Janssen Research & Development

Statistical Analysis Plan
for Clinical Study Report

Multicenter, randomized, double-blind, parallel-group extension to study AC-058B201 to investigate the long-term safety, tolerability, and efficacy of 10, 20, and 40 mg/day ponesimod, an oral S1P1 receptor agonist, in patients with relapsing remitting multiple sclerosis

Protocol AC-058B202 **; Phase [2b]**

JNJ-67896153/ACT-128800 (Ponesimod)

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

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VERSION HISTORY

Table [i] – SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1		Not Applicable	Initial release
0.1		Updates made for Final CSR.	Several updates captured in Section 6.2
0.2		Final CSR-SAP	
1		Final CSR-SAP	

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the analyses and presentation of all safety, tolerability and selected efficacy endpoints for the clinical study report (CSR) of the pooled AC-058B201 (core) and AC-058B202 (extension) studies.

For these analyses, the data for subjects in the core study is pooled with all data in the extension study. The pooled analyses described in this SAP focus on the period when subjects were treated with ponesimod, i.e., excluding the placebo period for those subjects who received placebo in the core study. The placebo data, however, includes certain disposition summaries to enable full traceability of subjects across the two studies.

Study data was initially collected in paper Case Report Forms (CRFs) and uploaded to a legacy database. Subsequently, on 9th August 2021, an electronic CRF (eCRF) was created and the study data was migrated to iMedidata RAVE EDC on 17th Nov. 2021.

Study Data Tabulation Model (SDTM) datasets are provided for both the core and extension and are considered the source data for the analyses. Throughout this SAP, SDTM201.XX refers to the SDTM domain XX for the core study, SDTM202.XX refers to the SDTM domain XX for the extension study, and SDTM.XX refers to the SDTM domain XX for either/both the core and extension studies.

The database lock date used for analyses described in this SAP will be specified in the Database Release Plan (DRP). All data (visits/occurrence dates) are planned to be entered in the database prior to this database lock date and will be included in the analyses.

Datasets and outputs related to the Covid-19 and Influenza Immunogenicity Analysis described in Appendices 11 and 12 respectively, as well as the Pharmacokinetics/Pharmacodynamics analysis described Sections 5.5.1 and 5.5.2, will be developed internally, whereas the rest of the analyses will be developed by a CRO.

1.1. Objectives

The objective of the extension study is to investigate the long-term effects of ponesimod, orally administered once daily (o.d.) at doses of 10, 20, or 40 mg, on safety, tolerability, and efficacy. All objectives are exploratory.

Specifically, the objectives are:

- To investigate the long-term safety and tolerability of ponesimod.
- To investigate the long-term efficacy of ponesimod.
- To explore the dose response relationship of 10, 20, and 40 mg ponesimod on lymphocyte count, magnetic resonance imaging (MRI) endpoints, annualized relapse rate (ARR), and safety endpoints. This objective was addressed in the Interim Analysis CSR in 2019. Furthermore, as stated in Appendix 2, Section 6.2.1, the placebo arm represents only a small percentage of the data, and modelling results without placebo data is difficult to interpret. Therefore, this objective will not be further addressed in the Final CSR.

1.2. Study Design and Flow

1.2.1. AC-058B201 study design (core study)

This was a prospective, multicenter, randomized, placebo-controlled, parallel-group, dose -finding study to evaluate the efficacy, safety, and tolerability of three doses of ponesimod in patients with relapsing-remitting multiple sclerosis (RRMS). Subjects were randomized (1:1:1:1) to one of four treatment groups (placebo, ponesimod 10 mg, ponesimod 20 mg, or ponesimod 40 mg daily) and treated for 24 weeks.

1.2.2. AC-058B202 study design (extension study)

This was designed as a prospective, multicenter, multinational, randomized, double-blind, multiple-dose, uncontrolled, parallel group extension study in subjects with RRMS who completed their regular Week 24 (End-of-treatment [EOT]) Visit of the core study while still on study treatment. Investigators, contract research organizations (CROs), and subjects were blinded to previous study treatment assignments during the core and at the time of transition to the extension study. The Sponsor was blinded during the core study and has been unblinded to the core dose assignments during the extension study follow-up in order to perform the final analyses of the core study. The Sponsor was also unblinded to the extension study dose assignments.

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

This extension study comprises three treatment periods: treatment period 1 (TP1; up to 96 weeks), and treatment periods 2 and 3 (TP2 and TP3; up to 540 weeks combined).

Per the original design of the extension study, subjects who received treatment with ponesimod (10, 20, or 40 mg) during the core study continued their treatment on the same dose during TP1 of the extension study. Subjects who received placebo in the core study were re-randomized 1:1:1 to 10, 20, or 40 mg ponesimod at the start of TP1.

The Sponsor was unblinded to the core study treatment allocation following the database lock and final analysis of the core study. The results of these analyses showed that ponesimod at doses of 10 and 20 mg were well tolerated. The 40 mg dose was associated with an increased incidence of adverse events (AEs) of dyspnea, peripheral edema, cough and, possibly, infection-related AEs, while no significant efficacy benefit was achieved with this dose as compared to 20 mg. Consequently, the Sponsor decided to discontinue the 40 mg treatment arm and offer the subjects who were randomized to 40 mg to be re-randomized to either ponesimod 10 or 20 mg. This option was introduced as TP2 in protocol Amendment 2 (16 February 2012 [D-12.087]).

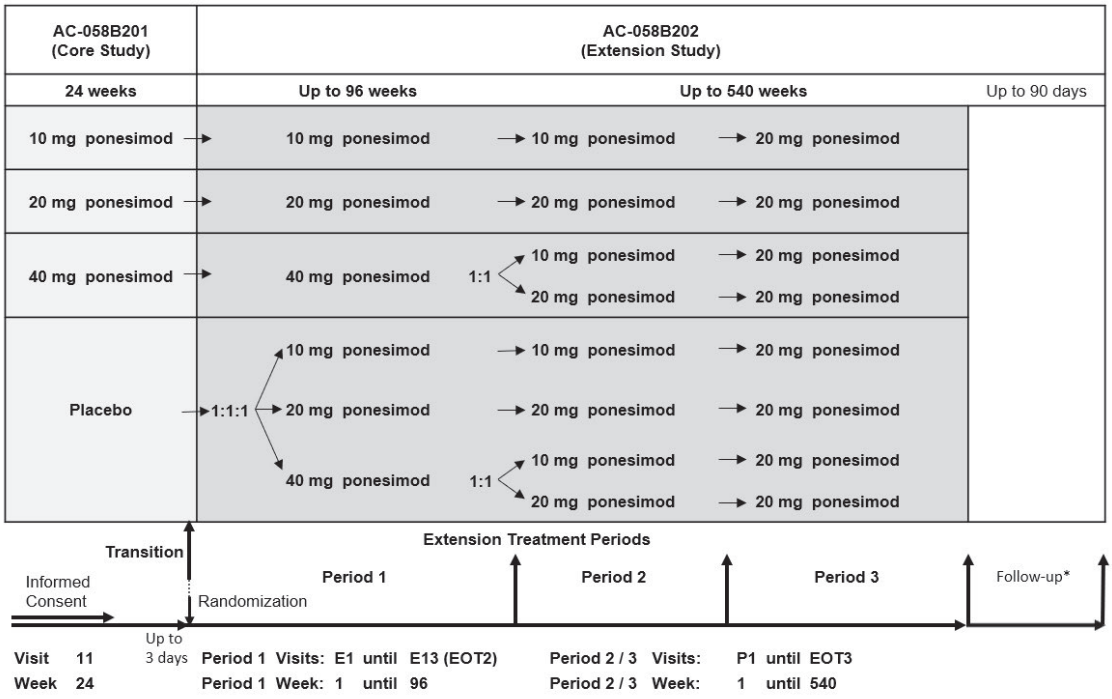
Subjects who completed at least Visit E9 (Week 48) of TP1 could be enrolled into TP2. In TP2, all subjects receiving 40 mg ponesimod in TP1 were re-randomized to 10 or 20 mg ponesimod in a 1:1 ratio. Subjects on 10 and 20 mg ponesimod continued with their previously allocated dose.

At the Independent Data Monitoring Committee (IDMC) meeting on 29 June 2016, the committee requested Actelion to perform a formal evaluation of the benefit-risk profile of the 10 and 20 mg dose arms in the ongoing extension, with the aim to potentially switch all subjects receiving ponesimod 10 mg to the 20 mg dose. The Sponsor performed the analyses given the study was already unblinded and presented the results without interpretation to the IDMC for the committee members to evaluate. Following a review of this analysis, the IDMC recommended on 6 December 2016 that the 10 mg dose arm should be discontinued and that all subjects should be offered to

continue on 20 mg. This switch from ponesimod 10 mg to the 20 mg dose in TP3 was introduced in protocol Amendment 7 (29 March 2017 [D-17.152]). Subjects who received 10 mg ponesimod during TP2 were switched to 20 mg ponesimod in TP3 and subjects on 20 mg ponesimod in TP2 continued with the same dose in TP3.

The changes in the original study design over the course of the study have resulted in significant additional complexity (see Figure 1 for a summary) and many possible treatment pathways through the study. In addition, at the transitions between core and extension studies and between TP1 and TP2, some subjects were allowed treatment interruptions of up to 3 months according to the protocol.

Figure 1: Study design: Treatments and Periods



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

EOT = End-of-treatment.

1.2.3. Treatment periods

The treatment periods defined here include all data, regardless of whether the patient was receiving treatment or not. Specific windows are defined later with more specific adherence to the treatment and these are analysis dependent. The following treatment periods are defined:

- **Core Treatment Period**

  The start date of the period is the date of first administration of ponesimod in the core study.

  For subjects who did not continue into the extension study, the end date of the period is last study date [see Section 5.1.1].

For subjects who did continue into the extension study, the end date of the period is the date of first administration of ponesimod in the extension study, minus 1 day.

- **Extension Treatment Period 1 (TP1)**

  The start date of the period is the date of first administration of ponesimod in TP1 of the extension study.

  For subjects who did not continue into TP2, the end date of the period is the last study date [see Section 5.1.1].

  For subjects who did continue into TP2, the end date of the period is the date of first administration of ponesimod in TP2, minus 1 day.

- **Extension Treatment Period 2 (TP2)**

  The start date of the period is the date of first administration of ponesimod in TP2.

  For subjects who did not continue into TP3, the end date of the period is the last study date [see Section 5.1.1].

  For subjects who did continue into TP3, the end date of the period is the date of first administration of ponesimod in TP3, minus 1 day.

- **Extension Treatment Period 3 (TP3)**

  The start date of the period is the date of first administration of ponesimod in TP3.

  The end date of the period is the last study date [see Section 5.1.1]

- **Ponesimod Treatment Period**

  The start date of the period is the date of first administration of ponesimod in either the core (for subjects treated with ponesimod in the core study) or in TP1 (for subjects treated with placebo in the core study).

  The end date of the period is last study date [see Section 5.1.1],

For all treatment periods, any treatment interruptions that occur between the start and end of the period are part of the treatment period.

2. STATISTICAL HYPOTHESES

All objectives in this SAP are exploratory.

3. SAMPLE SIZE DETERMINATION

As described in the Section 1.2.2, the sample sizes in the various phases of the study are determined by the treatment pathways starting with the core study.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

Table 1: Description of Analysis Sets

Analysis Sets	Description
All Randomized Set (RND)	The randomized analysis set includes all participants who were randomized in the core study.
Ponesimod Analysis Set (PAS)	This set includes all subjects who received at least one dose of ponesimod at any time during the core and/or the extension study.
Echocardiography Analysis Set (ECHO)	This includes all subjects in the PAS who have at least one echocardiography assessment after first dose of ponesimod.
Optical Coherence Tomography Analysis Set (OCT)	This includes all subjects in the PAS who have at least one OCT assessment after first dose of ponesimod.

An overview of the different analysis sets and their usage is given in Table 2 below.

Table 2: Usage of Analysis Sets

Analyses/Data Displays	RND	PAS	ECHO	OCT
Disposition	✓	✓		
Demographic characteristics		✓		
Baseline characteristics		✓		
Medical history		✓		
Previous and concomitant medications		✓		
Protocol deviations		✓*		
Treatment exposure		✓		
Efficacy: Relapse		✓		
Efficacy: MRI		✓		
Efficacy: Neurological		✓		
Efficacy: Ophthalmological				✓
Safety: Holter ECG		✓		

Safety: Echocardiography			✓	
Safety: All other endpoints		✓		
All subject listings		✓		

*Subset on subjects entering the extension study.
ECG = electrocardiogram; ECHO = Echocardiography analysis set; OCT = Optical coherence tomography analysis set; PAS = Ponesimod analysis set; RND = All-randomized analysis set.

5. STATISTICAL ANALYSES

5.1. General Considerations

5.1.1. Dates, times and days

Core study treatment start date: date of first administration of study drug (ponesimod or placebo) in AC-058B201.

Extension study treatment start date: date of first administration of ponesimod in AC-058B202.

Ponesimod start date (PSD): date of first administration of ponesimod:

- for subjects randomized to ponesimod in the core study, this is the date of the first study drug administration in the core study.
- for subjects randomized to placebo in the core study and enter the extension, this is the date of the first study drug administration in the extension study.

Ponesimod EOT / ponesimod end date: defined as the latest study treatment end date as recorded on the Study Drug Log (ECENDTC in SDTM.EC where ECCAT = 'STUDY DRUG LOG').

Extension End-of-Treatment (eEOT) / extension study treatment end date: equal to the Ponesimod EOT / Ponesimod end date as defined above for subjects entering the extension study. Missing for subjects not entering the extension study.

Core End-of-Study (cEOS) date: the EOS date in the core study, defined as DSSTDTC in SDTM201.DS, where DSSCAT='STUDY TERMINATION'. If the subject died, then EOS date is set to death date, where death date is defined as SDTM201.DD.DDDTC.

Extension End-of-Study (eEOS) date: the EOS date in the extension study, defined as DSSTDTC in SDTM202.DS, where DSSCAT='STUDY TERMINATION'. If the subject died, then EOS date is set to death date, where death date is defined as SDTM202.DD.DDDTC. Missing for subjects not entering the extension study.

Last study date: defined as core EOS date for subjects who did not enter the extension study, and Extension EOS date for subjects who did enter the extension study.

Ponesimod Study Day: defined as the number of days elapsed since ponesimod start date (PSD) plus 1 (e.g., Ponesimod Study Day 1 is the day of first administration of ponesimod). For dates prior to ponesimod start date (PSD), study day is the negative number of days elapsed between the date under consideration and the day of first administration of ponesimod. Therefore, the ponesimod study day is always different from 0.

5.1.2. Baseline and change from baseline

The ponesimod baseline is defined as the last non-missing assessment performed prior to the first administration of ponesimod in either the core study (for subjects randomized to ponesimod in AC-058B201) or the extension study (for subjects randomized to placebo in AC-058B201 and proceeding to the extension study).

Assessments that were taken on the date of the first intake of ponesimod will prioritize scheduled visit assessments over unscheduled visit assessments, unless the time is available and it indicates the unscheduled visit assessment was performed later than the scheduled assessment, but prior to the first administration of ponesimod.

5.1.3. Planned Pregnancy Interruptions

Planned pregnancy interruptions will be excluded for definition of exposure, treatment-emergent adverse events and other safety variables including AEs, laboratory tests, pulmonary function tests (PFTs), vital signs and ECGs.

Planned pregnancy interruptions will not be excluded for efficacy analyses or for study duration.

Interruptions for planned pregnancies are identified in the database as defined in Section 5.2.1.5. Determination of the period of planned pregnancy interruption is described in Section 5.1.4.

5.1.4. Treatment-emergent definition

For the purpose of safety evaluations, the treatment-emergent period is defined as the time from first administration of ponesimod up to 15 days (inclusive) after last administration of ponesimod as study drug.

Assessments on the date of first intake of ponesimod are considered treatment-emergent, unless they are clearly documented to be prior to first intake of ponesimod.

Note that, as per Section 5.1.3, planned pregnancy interruption period is excluded from treatment-emergent definition and other related variables.

The period of planned pregnancy interruption will be excluded from the treatment-emergent period for subjects with planned pregnancy interruption and restart of the treatment prior to the EOS date. Therefore, the treatment-emergent period for these subjects will consist of periods:
1. From the first dose on the ponesimod start date up to the last dose prior to the pregnancy interruption +15 days, and
2. From the first dose of study drug after the pregnancy interruption up to EOT+ 15 days.

In order to assess events that occur during the pregnancy interruption, a new “pregnancy interruption emergent period” is defined as from the last dose prior to pregnancy interruption + 16 days to the minimum of (first dose after pregnancy interruption – 1 day, EOS date).

Treatment-emergent definitions are applicable to all safety variables, e.g., AEs, laboratory tests, pulmonary function tests (PFTs), vital signs and ECGs.

5.1.5. Last on-treatment definition

Last on-treatment value/assessment is defined for all subjects at the last value observed for the subject up to the ponesimod EOT date + 1 day.

5.1.6. Post-treatment-emergent definition

The post-treatment-emergent period is defined as follows:

The start date of the period is the date of last administration of ponesimod as study drug plus 16 days (inclusive). See Section 5.1.4 for the definition of treatment-emergent, which is defined as the time from first administration of ponesimod up to 15 days (inclusive) after last administration of ponesimod as study drug.

The end date of the period is last study date [see Section 5.1.1].

5.1.7. Coding

The following coding dictionaries are used:

- Adverse events, Medical history, and ECHO findings are coded using MedDRA version 26.0
- Medications (previous and concomitant) are coded using the WHO-Drug Dictionary version March 2023 B3G
- ECG and Holter abnormalities are coded using ECG CDISC SDTM Controlled Terminology (Version 3.2 from 2017-09-29).

5.1.8. Visit Windows and Analysis Visits

The following windowing approach is applied to group data by time. Scheduled and unscheduled assessments at nominal pre-dose timepoints are grouped into analysis visits within each analysis period as indicated in Table 3.

At visits where the pre- and post-bronchodilator assessments are performed, both the pre- and the post-bronchodilator assessment are mapped to the same analysis visit.

Assessments during pregnancy interruptions that are not treatment-emergent will not be assigned to visit windows.

Table 3: Visit Windows

	Day relative to start of analysis period	
Analysis Visit	***Target***	***Range ****
Day 1 (Baseline)	1	-21 to 1
Week 1**	8	2 to 11
Week 2**	15	12 to 22
Week 4**	29	23 to 43
Week 8**	57	44 to 71
Week 12**	85	72 to 99
Week 16**	113	100 to 127
Week 20**	141	128 to 155
Week 24**	169	156 to 253
Week 48	337	254 to 421
Week 72	505	422 to 589

Week 96	673	590 to 757
Week 120	841	758 to 925
Week 144	1009	926 to 1093
Week 168	1177	1094 to 1261
Week 192	1345	1262 to 1429
Week 216	1513	1430 to 1597
Week 240	1681	1598 to 1765
Week 264	1849	1766 to 1933
Week 288	2017	1934 to 2101
Week 312	2185	2102 to 2269
Week 336	2353	2270 to 2437
Week 360	2521	2438 to 2605
Week 384	2689	2606 to 2773
Week 408	2857	2774 to 2941
Week 432	3025	2942 to 3109
Week 456	3193	3110 to 3277
Week 480	3361	3278 to 3445
Week 504	3529	3446 to 3613
Week 528	3697	3614 to 3781
Week 552	3865	3782 to 3949
Week 576	4033	3950 to 4117
Week 600	4201	4118 to 4285
Week 624	4369	4286 to 4453
Week 648	4537	4454 to 4621
Week 672	4705	4622 to 4789
Week 696	4873	4790 to 4956
Last-on-treatment ***	Defined as last non-missing value in the range	*2**** to ponesimod EOT date +1*
Day relative to last dose of ponesimod		
Analysis Visit ***	***Target***	***Range***
Follow-up Day 7 (FU7)	7	5 to 16
Follow-up Day 30 (FU30)	30	17 to 45
Follow-up Day 90 (FU90)	90	46 to end
Last Follow-up (Last FU)	Defined as last non-missing value in the range	5 to end

* If [ponesimod EOT date – ponesimod start date + 15 days] falls within the range then the upper bound of the range becomes [ponesimod EOT date – ponesimod start date+ 15 days]
** For the summary of EDSS over time, Week 1, 2, 4, 8, 12, 16 and 20 are not defined and Week 24 is defined with a range of 2 to 253
*** Not defined for EDSS
**** For ECG and Vital Signs (VS), Day 1 post-baseline assessments are also considered.

Except for last-on-treatment and last FU analysis visits, if more than one assessment falls in the same time window, the closest non-missing assessment to the target day will be taken (if equidistant then the earlier value is taken). Last-on-treatment and last FU analysis visits are always mapped to the last non-missing assessment within the window.

FU visits are derived separately from treatment-emergent visits and may result in additional records in the ADaM datasets (or flagging). Last on-treatment and FU visits are defined for AP3 only.

5.1.9. Analysis strategy for long-term safety and efficacy – analysis over the whole ponesimod period

To investigate the long-term safety and efficacy of ponesimod, analysis is performed over the combined core/TP1/TP2/TP3 periods (excluding the placebo period for subjects who received placebo in the core study). All data for all subjects who received at least one dose of ponesimod at any time are included. Analyses are performed by first randomized dose of ponesimod.

The following analysis periods are defined to support the objectives as defined in Section 1.1 and Analysis Strategy as defined above. This SAP focusses on AP3, however AP1 and AP2 are described here for historical continuity with previous analyses. See Figure 1 for an illustration of the treatment periods.

- Analysis Period 1 (AP1) (Core - TP1): analyses over core and extension TP1 periods combined;
- Analysis Period 2 (AP2) (Core - TP2): analyses over core, extension TP1 and TP2 periods combined;
- Analysis Period 3 (AP3) (Core - TP3): analyses over all periods combined.

The placebo period is excluded from all analyses described in this SAP, however the placebo visits and events are kept in the pooled B201/B202 analysis data model (ADaM) datasets. All analyses are performed by first randomized dose of ponesimod, i.e., ponesimod 10 mg, ponesimod 20 mg and ponesimod 40 mg. Additional disposition tables are provided including the placebo arm in order to provide a complete overview of the transition of patients through the two studies as shown above.

Table 4: Analysis Periods

Analysis Period	Start Date	End Date
AP1	Ponesimod start date	Minimum of [last study date, date of first administration of ponesimod in TP2 - 1 day]
AP2	Ponesimod start date	Minimum of [last study date, date of first administration of ponesimod in TP3 - 1 day]
AP3	Ponesimod start date	Last study date

Analyses for Analysis Periods 1 and 2 were conducted for the Interim Analysis CSR and are not planned to be repeated for the Final CSR. For the Final CSR, only analyses for Analysis Period 3 will be performed.

