Statistical Analysis Plan

A Multinational, Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Once Daily Oral Administration of Laquinimod (0.6 or 1.5 mg) in Patients with Primary Progressive Multiple Sclerosis (PPMS)

Study TV5600-CNS-20006

(ARPEGGIO - A Randomized Placebo-controlled trial Evaluating laquinimod in PPMS, Gauging Gradations In MRI and clinical Outcomes)

NCT02284568

Date: June 2017

TEVA BRANDED PHARMACEUTICAL PRODUCTS R&D, INC.

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Phase 2

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Prepared by: [redacted]

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1.0 Final	May, 2012	[redacted]	[redacted]
2.0, Final	June, 2017	[redacted]	[redacted]

SAP AMENDMENT RATIONALE VERSION 2.0 (JUNE 2017)

Following LAQ-MS-305 (CONCERTO) study results in RRMS, a gender effect was seen as a potential subpopulation for laquinimod treatment to be further explored. The sponsor decided to include a gender subgroup analysis for both the primary and all secondary endpoints.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

9HPT	9-Hole Peg test
BA	brain atrophy
BICAMS	Brief International Cognitive Assessment for Multiple Sclerosis
BMI	Body Mass Index
CDP	confirmed disability progression
CGR	Country/Geographical Region
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
CSF	cerebrospinal fluid
CSR	Clinical Study Report
ECG	electrocardiogram
EDSS	Expanded Disability Status Scale
ET	early termination
FDA	Food and Drug Administration
FSS	Functional System Score
ICH	International Conference on Harmonization
ITT	intent-to-treat
LCVA	low contrast visual acuity
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MRI	magnetic resonance imaging
MSWS-12	12-Item Multiple Sclerosis Walking Scale
MTR	magnetization transfer ratio
NABT	Normal-appearing brain tissue
OCT	optical coherence tomography
PGx	pharmacogenomic(s)
PP	per-protocol
PPK	population pharmacokinetic
PPMS	Primary Progressive Multiple Sclerosis
PVBC	Percentage in Brain Volume Change
SAP	Statistical Analysis Plan
SDMT	symbol digit modalities test
SDR	Study data review
ST	Safety (population)

T25FW	timed 25-foot walk
WHO drug	World Health Organization Dictionary of Medical Codes

PREFACE

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for TEVA Branded Pharmaceuticals Products R&D, Inc. study TV5600-CNS-20006 (ARPEGGIO) (A Multinational, Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Once Daily Oral Administration of Laquinimod [0.6 or 1.5 mg] in Patients with Primary Progressive Multiple Sclerosis [PPMS]), and was written in accordance with SOP GBP_RD_702 (Statistical Analysis Plan).

This phase 2 study is intended to serve as a proof of concept for potential treatment with laquinimod in patients with PPMS. The study also evaluated 2 doses of laquinimod in this population. The laquinimod 1.5mg dose was discontinued following the recommendations of the Data Monitoring Committee (DMC) on 31 December 2015.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA) and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): E9 Guidance on Statistical Principles in Clinical Trials. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association, and the Royal Statistical Society, for statistical practice.

The following documents were reviewed in preparation of this SAP:

- Clinical Study Protocol TV5600-CNS-20006 (ARPEGGIO) issued on 21-Jul-2014, protocol amendments issued on 01-Jul-2015, and on 01-Feb-2016.
- Case report form (CRF) for TV5600-CNS-20006 (ARPEGGIO).
- ICH E9 Guidance on Statistical Principles for Clinical Trials.
- ICH E3 Structure and Content of Clinical Study Reports (CSRs)

The reader of this SAP is encouraged to also read the clinical protocol for details on the conduct of this study, and the operational aspects of clinical assessments and timing for completing a patient in this study. When differences exist in descriptions or explanations provided in the protocol and this SAP, the SAP prevails; the discrepancies will be explained in the CSR.

1. SCOPE OF THIS SAP

The analyses described in this SAP will be performed using data collected during Part A (Core Study). Data collected during Part B will be used for additional exploratory analyses, which will be similar in methodology to the Part A analyses and are specified in this SAP as well.

2. STUDY OBJECTIVES

The objectives of this study are to assess the efficacy, safety, and tolerability of a once daily oral dose of laquinimod (0.6 or 1.5 mg) compared to placebo in PPMS patients.

3. STUDY DESIGN

3.1. General Design and Study Schema

This is a multinational, multicenter, randomized, double-blind, parallel-group, placebo-controlled study, to evaluate the efficacy, safety and tolerability of daily oral administration of laquinimod (0.6 or 1.5 mg) in patients with PPMS.

On 30 December 2015 the Data Monitoring Committee (DMC) for the CONCERTO and ARPEGGIO studies held an unscheduled meeting to review cardiovascular events. The DMC found an imbalance in serious cardiovascular events in the high dose treatment arms (1.2 mg in CONCERTO, 1.5 mg in ARPEGGIO): in CONCERTO there were 6 such cases in the 1.2 mg arm but none in the 0.6 mg or placebo arms, along with a myocardial infarction in the ARPEGGIO 1.5 mg dose group and a cerebral infarction in a 31-year old patient in the 1.2 mg arm of CONCERTO. Due to these events and the DMC recommendation to stop all laquinimod treatment arms above 0.6 mg in the MS trials, the 1.5 mg treatment arm in the ARPEGGIO study was discontinued as of 01 January 2016.

Prior to 01 January 2016, eligible patients were randomized in a 1:1:1 ratio into 1 of the following treatment arms:

1. Laquinimod 0.6 mg daily
2. Laquinimod 1.5 mg daily- in total 95 patients were randomized to this arm.
3. Daily placebo

As of 01 January 2016, following a decision to discontinue the laquinimod 1.5 mg dose arm, additional eligible patients who are enrolled will be randomized in a 1:1 ratio into one of the following treatment arms:

1. Laquinimod 0.6 mg daily
2. Daily placebo

A capped randomization procedure will be employed to ensure that the proportion of Expanded Disability Status Scale (EDSS) 6.0 and 6.5 patients will not exceed more than 20% of all enrolled patients.

The study will include screening up to 6 weeks and 2 parts: Part A (core study) and Part B (data analysis).

Part A will last at least 48 weeks, and individual patients will experience variable treatment durations, depending on the order of enrollment.

Once the last ongoing patient completes the week 48 visit, the sponsor will declare end of Part A and begin performing study analyses.

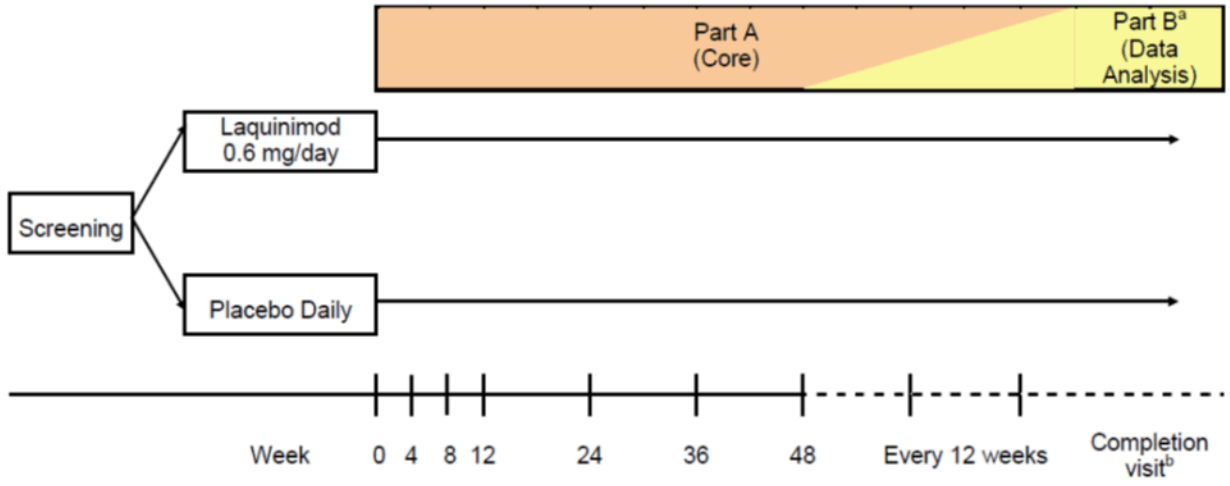
In Part B, patients will continue their randomly-assigned blinded treatments with visits every 12 weeks until the completion visit. After up to approximately 24 weeks of Part B, or once data analysis has been completed and the design of a potential extension study has been finalized (including blinded or open-label treatment allocation), patients will be invited to the clinic for the

completion visit and will be offered the opportunity to continue into an extension study, if applicable.

Patients will have the following study visits: screening visit (-6 weeks), baseline visit (week 0), weeks 4, 8, 12, 24, 36, 48, and every 12 weeks until study completion or early termination (ET).

The study schema is presented in Figure 1.

Figure 1: Overall Study Schema (from 01 January 2016)



Screening should occur up to 6 weeks prior to the baseline (week 0) visit

[a] Part B commences once the last ongoing patient completes week 48; consequently, individual patients will experience variable treatment durations, depending on the order of enrollment

[b] Patients will be invited for a completion visit once data analysis is complete and the design of a potential extension study has been finalized

Study assessments are detailed (by time point) in Sections 3.11.1 to 3.11.6 of the protocol.

In the event of neurological symptoms suggestive of a relapse, the definitions and procedures in Appendix A of the protocol apply. Confirmed relapses must be recorded in the CRF. Patients with a relapse may continue in the study. The suggested treatment for a relapse will be intravenous methylprednisolone 500 to 1000 mg/day for 3 to 5 consecutive days.

Pharmacogenomic (PGx) assessments will be performed in all patients, however this can be omitted if considered unacceptable per local regulations.

Ancillary studies include assessments of cerebrospinal fluid (CSF) and optical coherence tomography (OCT) to assess retinal thickness.

Visit-specific procedures and assessments are outlined in Table 1 (up to week 48) and in Table 2 (from week 60).

Table 1: Study Procedures and Assessments (up to Week 48)

Visit	Screening	Baseline	1	2	3	4	5	6	ET	Unscheduled Visit[a]
Study week[b]	**up to -6**	**0**	**4**	**8**	**12**	**24**	**36**	**48**		
Informed consent	X									
Eligibility criteria	X	X								
Medical and MS history	X									
Cardiovascular risk factor assessment and management[c]	X									
Prior and concomitant medication	X	X	X	X	X	X	X	X	X	X
Randomization		X								
First dose at site		X								
Adverse event	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X	X	X	
Vital signs[d]	X	X[d]	X	X	X	X	X	X	X	X
ECG	X	X[e]	X	X	X	X		X	X	
Chest X-ray[f]	X									
Anemia panel[g]		X	Anemia panel is performed if there is a confirmed hemoglobin decrease of >1 g/dL from baseline							
B12	X		B12 is analyzed if there is a confirmed hemoglobin decrease of >1 g/dL from baseline							
Safety laboratory tests[h]	X	X	X	X	X	X	X	X	X	X[i]
Fasting lipid profile[j]		X						X	X	
Thyroid function tests		X				X		X	X	
GFR[k]	X	X	X	X	X	X	X	X	X	X[i]
HTLV- I/II	X									
Urinalysis	X									
β-hCG[l]	X	X	X	X	X	X	X	X	X	
Home urine β-hCG test[m]					Every 28±2 days between visits; telephone confirmation within 72 hours of the scheduled home pregnancy test					
Ascertain use of acceptable contraception	X	X	X	X	X	X	X	X	X	X
Call IVRS/IWRS	X	X	X	X	X	X	X	X	X	

Visit	Screening	Baseline	1	2	3	4	5	6	ET	Unscheduled Visit[a]
Study week[b]	**up to -6**	**0**	**4**	**8**	**12**	**24**	**36**	**48**		
Study drug dispensing		X	X	X	X	X	X	X		
Study drug accountability			X	X	X	X	X	X	X	
MRI[n]		X				X		X	X[n]	
EDSS/FSS[o]	X	X			X	X	X	X	X	
T25FW[p]		X			X	X	X	X	X	
9HPT[p]		X			X	X	X	X	X	
SDMT[p,q]		X[q]			X	X	X	X[q]	X	
BICAMS[p,q]		X						X	X[r]	
LCVA		X				X		X	X	
MSWS-12		X			X	X	X	X	X	
Pharmacokinetic samples			X	X	X	X		X		X[i]
Potential biomarker samples		X				X		X		X[i]
Pharmacogenomic sample[s]		X								
Ancillary studies										
CSF assessment[t]								X		
OCT evaluation		X[u]						X	X[v]	

Patients who are discontinued from study treatment will be encouraged to continue all scheduled visits and procedures after study drug discontinuation (with the exception of procedures associated with drug dispensing and accountability, pregnancy testing, and pharmacokinetic sampling).

[a] An unscheduled visit may be performed at any time at the patient's request or per investigator's discretion. Only mandatory procedures are specified; additional assessments per clinical discretion. In addition, unscheduled urgent safety laboratory samples, pharmacokinetic blood samples, and/or samples for potential biomarker analyses may be collected at the discretion of the investigator or medical monitor at any time to assist with further investigations of cardiovascular events or other clinical event of interest. The samples should be collected as soon as possible in association with the event.

[b] For the purpose of scheduling study visits, a week is defined as 7±2 days.

[c] In addition, an evaluation should take place as soon as possible for patients already in the study, following approval of Global Amendment 2.

[d] Vital signs include temperature, pulse and blood pressure. Height will be measured at screening visit. Weight will be measured at all visits. At baseline (week 0), pulse and blood pressure will be measured pre dose as well as 30 and 60 minutes after onsite drug administration.

[e] At baseline (week 0), 3 ECG recordings 10 minutes apart are required before first dose.

[f] Chest X-ray can be omitted if the report of a chest X-ray performed within 24 weeks of screening is obtained, or if a screening chest X-ray is considered unacceptable per local regulations.

[g] Anemia panel includes blood smear, serum iron, ferritin, total iron binding capacity, folic acid, haptoglobin, IL-1, IL-6, IFN-γ, TNF-α, and hepcidin. Assessed at baseline and also at 1 subsequent time point (with B12) if hemoglobin decrease of >1 g/dL from the patient's hemoglobin level at baseline and the decrease is confirmed.

[h] Serum chemistry (including electrolytes, fibrinogen, glucose, urea, creatinine, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase, alkaline phosphatase, creatine phosphokinase, C-reactive protein, pancreatic amylase [lipase will be tested in case of abnormal pancreatic amylase results], total protein, albumin, direct and total bilirubin) and complete blood count (CBC) with differential. Coagulation to be tested only if required according to Guidance on Safety Monitoring.

[i] Unscheduled urgent safety laboratory samples, pharmacokinetic blood samples, and/or samples for potential biomarker analysis may be collected at the discretion of the investigator or medical monitor at any time to assist with further investigations of cardiovascular events or other clinical event of interest. The samples should be collected as soon as possible in association with the event.

[j] Fasting lipid profile includes total cholesterol, HDL, LDL (measured), and triglycerides.

[k] Patients who develop renal disease associated with moderate or severe functional impairment, defined as glomerular filtration rate (GFR) ≤60 mL/min/1.73 m^2, while participating in the study should stop study medication temporarily and the GFR assessment should be repeated. If the renal impairment is confirmed (GFR ≤60 mL/min/1.73 m^2), the patient should stop study medication permanently.

[l] For women of child-bearing potential serum β-hCG test will be done at each scheduled study visit. Urine β-hCG tests will be done at each study visit; in case of a positive result, study drug should not be dispensed until the serum β-hCG result is available. At baseline, serum β-hCG will be done within 7 days prior to randomization, such that the result is available prior to the first dose; urine β-hCG test will also be done on site prior to the first dose.

[m] Starting from week 12 visit, women of child-bearing potential will be provided with home pregnancy urine β-hCG test kits and will be instructed how to perform the test. The site staff will schedule the home test to be performed every 28 ±2 days between study visits.

[n] MRI scans (without and with gadolinium) will be performed at least 14 days but not more than 6 weeks before baseline. MRI (without gadolinium) will be performed within 14 days of the week 24 and week 48 visits. In case of steroid treatment, study MRI should be delayed to allow a minimum of 14 days but not more than 28 days from the completion of the steroid course. ET visit will only include MRI for patients who prematurely terminate treatment subsequent to the week 36 visit and prior to week 48. Patients who stop treatment before week 36 or after week 48 will not have MRI at ET visit.

[o] Only an Examining Neurologist will administer the EDSS/FSS. The Examining Neurologist will not have access to the patient's medical records or source documents, including previous EDSS/FSS forms or adverse events.

[p] Only a trained, blinded rater will administer the T25FW, 9HPT, BICAMS, and SDMT. The blinded rater will not have access to the patient's medical records or source documents, including previous T25FW, 9HPT, BICAMS, or SDMT forms.

[q] At baseline and at week 48, SDMT will be performed as part of the BICAMS assessment.

[r] ET visit will only include BICAMS for patients who prematurely terminate treatment subsequent to the week 24 visit and prior to week 48. Patients who stop treatment before week 24 or after week 48 will not have BICAMS at ET visit.

[s] If the pharmacogenomic sample is not obtained at baseline for any reason, it should be collected at the next possible visit. This can be omitted if mandatory pharmacogenomic sampling is considered unacceptable per local regulations.

