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BAF312A/Siponimod/Mayzent®

Clinical Trial Protocol 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, multi-center Phase IIIb study (EXCHANGE)

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List of abbreviations

AE	Adverse Event
AESI	Adverse Events of Special Interest
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
ANCOVA	Analysis of covariance
ARR	Annualized Relapse Rate
AST	Aspartate Aminotransferase
AV	Atrioventricular
BAF312	Siponimod
BBB	Blood Brain Barrier
BID	Twice a day
BMI	Body Mass Index
BLRM	Bayesian Logistic Regression Model
BRACE	Betaseron, Rebif, Avonex, Copaxone, Extavia and other interferons and glatiramer acetate
BUN	Blood Urea Nitrogen
CDP	Clinical Development Plan
CDS	Core Data Sheet
CK	Creatinine Kinase
ClinRO	Clinician Reported Outcomes
COA	Clinical Outcome Assessment
CO2	carbon dioxide
CRF	Case Report/Record Form (paper or electronic)
CO	Country Organization
CQA	Clinical Quality Assurance
CRO	Contract Research Organization
CDSGs	The Clinical Development Safety Guidelines
COPD	Chronic Obstructive Pulmonary Disease
CSR	Clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CTC	Common Terminology Criteria
CMO&PS	Chief Medical Office and Patient Safety
CV	coefficient of variation
DIN	Drug Inducted Nephrotoxicity
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DMT	Disease Modifying Therapy
DS&E	Drug Safety and Epidemiology
ECG	Electrocardiogram
eCOA	Electronic Clinical Outcome Assessment
e-C-SSRS	Electronic Columbia-Suicide Severity Rating Scale
EDC	Electronic Data Capture
EDSS	Expanded Disability Status Scale

ELISA	Enzyme-linked immunosorbent assay
EOI	End of Infusion
EOS	End of Study
EOT/S	End of Treatment/Study
eSource	Electronic Source
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
H	Hour
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	Human Chorionic Gonadotropin
HCP	Healthcare Professional
HCV	Hepatitis C virus
HEOR	Health Economics & Outcomes Research
HIV	Human immunodeficiency virus
HRQoL	Health-Related Quality of Life
IB	Investigator's Brochure
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
i.v.	intravenous
[redacted]	[redacted]
LFT	Liver function test
LDH	lactate dehydrogenase
LLOQ	lower limit of quantification
LLN	lower limit of normal
MAP	Manage Access Program
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
ml	milliliter(s)
MS	Multiple Sclerosis
MTD	Maximum Tolerated Dose
Nab	Neutralizing antibody
[redacted]	[redacted]
ObsRO	Observer Reported Outcomes
Q.D.	once a day
OCT	Optical Coherence Tomography
PA	posteroanterior

PC	Personal Computer
PD	Pharmacodynamic(s)
[redacted]	[redacted]
PerfO	Performance Outcomes
PK	Pharmacokinetic(s)
p.o.	oral(ly)
PRO	Patient Reported Outcomes
[redacted]	[redacted]
QRS	Quantron Resonance System
QTcF	QT interval corrected by Fridericia's formula
PT	prothrombin time
RAP/SAP	The Report and Analysis Plan (RAP) is a regulatory document which documents preplanned statistical analyses
RBC	red blood cell(s)
RDE	Recommended dose for expansion
REB	Research Ethics Board
RECIST	Response Evaluation Criteria In Solid Tumors
RMS	Relapsing Multiple Sclerosis
RRMS	Relapsing-Remitting Multiple Sclerosis
RP2D	Recommended phase two dose
RU	Resource Utilization
R Value	ALT/ALP x ULN
SAE	Serious Adverse Event
s.c.	subcutaneous
sCR	serum creatinine
SD	standard deviation
SDMT	Single Digit Modality Test
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reactions
TD	Study Treatment Discontinuation
TQSM-9	Treatment Satisfaction Questionnaire for Medication
ULN	upper limit of normal
ULQ	upper limit of quantification
WBC	white blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study patient
Cohort	A specific group of patients fulfilling certain criteria and generally treated at the same time
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q28 days)
Dosage	Dose of the study treatment given to the patient in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last patient or at a later point in time as defined by the protocol.
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications reduce the use of paper capture source data during clinical visits. eSource combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to Novartis and other oversight authorities, as appropriate.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug/treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Mis-randomized patients	Mis-randomized patients are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study
Other treatment	Treatment that may be needed/allowed during the conduct of the study (concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.

Patient	An individual with the condition of interest for the study- *Note: use "patient" in population section only, use "patient" in the rest of the document*
Period	The subdivisions of the trial design (e.g. Screening, Treatment, and Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Perpetrator drug	A drug which affects the pharmacokinetics of the other drug
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized patient
Run-in Failure	A patient who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to patient's intervention or treatment)
Screen Failure	A patient who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first patient.
Study treatment	Any single drug or combination of drugs or intervention administered to the patient as part of the required study procedures.
Study treatment discontinuation	When the patient permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Patient	A trial participant (can be a healthy volunteer or a patient)
Patient number	A unique number assigned to each patient upon signing the informed consent. This number is the definitive, unique identifier for the patient and should be used to identify the patient throughout the study for all data collected, sample labels, etc.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Variable	A measured value or assessed response that is determined from specific assessments and used in data analysis to evaluate the drug being tested in the study
Victim drug	The drug that is affected by the drug-drug interaction
Withdrawal of study consent	Withdrawal of consent is defined as when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already collected biologic material.

Amendment 05

Rationale for Amendment

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

Amendment 04

Rationale for Amendment

[redacted]

- Added Section 4.6 to address public health emergency mitigation procedures
- Section 6.7.2 to enable IMP home delivery of oral medication directly to a trial participant's home rather than dispensed as part of an on-site study visit.
- Updated Section 7 to enable remote consent
- Updated Section 8 (including sections 8.4 and 8.5) to enable virtual or phone efficacy and safety assessments or visits to the participant´s home, if possible, in the study, as well as remote COA data collection.
- Updated Section 11.4 Virtual Patient Cohort to include language on mitigation procedures for closure of the virtual patient cohort at discretion of the sponsor.

Amendment 4 removes the enrollment cap for Strata 1, referenced in the Amendment 3 rationale section, and allows patients with prior oral DMT (fumarates and teriflunomide) to continue to enroll. Real-world evidence indicates that the majority of siponimod patients transitioning from a prior DMT were most frequently taking another oral DMT (Shah et al, 2020). By lifting the enrollment cap for Strata 1, the amendment ensures that EXCHANGE generates clinical evidence that reflects real-world treatment paradigms and supports patients and providers.

Additional interim analyses may be conducted at additional time points based on study enrollment under Amendment 4 to evaluate continued efficacy and safety data (for example, 50% enrollment). These interim analyses will allow for an evaluation of the infusion strata, which was incorporated with Amendment 3.

Additional changes are listed below:

- Addition of Vumerity® (diroximel fumarate) and generic forms of dimethyl fumarate changed in Inclusion Criteria and throughout
- Added interim analysis description to Protocol Summary, Section 4.4, and Section 12.7
- Added language for clarity on ongoing virtual and traditional cohorts to Protocol Summary, Section 3, and Section 4.1
- Protocol Summary:
  - Correction made to Month 6 corresponding Visit number (Visit 5) for first interim analysis
  - Updated Study Design language in Section 11.4
- Table 8-1: Updated table as Hepatitis screen is only required at Screening
- Table 8-1: Correction made to footnote #8 to reflect correct reference section in protocol
- Section 4.4 and Section 12.7: Added language for conducting additional interim analyses
- Section 8.4.4: Updated language for guidance on pregnancy testing
- [redacted]
- Revised Inclusion Criteria:
  - #6: Addition of Vumerity® (diroximel fumarate) and generic forms of dimethyl fumarate
  - #7 removed from Protocol Summary, as this was not reflected and consistent with the main protocol
- Revised Exclusion Criteria:
  - #14: Added clarifying language to described history of or current significant cardiac disease

Amendment 03

Rationale for amendment

Amendment 3 broadens the pre-treatment groups to include natalizumab (an α4-integrin antagonist, humanized monoclonal antibody) and ocrelizumab (a humanized monoclonal antibody that targets the CD20 marker on B-lymphocytes) infusion therapies in order to characterize the short term safety profile after conversion. The generation of this data is important as it is expected that patients who are currently treated with natalizumab and/or ocrelizumab may convert to siponimod for reasons of safety, tolerability, effectiveness or access. There are no known safety or tolerability concerns with the co-administration of siponimod with natalizumab or ocrelizumab. The purpose of broadening the pre-treatment groups is to further understand this relationship (Leurs et al., 2018); (Kappos et al., 2015).

Sustained fingolimod induced receptor internalization of S1P receptors has been demonstrated in a number of separate studies (Jo et al., 2005); (Oo et al., 2007); (Mullershausen et al., 2009); (Snelder et al., 2016). Both siponimod and fingolimod are sphingospine 1-phosphate (S1P) receptor agonists causing complete internalization and down—regulation of the S1P1 receptor (Matloubian et al., 2004); (Chiba et al., 2006); (O'Sullivan et al., 2016); (Chun et al., 2010); (Subei and Cohen, 2015). It is postulated that the known immunomodulatory effect on lymphocytes and transient nature of the heart rate (HR) is most likely related to receptor internalization and degradation (Mullershausen et al., 2009)). This downregulation renders lymphocytes unresponsive to the normal S1P gradient, and deprives them of the obligatory signal that would ordinarily allow them to egress from lymphoid tissues and recirculate to the periphery (Chun et al., 2010). Long-term suppression of receptors and minimized transient effects on HR are maintained by subsequent regular dosing (Brown et al., 2019). Therefore, HR and atrioventricular (AV) conduction effects are not expected in patients converting from fingolimod therapy. Thus, Amendment 3 will omit the need for siponimod titration regimen for patients converting from fingolimod therapy in order to enhance understanding of the role of titration, or lack of, when converting between the two S1P receptor modulators. All study patients are dosed under the care of a healthcare practitioner. Fingolimod patients will receive an additional telephone call from site staff at the end of day 1 as part of additional safety measures.

In order to ensure each pre-treatment strata in this study has a sufficient and balanced number of subjects to assert a clinically meaningful outcome, a balanced stratification of 50 patients per strata will be adopted, and therefore increasing the enrollment number to a maximum of 400 patients.

Lastly, in an attempt to help 1) remove ambiguity, 2) clarify the protocol language for principal investigators, 3) be consistent with siponimod label and or 4) account for the aforementioned changes, revisions to the exclusion criteria (including adding time or scenario qualifiers), study design graphic and other applicable supporting areas, were warranted. Each revised section is supported by applicable rationale as outlined in the details below.

The purpose for Amendment 03 is to:

- Broaden pre-treatment groups to include infusion disease modifying therapies, specifically, natalizumab and ocrelizumab.
- Removal of titration regimen for patients converting from fingolimod treatment

- Expand study *n* to 300-400 patients
- Revise inclusion criteria:
  - #6: Include natalizumab and ocrelizumab to conversion options
- Revise exclusion criteria:
  - #4 & #5: Move post-menopausal women description from standalone exclusion and merge with existing pregnancy and contraception exclusion. The prior exclusion #5 was merely a description of women who are considered post-menopausal and not of child bearing potential and not a separate exclusionary criteria different from the pregnancy exclusion.
  - #12: Delete natalizumab, daclizumab and ocrelizumab from prohibited list. Natalizumab and ocrelizumab will be added to pre-treatment groups for inclusion; daclizumab is no longer commercially available.
  - #12: Added sub-criteria "more than 24 months prior treatment exposure to natalizumab". Based on critical assessment of the limited data available, combined with the opinion of steering committee members, it is suggested that patients with more than 24 months of prior natalizumab exposure may be at high risk for PML. Therefore, to minimize patient safety risks, added sub-bullet to exclusion #12.
  - #14: Added time qualifier to history of cardiovascular disease consistent with label "within last 6 months."
  - #14: Added therapeutic disease qualifier to patients receiving treatment with beta-blockers "for cardiac disease/comorbidities"
  - #17: Added exception to WBC count to include "while on injectable or oral DMT's at screening, except fingolimod" to reflect appropriate drop in WBC clinical lab values. Exception for fingolimod added given the direct effect on peripheral lymphocyte subpopulations including WBCs.
  - #17: Added new sub-bullet "for patients previously exposed to natalizumab, anti-JCV antibody positive and index > 1.5." Based on critical assessment of the limited data available, combined with the opinion of steering committee members, it is suggested that patients with an anti-JCV antibody index >1.5 are considered high risk for PML and therefore should be excluded if no MRI monitoring is part of the study design to help minimize risk of serious immunodeficiency.
- Updated study design figure 3-2.
- Clarify:
  - Section 1.2: Added identification of clinical gap and lack of data for conversion between S1P receptor modulators.
  - Section 1.2: Added rationale for broadening pre-treatment groups to include natalizumab and ocrelizumab.
  - Section 2: Added infusion to treatment options described in primary objective.
  - Section 3: Added definition of "immediate conversion" to be "cessation of existing DMT and initiation of siponimod within 24 hours, followed by subsequent 5-day dose titration." Additionally clarified teriflunomide treatment group will undergo accelerated elimination prior to initiating siponimod.

- Section 3: Added clarification that patients converting from fingolimod will not undergo titration period and instead immediately start 2mg dose, upon completion of required screening tests, including genotyping CYP2C9*1*1, as part of the inclusion/exclusion criteria.
- Section 3: Added clarification that patients converting from natalizumab will undergo at least 4 week washout period at time of consent prior to converting to dose-titrated siponimod.
- Section 3: Added clarification that patients converting from ocrelizumab will undergo at least 14 week washout period at time of consent prior to converting to dose-titrated siponimod.
- Section 3, Figure 3-2: Updated study design figure to reflect changes in section 3.
- Section 4.2: Added rationale for removal of titration regimen for patients converting from S1P receptor modulator, fingolimod.
- Section 5: Clarified functional definition of advancing RMS for purposes of this study.
- Section 5.1: Revised inclusion criteria to include infusion therapy, natalizumab and ocrelizumab.
- Section 5.2: Revised exclusion criteria as described above.
- Section 6.1.3: Clarifying titration language to include all patients except fingolimod group.
- Section 6.2.1.1: Clarifying language for patients treated with beta-blockers for non-cardiac treatment purposes.
- Section 6.2 Table: Removal of prohibited medication criteria “any other immunomodulatory of disease modifying MS treatment, including but not limited to, fingolimod, interferon beta, glatiramer acetate or systemic corticosteroids.” This statement is incorrect because we are allowing fingolimod, interferon beta and glatiramer acetate in this study. Added removal of systemic corticosteroids as there is no implication of this medication on patients in this study. Prohibition of steroids is only required when conducting MRI to minimize confounding of post-lesion repair mechanisms.
- Section 6.3.2: Clarification around titration regimen for all patients except those converting from fingolimod.
- Section 6.7.2: Clarification around titration regimen for all patients except those converting from fingolimod.
- Section 6.3 Table 6-3: Revised table header to “Treatment Schedule for All Pre-Treatment groups except Fingolimod” and added separate dose and treatment schedule for fingolimod patients.
- Section 8: Added disease modifying therapy washout regimen table and language for interferon-beta, dimethyl fumarate; accelerated elimination for teriflunomide; fingolimod; natalizumab and; ocrelizumab. Clarification language regarding pre-dose ECG, pre-dose HR, and post-dose HR collection methods.
- Section 8 Table 8-1: Added CD19+ B-cell titer at Screening only to support B-cell regeneration kinetic insights during conversion to siponimod. Added footnote

reflecting this is only needed for patients converting from ocrelizumab as that is the only B-cell therapy being introduced in this study.

