Novartis Research and Development

Mayzent (siponimod)

Synopsis/Clinical Trial Protocol CBAF312ADE03 / NCT04792567

An open-label multicenter study to assess response to SARS-CoV-2 modRNA vaccines in participants with secondary progressive multiple sclerosis treated with Mayzent (siponimod) (AMA-VACC)

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List of abbreviations

AE	Adverse Event
CDP	Clinical Development Plan
CDS	Core Data Sheet
CRO	Contract Research Organization
CSR	Clinical study report
CTC	Common Terminology Criteria
eSource	Electronic Source
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GCS	Global Clinical Supply
i.v.	intravenous
IB	Investigator's Brochure
ICF	Informed Consent Form
IEC	Independent Ethics Committee
PK	Pharmacokinetic(s)
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
s.c.	subcutaneous
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
WoC	Withdrawal of Consent

Amendment 2 (released 25-Sep-2021)

Amendment summary

The main changes introduced in this protocol amendment are a) termination of recruitment, b) optional treatment interruption according to SmPC also in cohort 1 in case of a booster vaccination and c) an additional study visit in case of a SARS-CoV-2 booster vaccination.

a) Termination of recruitment

With the advancement of the vaccination efforts in Germany participating centers of this study report that there are no more suitable MS patients for this study that have not yet received their initial SARS-CoV-2 vaccination cycle. Therefore, recruitment will be officially stopped with the approval of this amendment.

b) Optional treatment interruption for booster vaccination in cohort 1

The underlying study protocol already allows patients to receive a SARS-CoV-2 vaccination booster with any approved type of vaccination including but not limited to mRNA or vector based vaccines as part of clinical routine. Furthermore, according to SmPC all siponimod patients in cohort 1 and 2 will now be able to introduce a voluntary treatment break for the purpose of the booster vaccination e.g. if the immune response to the initial vaccination cycle was low or not detectable. The decision of a possible treatment break is at the discretion of the treating physician and patient.

c) Additional study visit after SARS-CoV-2 booster vaccination

At this point it is unclear if and at which point MS patients will be eligible for such a booster vaccination. In order to enable the assessment of the immune system to such a potential booster vaccination an additional study visit will be scheduled by the treating physician at one month after a potential booster vaccination. This additional visit will be termed ‘booster visit’ and will only be performed in a subgroup of patients receiving a booster vaccination. The additional booster visit includes all assessments conducted in the regular visit 3. If this additional visit would fall within +/-1 week of the regular visit 3, then the booster visit will not be performed as all required assessments are already part of the regular study visit 3. If the booster visit would be later than end of study at month 12 after the initial vaccination cycle then it will not be performed.

Changes to the protocol

Protocol summary

Sections 'study treatment' and 'study design': a sentence was added, that patients in cohort 1 and cohort 2 may also choose to conduct a treatment break for the purpose of a potential booster vaccination.

Section 2: Objectives and endpoints

A sentence was added to secondary endpoints that SARS-CoV-2 antibody levels and T-cell response will be assessed after a potential booster vaccination.

Section 3: study design

Explanations were added explaining that according to the EU SmPC all siponimod patients in cohort 1 and cohort 2 may introduce a treatment break for the purpose of the booster vaccination.

Section 4.2: Rationale for dose/regimen and duration of treatment

A sentence was added explaining that according to the EU SmPC all siponimod patients in cohort 1 and cohort 2 may introduce a treatment break for the purpose of the booster vaccination.

Table 6-1: Table 6-1 Investigational and control drug

Vector based SARS-CoV-2 vaccines were added to the list of IMPs in all treatment arms which are now allowed for booster vaccination as an alternative to mRNA vaccines

Section 6.1.3: Treatment arms

A sentence was added explaining that according to the EU SmPC patients in cohort 1 may introduce a treatment break for the purpose of the booster vaccination.

Section 6.3.2: Treatment assignment, randomization

A sentence was added that patients in cohort 1 may introduce a treatment break for the purpose of the booster vaccination.

Section 8: Visit schedule and assessments

An explanation was added during which time frame of the study a "booster visit" shall be performed to analyze the immune response to a potential booster vaccination.

Section 8.1: Documentation of IMPs

For the purpose of analyzing potential booster vaccinations the investigational period and end of study was extended to month 12 meaning that the study ends with the COVID-19 follow-up call in month 12. For individual patients the study duration therefore does not change.

Figure 3-1: Study design

The figure was amended to include a telephone contact in case of a booster vaccination and an additional study visit 1 month after a potential booster vaccination. A sentence was added to

the figure footer explaining during which time frame of the study a “booster visit” shall be performed to analyze the immune response.

Table 8-1: Assessment schedule

A sentence was added to the table footer explaining during which time frame of the study a “booster visit” shall be performed to analyze the immune.

Amendment 1 (released 25-May-2021)

Amendment summary

The main changes introduced in this protocol amendment are: a) prolongation of the visit window for investigational visit 1, b) classification of adverse events according to the Common Toxicity Criteria (CTC) AE grade (version 5 or higher) c) start and optional prolongation of screening period and d) optional booster/refresher SARS-CoV-2 vaccinations if suggested by local regulations e) more detailed description of IMP documentation.

Visit window: In this study, investigational visits will only be possible from Monday to Wednesday due to organizational reasons in the central laboratory. In order to still allow vaccinations on all weekdays, the visit window for investigational visit 1 will be extended from "7 +/- 1 days" to "8 +/-2 days after second dose of vaccination".

Adverse events: Severity assessment of (serious) adverse events was changed to CTCAE scale as this scale is more common in clinical trial setting and participating physicians are more accustomed to this kind of severity scale. Therefore, severity assessment of adverse events would be more comparable between different physicians resulting in more valuable data.

Screening period: In order to avoid screening failures and replacement of patients due to changes in the German vaccination regulation, guidance for physicians has been included in the protocol to contact the Novartis Medical Advisor in case a patient is not eligible for SARS-CoV-2 vaccination within one month after screening by local regulation to discuss further proceeding including re-evaluation of anti-SARS-CoV-2 antibody level and PCR test. Furthermore, length of the screening period was adjusted from 1-30 days to 3-30 days prior SARS-CoV-2 vaccination to ensure availability of SARS-CoV-2 PCR results before vaccination.

Booster/refresher SARS-CoV-2 vaccinations

It is currently under discussion to offer booster/refresher SARS-CoV-2 vaccinations to the population in general and patients under immune modulatory treatments especially. As AMA-VACC follows clinical routine it shall be possible for participants to receive such a booster/refresher vaccination if recommended by local regulations and conducted as part of clinical routine.

Detailed description of IMP documentation

A more detailed description of the required documentation of all IMPs (MS DMTs, SARS-CoV-2 vaccinations) was added to provide participating centers with an even clearer documentation guidance.

Changes to the protocol

Protocol Summary

Typos were corrected

Section 3: Study design

- Sentence has been added to clarify that PCR test results need to be available before a patient receives SARS-CoV-2 vaccination in this study.
- During COVID-19 follow up call, all confirmed COVID-19 infections will be recorded.
- Individual study duration will be 56-60 weeks (1-4 weeks between screening and vaccination 1, 3-4 weeks between vaccination 1 and 2 and 52 weeks until follow-up phone call)
- It is currently under debate that patients with immunosuppressive treatment may require additional booster/refresher SARS-CoV-2 vaccinations. Guidance was therefore added that booster/refresher SARS-CoV-2 vaccinations are allowed if performed according to local regulations and as part of clinical routine independent of the type of vaccination used.
- Guidance was included to contact the Novartis Medical Advisor in case a patient is not eligible for SARS-CoV-2 vaccination within one month after screening by local regulation to discuss further proceeding including re-evaluation of anti-SARS-CoV-2 antibody level and PCR test.
- Visit window for visit 1 was adapted to 6-10 days in section “3. Investigational period” and Figure 3-1

Section 4.5: Risks and benefits

Typo was corrected

Section 5.1: Inclusion criteria

Typo was corrected

Section 6.2.1: Concomitant therapy

Reference was corrected

Wording of updated Siponimod Investigators Brochure version 19 was included regarding vaccination guidance.

Section 6.3.1: Treatment arms

Typo was corrected

Section 8 Visiting schedule

An explanation regarding the possibility of unscheduled on-site (repeated sampling, safety) or telephone visits (booster/refresher vaccination) was added.

Section 8.1 Documentation of IMPs

This section was added for improved clarity on the parameters that need to be documented for all IMPs in this study (SARS-CoV-2 vaccine and all MS DMTs)

Table 8-1 assessment Schedule

Examination of vital signs, height and weight was included in the description of the full physical exam. Information on allowed booster/refresher SARS-CoV-2 vaccinations was added as well as the requirement of a negative SARS-CoV-2 PCR result prior to vaccination and guidance that information on MS relapses of the previous 2 years shall be collected.

Section 8.4: Safety

Examination of vital signs, height and weight was included in the description of the full physical exam.

Section 9.1.1: Study treatment discontinuation and study discontinuation

Visit window for visit 1 was adjusted to 6-10 days

Section 9.1.1.1 Replacement policy

Guidance was included to contact Novartis Medical Advisor in case a patient is not eligible for SARS-CoV-2 vaccination within one month after screening by local regulation to discuss further proceeding.

Section 10.1.1: Adverse events

Assessment and grading of adverse events will be done according to Common Terminology Criteria for Adverse Events (CTCAE) version 5 or higher.

Section 12.1: Analysis sets

Sentence was deleted because a more detailed description is given in the following paragraph.

