The CDA is confirmed ≥ 70/154 days, respectively for 12/24-week CDA, from the onset date of the progression (based on 84 days between assessments and ± 7 days of visit windows for 12-week CDA, so 84 days - two times 7-day visit time window, and based on 168 days between assessments - two times 7-day visit time window for 24-week CDA);

b. The EDSS assessments conducted during a relapse, i.e. from relapse start date (inclusive) to minimum of relapse end date and relapse start date + 90 days (exclusive) are not considered for confirmation;

c. Every EDSS score available (scheduled or unscheduled) between the CDA onset and the confirmation visit will be checked. If all EDSS scores meet the CDA criteria, the subject will be considered to have a 12/24-week CDA. If any EDSS within this period does not meet the CDA criteria, the CDA cannot be confirmed;

d. If a subject dies due to MS during the study, he/she will be considered as having a 12/24-week CDA with onset date being date of death. Deaths of subjects that are not study related will be censored, as described below.

3. The algorithm should check all possible onsets of a 12/24-week CDA for each subject, starting with the first possible onset, by date, up to the last possible onset. If at some time point a 12/24-week CDA is confirmed, the algorithm can stop and proceed with the next subject. If at none of the assessments a 12/24-week CDA could be confirmed, the subject is considered as not having 12/24-Week CDA. This subject will be censored according to the below rules. Subjects with a 12/24-Week CDA will be considered as having an event (‘0’), censored subjects as having no event (‘1’).

Handling of missing dates

Missing dates for EDSS assessments will be imputed as follows:

- Partial date: Maximum of ‘lower limit’, ‘previous scheduled EDSS assessment according to the visit label’ + 1 day (if available), and ‘randomization date’
- Missing date: do not impute and exclude from analysis/

See Section 6.13 for further details on handling missing dates.

Missing dates for relapse start and end dates will be handled as follows:

- Partial or missing relapse end date with available relapse start date: use relapse start date + 90 days or upper limit of partial end date if earlier.
- Partial relapse start date: If only day is missing, consider the relapse has started on the last day of the month (or on relapse end date − 1 day if earlier) and ended 60 days later or at (upper limit of a partial) relapse end date, if earlier. If the month or year are missing the relapse does not lead to non-consideration of an EDSS assessment.
- Missing relapse start date: Corresponding relapse does not lead to non-consideration of an EDSS assessment. Do not consider imputed relapse start dates.

5.3.1.3.2. Time to first 12 or 24-week CDA

Time to first 12- or 24-week CDA is defined as start date of the first 12- or 24-week CDA − date of randomization in the core study + 1 in days.

For a subject without a 12- or 24-week CDA, the censored time to 12- or 24-week CDA is defined as:

date of last EDSS assessment without an EDSS increase for subjects without a CDA (as defined above) − date of randomization in the core study + 1.

Subjects without post baseline assessment (without EDSS increase) are censored on randomization date. For subjects without baseline EDSS score missing values are assigned.

5.3.1.3.3. Change from baseline in EDSS

Absolute change from baseline in EDSS score by visit is derived, based on the overall EDSS score as reported by the investigator in the eCRF.

- The change from baseline in EDSS score will be calculated both for the Combined and the Extension Analysis Periods, using the core baseline for the Combined Analysis Period and the extension baseline for the Extension Analysis Period.

5.3.1.4. Other efficacy variables

5.3.1.4.1. NEDA-3 status up to extension EOS

No evidence of disease activity (NEDA)-3 up to extension EOS is defined by the absence of confirmed relapse, Gd+ T1 lesions, new or enlarging T2 lesions, and 12-week CDA. If at least one of the criteria is not fulfilled or the subject discontinues treatment prematurely, the subject is not considered to have achieved NEDA-3.

Derivation details

A subject is considered as having evidence of disease activity if at least one of the following applies:

- Any confirmed relapse up to extension EOS.
- Presence of Gd+ T1 lesions during the course of study until extension EOS.
- Presence of new or enlarging T2 lesions during the course of study until extension EOS.
- Any 12-week CDA up to extension EOS.

Subjects that discontinue treatment prematurely are considered as showing evidence of disease activity, irrespective of what the reason for treatment discontinuation is.

Subjects without evidence of disease activity as defined above, who have missing outcome for any component (absence of confirmed relapse up to extension EOS, absence of new Gd+ T1 lesions from Core baseline to Extension EOS, absence of new or enlarging T2 lesions from Core baseline to Extension EOS) are considered to have missing outcome for NEDA-3.

5.3.1.4.2. NEDA-4 status up to extension EOS

No evidence of disease activity (NEDA)-4 up to EOS is defined by the absence of confirmed relapse, Gd+ T1 lesions, new or enlarging T2 lesions, 12-week CDA until EOS, and absence of

annual brain volume decrease ≥ 0.4% **at all assessments** from Core Baseline up to Extension EOS. If at least one of the criteria is not fulfilled or the subject discontinues treatment prematurely, the subject is not considered to have achieved NEDA-4.

Derivation is as for NEDA-3, but in addition a subject is considered as having evidence of disease activity if the following applies:

- Annual brain volume at any assessment from core baseline to extension EOS decrease ≥ 0.4%. The annual brain volume change is defined in Section 5.3.1.2.4. If **at any visit** the percentage change is <= -0.4% then the criteria "Annual brain volume decrease ≥ 0.4%" is met

5.3.1.4.3. Change in Multiple Sclerosis Functional Composite (MSFC) Z-score from baseline by visit up to Extension EOS

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

MSFC will be assessed at pre-randomization (3 tests conducted on 3 days apart, where the first 2 are considered practice tests) and at post-baseline Visits as scheduled in the protocol.

For each assessment, the MSFC score will be calculated as the mean of the Z-scores of the 3 components:

(1) Timed 25-Foot Walk (T25FW) score (s)

(2) 9-Hole Peg Test (9-HPT) score (s)

(3) Paced Auditory Serial Addition Test (PASAT-3) score (Number correct).

Details for generating the MSFC Z-score and how to handle missing data are given in Section 6.14.1.

For analysis, baseline and nominal post-baseline visits are considered. See Section 5.1.10 for remapping of premature end of treatment or unscheduled visits (includes unscheduled visits due to relapse).

Baseline is defined as the last available MSFC score prior to or on randomization date. While this should usually present the subject's 3rd test, if that is missing, results from the practice test may be used. A flag is added indicating the number of tests conducted up to the baseline test inclusive.

5.3.1.4.4. Change in the symbol digit modalities test (SDMT) score from baseline by visit up to Extension EOS

The symbol digit modalities test (SDMT) measures attention and processing speed much like the PASAT. It is administered along with the MSFC at pre-randomization (3 tests, where the first 2 are considered practice tests) and at post-baseline visits as scheduled.

For analysis, baseline and nominal post-baseline visits are considered. See Section 5.1.9 for remapping of premature end of treatment or unscheduled visits.

Baseline is defined as the last available SDMT score prior to or on randomization date. While this should usually present the subject's 3rd test, if that is missing results from the practice test may be used. A flag is added indicating the number of tests conducted up to the baseline test inclusive.

5.3.2. Analysis Methods

5.3.2.1. Statistical methodology

5.3.2.1.1. Statistical methodology for count data

Count data will be analyzed assuming data is negative binomially (NB) distributed.

A generalized linear model with NB distribution will be assumed.

t_j denotes the length of observation (time in study) for subject j.
Y_j denotes the number of relapses for subject j during t_j.
μ_j denotes the mean of the NB distribution of Y_j.

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

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

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

The SAS code for the NB model is as follows:

```
proc genmod data=ADREL;
   model relnum_r = / dist=negbin link=log offset = log(Time);
run;
```

If the model does not converge the Poisson distribution will be used instead of the negative binomial distribution.

5.3.2.1.2. Statistical methodology for time to event data

The analysis of time-to-event data are conducted using Kaplan-Meier (KM) estimates of events over time. Estimates of the event rate are obtained for each study treatment group using the KM method as implemented in SAS proc lifetest. The reference time is the study day, i.e., days elapsed since first treatment. The KM estimates at different time points are plotted together with the 95% two-sided confidence limits (CLs), calculated using Greenwood's formula for the estimate of the standard error. Intervals will be displayed by 24 weeks up to last available time point.

The SAS code for the KM analysis is as follows:

```
proc lifetest data= method=KM;
  time survtime*censor(1);
run;
```

5.3.2.2. Analysis of relapse-related variables

5.3.2.2.1. Main analysis of ARR

The main statistical analysis will be performed on the FAS and EXTS using all data in the Combined Analysis Period. The model described in Section 5.3.2.1 for confirmed relapses will be used, with core study treatment as a factor and the logarithm of time in study (in years) from randomization up to the end of the Combined Analysis Period as an offset variable. ARR will be summarized descriptively by core treatment group in a table for confirmed relapses as follows:

- Number of confirmed relapses per subject: descriptive statistics;
- Number of confirmed relapses per subject: frequency counts and percentages for categories 0, 1, 2, 3, 4, 5-10 and 11+;
- Total number of confirmed relapses: frequency count:
- Total time in study (subject years): sum;
- Raw ARR: total number of confirmed relapses / total time in study.

Mean model-based estimates of the ARR (for confirmed relapses), by core study treatment group, as well as 95% CIs will be presented. A rate ratio comparing ponesimod with teriflunomide 14 mg will be derived from the model including 95% CIs.

The fit of the model will be assessed and other distributions such as the Poisson distribution will be considered in case of a lack of fit.

5.3.2.2.2. Additional analyses of ARR

All relapses will be analyzed for the Combined Analysis Period on the FAS and EXTS as described in Section 5.3.2.1.1, i.e., including the first summary table described (and adding the ARR estimate and 95% CI from a NB model).

This approach will also be used to analyze confirmed relapses on:the Extension Analysis Period using the EXTS and the EXTS and for all relapses on:

- the Extension Analysis Period using the EXTS;

with the logarithm of the appropriate observation time during the related period as an offset variable.

Additionally, for confirmed relapses, the ARR estimate and 95% CI from a Poisson model (as the NB model is not expected to converge for all time periods) will be determined by 24-week period (as defined in Section 5.3.1) using FAS and EXTS as follows. The log of observational time during each interval will be used as offset.

- Core Analysis Period (core weeks 0-24, 24-48, 48-72, 72-96, 96-core EOS);
- Extension Analysis Period (extension weeks 0-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168, 168-192, 192-216, 216-Extension EOS).

A line plot will be created to present the ARR estimate and the corresponding 95% CI by 24 weeks period.

Relapse characteristics will be summarized using descriptive statistics for the Combined Analysis Period on the FAS and for the Extension Analysis Period on the EXTS. This includes the following:

- Number (%) of subjects with at least one: relapse, relapse requiring hospitalization, relapse treated with corticosteroids; for all relapses up to EOS/cut-off and for confirmed relapses up to EOS/cut-off.
- Number (%) of relapses (out of total number of relapses) requiring hospitalization, treated with corticosteroids and descriptive statistics for continuous data for relapse duration (days); for all relapses up to EOS as well as for confirmed relapses up to EOS.

Full details of all relapses will be presented in a listing.

5.3.2.2.3. Time to first (confirmed) relapse

The analysis of time from randomization in the core study to first confirmed relapse during the Combined Analysis Period (up to EOS/cut-off for subjects entering the extension study or up to core EOS for subjects not entering the extension study) will be performed on the FAS and EXTS using KM methods.

Time to first confirmed relapse will be summarized on the FAS in a table including, the number of subjects with event / censored, KM estimates and corresponding CI (anticipated time points of 24-week intervals: 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264 and 288 weeks), and median (as well as 25th and 75th percentiles) of the survival function together with CIs. A graphical display presenting a KM plot going upward is presented, including CIs at specific time points. Intervals will be displayed 24 weeks up to the last time point.

Censoring rules are defined in Section 5.3.1.1.2. The analysis will be repeated for time to first relapse including all relapses.

Time to first relapse and time to first confirmed relapse data will be listed using the FAS.

5.3.2.3. Analysis of MRI-related variables

5.3.2.3.1. T1 Gd+ lesions

The total number of Gd+ T1 lesions per visit will be summarized descriptively as continuous data and in categories (anticipated categories: 0, 1, 2, 3, 4, 5, 6-10, 10+), for the Combined Analysis Period on the EXTS.

Descriptive statistics on absence of Gd+ T1 lesions (frequency and percentages of subjects with lesions absent, present) will be presented by visit, and cumulative for absence of Gd+ T1 lesions from Core baseline up to extension EOT will be tabulated. This analysis will be done for combined period using EXTS.

The total number of Gd+ T1 lesions will be analyzed by visit for the Combined Analysis Period on the EXTS using a negative binomial regression model: the response variable is the number of lesions at the respective visit, with core study treatment as a factor and no offset. Mean model-based estimates and corresponding 95% CIs will be presented. The corresponding plots will also be presented.

Total volume of T1 hypointense lesions and the change from core baseline per visit is summarized descriptively based on observed data, for combine analysis period using the EXTS. In addition, total volume of T1 hypointense lesions and the change from extension baseline per visit is summarized descriptively for extension period using EXTS. The total volume of T1 hypointense lesion data will be listed using FAS.

Descriptive statistics of the proportions of Gd+ T1 lesions at core baseline evolving to persistent black holes will be presented by visit in the subset of subjects with Gd+ T1 lesions present at baseline using the EXTS for combined period. Same analysis in relative to extension baseline (i.e. Core study EOT) will be repeated using EXTS during extension period. A listing will be prepared using the FAS.

Gd+ T1 lesions data will be listed on the FAS.

5.3.2.3.2. New or enlarging T2 lesions

The total number of new or enlarging T2 lesions per visit will be summarized descriptively as continuous and in categories (anticipated categories: 0, 1, 2, 3, 4, 5, 6-10, 11+), for the Combined Analysis Period on the EXTS.

The cumulative number of new or enlarging T2 lesions from core baseline up to extension EOS (Combined Analysis Period) (i.e. from baseline up to extension EOS) will be analyzed on the EXTS using a negative binomial regression model with core study treatment as a factor and the log of time up to last MRI (in years) considered for analysis as an offset variable. Mean model-based estimates and corresponding 95% CIs will be presented. The same model is applied for extension period on the EXTS.

Descriptive summary statistics for the cumulative number of new or enlarging T2 lesions from core baseline up to extension EOS on the EXTS will be presented by treatment group for continuous data and frequency per categories (anticipated: 0, 1–5, 6–10, 11-20, 20+), total counts and total cumulative observation time (time up to the last MRI scan in years) summed for all subjects, raw yearly rate (total count / total cumulative observation time). Descriptive summary statistics for the cumulative number of new or enlarging T2 lesions from extension baseline up to extension EOS on the EXTS will be presented in the same way.

Descriptive statistics on absence of new or enlarging T2 lesions by visit (frequency and percentages of subjects with lesions absent, present) will be presented by visit, and cumulative for absence of new or enlarging T2 lesions from Core baseline up to extension EOS will be tabulated. This analysis will be done for combined period using EXTS.

The total number of new or enlarging T2 lesions will be analyzed by visit for the Combined Analysis Period on the EXTS, using the negative binomial model, as described in Section 5.3.2.3.1, for the total number Gd+ T1 lesions per visit. The corresponding plots will also be presented.

Total volume of T2 lesions and change from baseline per visit is summarized descriptively based on observed data, for combine analysis period using the EXTS. Same analysis will be repeated using EXTS relative to Extension baseline during Extension period. The total volume of T2 lesion data will be listed using FAS.

T2 lesion data will be listed on the FAS.

5.3.2.3.3. Combined unique active lesions (CUAL)

The total number of CUAL lesions at Week 60 and at Week 108 of the core study, and Week 48, Week 96, Week 144, Week 192, Week 240, Week 288 and EOT of the extension study, will be analyzed by visit for the Combined Analysis Period on the FAS and EXTS, using the negative binomial model: the response variable is the number of CUAL at respective visit, with study treatment at core baseline as a factor and no offset. Model based estimates and the corresponding 95% CI will be tabulated. The corresponding plots will also be presented.

The total number of CUAL per visit will be summarized descriptively as continuous and in categories (anticipated categories: 0, 1–5, 6–10, 11-15, 16-20, 21-25, 26+), for the Combined Analysis Period on the FAS and EXTS.

The cumulative number of CUAL will be analyzed using a negative binomial regression model, similar as described in Section 5.3.2.3.2 for the cumulative number of new or enlarging T2 lesions, but using log of the total years from core baseline to last MRI scan as offset variable. CUAL will be analyzed from:

- Core baseline up to extension EOS (Combined Analysis Period) using EXTS;
- Extension baseline up to extension EOS (Extension Analysis Period) on the EXTS;

Descriptive summary statistics of the number of CUALs from core baseline up to extension EOS (Combined Analysis Period) using EXTS will be presented for continuous data and in categories (0, 1–2, 3–5, 6-10, 11-15, 16-20, 21-25, 26-30, 31-35, 36-40, 41+). The total number of CUALs as well as the total cumulative time up to the last MRI scan (summed for all subjects) will also be displayed. From the total number of CUALs and the total cumulative time up to the last MRI scan the raw number of CUALs per year will be calculated and summarized. Descriptive summary statistics for the number of CUALs from extension baseline up to extension EOS (Extension Analysis Period) on the EXTS will be presented in the same way.

In addition, the cumulative CUAL up to each visit during combined analysis period will be analyzed on FAS and EXTS using a negative binomial regression model, similar as described in Section 5.3.2.3.2 for the cumulative number of new or enlarging T2 lesions, but using log of the total years from core baseline to last MRI scan as offset variable. Model based estimates and the corresponding 95% CI will be tabulated. The corresponding plots will also be presented.

A listing of CUAL data will be presented using FAS.

5.3.2.3.4. Percent Change of Brain Volume from Baseline

PCBV from Core Baseline to Extension EOT will be summarized using descriptive statistics by visit based on observed data and listed using the FAS and EXTS.

PCBV from Core study EOT to Extension EOT will be summarized using descriptive statistics by visit based on observed data and listed using the EXTS.

Number and percentage of subjects with annual change from Core Baseline to Extension EOT in PCBV <= -0.4% will be summarized by visit using EXTS.

Number and percentage of subjects with annual change from Core study EOT to to Extension EOT in PCBV <= -0.4% will be summarized by visit using EXTS.

5.3.2.4. Analysis of neurological variables

5.3.2.4.1. Analysis of disability progression (12/24-week CDA)

The analysis of time from core study baseline to confirmed first 12- and 24-week CDA will be summarized in a similar manner to the time to first relapse variable, for the Combined Analysis Period, using FAS and EXTS.

A listing with 12/24-week CDA results will be produced.

5.3.2.4.2. Change in EDSS from baseline by visit up to EOS

The EDSS score and change from baseline in EDSS score by visit and core study treatment group will be summarized using descriptive statistics on the EXTS for the Combined Analysis Period as well as on the EXTS for the Extension Analysis Period. Mean changes from core baseline in EDSS score are also presented graphically with their standard error over time (plots starting with zero change at baseline), for the Combined Analysis Period on the EXTS.

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

A listing(s) of EDSS / functional system (FS) scores will be produced.

5.3.2.5. Analysis of other efficacy variables

5.3.2.5.1. NEDA-3 status up to EOS

Descriptive statistics of NEDA-3 status (Yes, No, Missing) up to Extension EOS including its components ([i] Presence of confirmed relapse, [ii] Presence of Gd+ T1 lesions, [iii] Presence of new or enlarging T2 lesions, [iv] 12-week CDA event, or [v] premature treatment discontinuation) will be presented using the EXTS. A listing will be prepared.

5.3.2.5.2. NEDA-4 status up to EOS

NEDA-4 status up to Extension EOS will be analyzed in the same way as NEDA-3 status on the EXTS.