- Section 8.4.1 Table 8-3: Added CD19+ titers to "additional tests" subsection.
- Section 8.4.3: Added clarifying language that the OCT test can be performed by referred ophthalmologist or clinically trained neurologist with expertise in assessing structural measurement of retinal nerve fiber layer thickness, optic nerve head and macular anatomy and is in possession of appropriate OCT equipment in-office.
- Section 12.4: Added clarifying language related to the primary objective.
- Section 12.8.1: Added revised language regarding sample size, precision estimates and infusion therapy *n.* in order to achieve balanced stratification.
- Appendix 16.6: Added clarifying guidance around accelerated elimination program for patients converting from teriflunomide.
- Appendix 16.8: Corrected Visit 3 to Visit 4 and added clarifying language regarding OCT as described in section 8.4.3.

- Additional changes are listed below:
  - Correction of "Siponimod" to lower case "siponimod throughout protocol.
  - Ensure CYP2C9 is marked in full form and not abbreviated.
  - Replacement of investigational compound name BAF312 to brand-name, Mayzent ® throughout protocol.
  - Minor clarifications to background introduction.

Amendment 02

Rationale for amendment

The purpose for Amendment 02 is to:

- Revised exclusion criteria #22 to also exclude CYP2C9*2/*3 and CYP2C9*1/*3 patients:
  - Genetic polymorphisms of the CYP2C9 enzyme are a major determinant of the inter-individual variability in the dosage requirements of siponimod. Per the Mayzent approved US Package Insert, Mayzent® is contraindicated in patients who have a CYP2C9*3/*3 genotype because of substantially elevated siponimod plasma levels. MAYZENT dosage adjustment to 1 mg is recommended in patients with CYP2C9*1/*3 or *2/*3 genotype because of an increase in exposure to siponimod. However, due to the current unavailability of a 1mg dosage form for Mayzent, patients with the CYP2C9*1/*3 and *2/*3 genotypes are dosed using the 0.25mg tablets (4 x 0.25mg = 1mg). Novartis will exclude the CYP2C9*3/*3, CYP2C9*2/*3, and CYP*1/*3 patients from the CBAF312AUS02 study and will only enroll patients who after titration, will take the 2mg recommended maintenance dose (CYP2C9 Genotypes *1/*1, *1/*2, or *2/*2).
- Revised ECG interval values to reflect PR interval: >200 msec; QRS duration ≥120 msec; QTcF >430 msec (males); QTcF >450 msec (females)
- Revised Exclusion #23: Concomitant use of MAYZENT and drugs that cause moderate CYP2C9 and moderate or strong CYP3A4 inhibition (Appendix 4).
- Added exclusion #24: Concomitant use of MAYZENT and drugs that cause moderate CYP2C9 and strong CYP3A4 induction (Appendix 4).
- Added exclusion #25: Use of cannabinoid or cannabidiol products 30 days prior to screening.
  a. At this time, there is no evidence of combination treatment with cannabinoid or cannabidiol products and siponimod. Thus, for patients' safety, the concomitant use of these products will be excluded from the study.
- Removed Visit 2/Day 7 (in office/home visit)
  a. In line with the approved US package insert for Mayzent, Novartis removes the Day 7 pre-dose ECG.
- Under Figure 3-1: Removed the managed access program and updated language for patient services hub for post-trial.

Additional changes are listed below:

- Exclusion criteria Note 2: Updated to reflect that each patient may be rescreened no more than 1 time.
- Section 4.4 and Section12.7: Update visit number from Visit 3 (Day 28) to Month 6 (Visit 5/Day 168).
- Section 8 Table 8-1 Assessment Schedule: Grayed out Visit 2 (Day 7) not to be performed.
  - Removed footnote #4 (12 Hour fasted food samples).

  - Added language to footnote #
- Section 8, Table 8-3 physical examination and neurological exam language was updated.
- Section 8.4.1 Laboratory Evaluations under CYP2CP testing language was updated.
- Section 8.4.2 Electrocardiogram language was updated.
- Sections 8, 10.2.2 and 16.7 (Appendix 7): Revision of pre-dose (< 55bpm) and post-dose (<45 bpm) bradycardia definition to be consistent throughout protocol.
- Section 15: Added references.
- Section 16.4: Updated Appendix 4.

All relevant section(s) of the protocol are updated to reflect the update in the exclusion criteria and removal of Day 7 pre-dose ECG.

Amendment 01

Rationale for amendment

The purpose for Amendment 01 is to update all relevant section(s) of the protocol related to:

- Drug supply, reflecting the details of how the drug is supplied and will be provided in a pharmacy manual.
- Additional cardiac monitoring for Day 1 and Day 7 prior to treatment
- The addition of ophthalmic assessment (optical coherence tomography; OCT) at Day 1 (baseline) and Day 84 for incidences of macular edema.

Additional changes are listed below:

- Table 2-1: Removed CSSRS from exploratory objectives.
- Section 5.2 – Updated Exclusion criteria #15 to be aligned with definition of high-risk cardiac patients in the CBAF312A2304 study.
- Section 6.1.1:
  a. Added a requirement of restarting titration, if a day or more of the 5-day titration is missed.
  b. Added that a pharmacy manual will be provided, with specific instructions, regarding study drug, titration and maintenance dose.
  c. Added sentence: "If the patient has missed greater than 30 consecutive days of treatment, using his/her best medical judgement, the PI should consider terminating the patient from the study."
- Section 6.5: Added "Siponimod dose adjustments are not permitted."
- Section 6.7: Added that supply of siponimod will be described in pharmacy manual.
- Section 6.7.2: Added that sites should refer to pharmacy manual for specific instructions on preparation and dispensation of study treatment.
- Section 8: Updated language in first bullet regarding assessment of vitals and heart rate at Visit 1 (Day 1).
- Table 8-1:
  a. Added visit windows (±days) for each clinical visit
  b. Updated visit names and numbering, as well as added heart rate assessment (pre-dose) at baseline visit.
  c. Updated height assessment, from being performed at every visit, to just done at screening and EOT/S visits.
  d. Included OCT assessment at Day 1 (baseline) and Day 84.
  e. Included ECG assessments at screening, Day 1 (baseline) pre-dose, and Day 7 pre-dose.
- Section 8.4.2: provided detailed direction on when to obtain ECG assessment (Day 1 and Day 7; pre-dose). Further, provided instructions should the patient be at cardiac risk.

- Section 8.4.5: We included the use of OCT as part of ophthalmologic assessments at baseline prior to siponimod treatment and on Day 84 (3 months post initial treatment with siponimod. The purpose of this assessment is to monitor incidences of macular edema in patients treated with siponimod. This inclusion can be found in the Table of Assessment (Table 8-1; Section 8.4.5 and Appendix 8)
- Section 10.2.2: Updated C-SSRS language including clarification regarding the method in which it will be administered.
- Section10.2.2: Added bradycardia as an adverse event of special interest
- Added Section 11.4: Potential Remote Patient Cohort. (These are patients who would potentially be allowed to participate, in the study, remotely, via online technology and telemedicine).
- Section 12.5.1: Added language that change in heart rate (and other vitals), from baseline to 6-hours post dose, may be summarized in secondary endpoint analysis.
- Section 12.7: Updated language to state that: an interim analysis on the safety data will be conducted at the time of approximately 50 patients completing Visit 3 (Day 28).
- Section 12.8.1: Updated language to state that: A sample size of 300 patients will provide us the precision (half-width of 95% confidence interval) of 5.6%.
- Section 16.7: Included treatment management for bradycardia.
- Section 16.8: Include guidelines for ophthalmic examination and management of macular edema

Protocol summary

Protocol number	CBAF312AUS02
Full Title	Exploring the safety and tolerability of conversion from oral injectable or infusion disease modifying therapies to dose-titrated Oral Siponimod in patients with advancing forms of relapsing multiple sclerosis: A 6-month open label, multi-center Phase IIIb study (EXCHANGE)
Brief title	Study of the safety and tolerability dose-titrated Oral Siponimod in patients with relapsing forms of multiple sclerosis.
Sponsor and Clinical Phase	Novartis Clinical Phase IIIb
Investigation type	Drug
Study type	Interventional, Open-label
Purpose and rationale	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 study 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.
Primary Objective(s)	The primary objective is to evaluate overall safety and tolerability profile of siponimod in advancing RMS patients (including a broader population that had not been previously studied with siponimod who are converting from currently approved oral, injectable or infusion RMS DMT).
Secondary Objectives	• Objective 1: To evaluate treatment satisfaction outcomes using the Treatment Satisfaction Questionnaire for Medication (TSQM-9) with siponimod in advancing RMS patients. • Objective 2: To evaluate cardiac safety, in the overall population during siponimod treatment initiation • Objective 3: To evaluate treatment adherence with siponimod.
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 DMT. This study consists of two parts: The Screening Period and Core Treatment Period, plus a 30-day follow-up telephone call. [redacted]

	[redacted]
Population	The study population will consist of out-patient, male and female patients, ≥18-65 years of age, with an EDSS score ≥ 2.0-6.5 with advancing RMS with or without progressive features. 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]
Key Inclusion criteria	Patients eligible for inclusion in this study must meet all of the following criteria: 1. Signed informed consent must be obtained prior to participation in the study. 2. Male or female aged 18 to 65 years (inclusive) at screening 3. Patients with advancing RMS as defined by the principal investigator 4. Prior history of relapsing MS (RMS), with or without progressive features, according to the 2010 Revised McDonald or Lublin criteria (Lublin et al, 2013) 5. Disability status at screening with an EDSS score of ≥2.0 to 6.5 (inclusive) 6. Having been continuously treated with beta-interferons, glatiramer acetate, fingolimod, fumarates, teriflunomide, natalizumab or ocrelizumab for at least 3 months at the time of consent 7. Patients desiring to start treatment with a DMT investigated in advancing stages of multiple sclerosis.
Key Exclusion criteria	Patients meeting any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator in order to ensure that the study population will be representative of all eligible patients: 1. Patients with an active chronic disease (or stable but treated with immune therapy) of the immune system other than MS (e.g., rheumatoid arthritis, scleroderma, Sjogren's syndrome, Crohn's disease, ulcerative colitis, etc.) or with a known immunodeficiency syndrome (AIDS, hereditary immune deficiency, drug-induced immune deficiency). 2. 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. 3. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless**

	they are using highly effective methods of contraception while taking study treatment and for 30 days *(30 = 5 times the terminal half-life of siponimod)* after stopping study treatment. Highly effective contraception methods include: • Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are **not** acceptable methods of contraception • Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment • Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient • Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment. • Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential. 4. Sexually active males unwilling to use a condom during intercourse while taking study treatment and for 30 days *(30 days = 5 times the terminal half-life of siponimod)* after stopping study treatment. A condom is required for <u>all</u> sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male participants must not donate sperm for the time period specified above. If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF.

	5. 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 whether there is evidence of local recurrence or metastases. 6. 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. 7. Diagnosis of macular edema 1 year prior to screening. 8. Patients with active systemic bacterial, viral, or fungal infections or known to have AIDS or have positive HIV antibody. 9. Positive results of screening period testing for serological markers for hepatitis A, B, C and E, indicating acute or chronic infection: • anti-HAV IgM • HBs Ag and/or anti-HBc IgM • anti-HEV IgM (if positive IgG and/or IgM, perform HEV-RNA PCR and if negative, patient can be included). Note: If the treating physician suspects false positive hepatitis serology results, such as an antibody pattern indicating acute hepatitis infection but no corresponding elevated liver enzymes and no signs or symptoms of liver disease, a HEV-RNA PCR will be performed and will be the deciding factor to determine whether the patient has hepatitis A, B, C, or E. If negative, the treating physician may document (in source data and in a eCRF comment) that the serology results are considered false positive and consider including the patient. 10. Negative for varicella-zoster virus IgG antibodies at Screening unless there is other evidence of immunity to VZV based on the CDC criteria (https://www.cdc.gov/chickenpox/hcp/immunity.html; see Appendix 1) 11. Have received any live or live-attenuated vaccines (including for varicella-zoster virus or measles) within 2 months of screening. 12. Have been treated with any of the medications listed below: • Intravenous immunoglobulin within 2 months prior to screening • Immunosuppressive/chemotherapeutic medications (e.g., azathioprine, methotrexate) within 6 months prior to screening • Cyclophosphamide within 2 years prior to screening • More than 24 months prior treatment exposure to natalizumab • Rituximab, ofatumumab, ublituximab or cladribine within 2 years prior to randomization • Alemtuzumab at any time

	• Any mitoxantrone during previous 2 years prior to randomization or evidence of cardiotoxicity following mitoxantrone or a cumulative life-time dose of more than 60 mg/m2 • If patients treated with teriflunomide cannot or will not undergo the accelerated elimination process (Appendix 6) • Stem cell transplantation • Lymphoid irradiation, bone marrow transplantation or other immunosuppressive treatments with effects potentially lasting over 6 months, at any time. 13. Patients with any medically unstable condition as determine by the investigator. 14. Any of the following conditions or treatments that may affect cardiovascular function within last 6 months: • Heart rate < 55 bpm at screening • Cardiac conduction disorders such as incomplete left bundle branch block or second degree AV block Mobitz type I (Mobitz I) (either history or observed at screening) • Minor ECG findings at screening PR interval: >200 msec; QRS duration ≥120 msec; QTcF >430 msec (males); QTcF >450 msec (females) • History of or current significant cardiac disease including cardiac failure (NYHA functional class II-IV), myocarditis, cardiomyopathy, angina pectoris or myocardial infarction (within 6 months), unstable angina (within 6 months), stroke (within 6 months), TIA (within 6 months), decompensated heart failure requiring hospitalization (within 6 months) or uncontrolled arterial hypertension • Patients receiving treatment with beta-blockers for cardiac disease/comorbidities. • Any other condition which, in the opinion of the investigator, has a potential for AV conduction suppression and/or other risk factors that may require expanded cardiac monitoring • Patients diagnosed with right bundle branch block, either at the screening visit for entry of the study or during the conduct of the study 15. Any of the following pulmonary conditions: • History of or active severe respiratory disease, including COPD, or pulmonary fibrosis, • Tuberculosis, except for history of successfully treated tuberculosis or a history of prophylactic treatment after positive PPD skin reaction • Patient with severe asthma or asthma requiring regular treatment with oral steroids

16. Patients with any of the following hepatic conditions prior to screening:
    - history of alcohol abuse, chronic liver or biliary disease
    - total or conjugated bilirubin greater than 1.5 times ULN range, unless in the context of Gilbert's syndrome
    - alkaline phosphatase (AP) greater than 1.5 times the ULN range
    - AST (SCOT), ALT (SGPT) or Gamma-glutamyl-transferase (GGT) greater than 3 times the ULN range within the last 6 months

17. Any of the following abnormal laboratory values prior to screening:
    - Serum creatinine > 1.7 mg/dL (150 umol/L)
    - White blood cells (WBC) count <3,500/mm3 (<3.5 x 10(9)/L), while on injectable or oral DMT's at screening, except fingolimod
    - Lymphocyte count <500/mm3 (<0.5 x 10(9)/L) while on all DMT's at screening except fingolimod
    - Serum potassium > ULN
    - Or other clinically significant laboratory assessment (i.e. hypomagnesemia or hypokalemia)
    - For patients previously exposed to natalizumab, anti-JCV antibody positive and index ≥ 1.5

18. Patients with the following neurological/psychiatric disorders prior to screening:
    - History of substance abuse (drug or alcohol) or any other factor (i.e. serious psychiatric condition) that may interfere with the patient's ability to cooperate and comply with the study protocol
    - Progressive neurological disorder, other than MS, which may affect participation in the study or require the use of medications not allowed by the protocol

19. Use of other investigational drugs at the time of enrollment or within prior 30 days; or five elimination half-lives, or until the expected pharmacodynamics effect has returned to baseline, whichever is longer.
20. History of hypersensitivity to the study drug or to drugs of similar chemical classes.
21. Homozygosity for CYP2C9*3/*3 or heterozygous for CYP2C9*2/*3 or CYP2C9*1/*3 (to be tested at screening) or refusal to test for CYP2C9 variants.
22. Concomitant use of MAYZENT and drugs that cause moderate CYP2C9 and moderate or strong CYP3A4 inhibition (Appendix 4).