Table 6-1: Investigational and control drug

Route of administration for vaccine will be i.m. according to EU SmPC

Table 8-1: Assessment schedule

- The visit window for investigational visit 1 has been adapted to 8 +/- 2 days.
- Screening period has been adapted to -30 to -3 days to make sure that PCR results will be available before vaccination (results will be available within 2 days).
- It was specified that at screening, all MS relapses within the last 2 years should be recorded.
- Assessment of current MS medication and concomitant medication should also be performed during telephone contacts after vaccination 1 and 2.
- Footnote regarding PCR test was amended with the statement that patients are only allowed to continue the study and receive SARS-CoV-2 vaccination within the study context after they received a negative PCR test result.
- Footnote was amended to allow possible booster/refresher vaccinations if they are suggested by local regulations and performed as part of clinical routine.

Section 12.5: Interim Analysis

To match the wording of section 4.4, a sentence was added to section 12.5 regarding additional interim analyses to support decision making concerning the current clinical study including an increase in participants (from 60 to 90), the sponsor's clinical development projects in general, or in case of any safety concerns.

Protocol summary

Protocol number	CBAF312ADE03
Full Title	An open-label multicenter study to assess response to SARS-CoV-2 modRNA vaccines in participants with secondary progressive multiple sclerosis treated with Mayzent (siponimod) (AMA-VACC)
Brief title	Study to assess SARS-CoV-2 vaccination response in siponimod treated SPMS patients
Sponsor and Clinical Phase	Novartis Pharma GmbH / clinical phase IV
Investigation type	Drug (Siponimod (BAF312))
Study type	Low-intervention, 3 cohorts
Purpose and rationale	MS disease modifying treatments generally target the immune system and may therefore interfere with vaccination responses. The purpose of this study is to understand whether participants can mount an immune response to SARS-CoV-2 modRNA vaccines administered either during continuous siponimod treatment or during a treatment break. Furthermore, the study will investigate the development of anti-SARS-CoV-2 antibody and T-cell titers over six months after participants' vaccination.
Primary Objective(s)	To estimate the proportion of those achieving seroconversion (i.e. having SARS-CoV-2 serum functional antibodies) after receiving a modRNA vaccine in participants treated concomitantly with siponimod and siponimod treatment break.
Secondary Objectives	• Describing SARS-CoV-2 serum functional antibody levels in participants treated concomitantly with siponimod versus siponimod treatment break versus first-line DMTs and in patients currently not on a DMT • Describing the T cell response to modRNA vaccines in participants treated concomitantly with siponimod versus siponimod treatment break versus first-line DMTs and in patients currently not on a DMT • Describing safety, incl. AEs related to discontinuation and new onset of siponimod treatment and patients developing COVID-19
Study design	This is a three cohort, multicenter, open-label, prospective study of 60 (optionally up to 90) MS patients currently treated with siponimod or a first-line DMT or without MS treatment in clinical routine planning to undergo a SARS-CoV-2 modRNA vaccination as part of clinical routine. • The first cohort will be participants not interrupting their current siponimod therapy for the purpose of a SARS-CoV-2 modRNA vaccination. In case of a booster vaccination, patients in this cohort may also undergo a treatment break which is also covered by the EU SmPC. • The second cohort will be participants interrupting their current siponimod therapy for the purpose of a SARS-CoV-2 modRNA vaccination (treatment interruption for about 2-3 months). • The third cohort will be participants receiving modRNA vaccine while on treatment with the following first-lineDMTs (dimethylfumarate,

	glatirameracetate, interferons, teriflunomide) or no current treatment in clinical routine.
Study population	The study population will consist of females and males at risk for SPMS or with SPMS diagnosis treated in clinical routine with either siponimod, a first line MS DMT or no current therapy.
Key Inclusion criteria	1. Signed informed consent must be obtained prior to participation in the study. 2. One of the following MS treatments as part of clinical routine: a. **Cohort 1**: Siponimod treatment according to EU SmPC **without interrupting daily dosing** for the purpose of vaccination with SARS-CoV-2 modRNA b. **Cohort 2**: Siponimod treatment according to EU SmPC **interrupting daily dosing** for the purpose of vaccination with SARS-CoV-2 modRNA c. **Cohort 3**: Dimethylfumarate, glatirameracetate, interferon, teriflunomide as per respective EU SmPC or no current treatment with diagnosis of SPMS or with RRMS at risk to develop SPMS (at the discretion of the treating physician) 3. Planning to receive a SARS-CoV-2 modRNA vaccination as part of clinical routine 4. No change regarding DMT within 4 weeks prior to inclusion to AMA-VACC, i.e. stable on current DMT according to dosing within label, no interruption, start or withdrawal of DMT in this period of time and no planned switch of DMT within following 2 months 5. Patients willing and eligible to receive a modRNA vaccine against COVID-19 as part of clinical routine
Key Exclusion criteria	1. History of COVID-19 2. SARS-CoV-2 antibodies at screening 3. Patients likely not being able or willing to complete the study 4. Use of other investigational drugs within 5 half-lives of enrollment/initiation of study treatment (e.g. small molecules) or until the expected pharmacodynamic effect has returned to baseline (e.g., biologics), whichever is longer 5. Patients with any medical or psychological condition that, in the investigators opinion, renders the patient unable to understand the nature, scope, and possible consequences of the study and who are therefore not able to comply with the requirements of the study and capable of giving informed consent 6. No person directly associated with the administration of the study is allowed to participate as a study subject 7. No family member of the investigational study staff is allowed to participate in this study 8. Known or suspected clinically relevant allergy, intolerance or hypersensitivity to peanuts, soya (only cohort 1 and 2) or to any of the study treatments designated for the individual subject (DMTs or mRNA vaccines) or drugs of similar chemical classes (active substance or excipients) 9. 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 10 days of study treatment after stopping medication. 10. For cohort 3: patients with contraindications for their current MS medication according to the respective EU SmPC

Study treatment	• **Cohort 1:** Siponimod (BAF312) treatment according to EU SmPC **without interrupting daily dosing** for the purpose of a SARS-CoV-2 modRNA vaccination In case of a booster vaccination, patients in this cohort may also undergo a treatment break which is also covered by the EU SmPC. • **Cohort 2:** Siponimod (BAF312) treatment according to EU SmPC **interrupting daily dosing** for the purpose of a SARS-CoV-2 modRNA vaccination (treatment interruption for about 2-3 months) • **Cohort 3:** Dimethylfumarate, glatirameracetate, interferon, teriflunomide as per respective EU SmPC or no current treatment without a change in treatment for the purpose of a SARS-CoV-2 modRNA vaccination
Treatment of interest	Siponimod (BAF312) / *SARS-CoV-2 modRNA vaccine*
Efficacy assessments	• Detection of SARS-CoV-2 serum functional antibodies • Detection of SARS-CoV-2 specific T-cells
Key safety assessments	• Patients developing COVID-19
Data analysis	The primary analysis will not use any statistical testing or modelling. The absolute numbers and the proportion of participants achieving seroconversion within each cohort will be calculated. It will be augmented by a (descriptive) 95% confidence interval (exact Clopper-Pearson). All secondary endpoints will be summarized descriptively as frequencies and percentages, or, for continuous data, mean, standard deviation, median, minimum, and maximum will be presented.
Key words	COVID-19, SARS-CoV-2, RNA vaccine, siponimod, secondary progressive multiple sclerosis

1 Introduction

1.1 Background

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was first observed in Wuhan, China, in December 2019. Since then, pandemic illness spread around the globe and currently affects millions of people, not only their health, but also their entire social and economic life. COVID-19 is associated with an increased risk of severe and potentially lethal disease especially among the elderly and among persons with preexisting medical conditions. Tremendous efforts are undertaken to develop a vaccine to SARS-CoV-2. The first promising data have recently been reported by BioNTech, Moderna and others using nucleoside-modified RNA (modRNA) vaccines encapsulated in lipid nanoparticles (Sahin et al, 2020; Jackson et al, 2020; press release BioNTech). Furthermore, the BioNTech and Moderna vaccines have just been granted marketing authorization by the European Medicines Agency (EMA).

Multiple sclerosis (MS) is a common cause of neurologic disability in young adults. In this disease, damage is caused by an autoimmune attack of the central nervous system. The majority of relapsing remitting multiple sclerosis (RRMS) patients convert to secondary progressive multiple sclerosis (SPMS) in their lifetime. Siponimod is indicated by the EMA for the treatment of SPMS patients with active disease as evidenced by relapse or MRI activity. Siponimod selectively targets S1P1 and S1P5 receptors present on lymphocytes inducing receptor internalization and therefore preventing egress of these cells from secondary lymphoid tissues (Behrangi et al, 2019).

In general, MS disease modifying treatments target the immune system and in doing so may diminish vaccine efficacy (Farez et al 2019). In a double-blind, placebo controlled study with siponimod in healthy volunteers, it was observed that concomitant siponimod was associated with no relevant effect on antibody response to pneumococcal polysaccharide vaccine and most of the patients met the EMA criteria of seroconversion for a T-cell dependent influenza vaccine although titers were lower (Ufer et al, 2017).

The current guidance for vaccination of siponimod patients is based on the findings by Ufer et al., reflected in section *4.4 Special warnings and precautions for use* in the EMA SmPC (product information siponimod):

- *The use of live attenuated vaccines should be avoided while patients are taking siponimod and for 4 weeks after stopping treatment.*
- *Vaccinations may be less effective if administered during siponimod treatment. Discontinuation of treatment 1 week prior to planned vaccination until 4 weeks after is recommended. When stopping siponimod therapy for vaccination, the possible return of disease activity should be considered*

The modRNA vaccine BNT162b2 was shown to not only trigger a vaccine-induced antibody response against the receptor binding domain (RBD) of the SARS-CoV-2 spike protein but also a functional and proinflammatory CD4+ and CD8+ T-cell response in a phase I/II trial (NCT04380701) (Sahin et al, 2020). In the following phase III trial with 43,548 participants (NCT04368728), BNT162b2 mRNA vaccine has further been shown to be 95% effective in

preventing COVID-19 (Polack et al, 2020). Similar results were also shown for the mRNA vaccine developed my Moderna: the efficacy of mRNA-1273 in preventing COVID-19 in a phase III trial with 30,420 participants was 94.1% (NCT04470427) (Lindsay et al, 2021).

