STATISTICAL ANALYSIS PLAN FOR CLINICAL STUDY REPORT AC-058B302 POINT: POnesImod aNd Tecfidera

Multicenter, randomized, double-blind, parallel-group, add-on, superiority study to compare the efficacy and safety of ponesimod to placebo in subjects with active relapsing multiple sclerosis who are treated with dimethyl fumarate (Tecfidera®)

Purpose of Analysis	Synoptic Clinical Study Report
Investigational Drug	Ponesimod (ACT-128800)
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LIST OF ABBREVIATIONS AND ACRONYMS

%predFEV1	FEV1 expressed as % of predicted normal value
%predFVC	FVC expressed as % of predicted normal value
ACTH	Adrenocorticotropic hormone
ADaM	Analysis Data Model
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
ARR	Annualized relapse rate
AST	Aspartate aminotransferase
ATC	Anatomic therapeutic chemical
BMI	Body mass index
bpm	Beats per minute
CDA	Confirmed disability accumulation
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence interval
CRA	Clinical Research Associate
CRF	Case report form
CSR	Clinical study report
CUAL	Combined unique active lesions
DBP	Diastolic blood pressure
DMF	Dimethyl fumarate
ECG	Electrocardiogram
eCRF	Electronic case report form
eC-SSRS©	Columbia-Suicide Severity Rating Scale (electronic self-rated version)
EDSS	Expanded Disability Status Scale
EOS	End-of-Study

EOT	End-of-Treatment
EU	European Union
FAS	Full analysis set
FDA	(US) Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
FS	Functional system
FVC	Forced vital capacity
GCP	Good Clinical Practice
Gd+	Gadolinium enhancing
HR	Heart rate
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
INR	International normalized ratio
IRT	Interactive response technology
IVRS	Interactive voice response
JCV	John Cunningham virus
KM	Kaplan-Meier
LLOQ	Lower limit of quantification
MACE	Major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MS	Multiple Sclerosis
NAP	Not applicable
NB	Negative binomial
PCS	Physical component summary
PD	Pharmacodynamic
PEF	Peak expiratory flow
PFT	Pulmonary function test
PI	Principal Investigator

PML	Progressive multifocal leukoencephalopathy
PT	Preferred term
PTOP	Post treatment observation period
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
RRMS	Relapsing-remitting multiple sclerosis
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SCR	Screened analysis set
SD	Standard deviation
SDTM	Study Data Tabulation Model
SE	Standard error
SI	Standard international
SMQs	Standardized MedDRA Queries
SOC	System organ class
SPA	Special Protocol Assessment
SPMS	Secondary progressive multiple sclerosis with superimposed relapses
STS	Study treatment start
TBIL	Total bilirubin
ULN	Upper limit of the normal range
WBC	White blood cell
WHO	World Health Organization
WHODRUG	WHO drug dictionary

1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the analyses and presentation of the key efficacy, safety and pharmacodynamic (PD) endpoints for the synoptic clinical study report (CSR) of the AC-058B302 study (POINT).

Separate SAPs (not described here) are developed for analyses on:

- Vaccination specific antibody titers.

Source data for the analyses are provided as Statistical Analysis Software (SAS®) data sets according to Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM).

On 26 November 2019 it was decided to prematurely terminate the study.

This decision was made following the recommendation from the Independent Data Monitoring Committee (IDMC) at the IDMC meeting on 10 September 2019 to further evaluate the feasibility of the AC-058B302/POINT study. The study started enrolling subjects in March 2017, and after 2.5 years of recruitment had enrolled 136 subjects (22% of the targeted population). The IDMC recommendation was as follows:

- The IDMC recognized the Sponsor's efforts to increase enrolment but these were not successful. Therefore, the IDMC members are concerned that the study will not be finished in an adequate timeframe which will impair a proper assessment of safety, efficacy, and feasibility.
- With the current recruitment rate the IDMC members regard the study as futile.
- IDMC members request arguments against futility from the sponsor to continue the study as per protocol.

As a result of this evaluation, the Sponsor concluded that the current study design with the required sample size is unlikely to achieve the study objectives, and therefore prematurely terminated the study.

Following the decision to prematurely terminate the study, it was decided also to produce a synoptic CSR of the key efficacy and safety data only.

2 STUDY DESIGN AND FLOW

This is a prospective, multicenter, randomized, double-blind, parallel-group, add-on, placebo-controlled, Phase 3, superiority study. The study is designed to compare the efficacy, safety, and tolerability of add-on therapy with ponesimod 20 mg vs placebo in adult subjects with active relapsing multiple sclerosis (RMS) who are treated with dimethyl fumarate (DMF; Tecfidera®).

It was planned to randomize approximately 600 subjects who had been receiving DMF twice daily for at least 6 months in a 1:1 ratio to ponesimod 20 mg or placebo (approximately 300 subjects per

arm). Randomization is stratified by baseline Expanded Disability Status Scale (EDSS) score (EDSS ≤ 3.5, EDSS > 3.5).

At the time of the decision to terminate the study, a total of 136 subjects had been randomized at 54 sites (randomized subjects) in 17 countries in North America, and Eastern and Western Europe regions.

Following the decision to terminate the study:

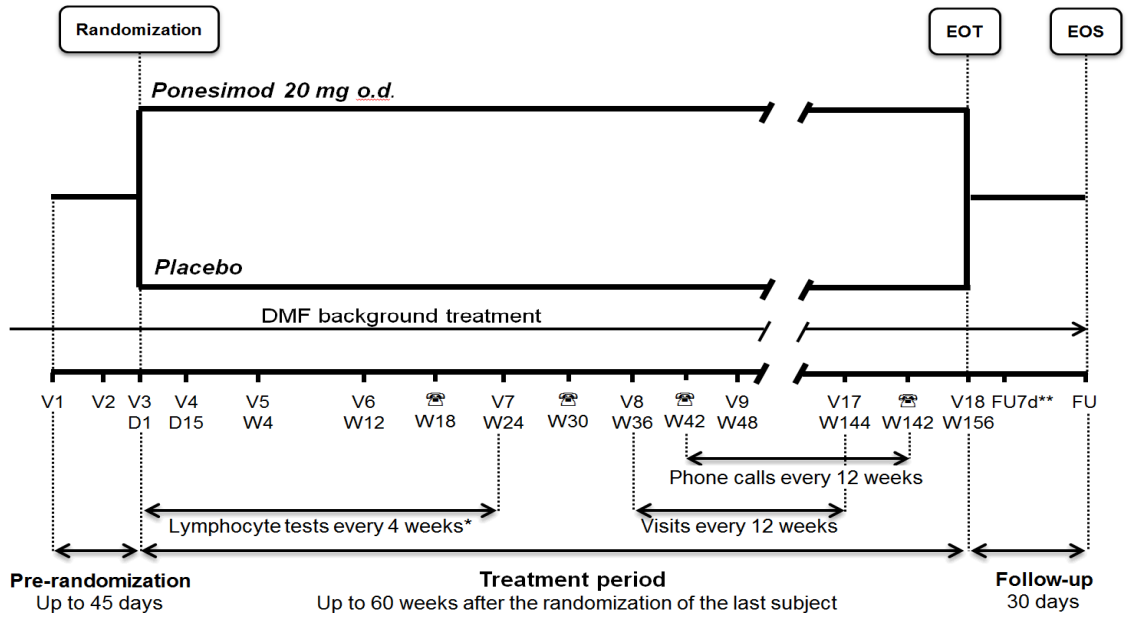
- Subjects in screening at the time of the announcement were required to be screen failed;
- Subjects on study treatment were required to perform the End-of-Treatment (EOT) visit within 8 weeks and the follow-up visits;
- Subjects in the post treatment observation period (PTOP) were required to perform the Visit 18A within 4 weeks.

2.1 Study design

The overall design of the two-arm study is shown in Figure 1.

Subjects who prematurely discontinue study drug and complete the 30-day safety follow-up including the FU visit, can enter the PTOP which lasts until 60 weeks after randomization of the last subject or until Week 156, whichever is first (i.e., planned EOT visit) irrespective of treatment completion.

Figure 1 Study Design



D = day; DMF = dimethyl fumarate; EOS = End-of-Study; EOT = End-of-Treatment; FU = follow-up; V = visit; W = week; *Lymphocyte tests every 4 weeks (± 3 days) until Week 24; ** Subjects participating in the lymphocyte subset sub-study will have an additional FU visit approximately 7 days after the last dose of study drug (FU7d).

2.1.1 Periods

The study consists of the following protocol defined periods:

- **Pre-randomization period** starts with signature of the Informed Consent Form (ICF) and ends with the subject's randomization and lasts up to 45 days (per screening attempt). Subjects can be re-screened once. It includes Visit 1 (Screening), Visit 2 (Baseline) and the pre-dose assessments of Visit 3 (Day 1).

- **Treatment period** starts on the day of randomization immediately after the first dose of study drug intake (Visit 3–Day 1 of the study). The double-blind treatment period has a variable duration from a minimum of 60 weeks (for the last subject randomized) to a maximum of 156 weeks (3 years) for the first subjects randomized in the trial. Average duration is expected to be approximately 2 years. It includes a randomization visit, visits at 2, 4, and 12 weeks after randomization, and 12-weekly visits thereafter until 60 weeks after the randomization of the last subject or 156 weeks of treatment (whichever occurs first). The treatment period consists of a titration and a maintenance phase.

  – A 2-week titration scheme is implemented on Day 1 (or at re-initiation following a treatment interruption of more than 3 days) to reduce the first-dose effects of ponesimod [see Table 1]. During the up-titration period, one tablet of ponesimod 2, 3, 4, 5, 6, 7, 8, 9, or 10 mg (or matching placebo) will be taken orally once daily.

  – The titration phase is followed by the maintenance phase with one tablet of ponesimod 20 mg (or matching placebo) administered orally once daily in the morning (from Day 15 to EOT).

- **Post-treatment period** starts immediately after the last dose of study treatment and ends when End-of-Study (EOS) visit has been completed. It comprises the post-treatment safety follow-up period and if applicable, is followed by the PTOP.

  – **Post-treatment safety follow-up period**
  All subjects will enter the safety follow-up period which lasts for at least 30 days after the last dose of study treatment and includes a safety follow-up visit approximately 30 days after the last dose of study treatment (FU visit). Subjects participating in the lymphocyte subset sub-study will have an additional follow-up visit approximately 7 days after the last dose of study drug (FU7d visit).

  – **Post-treatment observation period**
  Subjects who prematurely discontinue study drug and complete the 30-day safety follow-up including the FU visit, will enter the PTOP which lasts until 60 weeks after randomization of the last subject or until Week 156, whichever is first (i.e., planned EOT visit) irrespective of treatment completion. The PTOP consists of an abbreviated schedule of assessments at the time of the originally scheduled 12-weekly visits (i.e., not all assessments are performed, see visit schedule). Safety follow-up visits are conducted in addition, following the post-treatment safety follow-up period schedule.

- **End-of-study:** the study level EOS occurs after all subjects have completed the safety follow-up period or the last visit of the PTOP. For an individual subject, EOS is reached when treatment, post-treatment safety follow-up, and if applicable, the PTOPs have been completed:
  - For subjects who complete the treatment period, and for subjects who prematurely discontinue study treatment and do not enter the PTOP, the EOS visit corresponds to the 30-day follow-up visit (FU visit).
  - For subjects who prematurely discontinue study treatment and enter the PTOP period, the EOS visit corresponds to the last visit of the PTOP.

Table 1 Dosing scheme

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

- * Visit 4 is to take place at Day 15 ± 1 day.
- EOT = End-of-Treatment.

2.1.2 Blinding

This study is performed in a double-blind fashion. Refer to the protocol for aspects related to study drug material related blinding and functional blinding. To maintain functional blinding data are collected in two databases, a main database and a first dose database. During the conduct of the study, the Actelion trial team (with the exception of the Clinical Research Associate (CRA) / Site manager) does not have access to the first dose database. The main database contains all data except data collected on the day of the first dose or on the day of re-initiation until discharge of the subject for: adverse events (AEs), hourly vital signs and electrocardiogram (ECG) measurements, and will exclude all treatment-emergent data for the lymphocytes and white blood cell (WBC) laboratory parameters. In addition, spirometry data will not be available to Actelion Biostatistics until after database lock. Final analyses for the CSR described in this SAP will be presented from both main and first-dose databases combined.

2.1.3 Sub-studies

Two sub-studies were designed to evaluate specific safety variables and are conducted in a subset of sites and subjects.

2.1.3.1 Lymphocyte subset

A sub-study assessing lymphocyte subsets was conducted and it was planned to include approximately 200 subjects. Participation in the sub-study was mandatory for all subjects until at least the first 200 subjects were randomized to the main study. Due to the early termination of the study with 136 randomized subjects, it is expected that all are also participating in the lymphocyte sub-study. T cell, B cell, and NK cell counts as well as T cell subsets (e.g., $CD4^+$ naïve, $CD4^+$ effector memory, $CD4^+$ central memory, $CD8^+$ naïve, $CD8^+$ effector memory, $CD8^+$ central memory, $CD8^+$ terminally differentiated effector memory, Th17 cells, Treg cells, and Th1 cells) will be analyzed at the central laboratory. All subjects were to be analyzed for T cell subsets. In addition, approximately 50 subjects were to be analyzed for B cell subsets. Other lymphocyte subsets may also be analyzed. Selected lymphocyte subsets may also be analyzed functionally *ex vivo*. Results from the lymphocyte subsets sub-study will be blinded to site staff and the sponsor until study closure (i.e., database lock and unblinding).

2.2 Study visit and assessment schedule

Table 2 and Table 3 show a schematic representation of the assessments during the study. Table 4 shows a schematic representation of the assessments during the PTOP.

Table 2 Visit and assessment schedule (Part 1)

Periods	Name	**PRE-RANDOMIZATION** (1)		**TREATMENT PERIOD**						
	Duration	Up to 45 Days		Up to 60 weeks after the randomization of the last subject						
Visits	Number	1	2	3	4	5	6	7	8,10, 12, 14, 16	11, 15
	Name	Screening (1)	Baseline (1)	Rand	W2	W4	W12	W24	W36,W60, W84, W108, W132	W72, W120
	Time	Day −45 to −1		Day 1	Day 15	Day 28	Week 12	Week 24	Week 36, 60, 84, 108, 132	Week 72, 120
	Visit window				± 1 day	± 5 days	± 7 days	± 7 days	± 7 days	± 7 days
Informed consent*		X								
Inclusion/exclusion criteria*		X	X	X						
Demographics*		X								
Medical history / smoking status*		X								
MS history & treatment*		X								
McDonald criteria (Revision 2010)		X								
EDSS/FS*		X	X				X	X	X	X
Relapse* (2)			X	X (2)	◄	―	―	―	―	► X (2)
MSFC, SDMT*		X (3)	X (3)	X (3)			X	X		X
FSIQ-RMS** (4)			X				X	X		X
SF-36v2**			X				X	X		X
Health care resource utilization* (5)			X		X	X	X	X	X	X
WPAI:MS**			X				X	X		X
Chest X-ray* (6)		X								
eC-SSRS**			X							
MRI**			X					X		X
Concomitant medications*		X	X	X	X	X	X	X	X	X
Physical examination*		X	X					X		X
Body temperature*		X	X	X	X	X	X	X	X	X
Dermatological examination* (7)			X							
Body weight and height* (8)		X	X							
Systolic/diastolic blood pressure*		X	X	X (9)	X	X	X	X	X	X
12-lead ECG** (10)		X	X	X (11)	X	X	X (11)	X	X	X
Ophthalmological examination*(12)		X					X	X		
OCT*(12)			X				X	X		
Spirometry*			X				X			
Hematology/chemistry**		X	X		X	X	X	X	X	X
Urinalysis*		X					X	X		X

Lymphocytes** (13)	X	X		X	X (13) ⟷		X (13)	X	X
Lymphocyte subsets** (14)		X				X	X		
Tuberculosis test**	X								
Viral serology**	X								
JCV serology**		X							
Additional serum sample for viral serology		X							
Pregnancy test*/**	X (15)	X		X	X	X	X	X	X
PK sampling (pre dose, except Visit 3)*			X (16)			X (16)	X		
Study treatment dispensing & accountability (17)			X	X	X	X	X	X	X
AE*/SAE* (18)	X	X	X	X	X	X	X	X	X

* Data collected in the eCRF

** Electronically transferred to sponsor.

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

(1) At every study visit, subjects are reminded to contact their principal investigator / treating neurologist at the clinical site immediately in the event of the appearance of any new or worsened neurological symptoms. In addition, the site will contact the subject in-between the 12-weekly visits (e.g., Visit 6 – Week 12, Visit 7 – Week 24) in order to proactively inquire about any new or worsened neurological symptoms. These telephone calls will be conducted either at Weeks 18, 30, 42, 54, 66, 78, 90, 102, 114, 126, 138 and 150 (± 7 days), or 6 weeks after the last 12-weekly visit (± 7 days). Whenever between visits a subject experiences any new or worsened neurological symptoms, he/she must contact the principal investigator / treating neurologist, study nurse or clinical coordinator as soon as possible in order to complete a telephone questionnaire for relapse assessment [see Appendix 12]. After the occurrence of each confirmed relapse, subjects will be asked to re-consent to continue receiving study treatment [see Protocol Section 13.3].

(2) The symptoms scale (with a 24-hour recall) will be completed for 7 consecutive days (the day of the visit and the 6 days after the visit) with an average score being taken across these 7 days. At Visit 20 (FU), the FSIQ-RMS will be completed at home prior to the visit, ideally, during the 7 consecutive days preceding the visit.

(3) Healthcare resource utilization data, including number of hospital visits, length of stay, number of Intensive care unit admissions for MS relapses and emergency medical services facility visits for MS.

(4) In case of premature study treatment discontinuation, the chest X-ray at EOT does not need to be performed if the EOT visit occurs within 48 weeks of the pre-randomization chest X-ray.

(5) Dermatological examination to be performed by a dermatologist [see Protocol Section 7.3.12].

(6) SBP/DBP: Pre-dose and hourly (± 15 minutes) for at least 4 hours post-dose and up to 12 hours.

(7) Only pre-dose ECGs at all visits (if applicable) except EOT and re-initiation visits. At re-initiation, pre-dose and hourly (± 15 minutes) for at least 4 hours post-dose ECGs and up to 12 hours.

(8) OCT and/or ophthalmological examination to be performed at any visit in the presence of visual symptoms suggestive of macular edema or active uveitis.

(9) Lymphocyte subset analysis will be performed on a subset of at least 200 subjects randomized to the main study.

(10) Serum pregnancy test at FU. Urine pregnancy tests at all other visits. Urine pregnancy tests (performed at home) on a 4-weekly basis (± 4 days) between the visits until 4 weeks after last study treatment intake (results of the pregnancy test to be communicated by telephone call to the principal investigator / treating neurologist).

(11) Pre and post-vaccination sampling for vaccine-specific antibody titers for subjects having received non-live vaccines while on study treatment (sub-study).

(12) When possible, collect PK sample upon experiencing a SAE. Preferably, sample will be collected pre-dose, as early as possible after SAE onset, and within 7 days after the last dose of study treatment.

(13) Scheduled study medication dispensing/return procedures may be adapted according to the site practice.

(14) All AEs and SAEs that occur after signing the Informed Consent Form and up to 30 days after study treatment discontinuation must be reported.

(15) Unscheduled visits may be performed at any time during the study and may include all or some of the indicated assessments, based on the judgment of the investigator.

(16) Visit performed only for subject participating in the lymphocyte subset sub-study

(17) If a total lymphocyte count < 0.5×10^9/L is observed at FU an alert will be sent to the principal investigator and the sponsor. Discontinuation of DMF treatment should be considered in accordance with prescribing information [Tecfidera USPI, Tecfidera SmPC].
(18) Pulse rate to be assessed only if no 12-lead ECG is performed at this visit.

AE = adverse event; DBP= diastolic blood pressure; DMF = dimethyl fumarate; eCRF = electronic case report form; eC-SSRS = electronic self-rated version of the Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EDSS = expanded disability status scale; EOT = end-of-treatment; FU7d = FU visit approximately 7 days after the last dose of study drug; FS = functional system; FSIQ-RMS = fatigue symptoms and impacts questionnaire – relapsing multiple sclerosis; FU = follow-up; JCV = John Cunningham Virus; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSFC = multiple sclerosis functional composite; OCT = optical coherence tomography; PK = pharmacokinetics, SAE = serious adverse event; SBP = systolic blood pressure; SDMT = symbol digit modalities test; SF-36v2 = 36-Item Short Form Health Survey Version 2; SmPC = Summary of Product Characteristics; USPI = United States Prescribing Information; WPAI-MS = work productivity and activity impairment in MS.

Table 3 Visit and assessment schedule (Part 2)

Periods	Name	TREATMENT PERIOD		FOLLOW-UP		UNSCHEDULED			
	Duration	Up to 60 weeks after randomization of the last subject		30 Days					
Visits	Number	9, 13, 17	18	19	20	I1, I2, …		R1, R2, …	U1, U2, …
						d1	d15		
	Name	W48, W96, W144	EOT	FU7d (16)	FU (17)	Re-initiation		Relapse	Unscheduled (15)
						Day 1 of re-initiation	Day 15 after re-initiation		
	Time	Week 48, 96, 144	Up to Week 156 or earlier in case of premature discontinuation	Last study treatment intake + 7 days	Last study treatment intake + 30 days	Any day between Day 1 and EOT		Any day between Day 1 and EOS	
	Visit window	± 7 days	+ 7 days	± 2 days	+ 7 days	NA	± 1 day	+ 7 days	NA
EDSS/FS*		X	X		X			X	X
Relapse* (1)		X (1) ◄	———	———	► X (1)			X	
MSFC, SDMT*		X	X						
FSIQ-RMS** (2)		X	X		X			X	X
SF-36v2**		X	X					X	
Health care resource utilization* (3)		X	X					X	
WPAI:MS**		X	X						
Chest X-ray* (4)			X						
eC-SSRS**		X	X						
MRI**		X	X						X
Concomitant medications*		X	X		X			X	X
Physical examination*		X	X					X	X
Body temperature*		X	X		X	X	X	X	X
Pulse rate*								X	X (18)
Dermatological examination* (5)		X	X						X
Body weight*		X	X						X
Systolic/diastolic blood pressure*		X	X		X	X (6)	X		X
12-lead ECG** (7)		X	X		X	X (7)	X		X
Ophthalmological examination* (8)		X	X		X				X
OCT* (8)		X	X						X
Spirometry*		X	X		X				X
Hematology/chemistry**		X	X		X				X
Urinalysis*		X	X		X				X
Lymphocytes**		X	X		X				X
Lymphocyte subsets** (9)		X	X	X	X				
JCV serology**		X	X						

Pregnancy test*/** (10)	X	X		X				X
Serum sample vaccination* (11)								X
PK sampling pre dose*	X	X		X				X(12)
Study treatment dispensing & accountability (13)	X	X			X	X		X
AE*/SAE * (14)	X	X	X	X		X	X	X

* Data collected in the eCRF

** Electronically transferred to sponsor.

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

(1) At every study visit, subjects are reminded to contact their principal investigator / treating neurologist at the clinical site immediately in the event of the appearance of any new or worsened neurological symptoms. In addition, the site will contact the subject in-between the 12-weekly visits (e.g., Visit 6 – Week 12, Visit 7 – Week 24) in order to proactively inquire about any new or worsened neurological symptoms. These telephone calls will be conducted either at Weeks 18, 30, 42, 54, 66, 78, 90, 102, 114, 126, 138 and 150 (± 7 days), or 6 weeks after the last 12-weekly visit (± 7 days). Whenever between visits a subject experiences any new or worsened neurological symptoms, he/she must contact the principal investigator / treating neurologist, study nurse or clinical coordinator as soon as possible in order to complete a telephone questionnaire for relapse assessment [see Appendix 12]. After the occurrence of each confirmed relapse, subjects will be asked to re-consent to continue receiving study treatment [see Protocol Section 13.3].

