NOVARTIS

Clinical Development

BAF312A/Siponimod/Mayzent®

CBAF312AUS02 / NCT03623243

Exploring the safety and tolerability of conversion from oral, injectable or infusion disease modifying therapies to dose-titrated Oral Siponimod (Mayzent®) in patients with advancing forms of relapsing multiple sclerosis: A 6-month open label, multicenter Phase IIIb study (EXCHANGE)

Statistical Analysis Plan (SAP)

Author: [redacted]; Trial Statistician, [redacted]

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30-August-2022	Prior to DB lock	Protocol v05	Amendment 2.0	Section 1, 2

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List of abbreviations

AE	Adverse event
AESI	Adverse Event of Special Interest
ARR	Annualised Relapse Rate
CSR	Clinical Study report
DAR	Dose Administration Record
DMT	Disease Modifying Therapy
ECG	Electrocardiogram
EOS	End of Study
eCRF	Electronic Case Report Form
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MS	Multiple Sclerosis
[redacted]	[redacted]
[redacted]	[redacted]
PK	Pharmacokinetics
[redacted]	[redacted]
RMS	Relapsing Multiple Sclerosis
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMQ	Standardized MedDRA Query
SOC	System Organ Class
TFLs	Tables, Figures, Listings
TSQM-9	Treatment Satisfaction Questionnaire for Medication
WHO	World Health Organization

1 Introduction

This document contains details of the statistical methods which will be used in the phase IIIb clinical trial CBAF312AUS02. The statistical analysis described in this SAP is based on the study protocol no. BAF312AUS02 Amendment Version 05 and will be presented in the Clinical Study Report (CSR). This document will also describe planned analysis for an interim analysis.

The purpose of this study is to assess early phase safety and tolerability of converting patients from approved oral, injectable or infusion RMS DMTs to siponimod. The results of this phase IIIb clinical trial CBAF312AUS02 will guide clinically relevant decisions related to the transition from frequently used RMS DMTs to siponimod and provide clinically relevant data on safety and tolerability for healthcare providers who are considering converting patients from currently approved RMS DMT to siponimod.

1.1 Study design

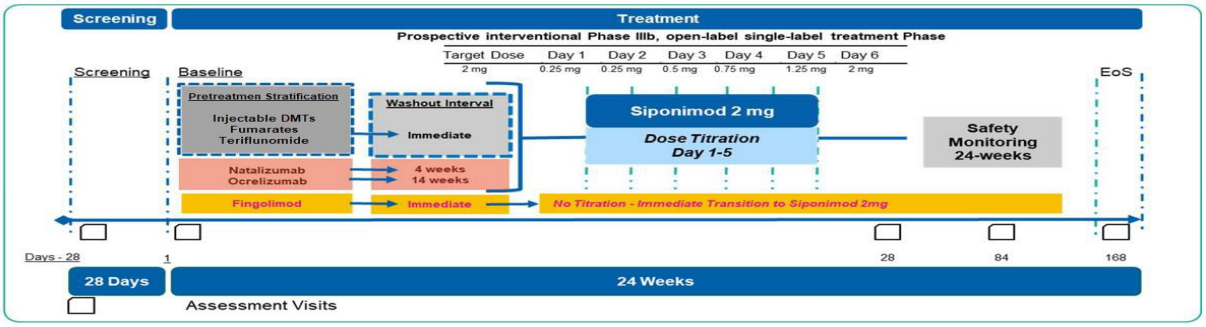
This is a 6-month, open-label, multi-center, single treatment arm design, including 300-400 advancing RMS patients, evaluating overall safety and tolerability profile when acutely converting to siponimod from oral, injectable or infusion RMS DMTs. This study consists of two parts: The Screening Period and Core Treatment Period.

- The patient cohort will be stratified by pre-treatment groups and may include injectable, oral or infusion DMTs used in RMS: interferon beta-1a (Avonex®, Rebif®), interferon beta-1b (Betaseron®, Extavia®), glatiramer acetate (Copaxone®, generic glatiramer acetate), peginterferon beta-1a (Plegridy®), teriflunomide (Aubagio®), fingolimod (Gilenya®, including generic forms of fingolimod), dimethyl fumarate (Tecfidera®, including generic forms of dimethyl fumarate, Vumerity® (diroximel fumarate)), natalizumab (Tysabri®), and ocrelizumab (Ocrevus®).
- Patients fulfilling the inclusion criteria, including genotyping, will undergo immediate conversion (please see below for exceptions) to siponimod, with “immediate” defined as cessation of the existing DMT and initiation of siponimod within 24 hours, followed by subsequent 5-day dose titration. Per inclusion criteria and screening phase testing requirements, fingolimod patients will undergo all required screening and/or Baseline testing, including genotyping for CYP2C9*1*1.

- Patients converting specifically from teriflunomide will undergo accelerated elimination prior to converting to siponimod over 11-14 days to allow for adequate drug elimination and minimize drug-drug interactions, in line with the Aubagio ® USPI.
- Patients converting from fingolimod will immediately convert to siponimod maintenance dose of 2mg, with no dose-titration.
- Patients treated with infusion DMT natalizumab (Tysabri®) will undergo at least a 4 week washout period at the time of consent, prior to converting to dose-titrated siponimod.
- Patients treated with infusion DMT ocrelizumab (Ocrevus®) will undergo at least 14 week washout period at the time of consent, prior to converting to dose-titrated siponimod.

- All patients initiating siponimod treatment, except those converting from fingolimod, will be titrated over 5 days to achieve a maintenance dose of 2mg by Day 6 with the following schedule of siponimod:

Figure 1: EXCHANGE study design



*Injectable DMTs: interferon beta-1a, interferon beta-1b, glatiramer acetate, peginterferon beta-1a
**Teriflunomide strata will undergo accelerated elimination over 11-14 days per product USPI
DMT, disease modifying therapy; EoS, End of Study
Novartis Data on File: BAF312A/Siponimod – Clinical Trial Protocol CBAF312AUS02

Approximately 300-400 patients will be enrolled in this study from up to 80 study sites in the USA. The study plans to screen approximately 570 patients. [redacted]

Since this is a single arm open-label trial, randomization is not being considered.

The primary aim of this study is to evaluate the overall safety and tolerability profile of siponimod 2 mg in patients with relapsing forms of MS who are converting from existing oral, injectable or infusion DMTs. The primary analysis will be performed at Visit 5 i.e. End of Study.