	23. Concomitant use of MAYZENT and drugs that cause moderate CYP2C9 and strong CYP3A4 induction (Appendix 4). 24. Use of cannabinoid or cannabidiol products 30 days prior to screening. 25. Any other disease or condition, which could interfere with participation in the study according to the study protocol, or with the ability of the patients to cooperate and comply with the study procedures. Note 1: If a patient fails on one or more laboratory (or other) assessment criteria, as part of the screening process, the assessment (s) may be repeated at the discretion of the investigator and the patient may be included if criteria are then met, provided the assessments are completed within the screening period. Note 2: In certain cases rescreening of patients that were previously determined ineligible may be permitted. When a patient is re-screened, a new patient identification number will be assigned and all screening assessments must be repeated. Each patient may be rescreened no more than one time. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.
Study treatment	All eligible patients will receive oral siponimod (Mayzent ®). The study treatment will be provided for the duration of the trial from baseline (Day 1) through last day of the treatment period.
Efficacy assessments	[redacted]
Key safety assessments	Physical examinations Monitoring of laboratory markers in blood (plasma/serum) Monitoring of macular edema through the use of OCT Electrocardiogram (ECG) Adverse event monitoring

Other assessments	An assessment of Patient reported outcomes is planned in this trial using [redacted] Patient reported outcomes (PRO)
Data analysis	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. 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% 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 above analyses will be conducted on the Safety Set. For the purpose of earlier dissemination, an interim analysis on the safety data will be conducted at the time of approximately 50 patients will complete their Month 6 (visit 5). Additional interim analyses may be conducted at additional time points based on study enrollment in order 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]
Key words	Siponimod, Disease Modifying Therapy , Multiple Sclerosis, Relapsing Multiple Sclerosis, Relapsing-Remitting Multiple Sclerosis, Secondary Progressive MS

1 Introduction

1.1 Background

Multiple Sclerosis (MS) is an immune-mediated disease of the central nervous system (CNS) characterized by inflammation, demyelination and axonal/neuronal destruction, ultimately leading to severe disability. It affects approximately 2.5 million individuals worldwide and has distinct clinical stages including relapsing remitting MS (RRMS), secondary progressive MS (SPMS) and primary progressive MS (PPMS). At the time of diagnosis, approximately 85% of patients have recurrent, acute relapses of neurological symptoms. More than 50% of patients with poorly treated RRMS transition to secondary progressive disease within 15-20 years (Tremlett et al, 2008). In progressive stages, relapses are absent or infrequent, yet disability continues to gradually worsen (MS Society, accessed 2018).

The McDonald Criteria (McDonald et al, 2001) was the first diagnostic criteria for MS to employ MRI measures alongside of clinical assessments. As more data and experience with MRI were acquired (Tintore et al. 2000; Swanton et al. 2006, 2007; Montalban et al. 2010)) the criteria evolved further with two subsequent revisions (Polman et al 2005, 2011). Currently, the 2010 revision of the McDonald Criteria is utilized to characterize the patients' clinical stage and determine the patients' eligibility to participate in the trial.

Currently, approved disease modifying therapies (DMTs) are indicated for use in relapsing forms of MS (RMS) in the USA. RMS includes RRMS and SPMS patients with superimposed relapses. The effect of drug in these SPMS patients is presumed to have increased effect on inflammatory activities (relapses and gadolinium enhancing lesions), efficacy on disability progression has not been confirmed in secondary progressive patients. Mitoxantrone is the only therapy approved for reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing, or worsening relapsing-remitting multiple sclerosis (i.e., patients whose neurologic status is significantly abnormal between relapses) in the USA. However, data demonstrating the efficacy of mitoxantrone in SPMS patients (Goodin et al, 2002) and the risks associated with mitoxantrone (heart failure, leukemia) limits its use.

Sphingosine-1-phosphate (S1P) receptor modulators possess a unique mechanism of action in the treatment of relapsing and progressive MS (Gergely et al, 2012). The S1P1 and S1P5 receptors are commonly found on the surface of astrocytes and oligodendrocytes, residing in the CNS, and are potentially implicated in mechanisms affecting CNS repair (O'Sullivan et al. 2016). Siponimod (Mayzent®), approved by the US FDA in March 2019 for treatment of relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing remitting disease and active secondary progressive disease in adults, is a S1P1/S1P5-selective agonist. It has scientific evidence for involvement with reducing T-cell migration to the CNS, astrogliosis, oligodendrocyte process modulation and increased cell survival (Chiba et al, 2012); (Sanna et al, 2004). The mechanism of action on immune cells is similar to the first-in-class drug, fingolimod, with S1P1-mediated trapping of lymphocytes in the peripheral lymphatic tissues. Siponimod, however, has a different chemotype than fingolimod, as it is not a prodrug and thus does not require a phosphorylation step *in vivo*. It readily crosses the blood-brain-barrier (BBB), and preclinical studies suggest: it may prevent synaptic neurodegeneration (Gentile et al, 2016); increases levels of myelin basic protein; promotes remyelination; and

activates pERK and pAKT signaling to promote internalization of S1P1 receptors to a greater extent (O'Sullivan et al, 2016) than S1P itself (Gentile et al, 2016); (O'Sullivan et al, 2016). In-vitro studies show that by binding to these specific receptors, siponimod may prevent the activation of these cells, helping to reduce loss of physical and cognitive function associated with MS (Aslanis et al, 2012).)

Next to its effects in lymphocyte trafficking and trapping in peripheral lymphatic tissue (similar to fingolimod), expression of S1P1 receptor ligands in atrial, septal and ventricular cardiac myocytes (as well as endothelial cells of cardiac vessels in humans) has been established and associated with the regulation of heart rate (HR) at treatment initiation in both healthy patients and in MS patients.

The half-life of siponimod compared to fingolimod is shorter (approximately 30 h versus 200 h), therefore drug effects cease more rapidly after discontinuation. 90% Recovery of the baseline lymphocyte counts after treatment withdrawal from steady state conditions should be achieved in one week at a daily siponimod dose of 2mg. However, residual pharmacodynamics effects, such as lowering effects on peripheral lymphocyte count may persist for up to 3 to 4 weeks after the last dose. Use of immunosuppressants within this period may lead to an additive effect on the immune system and therefore caution should be applied 3 to 4 weeks after the last dose.

The siponimod receptor selectivity and half-life has the potential to enable full efficacy in MS without targeting other S1P receptors (S1P3 and/or S1P4), which together with the more rapid washout may improve the safety profile.

The Phase I clinical pharmacology trials, siponimod was safe and generally well tolerated. The study detected a dose dependent bradyarrhythmic effect within 2-3 hours after intake of first dose.

A placebo-controlled Phase II study in patients (N=297) with RRMS was conducted to determine the dose-response curve for the MRI-based efficacy of siponimod, and to characterize its safety and tolerability (Selmaj et al 2013). A significant dose response relationship at Month 3 was observed (p=0.0001, Emax model). Siponimod treatment reduced the combined unique active lesion (CUAL) count by up to 80% vs. placebo, with the 2mg dose providing near-maximal efficacy. Annualized relapse rates (ARR) were 0.61, 0.20 and 0.30 for the 0.5, 2 and 10mg doses, respectively, vs 0.58 for placebo ($p<0.05$ for 2mg vs. placebo only).

- Five transient symptomatic bradyarrhythmic events without sequelae were observed with the two highest doses.
- Other safety findings included liver enzyme elevation (4.3% of patients at higher dose levels had transaminases >3x upper limit normal (ULN) and one case of macular edema in a patient with history of uveitis.
- Serious adverse events (SAEs) included one death (27 days post study drug discontinuation), likely due to coronary artery disease.

Due to the occurrence of bradyarrhythmic events during in the Phase I trial, a dose titration was implemented in the Phase II study, resulting in the attenuation of the earlier observed negative chronotropic and dromotropic effects. There were no symptomatic bradyarrhythmic events or asymptomatic AV-blocks of concern following the introduction of the initial-dose titration scheme.

The double-blind registration Phase III EXPAND trial, (N=1651) demonstrated unique effects on SPMS patients (Kappos et al, 2018). The majority of the study population had been on other DMTs prior to entering into the study. In patients randomized to the siponimod arm, approximately 69% of patients had previously been treated with either IFNβ-1a or IFNβ-1b while 26% of patients had been treated with glatiramer acetate. For patients on prior DMTs, there were specific washout requirements implemented without any monitoring during the washout. Given the development of additional S1P receptor modulators over the last few years, transition between S1P treatments has not broadly assessed. Theoretically, while both siponimod and fingolimod demonstrate persistent internalization and enhanced degradation of the S1P-receptor, there is clinical utility in understanding the role of titration, or lack of, when converting between the two S1P therapeutic options to ensure patients are not undertreated.

Safety results from the Phase III trial demonstrated that siponimod is safe and well tolerated

- 197 (18%) patients on siponimod and 83 (15%) on placebo had at least one serious adverse event.
- Headache, nasopharyngitis, urinary tract infection, and falls were the most frequent adverse events, being reported in more than 10% of patients in both treatment groups (siponimod vs placebo)
- Hypertension was reported in 115 patients (10%) on siponimod compared with 41 (8%) on placebo
- Four deaths occurred in each treatment group. Deaths in the siponimod group were due to metastatic gastrointestinal melanoma within 4 months of commencing siponimod; septic shock in a patient with terminal colon cancer; urosepsis more than 10 weeks after discontinuation of siponimod and after two doses of rituximab; and suicide.
- Cardiac effects: 1346 (82%) of 1651 patients underwent continuous mobile cardiac telemetry for up to 6 days.
- During double-blind treatment initiation, the maximum reduction in mean heart rate
  - On day 1 was 5.3 bpm in the siponimod group (4 h post-dose) and 1.2 bpm in the placebo group (1 h post-dose)
  - On day 7, mean reductions were 3.1 bpm and 2.0 bpm, in siponimod and placebo treated patients, respectively (3 h post-dose)
- For 68 patients (6%) receiving siponimod and 17 (3%) receiving placebo, bradycardia, decreased heart rate, or sinus bradycardia were reported as adverse events.
  - Two of these events on day 7 in the siponimod group were symptomatic, one leading to treatment discontinuation.
  - No cases of Mobitz type II or high degree atrioventricular block were observed during double-blind treatment

To date, phase III studies have not examined the safety considerations among RRMS or SPMS patients who had undergone acute conversion to siponimod from other DMT treatment. As the disease progresses with a need to convert from one DMT to another, assessing the effects (safety and efficacy) of this acute conversion from existing DMTs becomes important. In order to address the benefits and risk needs of a patient and public health relevance across a broad MS

population representative of clinical practice, it is necessary to understand the implications of overlapping immune effects, dose titration, washout intervals between therapies, direct conversion-related adverse events, conversion between S1P receptor modulators, patient tolerability and adherence, which are compulsory to appropriately address the benefit: risk needs of a patient. Furthermore, recent market research from the United States reported that there is a significant percentage of patients with transitioning RMS that are being treated with another class of drugs known as infusion DMTs, specifically, natalizumab (an α4-integrin antagonist, humanized monoclonal antibody) or ocrelizumab (a monoclonal antibody that targets CD20 marker on B-lymphocytes), for which a safety gap on DMT conversion continues to persist. Natalizumab, is broadly used in patients with advancing RMS. However, many patients need to switch to an alternative therapy due to safety, tolerability, effectiveness, or access reasons. Ocrelizumab has a prolonged immunosuppressive effect primarily resulting from a rapid reduction of lymphocyte B-cells, with a median time of 72 weeks (range 27-175 weeks) for this cell counts to return to normal after last infusion. It is expected that patients who are currently treated with natalizumab and/or ocrelizumab will convert to siponimod for reasons of safety, tolerability, effectiveness or access. Therefore it is critical to generate data to guide discussions between healthcare providers and patients at the time point of conversion, immediate and short term safety, and effectiveness after conversion.

1.2 Purpose

The purpose of this study is to assess initial safety and tolerability of converting patients from approved oral, injectable and infusion RMS DMTs to siponimod. The results of this study 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.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s) • 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.	**Endpoint(s) for primary objective(s)** • Occurrence of any study-drug related adverse events during 6-month treatment period
Secondary Objective(s) • To evaluate treatment satisfaction with siponimod in advancing RMS patients using outcomes based on the Treatment Satisfaction Questionnaire for Medication (TSQM-9). • To evaluate cardiac safety during siponimod treatment initiation	**Endpoint(s) for secondary objective(s)** • Occurrence of any adverse events • Change from Baseline in the TSQM-9 • Change from Baseline in heart rate to 6 hours after 1st treatment

Objective(s)	Endpoint(s)
• To evaluate treatment persistence with siponimod	• Occurrence of hospitalizations • Patient retention

[redacted]

3 Study design

This is a 6-month, open-label, multi-center, single arm design, including 300-400 advancing RMS patients, evaluating overall safety and tolerability profile when acutely converting to siponimod from oral or injectable or infusion RMS DMTs. This study consists of two primary parts: The Screening Period and the Core Treatment Period, plus a 30-day follow-up telephone call at the end of treatment/study visit. This study includes a virtual cohort of patients, i.e., the patient will remain in their own home and complete study assessments via an online technology. This virtual cohort of the study is being done in parallel to, but separate from, other sites that will conduct study visits in the traditional manner, i.e., with all assessments performed at the study center.

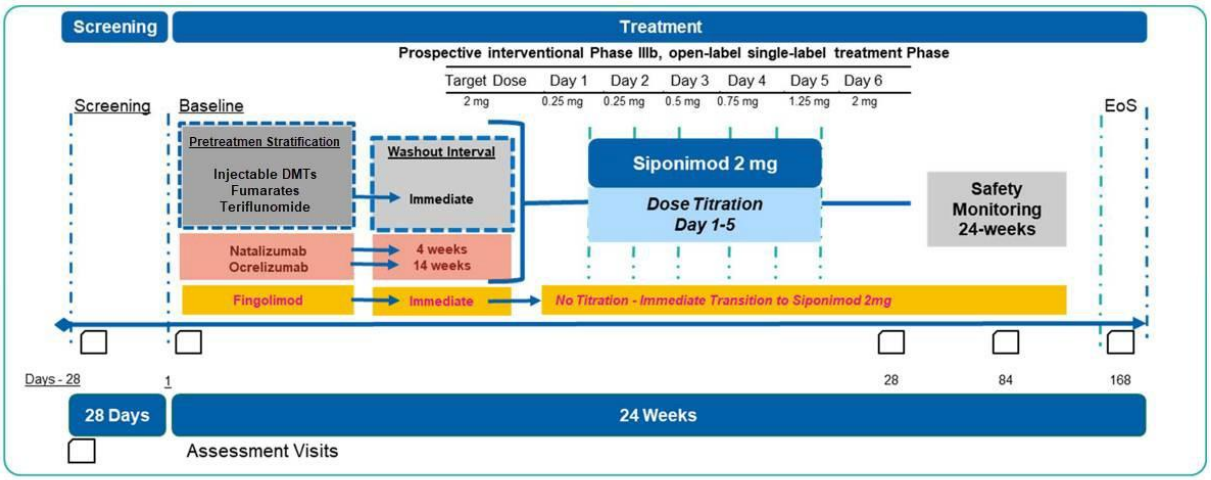
- The patient cohort will be stratified by pre-treatment groups and may include injectable, oral and infusion DMTs used in RMS: interferon beta-1a (Avonex®, Rebif®), interferon beta-1b (Betaseron®, Extavia®), glatiramer acetate (Copaxone®, generic glatiramer acetate), peginterferon beta-1a (Plegridy®), 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, expect 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 3-1 Siponimod Target Daily Dose