5.3.2.5.3. Change in MSFC Z-score from baseline by visit up to Extension EOS

MSFC Z-score as well as its subcomponents scores and changes from core baseline will be descriptively summarized for each treatment group by visit on the EXTS. Mean change (± SE) over time will be graphically presented by treatment group. Same analysis relative to extension baseline will be done on the EXTS during extension period. A listing will be prepared.

5.3.2.5.4. Change in the SDMT score from baseline by visit up to Extension EOS

SDMT scores and change from baseline will be descriptively summarized for each treatment group by visit on the EXTS. Mean change (± SE) over time will be graphically presented by treatment group. Same analysis relative to extension baseline will be done on the EXTS during extension period. A listing will be prepared.

5.4. Safety Analyses

All safety analyses will be based on the safety analysis set based on actual intervention received. Safety summaries for each analysis period will be based on the safety analysis sets described in Section 4, unless otherwise specified.

For all continuous safety variables, descriptive statistics by intervention group will include the N, mean, standard deviation, median, minimum, and maximum. To convey the uncertainty associated with the summary statistics, the line plots will incorporate standard error (defined as sample standard deviation divided by the square root of sample size) for continuous variables. Categorical variables will be summarized by intervention group using frequency counts and percentages.

5.4.1. Extent of Exposure

5.4.1.1. Definition of extent of exposure

5.4.1.1.1. Exposure (Time on treatment)

The following variables are defined for exposure during the **Extension Analysis Period**:

Duration of exposure to ponesimod in the extension (months) excluding interruptions is defined as the time elapsed between (the date of first study drug intake in the extension study and date of last study drug intake in the extension study + 1) × 12 / 365.25, excluding any temporary treatment interruptions.

Duration of exposure to ponesimod in the extension (months) is defined as the time elapsed between (the date of first study drug intake in the extension study and the date of last study drug intake in the extension study + 1) × 12 / 365.25, independent of any treatment interruptions (except for treatment interruption due to planned pregnancy).

In addition, the duration of exposure as derived above for each subject is categorized as follows:

- ≥ 1 day and ≤ 6 months;
- > 6 months and ≤ 12 months;
- > 12 months and ≤ 18 months;
- > 18 months and ≤ 24 months;
- > 24 months and ≤ 30 months;
- > 30 months and ≤ 36 months;
- > 36 months and ≤ 42 months;
- > 42 months and ≤ 48 months;
- > 48 months and ≤ 54 months;
- > 54 months and ≤ 60 months;
- > 60 months.

The following variables are defined for exposure to ponesimod treatment during the **Combined Analysis Period,** for subjects randomized to ponesimod in the core study only:

Combined duration of exposure to ponesimod (months) excluding interruptions is defined as the time elapsed between [the date of first ponesimod intake in the core study and the date of last

ponesimod intake in the extension study + 1 (in days)] × 12 / 365.25, excluding any temporary treatment interruptions.

Combined duration of exposure to ponesimod (months) is defined as the time elapsed between [the date of first ponesimod intake in the core study and the date of last ponesimod intake in the extension study + 1 (in days)] × 12 / 365.25, independent of any treatment interruptions (except for treatment interruption due to planned pregnancy).

In addition, the combined duration of exposure for each subject is categorized as follows:

- ≥ 1 day and ≤ 6 months;
- > 6 months and ≤ 12 months;
- > 12months and ≤ 18 months;
- > 18 months and ≤ 24 months;
- > 24 months and ≤ 30 months;
- > 30 months and ≤ 36 months;
- > 36 months and ≤ 42 months;
- > 42 months and ≤ 48 months;
- > 48 months and ≤ 54 months;
- > 54 months and ≤ 60 months;
- > 60 months and ≤ 66 months;
- > 66 months and ≤ 72 months;
- > 72 months and ≤ 78 months;
- > 78 months and ≤ 84 months
- > 84 months

5.4.1.1.2. Compliance with study treatment

Compliance is calculated as a percentage as:

Ponesimod exposure during the Analysis Period excluding interruptions / Ponesimod exposure during the Analysis Period independent of interruptions (except for treatment interruption due to planned pregnancy as defined above) × 100.

Compliance as derived above is categorized as < 80%, ≥ 80 – < 90 %, ≥ 90 – < 95 %, ≥ 95- <100%, 100% and >100%.

5.4.1.1.3. Treatment duration (days with intake documented) during up-titration period (extension study)

The number of days with intake documented is based on entries on the eCRF ‘Up-titration Summary’ and/or ‘Up-titration Ponesimod’.

For subjects where the investigator confirmed the up-titration has been conducted as planned, the ‘Up-titration Summary’ eCRF is filled out, collecting only start and end date of the entire titration period without collecting ‘number of tablets taken’. In that case the ‘Number of days with intake documented’ is derived and considered to be ‘titration end date - titration start date + 1 day’.

For all other subjects, information is collected on the ‘Up-titration Ponesimod’ eCRF, ‘Intake date’ resulting in potentially multiple records of up-titration drug intake (collecting in addition ‘number

of tablets taken'). In that case, 'Number of days with intake documented' for each record is derived in the same way as during the maintenance period.

5.4.1.1.4. Treatment duration (days with intake documented) during maintenance period (extension study)

Per protocol, one tablet of study drug is to be taken per day. On the 'Maintenance Ponesimod' eCRF log form, each record collects 'Treatment start date', 'Treatment end date', 'Daily Dose' (Default value 20 mg – Maintenance), and 'Total number of tablets taken'. If, for a record, the 'Number of tablets taken' is ≤ 'Treatment end date' − 'Treatment start date' + 1, it is assumed that the 'Number of tablets taken' represents the 'Number of days with intake documented' during that record's period of study drug intake. If, for a record, the 'Number of tablets taken' is > 'Treatment end date' − 'Treatment start date' + 1, 'Number of days with intake documented' is set to 'Treatment end date' − 'Treatment start date' + 1. These subjects are flagged as having taken > 1 capsule per day on at least one occasion.

5.4.1.1.5. Study treatment completion/discontinuation

Discontinuation from study treatment in the core study is used as derived in the core study. See the core study SAP for details.

Study treatment discontinuations in the extension study are collected on the extension eCRF page 'Premature Discontinuation of Study Treatment'.

A premature permanent treatment discontinuation in the extension study is defined as permanently stopping treatment prior to the extension EOT visit (Week 240/Week 288 for those Ukraine subjects, or at the time ponesimod is commercially available for treatment of MS in the subject's country, whichever occurs first).

Reasons for premature treatment discontinuation in the extension study are as follows:

- Death;
- Lost to follow-up;
- Pre-specified study treatment discontinuation criteria;
- Subject decision (further split into: Adverse event, Lack of efficacy, No reason provided, Other);
- Physician decision (further split into: Adverse event, Lack of efficacy, Other);
- Sponsor decision (further split into: Study termination, Other).

Study treatment completion records are collected on the extension eCRF page "Maintenance Ponesimod" where fields "Completed as per protocol" or "Approved Drug Available For Indication" are entered.

5.4.1.1.6. Study treatment interruptions

Study treatment interruptions in the core study is used as derived in the core study.

Temporary treatment interruptions refer to any period of time between a temporary study treatment end date and subsequent study treatment start date during which the subject did not receive study treatment. When considering the Combined Analysis Period, the time between end of treatment in the core study and start of treatment in the extension study is also a treatment interruption. The cumulative duration of all such treatment interruptions is derived for each subject.

In addition, for each subject, the number of interruptions > 3 days is counted.

5.4.1.1.7. Re-initiation of ponesimod

Re-initiations during the extension study are defined as any up-titration in the study drug log with a treatment gap of > 3 days before the start of new up-titration regimen. In case of an interrupted up-titration during a re-initiation, followed by another re-initiation, the subject is considered as having two re-initiations. Interruptions of > 3 days without new up-titration regimen are not counted as re-initiations, but will be flagged in the data. All relevant re-initiation information will be included in the exposure (ADEX) domains.

Re-initiations during the core study are used as derived in the core study ADaMs and not re-derived.

The first administration of ponesimod at the start of the extension study is not considered to be a re-initiation.

5.4.1.1.8. Study completion/discontinuation

Study discontinuation/completion in the core study is used as derived in the core study. See the core study SAP for details.

For an individual subject, extension EOS is reached when treatment has been completed/discontinued and safety follow-up (FU) has been completed. Thus, a subject is considered to have completed the study per protocol if they perform the EOS visit as scheduled (30–44 days after the permanent discontinuation of study treatment), even if they prematurely discontinued from study treatment. However, study withdrawal can happen at any time between premature treatment discontinuation/completion and the EOS/FU assessment. Such subjects are considered to have discontinued from the study, even if they completed treatment. Reasons for and date of study discontinuation are captured on the eCRF page “Study Discontinuation”.

Possible reasons for study withdrawal are as follows:

- Death;
- Lost to follow-up;
- Subject decision/ withdrawal of consent (further split into: Adverse event, Lack of efficacy, No reason provided, Other);
- Physician decision (further split into: Adverse event, Lack of efficacy, Other);
- Sponsor decision (further split into: Study termination, Other).

5.4.1.2. Analysis of extent of exposure

5.4.1.2.1. Exposure

Exposure to ponesimod treatment will be summarized descriptively, both for the Combined Analysis Period using the FAS (only for subjects included in the SAF who were initially treated with ponesimod 20 mg in the core study) and for the Extension Analysis Period by core study treatment group and overall, using the EXTS, as follows:

- Treatment exposure (months): descriptive statistics;
- Treatment exposure (months) by category (cumulative): frequency counts and percentages;
- Total subject years exposure

- Treatment exposure (months) excluding interruptions: descriptive statistics;
- Cumulative duration of interruptions: descriptive statistics;
- Number of treatment interruptions > 3 days: frequency;
- Number of subjects with at least 1 treatment interruption > 3 days: frequency counts and percentages;
- Number of subjects with at least 1 treatment re-initiation: frequency counts and percentages;
- Number of subjects with at least 2 treatment re-initiation: frequency counts and percentages;

5.4.1.2.2. Compliance with study treatment

Compliance with ponesimod treatment is summarized using descriptive statistics for continuous and categorical data both for the Combined Analysis Period using the FAS (only for subjects included in the SAF who were initially treated with ponesimod 20 mg in the core study) and for the Extension Analysis Period by core study treatment and overall, using the EXTS. Exposure and compliance are also presented in a subject data listing.

5.4.2. Adverse Events

5.4.2.1. General consideration in adverse events

An AE is any event reported by the investigator on the Adverse Event eCRF.

AEs that started in the core study and were still ongoing on Day 1 of the extension study are reported in the 'Ongoing Adverse Events from AC-058B301' extension eCRF form. If the event worsened in intensity/seriousness after start of study treatment in the extension study, such an event was reported in the usual Adverse Event eCRF Form.

All AEs are coded using the MedDRA dictionary (version 26.0).

For the summaries on the Combined Analysis Period, AEs from core and extension study (specifically AEs included in the extension eCRF as 'ongoing' from the core study and the original AEs included in the core eCRF) will be merged using a dedicated ID linking variable included in the related SDTM datasets. The following rules will be used by merging the SDTM datasets:

- If information regarding the seriousness of an ongoing AE is inconsistent between the two databases, the AE is conservatively considered to be serious;
- The outcome as entered in extension study will be used for the analysis;
- If the action taken for an ongoing AE is given as temporarily interrupted in the core study database, and the action taken is missing, none, not applicable, or unknown in the extension study database, then the value from the core will be retained. For all the other cases the action taken as entered in extension study will be used for the analysis;
- If an event entered on the form "Ongoing adverse events from AC-058B301" eCRF page in the extension, this AE will not be considered as treatment-emergent with respect to the Extension Analysis Period, and no dates or other variables will be imputed if missing or partial. Such events will appear in listings only.

For the Combined Analysis Period, cumulative data such as AEs and SAEs will only be summarized for subjects initially treated with ponesimod 20 mg in the core study.

5.4.2.2. Analysis variables in AE

5.4.2.2.1. Frequency of adverse events and AEs per 100 subject-years

AEs are summarized according to both frequency (number of subjects and percentages) and AEs per 100 subject-years (number of events and rate) and based on various grouping terms (for example MedDRA preferred term, or MedDRA primary system organ class).

For frequency of subjects experiencing an AE, AEs reported more than once for a subject within the Analysis Period (based on grouping term) are counted only once per subject.

AEs per 100 subject-years = Total cumulative number of events during the Analysis Period / Cumulative observation time in the treatment-emergent period over all subjects (100 years) per grouping term.

For total cumulative number of events, multiple records of the same MedDRA preferred term in the AE dataset for the same subject count as individual events (episodes of the same type of event) unless they have the same start date and, if available, time.

The observation time (in days) per subject for summaries of treatment-emergent AEs is calculated as:

- minimum (extension EOT + 15, extension EOS) − ponesimod start date in the extension study + 1, for the Extension Analysis Period;
- minimum (extension EOT + 15, extension EOS) – ponesimod treatment start date in the core study +1, for subjects in the Combined Analysis Period who had entered extension study.
- minimum (core EOT + 15, core EOS) – ponesimod treatment start date in the core study +1, for subjects in the Combined Analysis Period who did not enter extension study.

5.4.2.2.2. Treatment-emergent adverse events

Treatment-emergent adverse events (TEAEs) are defined as AEs occurring from start of treatment up to treatment end date + 15 days.

Treatment-emergence is considered with respect to the relevant Analysis Period, i.e., relative to the first dose of ponesimod in the core study for the Combined Analysis Period, and relative to the first dose of ponesimod in the extension study for the Extension Analysis Period.

AEs with completely missing start date will be considered treatment-emergent. If it is not clear whether the event is treatment-emergent or not (in case of partial dates), the event will be considered treatment-emergent (e.g., start date of AE is documented in the database as May 2016 and treatment start date 23 May 2016, see definition of handling of missing data in Section 6.13.3).

Extension study day of onset

Study day of onset (relative to the start of the extension study) is derived for all TEAEs in the Extension Analysis Period.

TEAEs on Day 1 of re-initiation of ponesimod treatment are those AEs that start at or after the time of the first administration of ponesimod on Day 1 of the re-initiation after study drug interruption, and before the following calendar date. Day of onset relative to the start of a re-

initiation is derived for all treatment-emergent adverse events in the Extension Analysis Period in the same way as described above for extension study day of onset.

AE duration (days)

AE duration in days is derived for all treatment-emergent adverse events with complete start and end dates only as AE end date − AE start date + 1. Furthermore, duration of AE is derived only if both start date and end date are complete.

5.4.2.2.3. Serious adverse events

An AE is considered to be an SAE if the field "Serious?" is answered "Yes" in the eCRF module 'Adverse Event', in case information on seriousness is missing, the AE is conservatively considered to be serious.

5.4.2.2.4. Adverse events leading to permanent discontinuation of study treatment

An AE is considered to be an AE leading to discontinuation if the field "Action taken with study drug" is answered "Permanently discontinued" in the eCRF module 'Adverse Event'.

5.4.2.2.5. Adverse events leading to temporary interruption of study treatment

An AE is considered to be an AE leading to discontinuation if the field "Action taken with study drug" is answered "Temporarily interrupted" in the eCRF module 'Adverse Event'.

5.4.2.2.6. Adverse events leading to hospitalization

AEs leading to hospitalization are those where the eCRF question 'Did the Adverse Event require subject hospitalization?' is recorded as 'Yes' on the Adverse Event eCRF.

5.4.2.2.7. Fatal adverse events

Fatal AEs are those with 'Fatal' reported as outcome.

5.4.2.2.8. Deaths

Death information (date of death and primary cause) is taken from the Death eCRF.

5.4.2.2.9. Post-treatment AEs and SAEs

Post-treatment (S)AEs are (S)AEs occurring after the last treatment administration + 15 days up to extension EOS.

5.4.2.2.10. Adverse events of special interest (AESI)

AESIs include the anticipated risks of treatment with study drug and events that may be related to MS comorbidities. The following safety areas are addressed by the pre-defined AESIs; detailed definition is given in Appendix 8:

- Bradyarrhythmia occurring post-first dose
- Macular edema
- Bronchoconstriction
- Severe liver injury
- Serious opportunistic infections including PML

- Skin cancer
- Non-skin malignancy
- Convulsions
- Unexpected neurological or psychiatric symptoms/signs (PRES, ADEM, atypical MS relapses)

5.4.2.2.11. Major adverse cardiovascular events (MACE)

Based on a pre-defined list of preferred terms belonging to relevant Standardized Medical Dictionary for Regulatory Activities Queries (SMQs), AEs are selected for the major adverse cardiovascular event (MACE) adjudication board evaluation. For each case sent for MACE adjudication, the board members individually assess whether the case is a myocardial infarction, a stroke, or another AE. For fatal cases, each member determines whether the death is considered of cardiovascular, non-cardiovascular, or undetermined cause. If not all individual assessments concur, the case is classified into the above listed categories based on a consensus meeting. For data analysis, each case is assigned to one of the following categories:

- cardiovascular death (if a death case is classified as cardiovascular);
- non-fatal myocardial infarction (if the case is classified as myocardial infarction but not as cardiovascular death);
- non-fatal stroke (if the case is classified as stroke but not as cardiovascular death);
- no MACE (if the case is classified as other adverse event, but not as cardiovascular death).

The onset date and treatment-emergent status of a MACE is determined by the onset date and treatment-emergent status of the corresponding AE. In case more than one AE is linked to the same MACE case, the earliest treatment-emergent AE onset date determines the MACE onset date; if none of the linked AEs are considered treatment-emergent, the earliest AE onset date determines the MACE onset date. This may lead to cardiovascular death MACE with an onset date prior to the date of death.

5.4.2.2.12. Intensity of adverse events

AE intensity is entered into the database as ‘Mild’, ‘Moderate’, or ‘Severe’. For AEs reported more than once for a subject, only the worst outcome is considered. AEs with missing severity assessment are imputed to be of ‘severe’ intensity.

5.4.2.2.13. Relationship of adverse events

Relationship to study treatment is entered into the database as ‘related’ or ‘not related’. For AEs reported more than once for a subject, only the worst relationship is considered. AEs with missing relationship are considered to be related.

5.4.2.3. Analysis of safety variables

If not otherwise stated, only safety data considered treatment-emergent (up to 15 days after the last treatment administration) in the respective Analysis Period will be included in tables and figures. Additionally, non-treatment-emergent data at Core Day-15 follow-up, Core Day-30 follow-up and extension EOS visits may also be included in certain tables and figures. All safety data will be included in listings, with flags for safety data considered to be treatment-emergent to a specific Analysis Period.

Generally, safety data are presented as follows:

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

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

5.4.2.3.1. Adverse events

Unless otherwise specified, all the AE summaries described below are produced for the Combined Analysis Period (only for subjects included in the SAF who were initially treated with ponesimod 20 mg in the core study) and for the Extension Analysis Period by core study treatment and overall, using the EXTS.

An overview of TEAEs is presented, per study treatment group, as the number and percentage of subjects having any AE, any severe AE, any drug-related AE, any AE leading to study drug discontinuation, any SAE, any drug-related SAE, or any fatal SAE. Similarly, an overview of TEAEs per 100 subject-years is also presented.

The following summary tables will be created to present the frequency and percentage of subjects with any AE, an AE in each primary SOC, and each individual AE (preferred term). SOCs are sorted by descending order of frequency in the ponesimod arm. If the frequencies of SOCs are the same, alphabetical order is used. The same rule applies for preferred terms within SOC:

- All AEs;
- TEAEs;
- TEAEs per 100 subject-years;TEAEs with onset on Day 1 of a re-initiation (all re-initiations summarized together, for subjects with at least one re-initiation), Extension Analysis Period only;
- TEAEs leading to permanent discontinuation of study treatment;
- TEAEs considered to be related to study drug;
- Severe TEAEs;
- Post-treatment AEs (subjects that entered the period between EOT date + 16 and EOS), Extension Analysis Period only.