It is therefore essential to understand the immune response to the novel class of modRNA vaccines in siponimod treated patients where S1P1 expressing Th17 cells are retained in lymph nodes (Behrangi et al, 2019) to develop a guidance for SARS-CoV-2 vaccination strategies in the vulnerable population of SPMS patients. This becomes even more important when considering that SARS-CoV-2 vaccination needs to be boosted after 3 or 4 weeks, resulting in a possible treatment interruption of about 2-3 months.

The detection of SARS-CoV-2 serum functional antibodies after vaccination in patients negative for this parameter at baseline is defined as seroconversion according to World Health Organization guidelines (WHO guideline, 2020). In this study, we will test for functional antibodies, i.e. antibodies that inhibit the binding of the viral spike protein to the human angiotensin-converting enzyme 2 (ACE2) receptor, which is the first and necessarily required step during SARS-CoV-2 infection (Yang et al, 2020). Vaccination response will be analyzed during continued siponimod treatment (cohort 1) or a short treatment interruption (cohort 2) in accordance with label recommendations / upon discretion of the treating physician to cover both scenarios taking place in clinical practice.

In order to set findings into relation to MS patients on disease modifying treatments (DMTs) with potentially less immunomodulatory effects, data will also be compared to cohort 3 with RRMS patients at risk of SPMS and SPMS patients either without treatment or on first-line therapies dimethylfumarate, glatirameracetate, interferons or teriflunomide.

These data are needed in a very timely manner to help physicians make an educated decision about vaccination in siponimod treated patients in the upcoming months. Therefore, the present study will be conducted in parallel to currently ongoing studies AMASIA (CBAF312ADE01) and PANGAEA 2.0 EVOLUTION (CFTY720DDE26), thereby leveraging established operational structures without influencing the non-interventional character of these trials. In case patients participating in AMASIA consider participation in AMA-VACC, for regulatory and safety reporting reasons, documentation in AMASIA needs to be paused for the time patients are participating in AMA-VACC.

1.2 Purpose

MS disease modifying treatments generally target the immune system and may therefore interfere with vaccination responses. The purpose of this study is to understand whether participants can mount an immune response to SARS-CoV-2 modRNA vaccines administered either during continuous siponimod treatment or during a treatment break. Furthermore, the study will investigate the development of anti-SARS-CoV-2 antibody and T-cell titers over six months after participants' vaccination.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
• To estimate the proportion of those achieving seroconversion (i.e. having SARS-CoV-2 serum functional antibodies) after receiving a modRNA vaccine in participants treated concomitantly with siponimod and siponimod treatment break.	Proportion of participants achieving seroconversion as defined by detection of SARS-CoV-2 serum functional antibodies one week after second dose of vaccine in participants treated concomitantly with siponimod and siponimod treatment break (yes/no)
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
• Describing SARS-CoV-2 serum functional antibody levels in participants treated concomitantly with siponimod versus siponimod treatment break versus first-line DMTs and in patients currently not on a DMT • Describing the T-cell response to modRNA vaccines in participants treated concomitantly with siponimod versus siponimod treatment break versus first-line DMTs and in patients currently not on a DMT • Describing safety, incl. AEs related to discontinuation and new onset of siponimod treatment and patients developing COVID-19	• SARS-CoV-2 serum functional antibody levels one week, one month and six months after second dose of vaccine and additionally one month after an optional booster vaccination in participants treated concomitantly with siponimod versus siponimod treatment break versus first-line DMTs and in patients currently not on a DMT • SARS-CoV-2 specific T-cell levels one week, one month and six months after second dose of vaccine and additionally one month after an optional booster vaccination in participants treated concomitantly with siponimod versus siponimod treatment break versus first-line DMTs and in patients currently not on a DMT measured by e.g. enzyme-linked immunosorbent spot (ELIspot) assay from peripheral blood mononuclear cells that were stimulated with SARS-CoV-2 peptide mix • AEs, SAEs, incl. patients with clinical confirmed COVID-19, events leading to discontinuation in participants treated concomitantly with siponimod versus siponimod treatment break versus first-line DMTs and in patients currently not on a DMT

2.1 Primary estimands

The primary clinical question in this trial is: What is the proportion of SPMS patients treated with siponimod within the three cohorts defined below which develop an immune response to a SARS-CoV-2 modRNA vaccine?

Of note, this is not a randomized trial, therefore no randomization needs to be preserved and the ITT-principle and the associated estimands framework do not apply. However, this protocol

will keep as close as appropriate to the terminology and the definitions established within that framework.

The justification for the primary estimand is that it will capture whether siponimod treated participants generate functional antibodies to SARS-CoV-2 vaccine as assessed by geometric mean titers.

The following attributes describe the primary estimand:

- **Population:** MS patients divided in three cohorts, each receiving a SARS-CoV-2 vaccination as part of clinical routine: (1) vaccination during continued siponimod treatment; (2) vaccination during a siponimod treatment interruption (of approx. 2-3 months); (3) vaccination in MS patients during continued treatment with first-line DMTs or no DMT. Patients who fail to receive their second dose of vaccine for whatever reason will be included in the analysis as non-responders. Patients who did receive their second dose of vaccine and do not have a valid determination of functional antibodies to SARS-CoV-2 for whatever reason will be excluded from the analysis of vaccine efficacy.
- **Variable:** Receiving the second dose of vaccine and achieving seroconversion as defined by detection of SARS-CoV-2 functional antibodies one week after second dose of vaccine (yes/no)
- **Treatment of interest:** siponimod either continuously applied or with a treatment break for the purpose of the vaccination, or first line DMTs or no treatment as part of clinical routine
- **Intercurrent events:** Failure to receive the second dose of vaccine: These patients will be counted as non-responders.
  Missing or invalid determination of functional antibodies to SARS-CoV-2: These patients will be excluded from the efficacy analyses (if they received their 2nd dose of vaccine)
- **Summary measure:** n.a., there will be no formal comparison between cohorts. Response rates will only be calculated within each cohort.

3 Study design

This is a three cohort, multicenter, open-label, prospective study of 60 (optional increase to 90) MS patients currently treated with siponimod or a first-line DMT (as per EU SmPC) or without MS treatment planning to undergo a SARS-CoV-2 modRNA vaccination as part of clinical routine and according to the respective EU SmPC. For each participant, total expected duration of the trial is 56-60 weeks.

- The first cohort will be participants not interrupting their current siponimod therapy for the purpose of a SARS-CoV-2 modRNA vaccination. In case of a booster vaccination, patients in this cohort may also undergo a treatment break which is also covered by the EU SmPC.
- The second cohort will be participants interrupting their current siponimod therapy for the purpose of a SARS-CoV-2 modRNA vaccination (treatment interruption of about 2-3 months).

- The third cohort will be participants receiving modRNA vaccine while on treatment with first-line DMTs (dimethylfumarate, glatirameracetate, interferons, teriflunomide) or no current treatment in clinical routine.

The interventional part of AMA-VACC is limited to the collection of blood samples at specified time-points to analyze levels of SARS-CoV-2 specific antibodies and T-cells as response to the modRNA vaccination in clinical routine.

There are 3 study periods:

1. Screening period:

Participants enter a screening period of up to 1 month to assess eligibility requirements including a blood draw and assessment of SARS-CoV-2 specific antibodies at baseline to exclude any prior exposure to the virus or a vaccination. In case the patient is not eligible for SARS-CoV-2 vaccination by local regulation within this time, the Novartis Medical Advisor should be contacted to discuss further proceeding including re-evaluation of anti-SARS-CoV-2 antibody level and PCR test. Furthermore, a SARS-CoV-2 PCR test will be performed at screening to exclude current COVID-19 infection. In case of a positive test result, the patient has to go into quarantine immediately. Patients are only allowed to continue within the study and receive SARS-CoV-2 vaccination once they received a negative PCR test result.

2. Vaccination period

Patients are vaccinated with a complete cycle of modRNA based SARS-CoV-2 vaccine at the discretion of the treating physician outside the study as part of clinical routine.

- Participants in cohort 1: vaccination will be administered according to EU SmPC under continued siponimod treatment. In case of a booster vaccination, patients in this cohort may also undergo a treatment break which is also covered by the EU SmPC.
- Participants in cohort 2: vaccination will be administered according to EU SmPC after start of the siponimod treatment break.
- Participants in cohort 3: vaccination will be administered according to EU SmPC during continued treatment with first-line MS DMTs or no current treatment.

If suggested by local regulations, patients will be allowed to receive additional SARS-CoV-2 vaccinations (booster or refresher) during the study according to the physician's discretion and as part of the clinical routine. This booster may be any type of SARS-CoV-2 vaccine, depending on local regulations. According to SmPC, siponimod patients in Cohort 1 and Cohort 2 may introduce a treatment break for the purpose of the booster vaccination e.g. in case there was no measurable immune response during the initial vaccination cycle. The decision for such a treatment break is at the discretion of the treating physician and patient.