An interim analyses on the safety data will be conducted at the time of approximately 50 patients complete their Visit 5 (Day 168).

[redacted]

1.2 Study objectives and endpoints

Objectives	Endpoints
Primary	
The primary objective is to evaluate overall safety and tolerability profile of siponimod in advancing RMS patients who are converting from currently approved oral, injectable or infusion RMS DMT.	Occurrence of any study-drug related adverse events during 6-month treatment period
Secondary	
To evaluate treatment satisfaction with siponimod in advancing RMS patients using outcomes based on the Treatment Satisfaction Questionnaire for Medication (TSQM-9).	Change from Baseline in the TSQM-9
To evaluate cardiac safety during siponimod treatment initiation	• Change from Baseline in heart rate to 6 hours after 1st treatment • Occurrence of any adverse Events • Occurrence of hospitalizations
To evaluate treatment persistence with siponimod	• Patient retention

[redacted]

2 Statistical methods

This section contains information that will be used to draft CSR Section 9.7 on statistical analysis.

2.1 Data analysis general information

All data will be analyzed by Novartis using the statistical software SAS version 9.4 or higher according to the data analysis Section 12 of the study protocol, which is available in Appendix 16.1.1 of the CSR. Important information is given in the following sections and details are provided, as applicable, in Appendix 16.1.9 of the CSR.

In general, for continuous data, number of observations, mean, standard deviation, minimum, 25th percentile, median, 75th percentile, and maximum will be presented. Categorical data will be presented as frequencies and percentages.

2.1.1 General definitions

2.1.1.1 Study treatment

The investigational drug siponimod is formulated in film coated tablet, which contains 0.25mg, 0.5mg, 1.0mg and 2.0mg siponimod as siponimod fumaric co-crystal (active ingredient).

All eligible patients in the core treatment period will start the treatment with a 5-day dose titration pack continuing to a maintenance dose of 2.0 mg.

Patients on fingolimod enrolled on / after Amendement 3 of the protocol, will directly start with the maintenance dose. Therefore, patients on fingolimod will have 2 groups:

1. Fingolimod with titration dose (patients enrolled in the Protocol versions 0, 1 and 2)
2. Fingolimod with direct maintenance dose (patients enrolled in Amendment 3 or after).

Figure 2 Siponimod Target Daily Dose

Treatment Schedule for All Pre-treatment groups (including Fingolimod under Protocol Version 0,1 and 2): **Titration Dose**	
Day of Treatment	**Target Dose**
1	0.25 mg
2	0.25 mg
3	0.5 mg
4	0.75 mg
5	1.25 mg
Maintenance Dose	
Day of Treatment	**Target Dose**
6 and beyond	2 mg

Treatment Schedule for Fingolimod Patients (enrolled in Amendment 3 or after): Maintenance Dose Only	
Day of Treatment	**Target Dose**
1 and beyond	2 mg

2.1.1.2 Study day

Study day is defined with respective to the first day on which treatment with Siponimod starts. The date of first administration of study medication is defined as Day 1 and the day before is defined as Day -1.

Therefore, for any particular date, study day will be calculated as follows:

- For dates on or after the first date of study medication administration,

  Study day = Assessment date – Date of first administration of study medication + 1;

- For dates prior to the first date of study medication administration,

  Study day = Assessment date – Date of first administration of study medication.

2.1.1.3 Baseline definition

Baseline visit (Visit 1) is defined as the day on which patients start with their first dose of Siponimod.
Baseline is defined as the last measurement on or prior to Baseline visit.

Post-Baseline assessments

Post-Baseline values are defined as assessments taken after the start of study treatment.

When change from Baseline is of interest, the following formula will be for each scheduled visit and time-point where Baseline and post-Baseline values are both available:

Change from Baseline = Post-Baseline value – Baseline value.

2.1.1.4 Visit Window

Visit-windows will be used for the data that is summarized by visit; they are based on the study evaluation schedule and comprise a set of days around the nominal visit day. For any assessment, there are the protocol defined scheduled visits around which visit windows were created to cover the complete range of days within the study. The visit windows are shown in Table 1. These apply to measurements taken at every visit. For assessments collected less often different visit windows will be applied as detailed below.

When visit windows are used, all visits will be re-aligned, i.e., they will be mapped into one of the visit windows. E.g., if the *Week 4* visit of a patient is delayed and occurs on Day 46 instead of on Day 29, say, it will be re-aligned to visit window *Week 8*. In the case of major deviations from the visit schedule, or due to unscheduled visits, several assessments of a patient may fall

in a particular visit window (either scheduled or unscheduled). Statistical approaches to handle multiple assessments in a given visit window are specified below.

Of note, patients are allowed to have gaps in visits.

Table 1 Assessment windows for scheduled visits

Visit Name	Days	Scheduled Day of Visit	Visit Window
Screening	-28 Days	-28	-28 days to Day 1*
Baseline (Visit 1)	Day 1	1	Day 1 - 4
Visit 2	Day 7	7	Day 5 - 18
Visit 3	Day 28	28	Day 19 - 56
Visit 4	Day 84	84	Day 57 - 126
Visit 5/EOS	Day 168	168	Day 127 - 183
Follow up visits	Follow up visits	198	Day 184 - 205

Day 1*: refers to the day 1 before dose administration.

For parameters which are not collected at every visit, visit windows defined in Table 1 will be combined. For example, if a parameter is measured at Day 28 and Day 84 only, Day 28 visit window will extend from Day 5 to Day 56 (combining Day 7 to Day 28 visit windows). If more than one assessment falls into the interval, the rules defined in Section 2.1.1.5 below are applied.

2.1.1.5 Multiple assessments within visit windows

When there are *multiple assessments* in a particular visit window, the following rules are applied to select one value "representing" the patient in summary statistics in a visit window (See **Table 1**).

For Baseline assessment, definition see Section 2.1.1.3. For post-Baseline visit windows the following applies (unless otherwise specified):

- For *quantitative variables*, the *closest* to the actual visit is chosen (if two assessments have the same distance, then the earlier one will be chosen);
- For *qualitative variables*, the *worst* record is selected. It is noted that in the analyses performed, *worst* case is always well defined.

In case qualitative variables are based on quantitative variables, the visit will be assigned to the quantitative variable, and this visit will be used for the derived qualitative variable.