The following summary tables will also be produced, presenting the frequency and percentage of subjects with any AE, and each individual AE (preferred term) by descending frequency:

- TEAEs;
- TEAEs per 100 subject-years;
- TEAEs leading to permanent discontinuation of study treatment;

- TEAEs reported in ≥ 5% of subjects in any group (after rounding into the 1st decimal in percentage, e.g. an event occurring in 4.955% of subjects will be rounded to be 5.0% and therefore be included in this summary table).

The following summary tables will also be produced, presenting the frequency and percentage of subjects with any AE, and each individual AE (preferred term) by maximum intensity:

- TEAEs.

AEs (preferred terms) reported more than once in a subject during the period summarized are counted once in frequency tables. Percentages are based on the SAF (ponesimod subjects) or on the EXTS as applicable.

5.4.2.3.2. Deaths

The number and percentage of subjects who died during the extension study are summarized per core study treatment group, including the reported primary cause of death.

A separate listing including all deaths will be provided; treatment-emergent deaths will be flagged as such in that listing.

5.4.2.3.3. Serious adverse events (SAEs)

SAEs are summarized by SOC and preferred term. The following summaries are presented:

- Treatment-emergent SAEs;
- Treatment-emergent SAEs per 100 subject-years;
- Treatment-emergent SAEs with onset on Day 1 of a re-initiation (for subjects with at least one re-initiation), Extension Analysis Period only;
- Treatment-emergent SAEs leading to permanent discontinuation of study treatment
- Treatment emergent SAEs with fatal outcome; (this will be tabulated only if there are more than 5 SAE-caused fatal events)

In addition, the following summary tables will also be produced, presenting the frequency and percentage of subjects with any SAE, and each individual SAE (preferred term) by descending frequency:

- Treatment-emergent SAEs;
- Treatment-emergent SAEs leading to premature discontinuation of study drug, Extension Analysis Period only.

SAEs, SAEs leading to hospitalization, and fatal SAEs will be presented in dedicated listings.

5.4.2.3.4. Treatment-emergent adverse events leading to study treatment discontinuation

AEs and SAEs leading to premature discontinuation of study drug are summarized by SOC and preferred term as listed above.

A listing for AEs leading to premature discontinuation of study drug will be presented.

5.4.2.3.5. Adverse events of special interest (AESIs)

For each of the AESI categories described in Section 5.4.2.2, the number and percentage of subjects with each AESI is summarized by core treatment group and preferred term for treatment-emergent AESIs. In addition, the number and percentage of subjects having any event of that category, having any serious event, any fatal event or any event leading to premature discontinuation of study drug is presented. Similarly, treatment-emergent AESIs per 100 subject-years are summarized per AESI category.

AESI are presented in dedicated listings (one for each AESI category).

5.4.2.3.6. Major adverse cardiovascular events (MACE)

A summary table will be produced for the Combined Analysis Period on the FAS and for the Extension Analysis Period on the EXTS presenting the frequency and percentage of subjects with any treatment-emergent MACE and having an event of the MACE subcategories (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) per core treatment group.

MACE are also presented in a dedicated listing.

5.4.3. Additional Safety Assessments

5.4.3.1. Clinical Laboratory Tests

5.4.3.1.1. Laboratory Test variables

Safety laboratory samples are centrally analyzed by ACM and the results are electronically transferred to sponsor's database. In exceptional cases, the protocol allows the utilization of local laboratories. Local laboratory analysis results are entered in the eCRF with some exceptions for blinding reasons (e.g., lymphocytes are not entered in the eCRF). Qualitative results like (marked) abnormality categorization, liver test elevation categories, etc., are derived from local laboratory data and summarized together with qualitative results derived from central laboratory data.

Safety laboratory assessments are conducted per schedule in section 6.12. Additional safety laboratory tests were allowed as per protocol at week 8, 16 and 20 and these assessments will also be tabulated.

Numerical results are converted into both conventional and SI units per QS document OTH-000005 (Definition of Marked Abnormalities in Laboratory Data). Results reported as below the lower limit of quantification (LLOQ) are set to the LLOQ value. Results reported as >XX are set to XX for calculation of summary statistics. For all quantitative safety laboratory data, core/extension baseline is flagged and absolute change from core/extension baseline and percent changes from core/extension baseline are calculated for each post-baseline value, as described in Section 5.1.6.

The Estimated Creatinine Clearance (eCLCr) is derived for analysis at each assessment (values based on Cockroft-Gault formula):

eCLCr (mL/min) = (140 − Age) × baseline Weight (in kg) × constant / serum creatinine (in µmol/L), where constant is 1.23 for men and 1.04 for women
Or
eCLCr (mL/min) = (140 − Age) × baseline Weight (in kg) × constant / (72 × serum creatinine (in mg/dL) where constant is 1 for men, 0.85 for women

If the assessment comes from the core study (excluding the ones used as baseline value for the Extension Analysis Period):

- Age is re-calculated at each assessment as follows:
  Age at core screening (or re-screening) + 0.5 + (Date of laboratory assessment − Date of core screening (or re-screening))/365.25.
- Baseline weight is the weight collected at core screening.

If the assessment comes from the core study but it is used as baseline for the Extension Analysis Period, or if the assessment comes from the extension study:

- Age is re-calculated at each assessment as follows:
  Age at start of extension + 0.5 + (Date of laboratory assessment – Extension enrollment date)/365.25.
- Baseline weight is the weight collected at start of extension.

Flags are derived according to project specific ranges for marked laboratory abnormalities, as documented in Appendix 10. Marked laboratory abnormalities are labeled to indicate the increasing severity of abnormally low ("LL", "LLL"), or high values ("HH", and "HHH") for each of the laboratory parameters listed. For INR, the general range specified in the protocol is applied to all subjects irrespective of concomitant treatment with anticoagulants.

The following flags will be derived for Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Total bilirubin (TBIL), and Alkaline phosphatase (ALP) at the subject/assessment level:

- ALT: ≥ 1 × ULN, ≥ 3 × ULN, ≥ 5 × ULN, ≥ 8 × ULN, ≥ 10 × ULN, ≥ 20 × ULN
- AST: ≥ 1 × ULN, ≥ 3 × ULN, ≥ 5 × ULN, ≥ 8 × ULN, ≥ 10 × ULN, ≥ 20 × ULN
- ALT or AST: ≥ 3 × ULN, ≥ 5 × ULN, ≥ 8 × ULN, ≥ 10 × ULN, ≥ 20 × ULN
- TBIL ≥ 2 × ULN
- ALT or AST ≥ 3 × ULN and TBIL ≥ 2 × ULN (at the same sample date)
- ALT or AST ≥ 3 × ULN and TBIL ≥ 2 × ULN + AP < 2 × ULN (at the same sample date)
- INR value (ratio) > 1.5 combined with ALT or AST ≥ 3 ULN (at the same sample date).

In addition, the following treatment-emergent alerts regarding lymphocyte counts will be flagged:
- < 0.2 10^9/L;
- ≥ 0.2 × 10^9/L – < 0.5 × 10^9/L;
- ≥ 0.5 × 10^9/L – < 0.8 × 10^9/L;
- ≥ 0.8 × 10^9/L – < 1.0 × 10^9/L;
- ≥ 1.0 × 10^9/L.

The following laboratory test will be presented in table and figure summaries. Other laboratory tests with abnormal findings will be presented in listings only.

Laboratory tests in standard unit
Erythrocytes (10^12/L)
Leukocytes (10^9/L)
Basophils (10^9/L)

Basophils/Leukocytes (%)
Eosinophils (10^9/L)
Eosinophils/Leukocytes (%)
Lymphocytes (10^9/L)
Lymphocytes/Leukocytes (%)
Monocytes (10^9/L)
Monocytes/Leukocytes (%)
Neutrophils (10^9/L)
Neutrophils/Leukocytes (%)
Platelets (10^9/L)
Hemoglobin (g/L)
Hematocrit (L/L)
Lactate Dehydrogenase (U/L)
Creatinine (umol/L)
Creatinine Clearance (mL/min)
Estimated Creatinine Clearance (mL/min)
Urea Nitrogen (mmol/L)
Urea (mmol/L)
Urate (umol/L)
Glucose (mmol/L)
Cholesterol (mmol/L)
Triglycerides (mmol/L)
Sodium (mmol/L)
Potassium (mmol/L)
Chloride (mmol/L)
Calcium (mmol/L)
Protein (g/L)
Albumin (g/L)
C Reactive Protein (mg/L)
Alanine Aminotransferase (U/L)
Aspartate Aminotransferase (U/L)
Alkaline Phosphatase (U/L)
Bilirubin (umol/L)
Prothrombin Intl. Normalized Ratio

5.4.3.1.2. Analysis of Laboratory Tests

The following tables will be produced for laboratory tests, both for the Combined Analysis Period, by core study treatment, using SAF (the summaries marked with § will include only the subjects who were initially treated with ponesimod 20 mg in the core study), and for the Extension Analysis Period, by core study treatment and overall, using the EXTS.

- Summary of absolute and absolute change from baseline values for laboratory tests (hematology, blood chemistry [excluding liver tests], liver tests): descriptive statistics by visit;
- Summary of percent change from baseline values for lymphocyte counts: descriptive statistics by visit;

- Incidence of marked laboratory abnormalities (LL, LLL, HH, HHH) as defined in Section 6.10: frequency counts and percentages, where percentages are based on the number of subjects with at least one post-baseline value in the Analysis Period (i.e., number of subjects at risk);§
- Incidence of special laboratory abnormalities for ALT, AST, Bilirubin, and ALP: frequency counts and percentages, where percentages are based on the number of subjects with at least one post-baseline value (i.e., number of subjects at risk);§
- Incidence of marked treatment-emergent laboratory abnormalities for lymphocyte counts: frequency counts and percentages, where percentages are based on the number of subjects with at least one post-baseline value (i.e., number of subjects at risk)§.

- A plot to evaluate Drug-Induced Serious Hepatotoxicity (eDISH plot) based on the highest observed treatment-emergent ALT and total bilirubin values will be provided for safety analysis set during combined period, as well as for extension period by treatment group. Individual subject's values expressed as × ULN are plotted on a log-log scatter plot (ALT on the horizontal axis, total bilirubin on the vertical axis); reference lines are drawn at Hy's law thresholds, i.e., at 3 × ULN for ALT and at 2 × ULN for total bilirubin.

For abnormalities, the worst case in each direction is considered and summarized in all applicable categories, i.e., a subject counted in LLL is also counted in LL for a given parameter; also, a subject maybe counted in both the high and the low category for a given parameter.

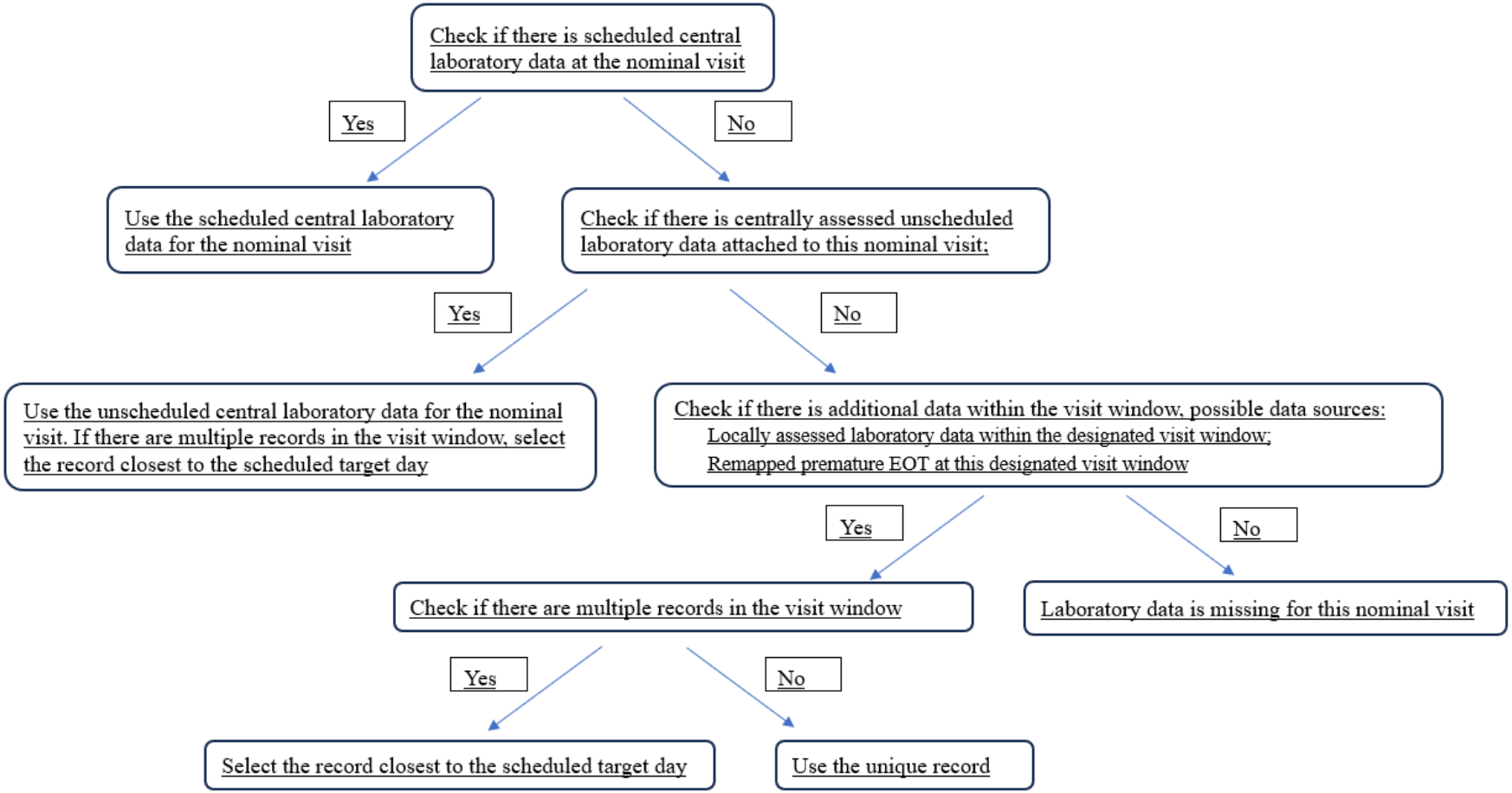
Unscheduled assessments that meet the pre-defined high/low criteria will be flagged and may be included in the corresponding incidence tables.

In general, local laboratory results with missing visits labels are not included in any summary tables. However, due to regional crisis or other reasons, Central lab testing was not available for some patients and the laboratory tests were performed only locally. Therefore, data from local laboratory might also be considered for summary tables. Below is the hierarchy of assigning laboratory data for a definite nominal visit.

1. For nominal laboratory visit listed in section 6.12 (as well as the additional safety visit at week 8, week 16 and week 20), if there is scheduled central laboratory data, the results from the central laboratory data at this nominal visit will be used.
2. If there is no available scheduled central laboratory data at this nominal visit, data from centrally assessed unscheduled laboratory data attached to this nominal visit will be considered.
3. If there is no available central laboratory data attach to this nominal visit (neither scheduled nor unscheduled assessments), data from the following sources will be considered, within the time window of the nominal visit (see Table 7 for the visit window).
    a. Locally assessed laboratory data within the designated visit window;
    b. Remapped premature EOT at this designated visit window.

In case there are multiple data within the same visit window, the record closest to the scheduled target day will be selected for summary statistics. In case there are two records with equal distance to schedule target day, the one occurs after target day will be used.

Figure 2: Flowchart of selecting laboratory data for nominal visit



In addition, the following figures will be produced for lymphocyte counts, both for the Combined Analysis Period, by core study treatment, using SAF, and for the Extension Analysis Period, using the EXTS:

- Summary of mean percent change from baseline values (and their standard error) for lymphocyte counts by visit: mean plot starting with zero change at baseline.

The specified abnormal findings (i.e. any laboratory test result of exceeding/not meeting the thresholds for marked laboratory abnormality in Section 6.10) in safety laboratory hematology, clinical chemistry and other laboratory parameters planned per protocol are also presented in subject data listings, for Extension Analysis Period only.

A listing will be created for all lymphocyte counts at each visit. The marked abnormality findings in lymphocyte count will be flagged in the listing.

For urinalysis no definitions and derivations necessary. Any resulting findings are recorded as adverse event (or medical history or relapse).

In addition, the following analysis will be performed for teriflunomide concentration which was measured at extension study day 1 for treatment group "Teriflunomide 14 mg / Ponesimod 20 mg".

- Number of subjects with teriflunomide concentration assessed.
- Number of subjects with non-detectable teriflunomide concentration
- Descriptive summary (N, arithmetic mean, SD, geometric mean, coefficient of variation [CV%], median, range, and IQ range) of the teriflunomide concentration in subjects whose sample were detectable.

A listing will be provided for all subjects with assessable teriflunomide concentration on extension study day 1.

5.4.3.2. Vital Signs

5.4.3.2.1. Definition of Vital Signs variables

5.4.3.2.1.1. Blood Pressure

Per protocol, blood pressure measurements, including systolic (SBP) and diastolic (DBP) blood pressure will be performed at all scheduled study visits, both during the core and the extension study.

Data is stored along with nominal visit and time point labels that will be used for the analysis. Data from both studies (core and extension) will be pooled for the analysis.

At all assessments (except the hourly post-dose assessments after first dose on Day 1 at re-initiation), blood pressure will be measured twice (i.e., two SBP measurements and two DBP measurements) and recorded in the eCRF. The average of the two values will be calculated on the eCRF and recorded as "Mean SBP" and "Mean DBP". For all data analysis, baselines, and for flagging of high or low values, these mean values will be used. If only one measurement is available, this is used for all further derivations and summary statistics.

Extension / core baseline is flagged and absolute and percent changes from extension/core baseline are calculated for each post-baseline value. In the same manner, pre-dose values are flagged and

absolute and percent change from pre-dose are calculated for the hourly post-dose assessments after first dose on extension study Day 1 at re-initiation.

For by-visit and by-hour tables presenting summary statistics of quantitative vital signs results, the latest (by date/time) transmitted measurement per nominal subject-visit / time point is used in case of multiple data available at that visit or visit / time point.

Assessments meeting the following conditions for **notable abnormalities** are flagged in the ADaM dataset:

- SBP ≤ 90 mmHg or ≥ 20 mmHg decrease from baseline;
- SBP ≤ 90 mmHg;
- ≥ 20 mmHg decrease from baseline in SBP;
- SBP ≥ 160 mmHg or ≥ 20 mmHg increase from baseline;
- SBP ≥ 160 mmHg;
- SBP ≥140 mmHg;
- ≥ 20 mmHg increase from baseline SBP;
- DBP ≤ 50 mmHg or ≥ 15 mmHg decrease from baseline;
- DBP ≤ 50 mmHg;
- ≥ 15 mmHg decrease from baseline in DBP;
- DBP ≥ 100 mmHg or ≥ 15 mmHg increase from baseline;
- DBP ≥ 100 mmHg;
- DBP ≥ 90 mmHg;
- ≥15 mmHg increase from baseline in DBP.

The above flags are derived for the Extension Analysis Period using extension baseline as a reference, and additionally for the Combined Analysis Period using the core baseline value as a reference.

For all hourly post-dose assessments after first dose on extension study Day 1 at re-initiations during the extension, flags are set for the following conditions:

- SBP ≤ 90 mmHg or ≥ 20 mmHg decrease from pre-dose;
- ≥ 20 mmHg decrease from pre-dose in SBP;
- DBP ≤ 50 mmHg or ≥ 15 mmHg decrease from pre-dose;
- ≥ 15 mmHg decrease from pre-dose in DBP.