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

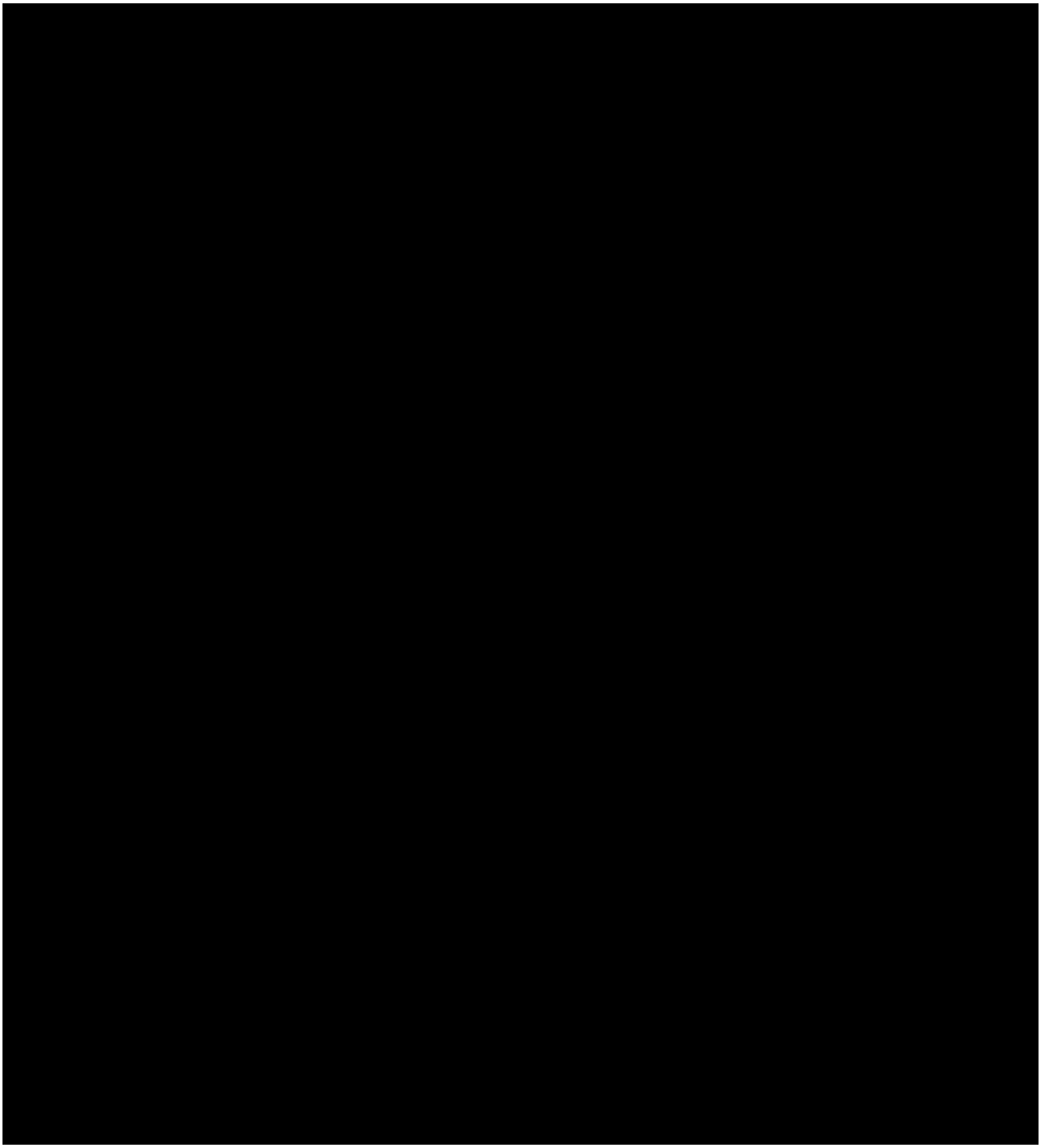
Patients who have completed the treatment period successfully, will be given the option to terminate from the study or be referred to the MAYZENT patient services hub for post-trial continuity of treatment programs, where the benefit risk is acceptable and discussed with the patient and investigator. Patients who terminate prior to the end of the treatment period or who withdraw permanently due to siponimod related AE or SAE should follow up with their primary neurologist for continued treatment options as quickly as possible.

Figure 3-2 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

[redacted]



4 Rationale

4.1 Rationale for study design

The clinical development program of siponimod has demonstrated both a favorable efficacy and benefit: risk profile in RMS and SPMS patients. While there is a fair amount of data on the overall safety profile of siponimod, less data exists to describe the safety and tolerability profile

during conversion from existing DMTs to siponimod in a broader population than included in the Phase II and Phase III development program and to determine how health outcomes changes when patients start treatment with siponimod both short- and long-term.

This prospective open-label treatment study design supports the need for increased human exposure to a new medicine to further evaluate the safety on the immediate conversion of oral injectable, and infusion DMTs to siponimod in patients with advancing RMS. A treatment period of 6 months will allow achieving assessment of potential overlapping immune effects from previous DMT at steady state of oral siponimod. Further, this 6-month treatment period will increase the knowledge of the safety profile of siponimod. The data from the study will give HCPs a better understanding of what the potential safety implications will be with an acute conversion of existing DMTs to siponimod.

This study will include a virtual cohort of patients, i.e., the patient will remain in their own home and complete study assessments via an online technology. This virtual cohort of the study is being done in parallel to, but separate from, other sites that will conduct study visits in the traditional manner, i.e., with all assessments performed at the study center. This study design element will potentially offer patients better access to a clinical trial

4.2 Rationale for dose/regimen and duration of treatment

In the siponimod Phase III (EXPAND) trial, siponimod treatment was initiated with a 5-day dose titration, starting with 0.25mg once daily on day 1 and 2, followed by once daily doses of 0.5mg on day 3 (two tablets of 0.25mg), 0.75 mg on day 4 (three tablets of 0.25mg) and 1.25mg on day 5 (five tablets of 0.25mg) to reach the maintenance dose of siponimod 2mg starting on day 6. It is currently unknown whether this titration regimen is needed among patients who are converting from existing S1P receptor modulators (e.g., fingolimod) to siponimod.

Given the recent development of S1P receptor modulators over the last few years in general, transition between emerging S1P treatments has not been broadly assessed. Sustained fingolimod induced receptor internalization of S1P receptors has been demonstrated in a number of separate studies (Jo et al., 2005); (Oo et al., 2007); (Mullershausen et al., 2009). Both siponimod and fingolimod are thought to act as a functional S1P1R antagonist, causing complete internalization and down—regulation of the S1P1 receptor found on lymphocytes (Matloubian et al., 2004); (Chiba et al., 2006); (O'Sullivan et al., 2016). Through this on-going study, there is clinical utility in substantiating the hypothesis that a direct switch between S1P receptor modulators is clinically safe and effective in sustaining therapeutic coverage. Therefore, in this study amendment, we suggest to omit the siponimod titration regimen for only those patients converting from fingolimod strata as part of the investigative approach in understanding the role of titration, or lack of, when converting between the two S1P receptor modulators to ensure patients are not undertreated.

The EXPAND trial demonstrated that 288 (26%) of 1096 patients receiving siponimod and 173 (32%) of 545 patients receiving placebo had 3-month CDP (hazard ratio 0.79, 95% CI 0.65–0.95; relative risk reduction 21%; p=0.013; (Kappos L et al Lancet 2018). Headache, nasopharyngitis, urinary tract infection, and falls were the most frequent adverse events, being reported in more than 10% of patients in both treatment groups. There were no observed cases of Mobitz type II or higher degree atrioventricular block.

Because of the success of siponimod in the EXPAND trial, the data was used as a reference and led to 2mg as the maintenance dose for all the patients in this Phase IIIb study with a 6-month treatment in the core treatment period for all patients. The data collected from this Phase IIIb study will be important to provide a better understanding of the safety profile when acutely converting advancing RMS patients to siponimod from standard of care oral, injectable or infusion DMTs.

4.3 Rationale for choice of control drugs

Not Applicable.

4.4 Purpose and timing of interim analyses/design adaptations

Shortly before the scheduled completion of enrollment in this study, an interim analysis will be performed. Since pre-specification of the parameters relevant for the sample size calculations (disease activity, enrollment rate, and dropout rate) has uncertainty, it is reasonable to re-assess the pre-study assumptions prior to the completion of the enrollment period. 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). This analysis may result in an increase in the total number of patients enrolled in the study. The maximum number of patients is specified in section 5. 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.

4.5 Risks and benefits

When adhering to the inclusion/exclusion criteria and PIs guidance on safety conditions, providing close clinical monitoring, avoiding prohibited treatments, the risk to patients in this trial will be minimized.

The risk profile of siponimod includes bradyarrhythmia (including conduction effects) occurring post-first dose in patients with heart rate (HR) less than 55 beats per min (bpm) and liver transaminase elevation. Risks associated with S1P modulators, but not observed with siponimod to date include clinically relevant bronchoconstriction, increased frequency of infections, hypertension and posterior reversible encephalopathy syndrome. There may be yet unknown risks to MS patients taking siponimod, which may be serious and unforeseen. There is little data from phase III/IIIb clinical trials asserting safety relevant to acute conversion of siponimod from current standard of care treatments.

With limited treatment options for patients with advancing RRMS and patients progressing to or currently diagnosed with SPMS, siponimod has demonstrated the potential to be an effective treatment that addresses the current unmet needs for this population.

Women of child bearing potential and sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study. Thus, they must agree to adhere to the contraception requirements outlined in the exclusion criteria in order to participate in the trial. If there is any question that the patient will not reliably comply, they should not be entered or continue in the study.

4.6 Rationale for public health emergency mitigation procedures

During a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, mitigation procedures to ensure participant safety and trial integrity are listed in relevant sections. Notification of the Public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

5 Population

This study includes advancing RMS patients. Because the transition of disease activity from RRMS to SPMS is not well-characterized, introducing a functional definition of advancing RMS for purposes of this study is aimed to help identify patients who may be demonstrate onset of relatively fixed impairment indicative or worsening disease activity or progressive disease activity.

The study population will consist of out-patient, male and female patients, ≥18-65 (inclusive) years of age, with an EDSS score ≥2.0-6.5, inclusive, with advancing RMS with or without progressive features. The diagnosis of MS with initial relapsing remitting disease course is defined by the 2010 revised McDonald criteria (Polman et al 2011). EDSS >2 defines the beginning of relatively fixed impairment. Worsening denotes an increase in neurological dysfunction and/or disability, with or without evidence of relapses or disease activity on MRI (Lublin et al 2013). Progression denotes the continuous or steady worsening of neurological impairment over at least 6 months (Rovaris et al 2006) not explained by incomplete recovery from relapses (Lublin et al 2013).

Patients who have been previously treated with other MS therapies, such as interferon beta-1a, interferon beta-1b, glatiramer acetate, fingolimod, fumarates (dimethyl fumarate, diroximel fumarate), teriflunomide, natalizumab or ocrelizumab for at least 3 months at the time of consent may participate. Approximately 300-400 patients will be randomized from up to 80 study sites in the USA. The study plans to screen approximately 570 patients.

At the time of enrollment, patients are eligible if they are identified as clinically appropriate advancing RMS patients and eligible to receive siponimod, as well as meeting all other eligibility criteria.

5.1 Inclusion criteria

Patients eligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study.

2. Male or female aged 18 to 65 years (inclusive) at screening
3. Patients with advancing RMS as defined by the principal investigator
4. Prior history of relapsing MS (RMS), with or without progressive features, according to the 2010 Revised McDonald or Lublin criteria (Lublin et al 2013)
5. Disability status at screening with an EDSS score of ≥2.0 to 6.5 (inclusive)
6. Having been continuously treated with beta-interferons, glatiramer acetate, fingolimod, fumarates (dimethyl fumarate, diroximel fumarate), or teriflunomide for at least 3 months at the time of consent OR having had last natalizumab dose at least 4 weeks before screening OR last ocrelizumab dose 14 weeks prior to screening.

5.2 Exclusion criteria

Patients meeting any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator in order to ensure that the study population will be representative of all eligible patients:

1. Patients with an active chronic disease (or stable but treated with immune therapy) of the immune system other than MS (e.g., rheumatoid arthritis, scleroderma, Sjogren's syndrome, Crohn's disease, ulcerative colitis, etc.) or with a known immunodeficiency syndrome (AIDS, hereditary immune deficiency, drug-induced immune deficiency).
2. 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.
3. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception while taking study treatment and for 30 days (30 days = 5 times the terminal half-life of siponimod) after stopping study treatment. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are **not** acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient
    - Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
    - In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

- Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

4. 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. A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male participants must not donate sperm for the time period specified above.

   If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF.

5. 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 whether there is evidence of local recurrence or metastases.
6. 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.
7. Diagnosis of macular edema 1 year prior to screening.
8. Patients with active systemic bacterial, viral, or fungal infections or known to have AIDS or have positive HIV antibody.
9. Positive results of screening period testing for serological markers for hepatitis A, B, C and E, indicating acute or chronic infection:
   - anti-HAV IgM
   - HBs Ag and/or anti-HBc IgM
   - anti-HEV IgM (if positive IgG and/or IgM, perform HEV-RNA PCR and if negative, patient can be included).

   Note: If the treating physician suspects false positive hepatitis serology results, such as an antibody pattern indicating acute hepatitis infection but no corresponding elevated liver enzymes and no signs or symptoms of liver disease, a HEV-RNA PCR will be performed and will be the deciding factor to determine whether the patient has hepatitis A, B, C, or E. If negative, the treating physician may document (in source data and in a eCRF comment) that the serology results are considered false positive and consider including the patient.
10. Negative for varicella-zoster virus IgG antibodies at Screening unless there is other evidence of immunity to VZV based on the CDC criteria (https://www.cdc.gov/chickenpox/hcp/immunity.html; see Appendix 1)
11. Have received any live or live-attenuated vaccines (including for varicella-zoster virus or measles) within 2 months of screening.
12. Have been treated with any of the medications listed below:

- Intravenous immunoglobulin within 2 months prior to screening
- Immunosuppressive/chemotherapeutic medications (e.g., azathioprine, methotrexate) within 6 months prior to screening
- Cyclophosphamide within 2 years prior to screening
- More than 24 months prior treatment exposure to natalizumab
- Rituximab, ofatumumab, ublituximab or cladribine within 2 years prior to randomization
- Alemtuzumab at any time
- Any mitoxantrone during previous 2 years prior to randomization or evidence of cardiotoxicity following mitoxantrone or a cumulative life-time dose of more than 60 mg/m2
- If patients treated with teriflunomide cannot or will not undergo the accelerated elimination process Appendix 6.
- Stem cell transplantation
- Lymphoid irradiation, bone marrow transplantation or other immunosuppressive treatments with effects potentially lasting over 6 months, at any time.