5.2. Participant Dispositions

5.2.1. Definitions

5.2.1.2. Screened subjects / screening failures

Subjects are not screened for entry into the extension study. Screening information for the core study is reported in the core study CSR.

5.2.1.3. Subjects randomized/entered

The following variables are defined:

- **Randomized in the core study**: a subject is considered as randomized in the core study if randomization date and number are recorded in the core study. Randomization date is stored in SDTM201.DS.DSSTDTC where DS.DSDECOD='RANDOMIZED', randomization number is stored in SDTM201.DS.DSREFID When DS.DSTERM = RANDOMIZED. Treatment assignment is stored in SDTM.DM.ARM. Note: 2 subjects in the core study were randomized and not treated. These subjects will not be included in any analyses described in this SAP.
- **Randomized/entered TP1**: a subject is considered as randomized/entered in TP1 if they have a randomization/enrollment date entered for TP1. Randomization date is stored in SDTM202.DS.DSSTDTC where DS.DSSCAT='ENROLLMENT IN TP1'.
- **Randomized/entered TP2**: a subject is considered as randomized/entered in TP2 if they have a randomization/enrollment date entered for TP2. Randomization date is stored in SDTM202.DS.DSSTDTC where DS.DSSCAT='ENROLLMENT IN TP2'.
- **Entered TP3**: a subject is considered to have entered TP3 if they have a record in the study drug log (SDTM202.EC and SDTM202.SUPPEC) indicating transition to TP3.
- **Entered Follow-up Phase:** a subject is considered to have entered the Follow-up Phase if they have at least one Follow-up visit after EOT.

5.2.1.4. Subjects treated

The following variables are defined:

- **Treated in the core study**: a subject is considered to have been treated with ponesimod in the core study if they have at least one record in SDTM201.EC with a valid date/time (ECSTDTC) where EC.ECCAT = 'STUDY DRUG INTAKE', and with SDTM201.DM.ACTARM is 'Ponesimod 10 mg', 'Ponesimod 20 mg' or 'Ponesimod 40 mg'.
- **Treated in TP1**: a subject is considered to have been treated in TP1 if they have at least one record in SDTM202.EC with a valid date/time (ECSTDTC) where EC.ECCAT = 'STUDY DRUG INTAKE, which is on or after date randomized/entered into TP1 (SDTM202.DS.DSSTDTC where DS.DSSCAT = 'ENROLLMENT IN TP1').
- **Treated in TP2**: a subject is considered to have been treated in TP2 if they have at least one record in SDTM202.EC with a valid date/time (ECSTDTC) where EC.ECCAT = 'STUDY DRUG INTAKE, which is on or after date randomized/entered into TP2 (SDTM202.DS.DSSTDTC where DS.DSSCAT = 'ENROLLMENT IN TP2').

- **Treated in TP3**: a subject is considered to have been treated in TP3 if they have at least one record in SDTM202.EC with a valid date/time (ECSTDTC) where EC.ECCAT = 'STUDY DRUG INTAKE, which is on or after date entered into TP3.

5.2.1.5. Subject treatment completion status

A subject is considered to have completed treatment as per protocol in the core study if a treatment completion record is documented in SDTM201.DS, i.e., where DSSCAT = 'TREATMENT TERMINATION' and DSDECOD is equal to 'COMPLETED'. Date of completion is the date in DSSTDTC for this record.

A subject is considered to have prematurely discontinued from study treatment in the core study if a reason for premature treatment discontinuation or date of treatment discontinuation is documented in SDTM201.DS, i.e., where DSSCAT = 'TREATMENT TERMINATION' and DSDECOD is not equal to 'COMPLETED'. Date of discontinuation is the date in DSSTDTC for this record and reason for discontinuation is stored in DSDECOD.

Possible primary reasons for premature discontinuation of study treatment in the core study are ‘Death’, ‘Adverse Event’ and ‘Other’. If the primary reason is 'Other', the specific reason is captured in DSTERM as free text.

A subject is considered to have completed treatment as per protocol in the extension study if a study completion record is documented in SDTM202.DS, i.e., where DSSCAT = 'TREATMENT TERMINATION' and DSDECOD is equal to 'COMPLETED'. Date of completion is the date in DSSTDTC for this record.

A subject who transitions to commercial study drug is considered to have completed study treatment as per protocol if DSSCAT = 'TREATMENT TERMINATION' and DSDECOD is equal to ‘APPROVED DRUG AVAILABLE FOR INDICATION’ in SDTM202.DS. Date of completion is the date in DSSTDTC for this record.

A subject is considered to have prematurely discontinued from study treatment in the extension study if:

- A permanent reason for discontinuation or date of discontinuation is documented in SDTM202.DS, i.e., where DSSCAT = 'TREATMENT TERMINATION' and DSDECOD is not equal to 'COMPLETED' or ‘APPROVED DRUG AVAILABLE FOR INDICATION’. Date of discontinuation is the date in DSSTDTC for this record and the reason for discontinuation is stored in DSDECOD.

Possible primary reasons for premature discontinuation of study treatment in the extension study are 'Death', 'Lost to follow-up', ‘Protocol specified withdrawal criterion met', ‘Withdrawal by Subject’, 'Physician decision' and 'Sponsor decision'. ‘Withdrawal by Subject’ is further categorized into: 'Tolerability related', 'Efficacy related', 'Other', and 'Not known'. Physician decision is further categorized into: 'Adverse event', 'Lack of efficacy/Treatment failure', and 'Other'. Sponsor decision is further categorized into 'Study terminated', and ‘Other'.

If the subject or investigator decision reason is 'Other', the specific reason is captured in DSTERM as free text.

- A reason for premature treatment discontinuation is documented in the extension study, where subjects are considered to have prematurely discontinued if the last chronological

interval has in SDTM202.SUPPEC.QLABEL = 'Reason for treatment end' and SUPPEC.QVAL is 'Death', 'Adverse Event' or 'Other'.

If a subject has discontinued treatment but reason is missing, then this is coded to 'Reason not provided'.

Subjects who enter TP2 are considered to have completed treatment in TP1, and subjects who enter TP3 are considered to have completed treatment in TP2. However, subjects may complete treatment as per protocol in a given treatment period and elect not to proceed to the following treatment period. Such subjects have a record in the study drug log (EX/SUPPEX) where QLABEL = “Reason for treatment end” and QVAL = “END OF TREATMENT”, and do not have a corresponding premature treatment discontinuation record in DS as defined above.

A subject is considered to have interrupted treatment for planned pregnancy if they have a record in SDTM.SUPPEX where QNAM = “REASTEND” and QVAL = “PLANNED PREGNANCY PER PROTOCOL”.

All subjects who interrupted treatment for a planned pregnancy and have not yet restarted study treatment will have treatment status “Interrupted treatment for planned pregnancy”. However, if a subject has restarted the treatment after the planned pregnancy interruption, they will be counted under their current treatment status either under “Prematurely Discontinued” or “Completed/Approved drug available”.

An additional parameter “Restarted treatment after planned pregnancy interruption” will be summarized and will present all subjects interrupting the treatment due to planned pregnancy and restarting the treatment before the EOS date.

Interruptions for planned pregnancy are identified in the database as follows: Drug administration end date recorded on study drug log with reason for treatment end “PLANNED PREGNANCY PER PROTOCOL”.

Restart of treatment after pregnancy are identified as follows: in the SV data set, the day of re-initiation is SVSTDTC for the record with SVUPDES = “RE-INITIATION OF STUDY DRUG X”. This record should follow records with SVUPDES = “POST-PLANNED PREGNANCY”.

The following variables are derived for treatment completion/discontinuation:

- Treatment completed in the core study;
- Treatment prematurely discontinued in the core study;
- Reason for premature treatment discontinuation in the core study;
- Treatment completed in TP1;
- Treatment prematurely discontinued in TP1;
- Reason for premature treatment discontinuation in TP1;
- Treatment completed in TP2;
- Treatment prematurely discontinued in TP2;
- Reason for premature treatment discontinuation in TP2;
- Interrupted treatment for planned pregnancy in TP2;

- Re-started treatment after planned pregnancy interruption in TP2;
- Treatment completed in TP3;
- Availability of commercial ponesimod in TP3 (as a subcategory of "Treatment completed in TP3")
- Treatment prematurely discontinued in TP3;
- Reason for premature treatment discontinuation in TP3;
- Interrupted treatment for planned pregnancy in TP3;
- Re-started treatment after planned pregnancy interruption in TP3;

For subjects who discontinued from study treatment, the time of treatment discontinuation (in days) is defined as:

- (Date of treatment discontinuation (in either the core or extension study) - date of first ponesimod administration + 1 day) - (End date of pregnancy interruption - Start date of pregnancy interruption + 1 day), for subjects with planned pregnancy interruption and restart of the treatment,
- (Date of treatment discontinuation (in either the core or extension study) - date of first ponesimod administration - ponesimod start date + 1 day), for all other subjects.

5.2.1.6. Subject study completion status

A subject is considered to have completed study in either the core or the extension if they completed the EOS Visit as per protocol. This definition is independent of treatment completion, i.e., a subject can prematurely discontinue from treatment but complete the study.

A subject is considered to have completed the core study as per protocol if a study completion record is documented in SDTM202.DS, i.e., where DSSCAT='STUDY TERMINATION' and DSDECOD is equal to 'COMPLETED'. Date of completion is the date in DSSTDTC for this record.

A subject is considered to have prematurely discontinued from the core study if a permanent reason for study discontinuation or date of study discontinuation is documented in SDTM201.DS, i.e., where DSSCAT = 'STUDY TERMINATION' and DSDECOD is not equal to 'COMPLETED'. Date of core study discontinuation is the date in DSSTDTC for this record and reason for discontinuation is stored in DSDECOD.

Possible main reasons for premature discontinuation in the core study are 'Death', 'Withdrawal of subject's consent', 'Lost to follow-up' and 'Administrative reason'.

A subject is considered to have completed the extension study as per protocol if a study completion record is documented in SDTM202.DS, i.e., where DSSCAT = 'STUDY TERMINATION' and DSDECOD is equal to 'COMPLETED'. Date of completion is the date in DSSTDTC for this record. A subject is considered to have completed study per protocol in a given period if they entered the period and completed the extension study whilst in that period.

A subject who transitions to commercial study drug is considered to have completed the extension study as per protocol and if DSSCAT = 'STUDY TERMINATION' and DSDECOD is equal to

'APPROVED DRUG AVAILABLE FOR INDICATION' in SDTM202.DS. Date of completion is the date in DSSTDTC for this record.

A subject is considered to have prematurely discontinued from the extension study if a reason for premature study discontinuation or date of study discontinuation is documented in SDTM202.DS, i.e., where DSSCAT = 'STUDY TERMINATION' and DSDECOD is not equal to 'COMPLETED' or 'APPROVED DRUG AVAILABLE FOR INDICATION'. Date of extension study discontinuation is the date in DSSTDTC for this record and reason for discontinuation is stored in DSDECOD.

Possible main reasons for premature discontinuation from the extension study are 'Death', 'Lost to follow-up', 'Withdrawal by Subject', 'Physician decision', 'Sponsor decision'. 'Withdrawal by Subject' is further categorized into: 'Tolerability related', 'Efficacy related', 'Other' and 'Not Known'. Physician decision is further categorized into: 'Adverse event', 'Lack of efficacy/Treatment failure', and 'Other'. Sponsor decision is further categorized into 'Study terminated', and 'Other'.

If the subject, investigator or sponsor decision reason is 'Other', the specific reason is captured in DS.DSTERM as free-text.

The following variables are defined for study completion/discontinuation:

- Completed the core study as per protocol;
- Prematurely discontinued study in the core;
- Reason for premature discontinuation in the core study;
- Completed the core study as per protocol and not entered in the extension;
- Completed TP1 as per protocol;
- Prematurely discontinued study in TP1;
- Reason for premature study discontinuation in TP1;
- Completed TP1 as per protocol and not entered in TP2;
- Completed TP2 as per protocol;
- Prematurely discontinued study in TP2;
- Reason for premature study discontinuation in TP2;
- Completed TP2 as per protocol and not entered in TP3;
- Completed TP3 as per protocol;
- Availability of commercial ponesimod in TP3*
- Prematurely discontinued study in TP3;
- Reason for premature study discontinuation in TP3;

*This will not be listed as a reason for premature study discontinuation as this is considered study completion as per protocol provided the subject had an EOS2 or EOS3 assessment.

5.2.1.7. Time on study

Time on study (years) is derived for the ponesimod period of the core and extension studies combined (i.e., excluding placebo period) as (last study date – [date randomized in core study (if

randomized to ponesimod in the core study) or date randomized/entered in TP1 (if randomized to placebo in the core study and continuing to the extension study)] + 1 day)/365.25.

Time on study is categorized into the following intervals: ≤ 6 months, > 6 months and ≤ 1 year, > 1 year and ≤ 2 years, > 2 years and ≤ 3 years, > 3 years and ≤ 4 years, > 4 years and ≤ 5 years, > 5 years and ≤ 6 years, > 6 years and ≤ 7 years, > 7 years and ≤ 8 years, > 8 years and ≤ 9 years, > 9 years and ≤ 10 years, > 10 years and ≤ 11 years, > 11 years and ≤ 12 years, > 12 years

5.2.2. Display of Subject Disposition

The following subject disposition tables are created to summarize the treatment disposition across the different treatment periods:

- Subject disposition during the core study, by randomized treatment in the core study (RND);
- Subject disposition during TP3, by randomized treatment pathway in core/TP1/TP2 (PAS).

For each of these tables, the number of subjects randomized/enrolled, treated, completed treatment, interrupted treatment for planned pregnancy (TP2/TP3 only), restarted treatment after planned pregnancy (TP2/TP3 only), prematurely discontinued treatment, reason for premature discontinuation of treatment, completed study as per protocol, prematurely discontinued study, reason for premature study discontinuation, completed study in the treatment period as per protocol and did not enter the following treatment period (Core, TP1 and TP2 only) are summarized. Percentages are based on the number of subjects who were randomized in the treatment period. All tables include a total column. Percentages for treatment completion/discontinuation variables are based on the number of subjects treated in the treatment period; percentages for study completion/discontinuation variables are based on the number of subjects randomized in the treatment period. Study and treatment completion due to “Approved Drug Available for Indication” will be a subcategory of study/treatment completion in the tables under “Availability of commercial ponesimod”.

An additional disposition table is created to summarize treatment disposition in AP3 on the PAS, by treatment period and treatment group and overall. For each treatment period (Core, TP1, TP2, TP3), the number of subjects randomized/enrolled, treated, completed treatment, prematurely discontinued treatment, completed study as per protocol, prematurely discontinued study, completed study in the treatment period as per protocol and did not enter the following treatment period (Core, TP1 and TP2 only), interrupted treatment for planned pregnancy (TP2 and TP3 only), restarted treatment after planned pregnancy (TP2 and TP3 only) are summarized. Study and treatment completion due to “Approved Drug Available for Indication” will be a subcategory of study/treatment completion in the tables under “Availability of commercial ponesimod”.

A further overview summary of disposition pooled across treatment periods is created for AP3 on the PAS, by treatment group and overall, to summarize the number of subjects randomized to ponesimod at any time, treated, completed treatment, prematurely discontinued treatment, interrupted treatment for planned pregnancy, restarted treatment after planned pregnancy, , completed study as per protocol, prematurely discontinued from study, completed study during a treatment period and not continuing to the next treatment period. Study and treatment completion due to “Approved Drug Available for Indication” will be a subcategory of study/treatment completion in the tables under “Availability of commercial ponesimod”.

An overall summary of condensed reasons for premature treatment discontinuation is created for AP3 on the PAS, by treatment group and overall, with condensed reasons for discontinuation categorized as described in Table 5 below.

A Kaplan-Meier plot for time to premature treatment discontinuation is produced for AP3 on the PAS.

Reasons for treatment discontinuation and reasons for study discontinuation are presented in separate listings.

A listing of start and end dates of each treatment period, together with treatment group and actual treatment in each period, is provided.

Table 5: Condensed reasons for treatment discontinuation

Collected Reason/Sub-reason	Displayed Reason
Death	Death
Lost to follow-up	Lost to follow-up
Protocol-specified withdrawal criterion met	Protocol-specified withdrawal criterion met
Subject decision – tolerability related	Tolerability related/adverse event
Subject decision – efficacy related	Efficacy related
Subject decision – other	Withdrawal by subject (other/unknown)
Subject decision – not known	Withdrawal by subject (other/unknown)
Withdrawal by subject – tolerability related	Tolerability related/adverse event
Withdrawal by subject – efficacy related	Efficacy related
Withdrawal by subject – other	Withdrawal by subject (other/unknown)
Withdrawal by subject – not known	Withdrawal by subject (other/unknown)
Physician decision – adverse event	Tolerability related/adverse event
Physician decision – lack of efficacy/treatment failure	Efficacy related
Physician decision – other	Investigator decision (other/unknown)
Physician decision – not known	Investigator decision (other/unknown)
Sponsor decision	Sponsor decision
Administrative reason	Administrative/other/unknown
Adverse event	Tolerability related/adverse event
Withdrawal of subject's consent	Withdrawal of consent
Protocol violation	Protocol violation
Administrative/other	Administrative/other/unknown
Investigator's decision	Investigator decision (other/unknown)
Withdrawal of consent	Withdrawal of consent
Approved drug available for indication *	Availability of commercial ponesimod
Other/not known	Administrative/other/unknown

*In compliance with the protocol, this will not be presented as one of the reasons for treatment discontinuation but will be listed as a sub-category under Treatment completion.

5.3. Analysis of Efficacy Variables

5.3.1. Relapse-related variables

Relapse data as assessed by the investigator are stored in SDTM.CE, SDTM.SUPPCE, SDTM.CM and SDTM.FA. The two corresponding SDTM datasets for each study are concatenated for the purposes of this analysis.

For each relapse the corresponding start and stop date/time of symptoms are stored in CE. Whether the relapse meets the criteria for a confirmed relapse is stored in FA.FAORRES (as "Y", "N"), where FATEST = "Relapse Criteria Met".

5.3.1.1. Annualized relapse rate up to end of Analysis Period

The annualized relapse rate (ARR) is defined as the number of relapses per subject-year.

The following variables are derived for the analysis of ARR:

- Number of confirmed/all relapses with start date in the Analysis Period;
- Length of observation for Analysis Period AP3 expressed in years, defined as: [Analysis Period end date − Analysis Period start date + 1] in days, divided by 365.25.

These variables are derived for each subject for the Analysis Period AP3 as defined in Section 5.1.9.

In addition, the number of confirmed relapses in each year in AP3 is derived for each subject (i.e., number of confirmed relapses in first year of ponesimod treatment, number of confirmed relapses in second year of ponesimod treatment, etc.). A year is defined as 365 days for this calculation with only the remaining days counted in the last year, e.g., if a subject has 900 days of follow-up, year 3 for that subject will only have 170 days. A similar analysis for the number of unconfirmed and confirmed (all) relapses will be provided.

For the statistical analysis of ARR, the corresponding logarithm of the length of observation is also derived.

For each Analysis Period, relapses are only considered if the start date of the symptoms ≥ date of first intake of ponesimod in that analysis period and ≤ end date of that analysis period.

5.3.1.2. ARR up to last treatment in the Analysis Period + 7 days

This endpoint was analyzed for the Interim Analysis and is not planned to be analyzed for the Final CSR, as noted below, in Section 5.3.2.4.

For subjects who completed the study at the end of an Analysis Period, who discontinued during an Analysis Period, or who had a treatment interruption between treatment periods, the Analysis Period end date may be up to 90 days after last intake of ponesimod in the Analysis Period.

To consider the on-treatment ARR, ARR up to last treatment date in the Analysis Period + 7 days is also derived.

The number of confirmed relapses and length of observation are derived as defined in Section 5.3.1.1 above, where end of the Analysis Period is capped at the minimum of [last treatment in the Analysis Period + 7 days, end of the Analysis Period] and only relapses with onset

in this period are included. The number of unconfirmed and confirmed (all) relapses is similarly derived.

ARR up to last treatment in the Analysis Period + 7 days is derived for AP3.

5.3.1.3. Time to first confirmed/any relapse up to end of the Analysis Period

Time to first confirmed release is derived for AP3 as follows:

The time to first confirmed relapse (in days) is defined as [Date of first confirmed relapse - ponesimod start date + 1] in days.

Subjects without any confirmed relapses during the Analysis Period are censored, and censored time is defined as the Analysis Period end date - ponesimod start date + 1, in days. In the listings censoring is displayed as 'End of Analysis Period' for subjects who did not have a relapse by the end of the Analysis Period. Relapses are labelled as either 'Confirmed Relapses' or 'Unconfirmed Relapses'.

The definition above is also applied for the derivation of time to first 'any' relapse for AP3, i.e., including confirmed and unconfirmed relapses.

5.3.1.4. Annualized relapse rate in the Post-treatment-emergent period

The following variables are derived for the analysis of ARR in the post-treatment-emergent period:

- Number of confirmed/all relapses with start date in the post-treatment emergent period; i.e. date of last administration of ponesimod plus 16 days, as defined in Section 5.1.6;
- Length of observation for the post-treatment-emergent period as defined in Section 5.1.6, expressed in years.

5.3.1.5. Other relapse-related characteristics

Relapses requiring hospitalization and relapses requiring treatment with corticosteroids are flagged in the ADaM dataset.

The need for hospitalization and treatment with corticosteroids is stored in SUPPCE. Any corresponding medications administered are recorded in SDTM.CM with CMCAT = "CORTICOSTEROIDS (IV) FOR TREATMENT OF RELAPSE".

In the legacy paper CRF, the question related to hospitalization for relapse was *'Relapse lead to hospitalization of patient?'* with responses "Yes" or "No". The reason for hospitalization was captured as a query response in free text. In RAVE, the question was amended to *'Relapse led to hospitalization of patient (for reasons other than administration of IV corticosteroids (e.g., relapse severity or medical complications due to relapse)'* with responses "Yes" or "No". There is a potential discrepancy between the response "Yes" to the question in the legacy CRF and the question in RAVE, since hospitalizations recorded in the legacy CRF would also include patients admitted only for the administration of corticosteroids.

Given this limitation, relapses requiring hospitalization will not be included in the summary tables due to the inconsistencies between the legacy CRF and RAVE described above, i.e., hospitalizations recorded originally in the legacy CRF also include patients admitted only for the administration of corticosteroids". However, the full characterization, including hospitalization, will be included in the listings.

Relapse severity is derived for each relapse according to the algorithm defined in Table 6.

Table 6: Severity of relapse

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

* excluding the bowel and bladder, and mental FS
FS = functional system.

The algorithm is applied by considering the EDSS assessment associated with the relapse (as linked in SDTM) relative to the last EDSS assessment that was performed prior to this linked relapse EDSS assessment and prior to the relapse. The change in EDSS score and corresponding FS scores between these two EDSS assessments is used to define the severity as classified in Table 6 above. If either EDSS assessment is missing, relapse severity is missing.