For details of the vital signs abnormality flags derived during the core study, see the core SAP [D-19.178]. These variables are used as derived in the core study, and are not re-derived for the extension analysis.

5.4.3.2.1.2. Weight

Weight is collected in the eCRF of the core study at Screening, Visit 10 (Week 60), EOT Visit (Week 108), and at unscheduled visits; and in the eCRF of the extension study at Visits 7, 11, 15, 19, and EOT (Weeks 48, 96, 144, 192, and 240), and at unscheduled visits.

Data is stored along with nominal visit and time point labels that will be used for the analysis. Absolute and percent change from core/extension baseline is calculated for each post-baseline weight (kg) value.

5.4.3.2.1.3. Body Temperature

Body temperature is collected at all visits in the Body Temperature eCRF as 'normal' or 'abnormal' both for the core and the extension studies.

No definitions and derivations (other than treatment day of assessment) are necessary.

5.4.3.2.1.4. Pulse rate

Pulse rate is collected as 'normal' or 'abnormal' at unscheduled visits in the Pulse Rate eCRF of the core and extension studies, and additionally at visits where no 12-lead ECG is performed during the extension study (as indicated in Protocol Table 12 and Table 13).

No definitions and derivations (other than treatment day of assessment) are necessary.

5.4.3.2.2. Analysis of Vital Signs

The following outputs will be produced for blood pressure (SBP and DBP) and body weight, both for the Combined Analysis Period, by core study treatment, using SAF (the summaries marked with § will include only the subjects who were initially treated with ponesimod 20 mg in the core study), and for the Extension Analysis Period, by core study treatment and overall using the EXTS:

- Summary of absolute values for blood pressure parameters and body weight: descriptive statistics by visit;
- Summary of absolute and absolute change from baseline values for blood pressure parameters and body weight: descriptive statistics by visit; mean changes from baseline in blood pressure are also presented graphically with their standard error over time (plots starting with zero change at baseline);
- Number and percentage of subjects with any treatment-emergent blood pressure result meeting the criteria defined in Section 5.4.3.2.1 Percentages are based on the number of subjects with at least one treatment-emergent result available for the corresponding parameter.[§]

The following outputs will be produced for blood pressure (SBP and DBP), for the Extension Analysis Period only, by core study treatment and overall using the EXTS:

- Summary of pre- and post-dose values for vital signs parameters on Day 1 of first reinitiation: descriptive statistics time point. Note: data from re-initiations beyond the first are listed only; Strictly speaking the Day 1 of extension study is also counted as "Day 1 of first re-initiation" as subjects had experienced study treatment interruption between end of core study and start of extension study. Nevertheless in this context the "Day 1 of first re-initiation" applies for re-initiation after a study drug interruption during extension period.
- Summary of absolute and absolute change from pre-dose to post-dose values for vital signs parameters on Day 1 of first re-initiation: descriptive statistics by time point. Note: data from re-initiations beyond the first are listed only;
- Number and percentage of subjects with any post-dose blood pressure result meeting the criteria defined in Section 5.4.3.2.1 on Day 1 of (any) re-initiation. Percentages are based on the number of subjects with at least one post-dose blood pressure result available for the corresponding parameter.

Unscheduled visits are not presented in summary tables by visit. Unscheduled assessments that meet the pre-defined high/low criteria will be flagged and included in the corresponding incidence tables.

The outputs summarizing high and low blood pressure will only use treatment-emergent data.

All notable abnormality in blood pressure (as specified above) are listed by core study treatment group and visit.

5.4.3.3. Electrocardiogram

5.4.3.3.1. Definition of ECG variables

5.4.3.3.1.1. ECG parameter measurements

The following variables are collected: Heart Rate (HR) (bpm), PR interval (ms), QRS (ms), QT (ms). Corrected QT values QTcF (ms) and QTcB (ms) (based on Fridericia's and Bazett's formulae) are provided by the central vendor and will not be recalculated.

Data are stored along with nominal visit and time point labels that will be used for the analysis. Extension/core baseline is flagged and absolute and percent changes from baseline are calculated for each post-baseline value. In the same manner, pre-dose values are flagged and absolute and percent changes from pre-dose are calculated for the hourly post-dose assessments after first dose on extension study Day 1 at re-initiations during the extension study.

For by-visit and by-hour tables presenting summary statistics of quantitative ECG results, the latest (by date/time) transmitted measurement per nominal subject-visit / time point is used in case of multiple data available at that visit or visit / time point.

Assessments meeting the following conditions for **notable abnormalities** are flagged in the ADaM dataset:

- Heart rate ≤ 50 bpm;
- Heart rate ≤ 45 bpm;
- Heart rate ≤ 40 bpm;
- PR interval > 200 ms and increase of > 20 ms compared to baseline assessment;
- QTcF/QTcB prolongation of > 500 ms;
- QTcF/QTcB prolongation of > 480 ms;
- QTcF/QTcB prolongation of > 450 ms;
- QTcF/QTcB increase from baseline of > 30 ms;
- QTcF/QTcB increase from baseline of > 60 ms;
- QTcF/QTcB prolongations of > 500 ms and increase from baseline of > 30 ms;
- QTcF/QTcB prolongations of > 500 ms and increase from baseline of > 60 ms;
- QTcF/QTcB prolongations of > 450 ms and increase from baseline of > 30 ms;
- QTcF/QTcB prolongations of > 450 ms and increase from baseline of > 60 ms.

Notable abnormalities are derived for the Extension Analysis Period using extension baseline as a reference, and additionally for the Combined Analysis Period using the core baseline as a reference.

In addition, assessments meeting the following conditions for notable abnormalities on Day 1 of re-initiation during the Extension Analysis Period are flagged in the ADaM dataset:

- PR interval > 200 ms and increase of > 20 ms compared to pre-dose assessment;
- QTcF/QTcB increase from pre-dose of > 30 ms;

- QTcF/QTcB increase from pre-dose of > 60 ms.

For details of the ECG notable abnormality flags derived during the core study. These variables are used as derived in the core study and are not re-derived for the extension analysis.

For presentation of these outliers in by-visit and by-hour tables, the most extreme (i.e., lowest heart rate and highest interval) is considered in case of multiple data available at that visit or visit / time point.

5.4.3.3.1.2. Morphological ECG findings

Morphological ECG findings are reported by the central reader, and mapped to CDISC standard (codelist C71153, with high level categories from codelist C71152) in the SDTM.

For details of the morphological ECG findings variables collected during the core study, see the core SAP [D-19.178]. These variables are used as derived in the core study, and are not re-derived for the extension analysis.

For analyses in tables the following categories are anticipated:

- Atrioventricular Conduction
- Axis and Voltage
- Chamber Hypertrophy or Enlargement
- Conduction
- Ectopy
- Intraventricular-Intraatrial Conduction
- Rhythm Not Otherwise Specified
- ST Segment, T wave, and U wave
- Sinus Node Rhythms and Arrhythmias
- Supraventricular Arrhythmias
- Supraventricular Tachyarrhythmias
- Ventricular Arrhythmias

Findings related to interpretation or technical issues are only included in listings.

Morphological ECG findings are flagged as “New” if not present at any assessment prior to first treatment in the Analysis Period, or “Pre-existing” if present at such assessment. For the Combined Analysis Period, in case of missing or non-evaluable pre-treatment ECG assessment, it is conservatively assumed that any treatment-emergent morphological ECG finding is “New”.

Morphological ECG findings on Day 1 of (any) re-initiation

Morphological ECG findings on Day 1 of a re-initiation are those findings that start at or after the time of the ponesimod administration on Day 1 of a re-initiation, and before the following calendar date.

Morphological ECG findings with onset on Day 1 of re-initiation are considered with respect to any re-initiation of ponesimod during the Extension Analysis Period. Morphological ECG findings on Day 1 of a re-initiation are considered to be “New” if they were not present at any pre-dose assessment on the day of re-initiation, or if no pre-dose assessment on day of re-initiation was performed.

For presentation of these findings in by-visit and by-hour tables, all reported abnormalities are considered in case of multiple assessments available at that visit or visit / time point.

5.4.3.3.2. Analysis of ECG

The following outputs will be produced for ECG, both for the Combined Analysis Period, by core study treatment, using SAF (the summaries marked with § will include only the subjects who were initially treated with ponesimod 20 mg in the core study), and for the Extension Analysis Period, by core study treatment and overall, using the EXTS:

- Summary of absolute values for ECG parameters (HR, PR, QRS, QT, and QTcF / QTcB): descriptive statistics by visit;
- Summary of absolute and absolute change from baseline values for ECG parameters (HR, PR, QRS, QT, and QTcF / QTcB): descriptive statistics by visit. Mean changes from baseline in heart rate are also presented graphically with their standard error over time (plots starting with zero change at baseline);
- Incidence of treatment-emergent notable abnormalities (PR prolongations and HR outliers as defined in Section 5.4.3.3.1.1): frequency counts and percentages, overall and by visit, where percentages are based on the number of subjects with at least one post-baseline value (i.e., number of subjects at risk);§
- Incidence of clinically relevant morphological ECG findings [as defined in Section 5.4.3.3.1.1], by abnormality and group term, overall and by visit: frequency counts and percentages;§

The following outputs will be produced for the Extension Analysis Period only, by core study treatment and overall, using the EXTS:

- Summary of pre- and post-dose values for ECG parameters (HR, PR, QRS, QT, and QTcF / QTcB) on Day 1 of first re-initiation: descriptive statistics time point. Strictly speaking the Day 1 of extension study is also counted as "Day 1 of first re-initiation" as subjects had experienced study treatment interruption between end of core study and start of extension study. Nevertheless in this context the "Day 1 of first re-initiation" applies for re-initiation after a study drug interruption during extension period.
- Summary of absolute and absolute change from pre-dose values for post-dose values of ECG parameters (HR, PR, QRS, QT and QTcF / QTcB) on Day 1 of first re-initiation: descriptive statistics by time point.
- Incidence of treatment-emergent PR prolongations and HR outliers [as defined in Section 5.4.3.3.1.1] on Day 1 of (any) re-initiation: frequency counts and percentages, overall post-dose and by post-dose time point, where percentages are based on the number of subjects with at least one post-dose value (i.e., number of subjects at risk).
- Incidence of clinically relevant morphological ECG findings on Day 1 of (any) re-initiation by abnormality and group term, overall and by time point: frequency counts and percentages.

Only newly occurring treatment-emergent abnormalities and findings are reported, i.e. if a subject has a particular event/finding prior to first treatment in the Analysis Period, and the same event/finding occurs again during the Analysis Period, it will not be reported in the summary table. "Pre-existing" findings will be only flagged in datasets and reported in listing. Unscheduled visits are not presented in summary tables by visit. Unscheduled assessments that meet the pre-defined high/low criteria will be flagged and may be included in the corresponding incidence tables.

All ECG notable abnormality data as specified above will be included in listings.

5.4.3.4. Spirometry and DL_{CO}

5.4.3.4.1. Definition of Spirometry and DL_{CO}

Spirometry tests are performed to assess pulmonary function.

In the core study, spirometry measurement data are collected using vendor machines from ERT and data are automatically submitted to ERT by the machine. In the extension study, spirometry measurement data are assessed at site and entered on the eCRF.

The following variables are collected in the extension study:

- FEV_1 (Forced Expiratory Volume in 1 Second) [L];
- FVC (Forced Vital Capacity) [L];

The following variables are derived for analysis (predicted values based on Quanjer [Quanjer 1993]):

- FEV_1 / FVC ratio = FEV_1 [L] / FVC [L];
- Predicted normal FEV_1[L] for male subjects = 4.30 × height (m) − 0.029 × *age* (years) at extension study enrollment − 2.49;
- Predicted normal FEV_1[L] for female subjects = 3.95 × height (m) − 0.025 × *age* (years) at extension study enrollment − 2.60;
- Predicted normal FVC[L] for male subjects = 5.76 × height (m) − 0.026 × *age* (years) at extension study enrollment − 4.34;
- Predicted normal FVC[L] for female subjects = 4.43 × height (m) − 0.026 × *age* (years) at extension study enrollment − 2.89.

For the predicted normal values derivations above, age as collected at study extension enrollment and height collected at core study screening are used; also *age* is set to 25 years if age is between 18 and 25 years and a conversion factor of 0.9 must be multiplied to the predicted normal value if subject race is other than 'White'.

- Percent of the corresponding predicted normal value is also calculated for FEV_1[L] and FVC[L] as follows:

  Percent of the predicted value (%) = [measured value] x100 / [predicted normal value]

The percent of the predicted normal values FEV_1 and FVC, as calculated by the vendor, for core study data will be used, and are not re-derived for the extension analysis.

For the core study assessments, analyses are based on best efforts, for details see CSR SAP for core study.

Core/extension baseline is flagged and absolute and percent changes from core/extension baseline are calculated for each post-baseline value.

Assessments meeting the following conditions are flagged in the ADaM dataset:

- Percent change from baseline in FEV_1: < −20%, < −30%;
- Percent change from baseline in FVC: < −20%, < −30%;
- Absolute change from baseline in %PRED FEV_1: < −20%, < −30%;

- Absolute change from baseline in %PRED FVC: < −20%, < −30%;
- FEV_1/FVC < 70%.

For details of the same conditions for the core study, see the core SAP. These flags are used as derived in the core study, and are not re-derived for the extension analysis.

Spirometry - DL_{CO}

Subjects who participated in the DL_{CO} sub-study during the core study were asked to continue their participation in the DL_{CO} sub-study during the extension study. Subjects who chose to continue participation provided consent under a separate informed consent for the DL_{CO} sub-study.

The DL_{CO} assessment is conducted at extension study Visits 3, 7, 11, 15, 19, EOT, and EOS. In addition, unscheduled DL_{CO} tests may be performed at any time during the study.

An assessment usually consists of multiple maneuvers. Among multiple maneuvers (reported within the same visit and assessment date), the mean value of the two highest DL_{CO} measurements are derived to represent the DL_{CO} at that assessment. If only one DL_{CO} measurement is available at an assessment, that measurement is used. Within the eCRF, DL_{CO} values are converted into 'mmol/min/kPA', which is the unit used in reporting.

Only these derived assessment-level values are used for any further derivations, the term 'DL_{CO} at visit' will refer to this value derived from the individual maneuvers measurements.

The following derivations are performed for DL_{CO} from all measurements:

- DL_{CO} adjusted for Hemoglobin (Hb) is derived based on the method of Cotes [Macintyre 2005] using the Hb reported by the central laboratory (or from local laboratory if missing) at the same nominal visit based on below formulae:
  - $DL_{CO\ Hb\ corrected} = DL_{CO} \times (10.22 + Hb\ [g/dL]) / (1.7 \times Hb\ [g/dL])$ for male subjects older than 14 years;
  - $DL_{CO\ Hb\ corrected} = DL_{CO} \times (9.38 + Hb\ [g/dL]) / (1.7 \times Hb\ [g/dL])$ for female subject subjects and all subjects ≤ 14 years;

  If no Hb value is available at the corresponding visit, this variable is missing.

- Predicted DL_{CO} corresponding to each assessment is derived based on Cotes [Cotes 1993] as follows:
  - $DL_{CO\ predicted} = 11.11 \times Height\ [m] - 0.066 \times Age\ [years] - 6.03$, for male subjects, age is set to 25 years if age below 25 years;
  - $DL_{CO\ predicted} = 8.18 \times Height\ [m] - 0.049 \times Age\ [years] - 2.74$, for female subjects, age is set to 25 years if age below 25 years;

  The age used in above formula is derived as follows: Age at baseline + 0.5 + (Date of assessment − Date of (re-)screening) / 365.25;

- Percent Predicted DL_{CO} is derived as:
  $100 \times DL_{CO\ Hb\ corrected} / DL_{CO\ predicted}$

Assessments meeting the following conditions **for notable abnormality** are flagged in the ADaM dataset:

- Percent change from baseline in DL_{CO}: < −20%;
- Percent change from baseline in hemoglobin corrected $DL_{CO\ d}$: < −20%;
- Absolute change from baseline in Percent predicted DL_{CO}: < −20%.

5.4.3.4.2. Analysis of Spirometry and DLCO

Spirometry:

The following outputs will be produced for PFTs, both for the Combined Analysis Period, using SAF, and for the Extension Analysis Period, using the EXTS:

- Summary of absolute values for PFT parameters (FEV_1, FVC, FEV_1/FVC ratio, %PRED FEV_1, %PRED FVC): descriptive statistics by visit;
- Summary of absolute change from baseline values for PFT parameters (FEV_1, FVC, FEV_1/FVC ratio, %PRED FEV_1, %PRED FVC): descriptive statistics by visit;
- Summary of percent change from baseline values for PFT parameters (FEV_1, FVC, FEV_1/FVC ratio, %PRED FEV_1, %PRED FVC): descriptive statistics by visit;
- Summary of absolute change from baseline values for PFT parameters (FEV1, FVC, FEV_1/FVC ratio, %PRED FEV_1, %PRED FVC): mean plot with core study treatment group color-coded (plot starting with zero change at baseline).
- Summary of percent change from baseline values for PFT parameters (FEV_1, FVC, FEV_1/FVC ratio, %PRED FEV_1, %PRED FVC): mean plot with core study treatment group color-coded (plot starting with zero change at baseline).

In addition, the following outputs will be produced both for the Combined Analysis Period, using the SAF and only for subjects who received ponesimod 20 mg in the core study, and for the Extension Analysis Period, using the EXTS:

- Incidence of treatment-emergent spirometry outliers [as defined in Section 5.4.3.4.1]: frequency counts, percentages, where percentages are based on the number of subjects with at least one treatment-emergent result available for the corresponding parameter.

Unscheduled visits are not presented in summary tables by visit. Unscheduled assessments that meet the pre-defined high/low criteria will be flagged and may be included in the corresponding incidence tables.

All notable abnormality in spirometry results (best effort results from core study and all results from extension study) will be listed by study treatment group and visit.

In addition, to understand the change in PFT parameters (FEV1, FVC, FEV1/FVC ratio, %PRED FEV1, %PRED FVC) after EOT, the following analyses will be done for subjects who continue any DMT (see section 6.5.1.4 for DMT list) after EOT date versus subjects who have no DMT after EOT date (irrespective of the original treatment group):

- Absolute values of PFT parameters over the following visits: Core baseline, Extension Baseline, Extension EOT, Extension EOS and the change from Core baseline using EXTS.

- A line graph to present the percent change from core baseline in PFT parameters over the following visits: Core baseline, Extension Baseline, Extension EOT, Extension EOS.

Note that the group labels in this analysis are “Any DMT” and “No DMT”, irrespective of the treatment group. Only subjects who have EOS visit and the EOS visit is at least 5 days after the EOT date are included in this analysis (refer to section 5.5.6 for more details).

Spirometry (Pulmonary Function Tests) - DL_{CO}

The following summary displays are provided, by study treatment group, for the Combined Analysis Period (the summaries marked with § will include only the subjects who were initially treated with ponesimod 20 mg in the core study) on the DLco sub-study safety analysis set, and for the Extension Analysis Period on the DLco sub-study extension analysis set:

- Treatment-emergent Hemoglobin corrected DLco, percent predicted DLco and DLco including absolute and percent change from core baseline, as described in Section 5.4.3.4.1, are presented, by parameter and visit. Except for 'Baseline', only treatment-emergent results from nominal scheduled visits are included; premature EOT visit is mapped to a scheduled visit. These are summarized descriptively and mean absolute and percentage changes from baseline are also presented graphically with their standard error over time (plots starting with zero change at baseline).
- Number and percentage of subjects with any occasion of treatment-emergent low Hemoglobin corrected DLco, Percent predicted DLco, and DLco values as defined in Section v are presented. Percentages are based on the number of subjects with at least one treatment-emergent result available for the corresponding parameter.[§]

All notable abnormality DL_{CO} results (derived mean values per assessment) are listed by study treatment group and visit.