2.2 Analysis sets

Safety set: The Safety Set includes all patients who received at least one dose of study treatment.
All analyses will be performed using the Safety Set.

2.2.1 Subgroup of interest

Summary tables can be analysed on the following prior RMS DMTs subgroups:

- Any Interferon Beta
- Glatiramer acetate
- Fingolimod patients (overall, with / without dose titration)
- Fumarates
- Teriflunomide
- Natalizumab
- Ocrelizumab

Population subgroups, Hispanic or Latino, Black or African American, White (excluding Hispanic or Latino), Hispanic or Latino (excluding white) [redacted] may also be performed based on clinical team's decision for analysis.

[redacted]

2.3 Patient disposition, demographics and other Baseline characteristics

All the patient demographic and Baseline characteristics will be summarized for the Safety Set in the CSR.

2.3.1 Patient disposition

Screening phase disposition and study phase disposition will be summarized.

The number and percentage of patients screened, screened passed and screen failed will be summarized for all the screened patients for the screening phase disposition.

For the study phase disposition, the overall number of patients who are screened passed i.e. entered into the study, completed the study and discontinued from the study (and/or treatment) will also be summarized with reasons for premature discontinuation on all enrolled patients.

Patient identification number and whether they completed or discontinued from the study (and/or treatment) will be listed, with date of last dose and primary reason for premature discontinuation.

For each protocol deviation (PD), the number and percentage of patients for whom the PD applies will be tabulated. A separate listing will be provided for the details on the patient identifier having met a specific PD.

The PD's will be distinguished in the below 5 categories as applicable:

- Selection Criteria Not Met - Inclusion/Exclusion criteria

- Patient Not Withdrawn As Per Protocol - Withdrawal criteria met but patient not withdrawn
- Treatment Deviation - Wrong treatment or incorrect dose
- Prohibited concomitant medication
- Other

2.3.2 Demographics and other Baseline characteristics

The following common background, demographics and Baseline characteristics data will be analyzed as described below:

Continuous variables:

- Age (which is derived from date of birth and the screening assessment date)
- Height (cm)
- Weight (kg)
- Body Mass Index (BMI)

Categorical variables:

- Age group (< =30 years, 31 - <= 40 years, 41 - <=50 years, 51 - <=60 years, > 60 years)
- Gender
- Race
- Ethnicity

Multiple Sclerosis History and the expanded disability status scale will also be presented with all the parameters collected according to the eCRF.

The above characteristics will be repeated on the required subgroups.

Unless otherwise specified, summary statistics will be presented for continuous variables for all patients (total) in the safety set. The number and percentage of patients in each category will be presented for categorical variables for all patients (total) in the safety set.

2.3.3 Medical history/current medical conditions

Medical history will be coded using the Medical Dictionary for Regulatory Activities terminology (MedDRA, current version at database lock). History/conditions and current medical conditions at Baseline will be summarized for the safety set by primary system organ class and preferred term, and overall. Verbatim recorded history/conditions will be listed together with the coded terms, date of diagnosis/surgery and whether the problem was ongoing at start of the study.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Duration of exposure to the study treatment (siponimod) will be calculated as the number of days exposed to the treatment with siponimod over the specified period (expressed as:

Duration of exposure = last known date of siponimod administration – first known date of siponimod administration + 1).

The duration of exposure (in days) will be summarized for the safety set as:

- a continuous variable with the standard descriptive statistics, and
- a categorical variable classified into <=4 weeks, >4 to <=8 weeks, >8 to <=12 weeks, >12 to <=16 weeks, >16 to <=20 weeks and >20 to <=24 weeks.

A data listing of the drug doses administered by patients will be provided.

Investigator reported compliance from eCRF

Compliance will be calculated based on the DAR data. Compliance data will be summarized descriptively as a continuous and categorical variable.

The number and percentages of patients in each of the compliance categories mentioned in the eCRF, i.e., Poor (< 25%), Average (≥ 25% to < 50%), Good (≥ 50% to <75%), Very good (≥ 75% to ≤100%) and Overdose or misuse (>100%) will be summarized. In case of over compliance (> 100%) the reason will be listed.

The compliance will be provided for overall study period, titration and maintenance phase.

The exposure will be presented for the overall population along with the subgroups, if needed.

2.4.2 Prior, concomitant and post therapies

Each medication has the start and end dates recorded. Prior medications are defined as those medications which were taken and stopped prior to the first dose of study drug. Concomitant medications are defined as those medications which were taken on or after the first dose of study drug but not prior to the first dose of study drug. Prior/concomitant medications are defined as those medications which were taken prior to and continued after the first dose of the study drug. All prior and concomitant medications will be summarized by primary system organ class and preferred term. All prior/concomitant medications will be summarized as concomitant medications, and will not be included in prior medication outputs.

Surgical and medical procedures (non-drug therapies) will be summarized by primary system organ class and preferred term. All summaries will be on the safety set.

2.4.3 Prior MS DMT treatment

Number and percentage of patients on prior MS DMT treatments will be presented. Along with the number and percentage, the duration of previous MS DMTs before switching to Siponimod will also be presented. The MS DMT information will also be repeated on the subgroups if needed.

2.5 Analysis of the primary objective

The primary objective is to evaluate overall safety and tolerability profile of siponimod in advancing RMS patients who are converting from currently approved oral, injectable or infusion RMS DMTs.

The primary aim of this study is to evaluate the overall safety and tolerability profile of siponimod 2mg in patients with relapsing forms of MS.

2.5.1 Primary endpoint

The primary endpoint is the occurrence of any study drug related treatment emergent adverse events during 6-month treatment period.

2.5.2 Statistical hypothesis, model, and method of analysis

The number (and percentage) of patients with treatment emergent adverse events suspected to be related to study medication will be summarized by primary system organ class and preferred term.

The 95% exact binomial confidence interval for the overall rate of adverse event suspected to be related to study medication will be calculated.

A patient with multiple adverse events within a category (overall, primary system organ class, or preferred term) is only counted once towards the total of that category.

The analysis of the primary variable will also be stratified by prior MS DMTs. Along with the overall treament emergent adverse events suspected to be related to study medication, a subgroup analysis by prior MS DMTs will also be provided.

Analysis of primary endpoint will be based on the Safety Set.

No formal hypothesis is being tested for the primary endpoint.

2.5.3 Handling of missing values/censoring/discontinuations

No missing data will be imputed. All analyses will be using observed-case approach.