Duration of relapse (days) is derived as relapse end date – relapse start date + 1 days. Relapses with missing or partially missing end dates are not included.

5.3.2. Analysis of relapse-related variables

Full details of all relapses are presented in a listing for AP3 on the PAS.

5.3.2.1. ARR up to end of Analysis Period

ARR for confirmed relapses up to the end of the Analysis Period is analyzed for AP3 on the PAS according to the NB model described in Section 6.12.1.

The model includes the number of confirmed relapses in the Analysis Period for each subject as the response variable, treatment as a factor and the logarithm of time in the Analysis Period (years) as an offset variable.

Mean model-based estimates of the ARR by treatment, as well corresponding 95% CIs are derived. In addition, rate ratios together with corresponding 95% CIs are derived for the following comparisons:

- ponesimod 20 mg *vs*. Ponesimod 10 mg;
- ponesimod 40 mg *vs*. Ponesimod 10 mg;
- ponesimod 40 mg *vs*. Ponesimod 20 mg.

The analysis of ARR for confirmed relapses is summarized in a table by treatment:

- 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, and 5+;
- Total number of confirmed relapses: sum;
- Total time in Analysis Period (subject years): sum;
- Raw ARR: total number of confirmed relapses/total time in Analysis Period;
- ARR estimate and 95% CI from a NB model, together with the dispersion parameter from the model;
- Rate ratios and 95% CIs for the comparisons listed.

ARR for all relapses is analyzed as described above for confirmed relapses

5.3.2.2. ARR in the Post-treatment-emergent Period

Summary statistics are presented for ARR in the post-treatment-emergent period, as defined in Section 5.3.1.4.

The following summary is presented for the Post-Treatment DMT subgroup (Any DMT, including ponesimod), No DMT)), where the Post-Treatment DMT subgroup is defined in Section 5.5.6 and the list of DMTs is provided in Table 11 in Section 6.5.1.

- 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, and 5+;
- Total number of confirmed relapses: sum;
- Total time in Analysis Period (subject years): sum;
- Raw ARR: total number of confirmed relapses/total time in Analysis Period;

This table is also presented for all relapses.

A listing of confirmed/all relapses in this period is also presented.

5.3.2.3. ARR by year

ARR by year for confirmed relapses is analyzed for AP3 on the PAS, as described for ARR up to the end of the analysis period in Section 5.3.2.1 above. A similar analysis for the number of unconfirmed and confirmed (all) relapses will be provided. Mean model-based estimates of the ARR by year and by treatment, as well corresponding 95% CIs are derived. A summary table and a bar chart are produced to present the ARR by year.

5.3.2.4. Sensitivity analyses of ARR

ARR up to last treatment in the Analysis Period +7

ARR for confirmed relapses up to last treatment in the Analysis Period + 7 days is analyzed separately for AP3 on the PAS, in the same way as described for ARR up to end of the Analysis Period in Section 5.3.2.1 above.

This sensitivity analysis was conducted for the Interim Analysis CSR and will not be conducted for the Final CSR.

ARR adjusted for additional baseline covariates

ARR for confirmed relapses up to end of the analysis period is analyzed for AP3 on the PAS using the same model as described in Section 5.3.2.1 above, adjusted by treatment, number of documented relapses (≤ 1 and ≥ 2) in the past 24 months prior to core[1] baseline, EDSS at ponesimod baseline (≤ 3.5 and > 3.5). A similar analysis for the number of unconfirmed and confirmed (all) relapses will be provided.

[1] Although the model considers relapses over the ponesimod period, the number of documented relapses in the past 24 months prior to extension baseline is not available, and so the value collected at the start of the core study is used as a proxy.

This sensitivity analysis was conducted for the Interim Analysis CSR and will not be conducted for the Final CSR.

5.3.2.5. Time to first confirmed/any relapse up end of the Analysis Period

Time to first confirmed relapse is analyzed for AP3 on the PAS, using the Kaplan-Meier method and Cox proportional hazards model, as described in Section 6.12.2.1 and 6.12.2.2.

The reference time is the study day, i.e., days elapsed since start of treatment with ponesimod.

The results of the Kaplan-Meier analysis are summarized in a table including:

- Number of subjects at risk, with an event and censored, KM estimates (unstratified) and corresponding CI, at intervals of 48 weeks;
- Median, 25th and 75th percentiles of the survival function together with corresponding CIs.

The hazard ratio and corresponding 95% CI based on a Cox proportional hazards model including treatment as a factor are presented in a separate table for the following comparisons:

- ponesimod 20 mg *vs*. Ponesimod 10 mg;
- ponesimod 40 mg *vs*. Ponesimod 10 mg;
- ponesimod 40 mg *vs*. Ponesimod 20 mg.

The results of Kaplan-Meier analysis are also presented graphically, including the KM estimates and corresponding CIs at the time points specified above up to the timepoint where at least 10% of subjects in each group are still at risk, as well as the hazard ratios and CIs from the Cox proportional hazards model.

Time to first 'any' relapse (all relapses) is analyzed as described above for confirmed relapses.

As a sensitivity analysis, time to first confirmed relapse is analyzed as described above, with a stratified log-rank test as described in Section 6.12.2.1 to include the additional baseline covariates: number of documented relapses (≤ 1 and ≥ 2) in the past 24 months prior to core baseline, EDSS at ponesimod baseline (≤3.5 and > 3.5). This sensitivity analysis was conducted for the Interim Analysis CSR and will not be conducted for the Final CSR.

5.3.2.6. Other relapse-related characteristics

Other relapse-related characteristics are summarized by treatment group separately for AP3 on the PAS. This includes the following:

- Number (%) of subjects with at least one: relapse, , relapse treated with corticosteroids; for all relapses up to end of the Analysis Period, confirmed relapses up to end of the Analysis Period.
- Number (%) of subjects without any (confirmed or total) relapse.
- Number (%) of relapses (out of total number of relapses) treated with corticosteroids and descriptive statistics for continuous data for relapse duration (days); for all relapses up to end of the Analysis Period as well as for confirmed relapses up to end of the Analysis Period.
- Number (%) of relapses classified as mild/moderate/severe; for all relapses up to end of the Analysis Period as well as for confirmed relapses up to end of the Analysis Period.
- Number of confirmed relapses, number of all relapses, ratio of confirmed vs. all relapses; for relapses up to end of the Analysis Period for all relapses up to end of the Analysis Period as well as for confirmed relapses up to end of the Analysis Period

As described in Section 5.3.1.5, relapses requiring hospitalization will not be included in the summaries.

A listing of all relapses including hospitalizations, administration of corticosteroids, severity of relapse will be presented.

5.3.3. MRI-related variables

MRI data are provided from a central reader (MIAC). The following parameters are evaluated by MIAC:

Table 7: MRI parameters

Name of MRI test	MRI test code	Unit of MRI test
Total number of T1 Gd+ lesions	T1Gd_R	
Total volume of T1 Gd+ lesions	T1Gd_Vol	mm^3
Number of new or enlarging T2 lesions (without gadolinium-enhancement)	T2New_R	
Total volume of T2 lesions	T2_Vol	mm^3
Percentage brain volume change since Visit 2 (AC-058B201)	PBVC_V2	%
Percentage brain volume change since Visit 11 (AC-058B201)	PBVC_V11	%

All available MRI data are considered valid.

5.3.3.1. T1 Gd+ lesions

For summaries of total number of T1 Gd+ lesions (T1Gd_R) and T1 Gd+ lesion volume (T1Gd_Vol) over time, MRI scans are remapped to the nearest timepoint via a windowing approach. If a subject has more than one assessment within a given window, the nearest

assessments to the (target) MRI timepoint within the window is taken. Only scheduled scans are remapped.

Time windows are derived from time since first administration of ponesimod according to the schedule defined in Table 8 below.

Table 8: MRI timepoint definition: scan mapping

Target timepoint displayed	Time window (weeks)
Baseline	Last non-missing prior or on day of 1st ponesimod dose
Week 24	1 (Day 2) - < 32
Week 48	32 - < 60
Week 72	60 - < 96
Week 120	96 - < 144
Week 168	144 - < 192
Week 216	192 - < 240
Week 264	240 - < 288
Week 312	288 - < 336
Week 360	336 - < 384
Week 408	384 - < 432
Week 456	432 - < 480
Week 504	480 - < 528
Week 552	528 - < 576
Week 600	576 - < 624
Week 648	624 - < 672
Week 696	672 - < 720

The following variables are derived for T1 Gd+ lesions per subject:

- Total number of T1 Gd+ lesions (T1Gd_R) per MRI timepoint (as defined in Table 8 above) in AP3, and corresponding number categorized (0, 1, 2, 3, 4+);
- Cumulative total number of T1 Gd+ lesions over the Analysis Period, for AP3, defined as the sum of the total number of T1 Gd+ lesions at each derived MRI (mapped) timepoint;
- Number of derived MRI (mapped) timepoints in the Analysis Period, for AP3;
- Absence of T1 Gd+ lesions (lesion-free) per MRI timepoint in AP3 (only mapped scans are considered);
- Total volume of T1 Gd+ lesions per MRI timepoint in AP3.

5.3.3.2. New or enlarging T2 lesions and T2 volume

For summaries of new or enlarging T2 lesions (T2New_R) over time, the number of lesions is assigned to the timepoint in which they fall, as defined in Table 9 below. As the number of new or enlarging lesions is always relative to the previous assessment, if the observation period for the scan crosses the boundary of a time window, the lesions are allotted **proportionally** to the time windows which they cross. For example, if a subject has a scan at Week 24, and the next scheduled scan occurs at Week 72, the Week 72 scan will count the number ("x") of new or enlarging T2 lesions since Week 24. In this case x/2 lesions would be allocated to the Week 0-48 window, and x/2 lesions would be allocated to the Week 48-96 window.

Time windows are derived from time since first administration of ponesimod according to the schedule defined in Table 9 below.

Table 9: MRI time window definition: scan mapping for new or enlarging T2 lesions

Time window displayed	Time window (weeks)
Week 0-48	0 - <48
Week 48-96	48 - <96
Week 96-144	96 - <144
Week 144-192	144 - <192
Week 192-240	192 - <240
Week 240-288	240 - <288
Week 288-336	288 - <336
Week 336-384	336 - <384
Week 384-432	384 - <432
Week 432-480	432 - <480
Week 480-528	480 - < 528
Week 528-576	528 - < 576
Week 576-624	576 - < 624
Week 624-672	624 - < 672
Week 672-720	672 - < 720

The following variables are derived for T2 lesions per subject using the above time windows:

- Number of new or enlarging T2 lesions (T2New_R) per MRI time window (as derived in Table 9 above) in AP3;
- No new or enlarging T2 lesions during each MRI time window in AP3.

The following additional variables are derived for T2 lesions per subject: Only scheduled scans are considered, however premature EOT scans are included.

- Cumulative number of new or enlarging T2 lesions over Analysis Period (for AP3), derived as the sum of the number of new or enlarging T2 lesions at each scheduled scan during the Analysis Period;
- Absence of new or enlarging T2 lesions over the Analysis Period (for AP3), derived where the sum of the number of new or enlarging T2 lesions at each scheduled scan during the Analysis Period is zero;
- Time (years) from first administration of ponesimod to last MRI scan at which T2 was measured in the Analysis Period (for AP3). Only scheduled scans are used for this derivation.
- T2 volume (T2_Vol) per MRI timepoint (as defined in Table 9 above) in AP3;
- Change from ponesimod baseline in total T2 lesion volume per MRI timepoint (as defined in Table 9 above) in AP3.

5.3.3.3. Combined unique active lesions (CUAL)

The following variables are derived per subject for CUAL:

- Total number of CUAL derived as the number of new or enlarging T2 lesions at each scheduled scan* within the Analysis Period, plus the number of T1 Gd + lesions at each corresponding scheduled scan within the Analysis Period where new or enlarging T2 lesions were measured (AP3), and corresponding number categorized (0, >0** – 5, >5 – 10, >10 -15, >15 --20, >20 -25, >25)
- Cumulative number of CUAL over the Analysis Period, derived as the sum of all new or enlarging T2 lesions at each scheduled scan* within the Analysis Period, plus the number of T1 Gd + lesions at each corresponding scheduled scan within the Analysis Period where new or enlarging T2 lesions were measured (AP3);
- Cumulative number of CUAL over the Analysis Period as derived above, categorized into the following categories: 0, 1-5, 6-10, 11-15, 16-20, 21-25, 26-30, 31-35, 36-40 and 41+ (AP3).

* Excluding T1 Gd+ lesions measured at the core scheduled visits at Week 4, 8, 16 and 20. This restriction is necessary to avoid double-counting lesions when the MRI scans are less than 12 weeks apart, as only total (new + persisting) T1 Gd+ lesions are collected, but the derivation of CUAL should consider only new T1 Gd+ lesions. As T1 Gd+ lesions are assumed not to enhance for more than 12 weeks, it is assumed that the number of T1 Gd+ lesions counted when the scans are at least 12 weeks apart is equivalent to the number of new T1 Gd+ lesions.

** Fractional values are possible and reflect allocation of T2 lesions proportionally to adjacent time-windows.

5.3.3.4. Brain volume

The following variables are derived per subject brain volume:

- Percentage change from ponesimod baseline* in brain volume per MRI timepoint (as defined in Table 8 above) in AP3.

* Percentage change in brain volume from Visit 2 of the core study, and percentage change in brain volume from Visit 11 of the core study are derived by MIAC and provided in SDTM. Percentage change from ponesimod baseline per scan is derived in the ADaM dataset as follows:

- For subjects randomized to ponesimod in the core study, percentage change in brain volume from ponesimod baseline is equal to percentage change in brain volume from Visit 2 of the core study (PBVC in the core study SDTM, PBVC_V2 in the extension study SDTM).
- For subjects randomized to placebo in the core study and continuing to the extension study, percentage change in brain volume from ponesimod baseline is equal to percentage change in brain volume from Visit 11 of the core study (PBVC_V11).

5.3.4. Analysis of MRI-related variables

5.3.4.1. T1 Gd + lesions

The cumulative total number of T1 Gd+ lesions is analyzed for AP3 on the PAS, according to the NB model described in Section 6.12.1. The model includes the cumulative total number of T1 Gd+ lesions in the Analysis Period for each subject as the response variable (as defined in

Section 5.3.3.1), treatment as a factor and the logarithm of the number of MRI timepoints in the Analysis Period (years) (as defined in Section 5.3.3.1) as an offset variable. This analysis was conducted for the Interim Analysis CSR and is not planned to be conducted for the Final CSR.

Mean model-based estimates of the total number of T1 Gd+ lesions by treatment, as well corresponding 95% CIs are presented, as well as rate ratios and 95% CIs for the comparisons between doses. This sensitivity analysis was conducted for the Interim Analysis CSR and is not planned to be conducted for the Final CSR.

As a sensitivity analysis, the cumulative total number of T1 Gd+ lesions is analyzed as described above, also including the additional baseline covariates included for the sensitivity analysis of ARR as described in Section 5.3.2.3. This sensitivity analysis was conducted for the Interim Analysis CSR and is not planned to be conducted for the Final CSR.

The total number of T1 Gd + lesions per MRI timepoint and the total volume of T1 Gd+ lesions at each MRI timepoint (as defined in Section 5.3.3.1) are summarized descriptively by treatment group for AP3 on the PAS. These data are presented in both a table and a figure.

The number of subjects with no T1 Gd+ lesions (lesion-free) at each MRI timepoint is summarized by treatment group for AP3 on the PAS: frequency counts and percentages. The denominator for percentages is the number of subjects with an MRI scan at the timepoint.

All T1 Gd+ lesion and volume data are presented in a listing for AP3 on the PAS.

5.3.4.2. New or enlarging T2 lesions

The cumulative number of new or enlarging T2 lesions (as defined in Section 5.3.3.2) is analyzed separately for AP3 on the PAS, as described in Section 5.3.4.1 for the cumulative total number of T1 Gd+ lesions. The logarithm of the time up to the last MRI scan at which T2 was measured in the Analysis Period (years) is used as an offset variable. This analysis was conducted for the Interim CSR and is not planned to be conducted for the Final CSR.

The number of new or enlarging T2 lesions per MRI time window (as defined in Section 5.3.3.2) is summarized descriptively by treatment group as described in Section 5.3.4.1 for the cumulative number of T1 Gd+ lesions, and is presented in both a table and a figure for AP3 on the PAS.

The total T2 lesion volume per MRI timepoint and corresponding change from ponesimod baseline in total T2 lesion volume per MRI timepoint are summarized descriptively in the same way.

The number of subjects with no new or enlarging T2 lesions (lesion-free) in the Analysis Period is summarized by treatment group separately for AP3 on the PAS: frequency counts and percentages. The denominator for percentages is the number of subjects with at least one MRI scan at which T2 was measured during the Analysis Period.

All T2 lesion and volume data are presented in a listing for AP3 on the PAS.

5.3.4.3. CUAL

The cumulative number of CUAL (as defined in Section 5.3.3.3) is analyzed for AP3 on the PAS, as described in Section 5.3.4.1 for the cumulative total number of T1 Gd+ lesions. The logarithm of the time up to the last MRI scan at which T2 was measured in the Analysis Period (years) is used as an offset variable.

The number of CUAL per MRI time window (as defined in Section 5.3.3.2) is summarized descriptively by treatment group, as described in Section 5.3.4.2 for the cumulative number of new or enlarging T2 lesions, and is presented in both a table and a figure for AP3 on the PAS.

Frequency counts and percentages for the categorical number of CUAL in the Analysis Period are presented by treatment group for AP3 on the PAS. The denominator for percentages is the number of subjects with at least one MRI scan at which T2 was measured during the Analysis Period.

All CUAL data is presented in a listing for AP3 on the PAS.

5.3.4.4. Brain volume

Descriptive statistics for percentage change from ponesimod baseline in brain volume by MRI timepoint are presented for AP3 on the PAS. Additionally, a line graph of percent change from baseline by MRI timepoint is presented.

All brain volume data is presented in a listing for AP3 on the PAS.

5.3.5. Neurological variables

EDSS and FS scores as assessed by the investigator are stored in SDTM.QS. The two QS datasets are concatenated for the purposes of this analysis.

5.3.5.1. Time to 24-week confirmed disability progression up to end of the Analysis Period

Time to 24-week confirmed disability accumulation from baseline is derived for AP3 using the ponesimod baseline.

Time to 24-week confirmed disability accumulation from baseline (the last non-missing measurement taken prior to first dose of ponesimod) up to end of the Analysis Period is derived based on the EDSS scores. Disability accumulation is defined as an increase of at least 1 point in the EDSS score if baseline EDSS was between 1 and 5.0, an increase of at least 1.5 points if baseline EDSS was 0, or an increase of at least 0.5 points if the baseline EDSS was equal or greater than 5.5.

A 24-week confirmed disability accumulation is defined as a 24-week sustained increase from baseline in the EDSS scores. i.e., every EDSS score (scheduled or unscheduled, with or without relapse) within a 24-week duration after the first accumulation should meet the accumulation criteria as specified above.

Data derivation for time to event analysis includes derivation of the event status and the time to event variables.

The steps to determine whether a subject has a 24-week confirmed disability accumulation or not (i.e., event status) and how the time to event variable is calculated are summarized in the numbered points below:

1. Detection of a disability accumulation onset:

   All available post-baseline EDSS assessments (scheduled or unscheduled, with or without relapse) are compared to the baseline EDSS to assess if the change from baseline meets the disability accumulation criteria as described above. The disability accumulation onset date is the date of the first EDSS meeting the disability accumulation criteria.

2. Confirmation of a disability accumulation:

   As a general rule, disability accumulation can only be confirmed at a scheduled visit and in the absence of a relapse. Note that the EOS/early discontinuation visit and the follow-up visit (in core, TP1, TP2, and TP3) are protocol specified visits and are treated as scheduled visits and thus can be used to confirm a disability accumulation if applicable. Specifically, the confirmation visit is the first scheduled visit meeting the following conditions.

   - This visit is ≥ 24 weeks (140* days) from the potential onset date;
   - The EDSS assessment is NOT performed during a relapse (between start and end date of a relapse, or if relapse end date is missing, then until start date of relapse + 90 days);
   - All available EDSS scores (scheduled or unscheduled, with or without relapse) between the disability accumulation onset and this visit meet the disability accumulation criteria;
   - The EDSS confirmation visit may be beyond the end of the Analysis Period, as long as the onset is prior to the end of the Analysis Period.

   * Note: In the extension study, visits are scheduled with a time window of +/- 14 days for conducting the EDSS assessment, the minimum per-protocol allowed time difference between two EDSS assessments scheduled 24 weeks apart is 140 days (24 weeks = 168 days minus a 14-day visit time window for each of the 2 visits, i.e., 168 days - 28 days = 140 days).

   If an EDSS increase cannot be confirmed due to no available EDSS assessment, but the subject dies due to MS (death with reason 'Multiple sclerosis') the CDA is also considered confirmed, with confirmation date being the death date and onset date of the initial EDSS increase.

3. If a confirmation visit cannot be found in step 2, then steps 1 and 2 are repeated to look for the next disability accumulation onset and its confirmation visit. If a confirmation visit is found in step 2, then the algorithm stops for this subject, otherwise steps 1 and 2 are repeated until the last disability accumulation onset is assessed.

4. If at none of the assessments a 24-week CDA is identified, but the subject dies due to MS (experiences a relapse with outcome death) the subject is considered to have a 24-week CDA with onset date being the death date.

5. Event status and time to event variables for time to event analyses:

   After steps 1, 2, 3 and 4 are performed, a subject is considered to have a 24-week confirmed disability accumulation if an accumulation onset with a confirmation visit is found. Otherwise, the subject is considered not to have a 24-week confirmed disability accumulation and is referred to as a censored subject.

   For subjects with a 24-week confirmed disability accumulation, the time to event variable (days) is calculated as (onset date – date of first treatment with ponesimod + 1). The onset date is based on the EDSS assessment date rather than the associated nominal visit date.

   For subjects without a 24-week confirmed disability accumulation, their time to event variable is calculated as (censoring date – date of first treatment with ponesimod + 1).

Censoring

The censoring date is defined as: Date of last EDSS assessment without an EDSS increase. Subjects without post baseline assessment (without EDSS increase) are censored on ponesimod

start date. Time to censoring is defined as censoring date minus date of date of first treatment with ponesimod + 1.

For handling of missing dates see Section 6.14.

5.3.5.2. Change from baseline in EDSS

The ponesimod baseline value is flagged in the ADaM dataset.

Absolute and percentage change from ponesimod baseline are derived for all post-(applicable) baseline EDSS assessments. All nominal visits are re-windowed based on the visit schedule in Section 5.1.7. See footnote on table, Weeks 1, 2, 4, 8, 12, 16 and 20 are not defined for EDSS. No last-on-treatment visit, follow-up visits or last follow-up visit are defined for EDSS as an intent-to-treat approach is used for efficacy.