5.4.3.5. Dermatological Examination

Collected in the Dermatological Examination eCRF. No definitions and derivations necessary. Any resulting findings are recorded as adverse event (or medical history). No additional statistical outputs are needed in this field.

5.4.3.6. Optical coherence tomography

Collected in the Optical coherence tomography (OCT) eCRF. No definitions and derivations necessary. Any resulting findings are recorded as adverse event (or medical history or relapse). No additional statistical outputs are needed in this field.

5.4.3.7. Ophthalmological Examination

Data will be taken from both Ophthalmological Examination eCRFs. No definitions and derivations necessary. Any resulting findings are recorded as adverse event (or medical history or relapse). No additional statistical outputs are needed in this field.

5.4.3.8. Physical examination

No definitions and derivations necessary. Any resulting findings are recorded as adverse event (or medical history or relapse). No additional statistical outputs are needed in this field.

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

5.4.3.9.1. Definition of eC-SSRS variables

The electronic self-rated version of the Columbia-Suicide Severity Rating Scale (eC SSRS©) is an assessment instrument that evaluates suicidal ideation and behavior. During an initial assessment it assesses lifetime as well as the recent history suicidality (scheduled at Core study

Visit 2-Baseline), and then prospectively monitors ideations and behaviors at subsequent follow up assessments since the last call throughout Core and Extension study.

The eC-SSRS outcome categories are provided below. The categories are ordered by increasing seriousness. Each category has a binary response (yes/no) and are numbered and ordered below for convenience

Table 8: eC-SSRS outcome categories

Suicidal category	Question category	Label in QSTEST in QS dataset
Suicidal Ideation (1-5)	Category 1: Wish to be dead	"CSS01-Wish to be Dead" and "CSS02-Wish to be Dead"
	Category 2: Non-specific active suicidal thoughts	"CSS01-Non-Specific Suicidal Thought" and "CSS02-Non-Specific Suicidal Thought"
	Category 3: Active suicidal ideation with any methods (not plan) without intent to act	"CSS01-Suicidal Ideation-No Intent" and "CSS02-Suicidal Ideation-No Intent"
	Category 4: Active suicidal ideation with some intent to act, without specific plan	"CSS01-Ideation With Intent, No Plan" and "CSS02-Ideation With Intent, No Plan"
	Category 5: Active suicidal ideation with specific plan and intent	"CSS01-Ideation With Plan/Intent" and "CSS02-Ideation With Plan/Intent"
Suicidal Behavior (6-10)	Category 6: Preparatory acts or behavior	"CSS01-Preparatory Acts/Behavior" and "CSS02-Preparatory Acts/Behavior"
	Category 7: Aborted attempt	"CSS01-Aborted Attempt" and "CSS02-Aborted Attempt"
	Category 8: Interrupted attempt	"CSS01-Interrupted Attempt" and "CSS02-Interrupted Attempt"
	Category 9: Non-fatal suicide attempt	"CSS01-Most Lethal Attempt Damage", "CSS01-Most Recent Attempt Damage", "CSS01-Most Lethal Attempt Potential", "CSS01-Most Recent Attempt Potential", "CSS02-Most Lethal Attempt Damage", "CSS02-Most Lethal Attempt Potential"
	Category 10: Completed suicide	

Furthermore, **self-injurious behavior without suicidal intent** is also an eC-SSRS outcome (although not suicide-related) and has a binary response (yes/no), this will be assigned as score 11 and to be summarized for subjects with these events.

The initial assessment has a lifetime and a recent history assessment. The recent history covers the last 1 month for suicidal ideation, and the last 3 months for suicidal behavior. Recent history questionnaire questions are only assessed for outcome categories with corresponding lifetime outcome question answered as yes. If the lifetime assessment for an outcome category is 'No', also the corresponding recent history outcome is considered 'No' for analysis. The "lifetime and a recent history assessment" is performed twice during the course of the study, respectively at core study baseline and at extension visit 7 – week 48.

Scoring: Scores are created at each assessment as follows:

- **Suicidal Ideation Score**: The maximum suicidal ideation category (1–5 on the eC-SSRS) present at the assessment. Assign a score of 0 if no ideation is present.
- **Suicidal Behavior Score:** The maximum suicidal behavior category (6–10 on the eC-SSRS) present at the assessment. Assign a score of 0 if no behavior is present.

For each assessment timepoint, a subject with multiple reported outcomes for suicidal ideation and suicidal behavior will be summarized under the worst reported outcome (i.e., max[1–5] and max[6–10], respectively).

Throughout all post-baseline assessments, a subject can have multiple suicidal ideation or suicidal behaviors, the worst reported outcome will be considered as the post-baseline outcome.

The following definitions will be used:

- **Suicidal ideation**: A "yes" answer to any one of the five suicidal ideation questions (Categories 1-5) on the eC-SSRS. Taken from the 'Reported most severe ideation level'.
- **Suicidal behavior**: A "yes" answer to any one of the five suicidal behavior questions (Categories 6-10) on the eC-SSRS.
- **Suicidal ideation or suicidal behavior**
- **Serious suicidal ideation (score ≥ 4) or suicidal behavior**

The definitions above will be defined at any time in the period from study treatment start up to Extension EOT + 15 days*, for pre-treatment lifetime, and for pre-treatment recent history.

Suicidal Ideation and Suicidal Behavior score categories: Shifts from baseline (worst outcome from pre-treatment recent history) to the worst outcome up to Extension EOT + 15 days (inclusive) will be derived using the following categories: No ideation (score 0), non-serious suicidal ideation (score 1–3), serious suicidal ideation (score 4–5), suicidal behavior (score 5–10).

*Only post-baseline assessments after study treatment start date from a 'since last call' questionnaires and the "Recently" questionnaire assessed at B303 extension week 48 (visit 7) are considered for the analysis.

Baseline is defined as last available recent history result (maximum score) up to study treatment start date at core study, i.e., pre-treatment recent history result at core baseline. This is taken from the answers to the "Recently" category questionnaires at core study baseline. If the lifetime assessment at core study baseline for an outcome category is 'No', also the corresponding recent

history outcome is considered 'No' for analysis. The core study baseline has already been derived and captured in B301 ADaM dataset and can be used directly.

5.4.3.9.2. Analysis of Columbia Suicide ideation or behavior

Number (%) of subjects with suicidal ideation (overall and by category), suicidal behavior (overall and by category), suicidal ideation score ≥ 4 or suicidal behavior and/or self-injurious behavior without suicidal intent will be tabulated by treatment group at Core baseline visit and at Extension week 48. The "Lifetime" and "Recently" results will be summarized separately. In addition, the worst outcome of post-core-baseline assessment up to Extension EOT + 15 days (including the assessment at Extesion week 48) will be presented. Analyses will be based on subjects in the SAF and EXTS who have at least one eC-SSRS measurement during Combined analysis period available.

For subjects who have in addition a core baseline eC-SSRS assessment available shifts from core baseline (maximum score from pre-treatment recent history) to the worst reported outcome (the maximum score) up to Extension EOT + 15 days will be tabulated by treatment group to demonstrate any changes in Suicidal Ideation and Suicidal Behavior score categories (i.e. No ideation, non-serious suicidal ideation, serious suicidal ideation , suicidal behavior).

A listing will be generated for subjects who have positive value of any Suicidal Ideation, Suicidal Behavior or Self-Injurious Behavior without Suicidal Intent of that visits. To be specific, if a subject had outcome "Y" in the Suicidal ideation category "1-Wish to be Dead" at Extension visit 11, all suicidality scores of that visit will be listed. On the contrary, if all outcomes of suicidality score are negative then this visit won't be listed.

5.5. Other Analyses

5.5.1. Pharmacokinetics

No Pharmacokinetics analysis is applied in this study.

5.5.2. Immunogenicity

Details of immunogenicity analyses conducted in this study are presented in Sections 6.11 for Covid-19

5.5.3. Pharmacodynamics

The pharmacodynamic (PD) marker evaluated in this study is Peripheral lymphocyte counts, which were measured as part of the clinical laboratory hematology tests.

To capture the abnormality in lymphocyte counts, among the treatment-emergent-flags abnormal values, the lowest lymphocyte counts through all post-baseline assessments are further categorized into the following categories. This will be done separately for combined period and for extension period.

- < 0.2 × 10^9/L;
- ≥ 0.2 × 10^9/L – < 0.5 × 10^9/L;
- ≥ 0.5 × 10^9/L – < 0.8 × 10^9/L;
- ≥ 0.8 × 10^9/L – < 1.0 × 10^9/L;
- ≥ 1.0 × 10^9/L.

The following analyses will be conducted:

- Peripheral lymphocyte counts and the associated percentage change from core baseline by visit and by treatment group during combined period using SAF, along with a line graph to present the percent change from core baseline in peripheral lymphocyte counts by treatment group over visit. Note that only the following nominal visits will be visualized in the plot: Core period -- Baseline, Week 2, Week 4, Week 12, Week 24, Week 48, Week 72, Week 96, Week 108, D15 FU, D30 FU; Extension period – Baseline, Week 2, Week 4, Week 12, Week 24, Week 48, Week 96, Week 144, Week 192, Week 240, Week 288, extension EOT, extension EOS.
- Peripheral lymphocyte counts and the associated percentage extension change from baseline by visit and by treatment group during extension period using EXTS, along with a line graph to present the percent change from core baseline in peripheral lymphocyte counts by treatment group over visit.
- Incidence of treatment-emergent marked abnormalities for blood lymphocyte counts for combined period using SAF and for extension period using EXTS.

In addition, to understand the change in lymphocyte counts after EOT, the following analyses will be done for subjects who continue any DMT after EOT date versus subjects who have no DMT after EOT date:

- Peripheral lymphocyte counts over the following visits: Core baseline, Extension Baseline, Extension EOT, Extension EOS visit and the change from Core baseline using EXTS.
- A line graph to present the percent change from core baseline in peripheral lymphocyte counts over the following visits: Core baseline, Extension Baseline, Extension EOT, Extension EOS.

Note that the group labels in this analysis are “Any DMT” and “No DMT”, irrespective of the treatment group. Only subjects who have EOS visit and the EOS visit is at least 5 days after the EOT date are included in this analysis(refer to section 5.5.6 for more details)..

5.5.4. Quality of life variables

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

The SF-36v2™ instrument is a generic health related quality of life assessment provided by the Medical Outcomes Trust, Boston, USA.

It contains 36 items measuring health across eight areas or domains: Physical Functioning (PF, 10 items: #3a – #3j); Social Functioning (SF, 2 items: #6 & #10); Role Limitations due to physical problems (RP, 4 items: #4a – #4d); Role Limitations due to emotional problems (RE, 3 items: #5a – #5c); Mental Health (MH, 5 items: #9b – # 9h); Vitality (VT, 4 items: #9a – #9i); Bodily Pain (BP, 2 items: #7 & #8) and General Health perceptions (GH, 5 items: #1, #11a – #11d) and an additional item on reported Health Transition to perceive changes in health status in the past 12 months (HT, 1 item: # 2).

In addition, Physical and Mental Component Summary (PCS and MCS) measures are calculated based on aggregate domain scores.

For each of the eight domains, scores will be coded, summed and transformed to generate a score from 0 (worst possible health state) to 100 (best possible health state). These domain scores as well as PCS and MCS will then be standardized to Z scores and then again will be transformed to create norm based scoring also known as t-scores. Scoring will be performed via licensed vendor QualityMetric using ProCore software. QualityMetric's 1998 US population weights will be used to generate norm-based scores, which is consistent with methods in core study AC 058B301 (OPTIMUM). Weighting for norm-based score calculation is embedded in the ProCore Software.

The SF-36v2™ is completed by the subject on an electronic device at defined visits up to extension EOS (see Section 6.12).

5.5.4.2. Analysis of SF-36v2™ Health Survey

Quality of life analysis based on the SF-36v2™ will be performed on the Combined period and Extension period using EXTS.

The eight normative (t-scores) domain scores, PCS and MCS will be summarized descriptively over time. In addition, the change from core baseline as well as change from extension baseline will be summarized by analysis visits.

5.5.5. Biomarkers

No biomarker analysis is applied in this study.

5.5.6. Subgroups analysis

To understand the change in some safety profiles after EOT, the following "Post-treatment DMT" subgroup is defined and the analysis by subgroup will be performed.

- Sub-population included in the analysis: This subgroup analysis includes the subjects who have an EOS visit and the start date of the EOS visit is at least 5 days after the EOT date.
- Post-treatment DMT subgroup definition: A patient in the above-defined sub-population will be assigned to the "Any DMT" category if meeting all the following conditions:
  1) There is a record in CMDECOD in SDTM.CM for any of the therapies listed in Section 6.5.1.4, and the medication is administered systemically via the following routes: Intravenous (IV), Oral, Subcutaneous (SC), Intramuscular (IM).
  2) The corresponding CMSTDTC is on or after the EOT date, or CMSTDTC is before EOT date and CMENDTC is after the EOT date, or CMSTDTC is before EOT date and CMENDTC is missing indicating that the medication is ongoing at EOS.

  Otherwise, the patient is assigned to the "No DMT" category.

5.5.7. Interim Analyses

An interim analysis was conducted in 2019 with data cut-off date of 2019-11-30. Details were documented in the interim analysis SAP.

5.5.8. Data Monitoring Committee (DMC) or Other Review Board

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

5.5.9. Covid-19 Impact Analyses

(i) In order to assess the impact of the Covid-19 pandemic on the ongoing study, the following additional outputs will be presented: the frequency of major PDs related to the pandemic and study drug compliance pre- and post-pandemic. A table of frequencies for major PDs related to the Covid-19 pandemic. This can be identified in SDTM.DV dataset by DVTERM which includes the prefix "Covid-19-related" and DVSCAT= "Major".

(ii) A listing of major PDs related to the Covid-19 pandemic will be presented.

(iii) A table for study drug compliance for the categories pre-Covid-19 and post-Covid-19 will be presented, where pre/post-Covid-19 is defined as pre/post-January 1, 2020. Interruptions occurred pre-Covid 19 is considered in pre-Covid 19 period but excluded from post-Covid 19 period.

(iv) The number of events of Covid-19 related discontinuations will be presented.

5.5.10. Regional Crisis Impact Analyses

In order to assess the impact of the regional crisis in Ukraine and Russia on the ongoing study, the following additional output will be presented:

(i) A listing of all major PDs related to the regional crisis.

(ii) A table for study drug compliance for categories pre-Regional Crisis and post-Regional Crisis will be presented for subjects from impacted countries (defined as Ukraine, Russia and Belarus) and for subjects from Ukraine. The pre/post-Regional Crisis is defined as pre/post February 24, 2022. Interruptions occurred pre-Regional Crisis is considered in pre-Regional Crisis period but excluded from post-Regional Crisis period.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

%PRED FEV1	FEV1 expressed as % of predicted normal value
%PRED FVC	FVC expressed as % of predicted normal value
ADaM	Analysis data sets
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ARR	Annualized Relapse Rate
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
BMI	Body mass index
bpm	Beats per minute
CDA	Confirmed disability accumulation
CDDM	Clinical Development Data Management
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence interval
CL	Confidence limit
CRF	Case report form
CSR	Clinical Study Report
CUAL	Combined unique active lesions
DBP	Diastolic blood pressure
DLco	Diffusing capacity of the lungs for carbon monoxide
DMTs	Disease modifying therapies for MS
ECG	Electrocardiogram
eCRF	Electronic case report form
EDSS	Expanded Disability Status Scale
EOS	End-of-Study
EOT	End-of-Treatment
EXTS	Extension Set
FAS	Full analysis set
FDA	(US) Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FS	Functional System
FU	Follow-up
FU	Follow-up
FVC	Forced vital capacity
Gd+	Gadolinium-enhancing
Hb	Hemoglobin

HR	Heart Rate
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
INR	International normalized ratio
KM	Kaplan-Meier
LLOQ	Lower limit of quantification
LT	Long Term
MAA	Marketing Authorization Application
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
MIAC	Medical Image Analysis Center
Min	Minimum
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSFC	Multiple Sclerosis Functional Composite
NB	Negative binomial
NDA	New Drug Application
PD	Protocol deviation
PFT	Pulmonary function test
PPS	Per-protocol analysis set
PCBV	Percent change from baseline in brain volume
PR	Pulse Rate
PTOP	Post-treatment observation period
QTcB	QT corrected for heart rate on the basis of Bazett's formula
QTcF	QT corrected for heart rate on the basis of Fridericia's formula
RMS	Relapsing multiple sclerosis
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis Software
SBP	Systolic Blood Pressure
SD	Standard deviation
SDTM	Study Data Tabulation Model
SE	Standard error
SMQs	Standardized Medical Dictionary for Regulatory Activities
SOC	System Organ Class
STS	Study treatment start
TBIL	Total bilirubin
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WHO	World Health Organization

6.2. Appendix 2 Changes to Protocol-Planned Analyses

6.2.1. Changes to the analyses planned in the study protocol

The following changes to the analyses planned in the study protocol have been implemented in this SAP for the interim analysis:

- Section 11.4.8.2 of the AC-058B303 protocol [D-18.056] describes the following QTcF prolongation flags: QTcF > 450 ms (male), > 470 ms (female), > 500 ms (male), and > 520 ms (female). These differ from the flags used in the core study, which are not differentiated for sex and are set at QTcF > 450 ms, > 480 ms, and > 500 ms. For consistency, the QTcF flags used in the core study will also be used in the extension study for QTcF as well as QTcB analyses.
- The adverse event of special interest (AESI) list was updated. The primary changes is adding Non-skin malignancy which was not defined in the protocol
- The safety endpoint for change in lung diffusion capacity as assessed by diffusing capacity of the lungs (DL_{CO}) will be analyzed for both the Combined and the Extension Analysis Periods (rather than only for the Combined Analysis Period, as initially planned in the protocol).
- In addition to frequency of adverse events (AEs), AEs will also be summarized as rate per 100 subject-years.
- In data listings, flags for safety data considered to be treatment-emergent with specific reference to the related analysis period will be included (rather than flags for safety data not considered treatment-emergent as reported in the protocol).
- DL_{CO} sub-study safety set and DL_{CO} sub-study extension set will be defined and used for the DL_{CO} sub-study.
- The derivation of the 'HH' and 'HHH' ranges for hemoglobin marked abnormalities were changed to better clarify how to derive pre-treatment assessments and post-treatment assessments when baseline is ≤ upper limit of normal (ULN).
- Per protocol set removed from analysis.
- The main efficacy analysis for final CSR focuses on combined period using EXTS. This is different from protocol Section 11.4.2.3. The argument is: given that long treatment duration in extension study (240 weeks) in comparison of core study (108 weeks), more focus should be placed in the population who have participated the extension study. The analysis using FAS in the combined period will still be conducted for key efficacy endpoints (see Section 4.2)
- The change from baseline for urinalysis depicted in protocol Table 9 is removed. Any resulting abnormal findings are recorded as adverse event (or medical history) and therefore no further analysis is needed. In addition, more urinalysis parameters are assessed in qualitative results and hence the analysis "change from baseline" is not applicable.
- The definition of NEDA 4 in terms of change in brain volume is updated in section 5.3.1.4.2 to be "Annual brain volume from core baseline to extension EOS decrease ≥ 0.4% at all assessment" This corrects the typo made in protocol table 6 "annual brain volume change ≥ -0.4% from baseline to all assessments".

6.2.2. Clarifications concerning endpoint definitions and related variables or statistical methods

The abnormality criteria for the international normalized ratio (INR) variously appears in the protocol as INR > 1.5 and INR ≥ 1.5 ULN. It is clarified here that the correct definition is INR > 1.5 and this will be used for all related definitions and analyses.