(2) The symptoms scale (with a 24-hour recall) will be completed for 7 consecutive days (the day of the visit and the 6 days after the visit) with an average score being taken across these 7 days. At Visit 20 (FU), the FSIQ-RMS will be completed at home prior to the visit, ideally, during the 7 consecutive days preceding the visit.

(3) Healthcare resource utilization data, including number of hospital visits, length of stay, number of Intensive care unit admissions for MS relapses and emergency medical services facility visits for MS.

(4) In case of premature study treatment discontinuation, the chest X-ray at EOT does not need to be performed if the EOT visit occurs within 48 weeks of the pre-randomization chest X-ray.

(5) Dermatological examination to be performed by a dermatologist [see Protocol Section 7.3.12].

(6) SBP/DBP: Pre-dose and hourly (± 15 minutes) for at least 4 hours post-dose and up to 12 hours.

(7) Only pre-dose ECGs at all visits (if applicable) except EOT and re-initiation visits. At re-initiation, pre-dose and hourly (± 15 minutes) for at least 4 hours post-dose ECGs and up to 12 hours.

(8) OCT and/or ophthalmological examination to be performed at any visit in the presence of visual symptoms suggestive of macular edema or active uveitis.

(9) Lymphocyte subset analysis will be performed on a subset of at least 200 subjects randomized to the main study.

(10) Serum pregnancy test at FU. Urine pregnancy tests at all other visits. Urine pregnancy tests (performed at home) on a 4-weekly basis (± 4 days) between the visits until 4 weeks after last study treatment intake (results of the pregnancy test to be communicated by telephone call to the principal investigator / treating neurologist).

(11) Pre and post-vaccination sampling for vaccine-specific antibody titers for subjects having received non-live vaccines while on study treatment (sub-study).

(12) When possible, collect PK sample upon experiencing a SAE. Preferably, sample will be collected pre-dose, as early as possible after SAE onset, and within 7 days after the last dose of study treatment.

(13) Scheduled study medication dispensing/return procedures may be adapted according to the site practice.

(14) All AEs and SAEs that occur after signing the Informed Consent Form and up to 30 days after study treatment discontinuation must be reported.

(15) Unscheduled visits may be performed at any time during the study and may include all or some of the indicated assessments, based on the judgment of the investigator.

(16) Visit performed only for subject participating in the lymphocyte subset sub-study

(17) If a total lymphocyte count $< 0.5 \times 10^9$/L is observed at FU an alert will be sent to the principal investigator and the sponsor. Discontinuation of DMF treatment should be considered in accordance with prescribing information [Tecfidera USPI, Tecfidera SmPC].

(18) Pulse rate to be assessed only if no 12-lead ECG is performed at this visit.

AE = adverse event; DBP= diastolic blood pressure; DMF = dimethyl fumarate; eCRF = electronic case report form; eC-SSRS = electronic self-rated version of the Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EDSS = expanded disability status scale; EOT = end-of-treatment; FU7d = FU visit approximately 7 days after the last dose of study drug; FS = functional system; FSIQ-RMS = fatigue symptoms and impacts questionnaire – relapsing multiple sclerosis; FU = follow-up; JCV = John Cunningham Virus; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSFC = multiple sclerosis functional composite; OCT = optical coherence tomography; PK = pharmacokinetics, SAE = serious adverse event; SBP = systolic blood pressure; SDMT = symbol digit modalities test; SF-36v2 = 36-Item Short Form Health Survey Version 2; SmPC = Summary of Product Characteristics; USPI = United States Prescribing Information; WPAI-MS = work productivity and activity impairment in MS.

Table 4 Visit and assessment schedule (Part 3)

Periods	Name	**Post-Treatment observation period (PTOP)** (to be performed after EOT, and FU)		
	Duration	Up to 60 weeks after randomization of the last subject		
Visits	Number	6A, 7A, 8A, 10A, 12A, 14A, 16A	11A, 15A	9A, 13A, 17A, 18A
	Name	W12A, W24A, W36A, W60A, W84A, W108A, W132A	W72A, W120A	W48A - W96A - W144A - W156A
	Time	Weeks 12, 24, 36, 60, 84, 108, 132	Weeks 72, 120	Weeks 48, 96, 144, 156
	Visit window	± 7 days	± 7 days	± 7 days
EDSS/FS*		X	X	X
Relapse* (1)		X (1) ◄	———	► X (1)
MRI**		X (Week 24 only)	X	X
FSIQ-RMS** (2)		X (only Weeks 12 and 24)	X	X
Concomitant medications*		X	X	X
Physical examination*		X (Week 24 only)	X	X
Body temperature*		X	X	X
Dermatological examination* (3)				X
Systolic/diastolic blood pressure*		X	X	X
12-lead ECG **				X
Spirometry*		X (Week 12 only)		X
Hematology/chemistry**		X	X	X
Urinalysis*		X	X	X
Lymphocytes**		X	X	X
Lymphocyte subsets**		X (only Weeks 12 and 24)		X
JCV serology**				X
Adverse events (AE)*		X	X	X
Serious adverse events (SAE)*		X	X	X

* Data collected in the eCRF

** Electronically transferred to sponsor.

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

(1) At every study visit, subjects are reminded to contact their principal investigator / treating neurologist at the clinical site immediately in the event of the appearance of any new or worsened neurological symptoms. In addition, the site will contact the subject in-between the 12-weekly visits (e.g., Visit 6A – Week 12, Visit 7A – Week 24) in order to proactively inquire about any new or worsened neurological symptoms. These telephone calls will be conducted either at Weeks 18, 30, 42, 54, 66, 78, 90, 102, 114, 126, 138 and 150 (± 7 days), or 6 weeks after the last 12-weekly visit (± 7 days). Whenever between visits a subject experiences any new or worsened neurological symptoms, he/she must contact the principal investigator / treating neurologist, study nurse or clinical coordinator as soon as possible in order to complete a telephone questionnaire for relapse assessment [see Appendix 12].

(2) The symptoms scale (with a 24-hour recall) will be completed for 7 consecutive days (the day of the visit and the 6 days after the visit) with an average score being taken across these 7 days. At Visit 18A (Week 156), the FSIQ-RMS will be completed at home prior to the visit, ideally, during the 7 consecutive days preceding the visit.

(3) Dermatological examination to be performed by a dermatologist [see Protocol Section 7.3.12].

ECG = electrocardiogram; EDSS = expanded disability status scale; EOT = End-of-Treatment; FS = functional system; FSIQ-RMS = fatigue symptoms and impacts questionnaire – relapsing multiple sclerosis; FU = Follow up; JCV = John Cunningham Virus; MRI = magnetic resonance imaging.

3 OBJECTIVES

3.1 Primary objective(s)

The primary objective of the study is to determine whether add-on therapy with ponesimod reduces relapse frequency as compared to placebo in subjects with active RMS who are treated with DMF (Tecfidera®).

3.2 Secondary objectives

- To assess the effect of add-on therapy with ponesimod vs placebo on disability accumulation and on other aspects of multiple sclerosis (MS) disease control in subjects with RMS who are treated with DMF (Tecfidera®);
- To assess the safety and tolerability of add-on therapy with ponesimod vs placebo in subjects with RMS who are treated with DMF (Tecfidera®).

4 CHANGES OR CLARIFICATIONS TO ANALYSES PLANNED IN THE STUDY PROTOCOL

4.1 Changes to the analyses planned in the study protocol

The early termination of the study has significant impact on the power of the study to detect differences, and some endpoints require a minimum time on study that is reached by very few subjects. As a synoptic CSR will be produced to report the study data, only key efficacy and safety data will be reported.

The following additional changes are also applied:

- In the study protocol section 6.1.2 (secondary efficacy endpoints), the derivation of the time to 12-week confirmed disability accumulation (CDA), states that "for the purpose of confirmation, only EDSS measured more than 30 days after the onset of a confirmed relapse will be used.". Relapses with unspecified end date are considered resolved at 90 days post onset. SAP Section 5.4.2.1 clarifies that the cutoff used will be 90 days rather than 30 days in line with this definition.
- The study protocol states that the mean number of combined unique active lesions (CUALs) and T2 lesions will be estimated per subject per scan, from negative binomial models including the log of the number of scans as an offset variable. However, the number of T2 lesions is expected to increase with observation time, and as the premature EOT magnetic resonance imaging (MRI) scan can occur at any time, 'number of MRI scans' is not necessarily expected to be a good approximation of the observation time for T2. This also applies to CUALs as with MRI scans scheduled every 24 weeks, the CUAL count is expected to be mainly driven by new T2 lesions. Therefore, instead, the mean number of CUALs and T2 lesions will be estimated per subject per year, from negative binomial models including the log of time up to last MRI scan as an offset variable.

- The protocol defines the treatment-emergent period as up to 30 days following study drug discontinuation. This is updated in this SAP to up to 15 days following study drug discontinuation, in-line with the approach used for analysis across the ponesimod MS program.
- The protocol states that "All safety data will be included in listings, with flags for safety data not considered to be treatment-emergent.". This approach will be reversed, i.e. the flags will be applied to treatment-emergent data points.
- The protocol states that "The lymphocyte count reversibility after EOT will be summarized by plotting the mean (and 95% CIs) change from baseline to EOT and change from baseline to EOS by treatment. A scatter plot will display the change from baseline to EOS versus the change from baseline to EOT on an individual subject level by study treatment.". This analysis will not be performed as the change from EOT does not consider the relationship to baseline and can therefore be misleading.

4.2 Changes in the conduct of the study / data collection

A total of 5 global protocol amendments were conducted. The main reasons are described below.

Protocol version 2, 4 December 2015: Main reason for the amendment was to address comments received after Special Protocol Assessment (SPA) review by the US FDA. The main changes were introduction of a standardized procedure for reporting and confirming relapses (relapse assessment questionnaire), clarification of the process for EDSS and functional system (FS) assessment, modifications and clarifications to the primary efficacy analysis and definitions associated with the primary endpoint, modification of the inclusion/exclusion criteria in the context of the SAP procedure, and clarification on the data review process by the IDMC during the study.

Protocol version 3, 9 March 2016: Main reason for the amendment was to add further clarification to address the comments received during the US FDA's review of the SPA.

Protocol version 4, 17 June 2016: Main reason for the amendment was to address the comments received during the Voluntary Harmonization Procedure review for this Clinical Trial Application in the EU. The main changes were the addition of a new section to describe the known and potential risks and benefits associated with the participation in the study, the introduction of the electronic self-rated version of the Columbia-Suicide Severity Rating Scale (eC-SSRS©) to monitor subjects for suicidal ideation or behavior during the study, the addition of further criteria to allow modification of treatment in case a subject experiences relapses/lack of efficacy during the study, and clarification that the hormonal methods of contraception are restricted to those which are associated with inhibition of ovulation. Additional changes were made to minimize the potential risks for subjects, to enhance subjects' safety monitoring, and to alleviate the burden on subjects and sites.

Protocol version 5, 8 December 2016: Main reason for the amendment is to clarify that subjects will be re-consented to continue receiving study drug if they meet one of the following conditions: completed at least 48 weeks of treatment in the study and has had at least one confirmed relapse which occurred after 12 or more weeks of treatment, experienced two confirmed relapses while on study treatment, or experienced an event of 24-week CDA while on study treatment.

Protocol version 6, 21 December 2017: Main reason for the amendment is to make changes to inclusion criteria 6, which is modified to include the presence of at least one new or one unequivocally enlarging T2 lesion on MRI on a pre-randomization scan as an alternative criterion of disease activity, and also to include the presence of T1 gadolinium enhancing (Gd+) lesions observed on the pre-randomization MRI scan as an alternative criterion of disease activity.

Additional local amendments were also created.

4.3 Clarifications concerning endpoint definitions and related variables or statistical methods

The following clarifications are applied:

- Mean number of CUALs up to EOS is given in the protocol as secondary efficacy endpoint. It is also listed as an exploratory MRI endpoint. It is clarified here that it is considered to be a secondary endpoint.
- The derivation of the 'HH' and 'HHH' ranges for hemoglobin marked abnormalities were changed to better clarify how to derive pre-treatment assessments and post-treatment assessments when baseline is ≤ upper limit of normal (ULN) [see Appendix C for details].

5 DEFINITIONS OF VARIABLES

This section provides the definitions and sources for all variables used in the analyses, including specifications for the derivations.

General recurrent definitions (e.g., study treatment start date, baseline, and EOS date) or unit conversions are described in Section 11.

5.1 Subject disposition

5.1.1 Screened subjects

A subject is considered screened if the subject has signed any informed consent (for the main study or the lymphocyte sub-study) and is assigned a subject number by the interactive response technology (IRT) provider. A screened subject is considered re-screened if a second screening visit date is documented in the electronic Case Report Form (eCRF). The same subject number is used in the case of re-screening.

5.1.2 Screening failures

A subject is considered a screening failure, if screened but not randomized into the study (as per the recording in the IRT system). Subjects screened more than once and subsequently randomized are not counted as screening failures.

The reason for not being randomized is documented on the randomization eCRF:

- Failure to meet randomization criteria ("Is subject eligible as per inclusion/exclusion criteria?" answered "No")

  OR

- "Subject withdrew consent" or "Other" (Reason provided following "Was the subject randomized?" answered with "No")

If a subject at a screening attempt is not randomized but no reason for not being randomized is reported, the reason is categorized as 'Unknown'. Two variables are derived to hold reason(s) for not being randomized:

- Reason for not being randomized at first attempt (not applicable [NAP], if subject randomized at first attempt; reason derived from first attempt, irrespective of existence and outcome of a second attempt)
- Reason for screening failure (NAP, if subject randomized; reason derived from first attempt if no second attempt, or from second attempt otherwise)

5.1.3 Subjects randomized

A subject is considered randomized if a randomization date and number are recorded in the IRT system.

5.1.4 Subjects treated

A subject is considered treated if they received at least one dose of study drug as documented in any study drug log eCRFs (see Section 5.3.1 for eCRFs involved).

5.1.5 Subject study treatment completion status

Due to the early termination of the study, no treatment completers as per protocol are expected as no subjects will have completed 156 weeks of treatment / 60 weeks of treatment following randomization of the last subject.

Subjects who complete study treatment up to study termination are defined as those meeting any of the following conditions:

- a record in the eCRF 'Maintenance Ponesimod/Placebo' form with reason for treatment end given as 'Completed as per protocol';
- reason 'Sponsor decision' with sub-reason 'Study termination' (for question 'Study treatment stopped due to') is reported on the eCRF form 'Premature Discontinuation of Study Treatment',
- the reason for treatment end is documented as 'Study Closure Announcement by Sponsor' on the eCRF 'Up-titration Ponesimod/Placebo' or 'Maintenance Ponesimod/ Placebo'.

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

- at least one reason ('Study treatment stopped due to') which is not 'Sponsor decision' with sub-reason 'Study termination' is reported on the eCRF form 'Premature Discontinuation of Study Treatment' and/or
- the reason for treatment end is documented as 'Premature Permanent Discontinuation' on the eCRF 'Up-titration Ponesimod/Placebo' or 'Maintenance Ponesimod/ Placebo'.

The date of treatment discontinuation is the last date study drug was taken [defined in Section 5.3.1.1]. In case of a (partially) missing discontinuation date, the date is imputed with the EOS date as defined in Section 5.1.6, or with the upper limit of the partial date if prior to EOS.

Reasons for premature discontinuation from study treatment are documented on the 'Premature Discontinuation of Study Treatment' eCRF with the following possible answers: 'Death', 'Lost to follow-up', 'Pre-specified study treatment discontinuation criteria', 'Subject decision' (further split into 'Adverse event', 'Lack of efficacy', 'No reason provided', or 'Other'), 'Physician decision' (further split into 'Adverse event', 'Lack of efficacy' or 'Other') or 'Sponsor decision' (sub-reason 'Other'). Whenever 'Other' is selected, free text can be provided in addition. Both recorded levels for treatment discontinuation (e.g., 'Subject decision' as well as 'Adverse event'), if pre-specified, are to be included in analyses, while any free text is not to be reported in tables, only listed. An additional category called 'Reason not provided' is defined for subjects where the reason is missing.

5.1.6 Subject study completion status

A subject is considered to have completed the study up to study termination if the corresponding entry on the 'Study Discontinuation' eCRF for question 'Study stopped due to' is answered with 'Sponsor decision' and corresponding specify field is answered with 'Study termination'. These subjects are considered to have completed study up to study termination.

All subjects not completing the study up to the early termination of the study as defined above are considered to have prematurely discontinued the study.

The EOS date is defined as the 'Date of Subject Decision' (if reason for study discontinuation was 'Subject Decision/Withdrawal of consent'), 'Date of Physician Decision' (if reason for study discontinuation was 'Physician Decision') collected on the 'Study Discontinuation' eCRF, or 'Date of recorded last study visit / assessment' (if reason for study discontinuation was 'Sponsor Decision'), unless a subject is lost to follow-up or dies, in which case 'Date of last successful contact' from the Study Discontinuation eCRF or 'Date of Death' from Death eCRF are used. If missing, the last recorded visit date (i.e., the latest assessment date within any visit) is considered as the EOS date.

For subjects prematurely discontinuing the study, reasons for premature discontinuation from study are: 'Death', 'Lost to follow-up', 'Subject decision/Withdrawal of consent' (further split into 'Adverse event', 'Lack of efficacy', 'No reason provided' and 'Other'), 'Physician decision' (further split into 'Adverse event', 'Lack of efficacy' and 'Other') or 'Sponsor decision' ('Other'). Whenever 'Other' is selected, free text can be provided in addition. An additional category 'Reason not provided' is defined for subjects where the reason is missing.

5.1.7 Time in study

Time in study (years) is derived as (EOS date − randomization date + 1 day) / 365.25.

Time in study (months) is derived as (EOS date − randomization date + 1 day) / 30.4375.

5.2 Subject characteristics

5.2.1 Demographics

The following demographic variables are derived:

- Sex, from the 'Demographics' eCRF (Male, Female)
- Age (years), from the 'Demographics' eCRF; if available, 'Age at re-screening' overwrites the initially entered 'Age'
- Age categories derived from the above as follows: < 18, 18–30, 31–40, 41–55, and ≥ 56 years. Age high-level categories: < 40, and ≥ 40. Age categories as per EudraCT requirement: < 12, 12–17, 18–64, 65–84, and ≥ 85
- Height (cm), from the 'Height & Body Weight' eCRF
- Weight (kg), from the 'Height & Body Weight' or from the 'Body Weight' eCRF:

The latest measurement available prior to study treatment start date is selected. If first intake is not documented, use the latest measurement available prior to randomization. If neither date is available (for screen failures), the latest weight assessment available is used.

- Body mass index (BMI; kg/m^2) derived as Weight (kg) / (Height (cm) / 100)^2
- BMI categories: < 18.5, ≥ 18.5 – < 25, ≥ 25 – < 30, and ≥ 30
- Race, from the 'Demographics' eCRF (Black or African American, American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, White, Other, and Not applicable)
- Ethnicity, from the 'Demographics' eCRF (Hispanic or Latino, Not Hispanic or Latino, and Unknown)
- Country based on site mapping performed on SDTM level
- Geographical region of site, countries are assigned to the following regions:
  - European Union (EU) + UK: Austria, Belgium, Bulgaria, Czech Republic, France, Germany, Greece, Hungary, Italy, Poland, Portugal, Spain, United Kingdom
  - Europe Non-EU + Russia: Russian Federation
  - North America: Canada, United States
  - Rest of World: Mexico

5.2.2 Baseline disease characteristics

Baseline characteristics variables are defined as follows:

Stratification variables from IRT

- **Baseline EDSS (from IRT)** (≤ 3.5, > 3.5) from the IRT system

Baseline disease characteristics variables from eCRF / non-IRT external data

- **Baseline EDSS score,** defined as the latest available EDSS score as entered in the EDSS/FS eCRF (i.e., not re-derived based on sub-scores) prior to or on the date of randomization
- **Baseline EDSS (from eCRF),** categorized as (≤ 3.5, > 3.5), derived from the baseline EDSS score
- **Time since first symptoms (years)**, defined as [Date of randomization – Date of first MS symptoms + 1] in days / 365.25. Taken from 'MS History – Disease Characteristics' eCRF at screening. Partial dates of first MS symptoms are imputed to the 1st day of the month (if the day is missing) and to the 1st of January (if the day and month are missing). No imputation is performed if the date is completely missing.
- **Time since initial diagnosis (years)**, defined as: [Date of randomization – Date of initial diagnosis + 1] in days / 365.25. Taken from 'MS History – Disease Characteristics' eCRF at screening. Partial dates of initial diagnosis are imputed to the maximum of [Date of first MS symptoms, 1st day of the month] (if the day is missing) and to the maximum of [Date of first MS symptoms, 1st of January] (if the day and month are missing). No imputation is performed if the date is completely missing.
- **MS subtype** (RRMS / SPMS), relapsing-remitting multiple sclerosis [RRMS], secondary progressive multiple sclerosis [SPMS] with superimposed relapses. Taken from 'MS History – Disease Characteristics' eCRF at screening; subtype at re-screening overwrites the initially entered subtype.
- **Time since most recent relapse (months) at screening**, defined as [Date of screening – Onset date of latest MS relapse prior to screening + 1] in days / 30.4375. From eCRF form 'MS History - Relapse' at screening. Take the most recent "Onset date of previous relapse" among all previous relapses entered on the 'MS History - Relapse' eCRF. Partial onset dates are imputed to the maximum of [Date of first MS symptoms, 1st day of the month] (if the day is missing) and to the maximum of [Date of first MS symptoms, 1st of January] (if the day and month are missing). Data collected at re-screening overwrites the initially entered data.
- **Number of relapses in the year prior to study entry**, as reported in the corresponding question on the 'MS History - Relapse' eCRF (i.e., not based on recorded onset dates of previous relapses). Data collected at re-screening overwrites the initially entered data.
- **Number of relapses in the 2 years prior to study entry** as reported in the corresponding question on the 'MS History - Relapse' eCRF (i.e., not based on recorded onset dates of previous relapses). Data collected at re-screening overwrites the initially entered data.
- **Prior MS treatment other than DMF (yes/no)** ('yes' if any MS treatment recorded on then 'MS Specific Treatment History' eCRF form or as prior concomitant medications on the

'Study-concomitant therapy - Disease-modifying treatment for MS' eCRF; otherwise 'no' if no such medications are recorded).

- **Months on DMF at screening** defined as [Date of screening – DMF start date] in days / 30.4375. DMF start date is defined as the earliest DMF start date documented in the Drug Log – DMF eCRF. In case of partially missing DMF start date, the start date is imputed to the latest possible date, see Section 12.1.1 for full details.
- **Relapses in the previous 6 months prior to study entry while on treatment with DMF (0, 1, ≥ 2)** number of relapses recorded in the 6 months prior to date of screening based on recorded onset dates of previous relapses ('MS History – Relapse' eCRF form) and recorded start/end dates of DMF treatment.
- **Presence of T1 Gd+ lesions (yes/no) in the previous 12 months prior to study**, as provided by sites (yes/no) - ('MS history - MRI' eCRF form).
- **Presence of T1 Gd+ lesions (yes/no)** on baseline MRI scan as provided by the MRI central reading.
- **Number of documented T1 Gd+ lesions** on baseline MRI scan as provided by the MRI central reading.
- **Presence of new or enlarging T2 (yes/no) in the previous 12 months prior to study**, as provided by sites (yes/no) - ('MS history - MRI' eCRF form).
- **Volume of T2 lesions** on baseline MRI scan as provided by the MRI central reading.
- **Smoking status** (Current smoker, Former smoker, Never smoked), taken from 'Smoking status' eCRF.