5.3.6. Analysis of Neurological variables

5.3.6.1. Time to 24-week CDA

Time to 24-week CDA is analyzed for AP3 on the PAS, using the Kaplan-Meier method and Cox proportional hazards model as described for time to first relapse in Section 5.3.4.1.

5.3.6.2. Change from baseline in EDSS

The absolute EDSS score and change from ponesimod baseline in EDSS score by analysis visit and treatment group are summarized using descriptive statistics for AP3 on the PASA corresponding listing of EDSS / functional system (FS) scores and indicating start date of a CDA / confirmation of a CDA is produced for AP3 on the PAS.

5.3.7. Ophthalmological variables

Ophthalmological variables as assessed by the investigator are stored in SDTM.OE. The two OE datasets are concatenated for the purposes of this analysis.

The following ophthalmological variables are collected at selected centers only:

- Retinal nerve fiber layer (RNFL) thickness;
- Central foveal thickness;
- Total macular volume;
- Number of letters correctly read.

The ponesimod baseline value is flagged in the ADaM dataset.

Absolute and percentage change from ponesimod baseline are derived for all post-baseline assessments. All nominal visits are re-windowed based on the visit schedule in Section 5.1.7.

In addition, absolute change from baseline in central foveal thickness is categorized as follows:

- < -40 µm;
- ≥ -40 and < -20 µm;
- ≥ -20 and ≤ 20 µm;
- > 20 and ≤ 40 µm;
- > 40 µm.

5.3.8. Analysis of ophthalmological variables

Absolute values and absolute change from ponesimod baseline values by analysis visit and treatment group are summarized using descriptive statistics for AP3 on the OCT for retinal nerve fiber layer (RNFL) thickness, central foveal thickness, total macular volume and number of letters correctly read.

Absolute change from ponesimod baseline in central foveal thickness by analysis visit is summarized using descriptive statistics and frequency counts and percentages for the categorical change, for AP3 on the OCT.

A listing of all ophthalmological variables is produced for AP3 on the OCT.

5.4. Other Safety Analyses

All safety analyses will be based on the PAS based on actual intervention received, unless otherwise specified.

For all continuous safety variables, descriptive statistics by intervention group will include the N, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by intervention group using frequency counts and percentages.

Unscheduled visits are not presented in summary tables or figures by visit unless mapped to a windowed analysis visit [see Section 5.1.8]. Any unscheduled assessments that meet the pre-defined high/low criteria are flagged and may be included in the corresponding incidence tables.

The outputs summarizing abnormalities only use treatment-emergent data.

Summaries of safety assessments over time are presented by analysis visit (see Section 5.1.9 for derivation of analysis visit). In these summary tables by analysis visit, except for values at baseline and follow-up visits, only treatment-emergent values are displayed.

5.4.1. Exposure and Compliance

5.4.1.1. Exposure to study treatment

All ponesimod drug administration data is taken from the study drug log and stored in SDTM.EC. ECSTDTC where EC.ECCAT = 'STUDY DRUG INTAKE'. The two EC datasets are concatenated for the purposes of this analysis.

Ponesimod exposure (years) for any given exposure period is derived as:

– [(Treatment end date - ponesimod start date + 1 day) - (End date of pregnancy interruption - Start date of pregnancy interruption + 1 day)] / 365.25, for subjects with planned pregnancy interruption and restart of the treatment,
– (Treatment end date - ponesimod start date + 1 day) / 365.25, regardless of interruptions, for all other subjects.

Duration of planned pregnancy study drug interruption (days) is defined as:
min (EOS date, end date of pregnancy interruption) – Start date of pregnancy interruption + 1 day

In case of multiple planned pregnancies, all intervals between start date and end date of each pregnancy interruption will be subtracted from exposure.

Duration of planned pregnancy is excluded from all definitions of exposure duration and compliance with study treatment.

The following variables are derived for ponesimod exposure:

Table 10: Ponesimod exposure variables

Exposure period	Start date	End date
Ponesimod exposure during the core study (years)	First administration of ponesimod in the core study	Last administration of ponesimod in the core study
Ponesimod exposure during TP1 (years)	First administration of ponesimod TP1	Last administration of ponesimod in TP1
Ponesimod exposure during TP2 (years)	First administration of ponesimod TP2	Last administration of ponesimod in TP2
Ponesimod exposure during TP3 (years)	First administration of ponesimod TP3	Last administration of ponesimod in TP3
Ponesimod exposure during AP3 (years)	First administration of ponesimod (in core or TP1)	Max of [last administration of ponesimod in the core study, last administration of ponesimod in TP1, last administration of ponesimod in TP2, last administration of ponesimod in TP3]

AP = Analysis Period; TP = Treatment Period.

If end date is missing on last record in EC (e.g., if a subject is lost to follow-up), then date of last administration is taken as DS.DSSDTC when DSSCAT = 'Study termination'.

For each of the variables defined in Table 10 above, the following corresponding exposure variables are derived:

- **Ponesimod exposure over defined exposure period, categorized** into the following intervals: ≤ 6 months, > 6 months and ≤1 year, > 1 year and ≤ 2 years, > 2 years and ≤ 3 years, > 3 years and ≤ 4 years, > 4 years and ≤ 5 years, > 5 years and ≤ 6 years, > 6 years and ≤ 7 years, > 7 years and ≤ 8 years, > 8 years and ≤ 9 years, > 9 years and ≤ 10 years, > 10 years and ≤ 11 years, > 11 years and ≤ 12 years, > 12 years .
- **Cumulative duration of interruptions during the defined exposure period (days):** the cumulative duration of interruptions is the sum of all interruptions during the period up to the date of last administration of ponesimod within the period (i.e., interruptions before the start of the next period are not included). Treatment interruption refers to any period during which the subject did not receive study treatment, i.e., one or more day without documented treatment intake (per the CRF Study Drug Log page). Each interruption is calculated as:

  Re-start date of ponesimod treatment - end date of previous ponesimod treatment - 1;
- **Ponesimod treatment exposure during the defined exposure period with interruptions excluded (years):** ponesimod exposure over the defined exposure period **-** (cumulative duration of corresponding interruptions)/365.25).

- **Number of treatment interruptions (> 3 days) during the defined exposure period:** an interruption with a duration is > 3 days.
- **Cumulative duration of interruptions during the defined exposure period (days):** the cumulative duration of interruptions is the sum of all interruptions (of any duration duration) during the period.

5.4.1.2. Compliance with study treatment

Data on capsules/tablets dispensed/returned are not collected on the CRF, and so compliance cannot be assessed in this way. As a proxy, compliance is assessed as a percentage, calculated as:

> (Cumulative exposure over defined exposure period with interruptions excluded / Cumulative exposure over defined exposure period with interruptions included) *100.

Corresponding categorical variables are derived for compliance in the categories: < 80%, ≥ 80 - < 90%, ≥ 90 - < 95%, ≥ 95 - <= 100%, =100%.

Compliance with study treatment is derived as:
– [duration of exposure with all interruptions excluded / duration of exposure with interruptions included (except interruption for planned pregnancy)] × 100.

All other exposure and compliance variables will be defined in the same way, i.e., excluding the planned pregnancy interruption periods. In addition, the planned pregnancy interruptions will not be counted/considered an interruption for the variables: number of subjects with at least an interruption, number of treatment interruptions (> 3 days) or cumulative duration of interruptions.

5.4.1.3. Study treatment re-initiation

A subject is considered to have a re-initiation of study treatment if they have a record in the study drug log where:

- There is a record in EX indicating ‘Up-titration’, ‘Re-initiation’, or ‘Transition’ with an associated administered dose of ponesimod 10 mg;
- This record follows a period of > 3 days where study drug was interrupted (either within a treatment period, or between two treatment periods).

The number of re-initiations per subject in AP3 is counted.

For subjects initially on placebo who had a treatment interruption before starting ponesimod treatment, the re-start of treatment after the interruption will not be considered as a re-initiation.

5.4.2. Analysis of Exposure

5.4.2.1. Exposure and compliance

Separate exposure tables are created for the AP3 exposure period as defined in Table 10 in Section 5.4.1.1 and for the corresponding compliance variables defined in Section 5.4.1.2 to present:

- Ponesimod exposure (years): descriptive statistics;
- Overall subject years exposure (sum over all subjects’ exposure);

- Ponesimod exposure by category (cumulative) (years): frequency counts and percentages;
- Ponesimod exposure with **interruptions excluded (years):** descriptive statistics;
- Ponesimod exposure by category with **interruptions excluded** (cumulative) **(years):** frequency counts and percentages**;**
- Number of treatment interruptions > 3 days: frequency counts and percentages;
- Number of subjects with at least 1 treatment interruption > 3 days: frequency counts and percentages;
- Cumulative duration (days) of interruptions > 3 days: descriptive statistics;
- Compliance (%): descriptive statistics (AP3 only);
- Compliance by category (%): frequency counts and percentages (AP3 only).

Corresponding listings of all exposure and compliance variables as defined in Sections 5.4.1.1 and 5.4.1.2 are provided separately for each defined exposure period.

All outputs for ponesimod exposure are based on the PAS.

5.4.2.2. Study treatment re-initiation

The following variables for treatment re-initiation are summarized for AP3 on the PAS:

- Number of subjects with at least 1 re-initiation during the Analysis Period: frequency counts and percentages;
- Number of re- initiations per subject during the analysis period; descriptive statistics.

5.4.2.3. Study drug batches

A listing of study drug batches received by each subject, including lot numbers and date dispensed, will be created for AP3 on the PAS.

5.4.3. Adverse Events

An AE is any event reported by the investigator on the CRF. All adverse events are stored in the appropriate SDTM.AE domain.

AEs collected in the core study are stored in SDTM201.AE. New AEs collected in the extension study are stored in SDTM202.AE, together with follow-up of AEs that were ongoing at the end of the core study. The two AE datasets are concatenated for the purposes of this analysis, and the additional follow-up details collected for AEs that were ongoing at the time of the end of the core study are merged onto the original records to create a single record for each such AE.

All AEs reported in both SDTM201.AE and SDTM201.AE are coded to the MedDRA version 26.0.

Adverse events with a missing end date are considered as ongoing, i.e., the end date is set to missing.

5.4.3.1. Duration of AE (days) is derived as min [AE end date, EOS date] – AE start date + 1 day. Treatment-emergent adverse events

Treatment-emergent adverse events (TEAEs) are defined according to the general definition of treatment-emergent for safety variables as described in Section 5.1.4.

AEs with completely missing start date will be considered as treatment-emergent unless it is otherwise clear (e.g., by end date) that the event occurred pre-treatment. If it is not clear whether the event is treatment-emergent or not (in case of partial dates), the event will be considered a TEAE if the AE start date is potentially on or after treatment start date. For example, an AE with partial date of "May 2016" and a treatment start date of "23 May 2016" is considered treatment-emergent. For imputation of partial dates see definition in Section 6.14.4.

AEs with an onset date during treatment interruptions (including periods between studies and study-periods) except the period of planned pregnancy interruptions (see Section 5.1.4) are considered treatment-emergent.

AEs considered treatment-emergent are flagged in the AdaM dataset.

5.4.3.2. Post-treatment-emergent adverse events

Post-treatment-emergent adverse events are defined as those AEs occurring from 16 days after last administration of ponesimod until last study date, i.e., AEs occurring during the post-treatment-emergent period (Section 5.1.6)

5.4.3.3. Intensity of adverse events

The maximum intensity of an AE is stored in SDTM.AE.AESEV, as 'Mild', 'Moderate', 'Severe' or 'Not applicable'. Adverse events with missing intensity are considered in any analysis as 'Severe'.

5.4.3.4. Relationship of adverse events to treatment

The possible relationship of an AE to study treatment is stored in SDTM.AE.AEREL, as 'Related' or 'Not Related'. If the relationship is missing for an AE, then it is considered to be related.

5.4.3.5. Outcome of adverse events

The outcome of an AE is stored in SDTM.AE.AEOUT, as 'Recovered/resolved', 'Recovered/resolved with sequelae', 'Not recovered/not resolved', 'Fatal', or 'Unknown'.

5.4.3.6. Deaths

Death information (date of death and cause of death) is stored in SDTM.DD. Date of death is in DDDTC and cause of death is in DDSTRESC.

5.4.3.7. Serious adverse events

The seriousness of an adverse events is stored in SDTM.AE.AESER as 'Y' or 'N'. If missing, the AE is considered to be serious.

5.4.3.8. Adverse events leading to discontinuation of study treatment

The action taken for an adverse event is stored in SDTM.AE.AEACN. An AE is considered to be an AE leading to discontinuation if AEACN = 'Drug withdrawn'.

5.4.3.9. Adverse events leading to temporary interruption of study treatment

The action taken for an adverse event is stored in SDTM.AE.AEACN. An AE is considered to be an AE leading to discontinuation if AEACN = 'Drug interrupted'.

5.4.3.10. Adverse events following first administration/re-initiation of ponesimod

The following TEAEs are flagged for their time of onset:

- TEAEs with onset on Day 1 following first ponesimod administration, i.e., those AEs that start on or after first ponesimod administration start date (on Day 1), by time and date, and before the following calendar date;
- TEAEs with onset on Days 2-7 following first ponesimod administration;
- TEAEs with onset on Days 8-14 following first ponesimod administration;
- TEAEs with onset on Days 15-21 following first ponesimod administration;
- TEAEs with onset on Day 1 following any re-initiation of ponesimod (for definition of a re-initiation, see Section 5.4.1.3).

5.4.3.11. Adverse events ongoing from the core study

Ongoing AEs are those in SDTM202.AE where AECAT = "ONGOING AE FROM AC-058B201".

5.4.3.12. Major adverse cardiovascular events

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 events (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 adverse event. 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 AE is 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.

5.4.4. Analyses of Adverse Events

5.4.4.1. Adverse events

All AEs captured from signature of informed consent up to EOS are reported in the subject listings.

- Unless otherwise specified, all summaries of adverse events are created separately for analysis period AP3, based on the PAS.

Summaries of AEs with onset on Day 1 of ponesimod administration are summarized on the PAS, and with a single column for ponesimod 10 mg (due to the up-titration scheme, all subjects receive ponesimod 10 mg on Day 1 regardless of randomized dose).

Summaries of AEs with onset on Day 1 were presented in the Interim Analysis CSR and are not planned to be presented in the Final CSR.

All summaries of AEs are presented by treatment group, and additionally overall for tables on AP3.

5.4.4.2. Frequency and AEs per 100 subject-years

AEs are summarized according to both frequency (number of subjects and percentage) 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 with the Analysis Period (based on grouping term) are counted only once per subject.

AEs per 100 subject-years is calculated as (Total cumulative number of events during the Analysis Period / Cumulative observation time over all subjects (years) during the Analysis Period) × 100, per grouping term. Pregnancy interruptions and events during pregnancy interruptions should be excluded from this calculation.

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.

The observation time (in days) per subject for summaries of treatment-emergent AEs is calculated as: minimum (date of last administration of ponesimod within the Analysis Period +15, EOS date) − ponesimod start date + 1. Pregnancy interruptions should be excluded from this calculation.

5.4.4.3. AE displays

The following types of summary display are used:

- Overview of AEs;
- AEs by primary system organ class (SOC) and preferred term (PT);
- AEs by preferred term (PT);
- AEs by AESI category and PT;
- AEs by maximum intensity and PT.

Overview of AE summaries display subjects having any AE, any severe AE, any drug-related AE, any AE leading to study drug discontinuation, any serious AE, any drug-related serious AE, or any fatal serious AE.

AE summaries by grouping term(s) (e.g., SOC, PT, AESI category, maximum intensity) display the number and percentage of subjects having any AE and having an AE in each grouping term. They are sorted by descending frequency of grouping term in the ponesimod 40 mg arm, then the ponesimod 20 mg arm, and finally the ponesimod 10 mg arm. If the frequencies in any grouping term are still the same, alphabetical order is used. Maximum intensity order is fixed as mild, moderate, severe.

5.4.4.3.1. All adverse events

The following summaries are presented:

- Overview of all AEs (frequency) (AP3 only);
- All AEs by SOC and PT (frequency) (AP3 only);

5.4.4.3.2. Treatment-emergent adverse events

The following summaries are presented:

- Overview of TEAEs (frequency);
- Overview of TEAEs (AEs per 100 subject-years);
- Treatment-emergent AEs by SOC and PT (frequency);
- Treatment-emergent AEs with onset on Day 1 of first ponesimod administration, by SOC and PT (frequency) – single table with a column for ponesimod 10 mg only;
- Treatment-emergent AEs with onset on Day 1 of any re-initiation by SOC and PT (frequency) (AP3 only, subjects with at least one re-initiation only);
- Treatment-emergent AEs by PT (frequency);
- Treatment-emergent AEs by PT (frequency): PTs occurring only in ≥ 5% subjects in at least one treatment group;
- Treatment-emergent AEs by PT and maximum intensity (frequency);
- Treatment-emergent AEs by SOC and PT (AEs per 100 subject-years);
- Treatment-emergent AEs by PT (AEs per 100 subject-years).

Treatment emergent AEs with onset of Day 1 of first ponesimod or Day 1 of any re-initiation by SOC and PT (frequency) were presented in the Interim Analysis CSR. This was presented in the Interim Analysis CSR and therefore, is not planned to be presented in the Final CSR.

A listing of all AEs is provided for AP3 based on the PAS.

5.4.4.3.3. Post-treatment-emergent adverse events

The following summaries are presented:

- Post-treatment-emergent AEs by SOC and PT (frequency; AP3 only, completed/discontinued subjects only).
- Post-treatment-emergent AEs by SOC and PT (frequency; AP3 only, completed/discontinued subjects only) by Treated (DMTs, including ponesimod), Not treated and Total.

A listing of all post-treatment AEs is provided based on the PAS.

5.4.4.3.4. Adverse events ongoing from the core study

A listing of all AEs ongoing from the core study is provided based on the PAS.

This listing was presented in the Interim Analysis CSR and is not planned to be presented in the Final CSR.

5.4.4.4. Deaths, other serious adverse events

5.4.4.4.1. Death

The number and percentage of subjects who died are summarized by treatment group, including the reported primary cause of death, for AP3 on the PAS.

All deaths during AP3 are listed on the PAS.

5.4.4.4.2. Serious adverse events

The following summaries are presented:

- Treatment-emergent SAEs by SOC and PT (frequency);
- Treatment-emergent SAEs with onset on Day 1 of first ponesimod administration, by SOC and PT (frequency) – single table with a column for ponesimod 10 mg only;
- All SAEs by SOC and PT (frequency);
- Treatment-emergent SAEs by SOC and PT (AEs per 100 subject-years).

Separate listings including all SAEs are provided for AP3 on the PAS.

Treatment emergent SAEs with onset of Day 1 of first ponesimod administration, by SOC and PT (frequency) was presented in the Interim Analysis CSR and is not planned to be presented in the Final CSR.

5.4.4.4.3. Treatment-emergent AEs leading to study treatment discontinuation

The following summaries are presented:

- TEAEs leading to study treatment discontinuation by SOC and PT (frequency);
- TEAEs with onset on Day 1 of first ponesimod administration leading to study treatment discontinuation, by SOC and PT (frequency) – single table with a column for ponesimod 10 mg only.

A separate listing including all AEs leading to study treatment discontinuation is provided for AP3 on the PAS.

Treatment emergent SAEs with onset of Day 1 of first ponesimod administration leading to study treatment discontinuation, by SOC and PT (frequency) was presented in the Interim Analysis CSR and is not planned to be presented in the Final CSR.

5.4.4.4.4. Treatment-emergent AEs leading to temporary interruption of study treatment

A listing including all AEs leading to temporary interruption of study treatment is provided for AP3 on the PAS.

5.4.4.4.5. Adverse events of special interest

The following summaries are presented:

- Treatment-emergent AESIs by AESI category and PT (frequency);
- Treatment-emergent AESIs by AESI category and PT (AEs per 100 subject-years).

The following additional (frequency) summaries are presented for the AESI category "Effect on heart rate and rhythm AESI (including hypotension)", for AEs relative to first administration of ponesimod:

- AEs by Day and PT, for Days 1-21;
- AEs on Days 1-7 (overall) by PT;
- AEs on Days 8-14 (overall) by PT;
- AEs on Days 15-21 (overall) by PT.

For summaries by Day following first ponesimod administration, subjects are summarized as follows:

- For Days 1-7 all subjects are summarized under ponesimod 10 mg;
- For Days 8-14 subjects randomized to ponesimod 10 mg are summarized under ponesimod 10 mg, whilst subjects randomized to ponesimod 20 mg or ponesimod 40 mg are summarized under ponesimod 20 mg;
- For Day 15-21 all subjects are summarized under their randomized dose.

This reflects the up-titration scheme and the doses that subjects were receiving at the time.

Time to first treatment-emergent AESI is analyzed separately for each AESI category for AP3 on the PAS using the Kaplan-Meier method, as described in for time to first relapse in Section 6.12.2.

A separate listing including all AESIs is provided based for AP3 on the PAS.

The above summary tables for Days 1-7, 8-14 and 15-21 for the AESI category "Effect on heart rate and rhythm AESI (including hypotension)", for AEs relative to first administration of ponesimod were presented in the Interim Analysis CSR. As no new data are expected, this is not planned to be presented in the Final CSR.

Additionally, Time to first treatment-emergent AESI for each AESI category for AP3, using the Kaplan-Meier method, was presented in the Interim Analysis CSR and is not planned to be presented in the Final CSR.

5.4.4.4.6. MACE

Based on the PAS, treatment emergent MACEs are summarized by presenting, per treatment group, the number and percentage of subjects having any MACE, and having an event of the MACE subcategories (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke. A listing of all events referred to the MACE adjudication committee (whether adjudicated to be MACE or not) is prepared for AP3 on the PAS.

5.4.5. Additional Safety Assessments

5.4.5.1. Clinical Laboratory Tests

Safety laboratory samples for hematology, blood chemistry, and urinalysis are taken at all scheduled visits. The samples are centrally analyzed by ACM or by local laboratories when necessary, and the results are electronically transferred to Actelion. The following parameters are planned to be collected as per protocol:

- **Hematology**: red blood cell count, total and differential white blood cell counts (basophils, eosinophils, lymphocytes, monocytes, neutrophils, band forms), platelet count, hemoglobin, hematocrit, mean corpuscular hemoglobin, mean corpuscular volume.
- **Blood chemistry**: Glucose (preferably under fasting conditions), alanine and aspartate aminotransferase (ALT, AST), alkaline phosphatase, total bilirubin, lactate dehydrogenase, creatinine, urea, cholesterol, triglycerides, sodium, potassium, chloride, calcium, total protein, albumin, C-reactive protein.
- **Urine/serum pregnancy test** (from visits E4 to EOT2 or EOT3 and at Follow-up visit E2 or Follow-up visit 2 [FU2], as applicable).