A subject is considered to have completed the study if they complete the End-of-Study (EOS) and safety follow-up assessments. It is clarified in this SAP that this is independent of treatment completion, i.e., a subject can prematurely discontinue from treatment but go on to complete the study per protocol.

6.3. Appendix 3 Demographics and Baseline Characteristics

6.3.1. Definition of demographic variables and baseline characteristics

For details of the demographic and baseline characteristics variables collected at the start of the core study, see the core SAP [D-19.178]. These variables are used as derived in the core study and are not re-derived for the extension analysis.

6.3.1.1. Demographics

The following demographic variables are derived at the start of the extension study:

- Sex, as collected on the 'Demographics' eCRF (Male, Female);
- Age at start of extension (years), from the 'Demographics' eCRF;
- Age categories derived from the above as follows: 18–30, 31–40, 41–55, ≥ 56 years;
- Weight at start of the extension study (kg), from the 'Body Weight' eCRF of the core study End-of-Treatment (EOT) visit;
- Body mass index (BMI) at start of the extension study (kg/m^2) derived as Weight (kg) / (Height (cm) / 100)^2;
- BMI categories: < 18.5; ≥ 18.5 – < 25; ≥ 25 – < 30; ≥ 30.

Height, race, ethnicity, country, and region are collected at the start of the core study and are used as derived in the core study.

6.3.1.2. Baseline disease characteristics

The following **baseline characteristics** variables are derived at the start of the extension study:

- **Expanded Disability Status Scale (EDSS) score at extension baseline,** defined as the latest available EDSS score as entered in the EDSS / FS eCRF (i.e., not re-derived based on sub-scores) of either the core or the extension study, that is prior to or on the date of first ponesimod administration in the extension study;

- **EDSS score at extension baseline, categorized** as (≤ 3.5, > 3.5), derived from the EDSS score at extension baseline above.

- **Time since first symptoms at start of extension (years)**, defined as [Extension enrollment date – Date of first MS symptoms + 1] / 365.25. Date of first MS symptoms is taken from 'MS History Disease Characteristics' core eCRF at screening. Partial dates of first MS symptoms, are imputed to the 1st day of the month (if the day is missing) and to the 1st of January (if the day and month are missing). No imputation is performed if the date is completely missing.

- **Time since initial diagnosis at start of extension (years)**, defined as: [Extension enrollment date − Date of initial diagnosis + 1] / 365.25. Date of initial diagnosis is taken from 'MS History Disease Characteristics' core eCRF at screening. Partial dates of initial diagnosis are imputed to the maximum of [Date of first MS symptoms, 1st day of the month] (if the day is missing) and to the maximum of [Date of first MS symptoms, 1st of January] (if the day and month are missing). No imputation is performed if the date is completely missing.

- **Time since most recent relapse (months) at start of extension**, defined as [Extension enrollment date − Start date of latest MS relapse prior to enrollment in the extension study + 1] in days / 30.4375.

For most recent relapse, the following sources of relapses are considered:

1) Relapses prior to entry into the core study: from the core eCRF, form 'MS History - Relapse' at screening. The most recent "Onset date of previous relapse" among all previous relapses entered on the 'MS History - Relapse' eCRF is used as derived in the core study.

2) Relapses occurring during the core study: from core eCRF, take the most recent "Start date of relapse" among all relapses entered on the 'Relapse Summary' eCRF form. Partial start dates are imputed to the maximum of [Date of previous relapse documented, 1st day of the month] (if the day is missing) and to the maximum of [Date of previous relapse documented, 1st of January] (if the day and month are missing). Data collected at re-screening overwrites the initially entered data.

Take the latest date from either of the above that is prior to extension enrollment date.

- **Number of documented MS relapses in the last year prior to start of extension**, defined as the number of MS relapses entered on the 'Relapse Summary' of the core eCRF for which the start date of the relapse is prior to the extension enrollment date and after the extension enrollment date – 365 days.
- **Number of documented MS relapses in the last 2 years prior to start of extension,** defined as the number of MS relapses entered on the 'Relapse Summary' of the core eCRF for which the start date of the relapse is prior to the extension enrollment date [see Section 5.1.9.1] and after the extension enrollment date − 730 days.
- **Presence of Gd+ T1 lesions (yes/no)** on extension baseline MRI scan as provided by the MRI central reading**.**
- **Number of documented Gd+ T1 lesions** on extension baseline MRI scan as provided by the MRI central reading**.**
- **Volume of T2 lesions** on extension baseline MRI scan as provided by the MRI central reading.

6.3.2. Analysis of demographic and baseline characteristics

6.3.2.1. Demographic characteristics

Demographic characteristics at start of the extension study will be summarized descriptively for subjects in the EXTS (and separately for subjects included in the DL_{CO} EXTS) in a single table, as follows:

- Sex: frequency counts and percentages;
- Race: frequency counts and percentages;
- Age at start of extension (years): descriptive statistics;
- Age at start of extension (years) by category: frequency counts and percentages;
- Race: frequency counts and percentages;
- Ethnicity: frequency counts and percentages;
- Height: descriptive statistics;
- Weight at start of extension: descriptive statistics;
- BMI at start of extension: descriptive statistics;
- BMI at start of extension by category: frequency counts and percentages;

- Geographical region / Country of enrolling site: frequency counts and percentages.

Height, race, ethnicity, geographical region, and country are used as derived in the core study.

Tables are presented by core treatment group and overall. All variables are also presented in a subject data listing.

6.3.2.2. Baseline characteristics

Baseline disease characteristics [defined in Section 6.3.1.2] are summarized using descriptive statistics for continuous and categorical data using EXTS. Tables are presented by core treatment group and overall. All variables are also presented in subject data listing(s) based on the EXTS.

In addition, core baseline characteristics will be summarized for the Core Analysis Period using EXTS.

All variables are also presented in a subject data listing.

6.4. Appendix 4 Protocol Deviations

This section refers to all protocol deviations as recorded in the database following the specifications provided in the protocol deviation code list.

Protocol deviations are categorized while being entered into the database into the following categories:

- **Important** protocol deviations (Yes/No)

In addition, protocol deviations are categorized by high-level topic in line with the Protocol Deviation code list.

Important protocol deviations for the extension study are summarized by category, by core treatment group, and overall on the EXTS.

A listing of important protocol deviations (coded term, reported term) by country and site is provided.

6.5. Appendix 5 Prior and Concomitant Medications

6.5.1. Definition of prior and concomitant medications

Therapies administered during the extension study are collected in the following eCRF pages: 'Concomitant Medications', 'Study-concomitant Therapy - Disease-modifying Treatment for MS', 'Corticosteroids for Treatment of Relapse'.

Therapies administered during the core study (core treatment-concomitant therapies) will be included as part of the concomitant therapies analysis for the Combined Analysis Period.

Terms are coded using the WHO drug code dictionary and the anatomic therapeutic chemical (ATC) class code (version dated March 2023).

Handling of partial or missing start and end dates is detailed in Section 6.13.

Therapies are flagged as previous/concomitant/after treatment with respect to the relevant Analysis Period.

Therapies that were started during the core study and are ongoing during the extension study (specifically therapies included in the extension eCRF as 'ongoing' from the core study and the original therapies included in the core eCRF) will have a record in the core database and a corresponding record in the extension database. These records will be merged in the ADaM dataset using a dedicated ID linking variable included in the related SDTM dataset.

6.5.1.1. Previous therapies

Previous therapies are therapies that were started and stopped prior to study treatment start date in the Analysis Period.

For the purpose of the analysis on the Extension Analysis Period, therapies reported in the core database that started after EOT in the core study and stopped prior to study treatment start date in the extension study, as well as therapies reported in the extension database that started and stopped prior to study treatment start date in the extension study, are flagged separately as "extension previous therapies".

6.5.1.2. Treatment-concomitant therapies: taken between treatment start and EOT

Treatment-concomitant therapies are all therapies that have been taken between the study treatment start date in the Analysis Period and EOT date (last study drug intake) + 30 days in the Analysis Period, with the exception of corticosteroids for treatment of relapse, for which the EOT + 7 days is used. This includes therapies ongoing at the start of the Analysis Period, as well as therapies starting after the start and before the end of the Analysis Period. DMT which is initiated on or after the study treatment start date and before the EOT date are also considered as concomitant. DMT which started on or after the EOT date is considered as "Post-treatment DMT" and not considered as treatment concomitant therapies.

Treatment-concomitant therapies that started during the core study and which were reported as ongoing at the start of the extension study (per the eCRF form 'Ongoing Concomitant medication from AC-058B301' with question 'Were any medication started in AC-058B301 and still ongoing at the time of the ICF signature in AC-058B303?' answered as 'Yes') are flagged to be summarized separately.

6.5.1.3. Therapies starting after EOT

Includes all therapies (except DMT) that have been started after the EOT (last drug intake) for the Extension Analysis Period only. This includes therapies with start date from EOT + 1 day onwards.

Therapies with missing start date will be considered to have started on treatment.

6.5.1.4. Disease modifying therapies for MS (DMTs)

Disease modifying therapies (DMTs) are defined as therapies which can favorably alter the course of the disease by reducing the rate and severity of relapses or delaying disease progression by preventing accumulation of disability. DMTs will be identified on an ingredient level if containing any of the text indicated in Table 9 below. Medications in ATC class S (non-systemic administration) will not be considered. Only the medications which are administered systemically via the following routes are considered as DMT: Intravenous (IV), Oral, Subcutaneous (SC), Intramuscular (IM).

In addition, any other potential DMT, i.e., medications with preferred drug name "INVESTIGATIONAL DRUG" or "BLINDED THERAPY" for multiple sclerosis (recorded either on the 'Study-treatment-concomitant therapy - Disease-modifying' eCRF) will also be taken into account.

Table 9: Disease modifying therapies for MS

ALEMTUZUMAB	MITOXANTRONE
AZATHIOPRINE	MYCOPHENOLIC ACID
CERALIFIMOD	NATALIZUMAB
CICLOSPORIN	OCRELIZUMAB
CLADRIBINE	OFATUMUMAB
CYCLOPHOSPHAMIDE	OZANIMOD
DACLIZUMAB	PEGINTERFERON BETA-1A
DIMETHYL FUMARATE	PLOVAMER
FINGOLIMOD	PLOVAMER ACETATE
GLATIRAMER ACETATE	RITUXIMAB
INTERFERON BETA-1A	SECUKINUMAB
INTERFERON BETA-1B	TERIFLUNOMIDE
LAQUINIMOD	SIPONIMOD
METHOTREXATE	IMMUNOGLOBULINS NOS
INTERFERON ALFA	ETRASIMOD
VUMERITY	BAFIERTAM
PONESIMOD	DIROXIMEL FUMARATE

A text search in ingredients will be conducted: Include all medications containing any of the text above to ensure salts (e.g., "Fingolimod Hydrochloride" …) and combination therapies are included.

6.5.2. Analysis of prior and concomitant medications

Treatment-concomitant therapies will be summarized, both for the Combined Analysis Period (therapies taken during the combined period), and for the Extension Analysis Period (therapies taken during the extension period), by core study treatment and overall, using the EXTS. Treatment-concomitant therapies that were originally recorded in the core study database and which were ongoing at extension study start will be summarized additionally on the EXTS.

Number and percentages of subjects having taken at least one treatment will be presented by ATC class and individual preferred term within each ATC class (ATC class level 4). All summaries are tabulated by ATC class, and individual preferred terms within each ATC class.

ATC classes are sorted by descending order of frequency overall. If the frequencies of ATC class are the same, alphabetical order is used. The same rule applies for preferred terms within ATC class. If the frequencies of ATC class are the same, alphabetical order is used. The same rule applies for preferred terms within ATC class.

Previous therapies (with respect to the Extension Analysis Period directly[a]) as well as therapies started after the extension EOT will be listed.

*Previous therapies for the Extension Analysis Period include those therapies that started after EOT in the core study and stopped prior to study treatment start date in the extension study, as well as therapies that started and stopped prior to study treatment start date in the core study that were newly reported in the extension study database. Previous therapies that started and ended prior to the start of the core study, or which were concomitant in the core study (and are previous relative to the extension) will be reported in the core study only.

Previous therapies with respect to the Core Analysis Period (i.e. those therapies started and stopped prior to study treatment start date in the core study) are not reported in any analysis output (both on combined or extension analysis period).

All therapies taken are reported in subject listings with all information collected on the eCRF presented, using flags to mark previous, extension/combined Analysis Period concomitant, as well as ongoing at extension study treatment start.

6.5.2.1. Disease modifying therapies (DMTs) for MS

Treatment-concomitant DMTs for MS are summarized in the same way as for the concomitant therapies above by study treatment group and overall, for the Combined Analysis Period using the EXTS and for the Extension Analysis Period using the EXTS. Post-treatment DMT will also be summarized using EXTS.

All DMTs taken for MS are reported in subject listings using flags to mark previous, extension/combined Analysis Period concomitant as well as ongoing at extension study treatment start.

[a] Previous therapies for the Extension Analysis Period include those therapies that started after EOT in the core study and stopped prior to study treatment start date in the extension study, as well as therapies that started and stopped prior to study treatment start date in the core study that were newly reported in the extension study database. Previous therapies that started and ended prior to the start of the core study, or which were concomitant in the core study (and are previous relative to the extension), will be reported in the core study only.

6.6. Appendix 6 Medical History

6.6.1. Definition of medical history

6.6.1.1. General medical history

The following medical history is collected on the extension study eCRF:

- Ongoing Medical History (from the core study);
- Additional Medical History (not reported in the core study);

Reported terms are coded using MedDRA (version 26.0).

The question 'Does the subject have any clinically significant past or concomitant disease/diagnosis ongoing from AC-058B301?' (Yes/No) will be used to identify medical history ongoing at the start of the extension study.

The question 'Does the subject have any additional clinically significant past or concomitant disease/diagnosis not already reported in AC-058B301?' (Yes/No) will be used to identify new medical history reported during the extension study only.

Medical history in the extension study is not merged with the medical history collected in the core study. Only medical history collected in the extension study is reported as part of this SAP.

6.6.1.2. Specific MS medical history

Specific complications or symptoms associated with MS are recorded on a specific the eCRF pages 'MS History - Complication or Symptoms (AC-058B301) and ongoing at signature of Informed Consent in AC-058B303' as well as 'MS disease changes'. Complications and symptoms originating from these pages are flagged to be summarized separately. Only specific MS medical history that is ongoing at the start of the extension study will be summarized. The question 'Ongoing at Visit 1 – AC-058B303' (Yes/No) will be used to identify MS medical history ongoing at the start of the extension study. Only records with answer "Yes" will be considered as ongoing at start of the extension.

6.6.2. Analysis of medical history

Medical history ongoing at the start of the extension study will only be summarized for the Extension Analysis Period, by core study treatment and overall, using the EXTS. The number and percentages of subjects who had/have at least one event and had/have each disease/diagnosis (by system organ class [SOC] and preferred term) will be tabulated. SOCs are sorted by descending order of frequency overall. If the frequencies of SOCs are the same, alphabetical order is used. The same rule applies for preferred terms within SOC.

Any additional medical history collected in the extension (not reported in the core study) will be listed only.

Complications or symptoms associated with MS ongoing at the start of the extension study are summarized by study treatment group and overall, by tabulating the number and percentages of subjects who had/have each complication/symptom (by predefined term sorted by descending order of frequency overall).

MS disease changes since entry into the core study will be listed separately (these data are not coded).

All variables including – as applicable – the treatment day relative to study treatment start date of start and end date of diagnosis/disease are presented in a subject data listing.

6.7. Appendix 7 Intervention Compliance

Compliance calculation is not applicable for this study.

6.8. Appendix 8 Adverse Events of Special Interest

The definitions for AESIs are based on the systematic approach using Standardized MedDRA Queries (SMQ). The definitions for AESIs are based on the systematic approach using Standardized MedDRA Queries (SMQ) / MedDRA version 26.0.The following safety areas are addressed by the pre-defined AESIs:

Table 10: AESI

AESI	SMQ	PT
Bradyarrhythmia occurring post-first dose	Bradyarrhythmias (including conduction defects and disorders of the sinus node function)	Blood pressure ambulatory decreased, Blood pressure decreased, Blood pressure decreased, Blood pressure diastolic decreased, Blood pressure fluctuation, Blood pressure orthostatic decreased, Blood pressure systolic decreased, Bradycardia, Central bradycardia., Chronotropic incompetence, Circulatory collapse, Diastolic hypotension, Electrocardiogram RR interval prolonged, Heart rate decreased, Hypotension, Labile blood pressure, Loss of consciousness, Mean arterial pressure decreased, Orthostatic hypotension, Presyncope, Procedural hypotension, Syncope
Macular edema		Cystoid macular oedema, Diabetic retinal oedema, Macular cyst, Macular hole, Macular oedema, Macular pseudohole, Macular rupture, Papilloedema, Pseudopapilloedema, Retinal oedema
Bronchoconstriction	Asthma/bronchospasm (narrow and broad) Interstitial lung disease (narrow and broad)	

Table 10: AESI

AESI	**SMQ**	**PT**
Severe liver injury	Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (narrow) Hepatitis, non-infectious (narrow)	
Serious opportunistic infections including PML	Opportunistic infections (narrow)	
Skin cancer	Skin neoplasms malignant and unspecified (narrow and broad)	
Non-skin malignancy	Malignant or unspecified tumours (narrow and broad) excluding the PTs included in the SMQ Skin neoplasms malignant and unspecified (narrow and broad)	
Convulsions	Convulsions (narrow)	
Unexpected neurological or psychiatric symptoms/signs (PRES, ADEM, atypical MS relapses)		Acute disseminated encephalomyelitis, Posterior reversible encephalopathy syndrome, Multiple sclerosis relapse

6.9. Appendix 9 Medications of Special Interest

No concomitant medications of special interest are defined.

6.10. Appendix 10 Thresholds for marked laboratory abnormalities

Table 11: Thresholds for marked laboratory abnormalities

Parameter (SI unit)	LL	LLL	HH	HHH
Hemoglobin (g/L)	< 100	< 80	> 20 g/L above ULN (for pre-treatment assessments, and post-treatment assessments when baseline ≤ ULN) or increase from baseline > 20 g/L (for post-treatment assessments when baseline is > ULN)	> 40 g/L above ULN (for pre-treatment assessments, and post-treatment assessments when baseline ≤ ULN) or increase from baseline > 40 g/L (for post-treatment assessments when baseline is > ULN)
Hematocrit (L/L)	< 0.28 (female) < 0.32 (male)	< 0.20	> 0.55 (female) > 0.60 (male)	> 0.65
Platelet count (10^9 /L)	< 75	< 50	> 600	> 999
WBC count (10^9 /L)	NA	< 1.9	> 20.0	> 100.0
Lymphocyte (10^9 /L)	ND	< 0.2	> 4.0	≥ 8
Neutrophils (10^9 /L)	< 1.5	< 1.0	ND	ND
Eosinophils (10^9 /L)	ND	ND	> 5.0	ND
Polymorphonuclear leucocyte/Band cells (%)	ND	ND	> 90%	> 95%
AST (U/L)*	ND	ND	≥ 3 ULN	≥ 5 ULN
ALT (U/L)*	ND	ND	≥ 3 ULN	≥ 5 ULN
Total bilirubin (umol/L)	ND	ND	≥ 2 ULN ALERT: ≥ 2 ULN combined with ALT or AST ≥ 3 ULN	≥ 5 ULN
Alkaline Phosphatase (U/L)	ND	ND	> 2.5 ULN	> 5 ULN
INR*	ND	ND	> 1.5 ULN ALERT: ≥ 1.5 combined with ALT or AST ≥ 3 ULN	> 2.5 ULN
Creatinine (umol/L)*	ND	ND	>1.5 ULN or >1.5 × baseline	> 3 ULN or >3 × baseline
Creatinine clearance (mL/min)	< 60	< 30	ND	ND
Urea (mmol/L)	ND	ND	> 2.5 ULN	> 5 ULN
Urea Nitrogen (mmol/L)	ND	ND	> 2.5 ULN	> 5 ULN
Urate (umol/L)	ND	ND	> 1 ULN	ND
Albumin (g/L)	< 30	< 20	ND	ND
Glucose (mmol/L)	< 3.0	< 2.2	> 8.9	>13.9
Potassium (mmol/L)	< 3.2	< 3.0	> 5.5	> 6.0
Sodium (mmol/L)	ND	< 130	> 150	> 155
Calcium (mmol/L)	< 2.0	< 1.75	> 2.9	> 3.1
Chloride (mmol/L)	ND	ND	ND	ND
Triglyceride (mmol/L)	ND	ND	> 3.42	> 11.4

Parameter (SI unit)	LL	LLL	HH	HHH
Cholesterol (mmol/L)	ND	ND	> 7.75	> 12.92
Serum pregnancy test	ND	ND	ND	Positive
Teriflunomide (ng/mL)	ND	ND	ND	> 20

* HH and HHH based on CTCAE 2010 v4.03 [CTCAE 2010]. An ALERT will be sent when INR > 1.5 based on the guidance for monitoring liver test abnormalities from FDA [FDA 2009].