[t] CSF collection (in selected sites) will be performed for all patients who signed an appropriate, EC approved ICF.

[u] Week 0 OCT evaluation (in selected sites) will be performed up to 42 days prior to baseline, in all patients who signed an appropriate, EC approved ICF.

[v] ET visit will only include OCT for patients who prematurely terminate treatment subsequent to the week 24 visit and prior to week 48. Patients who stop treatment before week 24 or after week 48 will not have OCT at ET visit.

ET = early termination; MS = multiple sclerosis; ECG = electrocardiogram; GFR = glomerular filtration rate; HTLV-I/II = human T lymphotropic virus Type I and II; β-hCG = beta human chorionic gonadotropin; IVRS/IWRS = interactive voice response system/interactive web response system; MRI = magnetic resonance imaging; EDSS = Expanded Disability Status Scale; FSS = Functional System Score; T25FW = timed 25 foot walk; 9HPT = 9 Hole Peg test; SDMT = symbol digit modalities test; BICAMS = Brief International Cognitive Assessment for Multiple Sclerosis; LCVA = low contrast visual acuity; MSWS-12 =

12-Item Multiple Sclerosis Walking Scale; CSF = cerebrospinal fluid; OCT = optical coherence tomography; IL = interleukin; IFN = interferon; TNF = tumor necrosis factor; HDL = high density lipoprotein; LDL = low density lipoprotein; EC = Ethics Committee; ICF = informed consent form

Table 2: Study Procedures and Assessments (from Week 60)

Visit	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**Completion**[a]	**ET**	**Unscheduled Visit**[b]
Study week[c]	**60**	**72**	**84**	**96**	**108**	**120**	**132**[d]	**144**[d]	**156**[d]	**168**[d]			
Cardiovascular risk factor assessment and management[e]				X				X					
Prior and concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs[f]	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG		X		X		X		X		X	X	X	
Anemia panel[g]	Anemia panel is performed if there is a confirmed hemoglobin decrease of >1 g/dL from baseline												
B12	B12 is analyzed if there is a confirmed hemoglobin decrease of >1 g/dL from baseline												
Safety laboratory tests[h]	X	X	X	X	X	X	X	X	X	X	X	X	X[i]
Fasting lipid profile[j]				X				X			X	X	
Thyroid function tests		X		X		X		X		X	X	X	
GFR[k]	X	X	X	X	X	X	X	X	X	X	X	X	X[i]
β-hCG[l]	X	X	X	X	X	X	X	X	X	X	X	X	
Home urine β-hCG test[m]	Every 28±2 days between visits; telephone confirmation within 72 hours of the scheduled home pregnancy test												
Ascertain use of acceptable contraception	X	X	X	X	X	X	X	X	X	X	X	X	X
Call IVRS/IWRS	X	X	X	X	X	X	X	X	X	X	X	X	
Study drug dispensing	X	X	X	X	X	X	X	X	X	X	X[n]		
Study drug accountability	X	X	X	X	X	X	X	X	X	X	X	X	
EDSS/FSS[o]	X	X	X	X	X	X	X	X	X	X	X	X	
mRS		X											
T25FW[p]	X	X	X	X	X	X	X	X	X	X	X	X	
9HPT[p]	X	X	X	X	X	X	X	X	X	X	X	X	
SDMT[p,q,]	X	X	X	X[q]	X	X	X	X[q]	X	X	X	X	
BICAMS[p,q]				X				X					

Visit	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**Completion**[a]	**ET**	**Unscheduled Visit**[b]
Study week[c]	**60**	**72**	**84**	**96**	**108**	**120**	**132**[d]	**144**[d]	**156**[d]	**168**[d]			
LCVA		X		X		X		X		X	X	X	
MSWS-12	X	X	X	X	X	X	X	X	X	X	X	X	
Ancillary study													
OCT				X[l]									

Patients who are discontinued from study treatment will be encouraged to continue all scheduled visits and procedures after study drug discontinuation (with the exception of procedures associated with drug dispensing and accountability, pregnancy testing, and pharmacokinetic sampling).

[a] Once analyses are completed and the design of a potential extension study has been finalized, patients will be invited for a completion visit and offered the opportunity to enter into an anticipated extension study.

[b] An unscheduled visit may be performed at any time at the patient's request or per investigator's discretion. Only mandatory procedures are specified; additional assessments per clinical discretion. In addition, unscheduled urgent safety laboratory samples may be collected at the discretion of the investigator or medical monitor at any time to assist with further investigations of cardiovascular events or other clinical event of interest. The samples should be collected as soon as possible in association with the event.

[c] For the purpose of scheduling study visits, a week is defined as 7±2 days.

[d] It is anticipated that few patients will require visits beyond week 120, however the number of visits required will depend on order and duration of enrollment. After week 168, further visits occur every 12 weeks until completion. If necessary, the visit at week 180 would have identical procedures to week 132, the visit at week 192 would have identical procedures to week 144. If a visit beyond week 192 is necessary, contact Sponsor for guidance.

[e] In addition, an evaluation should take place as soon as possible for patients already in the study, following approval of Global Amendment 2.

[f] Vital signs include temperature, pulse and blood pressure. Weight will be measured at all visits.

[g] Anemia panel includes blood smear, serum iron, ferritin, total iron binding capacity, folic acid, haptoglobin, IL-1, IL-6, IFN-γ, TNF-α, and hepcidin. Assessed at baseline and also at 1 subsequent time point (with B12) if hemoglobin decrease of >1 g/dL from the patient's hemoglobin level at baseline and the decrease is confirmed.

[h] Serum chemistry (including electrolytes, fibrinogen, glucose, urea, creatinine, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase, alkaline phosphatase, creatine phosphokinase, C-reactive protein, pancreatic amylase [lipase will be tested in case of abnormal pancreatic amylase results], total protein, albumin, direct and total bilirubin) and complete blood count (CBC) with differential. Coagulation to be tested only if required according to Guidance on Safety Monitoring.

[i] Unscheduled urgent safety laboratory samples, pharmacokinetic blood samples, and/or samples for potential biomarker analysis may be collected at the discretion of the investigator or medical monitor at any time to assist with further investigations of cardiovascular events or other clinical event of interest. The samples should be collected as soon as possible in association with the event.

[j] Fasting lipid profile includes total cholesterol, HDL, LDL (measured), and triglycerides.

[k] Patients who develop renal disease associated with moderate or severe functional impairment, defined as glomerular filtration rate (GFR) ≤60 mL/min/1.73 m^2, while participating in the study should stop study medication temporarily and the GFR assessment should be repeated. If the renal impairment is confirmed (GFR ≤60 mL/min/1.73 m^2), the patient should stop study medication permanently.

[l] For women of child-bearing potential serum β-hCG test will be done at each scheduled study visit. Urine β-hCG tests will be done at each study visit; in case of a positive result, study drug should not be dispensed until the serum β-hCG result is available.

[m] Starting from week 12 visit, women of child-bearing potential will be provided with home pregnancy urine β-hCG test kits and will be instructed how to perform the test. The site staff will schedule the home test to be performed every 28 ±2 days between study visits.

[n] Study drug will be dispensed at completion visit for those patients continuing to the potential extension study.

[o] Only an Examining Neurologist will administer the EDSS/FSS. The Examining Neurologist will not have access to the patient's medical records or source documents, including previous EDSS/FSS forms or adverse events.

[p] Only a trained, blinded rater will administer the T25FW, 9HPT, BICAMS, and SDMT. The blinded rater will not have access to the patient's medical records or source documents, including previous T25FW, 9HPT, BICAMS, or SDMT forms.

[q] At week 96 and every 48 weeks thereafter, SDMT will be performed as part of the BICAMS assessment

[r] OCT evaluation (in selected sites) will be performed in all patients who signed an appropriate, EC approved ICF.

ET = early termination; ECG = electrocardiogram; β-hCG = beta human chorionic gonadotropin; IVRS/IWRS = interactive voice response system/interactive web response system; EDSS = Expanded Disability Status Scale; FSS = Functional System Score; mRS = modified Rankin scale; T25FW = timed 25 foot walk; 9HPT = 9 Hole Peg test; SDMT = symbol digit modalities test; BICAMS = Brief International Cognitive Assessment for Multiple Sclerosis; LCVA = low contrast visual acuity; MSWS-12 = 12-Item Multiple Sclerosis Walking Scale; OCT = optical coherence tomography; IL = interleukin; IFN = interferon; TNF = tumor necrosis factor; HDL = high density lipoprotein; LDL = low density lipoprotein; EC = Ethics Committee; ICF = informed consent form

3.2. Primary and Secondary Measures and Endpoints

3.2.1. Primary Efficacy Variable and Endpoint

The primary endpoint for this study will be brain atrophy (BA) as defined by the percentage in brain volume change (PBVC) from baseline to week 48.

3.2.2. Secondary Efficacy Variable and Endpoint

- Time to confirmed disability progression (CDP), defined as increase in EDSS of ≥1 point from baseline EDSS if EDSS at entry is ≤5.0, or increase of ≥0.5 point if EDSS at entry is ≥5.5. This increase should be confirmed after at least 12 weeks. Progression cannot be confirmed during a protocol defined relapse, although relapses are rare in PPMS.
- Time to CDP as measured by 2 types of events for each individual (progression cannot be confirmed during a protocol defined relapse):
  - An increase from baseline in EDSS score (≥1 point from baseline EDSS if EDSS at entry is ≤5.0, or increase of ≥0.5 point if EDSS at entry is ≤5.5), confirmed after at least 12 weeks, **or**
  - An increase of at least 20% from baseline in the timed 25-foot walk (T25FW) score, confirmed after at least 12 weeks.
- Change from baseline to week 48 in the timed 25 foot walk (T25FW) score.
- The number of new T2 brain lesions at week 48.

3.2.3. Exploratory Efficacy Variables and Endpoints

- Change from baseline to week 48 in the Brief International Cognitive Assessment for Multiple Sclerosis BICAMS score (CVLT-II, BVMT-R, and SDMT).
- New T1-hypointense lesions, changes in T1-hypointense lesion volume, and changes in T2 lesion volume.
- Other magnetic resonance imaging (MRI) parameters, including thalamic, cortical, white matter, and cervical cord atrophy, number of cervical cord T2 lesions, and normal-appearing brain tissue average magnetization transfer ratio (MTR).
- Time to CDP as measured by at least 1 of 4 types of events for each individual (progression cannot be confirmed during a protocol defined relapse):
  - An increase from baseline in EDSS score (≥1 point from baseline EDSS if EDSS at entry is ≤5.0, or increase of ≥0.5 point if EDSS at entry is ≥5.5), confirmed after at least 12 weeks **or**
  - An increase of at least 20% from baseline in T25FW test, confirmed after at least 12 weeks **or**
  - An increase of at least 30% from baseline in the 9-Hole Peg test (9HPT) score, confirmed after at least 12 weeks **or**

  - A decrease of at least 20% from baseline in the symbol digit modalities test (SDMT) score, confirmed after at least 12 weeks

- mRS (at week 72, visit 8)
- Time to CDP confirmed after at least 24 weeks.
- T25FW.
- 9HPT.
- Low contrast visual acuity (LCVA).
- 12-Item Multiple Sclerosis Walking Scale (MSWS-12).
- The primary endpoint of Brain Atrophy as defined by the percentage in brain volume change (PBVC) from baseline to week 48 by gender.
- Secondary endpoint of Time to confirmed disability progression (CDP), defined using EDSS by gender.
- Secondary endpoint of Time to CDP as measured using 2 types of events (EDSS or T25FW) by gender.
- Secondary endpoint of change from baseline to week 48 in the timed 25 foot walk (T25FW) by gender.
- Secondary endpoint of the number of new T2 brain lesions at week 48 by gender.

3.2.4. Other Variables and Endpoints

- Relapses.
- Pharmacokinetic measures (determination of plasma concentration of laquinimod).
- Pharmacogenomic (PGx) measures.
- Potential biomarker measures.
- Ancillary studies measures.

3.2.5. Safety Variables and Endpoints

The safety of laquinimod will be assessed throughout the study by evaluating adverse events, vital signs, electrocardiogram (ECG) findings, clinical laboratory parameters, and concomitant medication usage.

3.2.6. Tolerability Variables and Endpoints

- Proportion of patients (%) who prematurely discontinue treatment, reasons for discontinuation, and time to early termination (ET).
- Proportion of patients (%) who prematurely discontinue treatment due to adverse events, and time to ET due to adverse events.

3.2.7. Pharmacokinetic Variables and Endpoints

Blood samples for determination of plasma concentration of laquinimod will be collected at weeks 4, 8, 12, 24 and 48. The patient should be instructed to take the daily oral dose at the same time each day. The date and time of the blood sample, as well as the date and time of the last study drug dose prior to the sample will be recorded in the source document and on the CRF.

Pharmacokinetics of laquinimod will be evaluated in this study using a population pharmacokinetics (PPK) approach. Details of sample collection and processing are provided in the Laboratory Manual.

3.3. Sample Size and Power Considerations

Sample size calculations were based on the following assumptions:

- 2-sided alpha level of 5%
- treatment difference (delta) of 0.3 in PBVC
- standard deviation of 0.8
- drop-out date of 10%

Under the above assumptions in order to reach power of 80%, 125 patients per arm should be enrolled. Since initially, this study was planned to have 3 treatment arms, the original sample size was 375 patients. Although, the enrollment to 1.5 mg laquinimod arm was stopped as specified in Section 3.1 and included 95 randomized patients, the Sponsor decided to continue enrollment to the laquinimod 0.6 mg and placebo arms until the total sample size reaches the initially planned 375 patients. This will result in 140 patients per arm (lauqinimod 0.6 mg/placebo) which provides 84% power.

3.4. Randomization and Blinding

This is a randomized, double-blind, placebo-controlled study. Patients will be randomly assigned to receive treatment with laquinimod at a dosage of 0.6 or 1.5 mg/day, or placebo in a 1:1:1 ratio. From 01 January 2016, patients were randomly assigned to receive treatment with laquinimod at a dosage of 0.6 mg/day, or placebo in a 1:1 ratio. Patients, investigators, and study site personnel will remain blinded to treatment assignment during the study. Laquinimod and placebo will be packaged and administered in a blinded manner. A capped randomization procedure will be employed to ensure that the proportion of EDSS 6.0 and 6.5 patients will not exceed more than 20% of all enrolled patients.

For more details on randomization and blinding see section 3.3 of the protocol.

3.5. Sequence of Planned Analyses

3.5.1. Interim Analyses

No interim analysis is planned for this study.

3.5.2. Final Analyses and Reporting

All final, planned analyses identified in this SAP for part A and part B of this study will be performed only after the last patient has completed part A or part B of the study respectively. The randomization codes will not be unblinded until this SAP has been approved and database has been locked for part A analysis.

4. POPULATIONS /ANALYSIS SETS

4.1. Intent-to-Treat (ITT) Population

The intent-to-treat (ITT) population will include all randomized patients. In this population, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received.

4.2. Modified ITT1 (mITT1) Population

The modified ITT1 (mITT1) is a subset of the ITT population. It will include all patients in the ITT population with at least 1 post baseline PBVC assessment.

4.3. Modified ITT2 (mITT2) Population

The modified ITT2 (mITT2) is a subset of the ITT population. It will include all patients in the ITT population with at least 1 post baseline efficacy assessment (EDSS, SDMT, CVLT, BVMT, T25FW, 9HPT, LCVA and/or MSWS-12).

4.4. Safety (ST) Population

The safety (ST) population will include all randomized patients who receive at least 1 dose of study drug. In this population, treatment will be assigned based upon the treatment patients actually receive, regardless of the treatment to which they were randomized.

4.5. Per-Protocol Population

The Per-Protocol (PP) population is a subset of the mITT1 population and will consist of all patients with no major protocol violations. Details on the final criteria for exclusion from the PP analysis set will be discussed and documented in statistical data review (SDR) meeting prior to revealing the blind.

5. GENERAL ISSUES FOR DATA ANALYSIS

5.1. General

Due to the decision from 01 January 2016 to discontinue the laquinimod 1.5 mg dose arm, and a low study exposure at this time, the laquinimod 1.5 mg dose arm will be presented descriptively only, and will not be included in any inferential analyses.

In addition, both efficacy and safety analyses will be performed using measurements recorded during the study treatment period (i.e., data captured after treatment discontinuation will be excluded from the analyses). MRI parameters measured up to one month after the last dose of the study drug will be considered under study treatment. For all other parameters, data measured up to seven days after the last dose of the study drug will be considered under study treatment. Data captured after treatment discontinuation will be used to identify AEs which occurred after treatment termination.

Descriptive statistics for continuous variables include number, mean, and standard deviation, standard error, median, minimum, and maximum. Descriptive statistics for categorical variables include patient counts and percentages.

Summaries of abnormal and potentially clinically significant abnormal values will include all post baseline values (including scheduled, unscheduled, and early termination visits).

By-visit summaries will present all scheduled visits, including visits that appear after week 48, due to the variable treatment duration of the patients. For patients who perform an ET visit, this visit will be presented as well.

5.2. Specification of Baseline Values

The baseline value is the last observed data recorded prior or equal to the first dose date of study drug.