All laboratory results are stored in SDTM201.LB/SDTM202.LB together with nominal visit and timepoint information. The two LB datasets are concatenated for the purposes of derivations and analysis.

As per study protocol, urinalysis results were to be collected and recorded only if an abnormality/ finding would constitute an (S)AE. The limited number of available data does not allow for performing the planned analyses (i.e., change in urinalysis parameters) as described in Section 3.10.2 of the protocol, and therefore will not be presented in the final CSR.

This approach would also apply to pregnancy test results not collected in CRF.

Numerical results are converted into both conventional and SI units as per Quality system 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.

All analyses are based on the standardized SI values.

The ponesimod baseline value (as described in Section 5.1.2) is flagged in the AdaM dataset.

Absolute and percentage change from ponesimod baseline are derived for all post-baseline assessments.

All nominal visits are re-windowed based on the visit schedule in Section 5.1.7.

Flags are derived according to project specific ranges for marked laboratory abnormalities as described in Section 6.7 (Appendix 8). Marked laboratory abnormalities are flagged to indicate the increasing severity of abnormally low (“LL”, “LLL”), or high values (“HH”, and “HHH”) for each of the laboratory parameters listed.

In addition, the following abnormality flags are derived for ALT, AST, total bilirubin (TBIL), and alkaline phosphatase (ALP):

- ALT: ≥ 1 × upper limit of normal range (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).

The following summaries will be produced for quantitative laboratory results by treatment group:

- Summary of absolute values for laboratory parameters: descriptive statistics by analysis visit (AP3 on the PAS);
- Summary of absolute values and absolute change from ponesimod baseline values for laboratory parameters: descriptive statistics by analysis visit (AP3 on the PAS);
- Summary of absolute values for ALT, AST, bilirubin and ALP: descriptive statistics by analysis visit (AP3on the PAS);
- Summary of absolute values for lymphocytes: descriptive statistics by analysis visit (AP3 on the PAS);
- Summary of absolute values and absolute change from ponesimod baseline values for ALT, AST, bilirubin and ALP: descriptive statistics by analysis visit (AP3 on the PAS);
- Summary of absolute values and absolute change from ponesimod baseline values for lymphocytes: descriptive statistics by analysis visit (AP3 on the PAS);
- Summary of percent change from ponesimod baseline values for lymphocytes: descriptive statistics by analysis visit (AP3 on the PAS);
- Summary of absolute values at ponesimod baseline, at last on-treatment and at each follow-up visit (FU7, FU30, FU90 and Last FU) for lymphocytes (completed/discontinued subjects with at least one follow-up value only): descriptive statistics (AP3 on the PAS); by Post-Treatment DMT subgroup ((Any DMT, including ponesimod), No DMT).
- Summary of percent change from ponesimod baseline to last on-treatment and to each follow-up visit (FU7, FU30, FU90 and Last FU) for lymphocytes (completed/discontinued subjects with at least one follow-up value only): descriptive statistics (AP3 on the PAS); by Post-Treatment DMT subgroup ((Any DMT, including ponesimod), No DMT).
- Incidence of treatment-emergent marked laboratory abnormalities (LL, LLL, HH, HHH) as defined in Section 6.8 (Appendix 8): frequency counts and percentages, where percentages are based on the number of subjects with at least one treatment-emergent post-baseline value for the specific parameter during the analysis period (i.e., number of subjects at risk; AP3 on the PAS);
- Incidence of treatment-emergent 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 treatment-emergent post-baseline value during the analysis period (i.e., number of subjects at risk; AP3 on the PAS).

The following plots are produced for quantitative laboratory results by treatment group:

- Plot of percent change from ponesimod baseline values for lymphocytes: mean ± SE by analysis visit (AP3 on the PAS).
- Plot of absolute values at ponesimod baseline, at last on-treatment and at each follow-up visits (FU7, FU30, FU90 and Last FU) for lymphocytes (completed/discontinued subjects with at least one follow-up value only): mean ± SE (AP3 on the PAS by Post-Treatment DMT subgroup ((Any DMT, including ponesimod), No DMT).
- Plot of percent change from ponesimod baseline to last on-treatment and follow-up visits (FU7, FU30, FU90 and Last FU) for lymphocytes (completed/discontinued subjects with at least one follow-up value only): mean ± SE (AP3 on the PAS), by Post-Treatment DMT subgroup ((Any DMT, including ponesimod), No DMT).
- A plot to evaluate Drug-Induced Serious Hepatotoxicity (eDISH plot) based on the highest observed treatment-emergent ALT and total bilirubin values. 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. Footnote presented which provides, for each treatment group, the number and percentage of subjects falling in each of the 4 quadrants defined by these reference lines (AP3 on the PAS).

The following listings are produced for laboratory results by treatment group and visit for AP3 on the PAS: Listings will only be produced for abnormal values for a patient for a given parameter.

- Listing of specified abnormalities for ECG and Blood Pressure.
- Listing of specified liver function test abnormalities;
- Listing of marked laboratory abnormalities as specified in Appendix 8.

In addition, a listing of all lymphocyte values will also be provided.

5.4.5.2. Vital Signs and Physical Examination Findings

All vital signs results are stored in SDTM201.VS/SDTM202.VS together with nominal visit and timepoint information. The two VS datasets are concatenated for the purposes of derivations and analysis.

5.4.5.2.1. Blood pressure

Measurements of systolic (SBP) and diastolic (DBP) blood pressure (mmHg) are collected pre-dose at all scheduled study visits. In addition, pre-dose and post-dose (1h, 2h, 3h, 4h, 5h, 6h) measurements are collected on Day 1, Day 8 and Day 15 of ponesimod administration, at re-initiation visits, and at the visit for the transition from TP2 to TP3.

The ponesimod baseline value (as described in Section 5.1.2) is flagged in the AdaM dataset.

Absolute change from ponesimod baseline are derived for all post-baseline assessments. All nominal visits (excluding **post-dose** assessments collected on Day 1, Day 8 and Day 15 of ponesimod administration and at re-initiation visits) are re-windowed based on the visit schedule in Section 5.1.7. All assessments, including post-dose assessments, are used for the derivation of "Last on treatment" and "Last follow-up" values.

For by-visit and by-hour tables presenting summary statistics of SBP and DBP results, the latest (by datetime) transmitted measurement per nominal subject-visit/timepoint is used in case of multiple data available at that visit or visit/timepoint.

Assessments meeting the following conditions are flagged in the AdaM dataset for all assessments (whether scheduled or unscheduled, and whether windowed or not):

Low blood pressure

- SBP ≤ 90 mmHg or ≥ 20 mmHg decrease from ponesimod baseline;
- SBP ≤ 90 mmHg;
- ≥ 20 mmHg decrease in SBP from ponesimod baseline;
- DBP ≤ 50 mmHg or ≥ 15 mmHg decrease from ponesimod baseline;
- DBP ≤ 50 mmHg;
- ≥ 15 mmHg decrease in DBP from ponesimod baseline**.**

High blood pressure

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

Each condition listed above is flagged separately.

Pre-dose values on Day 1, Day 8 and Day 15 following first ponesimod administration and on Day 1 of a re-initiation are flagged, and absolute and percent change from pre-dose on each day are calculated for the hourly post-dose assessments.

For all hourly post-dose assessments on Day 1, 8 and 15 following first ponesimod administration and on Day 1 of a re-initiation, 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.

Pre-dose values on Day 1, Day 8 and Day 15 following first ponesimod administration and on Day 1 of re-initiation were presented in the Interim Analysis CSR. It was determined that this was no longer required and istherefore not planned to be presented in the Final CSR.

The following summary will be produced for blood pressure abnormalities, as defined above, by treatment group:

- Incidence of treatment-emergent blood pressure abnormalities for SBP and DBP: frequency counts and percentages, where percentages are based on the number of subjects with at least one treatment-emergent post-baseline value during the analysis period (i.e., number of subjects at risk; AP3 on the PAS).

All abnormal blood pressure results are listed by treatment group and visit for AP3 on the PAS.

5.4.5.2.2. Body weight

Body weight (kg) is collected at selected scheduled visits.

The ponesimod baseline value (as described in Section 5.1.2) is flagged in the AdaM dataset.

Absolute change from ponesimod baseline is calculated for all post-baseline assessments. All nominal visits are re-windowed based on the visit schedule in Section 5.1.7.

5.4.5.3. Electrocardiogram

It is noted that the criteria to define abnormality in ECG findings has changed during the course of the study, subsequent to the Interim Analysis conducted in 2019, as reflected in the SDTM data.

5.4.5.3.1. 12-Lead ECG

A 12-lead ECG is performed pre-dose at all scheduled visits. In addition, ECGs are pre-dose and hourly post-dose (1h, 2h, 3h, 4h, 5h, 6h) on Day 1, Day 8 and Day 15 of ponesimod intake, at re-initiation visits, and at the visit for the transition from TP2 to TP3. In the event of a clinically relevant change from baseline in HR or other ECG parameters persisting after the 6-hour post-dose monitoring, additional ECGs are performed every 2 hours after 6 hours.

All 12-lead ECG results are stored in SDTM201.EG/SDTM202.EG together with nominal visit and timepoint information. The two EG datasets are concatenated for the purposes of derivations and analysis.

All nominal visits (excluding **post-dose** assessments collected on Day 1, Day 8 and Day 15 of ponesimod administration and at re-initiation visits) are re-windowed based on the visit schedule in Section 5.1.8. All assessments, including post-dose assessments, are used for the derivation of "Last on treatment" and "Last follow-up" values.

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

ECG parameter measurements

The following parameters are transferred by the central vendor (eRT): heart rate, RR, PR, QRS, QT, and are used as derived by eRT and are not re-calculated.

Corrected QT values QTcF and QTcB are available in SDTM.EG. The derivation based on Fridericia's and Bazett's formulae is as follows:

- QTcB (ms) = QT (ms)/RR (sec)^0.5
- QTcF (ms) = QT (ms)/RR (sec) ^1/3

These values are then rounded.

The ponesimod baseline values (as described in Section 5.1.2) are flagged in the AdaM dataset.

Absolute and percentage change from ponesimod baseline are derived for all post-baseline assessments.

All nominal visits (excluding post-dose assessments collected on Day 1, Day 8 and Day 15 of ponesimod administration and at re-initiation visits) are re-windowed based on the visit schedule in Section 5.1.8.

All nominal assessments meeting the following conditions are flagged in the AdaM dataset:

- Heart rate ≥ 100 bpm;
- Heart rate ≤ 50 bpm;
- Heart rate ≤ 45 bpm;
- Heart rate ≤ 40 bpm;
- PR interval > 200 ms and increase of > 20 ms from to ponesimod baseline assessment;
- QTcF/QTcB prolongation of > 500 ms;
- QTcF/QTcB prolongation of > 480 ms;
- QTcF/QTcB prolongation of > 450 ms;
- QTcF/QTcB increase from ponesimod baseline of > 30 ms;
- QTcF/QTcB increase from ponesimod baseline of > 60 ms;
- QTcF/QTcB prolongation of > 500 ms and increase from ponesimod baseline > 30 ms;
- QTcF/QTcB prolongation of > 500 ms and increase from ponesimod baseline > 60 ms;
- QTcF/QTcB prolongation of > 450 ms and increase from ponesimod baseline > 30 ms;
- QTcF/QTcB prolongation of > 450 ms and increase from ponesimod baseline > 60 ms.

Pre-dose values on Day 1, Day 8 and Day 15 following first ponesimod administration and on Day 1 of a re-initiation are flagged, and absolute and percent change from pre-dose on each day are calculated for the hourly post-dose assessments.

Post-dose assessments on Day 1, Day 8 and Day 15 following first ponesimod administration and on Day 1 of a re-initiation meeting the following conditions 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 assessment of > 30 ms;
- QTcF/QTcB increase from pre-dose assessment of > 60 ms.

Clinically relevant morphological ECG findings

Morphological ECG findings are reported by the eRT and are mapped to Clinical Data Interchange Standards Consortium (CDISC) standard (code list C71150, with high level categories from code list C71152) in the SDTM.

For analyses in tables the following categories are anticipated:

- Atrioventricular Conduction
- Axis and Voltage
- Chamber Hypertrophy or Enlargement
- Conduction
- Ectopy
- Intraventricular-Intratrial 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 intake of ponesimod (including assessments taken during the placebo period) or 'Pre-existing' if present at any assessment prior to intake of ponesimod. If a subject has no evaluable ECG assessment prior to first dose of ponesimod, it is conservatively assumed that any treatment-emergent morphological ECG finding is 'New'.

Quantitative ECG parameter measurements

The following summaries are produced for quantitative ECG parameters (heart rate, PR, QRS, QT and QTcF / QTcB) by treatment group:

- Summary of absolute values for ECG parameters: descriptive statistics by analysis visit (AP3 on the PAS);
- Summary of absolute values and absolute change from ponesimod baseline values for ECG parameters: descriptive statistics by analysis visit (AP3 on the PAS);
- Summary of pre- and post-dose absolute values for ECG parameters on nominal Day 1, 8 and 15 relative to first ponesimod administration: descriptive statistics by nominal day and nominal timepoint (PAS)*;
- Summary of absolute values and absolute change from pre-dose values for ECG parameters on nominal Day 1, 8 and 15 relative to first ponesimod administration: descriptive statistics by nominal day and nominal timepoint (PAS)*;
- Incidence of treatment-emergent abnormalities [as defined above]: frequency counts, percentages, where percentages are based on the number of subjects with at least one post-baseline value during the analysis period (i.e., number of subjects at risk) (AP3 on the PAS);
- Incidence of treatment-emergent abnormalities [as defined above] on nominal Day 1 relative to first ponesimod administration: frequency counts, percentages, where percentages are based on the number absolute of subjects with at least one post-dose value on Day 1 (i.e., number of subjects at risk) (PAS)*.
- Incidence of treatment-emergent PR and QTc prolongations (including increase from pre-dose) and HR outliers on Day 1 of treatment re-initiation after treatment interruption

The following plots are produced for ECG parameters (HR, PR, QRS, QT and QTcF / QTcB) by treatment group:

- Plot of pre- and post-dose absolute values for ECG parameters on nominal Day 1, 8 and 15 relative to first ponesimod administration: mean ± SE by nominal day and nominal timepoint (PAS)*;

- Plot of absolute change from pre-dose values for ECG parameters on nominal Day 1, 8 and 15 relative to first ponesimod administration: mean ± SE by nominal day and nominal timepoint (PAS)*.
- Plot of absolute values for heart rate: mean ± SE by analysis visit (AP3 on the PAS);
- Plot of absolute change from ponesimod baseline values for heart rate: mean ± SE by analysis visit (AP3 on the PAS).

All abnormal ECG parameter results are listed by treatment group and visit based on the PAS.

Summary tables and plots of ECG parameters on nominal Day 1, 8 and 15 relative to first ponesimod administration were presented in the Interim Analysis CSR and are not planned to be presented in the Final CSR.

Incidence of treatment-emergent abnormalities on nominal Day 1 relative to first ponesimod administration were presented in the Interim Analysis CSR and are not planned to be presented in the Final CSR.

Incidence of treatment-emergent PR and QTc prolongations (including increase from pre-dose) and HR outliers on Day 1 of treatment re-initiation after treatment interruption were presented in the Interim Analysis CSR and are not planned to be presented in the Final CSR.

Clinically relevant morphological ECG findings

The following summaries are produced for morphological ECG findings by treatment group:

- Incidence of clinically relevant morphological ECG findings [as defined above], by preferred term: frequency counts and percentages (AP3 on the PAS);
- Incidence of clinically relevant morphological ECG findings on nominal Day 1, Day 8 and Day 15 relative to first ponesimod administration, by nominal day and preferred term: frequency counts and percentages (PAS)*.

*For summaries/plots on nominal Days 1, 8 and 15 following first ponesimod administration, subjects are summarized as follows:

- For nominal Day 1 all subjects are summarized under ponesimod 10 mg;
- For nominal Day 8 subjects randomized to ponesimod 10 mg are summarized under ponesimod 10 mg, whilst subjects randomized to ponesimod 20 mg or ponesimod 40 mg are summarized under ponesimod 20 mg;
- For nominal Day 15 all subjects are summarized under their randomized dose.

This reflects the up-titration scheme and the doses that subjects were receiving at the time.

Post-dose hourly assessments are not included in summaries/plots by visit.

For tables reporting treatment-emergent abnormalities/findings, all assessments are considered, whether scheduled or unscheduled, pre-or post-dose.

All ECG morphological abnormalities are listed by treatment group and visit based on the PAS.

Summary tables and plots of incidence of clinically relevant morphological ECG findings on nominal Day 1, Day 8 and Day 15 relative to first ponesimod administration were presented in the Interim Analysis CSR and are not planned to be presented in the Final CSR.

5.4.5.3.2. 48-hour Holter ECG

Holter ECG is reported in SDTM202.XH. This data is not combined with that of the core, as Holter ECG monitoring is performed only for 4 subjects in Germany during the extension study.

Holter ECG monitoring is performed at Visit E1 (Day 1), Visit E2, Visit E3, Visit E7 (Week 24) and Visit E9 (Week 48) of TP1. For subjects enrolled into TP2, a 48-hour Holter ECG monitoring is performed in case of study drug re-initiation (followed by dose up-titration) on the day of re-initiation and of dose up-titration. Holter ECG monitoring is also performed at the visit for the transition from TP2 to TP3.

The Holter ECG is assessed by eRT as 'Normal' or 'Abnormal'. If 'Abnormal', the specific abnormalities are captured as free-text.

A listing of all Holter ECG data collected during the extension study is provided based on the Holter analysis set.

Holter ECG data was presented in the Interim Analysis CSR and as no new data is expected, is not planned to be presented in the Final CSR.

5.4.5.4. Echocardiography

Standard 2D/Doppler echocardiography is performed at a subset of centers. Echocardiography assessments in AC-058B202 are only conducted in subjects who were assessed during the core study.

All echocardiography results are stored in SDTM201.MO/SDTM202.MO together with nominal visit and timepoint information. The two MO datasets are concatenated for the purposes of derivations and analysis. The corresponding coded preferred terms are stored in SDTM201.SUPPMO/SDTM202.SUPPMO where QNAM is MODECOD.

Echocardiography parameters

The following quantitative echocardiography parameters are evaluated by the central reader (Methodist): left ventricular ejection fraction (LVEF) diameters (%), left ventricular (LV) diastolic dimension (cm), LV mean thickness (cm), LV posterior wall (LVPW) diastolic thickness (cm), IVS (cm), left atrial single plane area (cm^2), left atrial single plane volume (mL), aortic root diastolic diameter (cm).

The ponesimod baseline value (as described in Section 5.1.2) is flagged in the AdaM dataset.

Absolute and percentage change from ponesimod baseline are derived for all post-baseline assessments.

All nominal visits are re-windowed based on the visit schedule in Section 5.1.7.

Echocardiography findings

Echocardiography findings are evaluated centrally and coded using MedDRA version 26. Treatment-emergent findings are flagged in the AdaM dataset. Treatment-emergent findings are

any findings that were reported after first dose of ponesimod and within 15 days of last dose of ponesimod, and that either were not present at any assessment prior to first dose of ponesimod, or worsened from an assessment observed prior to first dose of ponesimod (per the rules described below).

Echocardiography findings include the following:

- All coded findings that were not present at any assessment prior to first dose of ponesimod.
- Cardiac Valves Regurgitation findings defined as:

  No regurgitation finding at any assessment prior to first dose of ponesimod and present as 'Trace', 'Mild', 'Moderate' or Severe' at any assessment after first dose of ponesimod.

  Regurgitation finding present at one or more assessments prior to first dose of ponesimod and worsening after first dose of ponesimod, e.g., ticked 'Trace' at the screening and 'Mild' at any post-baseline visit.

The following summaries are produced for quantitative echocardiography parameters (LVEF diameters, LV diastolic dimension, LV mean thickness, LVPW diastolic thickness, IVS, left atrial single plane area, left atrial single plane volume, aortic root diastolic diameter) by treatment group:

- Summary of absolute values for echocardiography parameters: descriptive statistics by analysis visit (AP3 on the echocardiography analysis set);
- Summary of absolute values and absolute change from ponesimod baseline values for echocardiography parameters: descriptive statistics by analysis visit (AP3 on the echocardiography analysis set);
- Summary of percent change from ponesimod baseline values for echocardiography parameters: descriptive statistics by analysis visit (AP3 on the echocardiography analysis set);

The following summaries are produced for echocardiography findings by treatment group:

- Incidence of new treatment-emergent MedDRA (i.e. not present at ponesimod baseline) coded echocardiography findings [as defined above], by preferred term: frequency counts and percentages (AP3 on the echocardiography analysis set);
- Treatment-emergent Cardiac Valves Regurgitation findings are summarized as follows (examples) percentages (AP3 on the echocardiography analysis set):
  - Aortic Valve Regurgitation: Mild;
  - Aortic Valve Regurgitation: Moderate;
  - Mitral Valve Regurgitation: Trace;
  - Mitral Valve Regurgitation: Moderate.

Each abnormal finding is only counted once. The worst outcome reported post-baseline is considered. Tables present the number and percentage of subjects having any new abnormality and having each specific new abnormality.

A full listing of all echocardiography data is provided based on the echocardiography analysis set.

Note that the core study B201 used a different dictionary (PSID) than that being used for the current study for Echocardiography findings. As certain terms may differ between the two dictionaries, and since a finding is defined relative to the first dose of ponesimod, this has an impact on what is identified as an Echocardiography finding. A footnote will be added to the echocardiography outputs to indicate that not all identified findings may indeed be findings (i.e. appearing for the first time).

5.4.5.5. Pulmonary Function Tests

All pulmonary function test (PFT) results are stored in SDTM201.RE/SDTM202.RE together with nominal visit and timepoint information. The two RE datasets are concatenated for the purposes of derivations and analysis.

Note that, as of the implementation of Global Protocol version 12, the bronchodilator assessment is no longer required.

PFTs are performed pre-dose at the following assessments, and the parameters forced expiratory volume in 1 second (FEV_1; L) and forced vital capacity (FVC; L) are collected at the following visits in the extension study:

- TP1: at Visits E2 and E3 (Days 8 and 15), Visits E4 to E7, E9, E11 and E13;
- TP2 and TP3: at every other visit (from P1 to EOT3);
- Follow-up: at Visits E1 and E2 or FU1, FU2 and FU3 (EOS3).

At selected visits a bronchodilator assessment is performed (required yearly from Visit P1 during TP2 and recommended yearly during TP3). At such visits, two pre-dose PFT assessments are performed:

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

The following additional PFT parameters variables are derived in the AdaM dataset:

- **FEV_1/FVC(%)**

  The ratio (in %) between FEV_1 and FVC is calculated as:

  $$FEV_1/FVC\ (\%) = \frac{FEV_1}{FVC} * 100$$

- **Predicted normal values for FEV_1 and FVC**
  Predicted normal values for FEV_1 and FVC are calculated based on the following formulas [Quanjer 1993], where height and race are used as recorded at screening of the core study. Age is re-calculated at each assessment, by adding the time since the assessment where age was originally recorded to the original age value.