2.5.4 Sensitivity and Supportive analyses

Neither sensitivity analysis nor supportive analysis is planned for the study.

2.6 Analysis of secondary objectives

The following are the secondary objective(s) planned for the study:

1. To evaluate treatment satisfaction with siponimod in advancing RMS patients using outcomes based on the Treatment Satisfaction Questionnaire for Medication (TSQM-9).
2. To evaluate cardiac safety during siponimod treatment initiation
3. To evaluate treatment persistence with siponimod

All secondary analyses will also be based on the Safety Set.

2.6.1 Secondary endpoints

2.6.1.1 Treatment Satisfaction Questionnaire for Medication (TSQM-9)

Please refer to Section 2.10 for details.

2.6.1.2 Change from Baseline in heart rate

The change from Baseline in heart rate to 6 hours after 1st treatment will be summarized by number of observations, mean, standard deviation, minimum, 25th percentile, median, 75th percentile, and maximum.

The above analysis will also be performed on the subgroup of prior MS DMTs.

2.6.1.3 Occurrence of any adverse events

Refer to Section 2.7.1 for details on the occurrence of any adverse events.

2.6.1.4 Occurrence of hospitalizations

Summary statistics will be provided for number of hospitalizations per patient occurred during treatment period. Number and percentages of patients having at least one hospitalization during treatment period will be provided.

2.6.1.5 Patient retention

The number of patients who complete the study will comprise patient retention. Number (and percentage) of patients completed study will be provided. Number of patients who are enrolled into the study, continued the study and discontinued the study will be presented.

2.6.2 Statistical hypothesis, model, and method of analysis

No formal hypothesis is being tested for the secondary endpoint.

2.6.3 Handling of missing values/censoring/discontinuations

No missing data will be imputed.

2.7 Safety analyses

All safety analyses will be based on the Safety Set. Subgroup analysis will be performed on the AE tables as required.

2.7.1 Adverse events (AEs)

The number (and percentage) of patients with treatment emergent adverse events (events started after the first dose of study medication to 30 days after the date of the last actual administration of any study treatment or events present prior to start of treatment but increased in severity based on preferred term) will be summarized.

AEs will be listed separately.

Adverse events by System Organ Class and Preferred Term

All adverse events starting on or after the first treatment will be coded utilizing the MedDRA version xx (during the database lock) dictionary, tabulated, and analyzed by primary system organ class and preferred term.

Primary system organ classes will be sorted alphabetically and, within each primary system organ class, the preferred terms will be sorted in descending order of frequency.

If a patient reported more than one adverse event with the same preferred term, the adverse event will be counted only once. If a patient reported more than one adverse event within the same primary system organ class, the patient will be counted only once at the system organ class level.

All adverse events will also be summarized by Standardized MedDRA Query (SMQ) and preferred term.

AEs by severity

All adverse events will be summarized by maximum severity, primary system organ class and preferred term. If a patient reports more than one adverse event within the same primary system organ class, only one adverse event will be counted for that patient at the highest severity level in the total row for each primary system organ class. If a patient reported more than one adverse event with the same preferred term, the highest (maximum) severity will be presented. Missing severity will be assumed to be severe in the summary table.

AEs leading to permanent study drug discontinuation

Treatment emergent adverse events leading to permanent study drug discontinuation, regardless of study drug relationship, will be summarized by primary system organ class and preferred term.

AEs requiring dose adjustment or interruption

Treatment emergent adverse events requiring dose adjustment or interruption, regardless of study drug relationship, will be summarized by primary system organ class and preferred term.

AEs requiring occurrence of hospitalization

Treatment emergent adverse events leading to hospitalization, regardless of study drug relationship, will be summarized by primary system organ class and preferred term.

Number of hospitalizations

Summary statistics using frequency and percentage will be provided for number of hospitalizations per patient occurred during treatment period.

[redacted]

2.7.2 Serious adverse events

Number and percentage of patient with serious adverse events, regardless of study drug relationship, will be presented by primary system organ class and preferred term.

SAEs will also be listed separately.

2.7.3 Adverse events of special interest / grouping of AEs

The number (and proportion) of patients with adverse events of special interest/related to identified and potential risks will be summarized by primary system organ class and preferred term.

The following will be considered as an AESI for the study:

1. Infections and Infestations (VZV infections, herpes virus infections),
2. Bradyarrhythmia/bradycardia,
3. Elevated liver functions tests,
4. Malignancies (basal cell carcinoma),
5. Thromboembolic events,

6. Convulsions,
7. Macular edema,
8. Bronchoconstriction,
9. Hypertension

2.7.4 Deaths

A listing for death including on treatment and post treatment deaths will be provided. The on-treatment period lasts from the date of first administration of study treatment to 30 days after the date of the last actual administrations of any study treatment.

2.7.5 Laboratory data

The summary of laboratory evaluations will be presented for the following groups of laboratory tests (hematology, clinical chemistry, serology, CYP2C9 Testing and [redacted]). Descriptive summary statistics for the change from Baseline to each study visit will be presented in the tabular form.

All laboratory data will be listed by patient and visit/time and if normal ranges are available abnormalities will be flagged.

In addition, shift tables will be provided for all parameters to compare a patient's Baseline laboratory evaluation relative to the visit's observed value. For the shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value was normal, low, or high for each visit value relative to whether or not the Baseline value was normal, low, or high.

The following laboratory parameters will be analyzed:

Hematology will include red blood cell count, total and differential WBC count (basophils, eosinophils, lymphocytes, monocytes, neutrophils), platelet count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration and red blood cell morphology.

Clinical Chemistry will include electrolytes (Na, K, Cl, bicarbonate, Ca, Mg, P), random glucose, albumin, alkaline phosphatase, creatinine, ALT, AST, GGT, amylase, total bilirubin, conjugated bilirubin, total cholesterol, CRP, triglycerides, HDL and LDL.

Shift tables using the low/normal/high/ (low and high) classification will be used to compare Baseline to the worst on-treatment value.