For vital signs parameters, measures that are taken at the latest time prior to drug administration will be defined as baseline values.

For MRI, baseline values are those taken up to 14 days following first dose of study drug.

For ECG, the mean value for 3 pre-dose assessments will define the baseline value. Worst case scenario will be used for character values.

5.3. Multiple Comparisons and Multiplicity

The overall significant level for this study is 5%, using two-tailed tests and/or two-sided confidence intervals with 95% confidence level. In order to protect the study from type-I error inflation, the secondary endpoints will be interpreted inferentially only if a statistically significant treatment effect is detected in the primary analysis. Type-I error will be further controlled by employing the Hierarchical Approach, (i.e. each secondary endpoint will be analyzed only in case the preceding endpoint will have a p-value less or equal to 0.05) according to the following order:

1. Time to CDP as measured by EDSS

2. Time to CDP event as measured by EDSS or T25FW
3. Change from baseline to week 48 in the T25FW test
4. The number of new T2 lesions at week 48

5.4. Definition of Country/Geographical Region (CGR)

Country will be added as a covariate in all analyses. All centers within a country will be pooled. Out of all countries participating in the study, there may be some countries with low number of patients in the ITT population. These countries may be pooled with neighboring countries or countries having similar standard of care to form larger geographical regions. Details of such pooling will be discussed and documented in SDR prior to revealing the blind.

5.5. Handling Withdrawals and Missing Data

If a patient performs an early termination (ET) visit, then this ET visit will be considered as next scheduled visit for the summaries and analyses of the following items: MRI data (following week 36 only), T25FW, 9HPT, EDSS, SDMT, CVLT (following week 24 only), BVMT (following week 24 only), LCVA and MSWS-12. Listings will present early termination visit records as they appear in the data.

The total EDSS score is composed of eight functional system scores (FSS). If any of the FSS are missing at a particular time point, the total EDSS score will also be considered missing at that time point.

Missing dates will be imputed as follows for data related to PPMS history (see Section 6.3):

1. In cases where only day is missing/unknown, then the 1st of the month will be imputed.
2. In cases where both day and month are missing/unknown, then the1st of January will be imputed.
3. In cases where the whole date is missing, the date will be considered as missing.
4. In listings, dates will appear as they are in the data (i.e., missing/unknown values as "UNK").

The MSWS-12 score will be calculated as the sum of the 12 items of the questionnaire. In case there are one or two items missing, the mean of the non-missing items per patient will be imputed. In a case with more than 3 items missing, the total score will be considered missing as well. Listings will present the item data as appears in the data.

Following CDP related endpoints definition (see Section 7.4.1), a CDP cannot be confirmed during a protocol defined relapse, whereas relapse occurrence is identified by relapse onset and approximate stabilization date. If a relapse onset is partial then assessment date of the relapse will be used instead. If a relapse stabilization date is partial, then the last day of the relevant month will be used in that date. Similar imputation of relapse onset and stabilization dates will be done for definition of protocol defined relapses (see Section 7.5.18) if needed. Listings will present relapse related information as appears in the data.

For all other variables, only the observed data from the patients up to study completion or study withdrawal will be used in the statistical analyses, i.e., there is no plan to impute missing data for other variables.

5.6. Study days and visit windows

Study days will be numbered relative to the 1st day of study drug administration. The start of treatment (day 1) is defined as the date on which a patient takes the 1st dose of study drug. Days will be numbered relative to study start (i.e., ..., –2, –1, 1, 2, ...; with day 1 being the start of study drug and day –1 being the day before the start of study drug). No windows schemes will be applied to the data.

For by-visit summaries, if there are multiple assessments at a post baseline time point then the last non-missing assessment at that visit will be used for the summary.

6. STUDY POPULATION

6.1. General

The ITT population will be used for all study population summaries unless otherwise noted. Summaries will be presented by treatment group, and overall, unless otherwise noted.

6.2. Patient Disposition

Patients screened, patients screened but not in the ITT population, and the reason the patients were not in the ITT population will be summarized only for all patients using patient counts. Patients in the ITT population, patients in the ITT population who were not treated, patients in the safety population, mITT1, mITT2, PP population, patients who completed part A of the study, patients who completed part B of the study, patients who performed an ET visit during part A, and patients who performed an ET visit during part B will be summarized using descriptive statistics. Patients who perform an ET visit during part A or part B will also be summarized using descriptive statistics by reason for ET. In addition, patients who performed an ET visit during part A or part B, but continue to come for follow-up visits will be presented as well. Patients who completed part A of the study will be defined as patients who did not perform an early termination visit prior to the database lock of part A of the study. This summary will include all patients screened into the study. The denominator for calculating the percentages will be the number of patients in the ITT population.

In addition, the distribution of ITT patients by county, and by country and site will be summarized using descriptive statistics.

6.3. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be presented for the following populations: ITT, mITT1, patients who performed an ET visit during part A of the study, patients who completed part A of the study, patients who performed an ET visit during part B of the study, patients who completed part B of the study.

Patient demographics and baseline characteristics will be examined to assess the comparability of the treatment groups. The continuous variables of patient age, weight, height, and body mass index (BMI), will be summarized using descriptive statistics. The categorical variables of patient sex, race and ethnicity will be summarized using descriptive statistics for each category. Missing categories will be presented if necessary.

Baseline PPMS characteristics will be presented in a separate table. Continuous variables of time from 1st MS symptom (years) to informed consent, time from PPMS diagnosis (years) to informed consent, EDSS will be summarized using descriptive statistics. The categorical variables of previous use of disease modifying treatments, combination of tests used to meet PPMS criteria (at least two), patients with positive CSF, areas with evidence of clinical disability progression in the 2 years prior to screening, EDSS raw score and EDSS score defined as ≤4.5 and >4.5 will be summarized using descriptive statistics for each category. Missing categories will be presented if necessary.

Baseline MRI measurements will be presented in a separate table as well. Continuous variables of normalized brain volume, T2 lesion volume, and number of T1 enhancing lesions will be summarized using descriptive statistics. The categorical variable of patients with T1 enhancing lesions at baseline will be summarized using descriptive statistics for each category

Tobacco usage will also be summarized using descriptive statistics.

The following statistical tests will incorporated for baseline tabulations between 0.6mg and placebo:

- Analysis of variance (ANOVA) with treatment group and CGR as factors will be used for all continuous variables presented for demography, PPMS history and normalized brain volume.
- Wilcoxon-Mann-Whitney test will be used for EDSS and for T2 lesion volume.
- Cochran-Mantel-Haenszel (CMH) test, stratified by CGR will be used for all categorical variables.

6.4. Medical History

All medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Patients with at least 1 abnormal medical history finding and abnormal findings for each system organ class and preferred term will be summarized using descriptive statistics. Patients are counted only once in each system organ class, and only once in each preferred term category.

6.5. Prior Medications

All prior medications will be coded using the World Health Organization dictionary of medical codes (WHO Drug). The incidence of prior medications use will be summarized using descriptive statistics by therapeutic class and preferred term. Patients are counted only once in each therapeutic class category, and only once in each preferred term category. Prior medications will include all medications taken prior to the first day of study drug treatment.

6.6. MS Disease Modifying Treatment History

All treatments will be coded using WHO Drug. The incidence of treatments will be summarized using descriptive statistics by therapeutic class and preferred term. Patients are counted only once in each therapeutic class category, and only once in each preferred term category.

6.7. Electrocardiogram

Electrocardiogram findings at baseline based on investigator interpretation (normal, abnormal not clinically significant, abnormal clinically significant, and missing) and based on ERT interpretation (normal, abnormal and unable to evaluate) will be summarized using descriptive statistics. The denominator for calculating percentages of patients with scans for each category will be a number of patients with available electrocardiogram scans at baseline.

6.8. Protocol Violations

Patients with at least 1 protocol violation as recorded on the CRF for each category will be summarized using descriptive statistics.

When the study is completed, the table of protocol violations will be generated again to include both part A and part B.

7. EFFICACY ANALYSIS

7.1. General

The mITT1 or mITT2 populations will be used for all efficacy analyses unless otherwise noted. Summaries will be presented by treatment group.

7.2. Primary Efficacy Variable and Analysis

The primary efficacy variable for this study is BA as measured by the PBVC from baseline to week 48. This endpoint will be analyzed using the mITT1 population and will include all the assessments done up to one month after the last dose of the study drug (all the following assessments will be excluded from this analysis). BA will be analyzed using baseline-adjusted repeated measures analysis of covariance (ANCOVA- SAS® PROC MIXED) in which 1 contrast will be constructed in order to compare between laquinimod 0.6 mg and placebo.

The model will be comprised from the treatment group as a class variable (2 levels). In addition to the treatment group, week (categorical, 2 levels), treatment by week interaction, normalized brain volume at baseline, natural logarithm of T2 lesion volume at baseline, and CGR will be used as covariates. Additionally, week (categorical) will be specified as a repeated effect and unstructured (UN) correlation matrix will be used to model intra-subject correlation. In case a convergence issue will arise using the UN correlation matrix, (1) AR1 or (2) Compound Symmetry (CS) will be used to enable model convergence (in this order). The SAS code for this analysis is as follows:

```
PROC MIXED;
  CLASS SUBJID ARM WEEK CGR;
  MODEL BA=ARM WEEK ARM*WEEK NBVBASE LT2BASE CGR / SOLUTION CL;
  REPEATED WEEK / TYPE=UN SUBJECT=SUBJID R RCORR;
  ESTIMATE 'Laq 0.6 to Plb on Week 48' ARM   1   -1  ARM*WEEK  0 1    0 -1 / CL;
  LSMEANS ARM*WEEK / PDIFF CL;
 WHERE ARM in ('Laquinimod 0.6 mg', 'Placebo');
RUN;
```

In addition, mean values of the BA as measured by the PBVC from baseline to weeks 24 and 48 will be summarized using descriptive statistics.

Since for the purpose of this analysis scans of patients who discontinue the study after week 36 are considered as scans at week 48 (see Section 5.5), PBVC measures from the scans of these patients will be presented also separately using descriptive statistics.

The assumption of a no treatment-by-covariate interaction will be evaluated by a separate repeated measures ANCOVA model (SAS® PROC MIXED) with the items treatment, week (categorical), week by treatment interaction, CGR, baseline covariate, and treatment-by-baseline covariate interaction included in the model. If there is evidence of treatment-by-covariate interaction ($p \leq 0.10$), further exploration of this interaction will be done graphically/descriptively and the treatment p-values will still be reported from the main effects model (repeated measures ANCOVA from above).

The consistency of treatment effects among different CGR will be evaluated by a separate repeated measures ANCOVA model (SAS® PROC MIXED) with treatment, week (categorical), and week by treatment interaction, CGR, and treatment-by-CGR interaction in the model. If there is evidence of a treatment-by-CGR interaction ($p \leq 0.10$), a descriptive summary of treatment differences for each CGR will be used to identify the Country (or Countries) for which the treatment effects are consistent with the remaining countries. This will be an exploratory analysis and the treatment p-values will still be reported from the main effects model (repeated measures ANCOVA from above).

7.3. Sensitivity Analyses for Primary Efficacy Variable

The robustness of the primary analysis results will be explored by applying it, as described in the previous section, to the PP population as well. In addition the, following sensitivity analysis will be performed:

- Repeat of the primary analysis without introduction of covariates except for the treatment group, week and week by treatment interaction.
- Repeat the primary analysis when introducing additional baseline covariates variables that differ appreciably between the laquinimod 0.6 mg and placebo treatment groups, if any, i.e. p-value≤0.05. The additional baseline covariates are:
  - Gender,
  - Age at baseline,
  - Time from first MS symptom (years),
  - Time from PPMS diagnosis (years),
  - Proportion of patients with GdE at baseline,
  - Proportion of patients whose PPMS diagnostic criteria includes positive CSF,
  - Proportion of patients with baseline EDSS ≤4.5 vs >4.5.

7.4. Secondary Efficacy Variables and Analysis

7.4.1. Time to CDP as measured by EDSS.

Time to CDP will be defined as increase in EDSS of ≥1 point from baseline EDSS, if EDSS at entry is ≤5.0 or increase of ≥0.5 point, if EDSS at entry is ≥5.5. This increase should be confirmed after at least 12 weeks. Progression cannot be confirmed during a protocol defined relapse.

To calculate the time of CDP, the following algorithm will be used:

Let E_t be an EDSS measurement of the patient under consideration observed at time (measured by weeks from the patient's baseline date).

Let E_0 be the baseline EDSS measurement for that patient.

Let $s = t + 12$.

The time to CDP for the patient under consideration is defined as t if all the following conditions hold:

1. If $0 \le E_0 \le 5$ then let $\Delta = 1$. Otherwise, let $\Delta = 0.5$.
2. $E_t \ge E_0 + \Delta$.
3. For any $t < q_1 < s$, if the patient's EDSS was evaluated at time q_1, then $E_{q1} \ge E_0 + \Delta$
4. $E_{q2} \ge E_0 + \Delta$ for some $q_2 \ge s$, and at time q_2, the patient was not experiencing a relapse (i.e. q_2 is not between onset and stabilization date of a relapse).
5. t is the earliest time point during the study in which conditions 2-4 hold.

If no such *t* exists, then the time to confirmed progression will be right censored by the patient's last EDSS evaluation date from Part A (or part B if the data from both part A and part B is used for analysis) of the study. In case time t exists without fulfilling conditions 3 and 4 because time q_2 is after the patient completed Part A (or part B if the data from both part A and part B is used for analysis) of the study (or performed ET), and therefore cannot be seen, then the right censored will be on time t and not in the last EDSS evaluation.

If a patient died due to MS disease progression, then this patient will be analyzed as having CDP and the time to CDP will be calculated using the onset date of progression.

If a patient died due to MS before having progression, then the time to disability progression will be censored using the date of death.

Time to CDP as measured by EDSS confirmed after at least 12 weeks will be analyzed using the ITT population and will include data from all the study assessments done up to seven days after the last dose of the study drug (all the following assessments will be excluded from this analysis). This analysis will be performed using a baseline adjusted Cox's proportional hazards regression model (SAS® PROC PHREG) in which 1 contrast for comparing laquinimod 0.6 mg to placebo will be constructed. In addition to treatment group, categorical EDSS at baseline (≤4.5 or >4.5), age at baseline, natural logarithm of T2 lesion volume at baseline, and CGR will be used as covariates. The SAS code for this analysis is as follows:

```
PROC PHREG;
  CLASS ARM EDSSBASE CGR;
  MODEL TIME_TO_PROGRESSION*CENSOR(1,2,3)=ARM EDSSBASE AGE LT2BASE CGR / COVB RL;
  CONTRAST 'Laq 0.6 to Plb' ARM  1    / ESTIMATE=EXP;
 WHERE ARM in ('Laquinimod 0.6 mg', 'Placebo');
RUN;
```

In case the above model will not converge due to CGR variable, then CGR will be removed from the model.

The adequacy of the proportional hazards assumption will be confirmed by including a time-dependent covariate of laquinimod 0.6 mg (as dummy variables) by log (time) interaction in the analysis model and testing it at the 5% level. In case the proportional hazards assumption will

be rejected, the log rank test (SAS® PROC LIFTEST) will be used for statistical inference. The SAS code for checking the proportional hazards assumption is as follows:

```
PROC PHREG;
  CLASS ARM EDSSBASE CGR;
  MODEL TIME_TO_PROGRESSION*CENSOR(1,2,3)=ARM ARMT  EDSSBASE AGE LT2BASE CGR ;
   ARMT  = ARM*log(TIME_TO_PROGRESSION);
 PROP_HAZARDS_TEST_LAQ_0_6: test ARMT;
 WHERE ARM in ('Laquinimod 0.6 mg', 'Placebo');
RUN;
```

In case the above model will not converge due to CGR variable, then CGR will be removed from the model.

In addition, patients with CDP will be summarized using descriptive statistics. The time to CDP will be presented by Kaplan-Meier curves stratified by treatment group.

EDSS scores and changes from baseline to each visit will be summarized using descriptive statistics.

All analyses presented in the section will be repeated to include both part A and part B when the study is completed.

7.4.2. Time to CDP event as measured by EDSS or T25FW

Time to CDP as measured by EDSS or T25FW will be defined by reaching at least 1 of the following 2 types of event for each individual:

- An increase from baseline in EDSS score (≥1 point from baseline EDSS, if EDSS at entry is ≤5.0 or increase of ≥0.5 point, if EDSS at entry is ≥5.5), confirmed after at least 12 weeks, **or**
- An increase of at least 20% from baseline in the T25FW test, confirmed after at least 12 weeks

Progression cannot be confirmed during a protocol defined relapse. A similar algorithm to that described for CDP as measured by EDSS will be used for definition and censoring rules of this variable (see Section 7.4.1).

T25FW will be calculated as a mean time of two T25FW trials at each visit. In cases when a patient could not complete a T25FW trial due to the physical limitations a value of 180 seconds will be assigned for that trial (this is the maximal possible value for the T25FW test).