Note: *For re-screened subjects, information for baseline characteristics 'at screening' is taken from the last Re-screening Visit, if available, instead of the Screening Visit.*

Handling of missing/partial dates: In case of partial dates for required dates (MS symptoms, initial diagnosis, latest MS relapse prior to Screening), the lower limit is used in derivations. Missing dates are not replaced; the corresponding variable is considered missing.

5.2.3 Previous and concomitant therapies

Therapies are collected in the following CRF pages: 'Previous Medications', 'Concomitant Medications', 'Interferon beta-1a history', 'Interferon beta-1b history', 'Glatiramer acetate history', 'Natalizumab history', 'Mitoxantrone history', 'Alemtuzumab concentrate history', 'Teriflunomide history', 'Daclizumab history', 'Ocrelizumab history', 'Cladribine history', 'Other MS Specific Treatment History', 'Study-concomitant therapy - Disease-modifying treatment for MS', 'Corticosteroids for Treatment of Relapse'.

Terms are coded using the World Health Organization (WHO) drug code dictionary (WHODRUG) and the anatomic therapeutic chemical (ATC) class code (version dated 1 March 2018 or later).

Handling of partial or missing start and end dates is detailed in Section 12.1.

5.2.3.1 Previous therapies

Previous therapies are therapies that were started and stopped prior to study treatment start date.

5.2.3.2 Treatment concomitant therapies

Includes all therapies that have been taken after study treatment start date up to EOT (last drug intake) + 15 days. This includes therapies ongoing at study start, as well as therapies starting after study treatment start date.

Handling of partial or missing start and end dates is detailed in Section 12.1.

5.2.3.3 Therapies starting after EOT

Includes all therapies that have been started after EOT (last drug intake). This includes therapies with start date from EOT + 1 day onwards.

Handling of partial or missing start and end dates is detailed in Section 12.1. Therapies with missing start date will be considered to have started on treatment.

5.3 Exposure and compliance

5.3.1 Study treatment exposure and compliance

Exposure and compliance with ponesimod / placebo information will be taken from the Study Drug Log eCRFs:

- **Up-titration Summary Ponesimod/Placebo eCRF** (collects information on up-titrations conducted as planned as per protocol, recording start and end date of up-titration);
- **Up-titration Ponesimod/Placebo eCRF** (collects information on up-titration if not conducted as planned as per protocol, separately for up-titration tablets on daily basis);
- **Maintenance Ponesimod/Placebo eCRF** (collects information on maintenance study drug intake based on maintenance tablets).

To derive the study treatment start date and time, in addition information collected on Study drug administration eCRFs ('Study Drug Administration - Day 1/Re-initiation', 'Study Drug Administration') is considered.

In addition, subjects filled an electronic study treatment diary (eDiary). Sites were instructed to review the entries in the subject study treatment diary versus the protocol-mandated drug intake regimen and versus the number of tablets dispensed and returned. Any discrepancy was to be clarified during the site visits, and actual drug intake was to be recorded in the eCRF, hence the

information from the eCRF is considered to be the most reliable, and all exposure derivations including derivation of EOT date are only based on eCRF data.

5.3.1.1 Study treatment exposure

Study treatment start date is defined as the earliest study drug start date documented in the study drug administration or study drug log eCRF pages, as listed above.

The time of study treatment start (time of first exposure to treatment) is taken from the study drug administration eCRF, where the date is equal to the study treatment start date, if available.

The EOT date is defined as the latest study treatment end date, as recorded on the Study Drug Log eCRFs listed above.

The following exposure variables are derived:

Duration of Study Treatment (days) = EOT date - Study treatment start date + 1 day. Duration of Study Treatment is also derived in weeks (days divided by 7), months (days divided by 30.4375), and years (days divided by 365.25).

Duration of Study Treatment is categorized as follows: ≤ 24 weeks (168 days), > 24 weeks to ≤ 48 weeks (336 days), > 48 weeks to ≤ 72 weeks (504 days), > 72 weeks to ≤ 96 weeks (672 days), > 96 weeks to ≤ 120 weeks (840 days), > 120 weeks to ≤ 144 weeks (1008 days), > 144 weeks (1008 days).

'**Study treatment exposure, interruptions excluded**' equals the 'Number of days with intake documented' for a subject overall as defined as part of the compliance derivations described in Section 5.3.1.2.1.

5.3.1.2 Compliance with study treatment

5.3.1.2.1 Compliance as percentage of days on study drug

Compliance is assessed as the percentage of days from the date of first intake until EOT with study drug intake documented in the eCRF:

$$\frac{\text{no. of days with intake documented}}{(\text{date of EOT-study treatment start date}) + 1\ \text{day}} \times 100$$

Note: Compliance below 100% is not necessarily indicative of a deviation from the protocol since the protocol mandates dose interruptions for certain very specific safety scenarios as well as based on investigator's judgment.

For reporting, the calculated compliance is categorized as follows: 100%, 99% – < 100%, 80% –< 99%, 50% – < 80%, > 0% – < 50%, 0%.

The number of days with study drug intake documented is derived as follows:

During up-titration period

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

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

For all other subjects, information is collected on the 'Up-titration Ponesimod/Placebo' eCRF, 'Treatment start date' resulting in potentially multiple records of up-titration drug intake (collecting in addition 'number of tablets taken'). In that case 'Number of days with intake documented' for each record is derived in the same way as during the maintenance period but based on the dose form with active drug only.

During maintenance period

As per protocol, one tablet of study drug is to be taken per day. On the 'Maintenance Ponesimod/Placebo' eCRF log form, each record collects 'Treatment start date', 'Treatment end date', and 'Number of tablets taken'. If, for a record, the 'Number of tablets taken' is ≤ 'Treatment end date' − 'Treatment start date' + 1, it is assumed that the 'Number of tablets taken' represents the 'Number of days with intake documented' during that record's period of study drug intake. If, for a record, the 'Number of tablets taken' is > 'Treatment end date' − 'Treatment start date' + 1, 'Number of days with intake documented' is set to 'Treatment end date' − 'Treatment start date' + 1 for the compliance calculation. These subjects are flagged as having taken > 1 tablet per day on at least one occasion.

The 'Number of days with intake documented' for a subject overall is derived as the sum across all study drug log records (sum across up-titration, or maintenance records; multiple periods of study drug intake during up-titration or maintenance are possible, e.g., due to interruptions, or detailed up-titration eCRF filled).

The following deviations from the protocol-intended study drug maintenance are identified from the 'Maintenance Ponesimod/Placebo' eCRF log form and flagged on a subject basis:

- More than 1 tablet of study drug taken per day on at least one occasion (derivation see above);
- At least one occasion of treatment interruption of more than 3 days documented, but maintenance treatment resumed or started without up-titration. This includes occasions when maintenance treatment started more than 4 days after the day up-titrations stopped.

5.3.2 Study treatment adjustments or interruptions

Study-specific criteria for interruption and discontinuation of study treatment were pre-specified in the protocol section 5.1.12. The protocol did not allow any study treatment dose adjustments.

Study treatment interruptions are assessed via the compliance variables described in Section 5.3.1.2 and the assessment AEs leading to changes in study treatment as described in Section 5.5.5.

Subjects with at least one interruption: Derived as subjects with 'Study treatment exposure, interruptions excluded' < 'Duration of Study Treatment', based on the definitions in Section 5.3.1.1.

Total duration of interruption(s) (days) is derived as 'Duration of Study Treatment'−'Study treatment exposure, interruptions excluded'.

5.3.3 DMF exposure and compliance

Exposure and compliance with DMF information will be taken from the Drug Log - DMF (Tecfidera) eCRF (collects information on DMF start date, end date, dose, frequency and reason for treatment end). All DMF dose changes, interruptions and discontinuations are to be reported here.

5.3.3.1 DMF exposure during study treatment

The on-study DMF start date is defined as:

- the study treatment start date (as defined in Section 5.3.1.1) for subjects who were receiving DMF on study treatment start date, as documented in the Drug Log – DMF eCRF;
- the earliest DMF start date documented in the Drug Log – DMF eCRF that is after the study treatment start date, for subjects who were not DMF on study treatment start date, as documented in the Drug Log – DMF eCRF.

The DMF end date is defined as latest DMF end date documented in the Drug Log – DMF eCRF. If the end date of the DMF record with the latest start date is missing, DMF is assumed to be ongoing at study treatment EOT and the DMF end date is imputed with study treatment EOT.

The following exposure variables are derived:

Duration of DMF treatment on study (days) = DMF end date – on-study DMF start date + 1 day. Duration of DMF Treatment on study is also derived in weeks (days divided by 7), months (days divided by 30.4375), and years (days divided by 365.25).

Duration of DMF Treatment on study is categorized as follows: ≤ 24 weeks (168 days), > 24 weeks to ≤ 48 weeks (336 days), > 48 weeks to ≤ 72 weeks (504 days), > 72 weeks to ≤ 96 weeks (672 days), > 96 weeks to ≤ 120 weeks (840 days), > 120 weeks to ≤ 144 weeks (1008 days), > 144 weeks (1008 days).

'DMF treatment exposure, interruptions excluded' equals the 'Number of days with DMF intake documented' between study treatment start date and study drug EOT for a subject overall as defined as part of the compliance derivations described in Section 5.3.3.2

5.3.3.2 Compliance with DMF treatment during study treatment

Compliance is assessed as the percentage of days from the date of first study drug intake until EOT with DMF intake documented in the eCRF:

$$\frac{\text{no. of days with DMF intake documented}}{(\text{date of EOT-study treatment start date}) + 1\text{ day}} \times 100$$

Note: Compliance below 100% is not necessarily indicative of a deviation from the protocol since the protocol mandates dose interruptions for certain very specific safety scenarios as well as based on investigator's judgment.

For reporting, the calculated compliance is categorized as follows: 100%, 99% – < 100%, 80% –< 99%, 50% – < 80%, > 0% – < 50%, 0%.

The number of days with DMF intake documented is derived as follows:

On the 'Drug Log - DMF' eCRF log form, each record collects 'DMF start date', 'DMF end date', and 'Individual dose'. If, for a record, the 'Individual dose' is > 0, it is assumed that the subject took DMF for each day covered by the record. For each record, the start date is defined to be the maximum of (DMF start date associated with the record, study treatment start date), and the end date is defined to be the minimum of (DMF end date associated with the record, EOT date).

The 'Number of days with DMF intake documented' for a subject overall is derived as the sum across all DMF drug log records.

5.4 Efficacy variables

5.4.1 Primary efficacy variable(s): ARR up to EOS

The primary endpoint is the Annualized Relapse Rate (ARR) up to EOS, based on confirmed relapses according to the treating neurologist / principal investigator. ARR is defined as the number of confirmed relapses per subject-year.

A confirmed relapse is defined as a record with 'Relapse meeting the criteria for a confirmed relapse?' answered 'Yes' on the 'Relapse Summary' eCRF. All confirmed relapses from randomization up to EOS will be included in the analysis.

For the statistical analysis of ARR, the following data will be used:

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

The logarithm of the length of observation up to EOS will be used as an offset variable in the primary efficacy and sensitivity analyses.

Confirmed relapses 'from date of randomization up to EOS date' includes all confirmed relapses unless starting prior to randomization.

5.4.1.1 General derivation details for relapses

A relapse (confirmed or unconfirmed) is identified from the 'Relapse Summary' eCRF with 'Did the subject experience a relapse' ticked as 'Yes'. For each relapse the corresponding start and end date/time, as well as outcome, treatment with corticosteroids, action taken with study drug and need for hospitalization, and whether an EDSS was completed are recorded. For relapses with completed EDSS it is collected whether it qualifies as a confirmed relapse (see definition details for primary efficacy variable above). A relapse which is not a confirmed relapse is considered an 'unconfirmed relapse'.

Relapses 'from date of randomization up to EOS date' include all relapses unless starting prior to randomization.

Note: Relapses with missing start date are considered to have started on randomization date for analysis. Relapses with partial start date are considered to have started at the lower limit (but earliest on randomization date).

5.4.1.2 Variables for supplementary analyses of primary endpoint

5.4.1.2.1 ARR up to EOS for all relapses

The variable considers all relapses (confirmed and unconfirmed) up to EOS:

- The subject's number of all relapses from date of randomization up to date of EOS;
- Length of observation expressed in years, defined as: [EOS date − date of randomization + 1] in days, divided by 365.25.

5.4.2 Secondary efficacy variables

5.4.2.1 Time to 12-week confirmed disability accumulation (CDA) up to EOS

Time to first 12-week CDA is defined as the time from start date of the first onset of 12-week CDA minus date of randomization + 1 in days. Subjects without 12-week CDA are censored, following the rules below. It is assessed from baseline up to EOS.

Assessing disability by EDSS

Disability as measured by EDSS is assessed in all subjects at screening, baseline, and thereafter at scheduled visits every 12 weeks until the end of study. Additional EDSS assessments for individual patients may be conducted between scheduled visits (i.e., during an MS relapse). The EDSS is a disability scale that ranges from 0 (normal) to 10.0 (death) in 0.5-point steps (1-point step from 0 to 1). It is based on standard neurological examination in conjunction with observations concerning ambulation. For analysis the overall EDSS score as reported by the investigator from the eCRF is considered (Field: 'Expanded disability status scale').

EDSS increase criteria for disability accumulation

The following criteria for an increase in EDSS in derivation of disability accumulation apply:

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

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

12-week CDA

A 12-week CDA is an increase in EDSS as compared to baseline according to the criteria above which is confirmed at a scheduled visit after 12 weeks. The increase needs to be persistent at all EDSS assessments (scheduled or unscheduled) between onset (first EDSS increase in the considered period) and confirmation. 12-week CDA is assessed sequentially up to the last available EDSS assessment for a subject in the study following the algorithm detailed below.

Disability progression can only be confirmed at a scheduled visit, where the EOT (Up to Week 156 or earlier or premature EOT visit), and FU visits count as scheduled visits, outside of an ongoing relapse. In this context, relapse duration is defined as period between start date (inclusive) and end date (exclusive) if available and limited to 90 days from onset if end date is not available or duration is longer than 90 days.

Algorithm for deriving 12-week CDA

1. For all post-baseline EDSS assessments (scheduled or unscheduled) assess if the absolute change from baseline meets the EDSS increase criteria for disability accumulation, described above. Start with the first EDSS assessment that meets the criteria for EDSS increase. Onset date of the corresponding potential 12-week CDA is the EDSS assessment date.
2. Confirmation of EDSS increase:
    a. An EDSS increase of a potential 12-week CDA has to be confirmed by an EDSS increase at a scheduled visit, at least 70 days*, from the onset date of the potential 12-week CDA.

        * Note: As visits are scheduled every 12 weeks with a time window of ± 7 days for conducting the EDSS assessment, the minimum per-protocol allowed time difference between two EDSS assessments scheduled 12 weeks apart is 70 days (12 weeks = 84 days minus a 7-day visit time window for each of the 2 visits, i.e., 84 days − 14 days = 70 days).

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

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

b. A confirmed EDSS increase as per (a) is considered persistent if every EDSS score available (scheduled or unscheduled) between the onset and the confirmation date of a potential 12-week CDA meets the EDSS increase criteria. The initial EDSS increase is considered a 12-week CDA.

   If any EDSS from onset to confirmation does not meet the EDSS increase criteria, the increase is not persistent and the initial EDSS increase is not considered a 12-week CDA.

3. Repeat step 2 for all EDSS assessments with an EDSS increase as per the criteria above for disability accumulation, starting with the first possible onset, by date, up to the last possible onset. Once a 12-week CDA is identified the algorithm can stop.
4. If at none of the assessments a 12-week CDA is identified, but the subject dies due to MS (experiences a relapse with outcome death) the subject is considered to have a 12-week CDA with onset date being the death date.
5. If no 12-week CDA is identified, the subject is considered censored with the censoring date derived according to the rules below.

Censoring

Censoring date is defined as: Date of last EDSS assessment without an EDSS increase. Time to censoring is defined as censoring date minus date of randomization + 1.

Subjects without post-baseline assessment are censored on randomization date. Similar, subjects without CDA who have only EDSS assessments with an EDSS increase that cannot be confirmed, are censored on randomization date. For subjects without baseline EDSS score, missing values are assigned.

Handling of missing dates

Missing dates for EDSS assessments will be imputed as follows:

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

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

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

5.4.2.2 Time to first confirmed relapse

The time to first confirmed relapse (in days) is defined as [Date of first confirmed relapse − Date of randomization + 1] in days.

Subjects without any confirmed relapses will be censored at the EOS date, and the time is defined as [Date of EOS − Date of randomization + 1] in days.

Derivation of confirmed relapses from randomization up to EOS is detailed in Section 5.4.1. Among these confirmed relapses, the earliest relapse start date is the 'Date of first confirmed relapse'. For analysis the variable is displayed in weeks: variables in days divided by 7.

5.4.2.3 Number of combined unique active lesions (CUAL) up to EOS

The cumulative number of CUAL from baseline to EOS is calculated as the sum of new T1 Gd+ lesions and new or enlarging T2 lesions without Gd enhancement on T1 at all post-baseline MRI visits up to EOS.

MRI scans are scheduled at Baseline, and every 24 weeks thereafter, i.e., at the visits at Week 24, Week 48, Week 72, Week 96, Week 120, Week 144 Visit and at the EOT visit. For subjects who prematurely discontinue treatment, an additional premature EOT visit MRI is scheduled. Unscheduled MRI scans may be conducted in addition.

MRI data are read centrally and provided to the sponsor.

To account for varying observation time, e.g., in case of premature study withdrawal or missing MRI assessments, the analysis will be adjusted by: Time up to the last MRI (years) = (Date of last MRI considered in derivation of CUAL − Randomization date + 1) / 365.25 days.

Rationale: Due to the fact that MRI scans are scheduled every 24 weeks, the CUAL count is expected to be mainly driven by new T2 lesions. The number of T2 lesions is expected to increase with observation time. In contrast, in studies where MRI scans are scheduled more regularly, the CUAL count is mainly driven by new T1 Gd+ lesions which are expected to increase with the 'Number of MRI scans' conducted. Also, in this study, there is an additional MRI following premature treatment discontinuation which can occur at any time, and which does not occur per

the planned schedule for any subjects and so the 'number of MRI scans' is not necessarily expected to be a good approximation of the observation time.

5.4.2.3.1 Derivation details

The central reader provides the 'Number of new T1 Gd+ enhancing lesions' (variable T1GdNew_R) and 'Number of new T2 lesions without Gd enhancement' (variable T2New_R) at a visit as compared to the last scheduled MRI scan (with premature EOT visit being considered a scheduled MRI). At the first scheduled post-baseline visit comparison is made to baseline (with baseline defined as the Baseline Visit 2, or Visit 2 - 2nd attempt if available [see Section 5.4.3] for details and a rationale).

Cumulative CUAL from baseline to EOS is derived as the sum of 'Number of new T1 Gd+ enhancing lesions' and 'Number of new T2 lesions without Gd enhancement on T1' across all post-baseline MRI visits up to up to EOS irrespective of whether a visit is conducted during PTOP or not.

As only the number of new lesions as compared to the last scheduled visit is recorded by the central reader, lesions are not expected to be double counted when summing over scheduled visits.

In the rare event that the baseline MRI visit is conducted after randomization date, the variable is derived in the same way, i.e., based on the nominal visit. Note that effectively the derived variable then covers a period starting slightly after randomization. If the baseline MRI is missing, new or enlarging T2 lesions as compared to baseline cannot be assessed and consequently the endpoint is considered missing. The baseline MRI is considered missing if presence of T1 Gd+ lesions at baseline is missing.

For subjects with at least one unscheduled post-baseline MRI scan, care needs to be taken in the derivation to avoid double counting of lesions and the following algorithm applies:

- If a subject has an unscheduled MRI which is the last available MRI in the time period considered: Include that last unscheduled MRI when deriving CUAL in the same way as for scheduled visits.
- If a subject has an unscheduled MRI which is not the last available MRI for the subject: Do not include that unscheduled MRI. Rationale: New / enlarging lesions at the unscheduled MRI as well as at the later scheduled MRI are reported in reference to the previous scheduled visit. Including both may result in double counting.

5.4.3 Exploratory MRI efficacy variables

MRI data are provided from a central reader.

Baseline

The central reader defines the result from 'Visit 2 - Baseline' as baseline (or 'Visit 2a - Baseline 2nd attempt' if available) and uses that Baseline visit as a reference in derivations of various variables (e.g., new or enlarging T2 lesions).

For analysis, baseline for MRI variables is defined in the same way, i.e., Visit 2 unless Visit 2a is available. In the unexpected case a Visit 2 scan is conducted after randomization, it is still considered as baseline.

MRI at post-baseline scheduled visits - visit windowing

MRI variables at scheduled visits are based on the result from the corresponding nominal visit (or from a re-mapped premature EOT visit [see Section 11.3]). In case of missing results, MRI results from an unscheduled visit can be re-mapped to a scheduled visit if conducted during the time window specified in Section 11.3. Care needs to be taken however in derivation of cumulative variables where occasionally unscheduled MRIs are not included, as per the respective derivation details.

5.4.3.1 Number of CUALs

The cumulative number of CUALs from baseline to Week 24, Week 48, Week 72, Week 96 and EOT is derived in the same way as for CUAL from baseline to EOS [see Section 5.4.2.3], but only including MRI scans up to the applicable MRI visit (if missing, up to remapped equivalent) as applicable.

Note that if an unscheduled MRI becomes the last available MRI in the considered time period it is to be included in deriving the sum of lesions.

5.4.3.2 Number of T1 Gd+ lesions

The **number of T1 Gd+ lesions per visit** is derived as the sum of 'number of new T1 Gad.-enhancing lesions' (T1GdNew_R) + 'number of persisting T1 Gad.-enhancing lesions' (T1Gd_R) as provided by the central reader at that visit.

Handling of missing MRI results at scheduled visits follows the general rules for MRI data described in Section 5.4.3 above.

The **cumulative number of new T1 Gd+ lesions from baseline to Week 48** is derived as the sum of number of **new** T1 Gd+ lesions at all post-baseline MRI scans up to the Week 48 MRI visit. This includes premature EOT scans if available. It may include unscheduled scans if it is the last available scan, following selection of unscheduled MRIs as per derivation of CUAL [Section 5.4.2.3]. To account for a potentially varying number of scans contributing to the variable, the analysis will be adjusted by the 'Number of MRI scans' included in the derivation.

Note: The number of T1 Gd+ lesions at baseline is taken from the variable 'Number of T1 Gad.-enhancing lesions at V2 – Baseline/Number of persisting T1 Gad.-enhancing lesions' (T1Gd_R). At baseline new T1 Gd+ lesions are not available, thus no corresponding record is expected.

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

- *If at a visit, number of persisting T1 Gd+ lesions are not recorded, the number of Gd+T1 lesions is the number of new T1 Gd+ lesions. Rationale: As per central reader processes*

persisting T1 Gd+ lesions are not assessed for subjects with scheduled MRIs scheduled more than 12 weeks apart (i.e., MRIs are scheduled every 24 weeks).

- *If at a MRI scan which is > 12 weeks (84 days) since the last previous scheduled MRI scan a persisting lesion count > 0 is recorded, these persisting lesions are considered implausible and therefore not to be considered in derivations of total T1 Gd+ counts.*

The cumulative number of new T1 Gd+ lesions from baseline will also be derived in the same way as described above for cumulative up to Week 48 for the following timepoints: Week 24, Week 72, Week 96, and EOT and EOS.