  Predicted normal value for FEV_1 (L); H: standing height (m); A: age (years):

Sex	Equation
Male	4.30 H – 0.029 A* – 2.49
Female	3.95 H – 0.025 A* – 2.60

Predicted normal value for FVC (L); H: standing height (m); A: age (yr):

Sex	Equation
Male	5.76 H – 0.026 A* – 4.34
Female	4.43 H – 0.026 A* – 2.89

*If age is between 18 and 25 (limits included), substitute with 25.

For patients of ethnic groups (race) other than 'Caucasian/White' the above predicted normal value must be multiplied by a conversion factor of 0.9 [Quanjer 1993].

- **Percent of the predicted normal values for FEV_1 and FVC**

  Percent of the corresponding predicted normal value is calculated for FEV_1 and FVC as follows:

  - Percent of the predicted value (%) = [measured value] × 100 / [predicted normal value].

For all collected and derived PFT parameters, the following variables are derived:

The ponesimod baseline values (as described in Section 5.1.2) are flagged in the AdaM dataset. At visits where both pre- and post- bronchodilator assessments are taken, only the pre-bronchodilator assessment is considered for baseline.

Absolute and percentage change from ponesimod baseline are derived for all post-baseline assessments (except post-bronchodilator assessments).

At assessments where the bronchodilator is administered, absolute and percentage change from pre-bronchodilator to post-bronchodilator value is derived.

All nominal visits are re-windowed based on the visit schedule in Section 5.1.7.

Nominal assessments meeting the following conditions are flagged in the AdaM dataset:

Outliers:

- Percent change from ponesimod baseline in FEV_1: < -20 %, < -30%;
- Percent change from ponesimod baseline in FVC: < -20 %, < -30%;
- Absolute change from ponesimod baseline in % predicted FEV_1: < -20 %, < -30%;
- Absolute change from ponesimod baseline in % predicted FVC: < -20 %, < -30%;
- FEV_1/FVC < 70%.

Positive test for bronchodilator:

- Absolute change from pre- to post-bronchodilator in FEV_1 > 200 mL and percent change from pre to post-bronchodilator in FEV_1 > 12 %;
- Absolute change from pre- to post-bronchodilator in FVC > 200 mL and percent change from pre to post-bronchodilator in FVC > 12 %.

By Treatment group

The following summaries are produced for PFT parameters (FEV_1, FVC, FEV_1/FVC, %pred FEV_1, %pred FVC) by treatment group (post-bronchodilator assessments are not included):

- Summary of absolute values for PFT parameters: descriptive statistics by analysis visit (AP3 on the PAS) by treatment group;
- Summary of absolute change from ponesimod baseline values for PFT parameters: descriptive statistics by analysis visit (AP3 on the PAS) by treatment group;
- Summary of percent change from ponesimod baseline values for PFT parameters: descriptive statistics by analysis visit (AP3 on the PAS) by treatment group;
- Incidence of treatment-emergent PFT outliers [as defined above frequency counts, percentages, where percentages are based on the number of subjects at risk, i.e. number of subjects with at least 1 post-baseline value in that category during the analysis period (AP3 on the PAS) by treatment group.

The following plot is produced:

A plot of %pred FEV_1 values over time (including FU visits), by analysis visit (AP3 on the PAS) by treatment group;

By Post-Treatment DMT Subgroup

The following summaries are produced for PFT parameters by Post-Treatment DMT subgroup, as defined in Section 5.5.6 (pooling across all treatment groups):

- Summary of absolute values at ponesimod baseline, at last on-treatment and at each follow-up visit (FU7, FU30, FU90 and Last FU) for PFT parameters: descriptive statistics by analysis visit (AP3 on the PAS), by Post-Treatment DMT subgroups ((Any DMT, including ponesimod), No DMT).
- Summary of absolute change from ponesimod baseline to last on-treatment and each follow-up visit (FU7, FU30, FU90 and Last FU) for PFT parameters: descriptive statistics by analysis visit (AP3 on the PAS), by Post-Treatment DMT subgroup ((Any DMT, including ponesimod), No DMT).
- Summary of percent change from ponesimod baseline to last on-treatment and each follow-up visit (FU7, FU30, FU90 and Last FU) for PFT parameters: descriptive statistics by analysis visit (AP3 on the PAS), by Post-Treatment DMT subgroup ((Any DMT, including ponesimod), No DMT).

The following plots are produced:

- A plot of ponesimod baseline, last-on-treatment and follow-up values for %pred FEV_1, by analysis visit (AP3 on the PAS), by Post-Treatment DMT subgroup ((Any DMT, including ponesimod), No DMT).
- A plot of absolute change from ponesimod baseline to last-on-treatment and follow-up values for %pred FEV_1, by analysis visit (AP3 on the PAS), by Post-Treatment DMT subgroup ((Any DMT, including ponesimod), No DMT).

By Total Exposure Duration Subgroup:

The following summaries are produced for PFT parameters by the Total Exposure Duration subgroup, as defined in Section 5.5.6 (pooling all treatment groups).

- Summary of absolute values at ponesimod baseline, at last on-treatment and at each follow-up visit (FU7, FU30, FU90 and Last FU) for PFT parameters: descriptive statistics by analysis visit (AP3 on the PAS), by the Total Exposure Duration subgroup.
- Summary of absolute change from ponesimod baseline to last on-treatment and each follow-up visit (FU7, FU30, FU90 and Last FU) for PFT parameters: descriptive statistics by analysis visit (AP3 on the PAS), by the Total Exposure Duration subgroup.
- Summary of percent change from ponesimod baseline to last on-treatment and each follow-up visit (FU7, FU30, FU90 and Last FU) for PFT parameters: descriptive statistics by analysis visit (AP3 on the PAS), by the Total Exposure Duration subgroup.

The following plots are produced:

- A plot of ponesimod baseline, last-on-treatment and follow-up values for %pred FEV_1, by analysis visit (AP3 on the PAS), by the Total Exposure Duration subgroup.
- A plot of absolute change from ponesimod baseline to last-on-treatment and follow up values for %pred FEV_1, by analysis visit (AP3 on the PAS), by the Total Exposure Duration subgroup.

The following summaries are produced for PFT parameters (FEV_1, FVC, FEV_1/FVC, %pred FEV_1, %pred FVC) for pre-/post-bronchodilator assessments by treatment group:

- Summary of absolute values for PFT parameters at pre- and post-bronchodilator assessments: descriptive statistics by analysis visit (AP3 on the PAS);
- Summary of absolute change from pre- to post-bronchodilator assessment for PFT parameters: descriptive statistics by analysis visit (AP3 on the PAS);
- Summary of percent change from pre- to post-bronchodilator assessment values for PFT parameters: descriptive statistics by analysis visit (AP3 on the PAS);
- Incidence of positive test for bronchodilator [as defined above]: frequency counts, percentages, where percentages are based on the number of subjects at risk, i.e., number of subjects with at least 1 bronchodilator administration with pre and post PFT performed during the analysis period (AP3 on the PAS).

The following plots are produced for pre-/post-bronchodilator assessments of PFT parameters by treatment group:

- A plot of all pre/post-bronchodilator %FEV_1 values over time, by analysis visit (AP3 on the PAS).

A listing of outliers and positive tests for bronchodilators for PFT data is provided for AP3 on the PAS.

5.5. Other Analyses

5.5.1. Pharmacokinetics

Blood samples were collected in order to provide information about study drug exposure in the target population, at various time points during the study as specified in the protocol schedule, and summarized below, for pharmacokinetic (PK) and pharmacokinetic /pharmacodynamic (PK/PD) evaluations.

Plasma concentrations of ponesimod are determined at trough (pre-dose):

- **TP1**: on Days 8 and 15 (Visits E2 and E3) and at Visits E4 (Week 4), E7 (Week 24), E9 (Week 48), and E13 (EOT2)
- **TP2 and TP3**: P2 (Week 12), P7 (Week 72), P14 (Week 156) and P22 (Week 252), as applicable

Although plasma concentration results were intended to be collected at the visits mentioned above, the study design evolved to allow participants to transition from TP1 anytime after Week 48 up to 90 days after EOT2, and be enrolled into TP2 starting with Visit P1. Thus, not all participants had blood samples collected at all visits.

In addition, some participants also had plasma concentration samples collected at visits not assigned in the protocol.

To address the variability of transition from TP1 to TP2, the following rules will be instituted to map the plasma collection dates for a participant to the planned plasma collection timepoints in the protocol.

Based on the protocol the following windows are allowed at the different timepoints: Days 8, 15: +-1 day, Week 4: +- 2days, further Weeks: +- 14 days:

- If TP1start date ≤ Plasma collection date < start of TP2 start date or TP1 start date ≤ plasma collection date (for subjects who did not enter TP2):
  Let the time difference be denoted Diff = Plasma collection date – TP1 start date +1
  Day 8 (Visit E2): (7 ≤ Diff ≤ 9); Day 15 (Visit E3): (14 ≤ Diff ≤ 16);
  Week 4 (Visit E4): (26 ≤ Diff ≤ 30); Week 24 (Visit E7): (154 ≤ Diff ≤ 182);
  Week 48 (Visit E9): (322 ≤Diff ≤ 350); Week 96 (Visit E13 EOT2): 658 ≤ Diff ≤ 686)

- If TP2 start date <= Plasma collection date:
  Let the time difference, denoted Diff = Plasma collection date – TP2 start date +1
  Week 12 (Visit P2): (70 ≤ Diff ≤ 98); Week 72 (Visit P7): (490 ≤ Diff ≤ 518);
  Week 156 (Visit P14): (1078 ≤ Diff ≤ 1106); Week 252 (Visit P22): (1750 ≤ Diff ≤ 1778);

Descriptive statistics by treatment period and by dose for the following pre-dose samples will be presented:

- TP1: Days 8 and 15, and Weeks 4, 24, 48, and 96
- TP2 and TP3: Weeks12, 72, 156, and 252

The following summaries are produced for trough level plasma concentrations at each time point of measurement by treatment group:

- Summary of absolute values of PK parameters: descriptive statistics by analysis visit

5.5.2. Pharmacodynamics

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

The following parameters are collected:

- Absolute count in peripheral blood lymphocyte counts as a function of ponesimod dose and plasma concentrations at trough level (pre-dose) on Days 8 and15 (Visits E2 and E3) and at Visits E4, E7, E9, E13 (EOT2), P2, P7, P14, P22, P30 and EOT3, as applicable.
- Post-treatment lymphocyte recovery 8, 30, and 90 days (only at 90 days for patients performing TP2 and TP3, if applicable) after study drug discontinuation.

The following summaries for peripheral blood lymphocyte counts as a function of ponesimod dose, as described in Section 5.4.5.1, will be produced:

- Summary of absolute values and absolute change from ponesimod baseline values for lymphocyte counts: descriptive statistics by analysis visit (AP3 on the PAS);
- Summary of percent change from ponesimod baseline values for lymphocyte counts: descriptive statistics by analysis visit (AP3 on the PAS);

In addition, the following plot, as described in Section 5.4.5.1 will be produced:

- Plot of percent change from ponesimod baseline values for lymphocyte counts: mean ± SE by analysis visit (AP3 on the PAS);

The following summaries for post-treatment lymphocyte count recovery, as described in Section 5.4.5.1, will be produced:

- Summary of absolute values at ponesimod baseline, at last on-treatment and at each follow-up visits (FU7, FU30, FU90 and Last FU)) for lymphocyte counts (completed/discontinued subjects with at least one follow-up value only): descriptive statistics (AP3 on the PAS); by Post-Treatment DMT subgroup ((Any DMT, including ponesimod), No DMT).
- Summary of percent change from ponesimod baseline to last on-treatment and to each follow-up visit (FU7, FU30, FU90 and Last FU)) for lymphocyte counts (completed/discontinued subjects with at least one follow-up value only): descriptive statistics (AP3 on the PAS); by Post-Treatment DMT subgroup ((Any DMT, including ponesimod), No DMT).

In addition, the following plots, as described in Section 5.4.5.1, will be produced:

- Plot of absolute values at ponesimod baseline, at last on-treatment and at each follow-up (FU7, FU30, FU90 and Last FU)) for lymphocytes (completed/discontinued subjects with at least one follow-up value only): mean ± SE (AP3 on the PAS); by Post-Treatment DMT subgroup ((Any DMT, including ponesimod), No DMT).
- Plot of percent change from ponesimod baseline to last on-treatment and follow-up visits

(FU7, FU30, FU90 and Last FU)) for lymphocytes (completed/discontinued subjects with at least one follow-up value only): mean ± SE (AP3 on the PAS); by Post-Treatment DMT subgroup ((Any DMT, including ponesimod), No DMT).

5.5.3. Pharmacokinetic/Pharmacodynamic Relationships

The following endpoint, "Efficacy and safety parameters will be correlated with absolute lymphocyte counts and magnitude of reduction of lymphocyte counts on an exploratory basis." was added to explore the objective: dose response relationship of 10, 20, and 40 mg ponesimod on lymphocyte count, magnetic resonance imaging (MRI) endpoints, annualized relapse rate (ARR), and safety endpoints.

Analyses to address dose decisions were presented in the Interim Analysis CSR and are not planned to be addressed in the Final CSR.

5.5.4. Biomarkers

Not applicable

5.5.5. Health Economics

Not applicable

5.5.6. Definition of Subgroups

The following subgroups are defined for the Follow-up Phase:

(i) Post-treatment DMT: A patient in the Follow-up Phase is assigned to the "Any DMT, including ponesimod" category if there is a record in CMDECOD in SDTM.CM for any of the therapies listed in Table 11 in Section 6.5.1 and the corresponding CMENDTC in SDTM.CM is on or after the ponesimod EOT date or ongoing at EOS date. In cases where CMENDTC is missing and CM is not ongoing, it should be checked whether CMSTDTC is on or after the ponesimod EOT date. Otherwise, the patient is assigned to the "No DMT" category.

(ii) Total Exposure Duration: A patient in the Follow-up Phase is assigned to one of the following categories "Less than or equal to 4 years", "Greater than 4 and Less than or equal to 8 years", "Greater than 8 years", based on their Ponesimod exposure duration during AP3 (years), as defined in Table 10 in Section 5.4.1.1. This subgroup will be considered only for PFT.

5.5.7. Immunogenicity Analysis

Details of immunogenicity analyses conducted in this study are presented in Sections 6.10 for Covid-19 and in Section 6.11 for Influenza.

5.5.8. Covid-19 Impact Analyses

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.

(i) 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 Total Compliance for the periods pre-Covid-19 and post-Covid-19 will be presented, where pre/post-Covid-19 is defined as pre/post-January 1, 2020. Interruptions spanning across these two periods will be assigned to the pre-Covid-19 period.

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

5.5.9. 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.

5.6. Interim Analyses

An iCSR SAP AC-058B202_SAP_V3_2307_EDMS-ERI-197686018_3.0 was prepared, describing the analyses and presentation of all safety, tolerability and selected efficacy endpoints, for the interim clinical study report (iCSR) (EDMS-ERI-181610698, 1.0) of the pooled AC-058B201 (core) and AC-058B202 (extension) studies, to support the ponesimod New Drug Application (NDA) / Marketing Authorization Application (MAA)

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

A DMC convened for the ponesimod program was disbanded on 30th Sept. 2021.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

%pred FEV_1	FEV_1 expressed as % of predicted normal value
%pred FVC	FVC expressed as % of predicted normal value
ADaM	Analysis data model
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AP1	Analysis period 1
AP2	Analysis period 2
AP3	Analysis period 3
ARR	Annualized relapse rate
AST	Aspartate aminotransferase
ATC	Anatomic therapeutic chemical
BP	Blood pressure
bpm	Beats per minute
CDA	Confirmed disability accumulation
CDISC	Clinical Data Interchange Standards Consortium
CFR	(US) Code of Federal Regulations
CI	Confidence interval
CL	Confidence limit(s)
CRF	Case report form
CRO	Contract research organization
CSR	Clinical study report
CUAL	Cumulative unique active lesions
DBP	Diastolic blood pressure
DMTs	Disease modifying therapies for MS
ECG	Electrocardiograph
EDSS	Expanded Disability Status Scale
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOS	End-of-study

EOT	End-of-treatment
FAS	Full analysis set
FDA	(US) Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FS	Functional system
FU	Follow-up
FVC	Forced vital capacity
GCP	Good Clinical Practice
Gd+	Gadolinium enhancing
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MS	Multiple Sclerosis
OCT	Optical coherence tomography
PAS	Ponesimod analysis set
PD	Pharmacodynamic
PK	Pharmacokinetic
PPS	Per-protocol analysis set
PT	Preferred term
QT_C	Corrected QT interval
QT_CB	QT interval corrected for heart rate using Bazett's formula
QT_CF	QT interval corrected for heart rate using Fridericia's formula
RMS	Relapsing multiple sclerosis
RNFL	Retinal nerve fiber layer
RRMS	Relapsing-remitting multiple sclerosis
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SAS	Statistical analysis system
SBP	Systolic blood pressure

SBP	Systolic blood pressure
SCR	Screened analysis set
SD	Standard deviation
SDTM	Study Data Tabulation Model
SE	Standard error
SI	Standard International
SOC	System organ class
SOP	Standard operating procedure
SPMS	Secondary progressive multiple sclerosis with superimposed relapses
TBIL	Total bilirubin
TEAE	Treatment-emergent adverse event
TP1	Treatment Period 1
TP2	Treatment Period 2
TP3	Treatment Period 3
ULN	Upper limit of the normal range
WHO	World Health Organization
WHODRUG	WHO drug dictionary

6.2. Appendix 2 Changes or Clarifications to Protocol-Planned Analyses

6.2.1. Changes to the analyses planned in the study protocol

Protocol section	Change	Rationale
5.2	It is stated that "Baseline is defined as the last assessment performed prior to the first administration of study treatment in AC-058B201 for the analyses comparing treatment groups as randomized in AC-058B201 including the placebo treatment period", however, no analyses including the placebo period are performed as part of this SAP.	An analysis by treatment groups as randomized in AC-058B201 would analyze subjects who have been receiving ponesimod for 8+ years as placebo, although they received placebo only for the first 6 months. Therefore, the placebo period is excluded. It is also considered important from a safety perspective that baseline is defined immediately prior to the initiation of ponesimod.
5.2	The following populations are defined: **"Modified intent-to-treat set (mITT) – extension population":** This analysis set includes all randomized patients who received at least once ponesimod dose in the combined studies AC-058B201 and AC-058B202 and had at least one post-baseline MRI examination. **Per-protocol (MRI) – extension population** "The Per-protocol (MRI) – extension population includes all patients of the Per-protocol (MRI) set for AC-058B201 who completed at least Visit E7 of AC-058B202 and did not have any major protocol violation in AC-058B202". These are not used for any analyses in this SAP.	These populations were not deemed necessary as the objectives of the analysis are exploratory in nature.
5.3	It is stated that "The treatment groups will be analyzed as randomized in AC-058B201, by pooled dose groups and by treatment pathway across the combined core study and extension study and by individual treatment periods in the extension study." No analyses by treatment pathway or as randomized by AC-058B201	An analysis by treatment groups as randomized in AC-058B201 would analyze subjects who have been receiving ponesimod for 8+ years as placebo, although they received placebo only for the first 6 months. There are 8 different treatment pathways across the core and extension studies combined. This was not foreseen at the time of

	are planned as part of this SAP. Subjects are summarized by pooled dose groups (based on first randomized dose of ponesimod) only.	protocol writing. Such an analysis would not be interpretable.
5.3	For ARR, it is stated that "In addition, the treatment effect on aggregate ARR will be tested by means of negative binomial regression adjusted by treatment, region, number of documented relapses (≤ 2 and > 2) past 24 months prior to screening, EDSS [Expanded Disability Status Scale] at baseline (CRF Visit 2) and total number of T1 Gd+ [gadolinium-enhancing] lesions at baseline." This is similarly applied for the Cox proportional-hazard regression model for time to first relapse, and negative binomial model for MRI endpoints. Only two covariates will be included in the adjusted models: EDSS score category (≤ 3.5 and > 3.5) based on extension baseline, and relapses in the 2 years prior to screening in the core study (≤ 1 and ≥ 2). EDSS is defined as a categorical variable. Number of documented relapses categorization is modified from "≤ 2 and > 2" to "≤ 1 and ≥ 2".	"Number of documented relapses in a fixed 24-month period cannot be determined for ponesimod baseline (of placebo switchers) and so the value prior to start of the core is used. The categories are modified as only a very small proportion of subjects would fall into a > 2 category. EDSS is categorized as the log-rank test (which is displayed alongside the Cox regression results) can only take categorical variables as covariates. Given the small sample size only the two more important covariates are selected. The same two covariates are used for all adjusted analyses (i.e., also for the negative binomial model for ARR and MRI) for consistency.
5.3	It is stated that "Different methods will be applied to handle missing data and to perform sensitivity analyses to address potential bias as a result of missing information. The methods will include an analysis which treats missing values as a success, and an analysis which treats missing values as a failure.". These sensitivity analyses are not planned in this SAP for some of the endpoints.	The interim analysis covers a period of almost 9 years and higher drop-outs are not unexpected over such a long period. Imputation of missing data over this long of a period would be difficult to interpret.
5.4	The dose response relationship will be explored for lymphocyte count, MRI related endpoints (number of total T1 Gd+ lesions, number of	Without a placebo arm only represents less than 10% of the follow-up for patients originally randomized to placebo so for reason

	combined unique active lesions, number of new or enlarging T2 lesions) and ARR using modeling techniques as described by Bretz et al [Bretz 2005]. This modeling is not planned in this SAP.	previously discussed placebo is being excluded from the analysis. MCP-Mod without a placebo (0 dose) makes the analysis difficult to interpret. Dose response was instead summarized in a more descriptive manner.
5.6	It is stated that "AEs, SAEs, and abnormalities are defined as treatment-emergent when occurring during study drug administration plus 7 days after study drug discontinuation.". The definition of treatment-emergent is updated to 15 days after last study drug administration in this SAP.	15 days is consistent with the Phase 3 program.
5.6	It is stated that "In addition, AEs of clinical interest will be summarized by the dose the patient received as per-protocol at time of onset.". This summary is not planned in this SAP.	Due to the potential carry over effect when subjects switch from one ponesimod dose to another, AEs will not be summarized by dose at onset.
3.10.1	Appendix 11: Planned Covid-19 analyses	Added to address efficacy endpoint No. 8 related to Covid-19 vaccine in Protocol Amendment 11.
2	Section 1.1: Objective: To explore the dose response relationship of 10, 20, and 40 mg ponesimod on lymphocyte count, magnetic resonance imaging (MRI) endpoints, annualized relapse rate (ARR), and safety endpoints	This objective was addressed in the Interim Analysis CSR in 2019 and will not be further addressed in the Final CSR.
5.1.9	Section 5.1.9 Analysis Strategy for long term efficacy and safety	Only AP3 will be considered for the Final CSR as it encompasses the entire ponesimod treatment period. Further, AP1 and AP2 were addressed in the Interim Analysis CSR in 2019.
3.10.1	Appendix 12: Influenza Analyses	Added to address efficacy endpoint No. 8 related to influenza vaccine in Protocol Amendment 11.
	Section 5.5.8. Added Covid-19 Impact Analyses in SAP.	This analysis was deemed important to assess due to the pandemic that occurred while the study was ongoing.
	Section 5.5.9 Added Regional Crisis Impact Analyses in SAP.	This was deemed important to assess due to the regional crisis that

		occurred while the study was ongoing.