Table 2 Criteria for notable abnormalities

Laboratory Variable	**Standard Units**	
SI Units		
LIVER FUNCTION AND RELATED VARIABLES		
SGOT (AST)	>82 U/L	>82 U/L
SGPT (ALT)	>90 U/L	>90 U/L
Gamma Glutamyltransferase (GGT)	> 130 U/L	> 130 U/L
Bilirubin (total)	>= 2.0 mg/dL	>= 34.2 mol/L
Alkaline phosphatase, serum	>280 U/L	>280 U/L
RENAL FUNCTION / METABOLIC AND ELECTROLYTE VARIABLES		
Glucose	>= 200 mg/dL	>= 11.11 mmol/L
Creatinine	>= 2.0 mg/dL	>= 176 umol/L
Amylase	>= 300 U/L	>= 300 U/L
Cholesterol (total)	>= 240 mg/dL	>= 6.21 mmol/L
Triglycerides	>= 300 mg/dL	>= 3.39 mmol/L
HEMATOLOGY VARIABLES		
Haemoglobin	<= 10.0 g/dL	<= 100 g/L
Platelet count (direct)	<= 100 k/mm3	<= 100 x 109/L
	>= 600 k/mm3	>= 600 x 109/L
WBC (total)	<= 2.0 k/mm3	<= 2.0 x 109/L
	>= 15 k/mm3	>= 15 x 109/L
HEMATOLOGY VARIABLES: DIFFERENTIAL		
Neutrophils (Seg. + Bands)	<= 1,000 /mm_3	<= 1 x 10_9/L
	>= 12000/mm_3	>= 12 x 10_9/L
Lymphocytes	< 200/mm_3	< 0.2 x 10_9/L
	>= 8000/mm_3	>= 8 x 10_9/L
RBC	< 3,300,000/mm_3	< 3.3 x 10_{12}/L
	> 6,800,000/mm_3	> 6.8 x 10_{12}/L

Table 3 Criteria for abnormal criteria for by visit summaries

Laboratory Variable (unit)	Criteria
Albumin (g/L)	<LLN
Bilirubin (direct/conjugated)(umol/L))	>ULN
	>2xULN
Gamma Glutamyltransferase (GGT)(U/L)	>ULN
	>3xULN
Glucose (mmol/L)	>ULN
Cholesterol (HDL) (mmol/L)	>ULN
Cholesterol (LDL) (mmol/L)	>ULN
SGOT (AST) (U/L)	>ULN
	>2xULN
	>3xULN
SGPT (ALT) (U/L)	>ULN
	>2xULN
	>3xULN
	>5xULN
Cholesterol (total) (mmol/L)	>ULN

2.7.6 Other safety data

2.7.7 ECG

Twelve-lead ECGs will be performed for all patients at Screening and will be presented. All ECG data will be listed by patient and visit/time, abnormalities will be flagged. Summary statistics for observed and change from Baseline will be provided by visit.

2.7.8 Pregnancy and assessments of infertility

For pregnancy, serum/urine test will be performed. Summary for the tests will be presented at Baseline and Week 24.

2.7.9 Vital signs

Vital signs measurements include pulse, systolic blood pressure, diastolic blood pressure, temperature, body weight and heart rate. The following summaries will be presented on the safety set.

2.7.9.1.1 Summary of absolute values and change from Baseline

Vital signs including the changes from Baseline will be summarized at the scheduled visits and time points.

Change in heart rate from Baseline to 6-hour after first treatment will be summarized as the secondary endpoint.

All vital signs data will be listed by patient and visit/time and if ranges are available, abnormalities will be flagged.

2.7.9.1.2 Notable absolute values and change from Baseline

The number and percentage of patients with newly occurring or worsening notable values, including notable change from Baseline, will be summarized by vital sign parameter and post-Baseline visit. An additional section will be included for abnormalities occurring at any time point over the treatment period, considering all post-Baseline data from scheduled, unscheduled and premature discontinuation visits. Notable absolute values and notable changes from Baseline for each vital sign parameter are defined in the Table 4 :

Table 4 Criteria for notable vital sign abnormalities

Vital Sign Variable	Notable Criteria
Pulse (beats/min)	>120 bpm Or < 50 bpm
Systolic BP (mmHg)	≥ 160 mmHg Or ≤ 90 mm Hg
Diastolic BP (mmHg)	≥ 100mmHg Or ≤ 50 mmHg
Temperature (°C)	>38.3 °C/ 101°F
Body weight (kg)	± 7% from Baseline weight

2.8 Pharmacokinetic endpoints

Not Applicable.

2.9 PD and PK/PD analyses

Not Applicable.

2.10 Patient-reported outcomes

Treatment Satisfaction Questionnaire for Medication (TSQM-9) will be assessed as a PRO for the study.

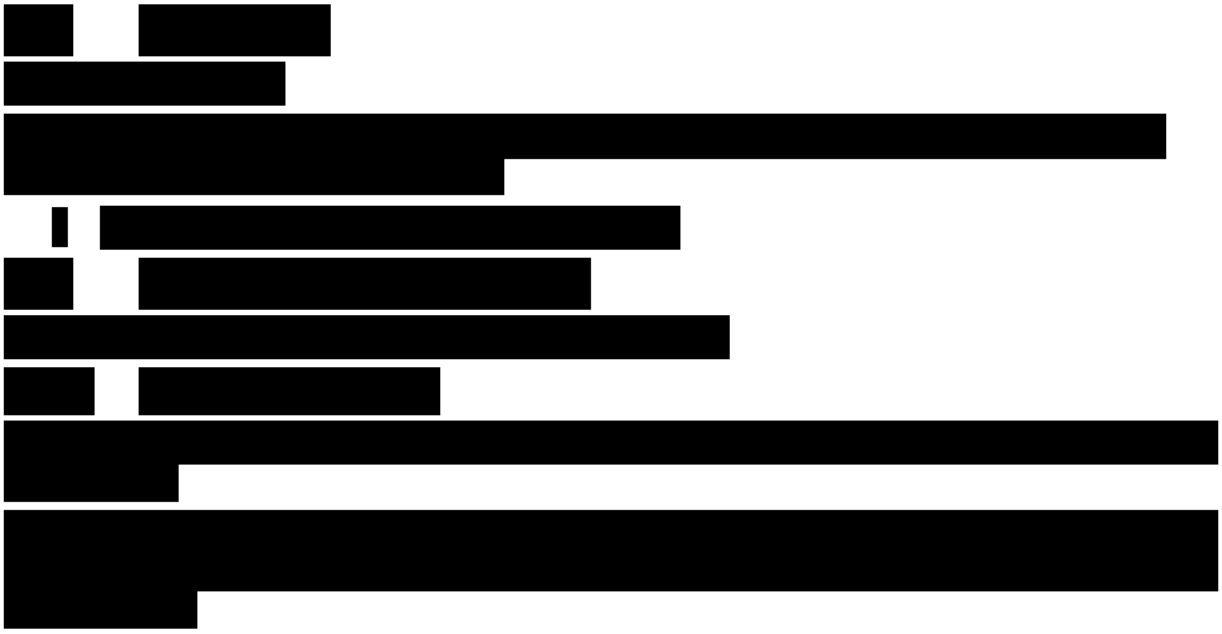
The Treatment Satisfaction Questionnaire for Medication (TSQM-9) will be used to psychometrically evaluate the patients' satisfaction with Siponimod. The TSQM-9 is a sound and valid measure of the major dimensions of patients' satisfaction with medication and a good predictor of adherence across different types of medication and patient population.