5.4.3.3 Number of new or enlarging T2 lesions

New or enlarging T2 lesions as compared to the previous scheduled visit are recorded by the external reader in two distinct categories: 'Number of new or enlarging T2 lesions without Gad. enhancement on T1' (T2New_R) and 'Number of new or enlarging T2 lesions with Gad. enhancement on T1' (T2NewGd_R) at a visit as compared to the previous scheduled visit. The sum of both is the 'number of new or enlarging T2 lesions' at that visit compared to the previous scheduled visit. For subjects with missing baseline MRI, the number of new or enlarging T2 lesions from baseline cannot be assessed and the endpoint is considered missing. The baseline MRI is considered missing if presence of T1 Gd+ lesions at baseline is missing.

The cumulative number of new or enlarging T2 lesions from baseline to Week 24, Week 48, Week 72, Week 96, EOT and EOS is calculated as the sum of lesions at all post-baseline MRI visits up to the applicable MRI visit.

The cumulative number of new or enlarging T2 lesions from baseline up to the applicable MRI visit is derived as the sum of the 'number of new or enlarging T2 lesions' at all scheduled post-baseline MRI visits, including premature EOT visit if applicable (irrespectively if a visit is conducted during PTOP or not), for subjects with only scheduled post-baseline MRI scans.

For subjects with at least one unscheduled post-baseline MRI scan, care needs to be taken in the derivation to avoid double counting of lesions and the following algorithm applies:

– If a subject has an unscheduled MRI which is the last available MRI in the time period considered: Include that last unscheduled MRI when summing over 'number of new or enlarging T2 lesions' in the same way as the scheduled visits.
– If a subject has an unscheduled MRI which is not the last available MRI for the subject in the time period considered: Do not include that unscheduled MRI. Rationale: New / enlarging lesions at the unscheduled MRI as well as at the later scheduled MRI are reported in reference to the previous scheduled visit. Including both would result in double counting.

To account for varying observation time the analysis will be adjusted by: Time up to the last MRI (years) = Date of last MRI considered in derivation − Randomization date + 1 divided by 365.25 days.

Rationale: The number of T2 lesions is expected to increase with observation time, not solely by the 'Number of MRI scans'. Therefore, adjustment by observation time is conducted. As in this study an additional MRI following premature treatment discontinuation is scheduled, the 'number of MRI scans' is not necessarily expected to be a good approximation of the observation time.

5.4.4 Other clinical efficacy variables

5.4.4.1 Time to 24-week CDA

The derivation of the variables for Time to 24-week CDA up to EOS follows the same approach as described in Section 5.4.2.1, but onset of progression is to be confirmed after 24 weeks (≥ 154 days, i.e., 168 days − two times 7-day visit time window) instead of after 12 weeks. The progression has to be persistent between onset and confirmation.

5.4.4.2 Change in EDSS from baseline by visit up to EOS

Absolute changes from baseline in EDSS score by visit are derived, based on the overall EDSS score as reported by the investigator in the eCRF. For subjects prematurely discontinuing treatment, results collected during PTOP are considered at the corresponding nominal visit in the same way as for subjects completing treatment as planned (e.g., by visit analysis at Week 24, considers both 'Week 24' and 'PTOP Week 24' visits). Baseline EDSS is defined as in Section 5.4.2.1.

On-treatment EDSS assessments will be flagged, i.e., EDSS assessments performed after study treatment start (date/time) and prior to EOT + 7 days.

5.5 Safety variables

5.5.1 Definition of treatment-emergent, baseline and change-from-baseline, last on treatment, follow-up assessments for safety variables

For all safety data analyses described in this SAP, baseline is considered to be the last valid assessment prior to first study drug intake. Assessments at Visit 1 (Screening) and Visit 2 (Baseline), with date on or prior to the date of first intake of study treatment, and with no time collected, are considered eligible for baseline.

For each individual safety variable, baseline is defined to be the last valid measurement available before the date and time of first dose intake of study treatment, unless otherwise specified. On days where study drug is initiated or re-initiated, the pre-dose assessment for that day is defined as the last non-missing assessment prior to the study drug intake on that day. The pre-dose assessment on Day 1 (if available) is identical to baseline; however, missing pre-dose data on Day 1 is not imputed with baseline. In case of (partially) missing assessment dates/times, or for assessments reported on Day 1 (or day of re-initiation) with recorded assessment time contradicting the timepoint label (e.g., pre-dose, 2 hours post-dose), the nominal visit and timepoint labels will be used to determine whether an assessment is considered for baseline (for example a blood pressure measurement with an assessment date on Day 1 but with a missing assessment time or an assessment time prior to the reported time of first study drug intake, will not be considered for

baseline if reported under the timepoint "2 hours post-dose" in the eCRF, however it will be considered if reported as "Pre-dose" in the eCRF).

Absolute changes from baseline are defined as post-baseline value minus baseline value, i.e., a positive sign indicates an increase compared to baseline.

A percentage change from baseline is defined as the absolute change from baseline divided by the baseline value (if the baseline value is > 0) and then multiplied by 100.

Absolute and percent change from baseline is calculated and stored for all continuous safety data.

In addition, the following assessments are flagged or derived per parameter:

- Last on-treatment assessment: Last assessment prior to or on EOT date +1 day (last on treatment may come from a scheduled or an unscheduled visit)
- Day-30 follow-up, between EOT + 16 days and EOT + 37 days [see Section 11.4]

A safety assessment (ECG, vital signs, laboratory) is considered treatment-emergent, if the assessment date is on or after the study treatment start date and prior to or on the study treatment end date + 15 days (inclusive). If both, the assessment date/time and the date/time of study treatment start are available, only events with date/time on or after the date/time of study treatment start are considered to be treatment-emergent. In case of (partially) missing assessment dates/times, or for assessments on treatment Day 1 with reported assessment time contradicting the timepoint label, the nominal visit and timepoint labels will be used to determine whether an assessment is considered as treatment-emergent or not. For example, a blood pressure measurement with an assessment date on Day 1 but a missing assessment time or an assessment time after the time of first study drug intake, will not be considered treatment-emergent if reported under the timepoint "Pre-dose" in the eCRF, however it will be considered if reported as "2 hours post-dose" in the eCRF.

A safety event (AE, serious AE [SAE], Death) is considered treatment-emergent if the onset date/date of occurrence is on or after the study treatment start date and prior to or on the EOT date + 15 days (inclusive). Missing or partially missing onset or occurrence dates are imputed as described in Section 12.3. If both the onset/occurrence date/time and the date/time of study treatment start are available, only events with date/time on or after the date/time of study treatment start are considered to be treatment-emergent.

5.5.2 Adverse events

An AE is any event reported by the investigator on the Adverse Event eCRF of the main database or the first dose database. All AEs are coded using MedDRA dictionary (version 21.0).

5.5.2.1 Frequency and prevalence of adverse events

AEs are summarized according to both frequency and prevalence and based on various grouping terms (for example MedDRA preferred term [PT], or MedDRA primary system organ class[SOC]).

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

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

5.5.2.2 Intensity of adverse events

For AEs reported more than once for a subject, only the worst outcome is considered. AEs with missing severity assessment are imputed to be of 'severe' intensity.

5.5.2.3 Relationship of adverse events to study treatment

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

5.5.2.4 Relationship of adverse events to DMF

Relationship to DMF is entered into the database as 'related' or 'not related'. For AEs reported more than once for a subject, only the worst relationship is considered (i.e., 'related'). AEs with missing relationship are considered to be related.

5.5.2.5 Fatal adverse events

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

5.5.3 Deaths

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

5.5.4 Serious adverse events

An AE is considered serious if the question 'Serious?' on the Adverse Event eCRF is answered with 'Yes'. AEs with seriousness criteria missing are considered to be SAEs.

5.5.5 Adverse events leading to discontinuation of study treatment

AEs leading to discontinuation of study treatment are those with 'Action taken with study drug' reported as 'Permanently discontinued'.

5.5.6 Adverse events leading to temporary interruption of study treatment

AEs leading to temporary interruption of study treatment are those with 'Action taken with study drug' reported as 'Temporarily interrupted'.

5.5.7 Adverse events leading to hospitalization

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

5.5.8 Adverse events on Day 1 and Day 1 of re-initiation of study treatment

Treatment-emergent AEs on Day 1 of study treatment are those AEs that start on or after study treatment start (on Day 1), by time and date, and before the following calendar date.

Treatment-emergent AEs on Day 1 of re-initiation of study treatment are those AEs that start on the date of a study treatment re-initiation.

Note: AEs in the first dose database with a different onset date than the first study drug intake or Day 1 of re-initiation of study treatment are not considered as 'Day 1' / 'Day 1 of re-initiation of study treatment' events.

5.5.9 Other significant adverse events

5.5.9.1 Adverse events of special interest

Adverse events of special interest (AESI) include the anticipated risks of treatment with study drug and events that may be related to MS comorbidities. The following safety areas are addressed by the pre-defined AESI, detailed definition is given in Appendix A:

- Effect on heart rate and rhythm AESI (including hypotension)
- Hypertension AESI
- Hepatobiliary disorders / Liver enzyme abnormality AESI
- Pulmonary AESI
- Macular edema AESI
- Infection AESI
- Herpetic infection AESI
- Skin malignancy AESI
- Non-skin malignancy AESI
- Seizure AESI

5.5.9.2 Major adverse cardiovascular events

Based on a pre-defined list of PTs belonging to relevant Standardized MedDRA 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 AE. For fatal cases, each member determines whether the death is considered of cardiovascular, non-cardiovascular, or undetermined cause. If not all individual assessments concur, the case is classified into the above listed categories based on a consensus meeting. For data analysis, each case is assigned to one of the following categories:

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

5.5.10 Vital signs and body weight

Blood pressure data are collected in the eCRFs for both the main database and the first dose database. Weight and height are collected in the eCRF of the main database only.

5.5.10.1 Blood pressure

Systolic (SBP) and diastolic blood pressure (DBP) are measured twice (i.e., two SBP measurements and two DBP measurements) at all assessments (except the hourly post-dose assessments after first dose on Day 1 and on study drug re-initiation). For all data analyses, for derivation of baseline, last on-treatment, Day-30 follow-up, and for flagging of high or low values, the average of the first and second measurements is considered. The average calculated in the eCRF irrespective of position of the subject (supine, standing, sitting) or arm (right, left) is used. If only one measurement is available, this is used for all further derivations and summary statistics.

Baseline is flagged and absolute and percent changes from baseline are calculated for each post-baseline value, as described in Section 5.5.1. In the same manner, pre-dose values are flagged and absolute and percent change from pre-dose are calculated for the hourly post-dose assessments after first dose on Day 1 or at re-initiation.

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

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

- SBP ≤ 90 mmHg or ≥ 20 mmHg decrease from baseline
- SBP ≤ 90 mmHg
- ≥ 20 mmHg decrease from baseline in SBP

- SBP ≥ 160 mmHg or ≥20 mmHg increase from baseline
- SBP ≥ 160 mmHg
- SBP ≥ 140 mmHg
- ≥ 20 mmHg increase from baseline SBP

- DBP ≤ 50 mmHg or ≥ 15 mmHg decrease from baseline
- DBP ≤ 50 mmHg
- ≥ 15 mmHg decrease from baseline in DBP

- DBP ≥ 100 mmHg or ≥ 15 mmHg increase from baseline

- DBP ≥ 100 mmHg
- DBP ≥ 90 mmHg
- ≥ 15 mmHg increase from baseline in DBP

For all hourly post-dose assessments after first dose on Day 1 or at 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.

5.5.10.2 Height and Weight

Height (cm) will only be summarized in the baseline characteristics and thus no derivations (other than treatment day of assessment) are required. Absolute and percent change from baseline is calculated for each post-baseline weight (kg) value, as described in Section 5.5.1.

5.5.10.3 Body Temperature

Collected at all visits in the Body Temperature eCRF as 'normal' or 'abnormal'. No definitions and derivations (other than treatment day of assessment) necessary.

5.5.10.4 Pulse rate

Collected at unscheduled visits in the Pulse Rate eCRF as 'normal' or 'abnormal'. No definitions and derivations (other than treatment day of assessment) necessary.

5.5.11 12-Lead Electrocardiogram

Only the visit, date and time information of the ECG data is collected on the eCRF for both the main database and the first dose database. ECG measurement data is collected using vendor machines from ERT (central ECG provider). Data is automatically submitted to ERT by the machine, centrally read, and transferred from ERT to Actelion.

5.5.11.1 Quantitative ECG variables

Central reader ECG data contains the following quantitative measurements and derived variables: Heart rate (HR) (bpm), PR interval (ms), QRS duration (ms), QT interval (ms), QT_CB (ms) and QT_CF (ms). Heart rate is labeled "Mean heart rate" in the data transferred, however for consistency with earlier studies and to avoid misinterpretation with values coming from Holter monitoring, the label used in the CSR is "Heart rate". Baseline is flagged and absolute and percent changes from baseline are calculated for each post-baseline value as described in Section 5.5.1. In the same manner, pre-dose values are flagged and absolute and percent changes from pre-dose are calculated for the hourly post-dose assessments after first dose on Day 1 or at re-initiation.

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

All assessments meeting the following conditions are flagged in the ADaM dataset:

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

In addition, similar notable abnormality flags are derived in relation to the pre-dose measurements for the post-dose assessments on Day 1 and start of study drug re-initiation, and for the 3-hours post-dose measurement at Week 12 visit:

- 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

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

5.5.11.2 Qualitative ECG variables

Morphological ECG findings are reported by the central reader, and mapped to CDISC standard (codelist C71150, with high level categories from codelist 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-Intraatrial Conduction
- Rhythm Not Otherwise Specified
- ST Segment, T wave, and U wave
- Sinus Node Rhythms and Arrhythmias
- Supraventricular Arrhythmias
- Supraventricular Tachyarrhythmias
- Ventricular Arrhythmias

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

Morphological ECG findings are flagged as "New" if not present at any pre-treatment assessment (i.e., at any ECG assessed prior to the study treatment start) or "Pre-existing" if present at any pre-treatment assessment. In case of missing or non-evaluable pre-treatment ECG assessment, it is conservatively assumed that any treatment-emergent morphological ECG finding is "New".

5.5.12 Laboratory

Laboratory tests will be performed at Visit 1 (Screening), Visit 2 (Baseline), Visit 4 (Week 2), Visit 5 (Week 4), Visit 6 (Week 12) and every 12 weeks thereafter up to Visit 18 (EOT), and at Visit 20 (FU) and, if applicable, at all corresponding visits in the PTOP. Unscheduled laboratory tests may be performed at any time during the study (Visits U1, U2, U3, etc.).

Additional lymphocyte count measurements will be performed every 4 weeks up to Week 24.

Safety laboratory samples are centrally analyzed by Covance and the results are electronically transferred to Actelion. In exceptional cases, the protocol allows the utilization of local laboratories. Local laboratory analysis results are entered in the eCRF with some exceptions for blinding reasons (e.g., lymphocytes are not entered in the eCRF, see protocol). Quantitative results from local laboratories are not summarized (i.e., not included in summary statistics or graphical representations). Qualitative results like (marked) abnormality categorization, liver test elevation categories, etc. are derived from local laboratory data and summarized together with qualitative results derived from central laboratory data.

Safety laboratory hematology, clinical chemistry and urinalysis comprise the following parameters planned as per protocol:

> **Hematology:** Red blood cell count, Total and differential WBC counts (basophils, eosinophils, lymphocytes, monocytes, neutrophils, band forms), Platelet count, Hemoglobin, Hematocrit.
>
> **Liver function tests and coagulation**: International normalized ratio (INR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), (alkaline phosphatase) AP, total bilirubin (TBIL).
>
> **Clinical chemistry (excl. liver tests)**: Lactate dehydrogenase, Creatinine, creatinine clearance (calculated by the central laboratory using Cockroft-Gault), Blood Urea Nitrogen, Urate, Glucose, Total cholesterol, Triglycerides, Sodium, potassium, chloride, calcium, Total protein, albumin, C-reactive protein.
>
> **Urinalysis (dipstick provided by central laboratory):** pH (5.0, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5), Glucose (Negative, Trace, +, ++, +++, ++++), Proteins (Negative, Trace, +, ++, +++, ++++), Occult Blood (Negative, Trace, +, ++, +++), Leukocytes (Negative, Trace, +, ++, +++), Bilirubin (Negative, +, ++, +++), Urobilinogen (3.2, 16, 33, 66, ≥131). Also, for each of those parameters it is collected whether the result is normal or abnormal, and - if abnormal - whether clinically significant (no/yes).

John Cunningham Virus (JCV) serology testing: JCV antibodies (positive/negative/indeterminate).

For the above protocol planned parameters for hematology, liver tests, and clinical chemistry, the derivations detailed in Section 5.5.12.1 will be performed.

Derivations (other than treatment day of assessment) are not performed for any other laboratory parameters, and only the raw information and treatment day of assessment are listed. This includes any laboratory parameters that were not planned to be collected per the protocol, and the following protocol planned parameters:

Hepatitis B Virus Surface Antigen, Varicella Zoster Virus IgG Antibody, HIV-1/2 Antibody, Hepatitis C Virus Antibody, M. tuberculosis IFN Gamma Response, pregnancy tests (Choriogonadotropin Beta, serum / urine).

5.5.12.1 Derivations

Numerical results are converted into both conventional and standard international (SI) units as per QS document OTH-000005 (Definition of Marked Abnormalities in Laboratory Data). Results reported as below the lower limit of quantification (LLOQ) are set to the LLOQ value. Results reported as > XX are set to XX for calculation of summary statistics. For all quantitative safety laboratory data, baseline, last on-treatment, and Day-30 follow-up assessments are flagged and absolute change from baseline and percent changes from baseline are calculated for each post-baseline value, as described in Section 5.5.1.

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

The following flags will be derived for alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), and alkaline phosphatase (AP):

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

* ULN = upper limit of the normal range.

5.5.13 Other safety variables

5.5.13.1 Pulmonary function tests - Spirometry

Spirometry tests to assess pulmonary function will be performed at Visit 2 (Baseline), Visit 6 (Week 12), Visit 9 (Week 48) and every 48 weeks thereafter until Visit 17 (Week 144), Visit 18 (EOT), Visit 20 (FU), and at unscheduled visits (U1, U2, etc.) if clinically indicated. If applicable, spirometry tests will also be performed at the corresponding visits in the PTOP.

Spirometry tests will be conducted at site according to the ATS/ERS guidelines [Miller 2005a, Miller 2005b]. The best (largest) forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC) and peak expiratory flow (PEF) values from the three acceptable and repeatable tests will be recorded in the eCRF as absolute volume in liters and as flow in liters/second (rounded to two decimal places). These values may come from separate maneuvers. The FEV_1/FVC ratio will be derived from the FVC and FEV_1 values recorded in the eCRF.

Prior to database lock and unblinding, spirometry data are not transferred to any member of Actelion biostatistics as these data are considered to carry a moderate risk of potential unblinding. The following parameters are collected on the eCRF at each visit:

- FVC (L),
- FEV1 (L),
- PEF (L/s).

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

- FEV1/FVC (%),
- Predicted normal FEV_1[L] for male subjects = 4.30 × height (m) − 0.029 × *age* (years) at study enrollment − 2.49;
- Predicted normal FEV_1[L] for female subjects = 3.95 × height (m) − 0.025 × *age* (years) at study enrollment − 2.60;
- Predicted normal FVC[L] for male subjects = 5.76 × height (m) − 0.026 × *age* (years) at study enrollment − 4.34;
- Predicted normal FVC[L] for female subjects = 4.43 × height (m) − 0.026 × *age* (years) at study enrollment − 2.89.

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

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

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

Baseline is flagged and absolute and percent changes from baseline are calculated for each post-baseline value, and last on-treatment and Day-30 follow-up assessments are derived as described in Section 5.5.1.

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

- Percent change from baseline in FEV1: < −20 %, < −30%
- Percent change from baseline in FVC: < −20 %, < −30%
- Absolute change from baseline in %predFEV1: < −20 %, < −30%
- Absolute change from baseline in %predFVC: < −20 %, < −30%
- FEV1/FVC < 70%
- Absolute change from baseline in FEV1 ≤ −200 mL or percent change from baseline in FEV1 ≤ −12 %
- Absolute change from baseline in FVC ≤ −200 mL or percent change from baseline in FVC ≤ −12 %
- Absolute change from baseline in FEV1 > −200 mL and percent change from baseline in FEV1 > −12 %
- Absolute change from baseline in FVC > −200 mL and percent change from baseline in FVC > −12 %

5.5.13.2 Suicidal ideation

The eC-SSRS© is an assessment instrument that evaluates suicidal ideation and behavior. During an initial assessment it assesses lifetime as well as the recent history suicidality (scheduled at Visit 2-Baseline), and then prospectively monitors ideations and behaviors at subsequent follow-up assessments since the last call (scheduled at Visit 9-Week 48, Visit 13-Week 96, Visit 17-Week 144 and Visit 18-EOT).

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

1 – Wish to be Dead
2 – Non-specific Active Suicidal Thoughts
3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan
5 – Active Suicidal Ideation with Specific Plan and Intent
6 – Preparatory Acts or Behavior
7 – Aborted Attempt
8 – Interrupted Attempt
9 – Actual Attempt (non-fatal)
10 – Completed Suicide

Furthermore, **self-injurious behavior without suicidal intent** is also an eC-SSRS© outcome (although not suicide-related) and has a binary response (yes/no). (Q07a)

The initial assessment has a lifetime and a recent history assessment. The recent history covers the last 1 month for suicidal ideation, and the last 3 months for suicidal behavior. Recent history questionnaire questions are only assessed for outcome categories with corresponding lifetime outcome question answered as yes. If the lifetime assessment for an outcome category is 'No', also the corresponding recent history outcome is considered 'No' for analysis.

Scoring: Scores are created at each assessment as follows:

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

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

The following definitions will be used:

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

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

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

* Only post-baseline assessments after study treatment start date from a 'since last call' (i.e., not from a lifetime) questionnaire are considered for the analysis.

Baseline is defined as last available recent history result (maximum score) up to study treatment start date, i.e., pre-treatment recent history result.

Lifetime (pre-treatment) is defined as any event (worst outcome) in recent history and lifetime evaluation(s) up to study treatment start date.

5.6 Pharmacodynamic variables

5.6.1 Total lymphocyte counts

The main PD marker is total lymphocyte count, which is measured as part of the hematology test from central laboratory. Absolute and change from baseline counts are derived, as described in Section 5.5.12.

Total lymphocyte counts are further categorized into the following categories:

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

For each subject in the SAF, the nadir (i.e., lowest) treatment-emergent lymphocyte value (up to EOT + 15 days) is flagged.

Subjects who have a value after Visit 5 (Week 4) (scheduled or unscheduled) which is both < 0.5 × 10^9/L and represents a decrease from Week 4 > 50%, and which is maintained at all visits (scheduled or unscheduled) for the next 24 weeks, will be flagged.

For example, if a subject has a value of 0.9 × 10^9/L at Visit 5 (Week 4), then a value of 0.4 × 10^9/L at Visit 6 (Week 12), a value of 0.35 × 10^9/L at Visit 7 (Week 24) and a value of 0.4 × 10^9/L at Visit 8 (Week 36), then the subject will be flagged as meeting the above criterion.

Subjects who have a value after Visit 5 (Week 4) (scheduled or unscheduled) which is both < 0.5 × 10^9/L and represents a decrease from Week 4 of > 50%, and who discontinue treatment within 24 weeks, will be flagged separately if this decrease is maintained at their remaining study scheduled visits, where EOT and FU are considered to be scheduled visits.

Total lymphocyte counts from central laboratory are flagged for analysis according to their sample dates as 'Baseline', 'Last on treatment' and 'Day-30 follow-up' following the rules described in Section 5.5.1 and Section 11.4.