3. Investigational period

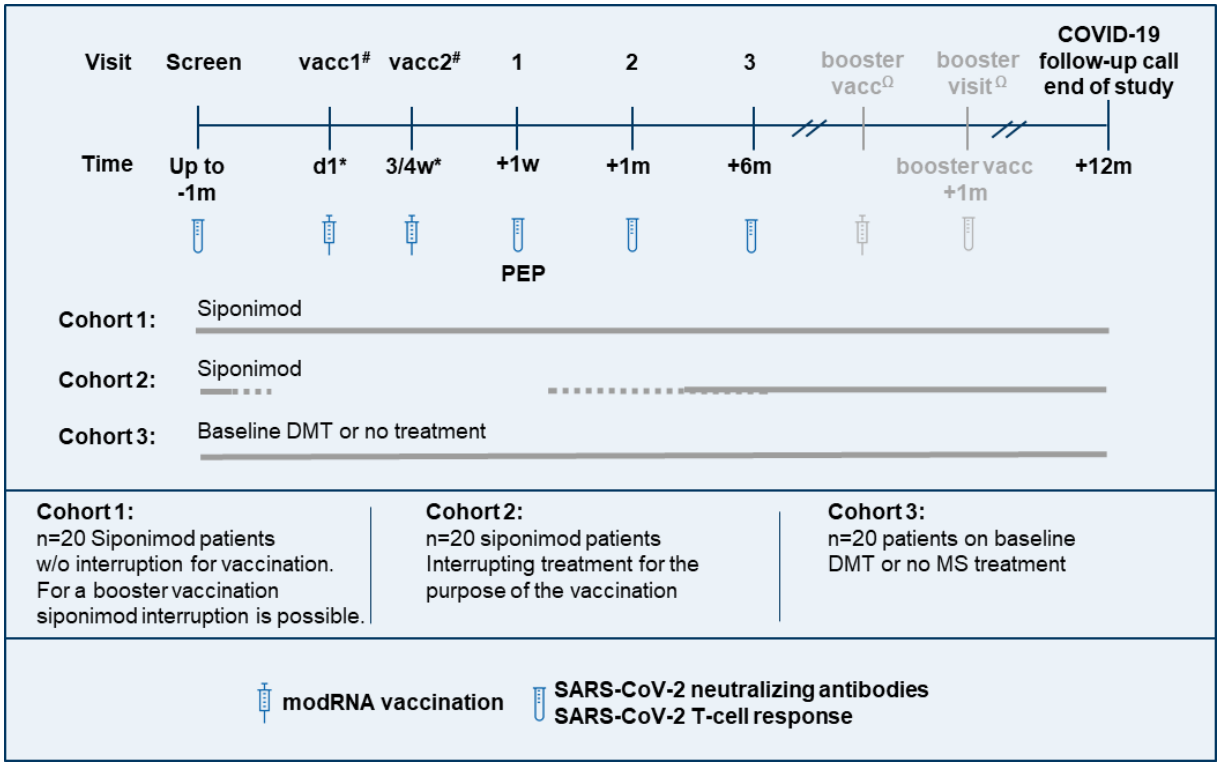
Blood samples for SARS-CoV-2 functional antibody titers and T-cells for primary and secondary endpoints will be drawn from all patients 1 week (day 6 - 10), 1 month (day 28 - 35)

and 6 months (week 25 - 27) after completion of vaccination. In case of booster vaccinations an additional blood sample will be collected one month (+/- 1 week after the booster vaccination).

12 months (week 50 – 54) after completion of the vaccination a COVID-19 follow-up call is scheduled to inquire about a possible confirmed COVID-19 disease after the end of the study.

In total, the study duration for each participant is 56-60 weeks, depending on the length of the screening period.

Figure 3-1 Study design



PEP: primary endpoint; d= day, w=week, m=month, vacc= vaccination independent of study site. # vaccination as part of clinical routine. * Number of Vaccinations required and interval depends on SmPC of respective modRNA vaccines. Any kind of SARS-CoV-2 booster/refresher vaccination is allowed in this study, if this is suggested by local regulations and applied as part of clinical routine. ΩIf booster vaccinations are performed as part of clinical routine an additional telephone contact (booster vacc) is scheduled. Furthermore, an additional study visit (booster visit) will be performed one month (+/- 1 week) after the booster vaccination matching all assessments of investigational visit 3. If this booster visit falls within +/-1 week of the regular visit 3 or later than the telephone contact in month 12, it will not be performed. Timing of visits 1-3: 1 week (day 6 - 10), 1 month (day 28 - 35) and 6 months (week 25 - 27) after completion of vaccination. COVID-19 follow-up call: 50-54 weeks after completion of vaccination

4 Rationale

4.1 Rationale for study design

A multicenter, multi-cohort, open-label, comparator design has been selected to enable feasible recruitment in a timely manner that allows fast generation of data in order to provide a guidance to physicians and patients how to apply SARS-CoV-2 vaccination in siponimod patients. The study therefore addresses two main questions:

- Can participants continuously treated with siponimod develop SARS-CoV-2 serum functional antibodies after receiving a modRNA vaccine?
- Can participants undergoing a siponimod treatment interruption for the purpose of a SARS-CoV-2 vaccination develop serum functional antibodies?

The third cohort comprising MS patients treated with first-line DMTs according to respective SmPC or no current MS therapy serves as a reference on the development of an immune response in MS patients.

As SPMS patients may be considered a vulnerable COVID-19 group these patients may be given access to the modRNA vaccines as one of the first groups in Germany (German ministry of health statement). In order to provide a guidance for vaccination of siponimod patients as early as possible a study design allowing fast implementation and execution was chosen. Therefore, immune responses to vaccination will be analyzed in patients receiving both MS treatment and modRNA vaccine in clinical routine. The intervention of AMA-VACC is limited to blood sampling and analysis of the immune response.

When considering possible randomization of siponimod patients into cohort 1 (continued treatment) and cohort 2 (treatment interruption) for the purpose of SARS-CoV-2 vaccination two perspectives are important: the SPMS disease and the possible vaccination response.

The siponimod SmPC suggests that patients may undergo vaccination with inactive agents either during continued siponimod treatment or during a treatment break. It is however also stated, that a return of disease activity has to be considered when interrupting the treatment. Therefore, physicians need to take the individual MS history into consideration when deciding about the most beneficial vaccination approach together with the patient. Randomization would overrule this decision process and may not lead to the most suitable result for the individual patient. One limitation of this approach however is that patient characteristics e.g. regarding age or MS parameters may not be completely matched in the two cohorts.

From a vaccination point of view two factors may influence the immune response: co-treatment with siponimod and patient characteristics. Interestingly, during clinical development of BNT162b2 which has recently been submitted to EMA and FDA, no impact of age was observed regarding the antibody response (Welch et al, 2020). Here, similar levels of S1-binding IgG antibodies were found in patients aged 18-55 and 65-85. With such a large range of ages studied it is not expected that these patient characteristics may lead to a strong bias in the development of an adequate immune response to modRNA vaccines in cohort 1 vs 2. The second possible impact factor – continued vs interrupted siponimod treatment – is part of the objectives of this study.

Therefore, randomization is not performed in AMA-VACC to allow patients and physicians to decide about the most suitable vaccination approach for the individual situation which also reflects the guidance of the siponimod SmPC.

Rationale for study population

In order to reflect the clinical routine of siponimod patients in Germany as close as possible no inclusion/ exclusion criteria regarding age or disease severity were implemented. This means, any siponimod patient willing to undergo a SARS-CoV-2 vaccination in clinical routine may be suitable for AMA-VACC as long as all other inclusion/exclusion criteria are met. During screening patients will be excluded if detectable levels of SARS-CoV-2 specific antibodies can be detected or if patients have a positive SARS-CoV-2 PCR test result at screening in order to ensure participants did not have previous contact to the virus or vaccination. This is necessary to assess whether siponimod patients can mount a response after vaccination.

Rationale for chosen endpoints

The primary endpoint was chosen in analogy to recently completed and ongoing clinical trials of the modRNA vaccine BNT162b2 (Walsh et al, 2020; ClinicalTrials.gov Identifier: NCT04368728). The endpoints will provide evidence addressing whether siponimod treated patients can mount an immune response to a SARS-CoV-2 modRNA vaccine.

4.2 Rationale for dose/regimen and duration of treatment

Siponimod

Patients in cohort 1 and cohort 2 are treated with siponimod as part of clinical routine with 2 mg or 1 mg siponimod daily depending on CYP2C9 metabolisation status. The siponimod SmPC allows vaccination with non-live or attenuated substances both during continued daily intake of siponimod (cohort 1) or a treatment break for the purpose of the vaccination (cohort 2, duration of treatment break will be around 2-3 months)). In case of a booster vaccination, patients in both cohorts may undergo a treatment break according to SmPC. The decision to continue siponimod treatment or to interrupt the treatment is at the discretion of the treating physician together with the patient independent of AMA-VACC and as part of clinical routine.

Vaccination

Several pharmaceutical companies have received or are awaiting approval of modRNA vaccines including but not limited to BNT162 (Biontech/Pfizer) and mRNA-1273 (Moderna). AMA-VACC participants will be vaccinated with any modRNA vaccine according to the respective EU SmPC at the discretion of the treating physician independent of AMA-VACC. If suggested by local regulations and performed as part of clinical routine any type of booster/refresher vaccination (e.g. mRNA, vector, peptide) is allowed in this study.

4.3 Rationale for choice of reference treatment

First-line DMTs

Dimethyl fumarate, glatiramer acetate, interferons and teriflunomide applied as per respective EU SmPC were chosen as reference therapy as these drugs are routinely used as first line MS treatments and negative effects on vaccination outcomes are not expected according to respective SmPCs. An interruption of treatment for the purpose of a SARS-CoV-2 vaccination is not indicated in the respective SmPCs.

4.4 Purpose and timing of interim analyses

An interim analysis is planned after all participants have completed the study visit at one week after the end of the SARS-CoV-2 vaccination cycle in the study. The week +1 data regarding antibody and T-cell response (along with relevant safety data) will be examined as a preliminary evaluation of proof of concept and are the basis for the primary endpoint of the study.

Additional interim analyses may be conducted to support decision making concerning the current clinical study including an increase in participants (from 60 to 90), the sponsor's clinical development projects in general, or in case of any safety concerns.

Additional information is presented in the interim analysis section.