ALERT = study-specific alerts that trigger specific actions by the investigator [see protocol Section 5.1.12]; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ND = not defined; may be complemented by definitions provided by the central laboratory (see central laboratory manual); ULN = upper limit of normal.

6.11. Appendix 11 Covid-19

This appendix describes the analyses and presentation of immunogenicity and clinical endpoints for objectives related to the assessment of immune response to Covid-19 vaccination in subjects in the AC-058B303 study.

Specific objectives are:

- To describe binding antibody concentrations to SARS-CoV-2 S protein as measured by ELISA
- To describe binding antibody concentrations to SARS-CoV-2 N protein as measured by ELISA
- To describe Covid-19 infection Adverse events (AEs).

6.11.1. Immunogenicity Variables

For Covid-19 vaccination, the following humoral immune responses are measured, including titers of neutralizing antibodies and S- and N-ELISA titers.

Humoral Assay	Purpose
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

6.11.2. Analysis of Immunogenicity Related to Covid-19 Vaccination:

6.11.2.1. Analysis related definitions:

Covid-19 vaccine analysis set: Study subjects who have a complete Covid-19 first vaccine regimen and at least one non-zero vaccine-specific antibody titers assessed within a timeframe (defined as any timepoint prior to the start of Covid-19 vaccine or within the 365 days after the 1st dosing or within 365 days after any boosters).

First Vaccine Regimen: For each subject, the 1st and 2nd doses of vaccine in the SDTM CM dataset are considered. Definition of 1st Vaccine Regimen for Janssen vaccine: Only the 1st dose is considered.

First Booster: The 1st subsequent dose of vaccine after first vaccine regimen is considered as the First Booster.

Second Booster: The 2nd subsequent dose of vaccine after first vaccine regimen is considered as the Second Booster.

Lymphocyte counts for a subject corresponding to a specific vaccination will be determined as the minimum of the last two available values within six months prior to the first vaccination date of first vaccine regimen. If only one value is available within this range, this value will be used. If none are available in the range, the lymphocyte value corresponding to the particular vaccination will be considered missing. Categories of "Lymphocyte Count < 500 mm^3" and "Lymphocyte Count >= 500 mm^3" will be used in the analysis.

Analysis based on BAU/ml: In order to calibrate across different assays, the WHO has proposed International Standards (WHO IS). The WHO IS assigned unit for quantifying immunoglobulins

is BAU/ml. Per Nexelis, the conversion of ELISA units (EU/ml) to BAU/ml is as shown below (see Attachment below):

Human SARS-CoV-2 Pre-Spike IgG ELISA

The results generated for the Human SARS-CoV-2 PreSpike IgG ELISA are reported with concentration units in "ELU/mL". When required, a correlation factor of 1/7.9815 [2] will be applied to convert the reported results from ELU/mL to BAU/mL. For example, a sample with reported anti-PreSpike IgG antibody concentration of 7981.5 ELU/mL will have a concentration equivalent to 1000 BAU/mL.

The following formula may be used for converting concentration units from ELU/mL to BAU/mL:

Result (BAU/mL) = Result (ELU/mL) / 7.9815

Human SARS-CoV-2 Nucleocapsid IgG ELISA

The results generated for the Human SARS-CoV-2 Nucleocapsid IgG ELISA are reported with concentration units in "ELU/mL". When required, a correlation factor of 1/10.3383 [3] will be applied to convert the reported results from ELU/mL to BAU/mL. For example, a sample with reported anti-Nucleocapsid IgG antibody concentration of 10338.3 ELU/mL will have a concentration equivalent to 1000 BAU/mL.

The following formula may be used for converting concentration units from ELU/mL to BAU/mL:

Result (BAU/mL) = Result (ELU/mL) / 10.3383

Antibodies assessment related to vaccine sequence:
Pre-vaccine antibodies assessment: for each subject, the antibodies assessment which is prior to and closest start date of 1st vaccine regimen, is considered as Pre-vaccine antibodies assessment.
Antibodies assessment post 1st vaccine regimen: for each subject, the antibody assessments on or after start of first vaccine regimen and before 1st booster are considered as antibody assessments post-1st vaccine regimen. The average of all values in a time frame of 365 days after the start of first vaccine regimen will be used as "Antibodies assessment post-1st vaccine regimen" in the analysis.
Antibodies assessment post 1st booster: for each subject, the antibody assessments on or after start of 1st booster and before the 2nd booster are considered as antibody assessments post-1st booster. The average of all values in a time frame of 365 days after the start of first booster will be used as the "Antibodies assessment post 1st booster" in the analysis.
Antibodies assessment post 2nd booster: for each subject, the antibody assessments on or after start of 2nd booster and before the 3rd booster are considered as antibody assessments post-2nd booster. The average of all values in a time frame of 365 days after start of second booster will be used as the "Antibodies assessment post 2nd booster" in the analysis.
Antibodies assessment post 3rd booster: for each subject, the antibody assessments on or after start of 3rd booster and before the 4th booster are considered as antibody assessments post-3rd booster. The average of all values in a time frame of 365 days after start of third booster will be used "Antibodies assessment post 3rd booster".

Prior Covid-19 infection evidence related to vaccine sequence:
If a subject encountered one or more Covid-19 infection AEs and the start date of AE is prior to or on the start date of 1st vaccine regimen, the subject is considered to have Prior Covid-19 infection evidence related to 1st vaccine regimen.
If a subject encountered one or more Covid-19 infection AEs and the start date of AE is prior to or on the date of 1st booster, the subject is considered to have Prior Covid-19 infection evidence related to 1st booster, irrespective if the start date of AE is prior to 1st vaccine regimen.

6.11.2.2. Analysis of Immunogenicity Related to Covid-19 Vaccination

A demographic table of study subjects who received Covid-19 vaccination will be provided including :
- number and percentage of subjects having pre-vaccination antibody assessment
- number and percentage of subjects having post-1st vaccine regimen assessment
- number and percentage of subjects having post-1st booster assessment
- number and percentage of subjects having post-2nd booster assessment
- number and percentage of subjects having post-3rd booster assessment
- age at time of 1st vaccination
- sex
- exposure (years) to ponesimod at time of 1st vaccination
- number and percentage of subjects in different vaccine type of the 1st vaccine regimen
- number and percentage of subjects with or without evidence of Covid-19 infection prior to 1st vaccine regimen
- number and percentage of subjects in different categories of lymphocyte count

In the above frequency tabulations, percentage is calculated based on number of subjects in Covid-19 Vaccine Analysis Set.

For S-ELISA and N-ELISA assays, the following results will be presented:
- N, geometric mean and corresponding 95% CI of the actual values of pre-vaccination, post-first vaccine regimen, post-first, post-second and post-third booster. Note that the analysis by timepoint will be performed only if more than 5 subjects have antibody concentration measured at that timepoint.
- Dot plots with dots for subject values with the corresponding geometric mean, 95% CI, minimum and maximum for each assay, for pre-, post- 1st vaccine regimen, post- 1st booster and post- 2nd booster will be presented. In the graphs, values in BAU/ml unit will be displayed on the log10 scale. Note that the analysis by timepoint will be performed only if more than 5 subjects have antibody concentration measured at that timepoint.
- The above analyses will be repeated for S-ELISA antibody concentrations for the following subgroups: vaccine type of the 1st vaccine regimen, evidence of Covid-19 infection prior to 1st vaccine regimen and categories of lymphocyte count. Box plot will be generated to visualize S-ELISA antibody concentrations for the above-mentioned subgroups. Note that the analysis by timepoint will be performed only if more than 5 subjects have antibody concentration measured at the timepoint.

Analyses of S-ELISA and N-ELISA antibody concentration will be presented in BAU/ml unit only.
For the calculation of the geometric mean and its corresponding 95% CI, the arithmetic mean and its corresponding 95% CI are calculated on the log10 transformed values. These values are back-transformed to provide the geometric mean and its corresponding 95% CI.

A listing containing assessment date, timepoint related to each vaccination and value of S-ELISA and N-ELISA assessment antibody concentration will be provided.
A listing of Covid-19 vaccinations will be provided.

6.11.3. Analysis of Adverse Events Related to Covid-19 Vaccination

A summary table will be provided for the following Covid-19 infection AEs for the Covid-19 Vaccine Analysis Set:

(i) any Covid-19 infection AEs.
(ii) any Covid-19 infection serious AEs.
(iii) any Covid-19 infection AEs sorted by severity (mild, moderate, severe).
(iv) any Covid-19 infection AEs leading to treatment discontinuation.
(v) any Covid-19 infection AE leading to death.

For each of the above, summary tables will include overall, and the following time-points:

(vi) any Covid-19 infection AEs prior to 1st dose of vaccination
(vii) any Covid-19 infection AE post 1st dose (Day 1) of vaccination

AE listing will include age at time of vaccination, days since 1st dose of vaccination, start and end dates, AE preferred/reported term, vaccine PT and AE severity.

6.12. Appendix 12 Study visit and assessment schedule

Table 12 and Table 13 show a schematic representation of the assessments during the extension study

Table 12: Visit and assessment schedule

Periods	Name	**AC-058B301 (core study)**		**AC-058B303 (extension study) TREATMENT PERIOD**							
	Duration	NA		Treatment may continue until 240 weeks or until ponesimod is commercially available (whichever occurs first)							
Visits	Number	NA		1	2	3	4	5	6, 8-10, 12-14, 16-18, 20-22	7, 11, 15, 19	23
	Name	FU1 Core Study	Abbreviated FU2 Core Study (1)	Enrollment	W2	W4	W12	W24	W36, W60, W72, W84, W108, W120, W132, W156, W168, W180, W204, W216, W228	W48, W96, W144, W192	EOT
	Time	NA	NA	Day 1(2)	Day 15	Week 4	Week 12	Week 24	Every 12 weeks	Every 48 weeks	W240 or earlier (14)
	Visit window	NA	NA	NA	−1 to +3 days	±7 days	±7 days	±14 days	±14 days	±14 days	14 days
Informed consent*				X							
Inclusion/exclusion criteria*				X							
Demographics				X							
Medical History*				X							
EDSS/FS*				X			X	X	X	X	X
Relapse*		X	X	← X (3) →							
SDMT*							X	X		X	X
MSFC*										X	X
SF-36**								X		X	X
eC-SSRS**										X	X
MRI**(15)										X	X
Concomitant medications*		X	X	X	X	X	X	X	X	X	X
Physical examination*				X				X		X	X
Dermatological examination* (4)										X	X
Body weight*										X	X
Body temperature*		X		X	X	X	X	X	X	X	X
Systolic/diastolic blood pressure*(5)		X		X(5)	X	X	X	X	X	X	X
12 Lead ECG**(6)		X		X						X	X
Pulse rate*					X	X	X	X	X		
Ophthalmological examination / OCT (7)*							X	X		X	X
Pulmonary function tests* (8)		X				X				X	X
Hematology/Chemistry**		X			X	← (9) →			X	X	X
Urinalysis*		X						X	X	X	X
Pregnancy test*/** (10)		X		X		X	X	X	X	X serum	X serum
Elimination procedure compliance		X	X								
Teriflunomide plasma concentration				X (11)							
Additional serum sample for viral serology*				X							
Study treatment dispensing & accountability (12)*				X	X	X	X	X	X	X	X
AEs* / SAEs*(13)		X	X	X	X	X	X	X	X	X	X

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

1) This visit will only take place if the compliance with the teriflunomide elimination procedure in the core study was not sufficient and has to be re-assessed prior to the study drug administration on Day 1.
2) Visit 1 includes a pre-treatment period which lasts from signing of the informed consent until first dosing of study treatment. Ideally, all assessments and procedures of Visit 1 (e.g., signing of the informed consent, first study treatment dosing and post-dose cardiac monitoring) should occur on the same day as the core study FU1 or abbreviated FU2 (whichever applies). In all cases, informed consent should be signed no later than one day after FU1 or FU2 visit (whichever applies) and all assessments and procedures of Visit 1 must be completed (i.e., study treatment start) no longer than 7 days after signing of the informed consent. The date of Day 1 corresponds to the date of the first dose of study treatment in the extension study. The investigator should make every effort to minimize the duration between EOT of the core study and Day 1 of the extension study. Ideally the treatment interruption should last no longer than 15 days.
3) At every study visit, subjects are reminded to contact their principal investigator / treating neurologist at the clinical site immediately in the event of the appearance of any new or worsening neurological symptoms. In addition, the site will contact the subject 6 weeks (± 7 days) after each visit starting with Visit 4 (Week 12) in order to proactively inquire about any new or worsened neurological symptoms. Whenever, between visits, a subject experiences any new or worsening neurological symptoms, he/she must contact the principal investigator / treating neurologist, study nurse or clinical coordinator as soon as possible in order to complete a relapse assessment questionnaire [see protocol appendix 10].
4) Dermatological examination to be performed by a dermatologist.
5) Systolic / diastolic blood pressure: Only pre-dose except Day 1. On Day 1 pre-dose and hourly (± 15 min) for at least 4 hours post-dose and up to 12 hours.
6) ECGs: Only pre-dose except Day 1. On Day 1 pre-dose and hourly (± 15 min) for at least 4 hours post-dose and up to 12 hours.
7) OCT and/or ophthalmological examination to be performed at any visit in the presence of visual symptoms suggestive of macular edema or active uveitis.
8) PFTs including spirometry to be performed in all subjects; DL_{CO} to be performed in a subset of subjects at selected sites only.
9) Monitoring of hematology/chemistry every 4 weeks for the first 24 weeks after enrollment (±7 days).
10) Between visits, urine pregnancy tests are done every 4 weeks (± 7 days) at home. At all visits, the methods of contraception will be reviewed and the contraceptive method form entered in the eCRF must be updated as applicable.
11) Blood sample for a teriflunomide test (results to be communicated to site only if needed, e.g., in the case of AEs where the measurement of exposure to teriflunomide is of relevance).
12) Scheduled study medication dispensing/return procedures may be adapted according to the site practice. No medication dispensed at EOT.
13) All AEs and SAEs that occur after signing the informed consent and up to 30 days after study treatment discontinuation (i.e., EOS) must be reported.
14) The EOT Visit will take place at Week 240 or earlier if ponesimod becomes commercially available in the subject's country or the subject prematurely discontinues from the study. In all cases, the EOT visit should take place 1 day after the last dose of study treatment but no later than 14 days after the last dose of study treatment.
15) In case of premature study treatment discontinuation, the MRI assessment at EOT does not need to be performed if the EOT visit occurs within 4 weeks of the MRI assessment at Visits 7, 11, 15, or 19 (Weeks 48, 96, 144, or 196).

AE = adverse event; DL_{CO} = diffusing capacity of the lungs, measured using carbon monoxide; ECG = electrocardiogram; eCRF = electronic Case Report Form; eC-SSRS = electronic self-rated version of the Columbia-Suicide Severity Rating Scale; EDSS = expanded disability status scale; EOS = End-of-Study; EOT = End-of-Treatment; FS = Functional System; FU = follow-up; MRI = magnetic resonance imaging; MSFC = Multiple Sclerosis Functional Composite; NA = not applicable; OCT = optical coherence tomography; PFT = pulmonary function test; SAE = serious adverse event; W = week.

Table 13: Visit and assessment schedule (Part 2)

Periods	Name	**FOLLOW-UP**	**UNSCHEDULED**							
	Duration	30 Days								
Visits	Number	24	R1, R2, …	U1, U2, …	I1, I2, …		P1, P2, …(9)			
					D1	D15				
	Name	EOS	Relapse	Unscheduled (8)	Re-initiation D1	Re-initiation D15	Interruption / planned pregnancy	Eligibility for re-initiation / planned pregnancy	Re-initiation D1 / pregnancy	Re-initiation D15 / pregnancy
					Day 1 of re-initiation	Day 15 of re-initiation	Unscheduled visit after drug interruption for planned pregnancy	Unscheduled visit prior to study drug re-initiation after interruption for planned pregnancy	Unscheduled visit following study drug interruption for planned pregnancy for re-start	Unscheduled visit following study drug interruption for planned pregnancy for re-start
	Time	Last study treatment intake + 30 days	Any day between Day 1 and EOS	Any day between Day 1 and EOS	Any day between Day 1 and EOS	Any day between Day 1 and EOS	Earliest after Visit 5 (Week 24) and until 6 weeks after the first of two consecutive tests showing teriflunomide plasma level < 0.02 mg/L and at least 30 days after study treatment discontinuation	30 days (± 5 days) days before study drug re-initiation		
	Visit window	+14 days	+7 days	NA	NA	± 1 day	± 7 days	NA	NA	NA
EDSS/FS*		X	X	X			X	X		
Relapse*		X	X	X(11)	X(11)	X(11)	X(11)	X	X	X(11)
MRI**				X			X	X		
Concomitant medications*		X	X	X	X		X	X	X	
Physical examination*			X	X			X	X		
Dermatological examination*				X			X			
Body weight*				X			X	X	X	
Body temperature*		X	X	X	X	X	X	X	X	X
Systolic/diastolic blood pressure*		X	X	X	X(1)	X	X	X	X(1)	X
12 Lead ECG**		X		X	X(2)	X	X	X	X(2)	X
Pulse rate*			X	X(12)			X(12)			
Ophthalmological examination/OCT* (3)		X		X			X	X		
Pulmonary function tests* (4)		X		X			X	X		
Hematology/Chemistry**		X		X			X	X		
Urinalysis*		X		X			X	X		
Teriflunomide plasma concentration (5) **				X						
Viral serology				X						
Pregnancy test*/**		X serum		X			X serum	X urine (first assessment)	X (first assessment; 10)	

Study treatment dispensing & accountability (6)*			X	X	X			X	X
AEs*/ SAEs* (7)	X	X	X	X	X	X	X	X	X

* Data collected in the eCRF.