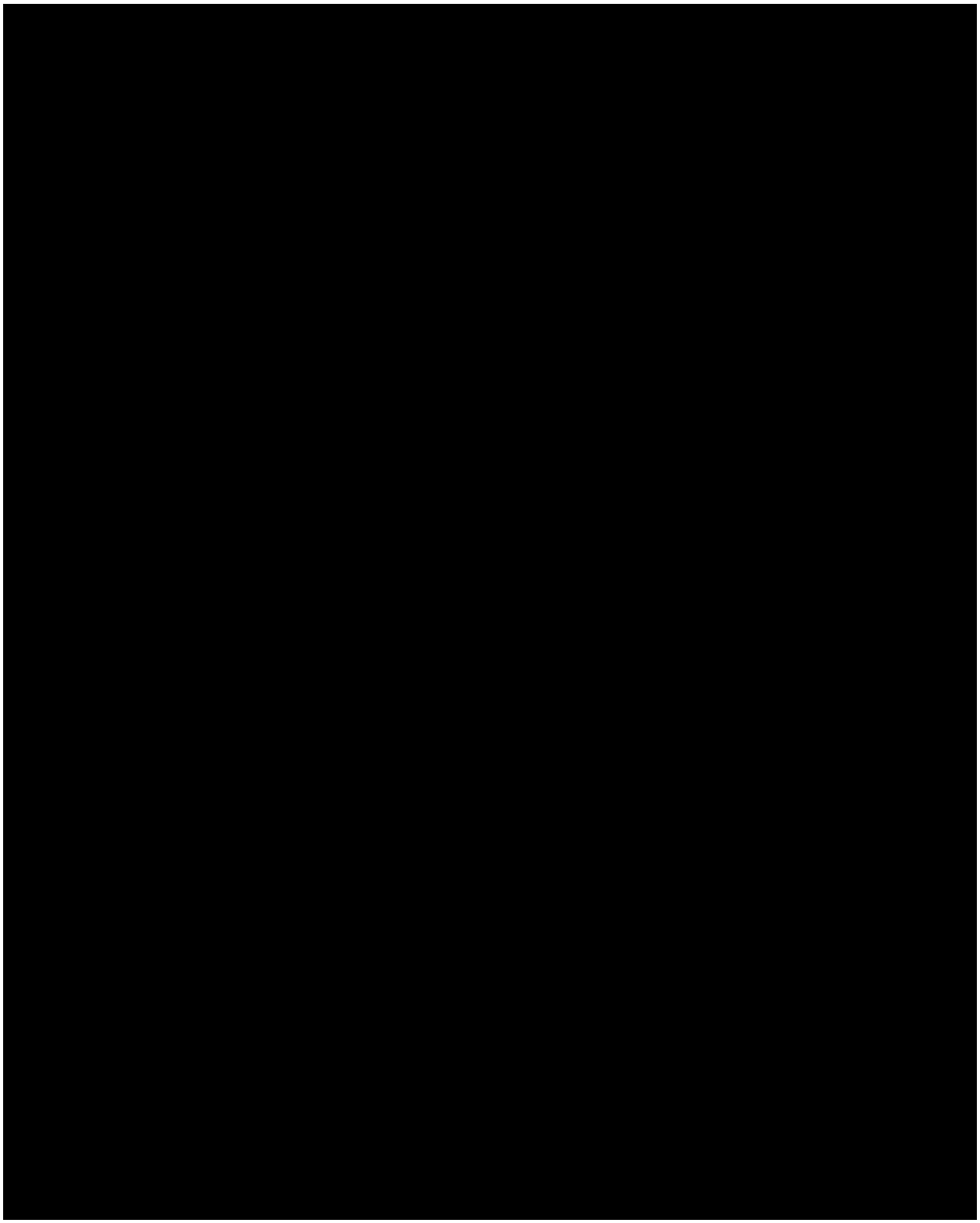
With the TSQM-9, scale scores are calculated by adding the items loading on each dimension. The lowest possible score is subtracted from this composite score and divided by the greatest possible score minus the lowest possible score. This provides a transformed score between 0 and 1 that should be multiplied by 100.

Effectiveness	([Sum (Item 1 + Item 2 + Item 3) – 3] divided by 18) * 100
	If one item is missing ([(Sum (Item 1 + Item 2 + Item 3)) – 2] divided by 12) * 100
Convenience	([Sum (Item 4 to Item 6) – 3] divided by 18) * 100
	If one item is missing ([(Sum (Item 4 to Item 6)) – 2] divided by 12) * 100
Global Satisfaction	([Sum (Item 7 to Item 9) – 3] divided by 14) * 100
	If either Item 7 or 8 is missing ([(Sum (Item 7 to Item 9)) – 2] divided by 10) * 100
	If Item 9 is missing ([(Sum (Item 7 and Item 8)) – 2] divided by 8) * 100

It should be noted that only one item may be missing from each scale before the subscale should be considered invalid for that respondent.

Change in TSQM-9 from Baseline with respect to domain scores to each post-Baseline time point will be summarized by providing: number of observations, mean, standard deviation, minimum, 25th percentile, median, 75th percentile, and maximum.





2.13 Interim analysis

For the purpose of earlier dissemination, an interim analysis on the safety data will be conducted at the time of approximately 50 patients completing their Visit 5 (Day 168).

Additional interim analyses may be conducted at additional time points based on study enrollment to evaluate continued efficacy and safety data (for example, 50% enrollment). These interim analyses will also allow for an evaluation of the infusion strata.