4.5 Risks and benefits

This study does not interfere with clinical routine treatment of MS patients regarding DMTs or SARS-CoV2 vaccinations. The only intervention is the blood sampling at specific time-points in the course of this trial. In the case that a blood sampling for antibody and T-cell response measurement is not related to a clinical routine blood draw, during patient's regular consultation, this blood draw could bear some minimal risk for the patient, associated with the sampling procedure (venous puncture). As of February 2021, for the currently EU approved mRNA vaccines (*COMIRNATY*® by BioNTech/Pfizer, *COVID 19 Vaccine Moderna* by Moderna), no data on safety and efficacy are available for patients with immunomodulating/immunosuppressive treatment as this condition was excluded from pivotal phase III clinical trials. However, as vaccines based on nucleoside modified RNA do not contain living viral particles, the risk to experience adverse events is considered similar as for healthy individuals. Thus, the risk evaluation for patients with immunomodulatory/immunosuppressive treatment is the same as for any other individual and the risks of the vaccine are considered much lower than the risks of suffering from (a severe course of) COVID-19 in the future.

However, this study involves the risk to reveal a reduced or insufficient immune response after vaccination in patients with immunomodulatory/immunosuppressive treatment. Although no data and recommendations are available for these circumstances, such a situation might require additional booster vaccination. Furthermore, the vaccine itself might have an effect on MS disease activity or on the anti-MS effect of the concomitant

immunosuppressing/immunomodulating therapy. However, no increased disease activity has been reported in MS patients in Israel that have received SARS-CoV-2 mRNA vaccination (DMSG statement, February 2021).

It is unlikely that there will be a direct benefit to the patient as a result of the participation in this study other than receiving the information whether measurable SARS-CoV-2 antibody and T-cell levels are reached after the vaccination. This information can then be used to decide whether an additional booster vaccination might be necessary in MS patients with/without concomitant immunosuppressing/immunomodulating therapy. Furthermore, the results of the study will contribute to a better understanding of immune responses to modRNA vaccines in siponimod treated SPMS patients. Findings can inform physicians and patients if risk factor management may need to be reviewed and potentially give additional guidance for vaccination with the novel class of modRNA vaccines in MS patients.

4.5.1 Blood sample volume

A volume smaller than a typical blood donation is planned to be collected over a period of up to 9 months, from each participant as part of the study. Additional samples may be required for safety monitoring.

Timings of blood sample collection are outlined in the assessment schedule (Table 8-1).

A summary blood log is provided in the laboratory manual. Instructions for sample collection, processing, storage and shipment information are also available in the laboratory manual.

Blood samples will be stored until the end of the study in case measurements need to be repeated.

5 Study Population

The study population will consist of 60 (optional increase to 90 after first interim analysis) females and males at risk for SPMS or with SPMS diagnosis treated in clinical routine with either siponimod, a first line MS DMT or no current therapy.

5.1 Inclusion criteria

Participants 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. One of the following MS treatments as part of clinical routine (according to respective SmPC):
    a. **Cohort 1**: Siponimod treatment according to EU SmPC **without interrupting daily dosing** for the purpose of vaccination with SARS-CoV-2 modRNA
    b. **Cohort 2**: Siponimod treatment according to EU SmPC **interrupting daily dosing** for the purpose of vaccination with SARS-CoV-2 modRNA

c. **Cohort 3**: Dimethylfumarate, glatirameracetate, interferon, teriflunomide as per respective EU SmPC or no current treatment with diagnosis of SPMS or with RRMS at risk to develop SPMS (at the discretion of the treating physician)

3. Planning to receive a SARS-CoV-2 modRNA vaccination as part of clinical routine
4. No change regarding DMT within 4 weeks prior to inclusion to AMA-VACC, i.e. stable on current DMT according to dosing within label, no interruption, start or withdrawal of DMT in this period of time and no planned switch of DMT within following 2 months
5. Patients willing and eligible to receive a modRNA vaccine against COVID-19 as part of clinical routine

5.2 Exclusion criteria

Participants meeting **any** of the following criteria are not eligible for inclusion in this study.

1. History of COVID-19
2. SARS-CoV-2 antibodies at screening
3. Patients likely not being able or willing to complete the study
4. Use of other investigational drugs within 5 half-lives of enrollment/initiation of study treatment (e.g. small molecules) or until the expected pharmacodynamic effect has returned to baseline (e.g., biologics), whichever is longer
5. Patients with any medical or psychological condition that, in the investigators opinion, renders the patient unable to understand the nature, scope, and possible consequences of the study and who are therefore not able to comply with the requirements of the study and capable of giving informed consent
6. No person directly associated with the administration of the study is allowed to participate as a study subject
7. No family member of the investigational study staff is allowed to participate in this study
8. Known or suspected clinically relevant allergy, intolerance or hypersensitivity to peanuts, soya (only cohort 1 and 2) or to any of the study treatments designated for the individual subject (DMTs or mRNA vaccines) or drugs of similar chemical classes (active substance or excipients)
9. 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 10 days of study treatment after stopping medication. Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the participant. 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 participants on the study, the vasectomized male partner should be the sole partner for that participant
- 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 bilateral 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.

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

10. For cohort 3: patients with contraindications for their current MS medication according to the respective EU SmPC:
    - Teriflunomide: Patients with severe hepatic impairment (Child-Pugh class C), severe immunodeficiency states (e.g. acquired immunodeficiency syndrome), significantly impaired bone marrow function or significant anemia, leucopenia, neutropenia or thrombocytopenia, severe active infection until resolution, severe renal impairment undergoing dialysis or severe hypoproteinaemia (e.g. nephrotic syndrome)
    - Dimethylfumarate: Patients with suspected or confirmed Progressive Multifocal Leukoencephalopathy (PML)
    - Interferons: Patients with current severe depression and/or suicidal ideation and patients with decompensated liver disease

6 Treatment

6.1 Study treatment

All study treatment is part of clinical routine. This trial does not interfere with the treatment of individual patients. All treatments will be performed according to respective EU SmPCs.

6.1.1 Investigational and control drugs

Table 6-1 merely serves as overview on the different treatments investigated in individual cohorts. This is not a guidance for treatment as all treatments are performed as part of clinical routine and according to respective EU SmPCs.

Table 6-1 Investigational and control drug

Treatment Arm	Type of Study Drug	Compound	Min Dose	Max Dose	Frequency	Admin. Route
Cohort 1	investigational	modRNA	Clinical routine (EU SmPC)	Clinical routine (EU SmPC)	Clinical routine (EU SmPC)	i.m. (EU SmPC)
	investigational	vector vaccine	Clinical routine (EU SmPC)	Clinical routine (EU SmPC)	Clinical routine (EU SmPC)	i.m. (EU SmPC)
	investigational	siponimod	1 mg (EU SmPC)	2 mg (EU SmPC)	Daily (EU SmPC)	Oral (EU SmPC)
Cohort 2	investigational	modRNA	Clinical routine (EU SmPC)	Clinical routine (EU SmPC)	Clinical routine (EU SmPC)	i.m. (EU SmPC)
	investigational	vector vaccine	Clinical routine (EU SmPC)	Clinical routine (EU SmPC)	Clinical routine (EU SmPC)	i.m. (EU SmPC)
	investigational	Siponimod treatment interrupted	1 mg (treatment interruption for vaccination) (EU SmPC)	2 mg (treatment interruption for vaccination) (EU SmPC)	Daily (EU SmPC)	Oral (EU SmPC)
Cohort 3	investigational	modRNA	Clinical routine (EU SmPC)	Clinical routine (EU SmPC)	Clinical routine (EU SmPC)	i.m. (EU SmPC)
	investigational	vector vaccine	Clinical routine (EU SmPC)	Clinical routine (EU SmPC)	Clinical routine (EU SmPC)	i.m. (EU SmPC)
	investigational	no treatment or first-line according to label	Clinical routine (EU SmPC)	Clinical routine (EU SmPC)	Clinical routine (EU SmPC)	Clinical routine (EU SmPC)

6.1.2 Supply of study treatment

All study treatment is part of clinical routine. There will be no supply.

6.1.3 Treatment arms

Participants will be assigned at screening to one of the following "3" treatment arms in a ratio of "1:1:1" based on the MS treatment received in clinical routine at this point. There is no randomization and no distribution of study drug within the trial.

- **Cohort 1:** Siponimod treatment **without interrupting daily dosing** for the purpose of a SARS-CoV-2 modRNA vaccination. In case of a booster vaccination, patients in this cohort may undergo a treatment break according to SmPC.
- **Cohort 2:** Siponimod treatment **interrupting daily dosing** (for approximately 2-3 months) for the purpose of a SARS-CoV-2 modRNA vaccination
- **Cohort 3:** Dimethylfumarate, glatirameracetate, interferon, teriflunomide according to respective EU SmPC or no current treatment without a change in treatment for the purpose of a SARS-CoV-2 modRNA vaccination

6.2 Other treatment(s)

Not applicable.

6.2.1 Concomitant therapy

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate Case Report Forms.

No studies have been performed to assess interactions of mRNA vaccines with other drugs or other vaccines.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

a) For cohort 1 and 2:

Antineoplastic, immune-modulating or immunosuppressive therapies

Siponimod has not been studied in combination with antineoplastic, immune-modulating or immunosuppressive therapies. Caution should be exercised during concomitant administration due to the risk of additive immune effects during such therapy and in the weeks after administration of any of these medicinal products.

Due to the characteristics and duration of alemtuzumab immune suppressive effects described in its product information, initiating treatment with siponimod after alemtuzmab is not recommended unless the benefits of treatment clearly outweigh the risks for the individual patient.

Anti-arrhythmic medicinal products, QT-prolonging medicinal products, medicinal products that may decrease heart rate

During treatment initiation siponimod should not be concomitantly used in patients receiving class Ia (e.g. quinidine, procainamide) or class III (e.g. amiodarone, sotalol) anti-arrhythmic medicinal products, QT-prolonging medicinal products with known arrhythmogenic properties, heart-rate-lowering calcium channel blockers (such as verapamil or diltiazem) or other substances that may decrease heart rate (e.g. ivabradine or digoxin) because of the potential additive effects on heart rate (see section 4.4 of Siponimod SmPC). No data are available for concomitant use of these medicinal products with siponimod. Concomitant use of these substances during treatment initiation may be associated with severe bradycardia and heart block. Because of the potential additive effect on heart rate, treatment with siponimod should generally not be initiated in patients who are concurrently treated with these substances (see section 4.4 of Siponimod SmPC). If treatment with siponimod is considered, advice from a cardiologist should be sought regarding the switch to non-heart-rate-lowering medicinal products or appropriate monitoring for treatment initiation.