5.6.2 Lymphocyte subsets

A sub-study assessing lymphocyte subsets will be conducted in approximately 200 subjects. Participation in the sub-study will be mandatory for all subjects until at least the first 200 subjects are randomized to the main study. T cell, B cell, and NK cell counts as well as T cell subsets (e.g., $CD4^+$ naïve, $CD4^+$ effector memory, $CD4^+$ central memory, $CD8^+$ naïve, $CD8^+$ effector memory, $CD8^+$ central memory, $CD8^+$ terminally differentiated effector memory, Th17 cells, Treg cells, and Th1cells) will be analyzed at the central laboratory. All subjects were to be analyzed for T cell subsets. In addition, the approximately 50 subjects were to be analyzed for B cell subsets. Other lymphocyte subsets may also be analyzed. Selected lymphocyte subsets may also be analyzed functionally *ex vivo*.

Blood samples for lymphocyte subset analysis will be taken from approximately 200 subjects at Visit 2 (Baseline), Visit 6 (Week 12), Visit 7 (Week 24), Visit 9 (Week 48), Visit 13 (Week 96), Visit 17 (Week 144), Visit 18 (EOT), Visit 19 (FU7d), and at Visit 20 (FU). If applicable, lymphocyte subsets will also be assessed at the corresponding visits in the PTOP (Visits 6A, 7A, 9A, 13A, 17A, and 18A).

Absolute and change from baseline values for lymphocyte subsets are derived as described in Section 5.5.12.

6 DEFINITION OF PROTOCOL DEVIATIONS

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

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

- **Important** protocol deviations (Yes/No)
- **Timing** (before Randomization / after Randomization / after end of treatment/ anytime during the study)

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

7 ANALYSIS SETS

7.1 Definitions of analysis sets

7.1.1 Screened analysis set

The Screened Analysis Set (SCR) includes all subjects who were screened and received a subject number.

7.1.2 Full analysis set

The full analysis set (FAS) includes all randomized subjects who were treated with at least one dose of study treatment and have at least one post-baseline efficacy assessment.

- In order to preserve the randomization, subjects will be evaluated according to the treatment they have been randomized to (which may be different to the treatment they have received) and stratum information used for randomization as recorded in the IVRS system (which may be different to the information available on the eCRF after data validation);
- Unless otherwise stated, all available efficacy data for the primary and secondary endpoints up to the EOS visit [see Section 11.4] will be included in the analysis, regardless of study treatment discontinuation and/or switches to alternative MS treatments.

7.1.3 Safety analysis set

The safety analysis set (SAF) includes all subjects who received at least one dose of study treatment. Irrespective of the randomized treatment group, subjects are summarized grouped:

- by actual treatment received, if the same kind of study treatment (ponesimod or placebo) was taken throughout the study.
- within the treatment group they were exposed to for the majority of time on study treatment in case both study treatments (ponesimod and placebo) were taken by a subject at some point

during the study. If a subject received ponesimod and placebo for exactly the same number of days, they are summarized within the treatment they are assigned to by randomization.

Some analyses are conducted based on the following safety set subsets:

- Subset of subjects with at least one re-initiation (based on eCRF Study Drug Administration - Re-Initiation).

7.1.4 Other analysis sets

The following other analysis sets are defined:

7.1.4.1 Post-treatment safety analysis set

Includes all subjects in the safety analysis set who have an EOS date > EOT + 15 days. Subjects are summarized in the same treatment group as in the safety analysis set.

7.1.4.2 Lymphocyte T cell subset analysis set

Includes all subjects in the safety analysis set who have at least one evaluable baseline and at least one evaluable post-baseline on-treatment sample for the lymphocyte T cell subset analysis.

7.1.4.3 Lymphocyte B cell subset analysis set

Includes all subjects in the safety analysis set who have at least one evaluable baseline and at least one evaluable post-baseline on-treatment sample for the lymphocyte B cell subset analysis.

7.2 Usage of the analysis sets

Table 5 provides an overview of the analysis set usage for the main variables of the study.

Table 5 Overview of the different main analysis sets and their usage

Analyses/Data Displays	Screened analysis set	Full analysis set	Safety analysis set
Inclusion/exclusion criteria	✓		
Demographic characteristics		✓	
Baseline characteristics		✓	
Previous and concomitant medications		✓	
Treatment exposure			✓
Efficacy: Primary endpoint		✓	
Efficacy: Secondary endpoints		✓	
Efficacy: Exploratory endpoints		✓	
Safety endpoints			✓
All subject listings		✓	

Main analysis of the primary efficacy endpoint is based on the Full analysis set, selected listings will be prepared on the Screened analysis set.

8 DEFINITION OF SUBGROUPS

Due to the low number of subjects recruited in this early terminated study, no subgroup analyses will be performed.

9 STATISTICAL ANALYSES

9.1 Overall testing strategy

9.1.1 Overall testing strategy

The primary endpoint (ARR using confirmed relapses) will be tested using a negative binomial regression model, comparing ponesimod with placebo. Due to the early termination of the study, analysis of the five secondary endpoints will be considered exploratory. No adjustment for multiplicity will be performed.

9.2 General rules for data presentations

This section describes the general rules applied for all data displays, unless otherwise specified in each corresponding section. Standard Guiding Rules and Principles and standard outputs are followed where applicable.

SAS version 9.4 is used for the preparation of all tables, listings and figures. Listings are sorted by treatment group, subject number (includes sorting by country and center) and timing (dates and/or visits as applicable). For analyses performed on multiple analysis sets, only one listing containing all analyzed subjects is presented. Names of outputs have a suffix that indicates the analysis set (e.g., _S for Safety set).

Data are listed and summarized using appropriate descriptive statistics:

- Number of non-missing observations, number of missing observations, mean, standard deviation, minimum, Q1, median, Q3, and maximum for continuous variables;
- Number of non-missing observations, and frequency with percentage per category (percentages based on the number of non-missing observations) for categorical endpoints;
- Some continuous variables are graphically presented based on mean change +/− standard error (SE) on a time axis scaled to the target days of the corresponding visit. The SE is derived as standard deviation (SD)/$\sqrt{N}$.
- All safety data will be included in listings, with flags for safety data considered to be treatment-emergent.

Example table layouts:

```
ACT-128800/JNJ-67896153                Protocol: AC-058B302<TITLE>
Analysis set: <Set>
_____________________________________________________________________
           Ponesimod 20 mg       Placebo          Total
            / DMF                / DMF
            N = XX               N = XX          N = xx
_____________________________________________________________________

<XXX>      XX                 XX                 XX
_____________________________________________________________________
```

Treatment groups are displayed in the order (left to right) of Ponesimod 20 mg / DMF, Placebo / DMF, Total (if applicable). For figures, ponesimod / DMF is displayed in red with solid line style and placebo / DMF is displayed in black with dashed line style.

9.3 Display of subject disposition, protocol deviations and analysis sets

9.3.1 Subject disposition

The number and percent of subjects in the FAS is summarized by country and site.

A listing including subject disposition is also provided on the FAS.

Furthermore, a listing of study initiation and completion dates is also provided.

The number and percent of subjects screened and re-screened (incl. reasons for screening failure), subjects randomized, subjects completing study up to study termination, subjects treated, and subjects completing study treatment up to study termination, as well as subjects completing both treatment and study up to study termination are summarized for the SCR. For subjects that failed screening more than once, only the reason of the last failure is reported in the summary table.

All reasons for screening failures are included in the listing. The listing also includes the date of screening / re-screening, an indicator variable ('Yes', 'No') for failed screening attempts, the randomization date, and the number of days from successful screening to randomization.

The number and percent of subjects by reason for premature discontinuation from study is tabulated for the FAS. The number and percent of subjects by reason for premature discontinuation from study treatment is tabulated for the SAF. Listings of subjects with premature study/treatment withdrawal and related reasons are also provided on FAS.

A listing of randomization scheme and codes (for randomized subjects only) as well as a listing with Informed Consent information are produced respectively on FAs and SCR.

9.3.2 Protocol deviations

Important protocol deviations are summarized by category (first timing, then high-level topic), per treatment group and overall on the FAS.

A listing of all protocol deviations (coded term, reported term) by country and site is provided on the SCR.

9.3.3 Analysis sets

Subject membership in the different analysis sets is presented in a listing.

9.4 Analyses of subject characteristics

9.4.1 Demographics

Demographic characteristics [defined in Section 5.2.1] are summarized using descriptive statistics for continuous and categorical data using the FAS. Tables are presented by treatment group and overall. All variables are also presented in a subject data listing based on the SCR.

9.4.2 Baseline disease characteristics

Baseline disease characteristics [defined in Section 5.2.2] are summarized using descriptive statistics for continuous and categorical data using the FAS. Tables are presented by treatment group and overall. All variables are also presented in subject data listings based on the SCR.

9.4.3 Previous and concomitant therapies

Number and percentages of subjects having taken at least one treatment are presented by at least one therapy, ATC class and individual PT within each ATC class (ATC class level 4). All summaries are tabulated by ATC class, and individual PTs within each ATC class, for the FAS, by treatment group and overall. ATC classes are sorted by descending order of frequency. If the frequencies of ATC class are the same, alphabetical order is used. The same rule applies for PTs within ATC class. If the frequencies of ATC class are the same, alphabetical order is used. The same rule applies for PTs within ATC class.

The above described frequencies are summarized by treatment group and overall for the following therapies:

- Treatment concomitant therapies (taken between study treatment start and EOT +15 days)

All therapies taken are reported in one subject listing with all information collected on the eCRF presented, using flags to mark previous, treatment concomitant, and therapies starting after EOT, as well as ongoing at study treatment start using the screened set.

9.5 Analysis of study treatment exposure and compliance

9.5.1 Study treatment exposure and compliance

9.5.1.1 Study treatment exposure

Exposure to study drug [defined in Section 5.3.1.1] is summarized using descriptive statistics for continuous and categorical data using the SAF. In addition, this table displays the overall subject year exposure (sum over all subjects' exposure). Tables are presented by treatment group. All variables are also presented in subject data listings, together with compliance, based on the SAF.

Subjects with at least one interruption as well as duration of interruptions will be summarized by treatment group on the SAF. Subject exposure to study drug is listed. Subjects with > 1 tablet taken on at least one day or maintenance treatment resumed without up-titration after an interruption of > 3 days are flagged.

9.5.1.2 Compliance with study treatment

Compliance with study treatment variables [defined in Section 5.3.1.2] are summarized using descriptive statistics for continuous and categorical data using the SAF. Tables are presented by treatment group. All variables are also presented in subject data listings, together with exposure, based on the SAF.

9.5.2 DMF exposure and compliance

9.5.2.1 DMF exposure during study treatment

Exposure to DMF [defined in Section 5.3.3.1] is summarized using descriptive statistics for continuous and categorical data using the SAF. In addition, this table displays the overall subject year exposure (sum over all subjects' exposure). Tables are presented by treatment group. All variables are also presented in subject data listings based on the SAF.

9.5.2.2 Compliance with DMF during study treatment

Compliance with DMF variables [defined in Section 5.3.3.2] are summarized using descriptive statistics for continuous and categorical data using the SAF. Tables are presented by treatment group. All variables are also presented in subject data listings based on the FAS.

9.6 Analysis of the primary efficacy variable

9.6.1 Hypothesis and statistical model

A generalized linear model with negative binomial distribution for the number of confirmed relapses will be assumed as described in Section 10.1.

Two-sided hypotheses are expressed in terms of the model parameters $\mu_{Ponesimod}$ and $\mu_{Placebo}$. The primary null hypothesis is that the ARR (μ) does not differ between ponesimod and placebo. The alternative hypothesis is that the ARR differs between ponesimod and placebo.

$$H_{0,\,ARR}: \mu_{Ponesimod} - \mu_{Placebo} = 0$$

vs

$$H_{1,\,ARR}: \mu_{Ponesimod} - \mu_{Placebo} \neq 0$$

The null hypothesis will be tested by a two-sided Wald test within the negative binomial regression model [see Section 9.6.2], with a two-sided significance level of 0.05.

9.6.2 Main analysis

The primary statistical analysis will be performed up to EOS on the FAS using a negative binomial (NB) regression model for confirmed relapses, with treatment as a factor and the binary stratification variable for EDSS category (EDSS $\leq$ 3.5 versus EDSS > 3.5) from IRT included in the model. The model also includes an offset variable defined as the log of time on study (in years) from randomization up to EOS. The effect size will be measured by the relative reduction in the model estimated mean ARR for ponesimod compared to placebo including two-sided 95% Wald confidence interval (CIs).

Mean model-based estimates of the ARR (for confirmed relapses), by treatment arm, as well as 95% CIs are presented. A rate ratio comparing ponesimod 20 mg with placebo will be derived from the model including 95% CIs and the corresponding p-value. The dispersion parameter will also be displayed.

Descriptive summary statistics of the number of confirmed relapses as a continuous variable and the number of confirmed relapses in categories (0, 1, 2, 3, 4, ≥ 5), by treatment arm will be presented. The total cumulative number of confirmed relapses, as well as the total cumulative time on study (summed for all subjects) will also be displayed. From the total number of confirmed relapses and the total time on study the raw unadjusted ARR, by treatment arm, will be calculated and summarized.

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

9.6.3 Sensitivity analyses to main analysis

No sensitivity analyses are planned.

9.6.4 Supplementary analyses

9.6.4.1 ARR based on all relapses up to EOS on the FAS

Same analysis as for the main analysis, but with number of all relapses up to EOS as a response variable. All other aspects of the model are as per the main analysis. This analysis is described to check the consistency of the treatment effect on all relapses and that no bias was introduced in the confirmation of relapses.

A listing of relapses and a listing for number of relapses will be prepared on FAS.

9.6.5 Subgroup analyses

No subgroup analyses are planned.

9.7 Analysis of the secondary efficacy variables

All analyses of secondary efficacy variables are considered to be exploratory.

9.7.1 Analysis of time to 12-week CDA

Time to first confirmed 12-week CDA up to EOS will be summarized on the FAS in a table including, number of subjects with event / censored, Kaplan-Meier estimates (unstratified) and corresponding CI (anticipated timepoints: 12, 24, …, 156 weeks), and median (as well as 25th and 75th percentiles) of the survival function together with CIs.

A listing of 12-week CDA data will be prepared.

9.7.1.1.1 Handling of missing data

See variable derivation in Section 5.4.2.1.

9.7.2 Time to first confirmed relapse

Time to first confirmed relapse will be summarized on the FAS in a table including, number of subjects with event / censored, Kaplan-Meier estimates (unstratified) and corresponding CI (anticipated timepoints: 12, 24, …, 156 weeks), and median (as well as 25th and 75th percentiles) of the survival function together with CIs. A graphical display presenting a Kaplan-Meier plot

(unstratified) going upward is presented including CIs at specific timepoints. Intervals will be displayed up to the time point where at least 10% of subjects are still at risk.

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

9.7.3 Analysis of cumulative unique active lesions (CUAL) from baseline up to EOS

The main analysis of the secondary endpoint CUAL will be performed on the FAS using a negative binomial regression model: response variable is the cumulative number of CUALs up to EOS, with treatment as a factor and the IRT stratification variable for EDSS (EDSS ≤ 3.5 versus EDSS > 3.5) included in the model. The model also includes an offset variable defined as the log of the time up to last MRI (in years) considered for analysis.

Mean model-based estimates of the number of CUALs per subject per year will be provided by treatment group, as well as 95% Wald CIs. A rate ratio comparing ponesimod 20 mg with placebo will be derived from the model including 95% Wald CIs and the corresponding p-value. The dispersion parameter will also be displayed.

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

Descriptive summary statistics of the number of CUALs from baseline up to EOS will be presented for continuous data and frequency per categories (0, 1–5, 6–10, 11+) anticipated. The total number of CUALs as well as the total cumulative time up to the last MRI scan (summed for all subjects) will also be displayed. From the total number of CUALs and the total cumulative time to the last MRI scan the raw number of CUALs per year will be calculated and summarized.

A listing of CUAL data will be presented.

9.8 Analysis of exploratory MRI efficacy variables

9.8.1 Number of CUALs

The cumulative number of CUALs from baseline up to Weeks 24, 48, 72, 96 and EOT will be analyzed on the FAS using a negative binomial regression model: response variable is the cumulative number of CUALs up to each timepoint, with treatment as a factor and EDSS category (IRT) as a covariate, and the log of the time up to last MRI scan for the timepoint (in years) as an offset. Mean model-based estimates for the number of CUALs per subject per year, rate ratio, and corresponding 95% CIs will be presented.

The cumulative number of CUALs from baseline up to each timepoint will be summarized descriptively using the FAS. The total number of CUALs as well as the total cumulative time up to the last MRI scan at the timepoint (summed for all subjects) will also be displayed. From the total number of CUALs and the total cumulative time to the last MRI scan the raw number of CUALs per year will be calculated and summarized.

CUAL data will be listed on the FAS.

9.8.2 Number of T1 Gd+ lesions

The cumulative number of T1 Gd+ lesions up to Weeks 24, 48, 72, 96, EOT and EOS will be analyzed on the FAS using a negative binomial regression model, with the cumulative number of T1 Gd+ lesions up to the timepoint as the response variable, treatment as a factor, EDSS stratification category as a covariate, and the log of the number of included scans up to the timepoint as an offset. Mean model-based estimates for the number of T1 Gd+ lesions per subject per scan, rate ratio, and corresponding 95% CIs will be presented.

The cumulative number of T1 Gd+ lesions from baseline up to each timepoint will be summarized descriptively using the FAS. The total number of T1 Gd+ lesions as well as the total number of included scans (summed for all subjects) will also be displayed. From the total number of T1 Gd+ lesions and the total number of included scans the raw number of T1 Gd+ lesions per scan will be calculated and summarized. For the number of T1 Gd+ lesions from baseline up to EOS the frequency per category will also be presented (anticipated categories: 0, 1, 2, 3, 4+).

Descriptive summary statistics of the number of T1 Gd+ lesions at each scheduled visit will also be presented.

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

9.8.3 Number of new or enlarging T2 lesions

The cumulative number of new or enlarging T2 lesions up to Weeks 24, 48, 72, 96, EOT and EOS will be analyzed on the FAS using a negative binomial regression model as described above in Section 9.8.1 for number of CUALs, with the cumulative number of new or enlarging T2 lesions up to the timepoint as the response variable.

The cumulative number of new or enlarging T2 lesions from baseline up to each timepoint will be summarized descriptively using the FAS. The total number of new or enlarging T2 lesions as well as the total cumulative time up to the last MRI scan at the timepoint (summed for all subjects) will also be displayed. From the total number of new or enlarging T2 lesions and the total cumulative time to the last MRI scan the raw number of new or enlarging T2 lesions per year will be calculated and summarized. For the number of new or enlarging T2 lesions from baseline up to EOS the frequency per category will also be presented (anticipated categories: 0, 1, 2, 3, 4+).

Descriptive summary statistics of the number of new or enlarging T2 lesions at each scheduled visit will also be presented.

T2 lesion data will be listed on the FAS.

9.8.1 Analysis of time to 24-week CDA

Analysis of time to 24-week CDA will be analyzed in the same way as analysis of time to 12-week CDA as described in Section 9.7.1.

9.8.2 Change in EDSS from baseline by visit up to EOS

The EDSS score and change from baseline in EDSS score by visit and treatment group will be summarized using descriptive statistics on the FAS. A listing of EDSS / FS scores will be produced on the FAS.

9.9 Analysis of safety variables

9.9.1 Adverse events

All AEs captured (i.e., from signature of informed consent up to EOS) are reported in the subject listings based on the SCR, treatment-emergent events are flagged.

Unless otherwise specified, the SAF is used for all analyses of AEs.

An overview of treatment-emergent AEs is presented, per treatment group, as the number and percentage of subjects having any AE, any severe AE, any drug-related AE, any AE leading to study drug discontinuation, any SAE, any drug-related SAE, or any fatal SAE.

Also, AEs are summarized by SOC and PT: Presenting, per treatment group, the number and percentage of subjects having any AE, having an AE in each primary SOC, and having each individual AE (PT). SOCs are sorted by descending order of frequency in the ponesimod arm. If the frequencies of SOCs are the same, alphabetical order is used. The same rule applies for PTs within SOC. The following summaries are presented:

- Treatment-emergent AEs
- Treatment-emergent AEs on Day 1
- Treatment-emergent AEs on Day 1 of re-initiation, for subjects with at least one re-initiation
- Treatment-emergent AEs leading to temporary interruption of study treatment
- Treatment-emergent AEs considered to be related to DMF
- Treatment-emergent AEs considered to be related to study drug
- Treatment-emergent AEs with fatal outcome

Also, treatment-emergent AEs are summarized by PT: presenting, per treatment group, the number and percentage of subjects having any AE, and having each individual AE (PT). PTs are sorted by descending order of frequency in the ponesimod arm. If the frequencies are the same, alphabetical order is used.

For the disclosure of the results to EudraCT and ClinicalTrials.gov (and inclusion in the CSR appendix), frequent treatment-emergent non-serious AEs, i.e., PTs reported in ≥ 5% of subjects in at least one treatment group, are summarized as follows:

1) The number and percentage of subjects having any frequent non-serious AE, and having each individual non-serious AE (PT).
2) The overall number of frequent non-serious AEs (i.e., reported episodes), and the number and percentage of frequent AEs (PT). Here the denominator is the overall number of frequent non-serious AEs.

9.9.2 Deaths, other serious adverse events

9.9.2.1 Death

A separate listing including all deaths is provided based on the SCR; treatment-emergent deaths are flagged as such in that listing.

9.9.2.2 Serious adverse events

Unless otherwise specified, the SAF is used for all analyses of SAEs.

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

- Treatment-emergent SAEs
- Treatment-emergent SAEs on Day 1
- Treatment-emergent SAEs on Day 1 of re-initiation, for subjects with at least one re-initiation
- Treatment-emergent SAEs considered to be related to study drug

For the disclosure of the results to EudraCT and ClinicalTrials.gov (and for inclusion in the CSR appendix), the overall number of treatment-emergent SAEs (i.e., reported episodes), and the number and percentage SAEs (PT) are summarized. Percentages of subjects are based on the number of subjects in the safety analysis set and the percentages of events are based on the total number of events.

9.9.2.3 Treatment-emergent adverse events leading to study treatment discontinuation

The SAF is used for all analyses of AEs leading to discontinuation. AEs leading to premature discontinuation of study drug are summarized by SOC and PT. The following summaries are presented:

- Treatment-emergent AEs leading to premature discontinuation of study drug.

9.9.2.4 Other significant adverse events

9.9.2.4.1 Adverse events of special interest

For each of the AESI categories described in Section 5.5.9.1, the following information is presented: The number and percent of subjects with each AESI is summarized by PT per treatment arm. In addition, the number and percentage of subjects having any event of that category, having any serious event, any fatal event or any event leading to premature discontinuation is presented.

AESI are presented in a dedicated listing.

9.9.2.4.2 Major adverse cardiovascular events

A listing of MACE events is prepared.

9.9.3 Electrocardiography (ECG)

The following summary displays are provided by treatment group, all based on the SAF:

- Quantitative ECG results and absolute change from baseline, as described in Section 5.5.11.1, are summarized descriptively, by parameter and visit. Except for data summarized under 'Baseline', 'last-on-treatment' and 'Day-30 follow-up', only treatment-emergent results from nominal scheduled visits are included, premature EOT visit is mapped to a scheduled visit [see Section 11.3];

- Quantitative ECG results and absolute change from pre-dose on Day 1, by timepoint (pre-dose, 1–4 hours post dose), are summarized descriptively;

- Number and percentage of subjects with any treatment-emergent PR, QTcF prolongations and HR outliers are presented overall. Percentages are based on the number of subjects with at least one treatment-emergent result available for the corresponding parameter. Abnormalities are presented cumulatively, i.e., a subject with a treatment-emergent QTcF result > 500 ms is also summarized in the category QTcF > 450 ms;

- Number and percentage of subjects with any 3-hr post-dose PR, QTcF prolongations and HR outliers on Day 1, Week 12 Visit, and Day 1 of any re-initiation. For this analysis the ECG results reported as 3-hours post-dose are considered, irrespective of actual time the ECG was performed. Percentages are based on the number of subjects with a result available for the corresponding parameter at 3-hours post-dose. Abnormalities are presented cumulatively;

- Number and percentage of subjects with new treatment-emergent morphological ECG findings, by abnormality and group term following CDISC terminology are presented;

- Number and percentage of subjects with new treatment-emergent post-dose morphological ECG findings on Day 1 or on Day 1 of any re-initiation, by abnormality and group term following CDISC terminology are presented.