6.2.2. Changes in the conduct of the study / data collection

None.

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

Protocol section	Change	Rationale
3.10.2.5	Regarding the bronchodilator assessment, it is stated that "This assessment is mandatory and will be performed at Visit P1 and on a yearly basis during TP1 and TP2. During TP3 bronchodilator test is recommended to be continued on a yearly basis (as deemed necessary by the investigator)." In fact, the bronchodilator assessment was not performed in TP1 at all and was only introduced at the start of TP2 (Visit P1).	Clarification.
3.9.1	It is stated that the endpoint "Time to 12-week confirmed disability progression up to end of the study" will be evaluated. This will not be done.	As EDSS is only scheduled every 24 weeks in TP1, it is not possible to determine time of 12-week CDA [Confirmed disability accumulation] during this period. Therefore only "Time to 24-week confirmed disability accumulation" was evaluated.
3.9.1	It is stated that the endpoint "Categorical change from baseline to all assessments in EDSS and FS [functional system] scores" will be evaluated. This will not be done.	This endpoint was evaluated in the core study as categorical change from baseline to Week 24, where categorical change is classed as stable, improved or worsening at Week 24 as compared to baseline. Due to the long running nature of the extension study and lack of defined endpoint, this endpoint will not be defined in the extension study.
3.9.1	It is stated that the safety and tolerability endpoints "Change in ophthalmological exam (best corrected visual acuity, low contrast visual acuity, visual fields, dilated	These safety ophthalmological data are assessed at site but not collected on the CRF.

	ophthalmoscopy, and at selected centers, OCT [optical coherence tomography]) from baseline to all assessments" will be derived. This will not be done.	
3.9.1	It is stated that the endpoints "Change in laboratory parameters (hematology, blood chemistry, and urinalysis) from baseline to all assessments" will be derived. This will be done for hematology and blood chemistry parameters, but not for urinalysis.	Urinalysis is performed locally, and results are not collected on the CRF.
AC-058B201 CSR SAP section 6.4.3.1	The EDSS assessment used for confirmation of disability accumulation must not be during a relapse. In the event of a missing relapse end date, the core study report considered relapse start date + 30 days. This SAP uses relapse start date + 90 days.	This derivation is updated to be in-line with the deviation as used in the Phase 3 program.
Section 5.1.3	Definition of Treatment emergent adverse events and other safety variables.	Definition updated to exclude pregnancy interruption period(s).
Various Sections	Disposition will include a new category corresponding to "Approved drug available for indication".	New reason in aCRF p.9 (Trial disposition) and p. 11 (Discontinuation of Study Treatment): "Approved drug available for indication".
Section 5.4.5.4		Echocardiogram: Criteria for defining abnormality have changed subsequent to 2019 IA and are reflected in the SDTM data.
Section 5.1.7	Coding Dictionaries: MedDRA Version 26.0 and WHO-Drug Dictionary version March 2023 B3G will be used.	Up-versioning to current dictionaries.
Section 5.1.3	Added Planned Pregnancy Interruptions: - excluded for definition of exposure, treatment-emergent adverse events and other safety variables. - not excluded for efficacy analyses or for study duration.	This rule was adopted for the Snapshot Analysis in 2022 and will be retained for the Final CSR.
Section 5.1.6	Added Definition: The post-treatment-emergent period.	This period was added to address analyses pertaining to relapses in Section 5.3.1.4 and for AEs in Section 5.4.4.3.3.

Section 5.1.8	Added additional Visit Windows	Added to cover the entire study period.
Section 5.2.1.3	Added Definition: Entered Follow-up Phase.	This definition is required for the identification of patients in the DMT subgroups.
5.2.2	Display of Subject Disposition: Kaplan-Meier plot for time to premature treatment discontinuation will not be presented.	This was presented in the Interim Analysis CSR and will not be presented in the Final CSR.
5.3.1.2	Removed Analyses for the endpoint: ARR up to last treatment in the Analysis Period + 7 days will not be performed.	This was presented in the Interim Analysis CSR and will not be presented in the Final CSR.
5.3.1.4	Added endpoint in Section 5.3.1.4: Annualized relapse rate in the Post-treatment-emergent period. Added planned analyses for this endpoint in Section 5.3.2.2.	This was added to assess disease reactivation.
5.3.1.5	Explanation added regarding the response to the question about relapse requiring hospitalization.	To address the discrepancy between the response "Yes" to the question in the legacy CRF and the question in RAVE.
5.3.2.1	Removed the presentation of p-values in this section; and elsewhere in the SAP.	All exploratory analyses.
5.3.2.4	Removed Sensitivity analyses for ARR	This was presented in the Interim Analysis CSR and will not be presented in the Final CSR.
5.3.2.5	Removed Sensitivity analyses for Time to first confirmed relapse	This was presented in the Interim Analysis CSR and will not be presented in the Final CSR.
5.3.3.3	Added endpoint definition: Combined unique active lesions (CUAL) at each timepoint	This was deemed important to assess.
5.3.4.1	Removed Analyses for the cumulative total number of T1 Gd+ lesions	This was deemed not important to address in the Final CSR. Instead this analysis will be conducted for CUALs.
5.3.4.1	Removed Sensitivity analyses for T1 Gd+ lesions.	This was presented in the Interim Analysis CSR and will not be presented in the Final CSR.

5.3.4.2	Removed Analyses for the cumulative total number of T2 lesions	This was deemed not important to address in the Final CSR. Instead this analysis will be conducted for CUALs.
5.3.4.2	Removed Sensitivity analyses for T2 lesions.	This was presented in the Interim Analysis CSR and will not be presented in the Final CSR.
5.3.4.3	Added analyses for the number of CUALs per MRI time window	This was deemed important to assess.
5.4.3.2	Added definition for Post-treatment adverse events	Definition required for table of post-treatment AEs.
5.4.4.1	Removed Summaries of AEs with onset on Day 1	This was presented in the Interim Analysis CSR and will not be presented in the Final CSR.
5.4.4.4	Removed outputs related to Treatment emergent AEs with onset of Day 1 of first ponesimod or Day 1 of any re-initiation	This was presented in the Interim Analysis CSR and will not be presented in the Final CSR.
	Removed Time to first treatment-emergent AESI for each AESI category for AP3, using the Kaplan-Meier method	This was presented in the Interim Analysis CSR and will not be presented in the Final CSR.
5.4.5	Only marked Laboratory abnormalities as defined in Appendix 8, and specified ECG, BP and liver function abnormalities will be presented in listings. However all lymphocyte values will be presented.	Given the long duration of the study, this was considered a reasonable approach As lymphocyte counts are a PD marker, all values will be presented.
5.4.5.1	Modified analyses for lymphocytes outputs related to ponesimod baseline, at last on-treatment and at each follow-up visit by Post-Treatment DMT subgroup.	This was deemed important to assess.
5.4.5.1	Added plot to evaluate Drug-Induced Serious Hepatotoxicity (eDISH plot)	This was deemed important to assess.
5.4.5.1	Urinalysis results were to be collected and recorded only if an abnormality/ finding would constitute an (S)AE.	The limited number of available data does not allow for performing the planned analyses
5.4.5.2.1	Removed outputs for Blood Pressure: Pre-dose values on Day 1, Day 8 and Day 15 following first ponesimod administration and on Day 1 of re-initiation.	This was presented in the Interim Analysis CSR and will not be presented in the Final CSR. This was deemed important to assess.

	Added: Summary for blood pressure abnormalities	
5.4.5.1	Modified: Lab Listings will only be produced for abnormal values	Given the long duration of the study, lab listings will be restricted to abnormal values only.
5.4.5.3	Electrocardiogram: Removed outputs related to ECG parameters on nominal Day 1, 8 and 15 relative to first ponesimod administration. Removed outputs related to incidence of treatment-emergent abnormalities, as well as PR and QTc prolongations.	This was presented in the Interim Analysis CSR and will not be presented in the Final CSR.
5.4.5.5	Modified analyses for PFT outputs related to ponesimod baseline, at last on-treatment and at each follow-up visit by Post-Treatment DMT subgroup. Added outputs based on Total Exposure Duration Subgroup.	This was deemed important to assess.
5.5.1	Added outputs related to Pharmacokinetics	This section was added to analyze the plasma concentration data collected in the study.
5.5.2	Link to outputs for lymphocytes that addressed the pharmacodynamic marker in the study.	The pharmacodynamic marker in the study was lymphocytes.
5.5.3	Pharmacokinetic/Pharmacodynamic Relationships	Analyses to address dose decisions were presented in the Interim Analysis CSR and will not be addressed in the Final CSR
5.5.6	Added definitions of subgroups Post-treatment DMT and Total Exposure Duration.	These subgroups were added to address the need for outputs based on the subgroups in the post-treatment-emergent period.
6.4	Only major PDs will be presented	Given the duration of the study. Also important PDs were a definition used in the legacy CRF and have been mapped to eCRF.
6.5	Definition of Treatment-concomitant therapies modified from "….that were initiated up to 15 days after the end of ponesimod treatment to "… that were	To ensure consistency with the definition of Post-treatment DMT subgroup.

	initiated upto the end of ponesimod treatment".	
6.5.1	Table 11 includes some medications that are not DMTs (etrasimod, sekukinumab), but will be retained for consistency with IA outputs.	
6.5	CMCLASS for Covid Vaccines updated	Updated based on current dictionaries.
6.8	Appendix 9 AESIs	Updated AESIs based on current coding dictionaries.

6.3. Appendix 3 Demographics and Baseline Characteristics

6.3.1. Demographics

Demographic data are collected at entry into the core study only. Demographic data include country, age, sex, race, weight and height. Date of birth is not available, and as the core study duration was only 6 months, age at start of extension is assumed to be the same as age at the start of the core. All demographic variables are stored in SDTM201.DM.

Age categories are derived from the above as follows: <18, 18-30, 31-40, 41-55, ≥56 years. Age high-level categories: <40, ≥ 40. Age categories as per EudraCT requirement: < 12 years, 12 - 17, 18 - 64, 65 - 84, ≥ 85.

Two categorizations are derived for region. The first categorization reflects the regions as they were defined in the core study report, with the following regions defined:

- Northern/Western Europe: Finland, Sweden, Belgium, Netherlands, Germany, UK, and Poland;
- South/Central Europe: Austria, France, Italy, Spain, Switzerland, Hungary, and Czech Republic;
- Eastern Europe / Israel: Bulgaria, Israel, Romania, Serbia, Russian Federation, and Ukraine;
- North America / Australia: USA, Canada, and Australia.

The second categorization is consistent with the Phase 3 program. The following regions are defined:

- European Union (EU) + UK + Switzerland: Austria, Belgium, Bulgaria, Czech Republic, Finland, France, Germany, Hungary, Italy, Netherlands, Poland, Romania, Spain, Sweden, Switzerland, and United Kingdom;
- Europe Non-EU + Russia: Russian Federation, Serbia, and Ukraine;
- North America: Canada, and United States;
- Rest of World: Australia, and Israel.

Region categorizations are based on the region of the site the subject was in at the start of the core study. Site changes that result in region changes are not considered.

Demographic characteristics are summarized using descriptive statistics for continuous and categorical data, by treatment group and overall for the PAS.

6.3.2. Baseline disease characteristics

The following baseline disease characteristics are collected at entry into the core study and analyzed as part of this SAP:

- Number of documented relapses within 12 months and within 24 months prior to screening in core study.

This variable cannot be determined prior to start of the extension study as not all the dates of pre-core relapses were collected (only the most recent).

The following baseline disease characteristics are derived relative to ponesimod baseline:

- Time (years) since first Multiple Sclerosis (MS) symptoms defined as ponesimod start date – date of first MS symptom;
- Time (years) since MS diagnosis defined as ponesimod start date – date of MS diagnosis;
- Time (months) since the most recent documented relapse prior to first dose of ponesimod defined as ponesimod start date – date of most recent documented relapse prior to ponesimod start date (including relapses in the core study for subjects randomized to placebo);
- Expanded Disability Status Scale (EDSS) score at ponesimod baseline, continuous and categorical (0, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, > 5.5);
- Number of T1 Gadolinium-enhancing (Gd+) lesions at ponesimod baseline;
- Proportion of subjects with at least one T1 Gd+ lesion at ponesimod baseline;
- Total volume of T2 lesions at ponesimod baseline.
- Number of documented relapses within 12 months and within 24 months prior to screening in the core study. A footnote in the tables should be added explaining that these are pre-screening rates.

See Section 5.1.1 for definition of ponesimod start date and Section 5.1.2 for definition of ponesimod baseline.

Baseline disease characteristics relative to ponesimod baseline are summarized using descriptive statistics for continuous and categorical data, by treatment group and overall for the PAS.

6.4. Appendix 4 Protocol Deviations

Protocol deviations are all those recorded in the database following the specifications provided in the protocol deviation code list. No major deviations are defined and no deviations lead to exclusion from the analysis sets.

All major protocol deviations recorded during the extension study are summarized by category, by treatment group and overall.

A listing of major protocol deviations (coded term, reported term) recorded during the extension study is provided.

Protocol deviations are summarized and listed for the PAS, subset on those subjects who entered the extension study only.

6.5. Appendix 5 Prior and Concomitant Medications

Previous and concomitant medications/therapies are stored in the SDTM.CM datasets. The two CM datasets SDTM201.CM and SDTM202.CM are concatenated for the purposes of this analysis. Terms are coded using the World Health Organization (WHO) drug code dictionary and the anatomic therapeutic chemical (ATC) class code (version dated September 2021 B3G).

A previous therapy is any treatment for which the end date of treatment is prior to the first dose of ponesimod (including medications with an end date in the core study for patients originally randomized to placebo).

Treatment-concomitant therapies are all treatments that are ongoing or initiated after first dose of ponesimod, or that were initiated up to the end of ponesimod treatment.

Post-treatment therapies are those which were initiated after the end of ponesimod treatment, i.e after the ponesimod EOT date as described in Section 5.1.1

Where start date of medication/therapy is missing or partial, the following medications/therapies are considered to be previous therapies:

- Medication end date is not missing and is < ponesimod treatment start date;
- If day is missing and the month/year of the medication end date is < month/year of the ponesimod treatment start date;
- If day and month are missing and the year of the concomitant medication end date is < year of treatment start date.

Otherwise, the medications/therapies with missing or partial start date are considered as treatment-concomitant. Medications considered treatment-concomitant where there is a possibility that they are previous will be flagged in listings, for example, if day is missing and month and year are same as month and year of ponesimod start date.

Beta blocking therapies will be listed for the pooled B201/B202 studies. Beta blocking agents are defined as medications with WHO-Drug anatomic therapeutic chemical (ATC) class level 2 code C07: BETA BLOCKING AGENTS". This is a sub-class of ATC class C "Cardiovascular system". Steroids used for the treatment of relapses are selected in SDTM.CM using CMCAT="CORTICOSTEROIDS (IV) FOR TREATMENT OF RELAPSE".

Covid-19 vaccines are selected in SDTM.CM using CMCLASS = "COVID-19 VACCINES" .

Assignment as prior, treatment-concomitant, and post-treatment therapy is derived using the definitions above.

An additional flag for therapies taken during planned pregnancy interruption will be derived and will include all therapies that started after last intake prior to pregnancy interruption + 15 days and stopped prior to the re-initiation date of study treatment after planned pregnancy.

A therapy with missing or partial start date will not be flagged as taken during planned pregnancy interruption.

6.5.1. Disease modifying therapies for MS

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. Previously, DMTs were identified on an ingredient level, using CM.CMINGL (Ingredients List) in SUPPCM. In the current SDTM, ingredients are listed under CM.CMDECOD and selected if they contain any of the text indicated in Table 11 below. Medications in ATC class S (sensory organs, i.e., ophthalmologicals and / or otologicals) will not be considered. The list in Table 11 will be updated periodically as new DMTs become available.

Table 11: 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

DMTs will be classified as previous or concomitant as defined in Section 6.5.

Previous and concomitant therapies (relative to first dose of ponesimod) are summarized for the PAS, by therapeutic organ class and preferred term.

For study reporting purposes, all previous and concomitant therapies are reported in the subject listings for AP3 on the PAS. Therapies are flagged to indicate whether they are previous, concomitant, or post-treatment.

Previous and concomitant DMTs are reported separately and summarized by therapeutic organ class and preferred term as described above for previous and concomitant therapies.

6.6. Appendix 6 Medical History

Medical history was primarily collected and reported in the core study and is therefore stored in SDTM201.MH. Additional medical history collected that was collected during the extension study is stored in SDTM202.MH.

Additional medical history collected in the extension study is listed on the PAS.

6.7. Appendix 7 Laboratory marked abnormalities

Table 12: Thresholds for marked laboratory abnormalities

Parameter (SI unit)	LL	LLL	HH	HHH
Hemoglobin (g/L)	< 100	< 80	Increase in > 20 g/L above ULN or above baseline (if baseline is above ULN)	Increase in > 40 g/L above ULN or above baseline (if baseline is above ULN)
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	> 8.0
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	≥ 5 ULN
Alkaline Phosphatase (U/L)	ND	ND	> 2.5 ULN	> 5 ULN
INR*	ND	ND	> 1.5 ULN	> 2.5 ULN
Creatinine (umol/L)*	ND	ND	>1.5 ULN or >1.5 x baseline	> 3 ULN or >3 x baseline
Creatinine clearance (mL/min)	< 60	< 30	ND	ND
Urea (mmol/L)	ND	ND	> 2.5 ULN	> 5 ULN
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
Triglyceride (mmol/L)	ND	ND	> 3.42	> 11.4
Cholesterol (mmol/L)	ND	ND	> 7.75	> 12.92

* HH and HHH based on CTCAE 2010 v4.03. 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.
Source: Protocol AC-058B301, Appendix 6.

6.8. Appendix 8 Adverse Events of Special Interest

Adverse events of special interest (AESIs) include the anticipated risks of treatment with ponesimod and events that may be related to MS co-morbidities.

The definitions for AESIs are based on the systematic approach using Standardized MedDRA Queries (SMQ). The additional relevant terms can be added to the search or deleted appropriately providing the rationale for the change. The proposal is based on MedDRA version 26.0. The following safety areas are addressed by the pre-defined AESIs:

The following categories for adverse events of special interest (AESI) are defined:

- 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)

Infection related AEs are identified by the AEs belonging to the MedDRA system organ class (SOC) “Infections and Infestations” (primary SOC), only if reported as serious or severe. If the intensity information is missing, the AE is conservatively considered to be of severe intensity.

See below for the search criteria (based on preferred terms and/or standardized MedDRA queries) used for pre-defined AEs to be included in the above safety areas of special interest.

The time to first treatment-emergent AESI in AP3 for each AESI category (in days) is defined as [date of first treatment-emergent AE in AESI category – ponesimod start date + 1] in days. If first treatment-emergent AE in AESI category is after the restart of treatment after pregnancy interruption period, then the time to first treatment-emergent AESI in AP3 (in days) is defined as: [date of first treatment-emergent AE in AESI category – ponesimod start date + 1 – (end of pregnancy interruption – (start of pregnancy interruption + 15) + 1)]

Subjects without any treatment-emergent AEs in a given AESI category during AP3 are censored, and censored time is defined as (the minimum of [last administration of ponesimod in AP3 +15 days, last study date] – ponesimod start date + 1. For subjects with pregnancy interruption: the minimum of [last administration of ponesimod in AP3 +15 days, last study date] – ponesimod start date + 1 – (end of pregnancy interruption – (start of pregnancy interruption + 15) + 1)

Table 13: AESI, SMQ and PTs

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)	
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

6.10. Appendix 10 Covid-19 Analyses

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 participants in the AC-058B202 study.

Specific objectives are:

- To describe binding antibody concentrations to SARS-CoV-2 S protein as measured by Enzyme-linked immunosorbent assay (ELISA)
- To describe binding antibody concentrations to SARS-CoV-2 N protein as measured by ELISA
- To describe SARS-CoV-2 neutralization as assessed by SARS-CoV-2 neutralization assays VNA (wild-type virus neutralization assay (wtVNA))
- To describe Covid-19 vaccine responders as assessed by binding antibody concentrations to SARS-CoV-2 S protein.
- To describe Covid-19 infection Adverse events (AEs).

6.10.1. Immunogenicity Variables

Patients receiving non-live vaccinations while on study treatment will have 5 mL of blood drawn prior to and at least 3 weeks after vaccination to explore changes in vaccine-specific antibody titers from pre- to post-vaccination.

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

Table 14: Types of SARS-CoV-2 Antibodies

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
SARS-CoV-2 neutralization (wtVNA)	Analysis of neutralizing antibodies to the wild-type virus

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

6.10.2.1. Analysis related definitions:

Baseline: The baseline for Covid-19 vaccine analyses is defined as the last pre-vaccination assessment. For participants missing a pre-vaccination assessment, summaries will be restricted to post-vaccination results only, where applicable.

Analysis Set: The Covid-19 Vaccinated Set (CVAS) is defined as all subjects in the PAS who reported receiving at least 1 dose of any Covid-19 vaccine.

Covid-19 vaccines are selected from the SDTM.CM data as described in Section 6.5.
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 count linked 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 for a given participant. If only one value is available within this time range, this value will be used. If none is available in the range, the lymphocyte count 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.

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.

Responder definition: for S-ELISA, N-ELISA, and wild type VNA assays separately:
A sample will be considered positive if the value is strictly greater than the LLOQ (> LLOQ). A participant will be considered a responder if one of the following conditions is satisfied:

- The baseline sample value is less than or equal to the LLOQ (≤ LLOQ) and the sample of post first vaccine regimen is strictly greater than the LLOQ (> LLOQ)

- The baseline sample value is strictly greater than the LLOQ (> LLOQ) and the sample value of post first vaccine regimen represents an at least 4-fold (≥ 4-fold) increase from the baseline sample value.

Participants with missing pre- or post- first vaccine regimen assessments will not be evaluated for the Responder definition.