13. Patients with any medically unstable condition as determine by the investigator.
14. Any of the following conditions or treatments that may affect cardiovascular function within the last 6 months:
    - Heart rate < 55 bpm at screening
    - Cardiac conduction disorders such as incomplete left bundle branch block or second degree AV block Mobitz type I (Mobitz I) (either history or observed at screening)
    - Minor ECG findings at screening PR interval: >200 msec; QRS duration ≥120 msec; QTcF >430 msec (males); QTcF >450 msec (females)
    - History of or current significant cardiac disease including cardiac failure (NYHA functional class II-IV), myocarditis, cardiomyopathy, angina pectoris or myocardial infarction (within 6 months), unstable angina (within 6 months), stroke (within 6 months), TIA (within 6 months), decompensated heart failure requiring hospitalization (within 6 months) or uncontrolled arterial hypertension
    - History of (within the 6 months) or current cardiac disease such as heart failure NYHA class I, history of myocardial infarction prior to enrollment.
    - Patients receiving treatment with beta-blockers for cardiac disease/comorbidities
    - Any other condition which, in the opinion of the investigator, has a potential for AV conduction suppression and/or other risk factors that may require expanded cardiac monitoring
    - Patients diagnosed with right bundle branch block, either at the Screening visit for entry of the study or during the conduct of the study
15. Any of the following pulmonary conditions:
    - History of or active severe respiratory disease, including COPD, or pulmonary fibrosis,
    - Tuberculosis, except for history of successfully treated tuberculosis or a history of prophylactic treatment after positive PPD skin reaction

- Patient with severe asthma or asthma requiring regular treatment with oral steroids

16. Patients with any of the following hepatic conditions prior to screening:
    - history of alcohol abuse, chronic liver or biliary disease
    - total or conjugated bilirubin greater than 1.5 times ULN range, unless in the context of Gilbert's syndrome
    - alkaline phosphatase (AP) greater than 1.5 times the ULN range
    - AST (SCOT), ALT (SGPT) or Gamma-glutamyl-transferase (GGT) greater than 3 times the ULN range within the last 6 months
17. Any of the following abnormal laboratory values prior to screening:
    - Serum creatinine > 1.7 mg/dL (150 umol/L)
    - White blood cells (WBC) count <3,500/mm3 (<3.5 x 10(9)/L), while on oral DMT's at screening, except fingolimod
    - Lymphocyte count <500/mm3 (<0.5 x 10(9)/L) while on all DMT's at screening except fingolimod
    - Serum potassium > ULN
    - Or other clinically significant laboratory assessment (i.e. hypomagnesemia or hypokalemia)
    - For patients previously exposed to natalizumab, anti-JCV antibody positive and index ≥ 1.5
18. Patients with the following neurological/psychiatric disorders prior to screening:
    - History of substance abuse (drug or alcohol) or any other factor (i.e. serious psychiatric condition) that may interfere with the patient's ability to cooperate and comply with the study protocol
    - Progressive neurological disorder, other than MS, which may affect participation in the study or require the use of medications not allowed by the protocol
19. Use of other investigational drugs at the time of enrollment or within prior 30 days; or five elimination half-lives, or until the expected pharmacodynamics effect has returned to baseline, whichever is longer.
20. History of hypersensitivity to the study drug or to drugs of similar chemical classes.
21. Homozygosity for CYP2C9*3/*3 or heterozygous for CYP2C9*2/*3 or CYP2C9*1/*3 (to be tested at screening) or refusal to test for CYP2C9 variants.
22. Concomitant use of MAYZENT and drugs that cause moderate CYP2C9 and moderate or strong CYP3A4 inhibition (Appendix 4).
23. Concomitant use of MAYZENT and drugs that cause moderate CYP2C9 and strong CYP3A4 induction (Appendix 4).
24. Use of cannabinoid or cannabidiol products 30 days prior to screening.
25. Any other disease or condition, which could interfere with participation in the study according to the study protocol, or with the ability of the patients to cooperate and comply with the study procedures.

Note 1: If a patient fails on one or more laboratory (or other) assessment criteria, as part of the screening process, the assessment (s) may be repeated at the discretion of the investigator and the patient may be included if criteria are then met, provided the assessments are completed within the screening period.

Note 2: In certain cases rescreening of patients that were previously determined ineligible may be permitted. When a patient is re-screened, a new patient identification number will be assigned and all screening assessments must be repeated. Each patient may be rescreened no more than 1 time.

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

Chemical Name: Siponimod

Other Names: BAF312, Mayzent ®

Classification: Oral sphingosine 1-phosphate receptor modulator

The investigational drug siponimod will be provided as film coated tablets. Please refer to the pharmacy manual provided for specific instructions.

The study medication will be administered orally, once daily, with or without food.

Should titrated patient miss one day of titration or more, the patient will need to restart the titration with Day 1 dosing (0.25mg), including Day 1 cardiac assessments (pre-dose ECG and 6-hour post dose heart rate). It is strongly recommended, during the titration phase, that a member of the study staff contact the patient, once daily via phone, to remind them to take their study medication as required. This is because restarting the titration will require the patient to come in for an unscheduled visit to do a pre-dose ECG assessment and 6 hour post-dose heart rate (holter telemetry monitoring).

Furthermore, if maintenance treatment (2mg) is interrupted for 4 or more consecutive daily doses, treatment must be re-initiated with the 5-day titration, including pre-dose ECG and 6-hour post-dose heart rate (holter telemetry monitoring) at an unscheduled visit. Treatment interruptions for up to 3 missed consecutive daily doses does not require re-titration, and treatment should be continued at the maintenance dose level.

If the patient has missed greater than 30 consecutive days of treatment, using his/her best medical judgement, the PI should consider terminating the patient from the study.

Table 6-1 Core Treatment Period

Treatment arm	# of patient's	Type of study drug	Compound	Min. Dose	Max. Dose	Frequency	Formulation	Admin Route	Generic acceptable
Arm 1	300 - 400	Investigational	Siponimod	0.25 mg	2 mg	Daily	Tablet	Oral	No

6.1.2 Additional study treatments

No other treatment beyond investigational drug and control drug are included in this trial.

6.1.3 Treatment arms/group

All patients, except those converting from fingolimod, will be assigned at visit 1 (Day 1) to the following single-treatment arm: Siponimod 0.25mg (initial dose). Following initial dose, the titration schedule will be as follows: Day 2 (0.25mg), Day 3 (0.5mg), Day 4 (0.75mg), Day 5 (1.25mg) and Day 6 and for the rest of the study (2.0mg) as shown in Table 6-3.

6.1.4 Treatment duration

The planned duration of the core treatment period is 6 months. Patients may discontinue from treatment earlier due to unacceptable toxicity, disease progression and/or at the discretion of the investigator or Novartis. For patients who in the opinion of the investigator are still deriving clinical benefit from siponimod, every effort will be made to continue study treatment.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the patient enrolls into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient enrolls into the study must be recorded on the appropriate Electronic Case Report Forms (eCRF). Each concomitant drug must be assessed against all exclusion criteria/prohibited medications. If in doubt, the investigator should contact the Novartis medical monitor before randomizing a patient or allowing a new medication to be started. If the patient is already enrolled, contact Novartis to determine if the patient should continue participation in the study.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the patient enrolls into the study.

Since heart rate is an important variable affecting the QT interval, starting medications affecting QT-prolongation (e.g. beta-blockers), during siponimod treatment initiation (e.g., the first 10 days) should be avoided whenever possible. Beta-blocker treatment for non-cardiac treatment purposes can be introduced in patients who are receiving a maintenance dose of study treatment.

Experience with siponimod is limited in patients receiving concurrent therapy with heart-rate lowering calcium channel blockers (such as verapamil or diltiazem), or other medications that may decrease heart rate (e.g., ivabradine or digoxin). Concomitant use of these medications during siponimod initiation may be associated with severe bradycardia and heart block; because

of these potential effects on heart rate, siponimod should not be initiated in patients who are concurrently treated with these medications.

6.2.2 Prohibited medication

Use of the medications displayed in Table 6-2 is NOT allowed throughout the study duration due to increased risk of immunosuppression with siponimod (CYP2C9 is the major metabolizing enzyme for siponimod).

If one of these prohibited medications is taken during the treatment period, the prohibited medication must be stopped immediately. Additional action may be required per the direction of the Novartis.

Table 6-2 Prohibited medication

Medication	Prohibition period	Action taken
Immunosuppressive/chemotherapeutic medications or procedures, including cyclosporine, azathioprine, methotrexate, cyclophosphamide, mitoxantrone, lymphoid irradiation and hematopoietic stem cell transplantation	duration of study	Discontinue or Interrupt study treatment, increase vigilance regarding infections. NOTE: Restarting study treatment in patients exposed to these medications must first be discussed with the Novartis Medical Advisor.
Monoclonal antibodies targeting the immune system, including, rituximab, ofatumumab, and alemtuzumab, ublitixumab	duration of study	Discontinue study treatment, increase vigilance regarding infections.
Any concomitant medication which inhibits cardiac conduction, e.g. verapamil-type and diltiazem-type calcium channel blockers or cardiac glycosides	duration of study	Discontinue study treatment
Potent inducers of CYP2C9 (Appendix 4)	duration of study	Discontinue study treatment

6.3 Treating the patient

6.3.1 Patient numbering

Each patient is identified in the study by a Patient Number (Patient No.), that is assigned when the patient consents and enters the screening period in the study; the number is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Patient Number consists of the Center Number, (as assigned by Novartis to the study site), with a sequential patient number suffixed to the Center Number. This provides each patient with a unique number across the entire database. Once assigned to a patient, the Patient Number will not be reused.

Upon signing the informed consent form, the patient is assigned the next sequential number by the investigator. The investigator or his/her staff will contact the IRT and provide the assigned patient study identification number along with the requested identifying information of the patient to register them into the IRT. The site will enter this number on the electronic case report form (eCRF) in the electronic data capture system (EDC).

If the patient fails to be assigned to treatment for any reason, the IRT must be notified within 2 days that the patient was not assigned to treatment. The reason for not being assigned to treatment will be entered on the Screening Phase Disposition eCRF.

6.3.2 Treatment assignment

Patients will receive siponimod on Day 1 (Visit 1). The initial dose given to all patients, except fingolimod strata, will be 0.25 mg. The initial siponimod dose given to patients converting from fingolimod will be given 2 mg. Fingolimod patients will receive an additional telephone call, from site staff, at the end of Day 1 as part of additional safety measures.

6.4 Treatment blinding

This is an open label study.

6.5 Dose escalation and dose modification

Siponimod dose adjustments are not permitted. Any dose interruptions due to adverse events should be documented in the eCRF and dose administration record.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the patient/caregiver. This information should be captured in the source document at each visit. Patient compliance should be at 100% during the titration period. During the maintenance treatment period, patient compliance should be at 80% minimum. The investigator and/or study personnel will counsel the patient if compliance is below 80%. Study drug accountability will also be determined by the site monitor while performing routine site visits and at the completion of the study.

Duration of the study titration and maintenance study drug exposure will be calculated based upon the start and stop dates recorded in the Dosage Administration Record eCRF.

6.6.2 Emergency breaking of assigned treatment code

Not applicable- Open label

6.7 Preparation and dispensation

Each study site will be supplied with siponimod as described in the pharmacy manual.

Siponimod will be administered to the patient orally.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

The designated personnel at the study site must receive investigational treatments, safely handled and properly stored, and kept in a secured location, where only the investigator and designees have access.

Upon receipt, all investigational treatment should be stored according to the instructions specified on the labels.

Clinical supplies are dispensed only in accordance with the protocol.

Medication labels will comply with the legal requirements of the USA. They will include storage conditions for the investigational treatment and medication number but not information on the patient.

The investigator must maintain an accurate record of the shipment and dispensing of investigational treatment in a drug accountability log. Monitoring of drug accountability will be performed by the field monitor during site visits and at the completion of the trial. Patients will be asked to return all unused investigational treatment and packaging at the end the treatment period of the study or at the time of discontinuation of investigational treatment. At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused investigational treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.7.1.2 Handling of additional treatment

No additional treatment is provided as part of the study

6.7.2 Instruction for prescribing and taking study treatment

During the treatment period, siponimod tablets should be taken once daily, preferably at the same time each day. It is advisable to take the study medication with or without food in the morning, normally before 12 noon.

At the start of the core treatment period, for all patients except those converting from fingolimod, siponimod is initially titrated from 0.25mg/day on day 1 to up to 2mg/day on day 6. For fingolimod patients, the titration regimen will be omitted and started directly on 2 mg maintenance dose. Please refer to the pharmacy manual for specific instructions.

Table 6-3 Dose and treatment schedule

Treatment Schedule for All Pre-treatment groups except Fingolimod:	
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: Maintenance Dose Only	
Day of Treatment	**Target Dose**
1 and beyond	2 mg

All kits of study treatment assigned by the IRT will be recorded in the IRT system.

The first siponimod dose in the core treatment period should be taken while the patient is at the study site. All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

The investigator should promote compliance by instructing the patient to take the study treatment exactly as prescribed and stating compliance is necessary for the patient's safety and validity of the study. The patient should be instructed to contact the investigator if he/she is unable for any reason to take the study medications.

In situations (i.e.: COVID-19 pandemic) that limit or prevent on-site study visits, delivery of IMP directly to a participant's home is generally permitted in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. Implementation will need to be discussed with Novartis. The dispatch of IMP from the site to the participant's home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 6-months supply. In this case, regular phone calls or virtual contacts should occur between the site and the participant for instructional purposes, safety monitoring, and discussion of the participant´s health status until the participants can again visit the site as applicable.

7 Informed consent procedures

Eligible patients may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If applicable, in cases where the patient's representative(s) gives consent (if allowed according to local requirements), the patient must be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB) *(and/or CDS for marketed drugs)*. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the patient.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

Male patients must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

Patients might be asked to complete an optional questionnaire to provide feedback on their clinical trial experience. This information is provided in the consent form and explains that the data will be kept anonymized, and will be used to understand where improvement can be made in the clinical trial process. This questionnaire would not ask about the patient’s disease or symptoms and therefore will not be considered to be trial data.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local Health Authority.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

8 Visit schedule and assessments

Assessment schedule Table 8-1 lists all of the assessments and when they are performed. All data obtained from these assessments must be supported in the patient’s source documentation.

Disease Modifying Therapy Washout Regimen

Pre-treatment strata drug name	Washout Interval Guidance
Interferon-beta/glatiramer acetate	None; immediate conversion to dose-titrated siponimod
Fumarates (dimethyl fumarate, diroximel fumarate)	None; immediate conversion to dose-titrated siponimod
Teriflunomide	11-14 day accelerated elimination protocol (Appendix 6) prior to starting dose-titrated siponimod
Fingolimod	None; immediate conversion to siponimod maintenance dose 2mg
Natalizumab	Last natalizumab dose at least 4 weeks prior to screening
Ocrelizumab	Last ocrelizumab dose at least 14 weeks prior to screening

No washout is required for patients converting from interferon-beta or fumarates (dimethyl fumarate, diroximel fumarate) prior to starting dose-titrated siponimod.

An accelerated elimination (Appendix 6) interval will be required for patients taking teriflunomide before the patient can start treatment with siponimod. At least 2 weeks with successful accelerated teriflunomide elimination procedure as described in the product label should be conducted for these patients. If accelerated elimination is not possible, the patient cannot participate in the study.

No washout period or titration regimen is required for patients converting from fingolimod to siponimod and CYP2C9 *1/*1, *1/*2, or *2/*2 genotyped patients will start directly on 2mg maintenance dose upon entering the treatment period.

At least a 4 week interval will be required for patients converting from natalizumab.

At least a 14 week interval will be required for patients converting from ocrelizumab.

- On Visit 1 (Day 1, baseline), patients who met eligibility criteria will have pre-dose body temperature, respiration rate, blood pressure, ECG and heart rate assessed prior to initial dose of siponimod. 6 hours after the initial dose of siponimod, heart rate will be measured again. The study site personnel will instruct the patient on how to obtain the 6-hour post dose heart rate. Pre-dose ECG may be obtained via vendor-supplied ECG vest and pre-dose HR may be obtained either manually (see below for guidance) or via ECG. Post-dose HR may be obtained via vendor-supplied HR monitoring device.
- During all other study visits, outside of Day 1 (screening, V2, V3, V4 and V5) a qualified study personnel, as determined by the PI, will assess the patient's heart rate.
- Patients will then follow the normal visit schedule in the treatment period and should complete all of the relevant assessments as indicated in Table 8-1.

Patients should have all visits/assessments as outlined in the Assessment schedule Table 8-1 or as close to the designated day/time as possible with an allowed visit window of +3 days for visit 1 (BSL), an allowed visit window of ± 5 days for visits 2, 3, 4, 5 and an allowed ±7 days for the 30-day telephone follow-up. Missed or rescheduled visits should not lead to automatic discontinuation.

Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the eCRF.

End of Treatment/Study (EOT/S) Visit Schedule

For patients who complete the core treatment period of the study, the end of treatment/study visit should be conducted. No study drug should be taken on the day of EOT/S.

For patients who discontinue study medication prematurely in the core treatment period, the end of treatment/study visit should be conducted when they stop taking study medication.