All ECG data including QTc parameters are listed by treatment group and subject based on the SCR. All marked abnormalities are flagged and morphological findings are listed.

9.9.4 Vital signs and body weight

The following summary displays are provided by treatment group, all based on the SAF:

- Blood pressure and body weight including absolute change from baseline, as described in Section 5.5.10, are summarized descriptively, by parameter and visit. Except for 'Baseline', 'Last on treatment' and 'Day-30 follow-up', only treatment-emergent results from nominal scheduled visits are included; premature EOT visit is mapped to a scheduled visit [see Section 11.3];

- Blood pressure including absolute change from baseline on Day 1, by timepoint (pre-dose, 1–4 hours post dose), are summarized descriptively;

- Number and percentage of subjects with any treatment-emergent blood pressure result meeting the criteria defined in Section 5.5.10.1. Percentages are based on the number of subjects with at least one treatment-emergent result available for the corresponding parameter;
- Number and percentage of subjects with post-dose blood pressure result on Day 1 meeting the criteria defined in Section 5.5.10.1 are presented overall post-dose hours. Percentages are based on the number of subjects with blood pressure results available for the corresponding parameter.

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

All blood pressure as well as body weight, body temperature and pulse rate results are listed by treatment group and visit based on the SCR. A listing for blood pressure measurements in subjects with at least one treatment-emergent marked blood pressure abnormality will also be presented on SCR.

9.9.5 Laboratory tests

Descriptive summary statistics by visit and treatment group are provided for laboratory test results reported by the central laboratory and corresponding absolute changes from baseline, based on the SAF. Except for 'Baseline', 'Last on treatment' and 'Day-30 follow-up', only treatment-emergent results from nominal scheduled visits are included; premature EOT visit is mapped to a scheduled visit [see Section 11.3]. Data are displayed in SI units as provided by the central laboratory. Values from unscheduled visits are not included in by visit summaries but are included in the listings and in the summaries for marked abnormalities and liver function test abnormalities.

For lymphocyte counts, this table is also provided on percent changes from baseline. The number of subjects with at least one treatment-emergent marked laboratory abnormality is summarized by treatment group, based on the SAF. The worst case in each direction is considered and summarized in all applicable categories, i.e., a subject counted in LLL is also counted in LL for a given parameter; also, a subject maybe counted in both the high and the low category for a given parameter. In addition, the number of subjects with treatment-emergent liver function test abnormalities is summarized by treatment group. The denominator for percentages is the number of subjects with at least one post-baseline assessment.

Safety laboratory hematology, clinical chemistry, urinalysis parameters planned as per protocol are also presented in subject data listings based on the SCR. All abnormalities and marked abnormalities including those at baseline are flagged in the listings.

A shift table of the frequency counts and percentages of number of subjects with positive, negative and indeterminate results at baseline and at EOS for JCV serology will be presented separately.

Other laboratory parameters are presented in a separate listing on the SCR.

Further analyses related to lymphocytes and lymphocyte subsets are described in Section 9.10.

9.9.6 Pulmonary function tests - Spirometry

The following summary displays are provided by treatment group, all based on the SAF:

- Treatment-emergent FEV1, FVC, FEV1/FVC, %predFEV1, and %predFVC including absolute and percent change from baseline, as described in Section 5.5.13.1, are summarized descriptively, by parameter and visit. Except for 'Baseline', 'Last on treatment' and 'Day-30 follow-up', only treatment-emergent results from nominal scheduled visits are included; premature EOT visit is mapped to a scheduled visit [see Section 11.3].

- Number and percentage of subjects with any occasion of treatment-emergent low spirometry values as defined in Section 5.5.13.1 are presented. Percentages are based on the number of subjects with at least one treatment-emergent result available for the corresponding parameter;

All spirometry results are listed by treatment group and visit based on the SCR. A listing of spirometry data in subjects with treatment-emergent decrease >= 0.2 L or >= 12% in FEV1 (or FVC) is also presented.

9.9.7 Columbia Suicide ideation or behavior

Suicidal Ideation, Suicidal Behavior or Self-Injurious Behavior without Suicidal Intent will be listed for each patient, at each assessment visit on the SCR. Events occurring during the period up to EOT + 15 days (treatment-emergent period) will be flagged.

Number (%) of subjects with suicidal ideation (overall and by category), suicidal behavior (overall and by category), suicidal ideation score ≥ 4 or suicidal behavior and/or self-injurious behavior without suicidal intent will be tabulated by treatment group up to EOT + 15 days (worst outcome). Analyses will be based on subjects in the SAF who have at least one treatment-emergent eC-SSRS© measurement available.

For subjects who have in addition a baseline eC-SSRS© assessment available shifts from baseline (maximum score from pre-treatment recent history) to the worst reported outcome (the maximum score) up to EOT + 15 days will be tabulated by treatment group to demonstrate any changes in Suicidal Ideation and Suicidal Behavior score categories.

All eC-SSRS© data will be presented in a listing on SCR.

9.10 Analysis of pharmacodynamic variables

9.10.1 Total lymphocyte counts

Descriptive analyses of lymphocyte data are described in Section 9.9.5. Only lymphocyte counts from central laboratory, irrespective of whether obtained at a scheduled or unscheduled visit, are included in any of the below described analyses.

For each subject in the SAF, the nadir (i.e., lowest) treatment-emergent lymphocyte value (up to EOT + 15 days) is summarized by means of frequency counts and percentages based on the categories specified in Section 5.6.

Frequency counts and percentages will be presented for the number of subjects with:

- Total lymphocyte counts < 0.5 × 10^9/L and > 50% decrease from baseline at Week 4, maintained at all visits for the next 24 weeks, where the denominator for percentages is the number of subjects with a total lymphocyte count at all scheduled visits for the next 24 weeks;
- Total lymphocyte counts < 0.5 × 10^9/L at any visit after Week 4 and > 50% decrease from Week 4, maintained at all visits for the next 24 weeks, OR total lymphocyte count < 0.5 × 10^9/L at any visit after Week 4 and > 50% decrease from Week 4, discontinuing for any reason within 24 weeks, with decrease maintained for remaining scheduled study visits, where the denominator for percentages is the number of subjects with a total lymphocyte count < 0.5 × 10^9/L and > 50% decrease from Week 4 at any visit after Week 4.

9.10.2 Lymphocyte subsets

All collected parameters from the T cell lymphocyte subset will be presented descriptively, with absolute values, as well as absolute and percent change from baseline values presented, using the T cell lymphocyte subset analysis set.

All collected parameters from the B cell lymphocyte subset will be summarized in the same way, using the B cell lymphocyte subset analysis set.

10 GENERAL STATISTICAL METHODOLOGY

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

10.1 Statistical methodology for count data

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

A generalized linear model with NB distribution will be assumed.

t_j denotes the length of observation 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, will be modeled by the following equation:

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

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

The SAS code for the NB model with 95% CI is as follows (considered "draft" until fully validated at analysis stage):

```
proc genmod data=ADREL;
     class Treat Strat Covar;
     model COUNTS = Treat Strat Covar / dist=negbin link=log
     offset = offset;
     lsmeans Treat / cl exp alpha = 0.05 OM;
     estimate 'Ponesimod - Placebo' ‖ Treat 1 -1 / exp alpha = 0.05;
run;
```

The offset variable used will be 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 will output the mean estimates for each of the treatment arms with 95% Wald CIs; the option OM ensures that the mean is derived for categorical covariates with weights as per observed marginal proportions.

The 'ESTIMATE' statement will output the rate ratio of the treatment effect with 95% Wald CIs. The direction of the estimate statement (governed by '1 – 1' or '−1 1') is chosen such that the rate ratio relative to placebo is provided (with rate ratio < 1 indicating ponesimod is better).

The number of covariates / stratification variables included in the model is different from analysis to analysis, and these are described in the respective analysis sections [see Section 9]. Interaction terms might be included in the model, depending on the analysis.

If the NB distribution is not considered to be appropriate (e.g., due to non-convergence), other distributions such as the Poisson and zero-inflated Poisson will be explored. For the Poisson distribution, a Poisson regression is conducted with model equation identical to the one for the negative binomial regression. The SAS code is as follows (considered "draft" until fully validated at analysis stage):

```
proc genmod data=ADREL;
     class Treat Strat Covar;
     model COUNTS = Treat Strat Covar / dist=poisson link=log
     offset = offset;
     lsmeans Treat / cl exp alpha = 0.05;
     estimate 'Ponesimod - Placebo' ‖ Treat 1 -1 / exp alpha = 0.05;
run;
```

10.2 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). Intervals will be displayed on plots up to the time point where at least 10% of subjects are still at risk.

10.2.1 Time to event

Estimates of the event rate are obtained for each treatment group using the Kaplan-Meier method as implemented in SAS Proc Lifetest. The graphical representation follows the recommendations from Pocock [Pocock 2002]. Two-sided CIs at specific timepoints 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 with the corresponding two-sided CIs calculated using the method of Brookmeyer [Brookmeyer 1982].

11 GENERAL DEFINITIONS AND DERIVATIONS

11.1 Dates, times and days

Study treatment start date see definition in Section 5.3.1.1.

End-of-Treatment (EOT) / Study treatment end date, defined as the latest study treatment end date as recorded on the Study Drug Log eCRFs [see Section 5.3.1.1].

End-of-Study (EOS) date is defined as the 'Date of Subject Decision' (if reason for study discontinuation was 'Subject Decision'), 'Date of Physician Decision' (if reason for study discontinuation was 'Physician Decision') collected on the 'Study Discontinuation' eCRF, or 'Date of recorded last study visit / assessment' (if reason for study discontinuation was 'Sponsor Decision'), unless a subject is lost to follow-up or dies, in which case 'Date of last successful contact' from the Study Discontinuation eCRF or 'Date of Death' from Death eCRF are used. If missing, the last recorded visit date (i.e., the latest assessment date within any visit) is considered as the EOS date [see Section 5.1.6].

Screening date defined as the visit date of the last available screening visit, i.e., date of Visit 1A for re-screened subjects, date of Visit 1 for all others.

Study Day refers to the number of days elapsed since randomization date plus 1 (e.g., Study Day 1 is the day of randomization). For dates prior to randomization, study day is the negative number of days elapsed between the date under consideration and the day of randomization. Therefore, the study day is always different from 0.

For efficacy analyses also referred to as 'Day'.

Treatment Day refers to the number of days elapsed since study treatment start date plus 1 (e.g., Treatment Day 1 is the day of study treatment start). For dates prior to study treatment start, treatment day is the negative number of days elapsed between the date under consideration and the day of study treatment start. Therefore, it is always different from 0.

For safety analyses also referred to as 'Day'.

11.2 Analysis period definitions

11.2.1 Efficacy study periods

The 'Efficacy Study Period' of primary interest in this study is the period from randomization up to the EOS date, defined as: [Randomization; EOS].

11.3 Re-assignment of premature EOT visits / Visit windowing

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

- Scheduled nominal visits, e.g., Week xx, are identified based on the eCRF recorded nominal visit label. Note that the eCRF allows for considering a visit under multiple visit labels, e.g., a Follow-up 1 or a Relapse visit can be considered in addition a Week xx visit. This 2nd visit label is collected on the Visit Summary eCRF under 'Corresponding visit'. In selecting results for a nominal scheduled visit both visit labels are considered. Priority is given to the 1st visit label, afterwards to the 2nd visit label. If at a scheduled nominal visit no result is available, premature EOT remapping is applied.

- If a result is missing for a scheduled visit, it can be replaced with a result from a premature EOT visit available in the respective visit window [see Table 6 and Table 7].

Table 6 Premature end of treatment remapping (except MRI)

Visit window	Nominal value Day	Lower limit for Day	Upper limit for Day
Week 2	15	2	22
Week 4	29	23	70
Week 12	85	71	126
Week 24	169	127	210
Week 36	253	211	294
Week 48	337	295	378
Week 60	421	379	462
Week 72	505	463	546
Week 84	589	547	630
Week 96	673	631	714
Week 108	757	715	798
Week 120	841	799	882
Week 132	925	883	966
Week 144	1009	967	1050
Week 156	1093	1051	Open end

Day refers to treatment day, i.e., days from study treatment start.

Table 7 Premature end of treatment remapping (MRI)

Visit window	Nominal value Day	Lower limit for Day	Upper limit for Day
Week 24	169	85	252
Week 48	337	253	420
Week 72	505	421	588
Week 96	673	589	756
Week 120	841	757	924
Week 144	1009	925	1050
Week 156	1093	1051	Open end

Day refers to treatment day, i.e., days from study treatment start.

11.4 Summaries by visit

Visit based safety and PD assessments are generally summarized according to the nominal visit. Except for Visit 18 (EOT/Week 156) in subjects prematurely discontinuing study treatment, Visit 19 (FU7d, Day 7 follow-up assessment for lymphocyte subset only), and Visit 20 (FU, Day 30 follow-up assessment). Those are derived following the rules below:

- Premature EOT visits are re-assigned following the visit windowing described in Section 11.3
- Day-7 follow-up assessment: Any assessment within EOT date + 6 days and EOT date + 15 days. If multiple assessments fall into that period, the one corresponding to the regular FU7d visit (Visit 19) is selected, if none of the multiple assessments corresponds to that visit, the one closest to EOT date + 7 days is selected, if there are two closest assessments, the later one is selected.
- Day-30 follow-up assessment: Any assessment within EOT date + 16 days and EOT date + 37 days. If multiple assessments fall into that period, the one corresponding to the regular FU visit (Visit 20) is selected, if none of the multiple assessments corresponds to that visit, the one closest to EOT date + 30 days is selected, if there are two closest assessments, the later one is selected.

In addition, the 'Last on-treatment' assessment is flagged. This is defined to be the latest assessment prior to or on EOT date + 1 day (last on treatment may come from a scheduled or an unscheduled visit).

Summaries by visit are presented by Baseline (derived), and further scheduled nominal visits up to Week 156 (irrespectively if conducted during PTOP or not), Last on-treatment, and derived Follow-up visits (FU7d, FU). Generally, by visit tables are tabulating the baseline and nominal and derived visits as follows:

- Baseline (Note: This is not a nominal visit but the derived baseline; see Section 5.5.1)
- Visit 4 - Week 2

- Visit 5 - Week 4
- Visit 6 - Week 12
- Visit 7 - Week 24
- Visit 8 - Week 36
- Visit 9 - Week 48
- Visit 10 - Week 60
- Visit 11 - Week 72
- Visit 12 - Week 84
- Visit 13 - Week 96
- Visit 14 - Week 108
- Visit 15 - Week 120
- Visit 16 - Week 132
- Visit 17 - Week 144
- Visit 18 - Week 156
- Last on-treatment (derived; see Section 5.5.1)
- Day-7 follow-up (derived) (lymphocyte subset only)
- Day-30 follow-up (derived)

Premature EOT visits are mapped to and summarized within a scheduled visit following the window approach described in Section 11.3; they will not be summarized as "Visit 18 - Week 156" unless they are mapped to this visit as per approach described in Section 11.3.

As per protocol, total lymphocyte counts will be assessed every 4 weeks up to Week 24 (i.e., there are 3 protocol mandated between-visit assessments for those tests at Week 8, Week 16, and Week 20 when no regular visit is scheduled).

These assessments are considered scheduled and are included in corresponding by-visit tabulations labeled as follows:

- Additional Visit - Week 8
- Additional Visit - Week 16
- Additional Visit - Week 20

Visit-based efficacy are summarized according to the nominal visit up to EOS, irrespective if conducted during PTOP or not:

- Baseline (Derived)
- Visit 4 - Week 2
- Visit 6 - Week 12
- Visit 7 - Week 24
- Visit 9 - Week 48
- Visit 11 - Week 72
- Visit 13 - Week 96

- Visit 15 - Week 120
- Visit 17 - Week 144
- Visit 18 - Week 156

Premature EOT visits are mapped to and summarized within a scheduled visit following the window approach described in Section 11.3; they will not be summarized as "Visit 18 - Week 156" unless they are mapped to this visit as per approach described in Section 11.3.

EOS visit is defined for efficacy endpoints and JCV:

- For subjects who complete the treatment period, and for subjects who prematurely discontinue study treatment and do not enter the PTOP, the EOS visit corresponds to the 30 day follow-up visit (FU) for efficacy endpoints, and for the last available visit for JCV.
- For subjects who prematurely discontinue study treatment and enter the PTOP period, the EOS visit corresponds to the last visit of the PTOP.

12 HANDLING OF MISSING/INCOMPLETE DATE 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*.

12.1 Previous / concomitant therapies

For previous and concomitant therapies with missing or partial start and end dates the following rules for assignation to previous therapies and treatment concomitant therapies are applied [see Table 8].

Table 8 Handling of missing or partial start and end dates for previous/concomitant therapies

eCRF page	Start date	End date	Previous / Concomitant
Prev*	Unless start date clearly after/on STS (Start date either: prior to STS date, partial with either lower or upper limit prior to STS date, or missing)	Unless end date after/on STS (Either prior STS, partial with either lower or upper limit prior STS, or missing)	Previous
Con**	Unless start date clearly after/on STS (as above)	Prior to STS date; or Partial with upper limit prior to STS date;	Previous
Con**	Start date confirmed prior STS (Start date either: prior to STS date, partial with upper limit prior to STS date)	End date on STS date and 'Ongoing at start of Treatment' ticked 'No'; or Partial with lower limit prior to STS date and upper limit after/on STS date and 'Ongoing at start of Treatment' ticked 'No';	Previous
Any	All other cases not listed above for which Start date prior to or on EOT+15 days (Start date either: prior to or on EOT+15 days, or partial with lower limit prior to or on EOT+15 days)	Any	Treatment concomitant
Any	All other cases not listed above for which Start date after EOT+15 days (Start date either: after EOT+15 days, or partial with lower limit after EOT+15 days)	Any	Post-treatment

STS = Study treatment start; For subjects randomized but not treated the randomization date is used instead of the STS.

* Includes 'Previous Medications' or any of the individual MS Specific Treatment History Log eCRFs (e.g., 'Interferon beta-1a history', 'Glatiramer acetate history' etc): On these forms as per CRF completion guidelines only medications that stopped prior to signature of informed consent are to be recorded.

** Includes all forms collecting therapies apart from 'Previous Medications' and any of the individual MS Specific Treatment History Log eCRFs.

Subjects randomized but not treated are not considered to have any treatment concomitant medications.

To further flag treatment concomitant therapies as 'ongoing at study treatment start' or 'started during study drug administration' medications the following rules apply:

- Study concomitant therapies with missing start date or partial start dates potentially falling into the treatment period (i.e., lower limit prior or on EOT) are considered to have been started during study drug administration unless 'Ongoing at start of Treatment' ticked 'Yes' then it is considered ongoing at study treatment start.

12.1.1 Previous / concomitant therapies date imputation

The following imputation of partial dates is made:

Previous therapies: Impute partial start date with lower limit, and partial end date with minimum of upper limit and study treatment start date − 1. Missing dates are not imputed.

Treatment concomitant therapies ongoing at study treatment start: Impute partial start date with lower limit and partial end date with upper limit. Missing dates are not imputed.

Treatment concomitant therapies not ongoing at study treatment start: Impute partial start date with maximum of lower limit and study treatment start date, impute partial end date with upper limit. Missing dates are not imputed.

12.2 Relapse

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

eCRF = electronic case report form.

12.3 Adverse event onset and death dates

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

- Onset day missing: If month and year is clearly on or after study treatment start (short: STS, the date of first study drug intake) month and year, and clearly before or on the month and year of last intake date + 15 days, consider the event as treatment-emergent. With regard to the date imputation, the following rules are applied:
  - If the record's origin is the First-Dose eCRF and month and year correspond to month and year of STS, impute onset date and time as the date and time of the first study drug intake.
  - If the record's origin is the First-Dose eCRF and month and year are clearly after STS month and year, but a date of re-initiation with corresponding month and year is documented, impute onset date and time as the date and time of this re-initiation study drug intake (in case more than one study drug re-initiations are documented in this month and year, impute with the date and time of the earliest of those).
  - If the record's origin is the First-Dose eCRF and month and year are clearly after STS month and year, but no date of re-initiation with corresponding month and year is documented, the onset date is imputed to the 1st day of the month and year given and time to 00:00.

  - If the record's origin is the main CRF and month and year is clearly on or after STS month and year, the onset date is imputed as the maximum of (date of Treatment Day 2, 1st day of the month and year given) and time is imputed to 00:00.
  - If event onset month and year is clearly prior to the STS month and year, the onset date is imputed to the last day of the given month (i.e., 28th, 29th, 30th, or 31st depending on month) and year and time is imputed to 00:00. This imputation is done irrespective of eCRF origin (First-Dose or Main).

- Onset day and month missing: If the year is the same year as the year of STS or later, and if the year is prior to or in the same year as the last intake date + 15 days, consider AE as treatment-emergent. With regard to the date imputation, the following rules are applied:
  - If the record's origin is the First-Dose eCRF and the year corresponds to the year of STS, impute onset date and time as the date and time of the STS.
  - If the record's origin is the First-Dose eCRF and the year is clearly after the year of STS, but a date of re-initiation with corresponding year is documented, impute onset date and time as the date and time of this re-initiation study drug intake (in case more than one study drug re-initiations are documented in this year, impute with the date and time of the earliest of those).
  - If the record's origin is the First-Dose eCRF and the year is clearly after the year of STS, but no date of re-initiation with corresponding year is documented, the onset date is imputed to January 1st of the given year and time to 00:00.
  - If the record's origin is the main CRF and year is clearly on or after the year of STS, the onset date is imputed as date of maximum of (Treatment Day 2, January 1st of the given year) and time is imputed to 00:00.
  - If the event onset year is clearly prior to the year of STS, the onset date is imputed to 31-December of the given year and time is imputed to 00:00. This imputation is done irrespective of eCRF origin (First-Dose or Main).

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

- Onset date is completely missing: Consider as treatment-emergent.
  The onset date and time is imputed as date and time of the STS (if death date or if AE onset date with record's origin is the First-Dose eCRF), if AE onset date with record origin in the main CRF, the onset date is imputed as Study Day 2.

12.4 Study treatment start and EOT

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

Details for assigning safety events and assessments to the treatment-emergent period, as described in Section 5.5.1, apply.

Type of date/time	Date/time is incomplete	Date/time is missing
Study treatment start date	Maximum of lower limit and randomization date.	Randomization date
Study treatment start time	See missing.	0:00 or randomization time if study treatment start date (after imputation) is equal to randomization date.
EOT	Earliest between treatment start date + 1092 days (156 weeks), the upper limit, EOS date, and Death date.	Earliest between treatment start date + 1092 days (156 weeks), EOS date and Death date.

EOS = End of Study; EOT = End of Trial.

13 LIST OF SUMMARY TABLES, LISTINGS AND FIGURES

The list of summary tables, listings, and figures is stored in a separate document in Excel format.

14 REFERENCES

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[Pocock 2002] Pocock SJ, Clayton TC, Altman DG. Survival plots of time-to-event outcomes in clinical trials: good practice and pitfalls. The Lancet. 2002;359:1686-9.

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15 ATTACHMENTS

Attachment 1 Protocol Deviation Code List

Protocol deviation code list version 4.0, 16 June 2020.