Beta blockers

Caution should be exercised when siponimod is initiated in patients receiving beta blockers due to the additive effects on lowering heart rate (see section 4.4 of Siponimod SmPC). Beta-blocker treatment can be initiated in patients receiving stable doses of siponimod. The negative chronotropic effect of co-administration of siponimod and propranolol was evaluated in a dedicated pharmacodynamic/safety study. The addition of propranolol on top of siponimod pharmacokinetic/pharmacodynamic steady state had less pronounced negative chronotropic

effects (less than additive) in comparison to addition of siponimod on top of propranolol pharmacokinetic/pharmacodynamic steady state (additive HR effect).

Vaccination

According to the IB the administration of any live or live-attenuated vaccine (including for measles) is prohibited while patients are receiving siponimod and for 4 weeks after siponimod discontinuation. They may be administered thereafter once there is confirmation that lymphocyte levels are in the normal range.

According to the IB non-live attenuated vaccines may be less effective if administered during siponimod treatment (Ufer et al., 2017). The decision whether to continue or pause the treatment with siponimod should be based on the benefit-risk assessment of the individual patient. The efficacy of vaccination is not considered to be compromised if siponimod treatment is paused 1 week prior to vaccination until 4 weeks after (see section 4.4 of Siponimod SmPC).

Potential of other medicinal products to affect siponimod pharmacokinetics

Siponimod is metabolised primarily by cytochrome P450 2C9 (CYP2C9) (79.3%) and to a lesser extent by cytochrome P450 3A4 (CYP3A4) (18.5%). CYP2C9 is a polymorphic enzyme and the drug-drug interaction (DDI) effect in the presence of CYP3A or CYP2C9 perpetrator drugs is predicted to be dependent on the CYP2C9 genotype.

CYP2C9 and CYP3A4 inhibitors

Because of a significant increase in exposure to siponimod, concomitant use of siponimod and medicinal products that cause moderate CYP2C9 and moderate or strong CYP3A4 inhibition is not recommended. 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.

The co-administration of fluconazole (moderate CYP2C9/strongCYP3A4 inhibitor) 200 mg daily at steady state and a single dose of siponimod 4 mg in healthy volunteers with a CYP2C9*1*1 genotype led to a 2-fold increase in the area under the curve (AUC) of siponimod. According to evaluation of the drug interaction potential using physiologically based pharmacokinetic (PBPK) modelling, a maximum of a 2-fold increase in the AUC of siponimod is predicted across genotypes with any type of CYP3A4 and CYP2C9 inhibitors except for patients with a CYP2C9*2*2 genotype. In CYP2C9*2*2 patients, a 2.7-fold increase in the AUC of siponimod is expected in the presence of moderate CYP2C9/CYP3A4 inhibitors.

CYP2C9 and CYP3A4 inducers

Siponimod may be combined with most types of CYP2C9 and CYP3A4 inducers. However, because of an expected reduction in siponimod exposure, the appropriateness and possible benefit of the treatment should be considered when siponimod is combined:

- with strong CYP3A4/moderate CYP2C9 inducers (e.g. carbamazepine) in all patients regardless of genotype.
- with moderate CYP3A4 inducers (e.g. modafinil) in patients with a CYP2C9*1*3 or *2*3 genotype.

A significant reduction of siponimod exposure (by up to 76% and 51%, respectively) is expected under these conditions according to evaluation of the drug interaction potential using PBPK modelling. The co-administration of siponimod 2 mg daily in the presence of 600 mg daily

doses of rifampin (strong CYP3A4 and moderate CYP2C9 inducer) decreased siponimod AUCtau,ss and Cmax,ss by 57% and 45%, respectively, in CY2C9*1*1 subjects.

b) For cohort 3:

Dimethylfumarate

Tecfidera has not been studied in combination with anti-neoplastic or immunosuppressive therapies and caution should, therefore, be used during concomitant administration. In multiple sclerosis clinical studies, the concomitant treatment of relapses with a short course of intravenous corticosteroids was not associated with a clinically relevant increase of infection.

Concomitant administration of non-live vaccines according to national vaccination schedules may be considered during Tecfidera therapy. In a clinical study involving a total of 71 patients with relapsing remitting multiple sclerosis, patients on Tecfidera 240 mg twice daily for at least 6 months (n=38) or non-pegylated interferon for at least 3 months (n=33), mounted a comparable immune response (defined as ≥2-fold increase from pre- to post-vaccination titer) to tetanus toxoid (recall antigen) and a conjugated meningococcal C polysaccharide vaccine (neoantigen), while the immune response to different serotypes of an unconjugated 23-valent pneumococcal polysaccharide vaccine (T-cell independent antigen) varied in both treatment groups. A positive immune response defined as a ≥4-fold increase in antibody titer to the three vaccines, was achieved by fewer subjects in both treatment groups. Small numerical differences in the response to tetanus toxoid and pneumococcal serotype 3 polysaccharide were noted in favour of non-pegylated interferon.

No clinical data are available on the efficacy and safety of live attenuated vaccines in patients taking Tecfidera. Live vaccines might carry an increased risk of clinical infection and should not be given to patients treated with Tecfidera unless, in exceptional cases, this potential risk is considered to be outweighed by the risk to the individual of not vaccinating.

During treatment with Tecfidera, simultaneous use of other fumaric acid derivatives (topical or systemic) should be avoided.

Glatiramer acetate

Interaction between Copaxone and other medicinal products have not been formally evaluated. There are no data on interaction with interferon beta.

An increased incidence of injection site reactions has been seen in Copaxone patients receiving concurrent administration of corticosteroids.

Interferons

No interaction studies have been performed with interferon beta-1a in humans.

Interferons have been reported to reduce the activity of hepatic cytochrome P450-dependent enzymes in humans and animals. Caution should be exercised when administering e.g. Rebif in combination with medicinal products that have a narrow therapeutic index and are largely

dependent on the hepatic cytochrome P450 system for clearance, e.g. antiepileptics and some classes of antidepressants.

Teriflunomide

The primary biotransformation pathway for teriflunomide is hydrolysis, with oxidation being a minor pathway.

Potent cytochrome P450 (CYP) and transporter inducers
Co-administration of repeated doses (600 mg once daily for 22 days) of rifampicin (a CYP2B6, 2C8, 2C9, 2C19, 3A inducer), as well as an inducer of the efflux transporters P-glycoprotein [P-gp] and breast cancer resistant protein [BCRP] with teriflunomide (70 mg single dose) resulted in an approximately 40% decrease in teriflunomide exposure. Rifampicin and other known potent CYP and transporter inducers such as carbamazepine, phenobarbital, phenytoin and St John's Wort should be used with caution during the treatment with teriflunomide.

Cholestyramine or activated charcoal
It is recommended that patients receiving teriflunomide are not treated with cholestyramine or activated charcoal because this leads to a rapid and significant decrease in plasma concentration unless an accelerated elimination is desired. The mechanism is thought to be by interruption of enterohepatic recycling and/or gastrointestinal dialysis of teriflunomide.

Pharmacokinetic interactions of teriflunomide on other substances

Effect of teriflunomide on CYP2C8 substrate: repaglinide
There was an increase in mean repaglinide Cmax and AUC (1.7- and 2.4-fold, respectively), following repeated doses of teriflunomide, suggesting that teriflunomide is an inhibitor of CYP2C8 in vivo. Therefore, medicinal products metabolised by CYP2C8, such as repaglinide, paclitaxel, pioglitazone or rosiglitazone, should be used with caution during treatment with teriflunomide.

Effect of teriflunomide on oral contraceptives: 0.03 mg ethinylestradiol and 0.15 mg levonorgestrel
There was an increase in mean ethinylestradiol Cmax and AUC0-24 (1.58- and 1.54-fold, respectively) and levonorgestrel Cmax and AUC0-24 (1.33- and 1.41-fold, respectively) following repeated doses of teriflunomide. While this interaction of teriflunomide is not expected to adversely impact the efficacy of oral contraceptives, it should be considered when selecting or adjusting oral contraceptive treatment used in combination with teriflunomide.

Effect of teriflunomide on CYP1A2 substrate: caffeine
Repeated doses of teriflunomide decreased mean Cmax and AUC of caffeine (CYP1A2 substrate) by 18% and 55%, respectively, suggesting that teriflunomide may be a weak inducer of CYP1A2 in vivo. Therefore, medicinal products metabolised by CYP1A2 (such as duloxetin, alosetron, theophylline and tizanidine) should be used with caution during treatment with teriflunomide, as it could lead to the reduction of the efficacy of these medicinal products.

Effect of teriflunomide on warfarin
Repeated doses of teriflunomide had no effect on the pharmacokinetics of S-warfarin, indicating that teriflunomide is not an inhibitor or an inducer of CYP2C9. However, a 25% decrease in

peak international normalised ratio (INR) was observed when teriflunomide was coadministered with warfarin as compared with warfarin alone. Therefore, when warfarin is co-administered with teriflunomide, close INR follow-up and monitoring is recommended.

Effect of teriflunomide on organic anion transporter 3 (OAT3) substrates
There was an increase in mean cefaclor Cmax and AUC (1.43- and 1.54-fold, respectively), following repeated doses of teriflunomide, suggesting that teriflunomide is an inhibitor of OAT3 in vivo. Therefore, when teriflunomide is coadministered with substrates of OAT3, such as cefaclor, benzylpenicillin, ciprofloxacin, indometacin, ketoprofen, furosemide, cimetidine, methotrexate, zidovudine, caution is recommended.