Time to CDP as measured by EDSS or T25FW, confirmed after at least 12 weeks will be analyzed using the ITT population and will include data from all the study assessments done up to seven days after the date of last dose of the study drug (all the following assessments will be excluded from this analysis). This analysis will be performed using baseline adjusted Cox's proportional hazards regression model (SAS® PROC PHREG) in which 1 contrast for comparing laquinimod 0.6 mg to placebo will be constructed. In addition to treatment group, categorical EDSS at baseline (≤4.5 or >4.5), age at baseline, T25FW at baseline, natural logarithm of T2 lesion volume at baseline, and CGR will be used as covariates. The SAS code for this analysis is as follows:

```
PROC PHREG;
  CLASS ARM EDSSBASE CGR;
  MODEL TIME_TO_PROGRESSION*CENSOR(1,2,3)=ARM EDSSBASE T25BASE AGE LT2BASE CGR /
COVB RL;
  CONTRAST 'Laq 0.6 to Plb' ARM  1    / ESTIMATE=EXP;
 WHERE ARM in ('Laquinimod 0.6 mg', 'Placebo'); RUN;
```

In case the above model will not converge due to CGR variable, then CGR will be removed from the model.

The adequacy of the proportional hazards assumption will be confirmed by including a time-dependent covariate of laquinimod 0.6 mg (as dummy variables) by log (time) interaction in the analysis model and testing it at the 5% level. If the proportional hazards assumption will be rejected, the log rank test (SAS® PROC LIFTEST) will be used for statistical inference. The SAS code for checking the proportional hazards assumption is as follows:

```
PROC PHREG;
  CLASS ARM EDSSBASE CGR;
  MODEL TIME_TO_PROGRESSION*CENSOR(1,2,3)=ARM ARMT  EDSSBASE T25BASE AGE LT2BASE
CGR ;
   ARMT  = ARM*log(TIME_TO_PROGRESSION);
  PROP_HAZARDS_TEST_LAQ_0_6: test ARMT;
 WHERE ARM in ('Laquinimod 0.6 mg', 'Placebo');
RUN;
```

In case the above model will not converge due to CGR variable, then CGR will be removed from the model.

In addition, patients with CDP as measured by EDSS or T25FW will be summarized using descriptive statistics. The time to CDP as measured by EDSS or T25FW will be presented by Kaplan-Meier curves stratified by treatment group.

All analyses presented in the section will be repeated to include both part A and part B when the study is completed.

7.4.3. Change from baseline to week 48 in the T25FW test

Change from baseline in the T25FW test at week 48 will be analyzed using the mITT2 population and will include all the assessments done up to seven days after the last dose of the study drug (all the following assessments will be excluded from this analysis). Since this variable might not follow normal distribution, the ranked values of this measurement will be defined and analyzed using baseline adjusted repeated measures ANCOVA (SAS® PROC MIXED) in which 1 contrast will be constructed in order to compare between laquinimod 0.6 mg and placebo. In addition to treatment group, T25FW test at baseline, week (categorical, 4 levels), treatment by week interaction and CGR will be used as covariates. Additionally, week (categorical) will be specified as a repeated effect and unstructured (UN) correlation matrix will be used to model intra-subject correlation. In case a convergence issue will arise using the UN correlation matrix, (1) AR1 or (2) Compound Symmetry (CS) will be used to enable model convergence (in this order). Due to the fact that the ANCOVA model will use ranked values and not the actual

changes in the T25FW, Hodges-Lehmann estimates will be used in order to present the magnitude of the treatment effect and the corresponding two sided 95% confidence limit.

The SAS code for defining ranked values and performing this analysis is as follows:

1. Ranked values assignment:

```
PROC RANK OUT=RANKED;
  VAR CHANGE T25BASE;
  RANKS CHANGERANK T25BASERANK;
 WHERE ARM in ('Laquinimod 0.6 mg', 'Placebo');
RUN;
```

2. Repeated measures ANCOVA model:

```
PROC MIXED DATA=RANKED;
  CLASS SUBJID ARM WEEK CGR;
  MODEL CHANGERANK=ARM WEEK ARM*WEEK T25BASERANK CGR;
  REPEATED WEEK / TYPE=UN SUBJECT=SUBJID R RCORR;
  ESTIMATE 'Laq 0.6 to Plb' ARM  1  0 -1  ARM*WEEK  0  0  0  1    0  0  0 -1 / CL;
  LSMEANS ARM*WEEK / PDIFF CL;
RUN;
```

3. HL estimates:

```
PROC NPAR1WAY HL;
  CLASS ARM;
  VAR CHANGE;
 WHERE WEEK=48 and ARM in ('Laquinimod 0.6 mg', 'Placebo');
RUN;
```

In addition, actual values of T25FW and changes from baseline to each visit will be summarized using descriptive statistics.

When the study is completed, actual values of T25FW and changes from baseline to each visit will be summarized using descriptive statistics to include both part A and part B. Also, the changes from baseline to each visit will be analyzed using similar statistical methodology as presented in this section for changes from baseline to week 48 in T25FW test.

7.4.4. The number of new T2 lesions at week 48

The number of new T2 lesions at week 48 compared to baseline will be analyzed using the mITT1 population and will include all the assessments done up to one month after the last dose of the study drug (all the following assessments will be excluded from this analysis). This analysis will be performed using baseline adjusted negative binomial regression model (SAS® PROC GENMOD) in which 1 contrast for comparing laquinimod 0.6 mg to placebo will be constructed. In addition to the treatment group, the natural logarithm of T2 lesion volume at baseline, age at baseline and CGR will be used as covariates. The SAS code for this analysis is as follows:

```
PROC GENMOD;
  CLASS ARM CGR;
  MODEL T2LES=ARM LT2BASE AGE CGR/ DIST=NB LINK=LOG TYPE3;
```

```
  LSMEANS ARM/ CL;
  ESTIMATE  'Laq 0.6 to Plb' ARM 1  -1 / ESTIMATE=EXP;
 WHERE ARM in ('Laquinimod 0.6 mg', 'Placebo');
RUN;
```

In addition, the number of new T2 lesions at week 48 will be summarized using descriptive statistics.

7.5. Exploratory/Other Efficacy Variables and Analysis

7.5.1. Change from baseline to week 48 in the CVLT-II score

CVLT-II scores will be calculated as a sum of total correct responses from five CVLT-II trials for each patient. If one of the five CVLT-II trials is missing, then the CVLT-II score will be considered missing as well.

Change from baseline in the CVLT-II score at week 48 will be analyzed using the mITT2 population. This analysis will be performed using baseline-adjusted Analysis of Covariance (ANCOVA, SAS® PROC GLM) in which a contrast for comparing laquinimod 0.6 mg to placebo will be constructed. In addition to treatment group, baseline CVLT-II score and CGR will be used as covariates. The SAS code for this analysis is as follows:

```
PROC GLM;
  CLASS ARM CGR ;
  MODEL CCVLT = ARM CVLTBASE CGR /CLPARM SOLUTION;
  LSMEANS ARM /STDERR CL;
  ESTIMATE  'Laq 0.6 to Plb' ARM 1  -1;
 WHERE ARM in ('Laquinimod 0.6 mg', 'Placebo');
RUN;
```

In addition, the CVLT-II scores and changes from baseline to each visit will be summarized using descriptive statistics.

When the study is completed, actual values of CVLT-II and changes from baseline to each visit will be summarized using descriptive statistics to include both part A and part B. Also, the changes from baseline to each visit will be analyzed using similar statistical methodology as presented in this section for changes from baseline to week 48 in CVLT-II test.

7.5.2. Change from baseline to week 48 in the BVMT-R score

BVMT-R scores will be calculated as a sum of total correct responses from three BVMT-R trials for each patient. If one of the three BVMT-R trials is missing, then the BVMT-R score will be considered missing as well.

Change from baseline in the BVMT-R score at week 48 will be analyzed by applying the same methodology used to analyze the change from baseline to week 48 in the CVLT-II score (see Section 7.5.1). Baseline CVLT-II score covariate will be replaced by BVMT-R at baseline. In addition, the BVMT-R scores and changes from baseline to each visit will be summarized using descriptive statistics.

When the study is completed, actual values of BVMT-R and changes from baseline to each visit will be summarized using descriptive statistics to include both part A and part B. Also, the changes from baseline to each visit will be analyzed using similar statistical methodology as presented in this section for changes from baseline to week 48 in BVMT-R test.

7.5.3. Time to CDP as measured by at least 1 of 4 types of events

Time to CDP as measured by at least 1 of 4 types of events for each individual will be defined if one of the below conditions holds (progression cannot be confirmed during a protocol defined relapse):

- An increase from baseline in EDSS score (≥1 point from baseline EDSS if EDSS at entry is ≤5.0, or increase of ≥0.5 point if EDSS at entry is ≥5.5), confirmed after at least 12 weeks **or**
- An increase of at least 20% from baseline in T25FW test (see Section 7.4.3 for definition), confirmed after at least 12 weeks **or**
- An increase of at least 30% from baseline in the 9HPT test, confirmed after at least 12 weeks **or**
- A decrease of at least 20% from baseline in the SDMT score, confirmed after at least 12 weeks

9HPT will be calculated as a mean time of two 9HPT trials for both dominant and non-dominant hands (4 trials overall) at each visit. In cases when a patient could not complete a 9HPT trial due to the physical limitations a value of 300 seconds will be assigned for that trial (this is the maximal possible value for the 9HPT).

Similar algorithm to that described for CDP as measured by EDSS confirmed after at least 12 weeks will be used for definition and censoring rules of this variable (see Section 7.4.1).

Time to CDP as measured by at least 1 of 4 types of events for each individual will be analyzed using the same methods as described for time to CDP as measured by EDSS in Section 7.4.1. In addition to treatment group, categorical EDSS at baseline (≤4.5 or >4.5), age at baseline, natural logarithm of T2 lesion volume at baseline, T25FW at baseline, 9HPT at baseline, SDMT score at baseline and CGR will be used as covariates.

In case the above model will not converge due to CGR variable, then CGR will be removed from the model.

The adequacy of the proportional hazards assumption will be checked using the same methodology as described for time to CDP as measured by EDSS in Section 7.4.1.

In addition, patients with CDP as measured by at least 1 of 4 types of events will be summarized using descriptive statistics. The time to CDP as measured by at least 1 of 4 types of events will be presented by Kaplan-Meier curves stratified by treatment group.

All analyses presented in the section will be repeated to include both part A and part B when the study is completed.

7.5.4. Time to CDP as measured by EDSS confirmed after at least 24 weeks.

Similar algorithm to that described for CDP as measured by EDSS confirmed after at least 12 weeks will be used for definition and censoring rules of this variable (see Section 7.4.1) with the distinction that the increase in EDSS should be sustained for at least 24 weeks instead of 12 weeks. The methodology and covariates for this analysis will be the same as for the primary analysis, including check of the proportional hazards assumption.

In addition, patients with CDP as measured by EDSS confirmed after at least 24 weeks will be summarized using descriptive statistics. The time to CDP as measured by EDSS confirmed after at least 24 weeks will be presented by Kaplan-Meier curves stratified by treatment group.

All analyses presented in the section will be repeated to include both part A and part B when the study is completed.

7.5.5. The number of new T1-hypointense lesions at week 48

The number of new T1-hypointense lesions at week 48 will be analyzed by applying the same methodology used to analyze the number of new T2 lesions at week 48 (see Section 7.4.4). Natural logarithm of baseline T2 lesion volume covariate will be replaced by natural logarithm of T1-hypointense lesion volume at baseline. In addition, the number of new T1-hypointense lesions at week 48 will be summarized using descriptive statistics.

7.5.6. Change from baseline to week 48 in T1-hypointense lesion volume

The change from baseline to week 48 in T1-hypointense lesion volume will be analyzed using the mITT1.

Since the change from baseline to week 48 in T1-hypointense volume might not follow normal distribution, the ranked values of this variable will be defined and analyzed using baseline-adjusted Analysis of Covariance (ANCOVA, SAS® PROC GLM) in which a contrast for comparing laquinimod 0.6 mg to placebo will be constructed. In addition to treatment group, natural logarithm of T1-hypointense lesion volume at baseline and CGR will be used as covariates. Due to the fact that the ANCOVA model will use ranked values and not the actual changes in the T1-hypointense volume, Hodges-Lehmann (HL) estimates will be used in order to present the magnitude of the treatment effect and the corresponding two-sided 95% confidence limit (i.e. p-values will be presented from the ANCOVA model and treatment effect with 95% confidence limits will be presented from the HL).

The SAS code for defining ranked values and performing this analysis is as follows:

1. Ranked values assignment:

```
PROC RANK OUT=RANKED;
  VAR CVOLT1 LVOLT1BASE;
  RANKS CVOLT1RANK LVOLT1BASERANK;
 WHERE ARM in (‘Laquinimod 0.6 mg’, ‘Placebo’);
RUN;
```

2. ANCOVA model:

```
PROC GLM DATA=RANKED;
  CLASS ARM CGR;
  MODEL CVOLT1RANK = ARM LVOLT1BASERANK CGR /CLPARM SOLUTION;
```

```
  LSMEANS ARM /STDERR CL;
  ESTIMATE  'Laq 0.6 to Plb' ARM 1   -1;
RUN;
```

3. HL estimates:

```
PROC NPAR1WAY HL;
  CLASS ARM;
  VAR CVOLT1;
 WHERE ARM in ('Laquinimod 0.6 mg', 'Placebo');
RUN;
```

In addition, T1-hypointence lesion volume and change from baseline to week 48 will be summarized using descriptive statistics.

7.5.7. Change from baseline to week 48 in T2 lesion volume

The change from baseline to week 48 in T2 lesion volume will be analyzed by applying the same methodology used to analyze the change from baseline to week 48 in T1-hypointence lesion volume (see Section 7.5.6). Natural logarithm of baseline T1-hypointense lesion volume covariate will be replaced by natural logarithm of baseline T2 lesion volume. In addition, T2 lesion volume and change from baseline to week 48 will be summarized using descriptive statistics.

7.5.8. Normalized Thalamic Volume percent change from baseline to week 48

Normalized thalamic volume percent change from baseline to week 48 will be calculated as change from baseline to week 48 in the normalized thalamic volume divided by normalized thalamic volume at baseline. In cases when a patient performs early termination, scan under at least 36 weeks of treatment will be used in this derivation (as specified in Section 5.5). This variable will be analyzed using the mITT1 population. This analysis will be performed using baseline-adjusted Analysis of Covariance (ANCOVA, SAS® PROC GLM) in which a contrast for comparing laquinimod 0.6 mg to placebo will be constructed. In addition to treatment group, normalized thalamic volume at baseline and CGR will be used as covariates. The SAS code for this analysis is as follows:

```
PROC GLM;
  CLASS ARM CGR;
  MODEL NTHALVOL = ARM BTHALVOL CGR /CLPARM SOLUTION;
  LSMEANS ARM /STDERR CL;
  ESTIMATE  'Laq 0.6 to Plb' ARM 1   -1;
 WHERE ARM in ('Laquinimod 0.6 mg', 'Placebo');
RUN;
```

In addition, the normalized thalamic volume percent change from baseline to week 48 will be summarized using descriptive statistics.

7.5.9. Mean Cortical Thickness percent change from baseline to week 48

The mean cortical thickness percent change from baseline to week 48 will be derived and analyzed by applying the same methodology used to define and analyze the normalized thalamic

volume percent change from baseline to week 48 (see Section 7.5.8 . Baseline normalized thalamic volume mean covariate will be replaced by cortical thickness at baseline. In addition, the mean cortical thickness percent change from baseline to week 48 will be summarized using descriptive statistics.

7.5.10. Normalized White Matter Volume percent change from baseline to week 48

The normalized white matter volume percent change from baseline to week 48 will be derived and analyzed by applying the same methodology used to define and analyze the normalized thalamic volume percent change from baseline to at week 48 (see Section 7.5.8). Baseline normalized thalamic volume mean covariate will be replaced by normalized white matter volume at baseline. In addition, normalized white matter volume percent change from baseline to at week 48 will be summarized using descriptive statistics.

7.5.11. Mean Upper Cervical Cord Area percent change from baseline to week 48

The mean upper cervical cord area percent change from baseline to week 48 will be derived and analyzed by applying the same methodology used to define and analyze the normalized thalamic volume percent change from baseline to at week 48 (see Section 7.5.8). Baseline normalized thalamic volume mean covariate will be replaced by mean upper cervical cord area at baseline. In addition, mean upper cervical cord area percent change from baseline to at week 48 will be summarized using descriptive statistics.

7.5.12. Number of T2 Cervical Cord Lesions at week 48

The number of T2 cervical cord lesions at week 48 will be analyzed by applying the same methodology used to analyze the number of new T2 lesions at week 48 (see Section 7.4.4). Natural logarithm of T2 lesion volume at baseline covariate will be replaced by number of T2 cervical cord lesions at baseline. In addition, the number of T2 cervical cord lesions at week 48 will be summarized using descriptive statistics.

7.5.13. Mean MTR Normal-Appearing Brain Tissue (NABT) percent change from baseline to week 48

The MTR NABT percent change from baseline to week 48 will be derived and analyzed by applying the same methodology used to define and analyze the normalized thalamic volume percent change from baseline to at week 48 (see Section 7.5.8). Baseline normalized thalamic volume mean covariate will be replaced by MTR NABT at baseline. In addition, MTR NABT percent change from baseline to at week 48 will be summarized using descriptive statistics.