1 PROTOCOL DEVIATIONS BEFORE RANDOMIZATION

Note: Applies to first screening attempt and re-screening, unless specified otherwise.

1.1 Informed consent and patient rights

Condition	Type	Identifier	Source/Instructions	Additional information expected?	Important PD
No informed consent form (ICF) signed	M	PD_MM.200	Monitor PD *PD to be reported even if subject is not randomized*		Yes
Informed consent form signed after first study procedure	P	PD_PP.201	eCRF [Inclusion Criterion 1] *Except subject number assignation - not a procedure* *PD to be reported even if subject is not randomized*		Yes
No ICF signed at re-screening	M	PD_MM.202	Monitor PD		Yes
Informed consent form signed after first study procedure at re-screening	P	PD_PP.203	eCRF [Inclusion Criterion 1 at re-screening] *Except subject number assignation - not a procedure* *PD to be reported even if subject is not randomized*		Yes
Informed consent procedures conducted by a non-qualified person	M	PD_MM.003	Monitor PD		Yes
During pre-randomization period, new ICF version not signed at first applicable visit	M	PD_MM.204	Monitor PD		Yes
Other violation of Informed consent procedures	M	PD_MM.205	Monitor PD		No

			e.g., wrong or draft version, wrong language, missing information (e.g., signature time…)		

1.2 General Eligibility

Condition	Type	Identifier	Source/Instructions	Additional information expected?	Important PD
Randomization performed without taking into account centrally provided quality review (MRI)	M	PD_MM.050	eCRF [MRI Summary] Monitor PD		No
Randomization performed based on local laboratory results	M	PD_MM.051	Monitor PD		No
Any pre-randomization safety assessment for eligibility not performed prior to randomization	M	PD_MM.206	eCRF Monitor PD *e.g., Dermatological exam, Blood pressure, Chest X-ray, Ophthalmological exam, OCT, Lab samples, Pregnancy tests, ECG, Spirometry* *Includes assessments not performed at all and assessments performed after randomization*		Yes
Any pre-randomization assessment not required for eligibility not performed prior to randomization	M	PD_MM.207	eCRF Monitor PD *e.g., Weight, Physical exam, Body temperature, Urinalysis, eC-SSRS, Smoking status, JCV serology, viral serology sample* *Includes assessments not performed at all and assessments performed after randomization*		No

Pre-randomization assessments not performed using centrally provided devices	M	PD_MM.054	Monitor PD *e.g., ECG*		No
Subject re-screened without sponsor approval	M	PD_MM.208	Monitor PD *GCS&E input*		No
Any pre-randomization safety assessment required for eligibility performed, but with at least one repeated assessment or test missing	M	PD_MM.209	Monitor PD / eCRF *e.g., V1 and V3 ECG confirming eligibility but V2 ECG not done; INR V1 available and V2 result unavailable*)		No
Any pre-randomization assessment required for eligibility performed, but results not available at randomization (subject retrospectively not eligible)	M	PD_MM.210	Monitor PD *e.g., Lab results available after randomization and not confirming eligibility*		Yes
Any pre-randomization assessment required for eligibility performed, but results not available at randomization (subject retrospectively eligible)	M	PD_MM.211	Monitor PD *e.g., Lab results available after randomization and confirming eligibility*		No
Any pre-randomization assessment required for eligibility not performed as per study protocol and not covered by another PD code	M	PD_MM.212	Monitor PD / eCRF		No
Pre-randomization EDSS not performed according to study protocol or performed after randomization	M	PD_MM.301	Monitor PD / eCRF [EDSS/FS forms] *Includes assessments not done*		Yes
Pre-randomization MRI not performed according to study protocol or performed after randomization	M	PD_MM.302	Monitor PD / eCRF [MRI Summary] *Includes assessments not done; MRI not repeated in case of unacceptable quality as per central overread, missing sequences*		Yes

Pre-randomization FSIQ-RMS not performed according to study protocol or performed after randomization	M	PD_MM.303	Monitor PD / eCRF [ePRO: FSIQ-RMS] *Includes assessments not done; FSIQ: e.g., symptoms domain not completed or completed less than 4 days, impact domain not completed; MRI: not repeated in case of unacceptable quality as per central over-read, missing sequences*		No

1.3 Inclusion Criteria

Condition	Type	Identifier	Source/Instructions	Additional information expected?	Important PD
Age < 18 or > 55 at Visit 1 (Screening)	P	PD_PP.007	eCRF [Inclusion Criterion 2]		Yes
Woman of childbearing potential without a negative serum pregnancy test at Visit 1 (Screening) or a negative urine pregnancy test at Visit 2 (Baseline)	P	PD_PP.008	eCRF [Inclusion Criterion 3a]		Yes
Woman of childbearing potential not agreeing to undertake monthly urine pregnancy tests during the study or up to 30 days after study treatment discontinuation	P	PD_PP.213	eCRF [Inclusion Criterion 3b]		Yes
Woman of childbearing potential not agreeing to use reliable methods of contraception until 30 days after study treatment discontinuation as described in protocol section 4.5.2	P	PD_PP.214	eCRF [Inclusion Criterion 3c]		Yes

Subject presenting no diagnosis of MS as defined by the revised (2010) McDonald Diagnostic Criteria for MS or with no relapsing course from onset (i.e., not RRMS or SPMS with superimposed relapses)	P	PD_PP.012	eCRF [Inclusion Criterion 4]		Yes
Subject not treated with DMF for at least 6 months prior to Visit 1 (Screening)	P	PD_PP.013	eCRF [Inclusion Criterion 5]		Yes
Subject with no active disease after at least 3 months of DMF treatment as per protocol inclusion criterion 6	P	PD_PP.215	eCRF [Inclusion Criterion 6a] [Inclusion Criterion 6b] [Inclusion Criterion 6c]		Yes
Subject not assessed as ambulatory or with EDSS > 6.0 at Visit 1 (Screening) or Visit 2 (Baseline)	P	PD_PP.016	eCRF [Inclusion Criterion 7]		Yes
Subject not meeting lymphocyte count requirements at Visit 1 (Screening) or Visit 2 (Baseline) as per protocol inclusion criteria 8	P	PD_PP.017	eCRF [Inclusion Criterion 8]		Yes

1.4 Exclusion Criteria

Condition	Type	Identifier	Source/Instructions	Additional information expected?	Important PD
Lactating or pregnant woman or woman intending to become pregnant during the study	P	PD_PP.018	eCRF [Exclusion Criterion 1]		Yes
Presenting with a diagnosis of MS with progressive course from onset (i.e., PPMS or PRMS)	P	PD_PP.019	eCRF [Exclusion Criterion 2]		Yes
Evidence of a relapse of MS within 30 days prior to baseline EDSS	P	PD_PP.020	eCRF [Exclusion Criterion 3]		Yes

assessment or between baseline EDSS assessment and randomization					
Treatment with beta-blockers, diltiazem, verapamil, digoxin or any other anti-arrhythmic or HR lowering systemic therapy within 15 days prior to randomization	P	PD_PP.021	eCRF [Exclusion Criterion 4a]		Yes
Treatment with adrenocorticotropic hormone (ACTH), systemic corticosteroids, or vaccination with live vaccines within 30 days prior to randomization	P	PD_PP.022	eCRF [Exclusion Criterion 4b]		Yes
Treatment with plasmapheresis, cytapheresis, intravenous immunoglobulin or with an investigational drug as specified in the protocol within 90 days prior to randomization	P	PD_PP.023	eCRF [Exclusion Criterion 4c]		Yes
Treatment with daclizumab (applicable since protocol v5), IFN beta-1a, IFN beta-1b, glatiramer acetate, other systemic immunosuppressive treatment, or fingolimod as specified in the protocol within 180 days prior to randomization	P	PD_PP.216	eCRF [Exclusion Criterion 4d]		Yes
Treatment with natalizumab or non-lymphocyte-depleting experimental biological agents within 12 months prior to randomization	P	PD_PP.217	eCRF [Exclusion Criterion 4e]		Yes

Treatment with lymphocyte-depleting biological agents (such as rituximab or ocrelizumab) or cladribine within 24 months prior to randomization	P	PD_PP.026	eCRF [Exclusion Criterion 4f]		Yes
Treatment with alemtuzumab, mitoxantrone, ponesimod, other investigational S1P modulators, stem-cell transplantation, leflunomide/teriflunomide (unless washed-out) at any time prior to randomization	P	PD_PP.027	eCRF [Exclusion Criterion 4g]		Yes
Any infection or infection risk as per exclusion criteria 5, 6 and 7	P	PD_PP.304	eCRF [Exclusion Criteria 5, 6, 7]		Yes
Known Progressive Multifocal Leukoencephalopathy (PML) infection / evidence of new neurological symptoms / MRI signs within 6 months prior to randomization compatible with a PML infection diagnosis	P	PD_PP.305	eCRF [Exclusion Criterion 8]		Yes
Any malignancy or pre-cancerous conditions as per protocol exclusion criteria 9 and 10	P	PD_PP.218	eCRF [Exclusion Criteria 9, 10]		Yes
Presence of macular edema	P	PD_PP.030	eCRF [Exclusion Criterion 11]		Yes
Any of the cardiovascular conditions as per protocol exclusion criteria 12	P	PD_PP.031	eCRF [Exclusion Criteria 12a to 12h]		Yes
Type 1 or 2 diabetes that is poorly controlled according to the investigator's judgment or diabetes complicated with organ involvement such as nephropathy or retinopathy	P	PD_PP.032	eCRF [Exclusion Criterion 13]		Yes

Subjects with a clinically significant pulmonary condition as per protocol exclusion criteria 14	P	PD_PP.033	eCRF [Exclusion Criteria 14a, 14b]		Yes
Active or latent TB, except if there is documentation that the subject has received adequate treatment for latent TB infection or TB disease previously as per protocol exclusion criteria 15	P	PD_PP.034	eCRF [Exclusion Criterion 15]		Yes
Any of the hematology abnormal laboratory values at Visit 1 (Screening) or Visit 2 (Baseline) as per protocol exclusion criteria 16	P	PD_PP.035	eCRF [Exclusion Criteria 16a to 16d]		Yes
Subject with known and documented moderate or severe hepatic impairment	P	PD_PP.036	eCRF [Exclusion Criterion 17]		Yes
Any abnormal liver laboratory values at Visit 1 (Screening) or Visit 2 (Baseline) as per protocol exclusion criteria 18	P	PD_PP.037	eCRF [Exclusion Criterion 18a to 18c]		Yes
Contraindications for MRI as per protocol exclusion criteria 19	P	PD_PP.038	eCRF Up to protocol version 4 included: [Exclusion Criteria 19a to 19d] From protocol version 6 onwards: [Exclusion Criteria 19a to 19c]		Yes
Subject with history of clinically significant drug or alcohol abuse	P	PD_PP.039	eCRF [Exclusion Criterion 20]		Yes
Subject with known allergy to any of the ponesimod formulation excipients	P	PD_PP.040	eCRF [Exclusion Criterion 21]		Yes
Subject with any other clinically relevant medical or surgical condition which, in the opinion of the	P	PD_PP.041	eCRF [Exclusion Criterion 22]		Yes

investigator, would put the subject at risk by participating in the study					
Subject unlikely to comply with protocol as per protocol exclusion criteria 23	P	PD_PP.042	eCRF [Exclusion Criterion 23]		Yes

1.5 Pregnancy and Contraception

Condition	Type	Identifier	Source/Instructions	Additional information expected?	Important PD
Woman of childbearing potential with a negative serum pregnancy test at Visit 1 (Screening) and a negative urine pregnancy test at Visit 2 (Baseline) performed < 21 days apart	M	PD_MM.009	Monitor PD / eCRF [Demographics] [Urine Pregnancy Test] [Central Lab] *e.g., serum and urine pregnancy tests performed 20 days apart*		No
Contraceptive methods requirements for WOCBP as described in protocol section 4.5.2 not followed by subject	M	PD_MM.219	Monitor PD / eCRF [Contraceptive Methods] *e.g., hormonal contraceptive started less than 30 days prior to randomization* *Note: To be used only if deviation occurred prior to randomization. If deviation occurred after randomization, use code MM.138*		No

1.6 Other

Condition	Type	Identifier	Source/Instructions	Additional information expected?	Important PD
Pre-randomization period > 45 days	P	PD_PP.055	eCRF [Randomization]		No

Any repeated assessment during pre-randomization period visits performed without respecting the minimum interval between assessments as defined per study protocol (except pregnancy tests)	M	PD_MM.056	Monitor PD / eCRF [Central lab] *For DM only: to be reported once*		No
Missing source documents related to pre-randomization period	M	PD_MM.058	Monitor PD		No
Incorrect stratum factor "EDSS <= or > 3.5" communicated to IVRS at randomization	P	PD_PP.220	eCRF		Yes

2 PROTOCOL DEVIATIONS AFTER RANDOMIZATION

Note: Applies any time after randomization, unless specified otherwise (e.g., during PTOP).

2.1 Informed consent and subject rights

Condition	Type	Identifier	Source/Instructions	Additional information expected?	Important PD
New ICF version not signed at first applicable protocol scheduled visit or signed after procedure related to new protocol version was performed	M	PD_MM.221	Monitor PD		No

2.2 Safety

Condition	Type	Identifier	Source/Instructions	Additional information expected?	Important PD
On Day 1 or on first day of re-initiation, any post-dose assessment not performed within 24 hours after pre-dose assessments	M	PD_MM.162	Monitor PD *To be reported in FDM database*		Yes

On Day 1 or on first day of re-initiation of study drug (when post-dose monitoring is required), subject discharged from hospital before 4 hour post-dose or before criteria for discharge were met	M	PD_MM.117	Monitor PD / eCRF [Systolic/Diastolic Blood Pressure − (Post-dose] [Discharge from Hospital] [12 Lead ECG − Post-dose] *To be reported in FDM database*		Yes
On Day 1 or on first day of re-initiation of study drug (when post-dose monitoring is required), post-dose monitoring not performed according to protocol	M	PD_MM.118	Monitor PD *To be reported in FDM database*		No
During maintenance period, any interruption > 3 days where study drug was re-initiated without up-titration or without post-dose cardiac monitoring	M	PD_MM.222	Monitor PD / eCRF [Study Drug Log]		Yes
Study drug not interrupted or discontinued (if applicable) upon reaching any of the cardiovascular discontinuation criteria	M	PD_MM.119	Monitor PD / eCRF [Premature Discontinuation of Study Treatment] [ECG] *Refer to section 5.1.12.1 of the study protocol*		Yes
Study drug not interrupted or discontinued (if applicable) upon reaching any of the hematological abnormalities discontinuation criteria	M	PD_MM.120	Monitor PD / eCRF [Study Drug Log] [Premature Discontinuation of Study Treatment] [Local Laboratory] [Central Lab] *Refer to section 5.1.12.2 of the study protocol*		Yes
Study drug not interrupted or discontinued (if applicable) upon	M	PD_MM.124	Monitor PD / eCRF [Study Drug Log]		Yes

subject experiencing an event of suspected opportunistic infection			[Local Laboratory] [AE] [Central Lab] *Refer to section 5.1.12.3 of the study protocol*		
Subject not monitored or discontinued (if applicable) from study drug upon reaching any of the respiratory system (PFT decrease and persistent respiratory AEs) monitoring and discontinuation criteria	M	PD_MM.125	Monitor PD / eCRF [Study Drug Log] [Premature Discontinuation of Study Treatment] [AE] [Spirometry forms] *GCS&E input* *Refer to section 5.1.12.4 of the study protocol*		Yes
Study drug not interrupted or discontinued (if applicable) upon pregnancy determination	M	PD_MM.126	Monitor PD / eCRF [Study Drug Log] [Premature Discontinuation of Study Treatment] [AE] *Refer to section 5.1.12.5 of the study protocol*		Yes
Study drug not interrupted or discontinued (if applicable) upon reaching any of the liver abnormalities monitoring and discontinuation criteria	M	PD_MM.128	Monitor PD / eCRF [Study Drug Log] [Premature Discontinuation of Study Treatment] [Local Laboratory] [AE] [Central Lab] *Refer to section 5.1.12.6 of the study protocol*		Yes
Study drug not interrupted or discontinued (if applicable) upon	M	PD_MM.129	Monitor PD / eCRF [Study Drug Log]		Yes

reaching any of the ocular abnormalities discontinuation criteria			[Premature Discontinuation of Study Treatment] [AE] *Refer to section 5.1.12.7 of the study protocol*		
No unscheduled OCT examination performed upon experiencing suspected clinically significant findings indicative of macular edema	M	PD_MM.223	Monitor PD / eCRF [AE] *e.g., blurred vision*		Yes
Subject not discontinued from study drug after discontinuation from DMF background therapy	P	PD_PP.132	eCRF [Study Drug Log] [Drug Log - DMF (Tecfidera)] *Refer to section 5.1.12.8 of the study protocol*		Yes
Subject remained on study drug but not re-consented to continue participation in the study after experiencing a confirmed relapse or a 24-week confirmed disability accumulation	M	PD_MM.133	Monitor PD / eCRF [Informed Consent]		Yes
Subject with active uveitis not monitored and managed as per guidance described in the study protocol	M	PD_MM.224	Monitor PD / eCRF [AE] *Refer to section 5.1.12.7.1 of the study protocol*		Yes
No follow-up monitoring provided until any event of clinical concern has resolved or until the condition has stabilized or until the change was regarded as no longer clinically relevant	M	PD_MM.225	Monitor PD		Yes
Treatment of relapse with ACTH or other corticosteroids, dose or route of	M	PD_MM.226	Monitor PD / eCRF [Relapse Summary]		No

administration than recommended per study protocol			[Corticosteroids for Treatment of Relapse] [Previous/Concomitant Medications] *Includes tapering, treatment > 5 days, IM administration*		
During treatment period, any start or dose increase of dalfampridine	M	PD_MM.140	Monitor PD / eCRF [Previous/Concomitant Medications]	\CM\CMSPID\\	Yes
During treatment period, any stop or dose decrease of dalfampridine	M	PD_MM.141	Monitor PD / eCRF [Previous/Concomitant Medications] [Coding]	\CM\CMSPID\\	No
During treatment period, QT-prolonging drug with known risk of Torsades de pointes started or increased in dose without adhering to recommendation defined in study protocol	M	PD_MM.227	Monitor PD / eCRF [Previous/Concomitant Medications] [Study Drug Log] [ECG] *Refer to Appendix 4 of the study protocol*		Yes
During treatment period, treatment with systemic corticosteroids and ACTH except for MS relapses and for short-term treatment with low dose or inhaled corticosteroids for pulmonary conditions	M	PD_MM.143	Monitor PD / eCRF [Relapse Summary] [Corticosteroids for Treatment of Relapse] [Previous/Concomitant Medications] [Coding]		Yes
During treatment period, treatment with any disease modifying drug for MS other than DMF and study drug prescribed as per protocol	M	PD_MM.144	Monitor PD / eCRF [Previous/Concomitant Medications] [Coding]	\CM\CMSPID\\	Yes
During treatment period, treatment with immunosuppressive (e.g., cladribine, mitoxantrone or other systemic immunosuppressive: azathioprine, cyclophosphamide,	M	PD_MM.145	Monitor PD / eCRF [Previous/Concomitant Medications] [Coding] *Refer to section 5.2.6 of the study protocol*		Yes

cyclosporine or methotrexate) except DMF					
During treatment period, treatment with intravenous immunoglobulins	M	PD_MM.146	Monitor PD / eCRF [Previous/Concomitant Medications] [Coding]		Yes
During treatment period, treatment with plasma exchange or total lymphoid irradiation	M	PD_MM.147	Monitor PD / eCRF [Previous/Concomitant Medications] [Coding]		Yes
During treatment period, vaccination with live vaccines	M	PD_MM.148	Monitor PD / eCRF [Previous/Concomitant Medications] [Coding]		Yes
During treatment period, treatment with another investigational drug	M	PD_MM.228	Monitor PD / eCRF [Previous/Concomitant Medications] [Coding]	\CM\CMSPID\\	Yes
During treatment period, treatment with beta-blockers, diltiazem, verapamil, digoxin, or any other anti-arrhythmic or HR-lowering systemic therapy	M	PD_MM.150	Monitor PD / eCRF [Previous/Concomitant Medications] [Coding]		Yes
During treatment period, any investigational therapeutic procedure for MS	M	PD_MM.151	Monitor PD / eCRF [Previous/Concomitant Medications] [Coding]	\CM\CMSPID\\	Yes
Lymphocyte repeat testing not performed or was performed out-of-time window	M	PD_MM.121	Monitor PD / eCRF [Local Laboratory] [Central Lab]		Yes
Spirometry repeat testing not performed or performed out-of-time window	M	PD_MM.122	Monitor PD / eCRF [Spirometry]		Yes
Liver function repeat testing not performed or performed out-of-time window	M	PD_MM.123	Monitor PD / eCRF [Local Laboratory] [Central Lab]		Yes

Any spirometry assessment not performed as per protocol	M	PD_MM.184	Monitor PD *e.g., less than 3 technically acceptable and repeatable traces, more than 8 expiratory manoeuvers*		No
Any repeated safety assessment not performed according to the time interval defined in the study protocol	M	PD_MM.171	Monitor PD / eCRF [Systolic/Diastolic Blood Pressure; Systolic/Diastolic Blood Pressure − Pre-dose; Spirometry; Ophthalmological examination; OCT; Body Weight; Physical Examination; Body Temperature; Pulse Rate; Dermatological Examination] [Central Lab] *For DM only: to be reported once*		No
Two consecutive safety assessments not performed or performed but results not available and no re-test done	M	PD_MM.229	Monitor PD / eCRF Vendor data *Valid for each following assessment if not performed as a whole: Spirometry, ECG, Physical exam, Body weight, Body temperature, Blood pressure, both Ophthalmology and OCT, Chemistry or Hematology*		Yes
Single scheduled non-blood safety assessment missing	M	PD_MM.230	Monitor PD / eCRF Vendor data *Valid for each following assessment if not performed as a whole: Spirometry, Urinalysis, Body temperature, Weight, eC-SSRS (if not done or if recorded on paper), ECG, both Ophthalmology and OCT* *Not valid if PD_MM.229 is applicable* *For DM only: to be reported once*		No

Any missing single blood safety assessment not performed or performed but with unavailable results	M	PD_MM.231	Monitor PD / eCRF Vendor data *Valid for whole Hematology or Chemistry* *Not valid if PD_MM.229 is applicable* *For DM only: to be reported once*		No
Any of the monthly total lymphocyte count assessments during the first 24 weeks of treatment not performed	M	PD_MM.174	Monitor PD		Yes

2.3 Contraception and Pregnancies

Condition	Type	Identifier	Source/Instructions	Additional information expected?	Important PD
Contraception requirement for woman of childbearing potential not followed	M	PD_MM.138	Monitor PD / eCRF [Contraception Log]		Yes
Any urine pregnancy test to be done at home or at site not performed or any test result not shared with study personnel	M	PD_MM.232	Monitor PD / eCRF [Urine Pregnancy Test forms]		No
Study personnel did not remind women of childbearing potential to use the methods of contraception defined for this study	M	PD_MM.177	Monitor PD		No
Absence of appropriate follow-up of a subject pregnancy	M	PD_MM.127	Monitor PD / eCRF [AE] *Refer to section 10.3.2 of the study protocol*		Yes