A follow-up telephone call, 30 days after the end of treatment/study visit, will be conducted for all patients who randomize.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowable by a local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) or visits by site staff/ home nursing staff to the participant´s home, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

Table 8-1 Assessment Schedule

Period	Screening		Treatment			End of Treatment/Study	Follow-up	Unplanned
Visit	Screening	Baseline[1]	Titration | Treatment Period			End of Treatment/Study	Safety	Unscheduled Visit
Visit Name	Screening Visit	V1	V2[12]	V3	V4	Exit/V5		UPV
Visit Number	1	110	120	130	140	1999		UPV
Days	-28 days	1 (+3 days)	7 (±1 day)	28 (±5 days)	84 (±5 days)	168 (±5 days)	30- Day Telephone (±7 days)	
Obtain informed consent	X							
MS History	X							
Demography	X							
Inclusion/Exclusion criteria	X	X						
Relevant Medical History	X							
[redacted]								
Physical Exam	S	S		S	S	S		S
[redacted]								
Neurological Exam[8]	X	X			X	X		X
Height	X					X		

[redacted]

Period	Screening		Treatment			End of Treatment/Study	Follow-up	Unplanned
Visit	Screening	Baseline[1]	Titration | Treatment Period			End of Treatment/Study	Safety	Unscheduled Visit
Visit Name	Screening Visit	V1	V2[12]	V3	V4	Exit/V5		UPV
Visit Number	1	110	120	130	140	1999		UPV
Days	-28 days	1 (+3 days)	7 (±1 day)	28 (±5 days)	84 (±5 days)	168 (±5 days)	30- Day Telephone (±7 days)	
Weight	X	X			X	X		
Body Temperature	X	X		X	X	X		X
Respiration Rate	X	X		X	X	X		X
Blood Pressure	X	X		X	X	X		X
Heart Rate	X	X[2]		X	X	X		X
Heart Rate 6 hours post Day 1 dose[2]		X						
Optical Coherence Tomography (OCT)[6]		X[6]			X			
CYP2C9 Haplotype	X							
Blood Chemistry/ Hematology	X	X		X	X	X		X
Coagulation and Thyroid	X	X		X	X	X		X
Hepatitis markers	X							
[redacted]								
CD19+ B-cell titer[10]	X							

[redacted]

Period	Screening		Treatment			End of Treatment/Study	Follow-up	Unplanned
Visit	Screening	Baseline[1]	Titration | Treatment Period			End of Treatment/Study	Safety	Unscheduled Visit
Visit Name	Screening Visit	V1	V2[12]	V3	V4	Exit/V5		UPV
Visit Number	1	110	120	130	140	1999		UPV
Days	-28 days	1 (+3 days)	7 (±1 day)	28 (±5 days)	84 (±5 days)	168 (±5 days)	30- Day Telephone (±7 days)	
VZV IgG Testing	X							
ECG (12 Lead)	X	X[7]						
Pregnancy Test serum	S	S				S		
Pregnancy Test Urine				S	S			
AE/ SAE Assessment	X	X		X	X	X	X	X
Prior/Concomitant Medications	X	X		X	X	X	X[5]	X
EDSS	X							
TSQM-9		X		X	X	X		
[redacted]								
C-SSRS		X				X		
Optional Trial Feedback Questionnaire[4]		S			S	S		
Dispensation of medication[11]		S		S	S			

[redacted]

Period	Screening		Treatment			End of Treatment/Study	Follow-up	Unplanned
Visit	Screening	Baseline[1]	Titration | Treatment Period			End of Treatment/Study	Safety	Unscheduled Visit
Visit Name	Screening Visit	V1	V2[12]	V3	V4	Exit/V5		UPV
Visit Number	1	110	120	130	140	1999		UPV
Days	-28 days	1 (+3 days)	7 (±1 day)	28 (±5 days)	84 (±5 days)	168 (±5 days)	30- Day Telephone (±7 days)	
Drug accountability		S		S	S	S		
Dosage Administration Record		X		X	X	X		
Washout[3]		S						
IRT Call	S	S		S	S	S		

X = assessment to be recorded in the clinical database or received electronically from a vendor
S = assessment to be recorded in the source documentation only

1. All baseline assessment are to be performed prior to siponimod dosing
2. Take another heart rate measure 6 hours post Day 1 dose (a Novartis-supplied portable heart rate monitor patch)
3. Patients currently taking or having taken teriflunomide in past 8 months will require a washout per label instructions prior to the baseline.
4. Patients may opt in or opt out of completing this questionnaire (optional).
5. Only SAEs and SAE related medications are to be collected.
6. OCT can be done 5 days prior to treatment or on Day 1 prior to treatment refer to Appendix 8.
7. ECG to be performed pre-dose on Day 1 (baseline) however, if the ECG assessment meets criteria in the protocol section 8.4.2., dosing cannot be initiated.
8. Neurological Exam refer to the protocol section 8.4 Table 8-2 for more details.
9. [redacted]
10. CD19+ titers only for patients previously exposed to ocrelizumab DMT.
11. Fingolimod patients will receive an additional telephone call from site staff at the end of BSL (Day 1) as part of additional safety measures.
12. There is no longer an ECG at Day 7 (visit 2). Therefore, visit 2 has been grayed-out and no longer applicable.

[redacted]

8.1 Screening

Screening Period: The duration of the screening period will be approximately 28 days from time of signed informed consent (ICF) to determine patients' eligibility for the study based on the inclusion/exclusion criteria and assessments listed below. Patients deemed eligible will enter the core treatment period at the Baseline visit. While all screening assessments for the patients enrolled at the traditional sites are expected to be conducted on-site, the option for home health nursing may be utilized to replace on-site study visits for the remainder of the trial.

The screening period will include the following assessments (approximately -28 Days):

- Obtain: signed ICF; patient history; demography; relevant medical history and current medical history; prior and concomitant medications
- Assess: EDSS, physical exam; if the patient is having a MS relapse; neurological exam; height; weight; body temperature; respiration rate; blood pressure; heart rate (taken at the clinic by a qualified study staff as determined by the PI); lab assessments (blood chemistry; pregnancy; [redacted] CYP2C9 haplotype); ECG (12-lead); CD19+ titer only for patients converting from ocrelizumab.
- Heart rate may be captured via ECG or manual reading. Should the heart rate need to be manually measured by a qualified study staff as determined by the PI, sitting heart rate should be taken three times after the patient has been sitting for five minutes with their back supported and both feet placed on the floor. Repeated sitting measurements should be made at 1-2 minute intervals. The average of the 3 heart rates assessed will be noted in the eCRF.
- Patients fulfilling the eligibility criteria may be enrolled into the study

Rescreening: Rescreening may be allowed under certain conditions. Each patient may be rescreened no more than once. Request from the investigator/site staff to rescreen patients will be handled on a case-by-case basis with Clinical Trial Lead approval required before proceeding with the rescreening. Rescreening cannot be done if a patient was previously enrolled in the study.

If a patient rescreens for the study, the patient must sign a new informed consent (ICF) and be issued a new patient number prior to any screening assessments being conducted under the new patient number. The date of the new informed consent signature must be entered on the Informed Consent eCRF to correspond to the new patient number.

8.1.1 Information to be collected on screening failures

All patients who have signed informed consent but not entered into the next period will have the study completion page for the screening period, demographics, inclusion/exclusion, and serious adverse event (SAE) data collected. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data. For all patients who have signed informed consent and are entered into the treatment period of the study will have all adverse events occurring after informed consent is signed recorded on the Adverse Event eCRF.

8.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data are to be collected on all patients include age, sex, race, and ethnicity. Relevant medical history/current medical condition data includes data until the start of study. Physical examination, vital signs, laboratory sampling, pregnancy testing, ECG, weight, and previous MS treatment, EDSS, [redacted] will be recorded on eCRF. Where possible, diagnoses and not symptoms, will be recorded. MS medications will be recorded on eCRFs designed to facilitate separation from non-MS medications. The last RMS DMT administered right before converting to siponimod will be recorded. Likewise, detailed MS history and other relevant medical history will be recorded on eCRFs separately from relevant non MS medical. In order to collect accurate information about study drug exposure, records of study medication dispensed and returned, doses administered and visit dates should be maintained for each patient and transcribed into the Dosage Administration record eCRF. Compliance will be assessed by the investigator and/or study personnel at each visit. The study monitor will perform and document drug accountability during site visits and at the end of the study.

8.3 Efficacy/Pharmacodynamics

Pharmacodynamics assessments are not measured in this study.

[redacted]

8.4 Safety/Tolerability

Safety assessments and tolerability will be assessed by collecting adverse events (AEs) and serious adverse events (SAEs) at all visits during the treatment period.

For details on AE collection and reporting, refer to AE section.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

Table 8-3 Physical Assessments

Assessment	Specification
Physical examination	Physical examination will be performed by a qualified licensed RN, PA or NP (MD/PI must be present) or neurologist (MD) at site clinic (traditional sites) or by a licensed RN for sites participating virtually (virtual sites) at the visits indicated in the treatment period assessment schedule and will include an assessment of skin, head, neck, lymph nodes, heart, lungs, abdomen, back, neurological function and comments on general appearance. All significant findings that are present prior to signing informed consent must be reported on the relevant medical history/current medical conditions eCRF. Significant findings made after singing the informed consent and being randomized meets the definition of an AE and must be recorded on the adverse events eCRF.
Neurological Exam	A concise neurological examination will be performed by a qualified licensed RN, PA or NP (MD/PI must be present) or neurologist (MD) at site clinic (traditional sites) or by a licensed RN for sites participating virtually (virtual sites) at the visits indicated in the treatment period assessment schedule and will include clinical history combined with a concise evaluation of the mental status, cranial nerves, coordination, sensory, motor and/or gait. In the event of a suspected relapse or exacerbation, a comprehensive neurological exam may be needed, at the discretion of the physician, to thoroughly evaluate cranial nerve II-XII, reflexes, strength, sensory and motor function and gait
Height and Weight	Height, in centimeters (cm) if possible, will be measured at screening visit and end of treatment/study visit. Body weight, to the nearest 0.1 kilogram (kg), in indoor clothing, but without shoes, will be measured at every visit except Visits 2.
Vital Signs	Vital signs will be assessed at every visit. This will include blood pressure and heart rate measurements. BP will be medium sized cuff and the noon-dominant arm in the sitting position after 5 minutes of rest. Every effort should be made to use the same arm for the patient for all vital signs assessments and where possible, the same person doing the assessment. Clinically notable vital signs are defined in Appendix 1.

8.4.1 Laboratory evaluations

Table 8-4 Laboratory Assessments

Test Category	Test Name
Hematology	Red blood cells, total White blood cells, Differential White blood cells (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, platelet count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration and red blood cell morphology
Chemistry	Alkaline phosphatase, ALT , AST , Gamma-glutamyl-transferase (GGT), Bicarbonate, Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Creatine kinase, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Glucose, amylase
Coagulation	Prothrombin time (PT) , Partial thromboplastin time (PTT)
Thyroid	T3 (free), T4 (free), TSH
Hepatitis markers	HBV-DNA, HbsAg, HbsAb, HbcAb, HCV RNA-PCR (baseline)
Additional tests	Serology: anti-hepatitis A virus IgM, hepatitis B surface antigen and anti-hepatitis B core antigen IgM, anti-hepatitis C virus IgG or IgM, anti-hepatitis E virus IgM (positive IgM and/or IgM: do HEV-RNA PCR; if negative, patient can be included), Anti-VZV IgG, CYP2C9 haplotype testing [redacted]

Test Category	Test Name
	CD19+ Titers
Pregnancy Test	Serum / Urine pregnancy test

Clinical Chemistry

Blood samples will be collected at the scheduled visits indicated in Table 8-1, and the parameters assessed 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.

Hematology

Blood samples will be collected at the scheduled visits indicated in Table 8-1, and the parameters assessed 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.

These will be measured at each visit by the central laboratory and will be communicated to the site in case of a notable abnormality which could result to a dose change.

Serology

Serology testing will be conducted at screening only in order to determine the patient's immune status and eligibility for inclusion in the study with respect to a number of viruses;

A positive result for HIV antibodies or for any of the following serological markers for hepatitis A, B, C, and E indicating acute or chronic infection is an exclusion criterion:

- anti-hepatitis A virus IgM
- hepatitis B surface antigen and anti-hepatitis B core antigen IgM
- anti-hepatitis C virus IgG or IgM
- anti-hepatitis E virus IgM (positive IgG and/or IgM: do HEV-RNA PCR: if negative, patient can be included).

NOTE: If the treating physician suspects false positive Hepatitis serology results, such as an antibody pattern indicating acute Hepatitis infection but no corresponding elevated liver enzymes and no signs or symptoms HEV-RNA PCR will be performed and will be the deciding factor to determine whether the patient has hepatitis A, B, C, or E. If negative, the treating physician may document (in source data and in a eCRF comment) that the serology results are considered false positive and consider including the patient in the study.

Anti-VZV IgG will be measured. Patients who are negative for varicella-zoster virus IgG antibodies at screening but may be re-screened after successful vaccination.

[redacted]

[redacted]

CYP2C9 Testing

CYP2C9 haplotype testing will be conducted once at the screening visit to determine the patient's eligibility to enter into the study.

[redacted]

[redacted]

8.4.2 Electrocardiogram (ECG)

Twelve-lead ECGs will be performed for all patients at Screening, Baseline (Day 1; Pre-dose). Clinically significant abnormalities should be recorded on the Medical History/Adverse event eCRF page.

If the Day 1 (pre-dose) 12- lead ECG assessment meets any of the following criteria, then dosing cannot be initiated.

The criterion are:

1. Heart rate < 55 bpm
2. Cardiac conduction disorders such as incomplete left bundle branch block or second degree AV block Mobitz type I (Mobitz I) (either history or observed at screening)
3. Minor ECG findings: PR interval >200 msec; QRS duration ≥120 msec; QTcF >430 msec (males); QTcF >450 msec (females)
4. Any other condition which, in the opinion of the investigator, has a potential for AV conduction suppression
5. Patients diagnosed with right bundle branch block

If none are met, then the patient can continue with treatment.

Additionally, on baseline Visit 1 (Day 1), heart rate will be monitored and measured for 6 hours on a holter telemetry device post initial dose of siponimod. If post-dose HR remains < 45 bpm at the end of 6-hour post-dose monitoring period, additional monitoring may be required (see Appendix 7).

8.4.3 Optical Coherence Tomography (OCT)

OCT is routinely utilized to assess changes or damages to the retina in a variety of diseases such as glaucoma, age-related macular degeneration or macular edema. To monitor changes in the patients retinal thickness, OCT assessment, measurement if retinal thickness, will be performed on Visit 1 (Day 1: prior to treatment; can be done 5 days prior to treatment or on Day 1 prior to treatment) and on Visit 4 (Day 84). The OCT machine used should preferably not be changed

during the duration of the study. The OCT can be performed by referring ophthalmologist or neurologists with clinical training and expertise to assess structural measurement of retinal nerve fiber layer thickness, optic nerve head, and macular anatomy AND currently possess appropriate OCT equipment in-office.

Please see Appendix 8 (Guidelines for Ophthalmic Examination and Management of Macular Edema) for further details and instructions.

8.4.4 Pregnancy and assessments of infertility

Serum pregnancy tests will be conducted for all women who are of child bearing potential at the screening, baseline, EOT/S visits of the treatment period.

Urinary pregnancy tests will be conducted for all women of childbearing potential at all other scheduled clinic visits as indicated in the schedule of assessments.

Relevant participants can perform the urine pregnancy test at home and report the result to the site. It is important that participants are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A communication process should be established with the participant so that the Site is informed of the pregnancy test results.

Assessments of Fertility

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child bearing potential must also be available as source documentation in the following cases:

1. surgical bilateral oophorectomy without a hysterectomy
2. reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, FSH testing is required of any female patient, regardless of reported reproductive/menopausal status at screening/baseline.

8.4.5 Other safety evaluations

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Treatment Satisfaction

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 (Atkinson et al 2004.)