7.5.14. Change from baseline to week 48 in 9-Hole Peg Test (9HPT)

The change from baseline to week 48 in the 9HPT test will be analyzed using the same methodology as described for the change from baseline to week 48 in the T25FW test in Section 7.4.3. Baseline T25FW covariate will be replaced by baseline 9HPT test.

In addition, actual values of the 9HPT and changes from baseline to each week will be summarized using descriptive statistics.

When the study is completed, actual values of 9HPT and changes from baseline to each visit will be summarized using descriptive statistics to include both part A and part B. Also, the changes

from baseline to each visit will be analyzed using similar statistical methodology as presented in this section for changes from baseline to week 48 in 9HPT test.

7.5.15. Change from baseline to week 48 in Symbol Digit Modalities Test (SDMT)

Change from baseline to week 48 in SDMT score will be analyzed for mITT2 population using baseline adjusted repeated measures analysis of covariance (ANCOVA SAS® PROC MIXED) in which 1 contrast will be constructed in order to compare between laquinimod 0.6 mg and placebo. The model will be comprised from the treatment group as a class variable (2 levels). In addition to the treatment group, week (categorical, 4 levels), treatment by week interaction, SDMT at baseline, and CGR will be used as covariates. Additionally, week (categorical) will be specified as a repeated effect and unstructured (UN) correlation matrix will be used to model intra-subject correlation. In case a convergence issue will arise using the UN correlation matrix, (1) AR1 or (2) Compound Symmetry (CS) will be used to enable model convergence (in this order). The SAS code for this analysis is as follows:

```
PROC MIXED;
  CLASS SUBJID ARM WEEK CGR;
  MODEL CSDMT=ARM WEEK ARM*WEEK SDMTBASE CGR / SOLUTION CL;
  REPEATED WEEK / TYPE=UN SUBJECT=SUBJID R RCORR;
  ESTIMATE 'Laq 0.6 to Plb' ARM  1   -1  ARM*WEEK 0  0  0  1    0  0  0 -1 / CL;
  LSMEANS ARM*WEEK / PDIFF CL;
 WHERE ARM in ('Laquinimod 0.6 mg', 'Placebo');
RUN;
```

In addition, actual values of the SDMT score and changes from baseline to each visit will be summarized using descriptive statistics.

When the study is completed, actual values of SDMT and changes from baseline to each visit will be summarized using descriptive statistics to include both part A and part B. Also, the changes from baseline to each visit will be analyzed using similar statistical methodology as presented in this section for changes from baseline to week 48 in SDMT test.

7.5.16. Change from baseline to week 48 in Low Contrast Visual Acuity (LCVA)

The changes from baseline to week 48 in LCVA will be analyzed for each chart type (100%, 2.5% and 1.25%) separately while using binocular values.

These analyses will be performed using the same methods as described for the primary efficacy variable in Section 7.2 and mITT2 population will be used. The age at baseline will also be included in the model. Baseline brain volume will be replaced by baseline LCVA.

In addition, actual values of LCVA and changes from baseline to each visit will be summarized using descriptive statistics.

When the study is completed, actual values of LCVA and changes from baseline to each visit will be summarized using descriptive statistics to include both part A and part B. Also, the changes from baseline to each visit will be analyzed using similar statistical methodology as presented in this section for changes from baseline to week 48 in LCVA test.

7.5.17. Change from baseline to week 48 in 12-Item Multiple Sclerosis Walking Scale (MSWS-12)

The change from baseline to week 48 in the MSWS-12 score will be analyzed using the same methodology as described for the change from baseline to week 48 in the SDMT score in Section 7.5.15. Baseline SDMT covariate will be replaced by baseline MSWS-12.

In addition, actual values of the MSWS-12 score and changes from baseline to each visit will be summarized using descriptive statistics.

When the study is completed, actual values of MSWS-12 and changes from baseline to each visit will be summarized using descriptive statistics to include both part A and part B. Also, the changes from baseline to each visit will be analyzed using similar statistical methodology as presented in this section for changes from baseline to week 48 in MSWS-12 test.

7.5.18. Relapses

Two types of relapses will be presented using descriptive statistics for relapsing and relapse-free patients:

1. Clinical relapse as captured by the clinical database.
2. Protocol defined relapse. In order to identify protocol defined relapses, all clinical relapses will be cross checked with EDSS evaluation data performed during the clinical relapse, i.e. between the onset and the stabilization date of the relapse. If several EDSS evaluations are available during relapse, then the closet evaluation to the relapse onset will be taken. A clinical relapse will be considered as protocol defined if one of the following conditions holds:
    - an increase of at least 0.5 in the EDSS score as compared to previous the evaluation
    - an increase of 1 grade in the score of 2 or more of the 7 functions from the FSS as compared to the previous evaluation
    - an increase of 2 grades in the score of 1 function from the FSS as compared to the previous evaluation

When the study is completed, the tables of clinical and protocol defined relapses will be generated again to include both part A and part B.

7.5.19. mRS at week 72

mRS at week 72 will be presented for mITT2 population as both continuous and categorical variable using descriptive statistics. This analysis will be repeated to include both part A and part B when the study is completed.

7.5.20. Time to CDP event as measured by T25FW

Time to CDP as measured by T25FW will be defined as an increase of at least 20% from baseline in T25FW test (see Section 7.4.3 for definition), confirmed after at least 12 weeks. Progression cannot be confirmed during a protocol defined relapse.

Similar algorithm to that described for CDP as measured by EDSS confirmed after at least 12 weeks will be used for definition and censoring rules of this variable (see Section 7.4.1).

Time to CDP as measured by T25FW for each individual will be analyzed using the same methods as described for time to CDP as measured by EDSS in Section 7.4.1. In addition to treatment group, T25FW at baseline and CGR will be used as covariates.

In case the above model will not converge due to CGR variable, then CGR will be removed from the model.

The adequacy of the proportional hazards assumption will be checked using the same methodology as described for time to CDP as measured by EDSS in Section 7.4.1.

In addition, patients with CDP as measured by T25FW will be summarized using descriptive statistics. The time to CDP as measured by T25FW will be presented by Kaplan-Meier curves stratified by treatment group.

All analyses presented in the section will be repeated to include both part A and part B when the study is completed.

7.5.21. By Gender Analyses

The aim of the following analyses is to examine gender effect in various key endpoints. The methodology will use the pre-specified models for each key endpoint while introducing gender and treatment by gender interaction. Corresponding contrasts will be created to test the treatment effect in males and females.

- Repeat the primary endpoint of Brain Atrophy as measured by Percent Brain Volume Change (PBVC) at week 48 by gender. This analysis will be performed on the mITT1 analysis set and will use the primary analysis model while adding gender and treatment by gender interaction terms. SAS code as example is specified below

```
PROC MIXED;
  CLASS SUBJID ARM WEEK CGR GENDER;
  MODEL BA= NBVBASE LT2BASE CGR ARM|WEEK|GENDER  / SOLUTION CL;
  REPEATED WEEK / TYPE=UN SUBJECT=SUBJID R RCORR;
  LSMEANS ARM*WEEK*GENDER / PDIFF CL;
 LSMESTIMATE TRTPN*WEEK*GENDER "MALES, WEEK 48, 0.6 MG VS PLACEBO" [-1, 1 2 1] [1, 2 2 1]/CL;
 LSMESTIMATE TRTPN*WEEK*SUBVAR "FEMALES, WEEK 48, 0.6 MG VS PLACEBO" [-1, 1 2 2] [1, 2 2 2]/CL;
  WHERE ARM in ('Laquinimod 0.6 mg', 'Placebo')  and  mITT1='Y' ;
RUN;
```

- Repeat the first secondary of Time to CDP as measured by EDSS by gender. This analysis will be performed using the ITT analysis set and will use the time to CDP measured by EDSS model together while adding gender and gender by treatment interaction terms as shown in the SAS code below.

```
PROC PHREG;
  CLASS ARM EDSSBASE CGR GENDER;
```

```
  MODEL TIME_TO_PROGRESSION*CENSOR(1,2,3)=ARM GEMDER ARM * GENDER EDSSBASE AGE
LT2BASE CGR / COVB RL;
 CONTRAST “MALES , 0.6 MG VS PLACEBO "    ARM 1  GENDER 0   ARM * GENDER 1    /ESTIMATE=EXP ;
 CONTRAST “FEMALES 0.6 MG VS PLACEBO "  ARM 1  GENDER 0   ARM * GENDER 0    /ESTIMATE=EXP;
 WHERE ARM in (‘Laquinimod 0.6 mg’, ‘Placebo’);
RUN;
```

- Repeat the second secondary of Time to CDP as measured by EDSS or T25FW by gender. This analysis will be performed using the ITT analysis set and will use the time to CDP measured by EDSS or T25FW model while adding with gender and gender by treatment interaction terms as shown for the first secondary endpoint of time to CDP measured by EDSS.
- Repeat the third secondary endpoint of change from baseline to week 48 in the T25FW test by gender. This analysis will be performed on the mITT2 analysis set and will use the original ranked model while adding gender and treatment by gender interaction terms.

```
PROC MIXED DATA=RANKED;
  CLASS SUBJID ARM WEEK CGR;
  MODEL CHANGERANK= T25BASERANK CGR ARM|WEEK|GENDER;
  REPEATED WEEK / TYPE=UN SUBJECT=SUBJID R RCORR;
  LSMEANS ARM*WEEK*GENDER / PDIFF CL;
  LSMESTIMATE arm*WEEK*GENDER "MALES, WEEK 48, 0.6 MG VS PLACEBO" [-1, 1 2 1] [1, 2 2 1]/CL;
  LSMESTIMATE arm*WEEK* GENDER "FEMALES, WEEK 48, 0.6 MG VS PLACEBO" [-1, 1 2 2] [1, 2 2 2]/CL;
RUN;
```

- Repeat the for the secondary endpoint of number of new T2 lesions at week 48 by gender. This analysis will be performed on the mITT2 analysis set and will use the original GENMOD model while adding gender and treatment by gender interaction terms.

```
PROC GENMOD;
  CLASS ARM CGR GENDER;
  MODEL T2LES=ARM  GENDER ARM * GENDER  LT2BASE AGE CGR/ DIST=NB LINK=LOG TYPE3;
  LSMEANS ARM*GENDER/ CL;
 lsmESTIMATE  arm*gender “MALE 0.6 MG VS PLACEBO "      [-1, 1 1] [1, 2 1]/exp;
 lsmESTIMATE arm*gender "FEMALE 0.6 MG VS PLACEBO "   [-1, 1 2] [1,2 2]/exp;
 WHERE ARM in (‘Laquinimod 0.6 mg’, ‘Placebo’);
RUN;
```

7.6. Tolerability Variables and Analysis

Tolerability analysis will be performed only for placebo and laquinimod 0.6 mg patients and will be presented by proportion of patients (%) who prematurely discontinued treatment and reason of discontinuation (including early termination due to AEs). Additionally the time to Early Termination (ET) and time to ET due to AEs will be presented by Kaplan-Meier curves. No statistical inference will be done.

All analyses presented in the section will be repeated to include both part A and part B when the study is completed.

8. SAFETY ANALYSIS

8.1. General

The safety population will be used for all safety analyses. Summaries will be presented by treatment group.

8.2. Study Drug Administration

Duration of treatment (days treated) is the number of days on treatment based on the first and last days of treatment with the study drug (last day of study drug – first day of study drug + 1). The last date of study drug for patients who are still ongoing in the study when part A is locked, will be defined as the latest of the following: last neurological evaluation date, last MRI scan date, last date of T25FW, 9HPT, SDMT, CVLT, BVMT, or MSWS, last date of safety evaluation including laboratory, ECG and vital signs data. Weeks on treatment using the categories ≤4 week, >4 to ≤8 weeks, >8 to ≤12 weeks, >12 to ≤24 weeks, >24 to ≤36 weeks, >36 to ≤48 weeks, and >48 weeks will be summarized using descriptive statistics. The last category of >48 weeks specified in the last sentence will include patients with variable treatment duration. In order to define treatment duration in weeks, 7 days will be used as denominator. Duration of treatment (days, weeks and years) will also be summarized using descriptive statistics, including the total number of days/weeks/years. In order to define treatment duration in years 365.25 days will be used as denominator.

In addition for patients who perform an ET visit and continue to come to the off-drug follow-up visits, the off-drug study duration will be presented and will be defined as following: last date in the study-last day of study drug+1. The last date in the study will be taken from the study completion form for patients who withdrew from the study prior to the lock of the part A, while for patients who didn't withdraw prior to the lock of part A, it will be defined as the latest of the following: last neurological evaluation date, last MRI scan date, last date of T25FW, 9HPT, SDMT, CVLT, BVMT, or MSWS, last date of safety evaluation including laboratory, ECG and vital signs data.

All the summaries presented in this section besides categorical week presentation will be repeated to include both part A and part B when the study is completed. Since all the patients will have treatment and study completion forms filled out at the end of the study, those forms will be used for definition of last day of study drug and last date in study respectively.

8.3. Adverse Events

All adverse events (AEs) will be coded using MedDRA. Summaries will be presented for all adverse events (overall and by severity), adverse events determined by the investigator to be treatment-related (overall and by severity), serious adverse events, adverse events causing discontinuation of the study drug, non-serious adverse events, and adverse events by outcome. The AEs will be presented by system organ class and preferred term. Each summary will include number of patients who experienced at least one AE within each category and corresponding percentage from the ST population, number of adverse events within each category and corresponding event rate. For incidence, patients will be counted only once in each system organ

class category and only once in each preferred term category. For frequency in cases when more than one AE with the same preferred term (PT) started on the same date for the same patient, these will be considered as duplicates and will be counted as one AE for that patient. If onset date of AEs with the same PT is partially unknown, then these AEs will be counted as separate AEs. An event rate will be defined as the total number of AEs divided by total exposure to study drug in patient years. Treatment-related adverse event summaries will include adverse events with missing relationship to study drug.

For the summaries by severity, for incidence patients are counted at the greatest severity, and for frequency when cases with duplicate AEs appear, the greatest severity will be assigned for that AE. Adverse events missing the flag indicating serious will be excluded from the summary of serious adverse events but included in the summary of non serious adverse events. For the summary by outcome, for incidence patients are counted at their worst outcome and for frequency when cases with duplicate AEs appear, the worst outcome will be assigned for that AE.

Treatment emergent AEs only which happened under study treatment will be included for all summaries and are defined as events with onset between (including) the date of first study drug dose , up to seven days after the date of last study drug dose. In addition, a summary of all AEs that happened following seven days after the last dose of the study drug will be presented as well.

All analyses presented in the section will be repeated to include both part A and part B when the study is completed.

All AEs will be presented in patient data listings.

Listings for deaths, serious adverse events, and adverse events leading to discontinuation will be presented.

8.4. Deaths

If a patient dies, all relevant information will be discussed in the patient's narratives included in CSR.

8.5. Clinical Laboratory Test

All laboratory tests will be presented in SI units. By-visit summaries for chemistry and hematology laboratory tests including actual values and changes from baseline to each visit will be summarized using descriptive statistics. Shifts (below, within, and above the normal range) from baseline to each visit will be summarized using descriptive statistics. In order to calculate the percentages for the shifts summary, the total number of patients with available laboratory test results at baseline and at the post baseline visit will be used as the denominator for each relevant laboratory test and time point.

The incidence of abnormal values (below or above normal range) and the incidence of potentially clinically significant abnormal values (PCSA) (according to criteria specified in Table 3) will be summarized for laboratory data using descriptive statistics. The denominator for calculating the percentage of patients with at least 1 abnormality/PCSA for the group of chemistry/hematology tests will be the number of patients with both baseline and post baseline

laboratory result for at least 1 of the chemistry/hematology tests in that group. The denominator for calculating the percentage of patients with at least 1 abnormality/PCSA for each separate test will be the number of patients with both baseline and post baseline result for that test.

In addition, shift analysis from baseline to any time during the study for abnormal values as well as for PCSA values will be summarized using descriptive statistics. The shift categories for abnormal values will be presented as following: from below/within normal range at baseline to above normal range during the study, from above/within normal range at baseline to below normal range during the study, and condition not changed/changed to normal range value. The shift categories for PCSA values will be presented as following: from low/non PCSA value at baseline to high PCSA value during the study, from high/ non PCSA value at baseline to low PCSA value during the study, and condition not changed/changed to non PCSA value. In addition shift analysis for PCSA will also be presented as shift from normal baseline values to PCSA any time during the study following baseline. The denominator for calculating the percentages of patients will be the number of patients with both baseline and post baseline measurements for a specific test.