[redacted]

Since there will be no hypothesis testing involved, statistical adjustment for the interim analysis will not be made at the stage of final analyses of efficacy and safety.

2.14 Sample size calculation

Primary endpoint

Sample size calculations were based on the rate of study drug related adverse events. During the first 6 months, such an AE rate was observed at 45% from the pooled data of patients treated with fingolimod 0.5 mg/day in studies CFTY720D2301 and CFTY720D2302. A sample size of 300 to 400 patients will provide us the precision estimates ranging from 4.9% to 5.6% precision (half-width of 95% confidence interval) of the estimated rate of AE. Of the total sample size, approximately 80-100 patients with prior infusion therapy exposure will be enrolled by balanced stratification.

[redacted]

3 Change to protocol specified analyses

Not Applicable.

4 Appendix

4.1 Imputation rules

4.1.1 Study drug

Siponimod will be used as the study drug.

Start and end date of the study drug will not be imputed.

4.1.2 AE date imputation

AE START DATE IMPUTATION (CBAF312AUS02)

where AE start date is XX-MON-YYYY and Treatment start date is XX-TRTM-TRTY,

If YYYY<TRTY and MON missing, then AE start date=1-JULY-YYYY which is prior to start of trt

If YYYY<TRTY and MON<TRTM, then AE start date=15-MON-YYYY which is prior to start of trt
If YYYY<TRTY and MON=TRTM, then AE start date=15-MON-YYYY which is prior to start of trt
If YYYY<TRTY and MON>TRTM, then AE start date=15-MON-YYYY which is prior to start of trt
If YYYY=TRTY and MON missing, then AE start date=TRTSTDT+1
If YYYY=TRTY and MON<TRTM, then AE start date=15-MON-YYYY which is prior to start of trt
If YYYY=TRTY and MON=TRTM, then AE start date=max (1-MON-YYYY, TRTSTDT +1)
If YYYY=TRTY and MON>TRTM, then AE start date=max (1-MON-YYYY, TRTSTDT +1)
If YYYY>TRTY and MON missing, then AE start date=1-JAN-YYYY
If YYYY>TRTY and MON<TRTM, then AE start date=max (1-MON-YYYY, TRTSTDT +1)
If YYYY>TRTY and MON=TRTM, then AE start date=max (1-MON-YYYY, TRTSTDT +1)
If YYYY>TRTY and MON>TRTM, then AE start date=max (1-MON-YYYY, TRTSTDT +1)

AE END DATE IMPUTATION (CQVA149A2340)

AE end date = min (last visit date, last know date of contact for discontinued patients, DEC 31, date of death), if MON is missing and YYYY is present.

AE end date = min (last visit date, last know date of contact for discontinued patients, last day of the Month, date of death), if day is missing, MON and YYYY present.

Impute Date Flag (CQVA149A2340)

If not a complete date:

• If year of the imputed date <> YYYY then date flag = Y (not possible since missing dates will not be imputed),
• else if month of the imputed date <> MON then date flag = M,
• else if day of the imputed date <> day of original date then date flag = D,
• else date flag = null.

4.1.3 Concomitant medication date imputation

CM start date imputation

Rules for imputing the CMD start date:

Here TRTSTDT = treatment start date,

1. If the CMD start date year value is missing, the imputed CMD start date is set to TRTSTDT-1, if not after the CMD end date. Thus the imputed CMD start date = minimum (TRTSTDT-1, CMD end date).

2. If the CMD start date year value is less treatment start date year value, the CMD started before treatment start. Therefore:
    a) If the CMD year is less than treatment start year and the CMD month is missing, the imputed CMD start date is set to 01JulYYYY.
    b) Else if the CMD year is less than the treatment start year and the CMD month is not missing, the imputed CMD start date is set to 15MONYYYY.

3. If the CMD start date year value is greater than treatment start date year value, the CMD started after treatment start. Therefore:
    a) If the CMD year is greater than the treatment start year and the CMD month is missing, the imputed CMD start date is set to 01JanYYYY.
    b) Else if the CMD year is greater than the treatment start year and the CMD month is not missing, the imputed CMD start date is set to 01MONYYYY.

4. If the CMD start date year value is equal to treatment start date year:
    a) If the CMD month is missing or the CMD month is equal to treatment start month, then the imputed CMD start date is set to the minimum (TRTSTDT-1, CMD end date).
    b) Else if the CMD month is less than the treatment start month, the imputed CMD start date is set to 15MONYYYY.
    c) Else if the CMD month is greater than the treatment start month, the imputed CMD start date is set to 01MONYYYY.

CMD end date imputing:

1. If the CMD end date is completely missing (and "Ongoing at final examination" was not answered "Yes"), the CMD end date will be the maximum of treatment end date +1 day and CMD start date.
2. If a partial CMD end date is reported (day is missing or day and month are missing), the CMD end date will be imputed by the maximum possible date, i.e.
    the end of the reported month if day is missing, or
    the end of the reported year if day and month are missing provided that the imputed date is not before the CMD start date, otherwise CMD end date will be equal to CMD start date.

3. CMTime since first symptoms of AD noticed by patient/caregiver (in years), for the partial dates in the data, the dates will be imputed as:

- If month and year are present, the 1st of the month is considered as the date. For example, if March 2015 is present, it will be imputed as 1st March 2015.
- If only year is present, January will be considered as the month and 1st as the date. For example, only 2015 is present, it will be imputed as 1st January 2015.

4.1.3.1 Prior therapies date imputation

Same as Concomitant medication date imputation.

4.1.3.2 Post therapies date imputation

Same as Concomitant medication date imputation.

4.2 AEs coding/grading

Latest version of MedDRA will be used.