Effect of teriflunomide on BCRP and /or organic anion transporting polypeptide B1 and B3 (OATP1B1/B3) substrates
There was an increase in mean rosuvastatin Cmax and AUC (2.65- and 2.51-fold, respectively), following repeated doses of teriflunomide. However, there was no apparent impact of this increase in plasma rosuvastatin exposure on the HMG-CoA reductase activity. For rosuvastatin, a dose reduction by 50% is recommended for coadministration with teriflunomide. For other substrates of BCRP (e.g., methotrexate, topotecan, sulfasalazine, daunorubicin, doxorubicin) and the OATP family especially HMG-Co reductase inhibitors (e.g., simvastatin, atorvastatin, pravastatin, methotrexate, nateglinide, repaglinide, rifampicin) concomitant administration of teriflunomide should also be undertaken with caution. Patients should be closely monitored for signs and symptoms of excessive exposure to the medicinal products and reduction of the dose of these medicinal products should be considered.

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial. The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis/Sponsor to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available.

6.3.2 Treatment assignment, randomization

No randomization will be performed in this study. The assignment of a participant to a particular cohort will be coordinated by the sponsor depending on the current MS treatment in clinical routine: Cohort 1: continued siponimod treatment without interruption for the purpose of a SARS-CoV-2 vaccination (except for a booster vaccination). Cohort 2: interruption of siponimod treatment for the purpose of a SARS-CoV-2 vaccination. Cohort 3: first-line MS treatment other than siponimod or no current treatment.

7 Informed consent procedures

Eligible participants may only be included in the study after providing, IRB/IEC-approved informed consent.

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 participant 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.

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

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Participants 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, the adverse event and concomitant medications should be recorded on the CRF. Unscheduled on-site visits are possible e.g. to repeat sampling in case of lost or unusable samples, in case of suspected safety issues. Additional telephone visits shall be scheduled in case of booster/refresher SARS-CoV-2 vaccinations to document type and date of the booster vaccination. Additionally, 1 month (+/- 1 week) after a potential booster vaccination a booster visit will be scheduled that includes all assessments performed in the regular study visit 3 including the drawing of blood samples. If this booster visit falls within +/-1 week of the regular visit 3 or later than the telephone contact in month 12, it will not be performed.

8.1 Documentation of IMPs

Both MS DMTs and SARS-CoV-2 vaccinations are considered as IMPs in this study. As part of drug accountability the following documentation of IMP treatment is required to allow a valid analysis of immune responses to vaccinations in combination with MS treatment.

Documentation of MS DMTs

- At screening
    - Documentation of the current prescription and lot number (Ch-B) of the currently applied MS DMT and number of remaining doses in the package. This information may also be obtained via telephone.
- Investigational epoch (Month 1-12 after vaccination)
    - Documentation of all re-newed MS-DMT prescriptions including lot numbers (Ch-B) of the medication packages. For this purpose, patients should bring any new and empty MS DMT packages (including empty blisters) to the next possible study visit for documentation purposes. Ch-B numbers may also be obtained via telephone contacts.

Should patients fail to bring new or empty MS DMT packages and blisters to the study center even after documented reminders it is also allowed to calculate the compliance from the interval of prescriptions. The compliance as judged by the treating physician shall be documented in the eCRF.

Documentation of SARS-CoV-2 vaccinations

- **Vaccination at external site**
    - A scan/copy of the "Impfpass" document

- Documentation timepoint of vaccination (date and hour)
- Documentation which external site performed vaccination

- **Vaccination within clinic but outside study site**
  - A scan/copy of the "Impfpass" document
  - Documentation timepoint of vaccination (date and hour)
  - Documentation of department and responsible person for vaccination
  - Confirmation that vaccination was performed according to clinical routine
  - Confirmation that temperature log cannot be obtained
- **Vaccination at study site**
  - **Preparation of syringes directly after delivery to study site**
    - Documentation DSL authorization
    - Documentation timepoint syringe preparation (to make sure 6h at room temperature is not exceeded)
    - Documentation temperature log of refrigerator (if used for storage)
    - A scan/copy of the "Impfpass" document
    - Documentation timepoint of vaccination (date and hour)
  - **Preparation of syringes NOT directly after delivery to study site**
    - Documentation DSL authorization
    - Documentation temperature log of refrigerator
    - Documentation timepoint syringe preparation (to make sure 6h at room temperature is not exceeded)
    - A scan/copy of the "Impfpass" document
    - Documentation timepoint of vaccination (date and hour)

8.2 Participant demographics/other baseline characteristics

Anamnesis, participant demographics (year of birth, sex, race) and relevant medical history/current medical conditions including MS disease and current treatment will be documented.

All prescription medications, over-the-counter drugs and significant non-drug therapies prior to the start and during the study must be documented. See the protocol Section 6.2.1 Concomitant Therapy for further details on what information must be recorded on the appropriate page of the eCRF.

8.3 Screening

Re-screening is not permitted.

8.3.1 Eligibility screening

At screening blood sampling and analysis is performed to check for pre-existing SARS-CoV-2 functional antibodies. If detectable levels are present, the patient is not eligible to further participate in the study. Furthermore, SARS-CoV-2 PCR testing will be performed at screening to exclude current COVID-19 infection. In case of a positive test result, the patient is sent to quarantine and is not eligible to further participate in the study.

8.3.2 Information to be collected on screening failures

Participants who sign an informed consent form and subsequently found to be ineligible will be considered a screen failure. The reason for screen failure should be entered on the applicable Case Report Form. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening phase (see SAE section for reporting details).

Table 8-1 Assessment schedule

Period	**Screening**	**Vaccination[#]**		**Investigational**					**COVID-19 follow-up call**
Visit	Screen	Vaccination 1[#]	Vaccination 2[#]	1	2	3	booster vaccination[Ω]	booster visit[Ω]	Call (end of study)
Day/Week/Month	Day -30 to -3	Day 1*	Week 3/4*	Week +1 (day 8 +/- 2)	Month +1 (day 28-35)	Month +6 (week 25-27)	any time	Month +1 (+/- 1 week) after booster vaccination	Month +12 (week 50-54)
Obtain informed consent	X								
Inclusion/exclusion criteria	X								
Demography, Relevant medical and MS history	X								
Physical exam including vital signs, height weight	F			S	S	F		F	
SARS-CoV-2 PCR test**	X								
Urine pregnancy test***	X					X		X	
Blood sampling	X			X	X	X		X	
MS relapse	X****	X	X	X	X	X	X	X	
Status MS- and concomitant medication	X	X	X	X	X	X	X	X	X
Documentation SARS-CoV-2 vaccination		X	X				X		
Telephone contact		X	X				X		X
AE/SAE	X	X	X	X	X	X	X	X	X

X = assessment to be recorded in the clinical database or received electronically from a vendor
F = full physical exam, S = short medical exam
[#] modRNA vaccination using the same type of compound in both vaccinations independent of study site at designated vaccination centers as part of clinical routine and depending on federal regulations; vaccination will be performed according to respective EU SmPC. Booster/refresher vaccinations are allowed in this study, if suggested by local regulations and performed as part of clinical routine. [Ω]If booster/refresher vaccinations are performed an additional telephone contact is required matching documentation parameters shown above for vaccination 1 and 2. [Ω]Furthermore, an additional study visit will be performed one month (+/- 1 week) after the booster vaccination matching all assessments of investigational visit 3. If this unscheduled visit falls within +/-1 week of the regular visit 3 or later than the telephone contact in month 12, it will not be performed. * Number of required vaccinations and interval depends on the SmPC of the respective modRNA vaccination. ** Patients need to be sent into quarantine immediately in case of positive test results. Patients in this study are only allowed to continue the study and receive SARS-CoV-2 vaccination after they received a negative PCR test result. *** Required minimum of sensitivity of the pregnancy test is HCG 25 mIU/mL. **** MS relapses within the last two years should be recorded.

8.4 Efficacy

Pharmacodynamic samples will be collected at the time-points defined in the Assessment Schedule (Table 8-1). Follow instructions outlined in the Laboratory manual regarding sample collection, numbering, processing, and shipment.

8.4.1 Efficacy assessment 1

SARS-CoV-2 vaccination efficacy is defined as seroconversion i.e. detection of SARS-CoV-2 serum functional antibodies one week after completion of the vaccination cycle.

8.4.2 Efficacy assessment 2

Additional efficacy assessments are:

- Longitudinal follow-up of SARS-CoV-2 serum functional antibody levels one week, one month and six months after second dose of vaccine and additionally 1 month after a potential booster vaccination
- Longitudinal follow-up of SARS-CoV-2 specific T-cell levels one week, one month and six months after second dose of vaccine and additionally 1 month after a potential booster vaccination

8.4.3 Appropriateness of efficacy assessments

Efficacy assessments in AMA-VACC are based on the study set up of the phase II clinical trial NCT04380701 (EudraCT: 2020-001038-36) for the SARS-COV-2 vaccination candidate BNT162b1 (Sahin et al., 2020). This study reports SARS-CoV-2 specific IgG antibodies one week after completion of the vaccination cycle at a stable level comparable to a later time-point. Similar results were also reported for mRNA-1273 by Jackson et al, 2020. The detection of specific antibody levels at one week post completion of the vaccination cycle was therefore chosen as primary endpoint.

Furthermore, BNT162b1 was shown to induce a $CD4^+$ and $CD8^+$ T-cell response (Sahin et al., 2020). Given the mode of action of siponimod targeting T_H17 lymphocytes – a subset of $CD4^+$ T-cells - it is of importance to understand the T-cell response to a SARS-CoV-2 vaccination in siponimod treated patients. This T-cell response was measured utilizing ex vivo IFNγ enzyme-linked immunosorbent spot (ELISpot) assays in the clinical development of BNT162b1 (Sahin et al., 2020) and was therefore also chosen to assess efficacy in the underlying trial.