Table 3: Criteria for Potentially Clinically Significant Laboratory Values

Test	Criterion value
Serum chemistry	
Sodium	≤ 130 mmol/L ≥ 150 mmol/L
Potassium	≤ 3.2 mmol/L ≥ 5.5 mmol/L
Calcium	≤ 1.87 mmol/L ≥ 2.75 mmol/L
Phosphate	≤ 0.65 mmol/L ≥ 1.61 mmol/L
Glucose	≤ 3 mmol/L ≥ 13.88 mmol/L
Blood Urea Nitrogen	≥ 11.16 mmol/L
Alanine aminotransferase (ALT)	≥3x ULN
Aspartate aminotransferase (AST)	≥3x ULN
Alkaline phosphatase	≥3x ULN
Gammaglutamyl Transpeptidase (GGT)	≥3x ULN
Creatine phosphokinase (CPK)	≥3x ULN
Creatinine	≥177 μmol/L
Bilirubin (total)	≥28 μmol/L
Albumin	≤ 25 g/L

Table 3: Criteria for Potentially Clinically Significant Laboratory Values (Continued)

Test		Criterion value
C Reactive Protein		≥3x ULN
Amylase, Pancreatic		≥3x ULN
Hematology		
Hemoglobin	Men	≤ 11.5 g/dL ≥ 20 g/dL
	Women	≤ 10 g/dL ≥ 18.5 g/dL
Leukocytes		≤2.5 x 10^9/L ≥21 x 10^9/L
Neutrophils		≤1.49 x 10^9/L
Platelets		≤100 x 10^9/L ≥600 x 10^9/L
Fibrinogen		≥1.5x ULN

ULN=upper limit of normal range.

Boxplots for all hematology tests, Fibrinogen, CRP and P-Amylase will be presented over time, including baseline, and all scheduled visits. Data recorded during unscheduled visits will not be included in the box plots.

In addition, for patients with a confirmed hemoglobin decrease of more than 1 g/dL who completed at least one of the tests in the anemia panel following baseline visit, data from the anemia panel/B12 tests and change from baseline will be presented using descriptive statistics.

Moreover, shift analysis of Common Terminology Criteria for Adverse Events (CTCAE) grade from baseline to any time during the study for Hemoglobin test will be presented using descriptive statistics. Grades of CTCAE will be defined according to CTCAE, v4 and are presented in Table 4. For the cases with normal hemoglobin value, the CTCAE grade will be assigned zero. The denominator for calculating the percentages of patients will be the number of patients with both baseline and post baseline Hemoglobin measurements.

Table 4: Common Terminology Criteria for Adverse Events for Hemoglobin, v4

Grade	Description
1	LLN - 10.0
2	10.0 - 8.0 g/dL
3	<8.0 g/dL
4	Life-threatening consequences; urgent intervention indicated
5	Death

Also, a graph for the evaluation of drug-induced serious hepatotoxicity (eDISH) will be presented. The following steps should be performed in order to construct this graph:

1. For each patient in the ST population, find maximal post baseline value for ALT. If the same maximal value occurs in two separate visits, then the earlier visit value should be taken into account. Following that find the maximal Bilirubin(Total) value occurring after (or same day) the maximum ALT measurement occurred.
2. The maximal values identified in step 1 then should be divided by the ULN for each test accordingly.
3. Values received in step 2 will be presented in the scatter plot with ALT values on the x-axis and Bilirubin values on the y-axis. Two reference lines indicating extreme limits of 3 X ULN for ALT and 2 X ULN for Bilirubin will be shown as well.

Maximal values of AST, ALT and GGT at any time after randomization in terms of the upper normal range multiples will be provided in a separate table for patients with normal AST, ALT and GGT at baseline using descriptive statistics. The following intervals for maximal values will be used for this table: <= 1xULN, > 1xULN and <= 3xULN, > 3xULN and <= 5xULN, > 5xULN and <= 8xULN, > 8xULN. The denominator for calculating percentages will be the number of patients with post baseline hematology tests.

All analyses presented in the section will be repeated to include both part A and part B when the study is completed.

Listings for clinically significant abnormal laboratory data will be presented.

8.6. Vital Signs

By-visit summaries for vital signs including actual values and changes from baseline to each visit will be summarized using descriptive statistics. The incidence of potentially clinically significant abnormal values will be summarized for selected vital signs using descriptive statistics.

Table 5 specifies the criteria for identifying vital signs as potentially clinically significantly abnormal. Note that in order to be identified as potentially clinically significantly abnormal, a value would need to meet both conditions below, ie, have a value beyond the criterion value and a change of at least the magnitude specified in the change from baseline column.

Table 5: Criteria for Potentially Clinically Significant Vital Signs

Vital Sign	Criterion value	Change relative to baseline
Pulse	≥120 bpm	Increase of ≥30
	≤45 bpm	Decrease of ≥30
Systolic blood pressure	≥180 mm Hg	Increase of ≥30
	≤90 mm Hg	Decrease of ≥30
Diastolic blood pressure	≥100 mm Hg	Increase of ≥20
	≤50 mm Hg	Decrease of ≥20

All analyses presented in the section will be repeated to include both part A and part B when the study is completed.

A listing for potentially clinically significant abnormal vital signs will be presented.

8.7. Electrocardiogram

ECG findings at each week will be summarized using descriptive statistics for investigator's interpretations (normal, abnormal not clinically significant, abnormal clinically significant, missing) and for ERT interpretation (normal, abnormal, unable to evaluate). Shifts from baseline to each visit will be summarized using descriptive statistics.

Summary statistics for electrocardiogram variables evaluated by ERT (Heart Rate, PR Interval, QRS Interval, QT Interval, QTc Interval Bazett, QTc Interval Fridericia, RR Interval) will be presented at baseline, and each visit. Actual values and changes from baseline to each visit will be summarized using descriptive statistics.

Categorical analysis of QTc Intervals (Bazett and Fridericia), according to International Conference on Harmonisation (ICH) guideline: E14 – "The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs", will be presented. Incidence of subjects within each category at baseline will be presented for each parameter. Shift analysis from baseline to each scheduled visit and to any time during study will be performed for each parameter.

All analyses presented in the section will be repeated to include both part A and part B when the study is completed.

The cut off points for categorical analysis of QTc Interval (msec) (Bazett and Fridericia) are defined in Table 6.

Table 6: Cut off Points for Categorical Analysis of QTc Interval (msec) (Bazett and Fridericia)

QTc Interval (msec)	<=450
QTc Interval (msec)	>450 and <=480
QTc Interval (msec)	>480 and <=500
QTc Interval (msec)	>500
QTc Interval (msec) Increase from Baseline	<=30
QTc Interval (msec) Increase from Baseline	>30 and <=60
QTc Interval (msec) Increase from Baseline	>60

8.8. Concomitant Medications

All concomitant medications will be coded using the WHO Drug. The incidence of concomitant medications will be summarized using descriptive statistics by therapeutic class and preferred term. Patients are counted only once in each therapeutic class category, and only once in each preferred term category. Concomitant medications will include all medications taken while a patient participated in the study.

When the study is completed, the table of concomitant medications will be generated again to include both part A and part B.

9. PHARMACOKINETIC ANALYSIS

A single blood sample will be collected from all patients at weeks 4, 8, 12, 24 and 48. Pharmacokinetics of laquinimod will be evaluated using a PPK approach. The effect of covariates on the pharmacokinetics of laquinimod will be evaluated. Possible covariates will include demographic variables (eg, age, gender, body weight and ethnicity), clinical variables, concomitant medications, blood and urine chemistry variables and markers of renal function (creatinine clearance and serum creatinine).

This analysis will be reported in a separate PPK report.

10. ANALYSIS OF ADDITIONAL EXPLORATORY PARAMETERS

The analysis of the following variable will be specified in separate documents:

- PGx measures
- Potential biomarker measures
- Ancillary studies measures

11. STATISTICAL SOFTWARE

All data listings, summaries, and statistical analyses will be generated using SAS®.

12. CHANGES TO PROTOCOL SPECIFIED ANALYSES

The following changes to protocol specified analyses are introduced in this SAP:

- Multiplicity adjustment at alpha level of 5% was added for the analyses of the primary and secondary endpoints.
- Sensitivity analyses for primary and secondary endpoints which use data recorded after patient early terminates treatment and continues to come to the follow up visits were removed.

13. LIST OF SUMMARIES AND LISTINGS

13.1. Summary Tables

Summary number	Title	Population	Data Lock
15.1.1	Patient Disposition by Treatment Group	All Patients	Part A
15.1.2	Patient Disposition by Treatment Group	All Patients	Part B
15.2	Distribution of Patients by Country and Treatment Group	ITT Population	Part A
15.3	Distribution of Patients by Country, Site, and Treatment Group	ITT Population	Part A
15.4.1	Demographics by Treatment Group	ITT Population	Part A
15.4.2	Demographics by Treatment Group	mITT1 Population	Part A
15.4.3	Demographics by Treatment Group	Patients who ET in Part A	Part A
15.4.4	Demographics by Treatment Group	Patients who Completed Part A	Part A
15.4.5	Demographics by Treatment Group	Patients who ET in Part B	Part B
15.4.6	Demographics by Treatment Group	Patients who Completed Part B	Part B
15.5.1	PPMS Characteristics by Treatment Group	ITT Population	Part A
15.5.2	PPMS Characteristics by Treatment Group	mITT1 Population	Part A
15.5.3	PPMS Characteristics by Treatment Group	Patients who ET in Part A	Part A
15.5.4	PPMS Characteristics by Treatment Group	Patients who Completed Part A	Part A
15.5.5	PPMS Characteristics by Treatment Group	Patients who ET in Part B	Part B
15.5.6	PPMS Characteristics by Treatment Group	Patients who Completed Part B	Part B
15.6.1	Baseline MRI Measurements by Treatment Group	ITT Population	Part A
15.6.2	Baseline MRI Measurements by Treatment Group	mITT1 Population	Part A
15.6.3	Baseline MRI Measurements by Treatment Group	Patients who ET in Part A	Part A
15.6.4	Baseline MRI Measurements by Treatment Group	Patients who Completed Part A	Part A
15.6.5	Baseline MRI Measurements by Treatment Group	Patients who ET in Part B	Part B
15.6.6	Baseline MRI Measurements by Treatment Group	Patients who Completed Part B	Part B
15.7.1	Tobacco Usage by Treatment Group	ITT Population	Part A
15.7.2	Tobacco Usage by Treatment Group	mITT1 Population	Part A
15.7.3	Tobacco Usage by Treatment Group	Patients who ET in Part A	Part A
15.7.4	Tobacco Usage by Treatment Group	Patients who Completed Part A	Part A

Summary number	Title	Population	Data Lock
15.7.5	Tobacco Usage by Treatment Group	Patients who ET in Part B	Part B
15.7.6	Tobacco Usage by Treatment Group	Patients who Completed Part B	Part B
15.8	Abnormal Medical History Findings by System Organ Class, Preferred Term and Treatment Group	ITT Population	Part A
15.9	Prior Medications by Therapeutic Class, Preferred Term, and Treatment Group	ITT Population	Part A
15.10	MS Disease Modifying Treatment History by Therapeutic Class, Preferred Term, and Treatment Group	ITT Population	Part A
15.11	Electrocardiogram Findings at Baseline Based on Investigator Interpretation by Treatment Group	ITT Population	Part A
15.12	Electrocardiogram Findings at Baseline Based on ERT Interpretation by Treatment Group	ITT Population	Part A
15.13.1	Protocol Violations by Treatment Group	ITT Population	Part A
15.13.2	Protocol Violations by Treatment Group	ITT Population	Part B
15.14	Major Protocol Violations by Treatment Group	ITT Population	Part A
15.15	Primary Analysis: Percentage Brain Volume Change (PBVC) from Baseline to Week 48	mITT1 Population	Part A
15.16	Primary Analysis Treatment by Covariate Interaction Evaluation: Percentage Brain Volume Change (PBVC) from Baseline to Week 48	mITT1 Population	Part A
15.17	Descriptive Statistics for Percentage Brain Volume Change (PBVC) by Visit and Treatment Group	mITT1 Population	Part A
15.18	Sensitivity Analysis for Primary Endpoint: Percentage Brain Volume Change (PBVC) from Baseline to Week 48	PP Population	Part A
15.19	Descriptive Statistics for Percentage Brain Volume Change (PBVC) by Visit and Treatment Group	PP Population	Part A
15.20	Sensitivity Analysis for Primary Endpoint: Percentage Brain Volume Change (PBVC) from Baseline to Week 48 – Unadjusted for Covariates	mITT1 Population	Part A
15.21	Sensitivity Analysis for Primary Endpoint: Percentage Brain Volume Change (PBVC) from Baseline to Week 48 – Adjusted for Additional Covariates	mITT1 Population	Part A
15.22.1	Secondary Analysis: Time to 12 Weeks Confirmed Disability Progression as Measured by EDSS	ITT Population	Part A
15.22.2	Exploratory Analysis: Time to 12 Weeks Confirmed Disability Progression as Measured by EDSS	ITT Population	Part B
15.23.1	Secondary Analysis Proportional Hazards Assumption Evaluation: Time to 12 Weeks Confirmed Disability Progression as Measured by EDSS	ITT Population	Part A

Summary number	Title	Population	Data Lock
15.23.2	Exploratory Analysis Proportional Hazards Assumption Evaluation: Time to 12 Weeks Confirmed Disability Progression as Measured by EDSS	ITT Population	Part B
15.24.1	Distribution of 12 Weeks Confirmed Disability Progression as Measured by the EDSS by Treatment Group	ITT Population	Part A
15.24.2	Distribution of 12 Weeks Confirmed Disability Progression as Measured by the EDSS by Treatment Group	ITT Population	Part B
15.25.1	Descriptive Statistics for EDSS Score and Change From Baseline to Each Visit by Treatment Group	ITT Population	Part A
15.25.2	Descriptive Statistics for EDSS Score and Change From Baseline to Each Visit by Treatment Group	ITT Population	Part B
15.26.1	Secondary Analysis: Time to 12 Weeks Confirmed Disability Progression as Measured by EDSS or T25FW	ITT Population	Part A
15.26.2	Exploratory Analysis: Time to 12 Weeks Confirmed Disability Progression as Measured by EDSS or T25FW	ITT Population	Part B
15.27.1	Secondary Analysis Proportional Hazards Assumption Evaluation: Time to 12 Weeks Confirmed Disability Progression as Measured by EDSS or T25FW	ITT Population	Part A
15.27.2	Exploratory Analysis Proportional Hazards Assumption Evaluation: Time to 12 Weeks Confirmed Disability Progression as Measured by EDSS or T25FW	ITT Population	Part B
15.28.1	Distribution of 12 Weeks Confirmed Disability Progression as Measured by EDSS or T25FW by Treatment Group	ITT Population	Part A
15.28.2	Distribution of 12 Weeks Confirmed Disability Progression as Measured by EDSS or T25FW by Treatment Group	ITT Population	Part B
15.29.1	Secondary Analysis: Timed 25-Foot Walk Score Change From Baseline to Week 48	mITT2 Population	Part A
15.29.2	Exploratory Analysis: Timed 25-Foot Walk Score Change From Baseline to Each Visit	mITT2 Population	Part B
15.30.1	Descriptive Statistics for Timed 25-Foot Walk Score and Change From Baseline to Each Visit by Treatment Group	mITT2 Population	Part A
15.30.2	Descriptive Statistics for Timed 25-Foot Walk Score and Change From Baseline to Each Visit by Treatment Group	mITT2 Population	Part B
15.31	Secondary Analysis: Number of New T2 Lesions at Week 48	mITT1 Population	Part A
15.32	Descriptive Statistics for the Number of New T2 Lesions at Week 48 by Treatment Group	mITT1 Population	Part A
15.33.1	Exploratory Analysis: CVLT-II Score Change From Baseline to Week 48	mITT2 Population	Part A
15.33.2	Exploratory Analysis: CVLT-II Score Change From Baseline to Each Visit	mITT2 Population	Part B

Summary number	Title	Population	Data Lock
15.34.1	Descriptive Statistics for CVLT-II Score and Change From Baseline to Each Visit by Treatment Group	mITT2 Population	Part A
15.34.2	Descriptive Statistics for CVLT-II Score and Change From Baseline to Each Visit by Treatment Group	mITT2 Population	Part B
15.35.1	Exploratory Analysis: BVMT-R Score Change From Baseline to Week 48	mITT2 Population	Part A
15.35.2	Exploratory Analysis: BVMT-R Score Change From Baseline to Each Visit	mITT2 Population	Part B
15.36.1	Descriptive Statistics for BVMT-R Score and Change From Baseline to Each Visit by Treatment Group	mITT2 Population	Part A
15.36.2	Descriptive Statistics for BVMT-R Score and Change From Baseline to Each Visit by Treatment Group	mITT2 Population	Part B
15.37.1	Exploratory Analysis: Time to 12 Weeks Confirmed Disability Progression as Measured by at least 1 of 4 Types of Events	ITT Population	Part A
15.37.2	Exploratory Analysis: Time to 12 Weeks Confirmed Disability Progression as Measured by at least 1 of 4 Types of Events	ITT Population	Part B
15.38.1	Exploratory Analysis Proportional Hazards Assumption Evaluation: Time to 12 Weeks Confirmed Disability Progression as Measured by at least 1 of 4 Types of Events	ITT Population	Part A
15.38.2	Exploratory Analysis Proportional Hazards Assumption Evaluation: Time to 12 Weeks Confirmed Disability Progression as Measured by at least 1 of 4 Types of Events	ITT Population	Part B
15.39.1	Distribution of 12 Weeks Confirmed Disability Progression as Measured by at least 1 of 4 Types of Events by Treatment Group	ITT Population	Part A
15.39.2	Distribution of 12 Weeks Confirmed Disability Progression as Measured by at least 1 of 4 Types of Events by Treatment Group	ITT Population	Part B
15.40.1	Exploratory Analysis: Time to 24 Weeks Confirmed Disability Progression as Measured by EDSS	ITT Population	Part A
15.40.2	Exploratory Analysis: Time to 24 Weeks Confirmed Disability Progression as Measured by EDSS	ITT Population	Part B
15.41.1	Exploratory Analysis Proportional Hazards Assumption Evaluation: Time to 24 Weeks Confirmed Disability Progression as Measured by EDSS	ITT Population	Part A
15.41.2	Exploratory Analysis Proportional Hazards Assumption Evaluation: Time to 24 Weeks Confirmed Disability Progression as Measured by EDSS	ITT Population	Part B
15.42.1	Distribution of 24 Weeks Confirmed Disability Progression as Measured by EDSS by Treatment Group	ITT Population	Part A
15.42.2	Distribution of 24 Weeks Confirmed Disability Progression as Measured by EDSS by Treatment Group	ITT Population	Part B
15.43	Exploratory Analysis: Number of New T1-Hypointense Lesions at Week 48	mITT1 Population	Part A