4.3 Laboratory parameters derivations

4.4 Refer to the main sections in SAP Statistical models

4.4.1 Primary analysis

Not Applicable

4.4.2 Key secondary analysis

Not Applicable

4.5 Rule of exclusion criteria of analysis sets

The protocol deviations defined for this study are the followings:

Table 5 Protocol deviations that cause patients to be excluded

Deviation Code	Text Description	Severity/ Analysis Classify action Code
INCL01	Signed informed consent not obtained prior to participation in the study	49
INCL02	ge of patient is not between 18 to 65 years (inclusive) at screening	49
INCL03	Patient is not with advancing RMS as defined by the principal investigator	49
INCL04	Not having prior history of relapsing MS (RMS), with or without progressive features, according to the 2010 Revised McDonald or Lublin criteria	49
INCL05	Disability status at screening is not defined as EDSS score of ≥2.0 to 6.5 (inclusive)	49
INCL06	Not treated with b-interferons, glatiramer acetate, fingolimod, dimethyl fumarate, or teriflunomide 3 months at IC, had last natalizumab 4 wks prior SCREEN, or had ocrelizumab 14 wks prior SCREEN	49
EXCL01	Patients with an active chronic disease of the immune system other than MS or with a known immunodeficiency syndrome (AIDS, hereditary immune deficiency, drug-induced immune deficiency)	49
EXCL02	Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive Hcg laboratory test	49
EXCL03a	Women of child bearing potential unless using highly effective methods of contraception while taking study treatment and for 30 days after stopping study treatment	49
EXCL03b	Post-menopausal women and not of child bearing potential if they had 12 months of natural amenorrhea or surgical bilateral oophorectomy, total hysterectomy or tubal ligation at least six week ago	49
EXCL04	Sexually active males unwilling to use a condom during intercourse while taking study treatment and for 30 days (30= 5 times the terminal half-life of Siponimod) after stopping study treatment	49
EXCL05	History of malignancy of any organ system other than localized basal cell carcinoma of the skin treated or untreated within the past 5 years regardless of evidence of local recurrence or metastases	49
EXCL06	Diabetes mellitus, unless well controlled and without known organ complications including but not limited to heart disease reduced renal function, significant retinal pathology or neuropathy	49
EXCL07	Diagnosis of macular edema 1 year prior to screening	49

EXCL08	Patients with active systemic bacterial, viral, or fungal infections or known to have AIDS or have positive HIV antibody	49
EXCL09	Positive results of screening period testing for serological markers for hepatitis A, B, C and E, indicating acute or chronic infection	49
EXCL10	Negative for varicella-zoster virus IgG antibodies at Screening unless there is other evidence of immunity to VZV based on the CDC criteria	49
EXCL11	Have received any live or live-attenuated vaccines (including for varicella-zoster virus or measles) within 2 months of screening	49
EXCL12	Treated with protocol restricted medication and therapies prior to screening and randomization as defined in exclusion criteria 12	49
EXCL13	Patients with any medically unstable condition as determine by the investigator	49
EXCL14	Any of the conditions or treatments that may affect cardiovascular function as listed in protocol	49
EXCL15	Pulmonary conditions History or active severe respiratory disease or prophylactic treatment or Tuberculosis, except history of successful treatment of TB or severe asthma or asthma with oral steroids	49
EXCL16	Patients with any of the hepatic conditions as described in protocol prior to screening	49
EXCL17	Abnormal laboratory values as defined in exclusion criteria prior to screening	49
EXCL18	Patients with the following neurological, psychiatric disorders prior to screening	49
EXCL19	Use of other investigational drugs at time of enrollment or within prior 30 day or five elimination half-lives or until expected pharmacodynamics effect has returned to baseline whichever is longer	49
EXCL20	History of hypersensitivity to the study drug or to drugs of similar chemical classes	49
EXCL21	Homozygosity for CYP2C9*3/*3 or heterozygous for CYP2C9*2/*3 or CYP*1*3 (to be tested at screening) or refusal to test for CYP2C9 variants	49
EXCL22	Concomitant use of MAYZENT and drugs that cause moderate CYP2C9 and moderate or strong CYP3A4 inhibition	49
EXCL23	Concomitant use of MAYZENT and drugs that cause moderate CYP2C9 and strong CYP3A4 induction	49
EXCL24	Use of cannabinoid or cannabidiol products 30 days prior to screening	49

EXCL25	Any other disease or condition which could interfere with participation in the study according to the study protocol or with ability of patient to cooperate and comply with study procedures	49
TRT01	Siponimod dose adjusted and/or interrupted	49
TRT02	Treatment is interrupted for 4 or more consecutive daily doses, and treatment not re-titrated per protocol	49
TRT03	treatment with Immunosuppressive/chemotherapeutic medications or procedures and hematopoietic stem cell transplantation but study treatment is not discontinued or interrupted	49
TRT04	Patient took Monoclonal antibodies targeting the immune system, including natalizumab, rituximab, ofatumumab, ocrelizumab and alemtuzumab but study treatment is not discontinued	49
TRT05	Patient took any other immunomodulatory or disease modifying MS treatment but study treatment is not interrupted	49
TRT06	Used any concomitant medication which inhibits cardiac conduction, e.g. verapamil-type and diltiazem-type calcium channel blockers or cardiac glycosides but study treatment is not discontinued	49
TRT07	Used Potent inducers of CYP2C9 but study treatment is not discontinued	49
COMD01	Patient took prohibited medication	49
OTHER01	Washout period is not there for taking teriflunomide before the patient can have their Day 1 visit (baseline) and start treatment with siponimod	49
OTHER02	Patients met eligibility criteria but does not have pre-dose body temperature; respiration rate; blood pressure; heart rate assessed	49
OTHER03	Study drug taken on the day of EOS	49
OTHER04	Pre-Dose vital signs; pre-dose ophthalmic exam; pre-dose ECG; screening labs (with exception of [redacted]); neurological exam	49
OTHER05	On-study Neurological exam not performed	49
OTHER06	Ophthalmology monitoring procedures not followed	49
OTHER07	Patient missed two consecutive lab assessments (with exception of [redacted])	49
OTHER08	Missed visit due to COVID-19	49
OTHER09	Visit done outside of study site due to COVID-19	49
OTHER10	Assessment / procedure changed due to COVID-19	49
OTHER11	Discontinuation due to COVID-19	49
TRT08	Post-dose cardiac monitoring not performed per protocol	49

TRT09	Study Drug Interruption of 4 or more consecutive days and re-started without first dose monitoring	49
TRT10	Drug supply method changed due to COVID-19	49
TRT11	Treatment not given due to COVID-19	49
OTHER12	Study Informed consent process not followed	49
OTHER13	SAE not reported to Sponsor in 24 hrs	49
OTHER14	Sample analyzed after withdrawal of consent	49

Table 6 Patient Classification

Analysis Set	PD severity codes that cause a patient to be excluded	Criteria that cause a patient to be excluded
SAF	8	

Table 7 Severity codes with action taken

Code	Action
8	Exclude from all analysis
49	Report relevant protocol deviation – include in all analyses

5 Reference

Not Applicable