2.4 Efficacy / Endpoint

Condition	Type	Identifier	Source/Instructions	Additional information expected?	Important PD
Any scheduled EDSS assessment not done	M	PD_MM.233	Monitor PD / eCRF		No
Any EDSS assessment not performed as per study protocol (impact on validity of EDSS score)	M	PD_MM.234	Monitor PD / eCRF *Any deviation not matching to codes PD_MM.306, PD_MM.307, PD_MM.152, PD_MM.233: To be reviewed by GCS&E for coding to either PD_MM.234 or PD_MM.235.*		Yes
Any EDSS assessment not performed as per protocol (no impact on EDSS score validity)	M	PD_MM.235	Monitor PD / eCRF *Any deviation not matching to codes PD_MM.306, PD_MM.307, PD_MM.152, PD_MM. 233: To be reviewed by GCS&E for coding to either PD_MM.234 or PD_MM.235*		No
No EDSS assessment performed to confirm a relapse	M	PD_MM.152	Monitor PD / eCRF [EDSS/FS forms]		Yes
EDSS assessment to confirm relapse performed after start of treatment with steroids	M	PD_MM.306	Monitor PD / eCRF [EDSS/FS forms] [Relapse Summary] [Corticosteroids for Treatment of Relapse] [Previous/Concomitant Medications]		Yes
EDSS assessment to confirm relapse performed >7 days after the onset of symptoms	P	PD_MM.307	Monitor PD / eCRF [EDSS/FS forms] [Relapse Summary]		No
FSIQ-RMS symptoms or impact domain at given visit or FSIQ-RMS	M	PD_MM.237	Monitor PD / Vendor data		No

impact domain not assessable at EOS visit			*e.g., symptoms domain not completed or completed less than 4 days, impact domain not completed; For DM only: to be reported once*		
Any MRI not performed as per protocol during treatment period or PTOP	M	PD_MM.308	Monitor PD / eCRF *e.g., not done or not repeated in case of MRI unacceptable as per central over-read, missing sequences, not as per protocol schedule*		Yes

2.5 Blinding

Condition	Type	Identifier	Source/Instructions	Additional information expected?	Important PD
At least one Actelion study team member (except site monitor, first dose monitor, first dose data scientist) had access to data potentially revealing treatment assignment as defined in study protocol	M	PD_MM.105	Monitor PD CTT PD *Except alerts as defined per protocol*		Yes
PI/study nurse, or any other personnel involved in the clinical care and management of subject deliberately tried to find out treatment assignment	M	PD_MM.238	Monitor PD *e.g., local lab results of lymphocytes*		Yes
Any site personnel had access to any post-randomization MRI report containing MS-related information without justification documented on the report	M	PD_MM.239	Monitor PD *Except in case of pre-defined threshold documented at site*		No

Treatment code broken before unblinding of the study for a reason not related to management of a clinical event	M	PD_MM.107	Monitor PD / eCRF [Subject Unblinding] Monitor to provide date of potential unblinding	\Date of Unblinding\\\	Yes
Efficacy assessor involved in clinical care and management or made aware of any data potentially revealing treatment assignment	M	PD_MM.240	Monitor PD *e.g., AEs, ECGs, lab results* *Monitor to provide date of potential unblinding*	\Date of potential unblinding\\\	Yes
PI/treating neurologist, clinical coordinator/study nurse or any other personnel involved in clinical care and management of subject who have had access to Day 1 or first day of SD re-initiation data	M	PD_MM.104	Monitor PD *Monitor to provide date of potential unblinding*	\Date of potential unblinding\\\	No
Any site personnel made aware of any data with unblinding potential assessed as high or moderate not related to management of a clinical event (except Day 1 or first day of re-initiation of study drug data)	M	PD_MM.309	Monitor PD *Data reviewed by at least one site member (except alerts as defined per protocol). Monitor to provide date. Unblinding type to be provided to CDDM based on "Potential Unblinding Event Documentation Form"); Type of unblinding to be reported for BST only for lymphocytes and/or WBC*	\Date of potential unblinding\ Type: Lymphocytes and/or Type: WBC\\	Yes
Any site personnel made aware of data with unblinding potential assessed as low (except Day 1 or day of re-initiation of study drug data)	M	PD_MM.310	Monitor PD *Data received but site claiming not reviewing the results (except alerts as defined per protocol); Monitor to provide date. Unblinding type to be provided to CDDM based on "Potential Unblinding Event Documentation Form");*	\Date of potential unblinding\ Type: Lymphocytes and/or Type: WBC\\	No

			Type of unblinding to be reported for BST only for lymphocytes and/or WBC		
Any site personnel involved in clinical care and management of subject who has reviewed Day 1 or re-initiation data	M	PD_MM.311	Monitor PD / *Monitor to provide date of unblinding*	\Date of potential unblinding\\\	Yes

2.6 Study drug

Condition	Type	Identifier	Source/Instructions	Additional information expected?	Important PD
Incorrect request of kit type via IVRS (i.e., up-titration kit instead of maintenance kit or vice-versa)	M	PD_MM.111	Monitor PD		Yes
Study drug taken from non-allocated kit	M	PD_MM.242	Monitor PD [Compliance from ePRO] *e.g., incorrect kit dispensed, accidental exchange* *NB: PD to be classified after unblinding into the following two protocol sub-deviations: 'Study drug taken from non-allocated kit: non-assigned treatment received' (PD_MM.242.1) or 'Study drug taken from non-allocated kit: assigned treatment received' at unblinding (PD_MM.242.2)*	Date of intake from incorrect kit (start and end date), incorrect kit number. I.e.: \Start date\End date\Kit number\	Yes
Lack of compliance with study drug during up-titration	M	PD_MM.243	Monitor PD / Vendor data [Compliance from ePRO] *e.g., study drug interrupted >1 day without restarting up-titration, drug not taken in the correct sequence*		Yes

			For DM only: to be raised manually in case of temporary interruption and no re-initiation.		
During up-titration period, at least one study drug dose not taken in the morning	M	PD_MM.244	Monitor PD *For DM only: to be reported once*		No
IMP temperature excursion of any dispensed kit with GQM (GMP-DP) approval for use	M	PD_MM.245	Monitor PD *For DM only: to be reported once*		No
IMP temperature excursion of any dispensed kit without GQM (GMP-DP) approval for use	M	PD_MM.246	Monitor PD *For DM only: to be reported once*		No
Misuse or abuse of the study treatment	M	PD_MM.137	Monitor PD / Vendor data / eCRF [Study Drug Log] *>3 doses taken on the same day*		Yes
Overdose of study treatment	M	PD_MM.312	eCRF / Monitor PD / *≤3 additional doses taken on the same day*		No
Study drug accountability and compliance check (if eDiary data available) not performed at least one applicable visit	M	PD_MM.247	Monitor PD *For DM only: to be reported once*		No
Subject did not return all used, partially used and unused study treatment blister packs at least one applicable visit	M	PD_MM.248	Monitor PD *For DM only: to be reported once*		No
Subject took study treatment on the day of study visit prior to visit assessment(s)	M	PD_MM.115	Monitor PD *For DM only: to be reported once*		No
Any missing recording of study drug intake in the eDiary	M	PD_MM.249	Monitor PD *e.g., no record at the time of study drug intake;*		No

			For DM only: to be reported once		
Study drug not available at site in due time	M	PD_MM.250	Monitor PD *Valid for late IMP delivery causing any interruption*		No

2.7 Other

Condition	Type	Identifier	Source/Instructions	Additional information expected?	Important PD
Any protocol scheduled visit not done (except follow-up and EOT visits)	M	PD_MM.251	Monitor PD / eCRF		No
Study drug administered but randomization not done per IRT system	M	PD_MM.252	Monitor PD / eCRF [Randomization] [Study Drug Log]		Yes
Study drug administered but date/time of first dose < date/time of randomization	P	PD_PP.253	eCRF		Yes
Any pre-dose assessment performed post-dose (except pre-dose PK sampling)	M	PD_MM.254	Monitor PD / eCRF *For DM only: to be reported once per visit if all assessments done post-dose*		No
Any randomized subject who never received study drug	M	PD_MM.101	Monitor PD *CRA: specify reason for not administering the study drug*		No
Any pre-dose PK sampling performed post-dose	M	PD_MM.255	Monitor PD / eCRF		No
Any PK sample not taken	M	PD_MM.256	Monitor PD / eCRF		No
Post-dose PK sampling performed out of time window	M	PD_MM.257	Monitor PD / eCRF		No
Missing source documents related to treatment period	M	PD_MM.179	Monitor PD		No

Vaccine-specific antibody titers assessment before and/or after non-live vaccination not performed	M	PD_MM.258	Monitor PD / eCRF		No
Any scheduled visit performed out of time window (except EOT and follow-up visits)	M	PD_MM.259	Monitor PD / eCRF [Visit Summary]		No

3 PROTOCOL DEVIATIONS AFTER END OF TREATMENT

Note: Applies any time after end of treatment unless specified otherwise.

3.1 Safety

Condition	Type	Identifier	Source/Instructions	Additional information expected?	Important PD
Any post-treatment safety follow-up not performed according to protocol	M	PD_MM.260	Monitor PD / eCRF [Visit Summary (FU Day30)] [Visit Summary (FU Day7)] [Study discontinuation] *e.g., follow-up performed out of time window, missing safety assessment*		No
Any applicable follow-up visits not done	M	PD_MM.313	Monitor PD / eCRF [Visit Summary (FU Day30)] [Visit Summary (FU Day7)]		Yes

3.2 Efficacy / Endpoint

Condition	Type	Identifier	Source/Instructions	Additional information expected?	Important PD
FSIQ-RMS symptoms domain not assessable at EOS visit	M	PD_MM.156	Monitor PD *e.g., not completed for at least 4 days*		No

Visit 18 (EOT) not performed within 7 days after study drug discontinuation for a subject who completed the treatment period as per study protocol	M	PD_MM.261	Monitor PD / eCRF [Visit Summary] *e.g., EOT visit performed out of time window*		No
Visit 18 (EOT) not performed within 7 days after study drug discontinuation for a subject who prematurely discontinued study drug	M	PD_MM.262	Monitor PD / eCRF [Visit Summary] *e.g., EOT visit performed out of time window*		No
Visit 18 (EOT) not performed for a subject who completed the treatment period as per study protocol	M	PD_MM.314	Monitor PD / eCRF *e.g., EOT visit not done*		Yes
Visit 18 (EOT) not performed for a subject who prematurely discontinued study drug	M	PD_MM.315	Monitor PD / eCRF *e.g., EOT visit not done*		Yes

4 PROTOCOL DEVIATIONS AT ANYTIME DURING THE STUDY

4.1 Safety and Pregnancy

Condition	Type	Identifier	Source/Instructions	Additional information expected?	Important PD
Any SAE reporting not performed as per protocol (e.g., delayed)	M	PD_MM.178	Monitor PD [AE]		Yes
Any pregnancy reporting not performed as per protocol	M	PD_MM.263	Monitor PD		Yes
Any MRI not reviewed by local radiologist or neurologist with MRI expertise	M	PD_MM.164	Monitor PD		Yes
Any assessment or procedure performed by a non-qualified or non-	M	PD_MM.264	Monitor PD		No

trained person (except EDSS and MRI) or by an non-delegated person					
PFT done without at least 5 minutes of rest prior to testing or done without refraining from taking SABA/LABA for 6/24 hours prior to testing	M	PD_MM.265	Monitor PD *For DM only: to be reported once*		No
Blood Pressure or ECG done without at least 5 minutes of rest prior to testing	M	PD_MM.266	Monitor PD *For DM only: to be reported once*		No
Any blood pressure assessment not measured in supine position	P	PD_PP.165	eCRF [Systolic/Diastolic Blood Pressure] *Visit 3 post-dose assessments: to be reported in FDM database* *For DM only: to be reported once*		No
Any Dermatology or Chest X-ray assessment not performed, or Chest X-ray: performed but results not available	M	PD_MM.267	Monitor PD / eCRF		No
Any lymphocyte sub-study assessment not performed or performed but with at least one test missing	M	PD_MM.173	Monitor PD / eCRF [Central Lab] *For DM only: to be reported once*		No
Blood pressure not measured on the same arm at every assessment	P	PD_PP.166	eCRF [Systolic/Diastolic Blood Pressure] *Visit 3 post-dose assessments: to be reported in FDM database* *For DM only: to be reported once*		No
Contraceptive methods not documented in the source notes	M	PD_MM.268	Monitor PD *For DM only: to be reported once*		No
Any safety or efficacy assessment or any questionnaire performed out of time window	M	PD_MM.172	Monitor PD / ePRO [SF-36v2™, WPAI:MS] *For DM only: to be reported once*		No

			Includes Phone Interviews		

4.2 Efficacy / Endpoint

Condition	Type	Identifier	Source/Instructions	Additional information expected?	Important PD
Any EDSS assessment performed by personnel not qualified or trained and certified (certification consists of the "Neurostatus e-Test" web-based interactive test)	M	PD_MM.102	Monitor PD / eCRF [EDSS/FS forms] *"Neurostatus e Test" web-based interactive test not passed or not re-certified as per protocol*		Yes
Any ophthalmology related EDSS assessment not performed by the efficacy assessor	M	PD_MM.269	Monitor PD *For DM only: to be reported once*		No
Any relapse assessment / symptom questionnaire not performed as per protocol at any time during the study	M	PD_MM.270	Monitor PD *Includes: - in-between visits telephone calls for relapse detection not done - any assessment for relapse detection not done (i.e.. questionnaires (RAQ, symptoms form, FSIQ-RMS, SF-36), Body temperature, Physical exam, Pulse rate or ECG) For DM only: to be reported for all missing relapse assessment / symptom questionnaire*		No
SF-36 or WPAI:MS questionnaire not performed or performed but with one or more question missing	M	PD_MM.271	Monitor PD / ePRO [SF-36v2™, WPAI:MS] *For DM only: to be reported once*		No
Any MSFC/SDMT missing or not performed as per protocol	M	PD_MM.272	Monitor PD		No

			Includes: Two PASAT forms (i.e. Form A and B) not administered in a counterbalanced way across visits (< 40% of one type) Incorrect sequence of tests or tests not timed; *For DM only: to be reported once*		

4.3 Other

Condition	Type	Identifier	Source/Instructions	Additional information expected?	Important PD
Any assessment performed not required by study protocol	M	PD_MM.273	Monitor PD *Except additional, repeated assessments or unscheduled visits which are required per protocol to follow-up on AEs or laboratory abnormalities* *e.g., extra labs, PFTs or MRIs;* *For DM only: to be reported once*		No
E-diary not used at any visit	M	PD_MM.274	Monitor PD *For DM only: to be reported once*		No
Data provided by site to external vendors containing potential patient identifiers	M	PD_MM.275	Monitor PD / Vendor data *e.g., real date of birth, subject's initials*		No
Any central laboratory report not signed / dated or signed / dated more than 5 calendar days after receipt	M	PD_MM.276	Monitor PD *For DM only: to be reported once*		No
Any applicable assessment not signed / dated (except central laboratory)	M	PD_MM.277	Monitor PD *e.g., ECG, PFT or MRI reports;* *Includes reports not signed and/or not dated;* *For DM only: to be reported once*		No

Any performed assessment not conducted as per protocol requirements	M	PD_MM.168	Monitor PD *Valid only if not covered by another PD code* *For DM only: to be reported once per deviation type*		No
Any other protocol deviation	M	PD_MM.186	Monitor PD *For DM only: to be reported once per type of issue*		No

16 APPENDICES

A. Adverse Events of Special Interest

AESIs include the anticipated risks of treatment with ponesimod and events that may be related to MS comorbitities.

The definitions for AESIs are based on the systematic approach using SMQs. 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 21.0. The following safety areas are addressed by the pre-defined AESIs:

- **Effect on heart rate and rhythm AESI (including hypotension)**

Effect on heart rate and rhythm AESI are identified by the PT in the following SMQ: Bradyarrhythmias (including conduction defects and disorders of sinus node function) (SMQ) [20000053]. In addition, the following PT will be added to the search for AEs addressing effects on heart rate and rhythm: 'Bradycardia', 'Electrocardiogram RR interval prolonged', 'Heart rate decrease', 'Presyncope', 'Syncope', 'Loss of consciousness', 'Chronotropic incompetence', and 'Central bradycardia'.

Hypotension will be identified searching the following PT: 'Blood pressure decreased', 'Blood pressure diastolic decreased', 'Blood pressure orthostatic decreased', 'Blood pressure systolic decreased', 'Diastolic hypotension', 'Hypotension', 'Mean arterial pressure decreased', 'Orthostatic hypotension', 'Procedural hypotension', 'Circulatory collapse', 'Blood pressure fluctuation', 'Labile blood pressure' and 'Blood pressure ambulatory decreased'.

- **Hypertension AESI**

Hypertension AESI are identified by the PT in the following SMQ: Hypertension SMQ (narrow scope) [20000147].

- **Hepatobiliary disorders / Liver enzyme abnormality AESI**

Hepatobiliary disorders/ Liver enzyme abnormality AESI are identified by the PT in the following SMQ: Drug related hepatic disorders – comprehensive (SMQ) (broad scope) [20000006]. This SMQ is included in the SMQ Hepatic disorder (SMQ) but only the PT included in Drug related hepatic disorders - comprehensive search (SMQ) are included to identify hepatobiliary disorders / Liver enzyme abnormality AESI.

- **Pulmonary AESI**

These AEs are identified by the PT the in the following SMQs: Asthma/bronchospasm (SMQ) (broad scope) [20000025] or Interstitial lung disease (SMQ) (broad scope) [20000042]. The PT 'Dyspnoea at rest', 'Dyspnoea', 'Dyspnoea exertional', 'Carbon monoxide diffusing capacity decreased', 'Pulmonary function test abnormal', 'Pulmonary function test decreased', 'Vital

capacity abnormal', and 'Vital capacity decreased' are added to the search pre-defined by SMQs Asthma/bronchospasm or Interstitial lung disease.

- **Macular edema AESI**

Macular edema AESI are identified by the following PT: 'Macular oedema', 'Macular hole', 'Macular pseudohole', 'Macular rupture', 'Macular cyst', 'Retinal oedema', 'Diabetic retinal oedema', 'Cystoid macular oedema', 'Papilloedema', and 'Pseudopapilloedema'.

- **Infection AESI**

Infection AESI are identified by the AEs belonging to the SOC Infections and Infestations (SOC), only if reported as serious or severe.

- **Herpetic infection AESI**

Herpetic infection AESI are identified by the PT in the following high level terms: Herpes viral infections and the following PTs will be added to the search for AEs addressing varicella zoster infection: 'Encephalitis post varicella', 'Herpes gestationis', 'Herpes simplex test positive', 'Human herpes virus 6 serology positive', 'Human herpes virus 8 test positive', and 'Herpes virus test abnormal'.

- **Skin malignancy AESI**

Skin malignancy AESI are identified by the PT in the following SMQs: Skin neoplasms malignant and unspecified (SMQ) (broad scope) [20000173].

- **Non-skin malignancy AESI**

Non-skin malignancy AESI are identified by the PT in the following SMQ: Malignant or unspecified tumours (SMQ) (broad scope) [20000091] excluding the PT which included in the following SMQs: Skin neoplasms, malignant and unspecified (SMQ) (broad scope) [20000173].

- **Seizure AESI**

Seizure AESI are identified by any PT in the following SMQ: Convulsions (narrow scope) (SMQ) [20000079].

B. Protocol deviation code list

Protocol deviations are defined as per the Protocol Deviation code list, version 4, 10 June 2020. Protocol deviations are categorized according to the categories in the Protocol Deviation code list (level 2 heading, e.g., 'Informed Consent and Patient Rights', 'General Eligibility', …) [Attachment 1].

C. Laboratory marked abnormalities

Table 9 Thresholds for marked laboratory abnormalities

Parameter (SI unit)	LL	LLL	HH	HHH
Hemoglobin (g/L)	< 100	< 80	> 20 g/L above ULN (for pre-treatment assessments, and post-treatment assessments when baseline ≤ ULN) or increase from baseline > 20 g/L (for post-treatment assessments when baseline is > ULN)	> 40 g/L above ULN (for pre-treatment assessments, and post-treatment assessments when baseline ≤ ULN) or increase from baseline > 40 g/L (for post-treatment assessments when baseline is > ULN)
MCH (pg/Cell)	ND	ND	ND	ND
MCV (fL)	ND	ND	ND	ND
Hematocrit (L/L)	< 0.28 (female) < 0.32 (male)	< 0.20	> 0.55 (female) > 0.60 (male)	> 0.65
Platelet count (10^9 /L)	< 75	< 50	> 600	> 999
RBC count (10^{12} /L)	ND	ND	ND	ND
WBC count (10^9 /L)	NA	< 1.9	> 20.0 **ALERT:** **> 20.0**	> 100.0
Lymphocyte (10^9 /L)	ND	< 0.2 **ALERT:** **< 0.2** **Decrease of > 50 % from the value of total lymphocyte count recorded at Visit 5 (Week 4) associated with a total lymphocyte count < 0.5 × 10^9/L recorded at two consecutive visits after Visit 5 (Week 4)**	> 4.0	≥ 8
Neutrophils (10^9 /L)	< 1.5	< 1.0	ND	ND

Eosinophils (10^9 /L)	ND	ND	> 5.0	ND
Monocytes (10^9 /L)	ND	ND	ND	ND
Basophils (10^9 /L)	ND	ND	ND	ND
Polymorphonuclear leucocyte/Band cells (%)	ND	ND	> 90%	> 95%
AST (U/L)*	ND	ND	≥ 3 ULN **ALERT:** **≥ 3 ULN**	≥ 5 ULN **ALERT:** **≥ 5 ULN** **≥ 8 ULN**
ALT (U/L)*	ND	ND	≥ 3 ULN **ALERT:** **≥ 3 ULN**	≥ 5 ULN **ALERT:** **≥ 5 ULN** **≥ 8 ULN**
Total bilirubin (umol/L)	ND	ND	≥ 2 ULN **ALERT:** **≥ 2 ULN combined with ALT or AST ≥ 3 ULN**	≥ 5 ULN
Alkaline Phosphatase (U/L)	ND	ND	> 2.5 ULN	> 5 ULN
INR*	ND	ND	> 1.5 ULN or > 1.5 times above baseline if on anticoagulation **ALERT:** **> 1.5 combined with ALT or AST ≥ 3 ULN**	> 2.5 ULN or > 2.5 times above baseline if on anticoagulation
Lactate deshydrogenase	ND	ND	ND	ND
Creatinine (umol/L)*	ND	ND	>1.5 ULN or >1.5 x baseline	> 3 ULN or >3 x baseline
Creatinine clearance (mL/min)	< 60	< 30	ND	ND
Urea (mmol/L)	ND	ND	> 2.5 ULN	> 5 ULN
Albumin (g/L)	< 30	< 20	ND	ND
Protein total (g/L)	ND	ND	ND	ND
C-reactive protein (mg/L)	ND	ND	ND	ND
Glucose (mmol/L)	< 3.0	< 2.2	> 8.9	>13.9
Potassium (mmol/L)	< 3.2	< 3.0	> 5.5	> 6.0
Sodium (mmol/L)	ND	< 130	> 150	> 155
Calcium (mmol/L)	< 2.0	< 1.75	> 2.9	> 3.1
Chloride (mmol/L)	ND	ND	ND	ND
Triglyceride (mmol/L)	ND	ND	> 3.42	> 11.4
Cholesterol (mmol/L)	ND	ND	> 7.75	> 12.92
Serum pregnancy test	ND	ND	ND	Positive **ALERT:** **Positive**

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

ALERT = study-specific alerts that trigger specific actions by the investigator [see Protocol Section 7.3.13.1]; ALT = alanine aminotransferase; AST = aspartate aminotransferase; NA = not applicable; INR = International Normalized Ratio; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; ND = not defined; may be complemented by definitions provided by the central laboratory (see central laboratory manual); RBC = red blood count; SI = international system of units; ULN = upper limit of normal; WBC = white blood cell.

Source: Protocol AC-058B302, appendix 6.

D. Document history

Version	Effective Date	Reason (main)
1.0	16 April 2020	New
2.0	16 June 2020	Reduction of scope and change to synoptic CSR