Summary number	Title	Population	Data Lock
15.44	Descriptive Statistics for the Number of New T1-Hypointense Lesions at Week 48 by Treatment Group	mITT1 Population	Part A
15.45	Exploratory Analysis: T1-Hypointense Lesion Volume Change From Baseline to Week 48	mITT1 Population	Part A
15.46	Descriptive Statistics for T1-Hypointense Lesion Volume and Change From Baseline to Week 48 by Treatment Group	mITT1 Population	Part A
15.47	Exploratory Analysis: T2 Lesion Volume Change From Baseline to Week 48	mITT1 Population	Part A
15.48	Descriptive Statistics for T2 Lesion and Volume Change From Baseline to Week 48 by Treatment Group	mITT1 Population	Part A
15.49	Exploratory Analysis: Normalized Thalamic Volume Percent Change From Baseline at Week 48	mITT1 Population	Part A
15.50	Descriptive Statistics for Normalized Thalamic Volume Percent Change From Baseline to Week 48 by Treatment group	mITT1 Population	Part A
15.51	Exploratory Analysis: Mean Cortical Thickness Percent Change From Baseline to Week 48	mITT1 Population	Part A
15.52	Descriptive Statistics for Mean Cortical Thickness Percent Change From Baseline to Week 48 by Treatment Group	mITT1 Population	Part A
15.53	Exploratory Analysis: Normalized White Matter Volume Percent Change From Baseline to Week 48	mITT1 Population	Part A
15.54	Descriptive Statistics for Normalized White Matter Volume Percent Change From Baseline to Week 48 by Treatment Group	mITT1 Population	Part A
15.55	Exploratory Analysis: Mean Upper Cervical Cord Area Percent Change From Baseline to Week 48	mITT1 Population	Part A
15.56	Descriptive Statistics for Mean Upper Cervical Cord Area Percent Change From Baseline to Week 48 by Treatment Group	mITT1 Population	Part A
15.57	Exploratory Analysis: Number of T2 Cervical Cord Lesions at Week 48	mITT1 Population	Part A
15.58	Descriptive Statistics for the Number of T2 Cervical Cord Lesions at Week 48 by Treatment Group	mITT1 Population	Part A
15.59	Exploratory Analysis: Mean MTR Normal-Appearing Brain Tissue Percent Change From Baseline to Week 48	mITT1 Population	Part A
15.60	Descriptive Statistics for Mean MTR Normal-Appearing Brain Tissue Percent Change From Baseline to Week 48 by Treatment group	mITT1 Population	Part A
15.61.1	Exploratory Analysis: 9-Hole Peg Test Score Change From Baseline to Week 48	mITT2 Population	Part A
15.61.2	Exploratory Analysis: 9-Hole Peg Test Score Change From Baseline to Each Visit	mITT2 Population	Part B
15.62.1	Descriptive Statistics for 9-Hole Peg Test Score and Change From Baseline to Each Visit by Treatment Group	mITT2 Population	Part A

Summary number	Title	Population	Data Lock
15.62.2	Descriptive Statistics for 9-Hole Peg Test Score and Change From Baseline to Each Visit by Treatment Group	mITT2 Population	Part B
15.63.1	Exploratory Analysis: Symbol Digit Modalities Test Score Change From Baseline to Week 48	mITT2 Population	Part A
15.63.2	Exploratory Analysis: Symbol Digit Modalities Test Score Change From Baseline to Each Visit	mITT2 Population	Part B
15.64.1	Descriptive Statistics for Symbol Digit Modalities Test Score and Change From Baseline to Each Visit by Treatment Group	mITT2 Population	Part A
15.64.2	Descriptive Statistics for Symbol Digit Modalities Test Score and Change From Baseline to Each Visit by Treatment Group	mITT2 Population	Part B
15.65.1	Exploratory Analysis: Low Contrast Visual Acuity Score (Chart Type 100%) Change From Baseline to Week 48	mITT2 Population	Part A
15.65.2	Exploratory Analysis: Low Contrast Visual Acuity Score (Chart Type 100%) Change From Baseline to Each Visit	mITT2 Population	Part B
15.66.1	Descriptive Statistics for Low Contrast Visual Acuity Score (Chart Type 100%) and Change From Baseline to Each Visit by Treatment Group	mITT2 Population	Part A
15.66.2	Descriptive Statistics for Low Contrast Visual Acuity Score (Chart Type 100%) and Change From Baseline to Each Visit by Treatment Group	mITT2 Population	Part B
15.67.1	Exploratory Analysis of Low Contrast Visual Acuity Score (Chart Type 2.5%) Change From Baseline to Week 48	mITT2 Population	Part A
15.67.2	Exploratory Analysis of Low Contrast Visual Acuity Score (Chart Type 2.5%) Change From Baseline to Each Visit	mITT2 Population	Part B
15.68.1	Descriptive Statistics for Low Contrast Visual Acuity Score (Chart Type 2.5%) and Change From Baseline to Each Visit by Treatment Group	mITT2 Population	Part A
15.68.2	Descriptive Statistics for Low Contrast Visual Acuity Score (Chart Type 2.5%) and Change From Baseline to Each Visit by Treatment Group	mITT2 Population	Part B
15.69.1	Exploratory Analysis: Low Contrast Visual Acuity Score (Chart Type 1.25%) Change From Baseline to Week 48	mITT2 Population	Part A
15.69.2	Exploratory Analysis: Low Contrast Visual Acuity Score (Chart Type 1.25%) Change From Baseline to Each Visit	mITT2 Population	Part B
15.70.1	Descriptive Statistics for Low Contrast Visual Acuity Score (Chart Type 1.25%) and Change From Baseline to Each Visit by Treatment Group	mITT2 Population	Part A
15.70.2	Descriptive Statistics for Low Contrast Visual Acuity Score (Chart Type 1.25%) and Change From Baseline to Each Visit by Treatment Group	mITT2 Population	Part B
15.71.1	Exploratory Analysis: 12-Item Multiple Sclerosis Walking Scale Score Change From Baseline to Week 48	mITT2 Population	Part A

Summary number	Title	Population	Data Lock
15.71.2	Exploratory Analysis: 12-Item Multiple Sclerosis Walking Scale Score Change From Baseline to Each Visit	mITT2 Population	Part B
15.72.1	Descriptive Statistics for 12-Item Multiple Sclerosis Walking Scale Score and Change From Baseline to Each Visit by Treatment Group	mITT2 Population	Part A
15.72.2	Descriptive Statistics for 12-Item Multiple Sclerosis Walking Scale Score and Change From Baseline to Each Visit by Treatment Group	mITT2 Population	Part B
15.73.1	Distribution of Clinical Relapsing Patients by Treatment Group	ITT Population	Part A
15.73.2	Distribution of Clinical Relapsing Patients by Treatment Group	ITT Population	Part B
15.74.1	Distribution of Protocol Defined Relapsing Patients by Treatment Group	ITT Population	Part A
15.74.2	Distribution of Protocol Defined Relapsing Patients by Treatment Group	ITT Population	Part B
15.75.1	Descriptive Statistics For mRS at Week 72 by Treatment Group	mITT2 Population	Part A
15.75.2	Descriptive Statistics For mRS at Week 72 by Treatment Group	mITT2 Population	Part B
15.76.1	Distribution of mRS at Week 72 by Treatment Group	mITT2 Population	Part A
15.76.2	Distribution of mRS at Week 72 by Treatment Group	mITT2 Population	Part B
15.77.1	Exploratory Analysis: Time to 12 Weeks Confirmed Disability Progression as Measured by T25FW	ITT Population	Part A
15.77.2	Exploratory Analysis: Time to 12 Weeks Confirmed Disability Progression as Measured by T25FW	ITT Population	Part B
15.78.1	Exploratory Analysis: Proportional Hazards Assumption Evaluation: Time to 12 Weeks Confirmed Disability Progression as Measured by T25FW	ITT Population	Part A
15.78.2	Exploratory Analysis Proportional Hazards Assumption Evaluation: Time to 12 Weeks Confirmed Disability Progression as Measured by T25FW	ITT Population	Part B
15.79.1	Distribution of 12 Weeks Confirmed Disability Progression as Measured by T25FW by Treatment Group	ITT Population	Part A
15.79.2	Distribution of 12 Weeks Confirmed Disability Progression as Measured by T25FW by Treatment Group	ITT Population	Part B
15.80.1	Tolerability by Treatment Group	ITT Population	Part A
15.80.2	Tolerability by Treatment Group	ITT Population	Part B
15.81.1	Study Drug Exposure by Treatment Group	Safety Population	Part A
15.81.2	Study Drug Exposure by Treatment Group	Safety Population	Part B
15.82.1	Off-Drug Follow-Up Study Duration by Treatment Group	Safety Population	Part A
15.82.2	Off-Drug Follow-Up Study Duration by Treatment Group	Safety Population	Part B

Summary number	Title	Population	Data Lock
15.83.1	Adverse Events by System Organ Class, Preferred Term, and Treatment Group	Safety Population	Part A
15.83.2	Adverse Events by System Organ Class, Preferred Term, and Treatment Group	Safety Population	Part B
15.84.1	Adverse Events by System Organ Class, Preferred Term, Severity, and Treatment Group	Safety Population	Part A
15.84.2	Adverse Events by System Organ Class, Preferred Term, Severity, and Treatment Group	Safety Population	Part B
15.85.1	Treatment-Related Adverse Events by System Organ Class, Preferred Term, and Treatment Group	Safety Population	Part A
15.85.2	Treatment-Related Adverse Events by System Organ Class, Preferred Term, and Treatment Group	Safety Population	Part B
15.86.1	Treatment-Related Adverse Events by System Organ Class, Preferred Term, Severity, and Treatment Group	Safety Population	Part A
15.86.2	Treatment-Related Adverse Events by System Organ Class, Preferred Term, Severity, and Treatment Group	Safety Population	Part B
15.87.1	Serious Adverse Events by System Organ Class, Preferred Term, and Treatment Group	Safety Population	Part A
15.87.2	Serious Adverse Events by System Organ Class, Preferred Term, and Treatment Group	Safety Population	Part B
15.88.1	Adverse Events Causing Discontinuation of the Study Drug by System Organ Class, Preferred Term, and Treatment Group	Safety Population	Part A
15.88.2	Adverse Events Causing Discontinuation of the Study Drug by System Organ Class, Preferred Term, and Treatment Group	Safety Population	Part B
15.89.1	Non-Serious Adverse Events by System Organ Class, Preferred Term, and Treatment Group	Safety Population	Part A
15.89.2	Non-Serious Adverse Events by System Organ Class, Preferred Term, and Treatment Group	Safety Population	Part B
15.90.1	Adverse Events by System Organ Class, Preferred Term, Outcome, and Treatment Group	Safety Population	Part A
15.90.2	Adverse Events by System Organ Class, Preferred Term, Outcome, and Treatment Group	Safety Population	Part B
15.91.1	Adverse Events That Occurred After Study Drug Discontinuation by System Organ Class, Preferred Term, and Treatment Group	Safety Population	Part A
15.91.2	Adverse Events That Occurred After Study Drug Discontinuation by System Organ Class, Preferred Term, and Treatment Group	Safety Population	Part B
15.92.1	Serum Chemistry Laboratory Test Results and Changes From Baseline to Each Visit by Treatment Group	Safety Population	Part A
15.92.2	Serum Chemistry Laboratory Test Results and Changes From Baseline to Each Visit by Treatment Group	Safety Population	Part B

Summary number	Title	Population	Data Lock
15.93.1	Hematology Laboratory Test Results and Changes From Baseline to Each Visit by Treatment Group	Safety Population	Part A
15.93.2	Hematology Laboratory Test Results and Changes From Baseline to Each Visit and by Treatment Group	Safety Population	Part B
15.94.1	Serum Chemistry Laboratory Tests Shifts From Baseline to Each Visit by Treatment Group	Safety Population	Part A
15.94.2	Serum Chemistry Laboratory Tests Shifts From Baseline to Each Visit by Treatment Group	Safety Population	Part B
15.95.1	Hematology Laboratory Tests Shifts From Baseline to Each Visit and by Treatment Group	Safety Population	Part A
15.95.2	Hematology Laboratory Tests Shifts From Baseline to Each Visit and by Treatment Group	Safety Population	Part B
15.96.1	Serum Chemistry Laboratory Tests Abnormal Results by Treatment Group	Safety Population	Part A
15.96.2	Serum Chemistry Laboratory Tests Abnormal Results by Treatment Group	Safety Population	Part B
15.97.1	Hematology Laboratory Tests Abnormal Results by Treatment Group	Safety Population	Part A
15.97.2	Hematology Laboratory Tests Abnormal Results by Treatment Group	Safety Population	Part B
15.98.1	Serum Chemistry Laboratory Tests Potentially Clinically Significant Abnormal Results by Treatment Group	Safety Population	Part A
15.98.2	Serum Chemistry Laboratory Tests Potentially Clinically Significant Abnormal Results by Treatment Group	Safety Population	Part B
15.99.1	Hematology Laboratory Tests Potentially Clinically Significant Abnormal Results by Treatment Group	Safety Population	Part A
15.99.2	Hematology Laboratory Tests Potentially Clinically Significant Abnormal Results by Treatment Group	Safety Population	Part B
15.100.1	Shift Analysis for Serum Chemistry Laboratory Tests Abnormal Values From Baseline to Any Time During the Study by Treatment Group	Safety Population	Part A
15.100.2	Shift Analysis for Serum Chemistry Laboratory Tests Abnormal Values From Baseline to Any Time During the Study by Treatment Group	Safety Population	Part B
15.101.1	Shift Analysis for Hematology Laboratory Tests Abnormal Values From Baseline to Any Time During the Study by Treatment Group	Safety Population	Part A
15.101.2	Shift Analysis for Hematology Laboratory Tests Abnormal Values From Baseline to Any Time During the Study by Treatment Group	Safety Population	Part A

Summary number	Title	Population	Data Lock
15.102.1	Shift Analysis for Serum Chemistry Laboratory Tests Potentially Clinically Significant Abnormal (PCSA) Values From Baseline to Any Time During the Study by Treatment Group	Safety Population	Part A
15.102.2	Shift Analysis for Serum Chemistry Laboratory Tests Potentially Clinically Significant Abnormal (PCSA) Values From Baseline to Any Time During the Study by Treatment Group	Safety Population	Part B
15.103.1	Shift Analysis for Hematology Laboratory Tests Potentially Clinically Significant Abnormal (PCSA) Values From Baseline to Any Time During the Study by Treatment Group	Safety Population	Part A
15.103.2	Shift Analysis for Hematology Laboratory Tests Potentially Clinically Significant Abnormal (PCSA) Values From Baseline to Any Time During the Study by Treatment Group	Safety Population	Part B
15.104.1	Shift Analysis for Serum Chemistry Laboratory Tests Potentially Clinically Significant Abnormal (PCSA) Values From Normal Values at Baseline to Any Time During the Study by Treatment Group	Safety Population	Part A
15.104.2	Shift Analysis for Serum Chemistry Laboratory Tests Potentially Clinically Significant Abnormal (PCSA) Values From Normal Values at Baseline to Any Time During the Study by Treatment Group	Safety Population	Part B
15.105.1	Shift Analysis for Hematology Laboratory Tests Potentially Clinically Significant Abnormal (PCSA) Values From Normal Values at Baseline to Any Time During the Study by Treatment Group	Safety Population	Part A
15.105.2	Shift Analysis for Hematology Laboratory Tests Potentially Clinically Significant Abnormal (PCSA) Values From Normal Values at Baseline to Any Time During the Study by Treatment Group	Safety Population	Part B
15.106.1	Anemia Panel/B12 Laboratory Tests Results and Change From Baseline by Treatment Group	Safety Population	Part A
15.106.2	Anemia Panel/B12 Laboratory Tests Results and Change From Baseline by Treatment Group	Safety Population	Part B
15.107.1	Shift Analysis of CTCAE Grade For Hemoglobin From Baseline to Any Time During the Study by Treatment Group	Safety Population	Part A
15.107.2	Shift Analysis of CTCAE Grade For Hemoglobin From Baseline to Any Time During the Study by Treatment Group	Safety Population	Part B
15.108.1	Distribution of Maximal AST, ALT, and GGT Values During Study by Treatment Group	Safety Population	Part A
15.108.2	Distribution of Maximal AST, ALT, and GGT Values During Study by Treatment Group	Safety Population	Part B
15.109.1	Vital Signs Values and Changes From Baseline to Each Visit by Treatment Group	Safety Population	Part A
15.109.2	Vital Signs Values and Changes From Baseline to Each Visit by Treatment Group	Safety Population	Part B