Analysis based on BAU/ml: In order to calibrate across different ELISA 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:

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

Identification of antibody concentrations related to each vaccination: As the doses are not labeled in the dataset, determination of the vaccination doses will be based on a combined assessment of the Covid-19 vaccination dates, available in the SDTM CM dataset, and the sample collection dates, available in the SDTM IS dataset, as follows:

- The sequence of vaccination and sample collection dates will be ordered.
- The sample preceding the 1st dose will be considered "**Pre-1st Vaccination Regimen**"
- The sample following the 2nd dose and preceding the 3rd dose will be considered "**Post-1st Vaccination Regimen**", unless the Vaccine Type is "Janssen", in which case, the sample following the 1st dose will be considered "Post-1st Vaccination Regimen".
- The samples preceding and following the 3rd dose will be considered the "**Pre-1st Booster**" and "**Post-1st Booster**", unless the Vaccine Type is Janssen, in which case the samples preceding and following the 2nd dose will be considered "Pre-Booster" and "Post-Booster".
- If there is only 1 sample between the 2nd dose and the 3rd dose, the "Planned Timepoint" (i.e. TP3-Pre or TP3-Post) will be used to determine whether the sample is "Post-1st Vaccination Regimen" or "Pre-1st Booster Regimen".
- The samples preceding and following the 4th dose will be considered the "**Pre-2nd Booster**" and "**Post-2nd Booster**", unless the Vaccine Type is Janssen, in which case the samples preceding and following the 3rd dose will be considered "Pre-2nd Booster" and "Post-2nd Booster". If there is only 1 sample between the 3rd dose and the 4th dose, the "Planned

Timepoint" (i.e. TP4-Pre or TP4-Post) will be used to determine whether the sample is "Post-2nd Vaccination Regimen" or "Pre-2nd Booster Regimen".
- The samples preceding and following the 5th dose will be considered the "**Pre-3rd Booster**" and "**Post-3rd Booster**", unless the Vaccine Type is Janssen, in which case the samples preceding and following the 4th dose will be considered "Pre-3rd Booster" and "Post-3rd Booster". If there is only 1 sample between the 4th dose and the 5th dose, the "Planned Timepoint" (i.e. TP5-Pre or TP5-Post) will be used to determine whether the sample is "Post-3rd Vaccination Regimen" or "Pre-3rd Booster Regimen".

Evidence of Prior Covid-19 infection: a subject is considered to be with evidence of prior Covid-19 infection if any of the following conditions are met:
- Subject has any Covid-19 AE records before first vaccination in SDTM AE dataset.
- Subject has N- and/or S- ELISA positive antibody concentrations prior to first vaccination.

6.10.2.2. Analysis of Immunogenicity Related to Covid-19 Vaccination

Missing and/or Unquantifiable Immune Response Data: Details in Section 6.14.6.

A demographic table of study participants 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 both pre- and post- 1st vaccine regiment 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 vaccination
- sex
- exposure (years) to ponesimod at time of first vaccination
- time interval (days) between 1st dose of vaccine and post-1st vaccination sample
- number and percentage of subjects in different vaccine type of the 1st vaccine regimen
- number and percentage of subjects with or without evidence of prior Covid-19 infection
- number and percentage of subjects in different categories of lymphocyte count

In the above frequency tabulations, percentage is calculated based on number of patients in Covid-19 Vaccinated Set.

For S-ELISA, N-ELISA, and wild type VNA 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 booster and post second booster.
- For participants with pre- and post-vaccination assessments, fold increases in comparison to baseline (geometric mean, 95% CI) will be presented for post-1st vaccine regimen, post-1st booster, post-2nd booster and post-3rd booster. Note that the analysis for post-2nd and post-3rd booster will be performed only if there are > 5 datapoints.
- Number of responders (percent and 95% CI) at post-1st vaccine regimen assessment will be tabulated.

- Dot plots with dots for participant values with the corresponding geometric mean, 95% CI, minimum and maximum for each assay, for pre-, post-1st vaccine regimen, post-1st booster, post-2nd booster and post-3rd booster will be presented. In the graphs, values in BAU/ml unit will be displayed on the log10 scale. Note that the analysis for post- 2nd booster and post- 3rd booster will be performed only if there are >5 datapoints.
- The analyses of the first three bullets will be repeated for S-ELISA antibody concentrations for the following subgroups: vaccine type of the 1st vaccine regimen, evidence of prior Covid-19 infection and categories of lymphocyte count. Box plot will be generated to visualize S-ELISA antibody concentrations for the above-mentioned subgroups. Note that for each booster timepoint, the subgroup analyses will be done only if >= 10 datapoints are available post each booster.

Analyses of S-ELISA and N-ELISA antibody concentration will be presented in BAU/ml unit only. Analyses of wild type VNA assays will be presented in original 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, N-ELISA and wild type VNA assessment antibody concentration will be provided.
A listing of Covid-19 vaccinations will be provided.

6.10.3. 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 VaccinatedSet:

(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 interruption.
(v) any Covid-19 infection AEs leading to treatment discontinuation.
(vi) any Covid-19 infection AE leading to death.

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

(vii) any Covid-19 infection AEs prior to 1st dose of vaccination
(viii) any Covid-19 infection AE post 1st dose (Day 1) of vaccination
(ix) any Covid-19 infection AE with onset at least 14 days (Day 15) post-vaccination (1st dose of any Covid-19 vaccination)
(x) any Covid-19 infection AE with onset at least 28 days (Day 29) post-vaccination (1st dose of any Covid-19 vaccination)

6.11. Appendix 11 Influenza Analyses

Seasonal influenza vaccine typically contains killed strains of Influenza type A and influenza type B. For subjects who have been administered seasonal influenza vaccine, antibody titers against influenza vaccine will be measured by hemagglutination inhibition (HAI) antibody titer (hemagglutination test) by ELISA.

The administration of influenza vaccine is stored in SDTM CM dataset (variable CMCLAS="INFLUENZA VACCINES"). The antibody titers concentration triggered by influenza vaccine(s) are stored in SDTM LB dataset.

The first documented influenza vaccine in the dataset is defined as "1st vaccination". For subjects with multiple influenza vaccinations over years, the subsequent doses are defined as "2nd vaccination", "3rd vaccination", "4th vaccination", etc.

Identification of vaccination sequence and antibody concentrations related to each vaccination:
As the doses are not labeled in the dataset, determination of the vaccination doses will be based on a combined assessment of the influenza vaccination dates, as follows:

- The sequence of vaccination and sample collection dates will be ordered.
- Only the samples assessed within 183 days prior to each vaccination are considered as pre-vaccination assessment. Only the samples assessed within 183 days on or after each vaccination are considered post-vaccination assessment. If the time frame between 2 vaccinations is less than 366 days the time frame for: Before vaccination to the subsequent vaccination is reduced respectively" (We will look 183 before and after a vaccination to assign "Pre"/"Post". In case the time between 2 vaccinations is less than 366 days the described rule was used).
- The nearest sample preceding the 1st dose will be considered "**Pre-1st Vaccination**". The same logic is used for detecting the sample for "Pre-2nd vaccination", "Pre-3rd vaccination", "Pre- 4th vaccination", etc.
- The sample following the 1st dose and preceding the 2nd dose will be considered "**Post-1st Vaccination**". In case there are multiple in this interval, the sample closest to 1st vaccination is considered. The same logic is applied to detect sample for "Post-2nd vaccination", "Post-3rd vaccination", "Post-4th vaccination", etc.

The following immunogenicity analysis related to influenza vaccine will be conducted:

- A listing will be provided to include influenza antibody concentration information.

6.12. General Statistical Methodology

This section describes in general terms the statistical models and methods applied.

6.12.1. Statistical methodology for count data

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

A generalized linear model with NB distribution is assumed.

T_j denotes the length of observation for subject j.
Y_j denotes the counts of interest 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, is modeled by the following equation:

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

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

Example SAS code for the NB model with 95% confidence interval (CI) is as follows:

```
proc genmod data=ADREL;
   class Treat;
   model COUNTS = Treat / dist=negbin link=log
   offset = offset;
        lsmeans Treat / cl exp alpha = 0.05;
   estimate 'A vs B' ' Treat 1 -1/ exp alpha = 0.05;
run;
```

The offset variable used is specified per analysis (e.g., for ARR it is the log-transformed observation time, for total T1 lesions it is the log-transformed number of available MRI scans).

The 'LSMEANS' statement is used to output the mean estimates for each of the treatment arms with 95% Wald CIs).

The 'ESTIMATE' statement is used to output the rate ratio of the treatment effect with 95% Wald CIs for any relevant comparisons.

In the event that the NB model does not converge, a Poisson model is used. For the Poisson distribution, a Poisson regression is conducted with model equation identical to the one for the negative binomial regression. Example SAS code for the Poisson model with 95% CI is as follows:

```
proc genmod data=ADREL;
   class Treat;
   model COUNTS = Treat / dist=poisson link=log
   offset = offset;
        lsmeans Treat / cl exp alpha = 0.05;
   estimate 'A vs B' ' Treat 1 -1/ exp alpha = 0.05;
run;
```

6.12.2. Statistical methods for time-to-event data

The analysis of time-to-event data are conducted using Kaplan-Meier estimates of events over time (including graphical representation), log-rank tests and Cox proportional hazard models.

6.12.2.1. Kaplan-Meier and (stratified) log-rank test

Estimates of the event rate are obtained from the Kaplan-Meier method using SAS PROC LIFETEST. The graphical representation follows the recommendations from Pocock [Pocock 2002]. Two-sided CIs at specific time points are constructed, with confidence limits calculated using Greenwood's formula for the estimate of the standard error. Median time to event, as well

as 25th and 75th percentiles for each group are provided. The corresponding two-sided CIs are calculated using the method of Brookmeyer [Brookmeyer 1982].

Example SAS PROC LIFETEST code is as follows, where the STRATA statement includes the treatment variable (treat), and the TIME statement includes a variable with times to event (time) and an indicator variable for right censoring (censor) with 1 representing censoring.

```
PROC LIFETEST data= method=km;
  TIME survtime*censor(1);
  STRAT treat;
run;
```

The stratified log-rank test is conducted with SAS Proc Lifetest where the STRATA statement includes the specified covariates and the GROUP option includes the treatment variable (treat). The TIME statement includes a variable with times to event (time) and an indicator variable for right censoring (censor) with 1 representing censoring.

```
Proc lifetest data= method=KM;
   time survtime*censor(1);
   strata STRAT COVAR / group=treat;
run;
```

6.12.2.2. Cox proportional hazards model

SAS PROC PHREG is used to estimate the hazard ratio and the CI of the hazard ratio (using Wald-based methods). The Cox regression model can be implemented using the following code:

```
PROC PHREG data =;
  CLASS treat;
  MODEL timeto*censor(1)= treat /risklimits ties=exact;
run;
```

6.13. Study visit and assessment schedule

The following tables: Table 15, Table 16, Table 17 and Table 18 correspond to Tables 1, 2, 3 and 4 in the study protocol. Section numbers in the footnotes refer to the protocol sections.

Table 15: Visit and assessment schedule (treatment period 1 – up to 96 weeks)

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

Table 16: Visit and assessment schedule (Safety Follow-up for patients discontinuing during or at the end of treatment period 1 only

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

*** Hematology/Blood chemistry**	**X**	**X**
*** Urinalysis**	**X**	**X**
*** Pregnancy Test**		**X**
Adverse Events	**X**	**X**
Serious Adverse Events	**X**	**X**

Table 17: Visit and assessment schedule (treatment period 2 and treatment period 3 – up to 540 weeks and Safety Follow-up)

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

Table 18: Visit and assessment schedule (unscheduled visits)

PERIODS	Name	UNSCHEDULED VISITS							
VISITS	Name	Relapse	Unscheduled	Re-initiation[20]		Interruption / planned pregnancy	Eligibility for re-initiation / pregnancy	Re-initiation D1 / pregnancy	Re-initiation D8 / pregnancy
				Day 1 of re-initiation	Day 15 of re-initiation	Unscheduled visit after drug interruption for planned pregnancy	Unscheduled visit prior to study drug re-initiation after interruption for planned pregnancy	Unscheduled visit for re-initiation of study drug following study drug interruption for planned pregnancy	Unscheduled visit for re-initiation of study drug following study drug interruption for planned pregnancy
	Time	Any day between Day 1 and FU3 (EOS3)		Any day between Day 1 and EOT3		30 days after study drug interruption for planned pregnancy	30 days (±5 days) before study drug re-initiation		

Visit window	+ 7 days	NA	NA	±1 day	±7 days	NA	NA	NA
EDSS / Functional Systems[16]	X	X			X	X		
* Chest X-ray								
* MRI		X			X	X		
Concomitant medications	X	X	X	X	X	X	X[19]	X
* Physical Examination	X	X[5]			X	X		
Systolic/diastolic blood pressure[6]	X	X	X	X	X	X	X	X
* 12-lead ECG[6]		X	X	X	X	X	X	X
Ophthalmologic examination[8]		X			X	X		
Pulmonary function tests[9]		X			X	X		
* Hematology/Blood chemistry		X			X	X		
* Urinalysis		X			X	X		
* Pregnancy Test[18]		X			X	X (first assessment)	X (first assessment)	
* Study Drug Dispensing/Return		X	X	X			X[19]	X
Adverse Events	X	X	X	X	X	X	X	X
Serious Adverse Events	X	X	X	X	X	X	X	X

Note: The footnotes apply to Table 15, Table 16, Table 17 and Table 18.

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

1. All Week 24 (EOT) assessments of the core study (AC-058B201) must be completed prior to randomization in the extension study. If a patient is going to enter the extension study the Visit E1 should be scheduled within 3 days after the Week 24 (EOT) visit of the core study. Patients will have to continue using their core study medication every day until and including the day prior to Visit E1.
2. Phone call: The site will call the patient for information on health status / adverse events.
3. In the event of treatment discontinuation prior to Week 96 (whatever the reason), all assessments planned at Visit E13 (EOT2) must be performed as soon as possible, but no later than 5 days following the date of the last dose of study drug.
4. Informed Consent Form of the extension study must be signed by the patient prior to participating in any study-related procedure of the extension study, and prior to continuing using their core study medication on the day of their Week 24 visit of the core study.
5. Physical examination must be performed at all study visits until P37, then yearly until P45, inclusive, and at EOT3, FU1, FU2, and FU3. Includes careful skin examination at each visit from E6 until P37, then at P41, P45, EOT3, and at FU2 and FU3. Body weight only at E7, E9, E11, E13, and yearly from P1 to EOT3.
6. Blood pressure must be performed pre-dose at all visits. ECG must be performed pre-dose at all study visits until P37, then yearly until Visit P45, inclusive. At the visit when the transition from treatment period 2 (TP2) to treatment period 3 (TP3) will occur, all patients must be monitored at the investigational site for at least 6 hours after dose administration [see Section 3.12.2]. In the event of re-initiation of study drug, blood pressure and ECG must be performed pre-dose (all patients) and hourly (±15 min) for at least 4 hours and up to 12 hours (only mandated for patients with cardiovascular risk factors and at the discretion of the investigator / treating neurologist for patients without cardiovascular risk factors) [see Appendix 5 and Section 3.12.5.3].
7. Standard 2D/Doppler echocardiography will assess regional wall abnormalities, aortic valve morphology and function, mitral valve morphology and function, and left ventricular ejection fraction. It will be performed at selected centers with adequate equipment and experience. During TP2 and TP3, echocardiography is performed at every other visit from P1 to P35, yearly from Visits P37 to P45, inclusive, and at EOT3.
8. Ophthalmological examination includes best corrected visual acuity, low contrast visual acuity, visual fields, dilated ophthalmoscopy, and optical coherence tomography (OCT) in case of suspicion of macular edema or active uveitis (OCT, only for subjects at risk). During TP2 and TP3, ophthalmologic examination is performed at every other visit from P1 to P35, yearly from Visits P37 to P45, inclusive, at EOT3 and FU2.
9. FEV_1 and FVC. Additional unscheduled pulmonary function tests (PFTs) will be conducted in the event of respiratory symptoms (e.g., dyspnea) or decreased lung function (FEV_1 and/or FVC <80% of baseline value) during the course of the study. During TP2 and TP3, PFTs are performed at every other visit from P1 to P35, yearly from Visits P37 to P45, inclusive, at EOT3 and FU visits.
10. Plasma sample at trough level (pre-dose).
11. Patients will have to continue using their core study medication until and including the day prior to Visit E1.

12. Dose uptitration or mock uptitration will take place on Days 8 and 15 during TP1. Study drug re-initiation during TP2 will require only one dose uptitration or mock uptitration on Day 8. Study drug re-initiation during TP3 will require only one dose uptitration on Day 8.
13. EOT3 visit has to be performed 1 day after the last study drug intake. For premature discontinuations EOT3 should be performed as soon as possible, but no later than 5 days after the last dose of study drug. Additionally, EOT3 visit has to be performed as soon as possible, but no later than 5 days after the last dose of study drug for patients not enrolling into TP3, or for patients completing study treatment due to availability of commercially available ponesimod [see Section 3.12.3.5]. Commercially available ponesimod may be initiated on the day after last intake of study drug.
14. The three Safety Follow-up visits must be performed:
    – following premature treatment discontinuation
    – following treatment discontinuation at EOT3
    – following treatment discontinuation for switching to commercially available ponesimod.
15. Patients completing the EOT2 (Visit E13) and having a chest X-ray done at this visit must not repeat the chest X-ray at Visit P1.
16. If the patient experiences a confirmed relapse she/he must be made aware by the primary investigator / treating neurologist of the possibility of withdrawal and of switching to standard treatments approved for RRMS. The patient's decision must be recorded in the medical records.
17. When feasible, patients will be transitioned from TP2 to TP3 at the earliest visit following approval of protocol version 8 by ECs/IRBs and health authorities and after having signed the revised Informed Consent Form. At this visit, all patients must be monitored at the investigational site for at least 6 hours after dose administration [see Section 3.12.2].
18. Women who interrupt the study drug because of planned pregnancy will be exempted from any protocol-mandated pregnancy tests after the first positive pregnancy test and until 30 (±5) days before study drug re-initiation.
19. Review and assess contraception methods and total duration of study drug interruption, which should not exceed 81 weeks.
20. As described in detail in Appendix 5, patients who miss taking the study drug for four or more consecutive days are required to re-initiate ponesimod treatment using the gradual uptitration scheme. In such cases, there will be one or two visits; one visit on the day of re-initiation (Day 1) for all patients. An additional visit 14 days (±1 day) after the day of re-initiation (Day 15) only mandated for patients with cardiovascular risk factors [see Appendix 5] but may be scheduled for any patient at the discretion of the investigator / treating neurologist.

6.14. Handling of Missing/Incomplete/Inconsistent Data and 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.

6.14.1. Medical history and baseline disease characteristics

Type of date/time	Date is incomplete	Date is missing
Medical history and baseline disease characteristics	Day missing: 15th of the month Day and month missing: 30th of June	No replacement

6.14.2. EDSS

Type of date/time	Date/time is incomplete	Date/time is missing
EDSS assessment date	Maximum of - lower limit - previous scheduled EDSS assessment according to the visit label + 1 day (if available) - date of first administration of ponesimod. Unless upper limit is prior to date of first administration of ponesimod, then upper limit	do not impute and exclude from analysis

6.14.3. Relapse

Type of date/time	Date/time is incomplete	Date/time is missing
Relapse start date	Maximum of lower limit and date of first administration of ponesimod Unless upper limit is prior to date of first administration of ponesimod, then upper limit	Date of first administration of ponesimod

6.14.4. Adverse event onset and resolution dates

The following imputation rules are applied for (partially missing) AE onset dates:

- Onset day missing:
  - If month and year put the event start date clearly on or after month and year of first administration of ponesimod in the Analysis Period, and clearly on or before the month and year of date of last administration of ponesimod in the Analysis Period + 15 days, the event is considered to be treatment-emergent, unless event occurred during pregnancy interruption as described in Section 5.1.4.
  - If the month and year correspond to the month and year of first administration of ponesimod in the Analysis Period, impute onset date of the AE as the date of the first administration of ponesimod in the Analysis Period.
  - If the month and year are clearly after the month and year of date of first administration of ponesimod in the Analysis Period, the onset date is imputed as the maximum of (date of Study Day 2, 1st day of the month and year given.

- If event onset month and year are clearly prior to the month and year of date of first administration of ponesimod in the Analysis Period, the onset date is imputed to the last day of the given month.

- Onset day and month missing:
  - If the year is the same year as the year of first administration of ponesimod in the Analysis Period or later, and if the year is prior to or in the same year as the date of last administration of ponesimod in the Analysis Period + 15 days, the event is considered to be treatment-emergent unless event occurred during pregnancy interruption as described in Section 5.1.4.
  - If the year is clearly on or after the year of first administration of ponesimod in the Analysis Period, the onset date is imputed as date of maximum of (Study Day 2, 1 January of the given year).
  - If the event onset year is clearly prior to the year of first administration of ponesimod in the Analysis Period, the onset date is imputed to 31-December of the given year.

- Onset date is completely missing:
  - The event is considered to be treatment-emergent.
  - The onset date is imputed as date of first administration of ponesimod in the Analysis Period.

- Resolution day missing:
  - If event resolution month and year are clearly prior to the month and year of the date of last administration of ponesimod in the Analysis Period, the resolution date is imputed to the last day of the given month.
  - If event resolution month and year are the same as the month and year of the date of last administration of ponesimod in the Analysis Period, the resolution date is imputed to date of last administration of ponesimod in the Analysis Period, and the event is considered to be ongoing.
  - If event resolution month and year are clearly after the month and year of the last ponesimod administration (EOT), the resolution date is imputed to the last day of the given month.

- Resolution day and month missing:
  - If event resolution year is clearly prior to the year of the date of last administration of ponesimod in the Analysis Period, the resolution date is imputed to 31-December of the given year.
  - If event resolution year is the same as the year of the date of last administration of ponesimod in the Analysis Period, the resolution date is imputed to date of last administration of ponesimod in the Analysis Period, and the event is considered to be ongoing.

- Onset date is on a date subsequent to the resolution date:
  - If event start date occurs at a date after the event resolution date, the event is considered to be treatment-emergent. However, neither the onset date nor the resolution date is changed.

6.14.5. Handling of missing and partially missing End-of-Treatment Dates

End-of-treatment date: the last drug administration date recorded on the study drug log.

If end date is missing on last record in SDTM.EC then:

- If the subject has discontinued early then date of last administration is taken as DS.DSSTDTC when DSSCAT = 'Study termination'.

If end date is partially missing on last record in SDTM.EC then:

- set as min(upper limit, DS.DSSTDTC where DSSCAT= 'Study termination',)

6.14.6. Missing and/or Unquantifiable Immune Response Data

Missing immune response data will not be imputed.

Values will be imputed based on the type of analysis. For the calculation of the geometric mean titer, values below LLOQ will be imputed to LLOQ/2. For the calculation of the geometric mean of the increase from baseline, values below LLOQ will be imputed to LLOQ. The LLOQ values per assay are available in the data base.

Data above the ULOQ will be imputed with the ULOQ.

7. REFERENCES

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