8.5 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

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

Assessment	Specification
Physical examination	A complete physical examination will include the examination of vital signs (blood pressure [SBP and DBP] and pulse), height, weight, general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. A short physical exam will include the examination of general appearance and vital signs (blood pressure [SBP and DBP] and pulse). A short physical exam will be at all visits starting from visit 3 except where a complete physical examination is required (see above). Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.

Special clinical laboratory evaluations

All abnormal lab results must be evaluated for criteria defining an adverse event and reported as such if the criteria are met. For those lab adverse events, repeated evaluations are mandatory until normalization of the result(s) or until the result is no longer considered to be clinically significant.

Test Category	Test Name
SARS-CoV-2 vaccination antibody response	Serum functional SARS-CoV-2 antibodies
SARS-CoV-2 vaccination T-cell response	Ex vivo IFNγ enzyme-linked immunosorbent spot (ELISpot)

9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

All medication is part of clinical routine.

Discontinuation of study treatment for a participant occurs when study treatment is stopped earlier than the protocol planned duration and can be initiated by either the participant or the investigator.

The investigator must discontinue study treatment for a given participant if, he/she believes that continuation would negatively impact the participant's well-being.

Study treatment must be discontinued under the following circumstances:

- Participant/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section
- New medical condition not allowing for continuation of study treatment
- Any situation in which study participation might result in a safety risk to the participant
- Adverse events, abnormal laboratory values or abnormal test result that indicate a safety risk to the participant.

Study discontinuation of a participants occurs under the following circumstances:

- Significant non-compliance
- Retroactive failure to fulfil inclusion/exclusion criteria
- Enrolment in any other clinical trial involving an investigational product or enrolment in any other type of medical research judged not to be scientifically or medically compatible with this study

Participants who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 9.1.2 'Withdrawal of Informed Consent' section). **Where possible, they should return for the assessments indicated** in the Assessment Schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the participant/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

Patients completing the vaccination cycle but do not come to the center for the blood draw one week later (6-10 days after second vaccination) will be excluded from the study.

9.1.1.1 Replacement policy

Patients failing the screening visit (detectable levels of SARS-CoV-2 serum functional antibodies) will be replaced. Patients successfully screened who do not receive a mod-RNA SARS-CoV-2 vaccination according to EU SmPC within 1 month after screening will be excluded from the study and replaced unless the patient is currently not eligible for SARS-CoV-2 vaccination by local regulation. In this case, the Novartis Medical Advisor should be contacted to discuss further proceeding including re-evaluation of anti-SARS-CoV-2 antibody level and PCR test. Patients developing symptoms of COVID-19 or have a SARS-CoV-2 infection (positive test result) between screening and first vaccination will be excluded from the study and will be replaced.

9.1.2 Withdrawal of informed consent

Participants may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a participant:

- Does not want to participate in the study anymore,

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw his/her consent and record this information.

Where consent to the use of personal and coded data is not required, participant therefore cannot withdraw consent. They still retain the right to object to the further use of personal data.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study discontinuation. A final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table.

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

For participants 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 participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a prematurely withdrawn participant. 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 participant's interests. The investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last participant finishes their Study Completion visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision.

All patients in the present study are treated as part of the clinical routine. The interventional character of the study is limited to collection and analysis of blood samples.

There is no plan for further treatment and medical care for the study participants after the end of the clinical trial. After completion, all study participants regardless of the reasons will continue to be cared for as part of the clinical routine and further treatment will be discussed individually with investigator.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual participant and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The Common Toxicity Criteria (CTC) AE grade (version 5 or higher):

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version. CTCAE grade 5 will be used to capture death information within the eCRF.

2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant
3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment.

   All adverse events must be treated appropriately. Treatment may include one or more of the following:
   - Dose not changed
   - Dose Reduced/increased
   - Drug interrupted/withdrawn
6. Its outcome (i.e. recovery status or whether it was fatal)

Conditions that were already present at the time of informed consent should be recorded in medical history of the participant.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 30 days following the last study visit (Covid-19 follow-up call).

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

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participant with the underlying disease.

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 participant 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 deterioration in condition
  - 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 participant'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 participant or may require medical or surgical intervention to prevent one of the outcomes listed above

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 participant 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).

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

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

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days after the last study visit must be reported to

Novartis safety immediately, without undue delay but not later than 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.

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 immediately, without undue delay but not later than 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.

Every SAE occurring to a subject after completion of the clinical trial has to be reported to the sponsor by the investigator if it is suspected to be causally related to the investigation product.

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.

10.1.4 Pregnancy reporting

Pregnancies

If a female trial participant becomes pregnant, the study treatment should be stopped, and the trial participant must be asked to read and sign pregnancy consent form to allow the Study Doctor ask about her pregnancy. To ensure participant 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 treatmentany pregnancy outcome. Any SAE experienced during pregnancy must be reported.

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, participant 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 CRF 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.

11 Data Collection and Database management

11.1 Data collection

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 CRFs) (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 participant 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 World Health Organization (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.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis 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 will apply 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 participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment. For this clinical trial, it will specifically be verified that patients have received a permitted SARS-CoV-2 mRNA vaccine during initial vaccination cycle by checking the patient's vaccination certificate. As this study aims at resembling the clinical routine as closely as possible, field monitors will confirm the patients' treatment adherence during on site monitoring visits by verifying the continuous prescription of the respective MS drug (prescription records or equivalent sources). Key study personnel must be available to assist the field monitor during these visits. 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 participant 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 CRFs must be traceable to these source documents in the participant's file. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

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 CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

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

12.1 Analysis sets

For all analysis sets, participants will be analyzed according to the study treatment(s) received.

The safety analysis set will include all participants that received any study drug.

The efficacy analysis sets at one week, one month and six month and additionally after a potential booster vaccination respectively will include all participants who have a valid determination of functional antibodies to SARS-CoV-2 at that time point plus those who failed to receive their second dose of vaccine for whatever reason. The latter will be counted as non-responders. Patients completing vaccination but fail to provide a blood sample at one week after the second vaccination will be excluded from the study and analysis.

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment group (Cohort 1-3) for the FAS.

The Safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

For Cohort 1, the continued siponimod intake after vaccination will be presented. For Cohort 2 the duration of discontinuation (time between last prior to vaccination and first dose after vaccination will be summarized. For Cohort 3, the various base DMTs will be summarized (type, doses and duration) as appropriate.

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, by cohort.

12.3 Analysis of the primary endpoint

The primary clinical question in this trial is: what is the proportion of SPMS patients treated with siponimod within the tree cohorts defined below which mount an immune response to a SARS-CoV-2 modRNA vaccine?

12.3.1 Definition of primary endpoint(s)/estimand(s)

The primary endpoint of the study is the proportion of participants achieving seroconversion as defined by detection of SARS-CoV-2 serum functional antibodies one week after second dose of vaccine in participants treated concomitantly with siponimod and siponimod treatment break (yes/no).

12.3.2 Statistical model, hypothesis, and method of analysis

The primary analysis will not use any statistical testing or modelling. The absolute numbers and the proportion of participants achieving seroconversion within each cohort will be calculated. It will be augmented by a (descriptive) 95% confidence interval (exact Clopper-Pearson).

12.3.3 Handling of remaining intercurrent events of primary estimand

Patients who fail to receive their second dose of vaccine for whatever reason will be included in the analysis as non-responders. Patients who did receive their second dose of vaccine and do not have a valid determination of functional antibodies to SARS-CoV-2 for whatever reason will be excluded from the analysis of vaccine efficacy.

12.3.4 Supportive analyses

Patient demographics and baseline characteristics among 3 cohorts will be compared in the data analysis. Also the treatment interruption time of the selected cohort 2 patients will be compared to that of other siponimod treated patients in AMASIA interrupting daily dosing as per label for the purpose of vaccination with SARS-CoV-2 modRNA as part of clinical routine. If major imbalance is discovered, the study results will be interpreted with more caution and post-hoc supportive analyses may be conducted to adjust for the imbalance.

12.4 Analysis of secondary endpoints

All secondary endpoints will be summarized descriptively as frequencies and percentages, or, for continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

12.4.1 Safety endpoints

For all safety analyses, the safety set will be used. All listings and tables will be presented by cohort.

Safety summaries (tables, figures) include only data from the on-treatment period which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary 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 month 12 COVID-19 follow-up call.

Adverse events

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

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

- by cohort, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation, and adverse events leading to dose adjustment.

A participant with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Vital signs

All vital signs data will be listed by treatment group, participant, and visit/time and if ranges are available, abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by treatment group (cohort 1-3), participant, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

12.5 Interim analyses

An interim analysis will be performed when all participants have completed study visit 1 (one week after SARS-CoV-2 vaccination cycle completion) as this reflects the primary endpoint. As all analyses in this study are purely descriptive, there is no need for any statistical adjustments. Additional interim analyses may be conducted to support decision making concerning the current clinical study including an increase in participants (from 60 to 90), the sponsor's clinical development projects in general, or in case of any safety concerns.

12.6 Sample size calculation

12.6.1 Primary endpoint(s)

The sample size of 20 participants per arm is selected based on need for early availability of results for the current covid-19 pandemic and the feasibility to recruit sufficient participants from AMASIA and PANGAEA 2.0 EVOLUTION. This sample size of 20 subjects will provide estimates of proportion responded with margin of error (half-width of a 95% confidence interval) of 20.1%, 19%, and 17.5% corresponding to response rates of 70%, 75%, and 80%, respectively. Adjusting for 10% drop-out, 22 subjects will be enrolled in each arm. In case of fast recruitment the sponsor is allowed to increase sample size in each arm by up to 10 additional patients to support the generation of meaningful data in a larger sample size.

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, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. 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 (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 participants 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 participant 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 participant 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.

15 References

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