Summary number	Title	Population	Data Lock
15.110.1	Vital Signs Potentially Clinically Significant Abnormal Values by Treatment Group	Safety Population	Part A
15.110.2	Vital Signs Potentially Clinically Significant Abnormal Values by Treatment Group	Safety Population	Part B
15.111.1	Electrocardiogram Findings Based on Investigator Interpretation at Each Visit by Treatment Group	Safety Population	Part A
15.111.2	Electrocardiogram Findings Based on Investigator Interpretation at Each Visit by Treatment Group	Safety Population	Part B
15.112.1	Electrocardiogram Findings Based on ERT Interpretation at Each Visit by Treatment Group	Safety Population	Part A
15.112.2	Electrocardiogram Findings Based on ERT Interpretation at Each Visit by Treatment Group	Safety Population	Part B
15.113.1	Electrocardiogram Findings Based on Investigator Interpretation Shifts From Baseline to Each Visit by Treatment Group	Safety Population	Part A
15.113.2	Electrocardiogram Findings Based on Investigator Interpretation Shifts From Baseline to Each Visit by Treatment Group	Safety Population	Part B
15.114.1	Electrocardiogram Findings Based on ERT Interpretation Shifts From Baseline to Each Visit by Treatment Group	Safety Population	Part A
15.114.2	Electrocardiogram Findings Based on ERT Interpretation Shifts From Baseline to Each Visit by Treatment Group	Safety Population	Part B
15.115.1	Electrocardiogram Variables Evaluated by ERT Results and Changes From Baseline to Each Visit by Treatment Group	Safety Population	Part A
15.115.2	Electrocardiogram Variables Evaluated by ERT Results and Changes From Baseline to Each Visit by Treatment Group	Safety Population	Part B
15.116.1	QTc Intervals (Bazett and Fridericia) at Baseline by Treatment Group	Safety Population	Part A
15.116.2	QTc Intervals (Bazett and Fridericia) at Baseline by Treatment Group	Safety Population	Part B
15.117.1	Shift Analysis For QTc Intervals (Bazett and Fridericia) From Baseline to Each Visit and Overall by Treatment Group	Safety Population	Part A
15.117.2	Shift Analysis For QTc Intervals (Bazett and Fridericia) From Baseline to Each Visit and Overall by Treatment Group	Safety Population	Part B
15.118.1	Concomitant Medications by Therapeutic Class, Preferred Term, and Treatment Group	Safety Population	Part A
15.118.2	Concomitant Medications by Therapeutic Class, Preferred Term, and Treatment Group	Safety Population	Part B

13.2. Individual Patient Data Listings

Listing Number	Title	Population	Data Lock
16.2.1.01.1	Patient Disposition by Treatment Group	ITT Population	Part A
16.2.1.01.2	Patient Disposition by Treatment Group	ITT Population	Part B
16.2.1.02	Patients Who Did Not Meet Screening Criteria		Part A
16.2.2.01.1	Protocol Violations by Treatment Group	ITT Population	Part A
16.2.2.01.2	Protocol Violations by Treatment Group	ITT Population	Part B
16.2.2.02	Major Protocol Violations by Treatment Group	ITT Population	Part A
16.2.4.01	Demographics by Treatment Group	ITT Population	Part A
16.2.4.02	Childbearing Potential by Treatment Group (Females Only)	ITT Population	Part A
16.2.4.03	Medical History by Treatment Group	ITT Population	Part A
16.2.4.04	PPMS History by Treatment Group	ITT Population	Part A
16.2.4.05	MS Disease Modifying Treatment History by Treatment Group	ITT Population	Part A
16.2.4.06	Chest X-Ray by Treatment Group	ITT Population	Part A
16.2.4.07	Informed Consent for Cerebrospinal Fluid and Optical Coherence Tomography by Treatment Group	ITT Population	Part A
16.2.4.08.1	Liver Disease Risk Factor Evaluation by Treatment Group	ITT Population	Part A
16.2.4.08.2	Liver Disease Risk Factor Evaluation by Treatment Group	ITT Population	Part B
16.2.4.09	Tobacco Usage by Treatment Group	ITT Population	Part A
16.2.5.01.1	Dosing by Treatment Group	ITT Population	Part A
16.2.5.01.2	Dosing by Treatment Group	ITT Population	Part B
16.2.5.02.1	Study Medication Interruption by Treatment Group	ITT Population	Part A
16.2.5.02.2	Study Medication Interruption by Treatment Group	ITT Population	Part B
16.2.5.03	Prior Drug Administration by Treatment Group	ITT Population	Part A
16.2.5.04.1	Study Drug Accountability by Treatment Group	ITT Population	Part A
16.2.5.04.2	Study Drug Accountability by Treatment Group	ITT Population	Part B
16.2.5.05.1	Pack Accountability by Treatment Group	ITT Population	Part A
16.2.5.05.2	Pack Accountability by Treatment Group	ITT Population	Part B
16.2.6.01	MRI Scan by Treatment Group	ITT Population	Part A
16.2.6.02	MRI Parameters by Treatment Group	ITT Population	Part A
16.2.6.03.1	Confirmed Disability Progression (CDP) by Treatment Group	ITT Population	Part A
16.2.6.03.2	Confirmed Disability Progression (CDP) by Treatment Group	ITT Population	Part B
16.2.6.04.1	Neurological Assessments by Treatment Group	ITT Population	Part A
16.2.6.04.2	Neurological Assessments by Treatment Group	ITT Population	Part B
16.2.6.05.1	CVLT-II by Treatment Group	ITT Population	Part A

Listing Number	Title	Population	Data Lock
16.2.6.05.2	CVLT-II by Treatment Group	ITT Population	Part B
16.2.6.06.1	BVMT-R by Treatment Group	ITT Population	Part A
16.2.6.06.2	BVMT-R by Treatment Group	ITT Population	Part B
16.2.6.07.1	T25FW by Treatment Group	ITT Population	Part A
16.2.6.07.2	T25FW by Treatment Group	ITT Population	Part B
16.2.6.08.1	9HPT by Treatment Group	ITT Population	Part A
16.2.6.08.2	9HPT by Treatment Group	ITT Population	Part B
16.2.6.09.1	SDMT by Treatment Group	ITT Population	Part A
16.2.6.09.2	SDMT by Treatment Group	ITT Population	Part B
16.2.6.10.1	LCVA by Treatment Group	ITT Population	Part A
16.2.6.10.2	LCVA by Treatment Group	ITT Population	Part B
16.2.6.11.1	MSWS-12 by Treatment Group	ITT Population	Part A
16.2.6.11.2	MSWS-12 by Treatment Group	ITT Population	Part B
16.2.6.12.1	Clinical Relapse by Treatment Group	ITT Population	Part A
16.2.6.12.2	Clinical Relapse by Treatment Group	ITT Population	Part B
16.2.7.01.1	Adverse Events by Treatment Group	ITT Population	Part A
16.2.7.01.2	Adverse Events by Treatment Group	ITT Population	Part B
16.2.7.02.1	Deaths by Treatment Group	ITT Population	Part A
16.2.7.02.2	Deaths by Treatment Group	ITT Population	Part B
16.2.7.03.1	Serious Adverse Events by Treatment Group	ITT Population	Part A
16.2.7.03.2	Serious Adverse Events by Treatment Group	ITT Population	Part B
16.2.7.04.1	Adverse Events Causing Discontinuation of Treatment by Treatment Group	ITT Population	Part A
16.2.7.04.2	Adverse Events Causing Discontinuation of Treatment by Treatment Group	ITT Population	Part B
16.2.7.05	Adverse Events in Patients Who Did Not Meet Screening Criteria		Part A
16.2.8.01	Laboratory Reference Ranges		Part A
16.2.8.02.1	Serum Chemistry Laboratory Tests Results by Treatment Group	ITT Population	Part A
16.2.8.02.2	Serum Chemistry Laboratory Tests Results by Treatment Group	ITT Population	Part B
16.2.8.03.1	Hematology Laboratory Tests Results by Treatment Group	ITT Population	Part A
16.2.8.03.2	Hematology Laboratory Tests Results by Treatment Group	ITT Population	Part B
16.2.8.04.1	Coagulation Laboratory Test Results by Treatment Group	ITT Population	Part A
16.2.8.04.2	Coagulation Laboratory Test Results by Treatment Group	ITT Population	Part B
16.2.8.05	Urinalysis Laboratory Tests Results by Treatment Group	ITT Population	Part A

Listing Number	Title	Population	Data Lock
16.2.8.06.1	Pregnancy Test Results by Treatment Group (Females Only)	ITT Population	Part A
16.2.8.06.2	Pregnancy Test Results by Treatment Group (Females Only)	ITT Population	Part B
16.2.8.07.1	Serology Tests Results by Treatment Group	ITT Population	Part A
16.2.8.07.2	Serology Tests Results by Treatment Group	ITT Population	Part B
16.2.8.08.1	Anemia Panel Tests Results by Treatment Group	ITT Population	Part A
16.2.8.08.2	Anemia Panel Tests Results by Treatment Group	ITT Population	Part B
16.2.8.09.1	Serum Chemistry Laboratory Tests Potentially Clinically Significant Abnormal Results by Treatment Group	ITT Population	Part A
16.2.8.09.2	Serum Chemistry Laboratory Tests Potentially Clinically Significant Abnormal Results by Treatment Group	ITT Population	Part B
16.2.8.10.1	Hematology Laboratory Tests Potentially Clinically Significant Abnormal Results by Treatment Group	ITT Population	Part A
16.2.8.10.2	Hematology Laboratory Tests Potentially Clinically Significant Abnormal Results by Treatment Group	ITT Population	Part B
16.2.8.11.1	Treatment Schedule	ITT Population	Part A
16.2.8.11.2	Treatment Schedule	ITT Population	Part B
16.2.8.12.1	Vital Signs Values by Treatment Group	ITT Population	Part A
16.2.8.12.2	Vital Signs Values by Treatment Group	ITT Population	Part B
16.2.8.13.1	Vital Signs Potentially Clinically Significant Abnormal Values by Treatment Group	ITT Population	Part A
16.2.8.13.2	Vital Signs Potentially Clinically Significant Abnormal Values by Treatment Group	ITT Population	Part B
16.2.8.14.1	Electrocardiogram Findings by Treatment Group	ITT Population	Part A
16.2.8.14.2	Electrocardiogram Findings by Treatment Group	ITT Population	Part B
16.2.8.15.1	Electrocardiogram Variable Results by Treatment Group	ITT Population	Part A
16.2.8.15.2	Electrocardiogram Variable Results by Treatment Group	ITT Population	Part B
16.2.8.16.1	Physical Examination Not Done Records by Treatment Group	ITT Population	Part A
16.2.8.16.2	Physical Examination Not Done Records by Treatment Group	ITT Population	Part B
16.2.8.17.1	Prior and Concomitant Medications by Treatment Group	ITT Population	Part A
16.2.8.17.2	Prior and Concomitant Medications by Treatment Group	ITT Population	Part B
16.2.8.18	Pharmacokinetic Sampling Times by Treatment Group	ITT Population	Part A
16.2.8.19.1	Optical Coherence Tomography by Treatment Group	ITT Population	Part A
16.2.8.19.2	Optical Coherence Tomography by Treatment Group	ITT Population	Part B
16.2.8.20.1	Reasons for Unscheduled Visit by Treatment Group	ITT Population	Part A
16.2.8.20.2	Reasons for Unscheduled Visit by Treatment Group	ITT Population	Part B
16.2.8.21.1	Liver or Biliary Tract Ultrasound by Treatment Group	ITT Population	Part A

Listing Number	Title	Population	Data Lock
16.2.8.21.2	Liver or Biliary Tract Ultrasound by Treatment Group	ITT Population	Part B
16.2.8.22.1	Other Diagnostics by Treatment Group	ITT Population	Part A
16.2.8.22.2	Other Diagnostics by Treatment Group	ITT Population	Part B

13.3. Graphs

Graph Number	Title	Population	Data Lock
17.1	Adjusted Means Percentage Brain Volume Change (PBVC) from Baseline to Each Visit.	mITT1 Population	Part A
17.2	Adjusted Mean Percentage Brain Volume Change (PBVC) from Baseline to Each Visit.	PP Population	Part A
17.3.1	Kaplan-Meier Curves for Time to 12 Weeks Confirmed Disability Progression as Measured by EDSS by Treatment Group	ITT Population	Part A
17.3.2	Kaplan-Meier Curves for Time to 12 Weeks Confirmed Disability Progression as Measured by EDSS by Treatment Group	ITT Population	Part B
17.4.1	Kaplan-Meier Curves for Time to 12 Weeks Confirmed Disability Progression as Measured by EDSS and T25FW by Treatment Group	ITT Population	Part A
17.4.2	Kaplan-Meier Curves for Time to 12 Weeks Confirmed Disability Progression as Measured by EDSS and T25FW by Treatment Group	ITT Population	Part B
17.5.1	Means Timed 25-Foot Walk Score Change from Baseline to Each Visit	mITT2 Population	Part A
17.5.2	Means Timed 25-Foot Walk Score Change from Baseline to Each Visit	mITT2 Population	Part B
17.6.1	Kaplan-Meier Curves for Time to 12 Weeks Confirmed Disability Progression as Measured by at least 1 of 4 Types of Events by Treatment Group	ITT Population	Part A
17.6.2	Kaplan-Meier Curves for Time to 12 Weeks Confirmed Disability Progression as Measured by at least 1 of 4 Types of Events by Treatment Group	ITT Population	Part B
17.7.1	Kaplan-Meier Curves for Time to 24 Weeks Confirmed Disability Progression as Measured by EDSS by Treatment Group	ITT Population	Part A
17.7.2	Kaplan-Meier Curves for Time to 24 Weeks Confirmed Disability Progression as Measured by EDSS by Treatment Group	ITT Population	Part B
17.8.1	Means 9-Hole Peg Test Score Change from Baseline to Each Visit	mITT2 Population	Part A
17.8.2	Means 9-Hole Peg Test Score Change from Baseline to Each Visit	mITT2 Population	Part B
17.9.1	Adjusted Means Symbol Digit Modalities Test Score Change from Baseline to Each Visit	mITT2 Population	Part A
17.9.2	Adjusted Means Symbol Digit Modalities Test Score Change from Baseline to Each Visit	mITT2 Population	Part B
17.10.1	Adjusted Means for Low Contrast Visual Acuity Score (Chart Type 100%) Change from Baseline to Each Visit	mITT2 Population	Part A

Graph Number	Title	Population	Data Lock
17.10.2	Adjusted Means for Low Contrast Visual Acuity Score (Chart Type 100%) Change from Baseline to Each Visit	mITT2 Population	Part B
17.11.1	Adjusted Means for Low Contrast Visual Acuity Score (Chart Type 2.5%) Change from Baseline to Each Visit	mITT2 Population	Part A
17.11.2	Adjusted Means for Low Contrast Visual Acuity Score (Chart Type 2.5%) Change from Baseline to Each Visit	mITT2 Population	Part B
17.12.1	Adjusted Means for Low Contrast Visual Acuity Score (Chart Type 1.25%) Change from Baseline to Each Visit	mITT2 Population	Part A
17.12.2	Adjusted Means for Low Contrast Visual Acuity Score (Chart Type 1.25%) Change from Baseline to Each Visit	mITT2 Population	Part B
17.13.1	Adjusted Means 12-Item Multiple Sclerosis Walking Scale Score Change from Baseline to Each Visit	mITT2 Population	Part A
17.13.2	Adjusted Means 12-Item Multiple Sclerosis Walking Scale Score Change from Baseline to Each Visit	mITT2 Population	Part B
17.14.1	Kaplan-Meier Curves for Time to 12 Weeks Confirmed Disability Progression as Measured by T25FW by Treatment Group	ITT Population	Part A
17.14.2	Kaplan-Meier Curves for Time to 12 Weeks Confirmed Disability Progression as Measured by T25FW by Treatment Group	ITT Population	Part B
17.15.1	Kaplan-Meier Curves for Time to Early Termination	ITT Population	Part A
17.15.2	Kaplan-Meier Curves for Time to Early Termination	ITT Population	Part B
17.16.1	Kaplan-Meier Curves for Time to Early Termination Due to Adverse Events	ITT Population	Part A
17.16.2	Kaplan-Meier Curves for Time to Early Termination Due to Adverse Events	ITT Population	Part B
17.17.1	Box Plots for Hematology Laboratory Tests Results Over Time by Treatment Group	Safety Population	Part A
17.17.2	Box Plots for Hematology Laboratory Tests Results Over Time by Treatment Group	Safety Population	Part B
17.18.1	Box Plots for Fibrinogen, CRP, and P-Amylase Laboratory Test Results Over Time by Treatment Group	Safety Population	Part A
17.18.2	Box Plots for Fibrinogen, CRP, and P-Amylase Laboratory Test Results Over Time by Treatment Group	Safety Population	Part B
17.19.1	Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) by Treatment Group	Safety Population	Part A
17.19.2	Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) by Treatment Group	Safety Population	Part B