Other assessments

MS is associated with a variable combination of symptoms, including sensory loss, imbalance, mobility loss, bladder and bowel dysfunction, cognitive dysfunction, spasticity, pain, and sexual dysfunction. Measurement of these wide-ranging effects of MS on the lives of patients is beyond the scope of clinician-reported endpoints commonly used to evaluate therapeutic effectiveness in MS studies. Patient-reported outcome (PRO) measures provide an empirical assessment from the patient's perspective of the benefits of treatment that cannot be gained from Magnetic Resonance Imaging (MRI), Expanded Disability Status Score (EDSS), or relapse measurement. The use of the C-SSRS (or equivalent) to detect suicidal ideation or behavior is currently mandated in studies of CNS active drugs.

Appropriateness of safety measurements

The safety assessments in this study are standard for S1P modulator treatment in this indication and patient population.

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

Patient reported outcomes (PRO)

The following PROs will be assessed in this study. These questionnaires will be administered to patients per scheduled visits listed in the schedule of assessments.

- Treatment Satisfaction Questionnaire for Medical (TSQM-9)

[redacted]

[redacted]

While all screening assessments are expected to be conducted on-site, the option for home health nursing may be utilized to replace on-site study visits for the remainder of the trial. In this case, home health nurses will provide technology to complete COAs.

Trial Feedback

At Visit 1 (baseline), Visit 4 (Day 84), and Visit 5 (Day 168/EOT/S), patients might be asked to complete an optional anonymized questionnaire, "Trial Feedback Questionnaire" to provide feedback on their clinical trial experience. Responses would be used to understand where improvements can be made in the clinical trial process. This questionnaire is not meant to collect data about the patient's disease, symptoms or adverse events and therefore would not be considered to be trial data. Should any spontaneous information be collected about AEs, it would be transferred to the safety database. Patients may opt in or opt out of completing this questionnaire. The data will be used to help understand and conduct clinical trials better in the future.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, COA data may be collected remotely.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.5.3 Other Assessments

No additional assessments/tests will be performed on patients entered into this study.

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Study treatment can be interrupted or discontinued based on investigator's judgement and overall clinical assessment, including in the following cases:

- Adverse event or serious adverse event (e.g., Serious infections, Symptomatic bradyarrhythmia)
- Abnormal laboratory value(s) including liver function tests
- Use of prohibited medications.

All dose changes must be recorded on the Dosage Administration Record eCRF.

Patients may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits or become lost to follow up for any other reason. If premature withdrawal occurs for any reason, the investigator must make every effort to determine the primary reason for a patient's premature withdrawal from the study and record this information on the corresponding patient's disposition eCRF page.

Study treatment should be discontinued under the following circumstances:

- Withdrawal of informed consent
- Pregnancy
- Protocol violation that results in a significant risk to the patient's safety
- Non-compliance with study treatment
- Lost to follow up
- Emergence of certain adverse events, such as malignancy (except successfully treated basal cell carcinoma), liver failure or, serious chronic infections (such as HIV).

Note 1: For a patient with a positive urine pregnancy test, study medication must be immediately discontinued and a serum pregnancy test conducted. If the serum test is negative, the patient may restart study medication; if siponimod treatment has been interrupted for 4 or more consecutive daily doses, treatment must be re-initiated with the 5-day titration pack. If the serum test is positive, the patient can either be discontinued from the study or remain in the study continuing all scheduled visits, as above. Restart of study medication after the pregnancy (and lactation) will be considered on a case by- case basis, as above. Women who need another disease modifying treatment during pregnancy will be withdrawn from the study.

The investigator must also contact the IRT to register any patient discontinuations from study treatment.

9.1.2 Withdrawal of informed consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent (WoC) occurs only when a patient does not want to participate in the study anymore; does not want any further visits or assessments and does not want any further study related contact.

At the time a patient withdraws consent, the investigator should make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information on the Study Completion eCRF. Study drug must be discontinued and no further assessments conducted. All biological material that has not been analyzed at the time of withdrawal must not be used. Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation.

9.1.3 Lost to follow-up

Study treatment should be discontinued if patient is lost to follow-up. For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient will not be formally considered lost to follow-up until all efforts to contact the patient have been exhausted.

9.1.4 Early study termination by sponsor

The study can be terminated at any time for any reason by Novartis. This may include reasons related to the benefit/risk assessment of participating in the study or for regulatory or medical reasons. Should this be necessary, the patient should be seen as soon as possible and treated for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs of the early termination of the trial.

9.2 Study completion and post study treatment

A patient will be considered a core treatment period completer when he/she has completed all treatment period visits, up to the EOT/S visit for the core treatment period and including follow-up visits where required.

The study will be considered completed when all individual patients have either completed or prematurely discontinued from the treatment period of the study. The maximum duration of a patient who completes the treatment Parts of the study could reach approx. 5 years.

The investigator must provide follow-up medical care for all patients who prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

Adverse events must be recorded in the Adverse Events eCRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information:

- mild: usually transient in nature and generally not interfering with normal activities
- moderate: sufficiently discomforting to interfere with normal activities
- severe: prevents normal activities

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- no action taken (e.g. further observation only)
- (investigational) treatment dosage increased/reduced
- (investigational) treatment interrupted/withdrawn
- concomitant medication or non-drug therapy given
- non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged (see Section 10.1.2 for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved; recovered/resolved with sequelae; fatal; or unknown)

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB). This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the medicinal product that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and has then to be discussed with the patient.

The investigator must also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

10.1.2 Serious adverse events

An SAE is defined as any adverse event (appearance of (or worsening of any pre-existing)) undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any study drug deterioration.
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - social reasons and respite care in the absence of any deterioration in the patient's general condition
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant". Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse *(please refer to the ICH-E2D Guidelines).*

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

10.1.3 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days (after the last study visit/ following the last administration of study treatment if there are post-treatment follow-up visits with no required procedures) must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. Any SAEs experienced after the 30 day period (after the last study visit/ following the last administration of study treatment if there are post-treatment follow-up visits with no required procedures) should only be reported to Novartis if the investigator suspects a causal relationship to study treatment

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a CMO & PS Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

The time of 30 days in the standard text above is the recommended minimum and the SAE form should be submitted to Novartis Safety. A longer duration may be appropriate for drugs with particularly long elimination half-lives or from drug classes with known late occurring effects, or when risk assessment/management objectives require prolonged safety monitoring. Please ensure the Informed Consent reflects this 30 day/Post Study Safety Contact.

10.1.4 Pregnancy reporting

To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same

form and should include an assessment of the possible relationship to the *investigational/study treatment.*

Any SAE experienced during pregnancy and unrelated to the pregnancy must be reported on a SAE form.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the, respective sections.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure patient safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Liver events are divided into two categories:

- Liver events of special interest (AESI) which consist of elevations of liver function tests (LFTs)
- Medically significant liver events which are considered as serious adverse events (SAEs) and which consist of marked elevations of LFTs and / or pre-specified adverse events.

Please refer to Appendix 2 for complete definitions of liver events.

Any liver event which meets the criteria for "medically significant" event as outlined should follow the standard procedures for SAE reporting. Every liver event as defined in Table 16-1 of Appendix 2 should be followed up by the investigator or designated personal at the trial site as summarized below:

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug if appropriate
- Hospitalization of the patient if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g., disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution.

These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion. All follow-up information, and the procedures performed should be recorded on appropriate eCRF pages, including the liver event overview eCRF pages.

NOTE: If local requirements for liver safety monitoring are more stringent than those outlined in this section of the protocol, then the local requirements will take precedence

10.2.2 Prospective suicidality assessment

The Columbia-Suicide Severity Rating Scale (C-SSRS) (Posner, 2011) is a questionnaire that prospectively assesses Suicidal Ideation and Suicidal Behavior. The C-SSRS tool is administered via interview with the subject.

The C-SSRS must be administered at the visits indicated in Table 8-1.

If the patient does not attend the End of Treatment/Study Visit, the C-SSRS should be completed if the site has become aware of a potential suicide-related thought or behavior by other communications.

If, at any time after screening the score is "yes" on item 4 or item 5 of the Suicidal Ideation section of the C-SSRS or "yes" on any item of the Suicidal Behavior section, except for the "Non-Suicidal Self-Injurious Behavior (NSSI) item, the patient must be referred to a mental health care professional for further assessment and/or treatment. The decision on whether the study treatment should be discontinued is to be taken by the investigator in consultation with the mental health professional to whom the patient is referred.

In addition, all life-threatening events during the study must be reported as SAEs. For example, if a patient answers "yes" to one of the questions in the Suicidal Behavior section, an SAE must be reported if the event was life-threatening.

All events of "Non-Suicidal Self-Injurious Behavior" (question in the Suicidal Behavior section) that meet the criteria for AEs (e.g. treatment emergent events or change in severity compared to baseline) should be reported as AEs. Patients reporting NSSI behaviors can be referred to a mental health care professional at the discretion of the investigator.

10.2.3 Bradycardia

This is considered an AESI. To ensure patient safety and enhance reliability in determining the bradycardia potential of an investigational drug, a standardized process for identification, monitoring and evaluation of bradycardia events has to be followed. (Please see Appendix 7 for instructions)

Bradycardia is defined as any pre-dose HR less 55 bpm or post-dose HR bpm less than 45.

11 Data Collection and Database management

11.1 Data collection

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on eCRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate

After final database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

11.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Randomization codes and data about all study treatment (s) dispensed to the patient and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system

will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis/ (or designated CRO) representative will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/delegated CRO/CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

11.4 Virtual patient cohort

This study includes a virtual cohort, i.e., the patient will remain in their own home and complete study assessments via an online technology. The patient interacts with study personnel using online communication tools which incorporate telemedicine. This virtual cohort of the study is being done in parallel to, but separate from, other sites that will conduct study visits in the traditional manner, i.e., with all assessments performed at the study center.

The rationale for the virtual cohort is to make the trial accessible to patients who do not live close enough to a traditional participating trial site; and to unburden patients who may have ambulatory challenges and/or who may have family and job responsibilities that would preclude their trial participation at a traditional trial site. Virtual assessments are less time-consuming, can be done independent of patient schedule, and do not require travel to a site.

For patients participating in the virtual cohort of the study, pre-screening is done remotely via a telephone call and informed consent is performed remotely using telemedicine and an electronic consent form. Study drug is shipped directly to the patient's home from a central certified and GCP compliant distribution center. Appropriate controls are used to ensure that the drug is received by the patient. Lab samples and ECG readings are collected from the patient, at the patient's home, by certified healthcare personnel such as a mobile nurse practitioner or phlebotomist. Local lab sample collection centers are also incorporated to collected patient samples locally.

Assessments will only be conducted virtually if they can be done without affecting the wellbeing of the patient during the study and with the same level of scientific integrity as assessments conducted in a physical study center. Some assessments (e.g., EDSS, [redacted]) may require the presence of a trained Registered Nurse, Nurse Practitioner or Physician Assistant in the patient's home. If completed in the patient's home, EDSS will be performed by a Registered Nurse, Nurse Practitioner or Physician Assistant certified (Level C) to perform the test.

While there are parts of study visits that require the virtual trial investigator to participate via telemedicine per protocol (for further detail please reference the Study Virtual Cohort Site Operations Plan), the virtual investigator may participate in any visits or parts thereof via telemedicine.

Data collected from patients participating in the virtual cohort will be collected electronically using purpose-built technology and will be entered into RaveX manually by a virtual study coordinator. The data is monitored remotely by CRAs. A central IRB is used for all investigators participating the virtual study model, if used. AE/SAE (reporting, assessing and follow-ups) will be handled similarly to a traditional model, with the patient contacting study personnel or engaging local care for emergencies.

The virtual patient cohort may terminate new study enrollment at the discretion of the sponsor. In this case, any ongoing patients in this cohort will be followed per protocol through end of study. Virtual study subject in prescreening will be offered alternative participation through our traditional cohort, when subject is amenable

12 Data analysis and statistical methods

The analysis will be conducted on all patient data at the end of the treatment phase of the study.

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

The Safety Set includes all patients who received at least one dose of study treatment.

All analyses will be performed using the Safety Set.

12.2 Patient demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively.

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

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term.

12.3 Treatments

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

The duration of exposure in (days) to study medication will be summarized by means of descriptive statistics.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system.

12.4 Analysis of the primary endpoint(s)

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.

12.4.1 Definition of primary endpoint(s)

The primary endpoint is the occurrence of adverse event suspected to be related to study medication.

12.4.2 Statistical model, hypothesis, 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% 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 pre-treatment.

12.4.3 Handling of missing values/censoring/discontinuations

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

12.4.4 Sensitivity and Supportive analyses

Sensitivity analyses

No sensitivity analyses are planned.

Supportive analyses

No supportive analyses are planned.

12.5 Analysis of secondary endpoints

12.5.1 Safety endpoints

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate listing for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (*treatment-emergent* AEs).

The on-treatment period lasts from the date of first administration of study treatment to 30 days after the date of the last actual administration of any study treatment.

Adverse events

All information obtained on adverse events will be displayed by patient.

The number (and percentage) of patients with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of open-label treatment but increased in severity based on preferred term) will be summarized in the following ways:

- By primary system organ class and preferred term
- By primary system organ class, preferred term and maximum severity
- By Standardized MedDRA Query (SMQ) and preferred term

Separate summaries will be provided for adverse events and other significant adverse events leading to discontinuation.

The number (and proportion) of patients with adverse events of special interest/related to identified and potential risks will be summarized.

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.

In addition, occurrence of hospitalization will be summarized using frequencies and percentages.

[redacted]

Vital signs

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

In addition, change in heart rate from Baseline to 6-hour after first treatment will be summarized.

12-lead ECG

All ECG data will be listed by patient and visit, abnormalities will be flagged. Summary statistics will be provided by visit.

In addition, change in heart rate (and other vitals) from Baseline to 6-hours after first treatment, may be summarized. Please see protocol Section 8.4.2

Clinical laboratory evaluations

All laboratory data will be listed by patient and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by visit/time. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

12.5.2 Patient report outcomes

Change in TSQM-9 from Baseline 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.

[redacted]

[redacted]

12.7 Interim analyses

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.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

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]

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, patient recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (***e.g., defined as last patient last visit***) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.) .