** Electronically transferred to the sponsor

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

1) SBP/DBP: Pre-dose and hourly (± 15 min) for at least 4 hours post-dose and up to 12 hours.
2) ECGs: Pre-dose and hourly (± 15 min) for at least 4 hours post-dose and up to 12 hours.
3) OCT and/or ophthalmological examination to be performed at any visit in the presence of visual symptoms suggestive of macular edema or active uveitis.
4) PFTs include spirometry to be performed in all subjects; DL_{CO} to be performed in a subset of subjects at selected sites only.
5) Teriflunomide plasma concentration may be assessed at Week 19 ± 7 days and at Week 21 ± 7 days and may be repeated at Visit 5 (Week 24) and at following visits if necessary until two consecutive test results confirming plasma concentration of teriflunomide < 0.02 mg/L are available.
6) Scheduled study medication dispensing/return procedures may be adapted according to the site practice.
7) All AEs and SAEs up to 30 days after study treatment discontinuation must be reported.
8) Unscheduled visits may be performed at any time during the study and the indicated assessments are optional, based on the judgment of the investigator.
9) The wish to become pregnant and stay in the study must be communicated by the female subject to the principal investigator / treating neurologist during a scheduled visit. Interruption of study treatment for planned pregnancy may only take place after Visit 5 (Week 24) and at earliest 6 weeks after the first of two consecutive tests confirming plasma teriflunomide level < 0.02 mg/L and at least 30 days after ponesimod interruption.
10) Review and assess contraception methods and total duration of study treatment interruption, which should not exceed 81 weeks.
11) Only if the subject is meeting the principal investigator / treating neurologist at unscheduled visits.
12) Only if no 12-lead ECG is performed at this visit.

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

6.13. Appendix 13 Handling of missing/incomplete date and the time fields

In the following, 'lower limit' and 'upper limit' refer to the minimum or maximum, respectively, of a possible date. For example, if the day is missing, the lowest limit is the first day of the given month and the upper limit is the last day of the given month. If the day and month are missing, the lower limit refers to the first day of the given year and the upper limit to the last day of the given year. *The earliest and the latest dates refer to the first or last date, respectively, when ordered in sequence.*

6.13.1. Previous / Concomitant therapies

For previous and concomitant therapies with missing or partial start and end dates the following rules for assignation to previous therapies and study concomitant therapies are applied [see Table 14].

Table 14: Handling of missing or partial start and end dates for previous/concomitant therapies

eCRF page	Analysis Period	Start date	End date	Previous / Concomitant
Prev*	Combined Analysis Period	Unless start date clearly after/on core STS (Start date either: prior to core STS date, partial with either lower or upper limit prior to core STS date, or missing)	Unless end date after/on core STS (Either prior core STS, partial with either lower or upper limit prior core STS, or missing)	Previous
Con**	Combined Analysis Period	Unless start date clearly after/on core STS (as above)	Prior to core STS date; or Partial with upper limit prior to core STS date;	Previous
Con**	Combined Analysis Period	Start date confirmed prior core STS (Start date either: prior to core STS date, partial with upper limit prior to core STS date)	End date on core STS date and 'Ongoing at start of Treatment' ticked 'No'; or Partial with lower limit prior to core STS date and upper limit after/on core STS date and 'Ongoing at start of Treatment' ticked 'No';	Previous
Con***	Extension Analysis Period	Unless start date clearly after/on extension STS (Start date either: prior to extension STS date, partial with either lower or upper limit prior to extension STS date, or missing)	Prior to extension STS date; or Partial with upper limit prior to extension STS date;	Previous
Con***	Extension Analysis Period	Start date confirmed prior extension STS (Start date either: prior to extension STS date, partial with upper limit prior to extension STS date)	End date on extension STS date and 'Ongoing at start of Treatment' ticked 'No'; or Partial with lower limit prior to extension STS date and upper limit after/on extension STS date and 'Ongoing at start of Treatment' ticked 'No';	Previous

Any	Combined/Extension Analysis Period	All other cases not listed above	All other cases not listed above	Treatment concomitant

Con = concomitant; eCRF = electronic Case Report Form; MS = multiple sclerosis; Prev = previous; STS = study treatment start.
For subjects randomized but not treated in the core study the randomization date is used instead of the core STS. For subjects enrolled but not treated in the extension study, the enrollment date is used instead of the extension STS.
* Includes core study core eCRF forms 'Previous Medications' or 'MS Specific Treatment History Log': On these forms as per CRF completion guidelines only medications that stopped prior to signature of informed consent are to be recorded.
** Includes all core study eCRF forms collecting therapies apart from 'Previous Medications' or 'MS Specific Treatment History Log eCRF.
*** Includes extension eCRF forms 'Concomitant Medications' and extension eCRF form 'Study-concomitant Therapy – Disease-modifying for MS'.

Concomitant medications entered on the eCRF page "Ongoing Concomitant Medication from AC-058B301" are considered to be concomitant in both the Combined and Extension Analysis Periods. Concomitant medications entered as "Ongoing at EOS" on the core study eCRF page are considered to be concomitant in both the Combined and Extension Analysis Periods for subjects that entered the extension, even if a corresponding "Ongoing Concomitant Medication from AC-058B301" has not been completed for the extension.
In this study subjects are allowed to switch to commercial ponesimod prior to week 240 / week 288, with the ponesimod medication documented in the concomitant medication eCRF page. In this regard, the commercial ponesimod is considered as post-EOT medication unless there is evidence showing that the commercial ponesimod is taken prior to EOT date. In case of partial CM start date, the commercial ponesimod is considered as a post-EOT medication if the month and/or year is the same as the EOT date. The commercial ponesimod is considered as a post-EOT medication in case of completely missing start date in the CM dataset.

6.13.2. Relapse Start Date

For the analysis of ARR in the Extension Analysis Period, the start date of the confirmed relapse as entered on the eCRF by the treating neurologist must be within the interval of [extension enrollment date; extension EOS].

For the analysis of ARR in the Combined Analysis Period, the start date of the confirmed relapse as entered on the eCRF by the treating neurologist must be within the interval of [date of randomization; extension EOS].

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

Every effort will be made to collect relapse information as completely as possible, with a focus on collecting all start dates and all EDSS/FS data required for the relapses to make a correct evaluation of relapse confirmation. All relapses with missing or incomplete start dates will be included in the efficacy analysis, unless it is clear that they have occurred prior to the start of the Analysis Period.

Type of date/time	Analysis Period	Date/time is incomplete	Date/time is missing
Relapse start date (collected on 'Relapse Summary' eCRF)	Core/Combined Analysis Period	Maximum of lower limit and randomization date Unless upper limit is prior to randomization date, then upper limit	Randomization date (for relapse reported in the core study) or enrollment date (for relapse reported in the extension study)

Type of date/time	Analysis Period	Date/time is incomplete	Date/time is missing
Relapse start date (collected on 'Relapse Summary' eCRF)	Extension Analysis Period	Maximum of lower limit and enrollment date Unless upper limit is prior to enrollment date, then upper limit	Enrollment date

6.13.3. Adverse events

In order to assign AEs into the different Analysis Periods, the following algorithms are applied.

6.13.3.1. Treatment-emergent AEs

Safety data with missing or partial onset dates/times (Adverse Events) are handled as follows:

For AEs reported during the core study as well as AEs between the core EOT date + 15 days and the first treatment in the extension, these variables are used as derived in the core study, and are not re-derived for the analysis of the Combined Analysis Period.

For AEs reported on the "Adverse Event" page for the extension study the following rules are applied:

- Onset day missing: If month and year is clearly on or after date of first study drug intake in the extension study month and year, and clearly before or on the month and year of minimum of (EOS, last intake date + 15 days), the event is considered to be treatment-emergent. For pregnancy interruptions, if month and year is clearly on or after date of first study drug intake in the extension study month and year and clearly before the last study drug intake date prior to pregnancy interruption + 15 days, or clearly on or after the re-initiation date of study treatment after planned pregnancy and prior to or on the minimum of [EOT date + 15 days, cut-off date], the event is considered to be treatment-emergent.
  - If the month and year correspond to month and year of date of first study drug intake (in the extension study), impute onset date and time as the date and time of the first study drug intake in the extension study. If the date/time of first study drug intake (in the extension study) is missing, then use enrollment date/time.
  - If the month and year are clearly after date of first study drug intake in the extension study month and year, but a date of re-initiation with corresponding month and year is documented, impute onset date and time as the date and time of this re-initiation study drug intake (if more than one study drug re-initiations are documented in this month and year, impute with the date and time of the earliest of those).
  - If the month and year are clearly after date of first study drug intake in the extension study month and year, but no date of re-initiation with corresponding month and year is documented, the onset date is imputed to the first day of the month and year given, and time to 00:00.
  - If neither date of first study drug intake in the extension study nor extension enrollment date are available, or if event onset month and year is clearly prior to the date of first study drug intake in the extension study month and year (or, if missing, the enrollment month and year), the onset date is imputed to the last day of the given month (i.e., 28th, 29th, 30th, or 31st, depending on the month) and year, and time is imputed to 00:00.

  - Onset day and month missing: If the year is the same year as the year of first study drug intake in the extension study or later, and if the year is prior to or in the same year as the minimum of (cut-off date, last intake date + 15 days), the AE is considered to be treatment-emergent. For pregnancy interruptions, if the year is the same year as the year of first study drug intake in the extension study or later, and if the year is prior to or in the same year as the minimum of (cut-off date, last intake date + 15 days), the AE is considered to be treatment-emergent.If the year corresponds to the year of first study drug intake (in the extension study), impute onset date and time as the date and time of the first study drug intake in the extension study. If first study drug intake (in the extension study) is missing, then use enrollment date/time.
  - If the year is clearly after the year of first study drug intake in the extension study, but a date of re-initiation with corresponding year is documented, impute onset date and time as the date and time of this re-initiation study drug intake (if more than one study drug re-initiations are documented in this year, impute with the date and time of the earliest of those).
  - If the year is clearly after the year of first study drug intake in the extension study, but no date of re-initiation with corresponding year is documented, the onset date is imputed to 1 January of the given year and time to 00:00.
  - If neither date of first study drug intake in the extension study nor extension enrollment date are available, or if the event onset year is clearly prior to the year of first study drug intake (or, if missing, year of enrollment), the onset date is imputed to 31 December of the given year and time is imputed to 00:00.

- Missing onset time is imputed to:
  - the time of the first study drug intake in the extension study, if the onset date equals the date of first study drug intake in the extension study.
  - the time of the study drug intake at re-initiation in the extension study, if the onset date equals the date of a documented study drug re-initiation.
  - 00:00, for any other onset date.

- Onset date is completely missing: considered to be treatment-emergent. The onset date and time are imputed as date and time of the first study drug intake in the extension study.

AEs with missing or partial onset date may be considered to be treatment-emergent as per the definitions above. However, they are not considered to be "Day 1" AEs and will not appear in summaries of AEs on Day 1.

For AEs reported on the "Ongoing Adverse Events from AC-058301" eCRF page for the extension study, no dates are imputed and the events are considered to be not treatment-emergent with respect to the Extension Analysis Period.

6.13.4. Study treatment start and EOT date

The following imputations of study treatment start and extension EOT date are considered for assigning safety events and assessments to the treatment-emergent period and used for deriving efficacy variables with definitions requiring extension EOT date. It is not considered for derivation of exposure variables.

Type of date/time	Date/time is incomplete	Date/time is missing
Study treatment start date	Maximum of lower limit and randomization/enrollment date.	Randomization/enrollment date
Study treatment start time	See missing.	0:00 or randomization time if study treatment start date (after imputation) is equal to randomization/enrollment date.
Extension EOT date	Earliest among the upper limit, date of first commercial ponesimod intake in CM dataset -1, and EOT visit date -1.	Earliest among the upper limit, date of first commercial ponesimod intake in CM dataset -1, and EOT visit date -1

6.13.5. Treatment exposure

Exposure data is entered as intervals on the eCRF with an exposure start and end date.

If both the start and end date of any interval is completely missing no date will be imputed.

6.14. Appendix 14 PRO and other composite assessment scoring and handling of missing data

6.14.1. MSFC

A more comprehensive description of the test and its administration is provided in the protocol appendix 6. The MSFC score will be calculated as the mean of the Z-scores of the 3 components:

(1) Timed 25-Foot Walk (T25FW)

(2) 9-Hole Peg Test (9-HPT)

(3) Paced Auditory Serial Addition Test (PASAT-3).

for each of the scheduled assessment visit using the following equation (MSFC administration and scoring manual, Fisher *et al*., 2001, National MS society).

$$\text{MSFC Z-score}_t = \frac{Z_{\text{arm, average t}} - Z_{\text{leg, average t}} + Z_{\text{cognitive t}}}{3}$$

In more details the score will be calculated as follows:

MSFC Z-score $_t$ = {[(Average 1/9-HPT $_t$ - Baseline Mean 1/9-HPT) / Baseline Std Dev (1/9-HPT)]
+ [- (Average T25FW $_t$ - Baseline Mean T25FW) / Baseline Std Dev T25FW]
+ [(PASAT-3 $_t$ - Baseline Mean PASAT-3) / Baseline Std Dev PASAT-3]} / 3

Where t = time, baseline mean and SD refer to the mean and standard deviation in the study independent of treatment arm (FAS) at baseline.

The average (1/9-HPT) and average T25FW are derived as follows.

Average 1/9-HPT= [1/Mean trials arm left +1/ mean trials arm right]/2

Average T25FW = mean of trials (i.e. trial 1 and trial 2) = (trial 1+ trial 2)/2

For the T25FW and 9-HPT, a higher raw score represents deterioration whereas, for the PASAT-3 a lower raw score represents deterioration. After the transformation to Z-scores the negative values Z-scores of each of the components as well as the MSFC Z-score indicate deterioration in the neurological function.

The subcomponents are considered in addition separately. These are: Average T25FW in seconds, PASAT-3 score in number correct, and the Average 9-HPT in seconds. The Average 9-HPT is defined as Average 9-HPT = mean (Mean trials arm left, mean trials arm right).

Handling of missing data for MSFC analysis

For assessments 9-HPT and T25FW, if only one trial is available that score is used instead of the mean, if more trials are available at the same visit the mean is derived based on all available trials.

For assessments 9-HPT, if only results from one arm are available, the reciproce is used for Average 1/9-HPT.

For overall composite MSFC score, if any of the three components is missing at that visit, the MSFC score is set to be missing, no imputation is conducted.

6.14.2. SF-36 analysis

6.14.2.1. SF-36 scoring

SF-36 scoring is performed via licensed vendor QualityMetric using PRO CORE software. The 36 questions are imported for processing and detailed process steps can be found in PRO CORE 1.4 manual.

The original SDTM QSTESTCD need to be transformed into imported test code requested by PRO CORE. Below are coding rules.

QSTESTCD	QSTEST	SF-36 coding for PRO CORE
SF36201	SF-36 v2.0 Standard-Question 1	GH01
SF36202	SF-36 v2.0 Standard-Question 2	HT
SF36203A	SF-36 v2.0 Standard-Question 3a	PF01
SF36203B	SF-36 v2.0 Standard-Question 3b	PF02
SF36203C	SF-36 v2.0 Standard-Question 3c	PF03
SF36203D	SF-36 v2.0 Standard-Question 3d	PF04
SF36203E	SF-36 v2.0 Standard-Question 3e	PF05
SF36203F	SF-36 v2.0 Standard-Question 3f	PF06
SF36203G	SF-36 v2.0 Standard-Question 3g	PF07
SF36203H	SF-36 v2.0 Standard-Question 3h	PF08
SF36203I	SF-36 v2.0 Standard-Question 3i	PF09
SF36203J	SF-36 v2.0 Standard-Question 3j	PF10
SF36204A	SF-36 v2.0 Standard-Question 4a	RP01
SF36204B	SF-36 v2.0 Standard-Question 4b	RP02
SF36204C	SF-36 v2.0 Standard-Question 4c	RP03
SF36204D	SF-36 v2.0 Standard-Question 4d	RP04
SF36205A	SF-36 v2.0 Standard-Question 5a	RE01
SF36205B	SF-36 v2.0 Standard-Question 5b	RE02
SF36205C	SF-36 v2.0 Standard-Question 5c	RE03
SF36206	SF-36 v2.0 Standard-Question 6	SF01
SF36207	SF-36 v2.0 Standard-Question 7	BP01
SF36208	SF-36 v2.0 Standard-Question 8	BP02
SF36209A	SF-36 v2.0 Standard-Question 9a	VT01
SF36209B	SF-36 v2.0 Standard-Question 9b	MH01
SF36209C	SF-36 v2.0 Standard-Question 9c	MH02
SF36209D	SF-36 v2.0 Standard-Question 9d	MH03
SF36209E	SF-36 v2.0 Standard-Question 9e	VT02
SF36209F	SF-36 v2.0 Standard-Question 9f	MH04
SF36209G	SF-36 v2.0 Standard-Question 9g	VT03
SF36209H	SF-36 v2.0 Standard-Question 9h	MH05
SF36209I	SF-36 v2.0 Standard-Question 9i	VT04
SF36210	SF-36 v2.0 Standard-Question 10	SF02

SF36211A	SF-36 v2.0 Standard-Question 11a	GH02
SF36211B	SF-36 v2.0 Standard-Question 11b	GH03
SF36211C	SF-36 v2.0 Standard-Question 11c	GH04
SF36211D	SF-36 v2.0 Standard-Question 11d	GH05

The normative score and the 0-100 scale score for individual domain, along with the normative score for PCS and MCS will be exported from PRO CORE. The exported code and the corresponding ADaM parameter code and descriptions are outlined below.

Outputed Parameter Code	**Parameter Code in ADaM**	**Parameter Description in ADaM**
BP	BP	Bodily Pain 0-100 Score
GH	GH	General Health 0-100 Score
MH	MH	Mental Health 0-100 Score
PF	PF	Physical Functioning 0-100 Score
RE	RE	Role-Emotional 0-100 Score
RP	RP	Role-Physical 0-100 Score
SF	SF	Social Functioning 0-100 Score
VT	VT	Vitality 0-100 Score
BP_NBS	BPT	Bodily Pain Normative Score
GH_NBS	GHT	General Health Normative Score
MH_NBS	MHT	General Health Normative Score
PF_NBS	PFT	Physical Functioning Normative Score
RE_NBS	RET	Role-Emotional Normative Score
RP_NBS	RPT	Role-Physical Normative Score
SF_NBS	SFT	Social Functioning Normative Score
VT_NBS	VTT	Vitality Normative Score
MCS	MCST	Normative Mental Component Summary Score
PCS	PCST	Normative Physical Component Summary Score

Descriptive statistics will be performed based on normative scores.

In addition, there is no transformation of item Health Transition. Analysis of Health Transition will be based on the original results.

6.14.2.2. ADaM domain generation

For combined analysis, only the composite score is stored in the ADaM dataset. The original SF-36 questionnaires will be kept in SDTM only.

6.14.2.3. Handling of duplicate entries on Questionnaire form for SF-36 scoring

For SF-36 scoring, unique assessment per subject per question item per day is required. In case a subject have duplicate entries within the same day for a question item, the following handling rules will be applied:

- If a respondent marks two responses which are adjacent to each other, then the worst case (lowest value) is selected. For questions BP01, BP02, GH01, GH03, GH05, VT01, VT02, SF01, MH03 and MH05, the record with higher score is considered "worst case". For other questions the record with lower score is considered "worst case".
- If a respondent marks two responses which are not adjacent to each other, then the score is missing for that item.
- If a respondent marks three or more responses then the score is missing for that item.

6.14.2.4. Selection of subset population for dry-run SF-36 scoring

Due to limited administrations licensed at PRO CORE, a subset of data from internal SDTM data (dated 30Oct2023) will be selected for Dry-run. The selection rules are outlined below:

1. To select subjects who have completed the study or subjects who have reached visit "Week 240".
2. To check SF-36 assessments for these subjects and exclude subjects with multiple assessments within the same date.
3. To include all assessments at any visits for the selected subjects for SF-36 scoring for Dry-run.
4. To keep subjects who have completed the study prior to 31-12-2022 or who have visit "Week 240".
5. In order to perform visit remapping for EOT visit of subjects who prematurely discontinue the study. The SF-36 assessments of the first 10 subjects who had discontinued the study are added for Dry-run analysis.

This results to approximately 1000 assessments to be included for Dry-run.

7. REFERENCES

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