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

14.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for patient safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

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16 Appendices

16.1 Appendix 1: Vital signs

Notable Vital Signs and Body Weight

Vital Sign Variable	Notable Criteria
Pulse (beats/min)	>120 bpm
Or	
< 55 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

16.2 Appendix 2: Liver event definition and follow up requirements

Table 16-1 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	• *3 x ULN < ALT / AST ≤ 5 x ULN* • *1.5 x ULN < TBL ≤ 2 x ULN*
LIVER EVENTS	• *ALT or AST > 5 × ULN* • *ALP > 2 × ULN (in the absence of known bone pathology)* • *TBL > 2 × ULN (in the absence of known Gilbert syndrome)* • *ALT or AST > 3 × ULN and INR > 1.5* • *Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN (mainly conjugated fraction) without notable increase in ALP to > 2 × ULN)* • *Any clinical event of jaundice (or equivalent term)* • *ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia* • *Any adverse event potentially indicative of a liver toxicity**

**These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms TBL: total bilirubin; ULN: upper limit of normal*

Table 16-2 Follow Up Requirements for Liver Events and Laboratory Triggers

Criteria	***Actions required***	***Follow-up monitoring***
Potential Hy's Law case[a]	• *Discontinue the study treatment immediately* • *Hospitalize, if clinically appropriate* • *Establish causality* • *Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate eCRF*	*ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)*
ALT or AST		
> 8 × ULN	• *Discontinue the study treatment immediately* • *Hospitalize if clinically appropriate* • *Establish causality* • *Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate eCRF*	*ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)*
> 3 × ULN and INR > 1.5	• *Discontinue the study treatment immediately* • *Hospitalize, if clinically appropriate* • *Establish causality*	*ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)*

Criteria	*Actions required*	*Follow-up monitoring*
	• *Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate eCRF*	
> 5 to ≤ 8 × ULN	• *Repeat LFT within 48 hours* • *If elevation persists, continue follow-up monitoring* • *If elevation persists for more than 2 weeks, discontinue the study drug* • *Establish causality* • *Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate eCRF*	*ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)*
> 3 × ULN accompanied by symptoms[b]	• *Discontinue the study treatment immediately* • *Hospitalize if clinically appropriate* • *Establish causality* • *Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate eCRF*	*ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)*
> 3 to ≤ 5 × ULN (patient is asymptomatic)	• *Repeat LFT within the next week* • *If elevation is confirmed, initiate close observation of the patient*	*Investigator discretion* *Monitor LFT within 1 to 4 weeks*
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• *Repeat LFT within 48 hours* • *If elevation persists, establish causality* • *Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate eCRF*	*Investigator discretion* *Monitor LFT within 1 to 4 weeks or at next visit*
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	• *Repeat LFT within 48 hours* • *If elevation persists, discontinue the study drug immediately* • *Hospitalize if clinically appropriate* • *Establish causality* • *Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate eCRF*	*ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)* *Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated (indirect) bilirubin)*
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	• *Repeat LFT within the next week* • *If elevation is confirmed, initiate close observation of the patient*	*Investigator discretion* *Monitor LFT within 1 to 4 weeks or at next visit*

Criteria	*Actions required*	*Follow-up monitoring*
Jaundice	• *Discontinue the study treatment immediately* • *Hospitalize the patient* • *Establish causality* • *Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate eCRF*	*ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)*
*Any AE potentially indicative of a liver toxicity**	• *Consider study treatment interruption or discontinuation* • *Hospitalization if clinically appropriate* • *Establish causality* • *Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate eCRF*	*Investigator discretion*

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN
[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

Based on investigator's discretion investigation(s) for contributing factors for the liver event can include: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

16.3 Appendix 3: Specific Renal Alert Criteria and Actions and Event Follow-up

Guidance on monitoring patients with elevated blood pressure: Patients who have at least two out of the three sitting readings of blood pressure (systolic BP ≥ 140 and/or diastolic BP ≥ 90 mmHg) should be followed up in one month by an unscheduled visit if the scheduled visit is not due. Should systolic BP ≥ 140 and/or diastolic BP ≥ 90 mmHg values will be confirmed in two sitting readings out of three in the second visit, the patient should be referred to his primary care physician, an independent internist or to the specialty hypertension clinic for evaluation, diagnosis and treatment of hypertension. A standard referral letter provided by Novartis should explain a reason for referral and the information about the investigational drug (BAF312).

Patients with BP values of >180/110 mmHg on any visit during the study should be immediately referred to evaluation, diagnosis and treatment of hypertension.

The study drug should not be discontinued, unless the physician has a reason to do so.

A newly diagnosed hypertension as well as an aggravation of a preexisting condition must be reported as an AE.

Guidance on monitoring of patients with notable lymphopenia: The absolute total WBC, neutrophil and lymphocyte counts will be measured at each visit by the central laboratory. If

the circulating lymphocyte level drops to <0.2 $x10^9$/L when the patient is receiving the minimum study drug dose allowed in the study protocol, the lymphocyte count should be repeated in one week by the central lab to confirm the reading. If the repeat test confirms the lymphocyte count is below $0.2x10^9$/L or 200 cells/mm^3, the study drug must be interrupted and the lymphocytes count needs to be monitored weekly until the level returns to 0.2 x 10^9/L, then monthly until the level reaches $0.6x10^9$/L values. The patient should be continuously evaluated and monitored for infections.

Re-initiation of the study drug can only be considered once the lymphocyte counts increase above $0.6x10^9$/L.

Guidance on monitoring of patients with symptoms of neurological deterioration inconsistent with MS course: Should a patient develop any unexpected neurological or psychiatric symptom/signs in the opinion of investigator (e.g. cognitive deficit, behavioral changes, cortical visual disturbances or any other neurological cortical symptoms/signs any symptom/sign suggestive of an increase of intracranial pressure) or accelerated neurological deterioration, the investigator should schedule a complete physical and neurological examination as soon as possible before beginning any treatment.

Guidance on monitoring of patients with infections: All infections that develop during the study will be reported as AEs on the respective AE eCRF pages. Treatment and additional evaluations will be performed at discretion of the investigator.

The investigator should remind the patient of the risk of infections and instruct them to promptly report any symptoms of infections to the investigator. The patients must also be reminded to always carry their Patient Information Card (with site contact information and which identifies them as participants in a clinical study with an investigational agent with potential immunosuppressive effects) and to show this to any local healthcare provider they may consult and ask that the Primary Treating Physician be contacted.

In the case of suspected or confirmed serious or atypical infection, BAF312 treatment interruption should be considered. The investigator should inform the Novartis Medical Advisor of any such cases. The elimination half-life of approximately 30 hours allows washout of the compound within a week.

When evaluating a patient with a suspected infection, the most sensitive tests available should be used (i.e. that directly detect the pathogen, as with PCR).

The investigator should consider early treatment with specific antimicrobial therapy on the basis of clinical diagnosis or suspicion thereof (e.g. antiviral treatment for herpes simplex or zoster) in consultation with infectious disease experts, as appropriate. The investigator should inform the Novartis Medical Advisor of any such cases.

Investigators should consider the added immunosuppressive effects of corticosteroid therapy for treatment of MS attack/relapse and increase vigilance regarding infections during such therapy and in the weeks following administration.

16.4 Appendix 4: List of generic names of potent inhibitors/inducers of CYP2C9/CYP3A4

The aim of this document is to provide a specific list of drugs that should not be co-administered with siponimod, and a list of drugs that should only be used with additional vigilance.

Due to the constant information arising on drugs, these lists are by no mean exhaustive and medical judgment should always prevail. These lists are adapted to the patient population and the exclusion criteria of the CBAF312AUS02.

Siponimod is extensively metabolized, mainly via CYP2C9 (79.3%), followed by CYP3A4 (18.5%). CYP2C9 is polymorphic and the genotype influences the fractional contributions of the two oxidative metabolism pathways to overall elimination. Physiologically based PK modeling indicates a differential CYP2C9 genotype-dependent inhibition and induction of CYP3A4 pathways. With decreased CYP2C9 metabolic activity in the respective genotypes, a larger effect of the CYP3A4 perpetrators on siponimod exposure is anticipated.

Because of a significant increase in exposure to siponimod, concomitant use of siponimod and drugs that cause moderate CYP2C9 and moderate or strong CYP3A4 inhibition is not allowed. This concomitant drug regimen can consist of a moderate CYP2C9/CYP3A4 dual inhibitor (e.g., fluconazole) or a moderate CYP2C9 inhibitor in combination with a separate - moderate or strong CYP3A4 inhibitor. Caution should be exercised for concomitant use of siponimod with moderate CYP2C9 inhibitors.

Because of a significant decrease in siponimod exposure, concomitant use of siponimod and drugs that cause moderate CYP2C9 and strong CYP3A4 induction is not allowed for all patients. This concomitant drug regimen can consist of moderate CYP2C9/strong CYP3A4 dual inducer (e.g., rifampin or carbamazepine) or a moderate CYP2C9 inducer in combination with a separate strong CYP3A4 inducer. Caution should be exercised for concomitant use of MAYZENT with moderate CYP2C9 inducers.

Table 16-3 Dual moderate CYP2C9/strong or moderate CYP3A4 inhibitors

Fluconazole	

Table 16-4 Moderate CYP2C9 inhibitors

Phenybutazone	Oxandrolone	Milk thistle
Ataciguat	AZD1981	Azapropazone
Tienilic acid	Piperine	Bucolome
Fluconazole	amiodarone	Benzbromarone

Table 16-5 Strong CYP3A4 inhibitors

Viekira Pak	Elvitegravir/ritonavir	Telithromycin
Indinavir/ritonavir	Saquinavir/ritonavir	Grapefruit juice DS

Tipranavir/ritonavir	Lopinavir/ritonavir	Ceritinib
Ritonavir	Itraconazole	Conivaptan
Cobicistat	Voriconazole	Nefazodone
Ketoconazole	Mifepristone	Nelfinavir
Indinavir	Mibefradil	Saquinavir
Troleandomycin	LCL161	Ribociclib
Telaprevir	Clarithromycin	Idelalisib
Danoprevir/ritonavir	Posaconazole	Boceprevir

Table 16-6 Moderate CYP3A4 inhibitors

Erythromycin	GSK2647544	Grapefruit juice
Fluconazole	Aprepitant	Tofisopam
Atazanavir/ritonavir	Casopitant	Cyclosporine
Darunavir	Amprenavir	ACT-178882
Diltiazem	Faldaprevir	Ciprofloxacin
Darunavir/ritonavir	Imatinib	Magnolia vine (Schisandra sphenanthera)
Dronedarone	Verapamil	Isavuconazole
Crizotinib	Ravuconazole	Cimetidine
Atazanavit	Nutepitant	FK1706
Letermovir	Nilotinib	

Table 16-7 Dual moderate CYP2C9/moderate or strong CYP3A4 inducers

Rifampin	Enzalutamide

Table 16-8 Moderate CYP2C9 inducers

Rifampin	Enzalutamide
Ritonavir	

Table 16-9 Strong CYP3A4 inducers

Rifampin	Carbamazepine
Mitotane	Enzalutamide
Avasimibe	St John's Wort extract
Rifapentine	Lumacaftor
Apalutamide	Rifabutin
Phenytoin	Phenobarbital

Table 16-10 Moderate CYP3A4 inducers

Ritonavir and St John's Wort	Nafcillin
Semagacestat	Talviraline
Efavirenz	Lopinavir
Tipranavir and ritonavir	Daclatasvir and asunaprevir and beclubuvir
Dabrafenib	Modafinil
Lesinurad	PF-06282999
Bosentan	Etravirine
Genistein	Lersivirine
Thioridazine	Telotristat ethyl

*Source: University of Washington, Drug Interaction Database (www.druginteractioninfo.org).

16.5 Appendix 5: Assessing Immunity to Varicella

(https://www.cdc.gov/chickenpox/hcp/immunity.html)

Evidence of immunity to varicella includes any of the following:

Documentation of age-appropriate varicella vaccination;

- Preschool-age children (i.e., age 12 months through 3 years): 1 dose
- School-age children, adolescents, adults: 2 doses

- Laboratory evidence of immunity or laboratory confirmation of disease
- Birth in the United States before 1980 (Should not be considered evidence of immunity for health care personnel, pregnant women, and immunocompromised persons)
- Diagnosis or verification of a history of varicella or herpes zoster by a health care provider

To verify a history of varicella, health care providers should inquire about:

- an epidemiologic link to another typical varicella case or to a laboratory confirmed case, or
- evidence of laboratory confirmation, if testing was performed at the time of acute disease

Persons who have neither an epidemiologic link nor laboratory confirmation of varicella should not be considered as having a valid history of disease. For these persons, a second dose of vaccine is recommended if they previously received only one dose. If a health care provider verifies the diagnosis based on the above criteria, then vaccination is not needed

16.6 Appendix 6: Teriflunomide Accelerated Elimination Program (for patients treated with teriflunomide at screening or within 8 months prior to screening)

All patients treated with teriflunomide at screening or within 8 months prior to screening should undergo accelerated teriflunomide elimination program. This can be done anytime during the Screening Period if a switch in therapy for the patient is imminent or during the Treatment Period, Visit 1, after all inclusion criterion are met by the patient.

Recommended rapid elimination procedure is the administration of oral cholestyramine 8 g three times per day for 11 days. If patients do not tolerate this regimen, then the dosage may be reduced to 4 g three times per day. Teriflunomide levels are not required for this study however could be completed as part of standard of care.

If tolerability issues persist, cholestyramine administration does not need to occur on consecutive days unless there is an acute need to lower teriflunomide levels.

As an alternative to cholestyramine, oral activated charcoal administered as 50 g twice a day for 11 days may be used.

It needs to be documented in the eCRF which elimination treatment was used.

16.7 Appendix 7: Recommendations for the management of bradycardia

Initiating treatment results in a decrease in HR. If any of the following abnormalities are present after 6 hrs. (even in the absence of symptoms), additional monitoring should be conducted:

- Day 1: HR 6 hrs. post-dose <45 bpm

If post-dose symptomatic bradycardia, bradyarrhythmia, or conduction related symptoms occur, or there is evidence of new-onset second-degree or higher AV block or QTc ≥500 msec, initiate appropriate management; monitor ECG and symptoms until resolved if no pharmacological treatment is required.

The study site personnel should be particularly mindful of patients who have a low pulse at baseline (spontaneously or through drug-induced ß-receptor blockade), prior to administration of the study drug. A cardiologist should be consulted if needed.

Atropine (subcutaneous or intravenous) is recommended as the first-line treatment of bradycardia, up to a maximum daily dose of 3 mg.

Furthermore, the common guidelines for treatment of bradycardia (e.g. ACLS guidelines) should be followed as appropriate:

- In case of clinical symptoms of bradycardia, administration of atropine 1 mg, with repeated administration in 3-5 minutes is recommended.
- If heart rate and/or blood pressure remain unresponsive, consider administration of dopamine drip 5-20 ug/kg/min or epinephrine drip 2-10 ug/min.
- Transcutaneous pacing may also be considered.
- In the setting of decreased blood pressure, isoproterenol should be avoided or used with caution.
- If a patient requires treatment for bradycardia/bradyarrhythmia during the first dose, the patient should be hospitalized for overnight monitoring and this monitoring procedure should be repeated for the second dose of study drug.

16.8 Appendix 8: Guidelines for Ophthalmic examination and management of Macular Edema

A complete ophthalmic examination and Optical Coherence Tomography (OCT) assessment are scheduled at baseline (Day 1) and Visit 4 (Day 84), as indicated in the assessment schedules for both CP study assessments (Table 8-1).

This appendix provides details of the ophthalmic examination requirements in the study.

A standard visual acuity chart with equal space between letters and between lines should be used for the visual acuity assessment. As noted in Section 8.4.5., the OCT machine used should preferably not be changed during the course of the study to allow for comparison of central foveal thickness within each patient across time points.

(1) Ophthalmic monitoring for general MS population Baseline visit:

At the baseline visit this eye examination will include;

- ophthalmic history
- best corrected visual acuity measurement
- ophthalmoscopy (may include contact lens biomicroscopy to examine the macula and optic disc).
- measurement of central foveal thickness by OCT (required for all patients regardless of the results of visual acuity or ophthalmoscopy).

N.B. Ophthalmic findings should be recorded.

If there is a suspicion of macular edema by ophthalmoscopy and increased central foveal thickness by OCT, then a fluorescein angiogram may be performed (at the discretion of the ophthalmologist). Patients with diagnosed macular edema at baseline should discontinue from the study.

Visit 4

At scheduled study visits the eye examination will include;

- ophthalmic history
- best corrected visual acuity measurement
- ophthalmoscopy (may include contact lens biomicroscopy to examine the macula and optic disc).
- measurement of central foveal thickness by OCT (required for all patients regardless of the results of visual acuity or ophthalmoscopy).

N.B. Ophthalmic findings should be recorded.

During the study if there are complaints of decreased vision or identification of worsening visual acuity (equal to or more than two lines on a standard eye chart using best corrected vision) then an unscheduled ophthalmic exam should be performed at which the eye examination will include;

- best corrected visual acuity measurement
- ophthalmoscopy (may include contact lens biomicroscopy to examine the macula and optic disc).
- measurement of central foveal thickness by OCT

N.B. Ophthalmic findings should be recorded.

The OCT can be performed by referring ophthalmologists or neurologists with clinical training and expertise to assess structural measurement of retinal nerve fiber layer thickness, optic nerve head, and macular anatomy AND currently possess appropriate OCT equipment in-office.

In case of suspected macular edema based on the ophthalmoscopy or if a relevant increase of central foveal thickness is observed, then a fluorescein angiogram may be performed to diagnose and characterize macular edema (at the discretion of the ophthalmologist), if present.