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Novartis Research and Development

Ofatumumab (OMB157)

Synopsis/Clinical Trial Protocol COMB157GDE01 / NCT04869358

Tracking the immune response to SARS-CoV-2 modRNA vaccines in an open-label multicenter study in participants with relapsing multiple sclerosis treated with ofatumumab s.c. (KYRIOS)

Document type:	Amended Protocol Version
EUDRACT number:	2021-000307-20
Version number:	03
Clinical Trial Phase:	IV
Release date:	28-Mar-2022

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List of abbreviations

AE	Adverse Event
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical study report
DQF	Data Query Form
ELISpot	Enzyme-linked immunospot
eSource	Electronic Source
GCP	Good Clinical Practice
GCS	Global Clinical Supply
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFN	Interferon
Nab	Neutralizing antibody
QMS	Quality Management System
s.c.	subcutaneous
SAE	Serious Adverse Event
SD	standard deviation
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TD	Study Treatment Discontinuation
WHO	World Health Organization
WoC	Withdrawal of Consent

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Cohort	A specific group of participants fulfilling certain criteria and generally treated at the same time
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant or at a later point in time as defined by the protocol
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained
Estimand	A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same patients under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Participant	A trial participant (can be a healthy volunteer or a patient)
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis

Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Run-in Failure	A participant who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to participant's intervention or other treatment)
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a participant does not want to participate in the study any longer and does not allow any further collection of personal data

Amendment 3

Amendment Summary:

Main changes in the amendment include termination of recruitment, addition of a study visit and omitting of study exclusion after use of prohibited medication.

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 who have not yet received their initial or booster SARS-CoV-2 vaccination and fit the inclusion/exclusion criteria (especially "no known prior COVID-19 infection"). Therefore, recruitment will be officially stopped with the approval of this amendment.

Addition of study visit: An additional visit will be performed 1 month after the second booster vaccine. Assessment of the immune response at the same time point after two consecutive vaccinations is necessary to draw conclusions on the formation of a memory immune response. In order to collect this information, an additional study visit is necessary.

Prohibited medication: Non-mRNA vaccines will still be listed as prohibited medication but patients receiving this kind of vaccine will no longer be excluded from the study. So far, there is only very limited information available with regards to the immune response in ofatumumab treated patients after SARS-CoV-2 vaccination. It is therefore essential to capture as much information about maintenance of immune response in this vulnerable patient cohort as possible in order to provide the best guidance for patients and physicians. As vaccination is the main tool to fight the pandemic, all patients are encouraged to receive booster vaccines. It is not planned that these boosters are non-mRNA vaccines but if it happens, this should not lead to study continuation but will instead be reflected in the analysis.

Changes to the protocol:

Section 3: Study design:

- Foot note below study design was changed to reflect that an additional visit should be performed after the second booster vaccine.
- Specification that patients in cohorts 1b and 2b have to receive their first SARS-CoV-2 mRNA booster during the study.

Section 6.2.2: Prohibited medication:

- Vaccination with non-mRNA vaccines won't lead to exclusion of these patients

Section 8: Visit schedule and assessments

- Visit schedules for all cohorts were updated to reflect additional visits after the second booster vaccine.

Section 12.4.4: Supportive analyses:

- Sentence was added to describe that it will be reflected in the analysis if patients should receive a non-mRNA vaccine as booster.

Amendment 2

Amendment Summary:

Main changes in the amendment include splitting of each cohort into two subcohorts, corresponding changes in the treatment schedule, adaption of the primary endpoint and the exclusion criteria as well as addition of an interim analysis.

Study design: Based on current discussions about the necessity of SARS-CoV-2 booster vaccines in immunocompromised patients, the immune response of patients with MS after booster vaccines should be investigated. The existing cohorts that receive SARS-CoV-2 vaccination either before or after starting ofatumumab treatment, were therefore divided into two subcohorts each: the first subcohort (cohort 1a and 2a) will receive their initial SARS-CoV-2 vaccination (1st and 2nd vaccine) within the study while the other subcohort (cohort 1b and 2b) will receive a booster shot during the study.

Primary endpoint: The primary endpoint was adjusted to reflect the new study design. In order to have comparable data after the initial vaccination cycle and the booster vaccine, the primary endpoint will be measured 1 month after either the 2nd SARS-CoV-2 vaccine (cohort 1a and 2a) or the booster vaccine (cohort 1b and 2b).

Exclusion criteria: As fully vaccinated patients are now allowed to be recruited to the study (into cohort 1b and 2b), the exclusion criteria were amended to exclude patients that have received any non-mRNA SARS-CoV-2 vaccination before the study

Interim analysis: In order to provide fast guidance on the currently discussed booster vaccines, an additional interim analysis should be performed when at least 10 patients have been vaccinated while being on stable ofatumumab treatment (cohort 2) or on January 10th 2022, whichever comes first.

Changes to the protocol:

List of abbreviations

- Deletion of unused abbreviations

Protocol Summary

- Change of primary endpoint
- Addition of secondary endpoint (level of T-cell response)
- Complement of secondary objective, which was added by amendment 1
- Addition of exclusion criterion (no previous non-mRNA vaccine)
- Study treatment was adjusted to new subcohorts

Section 1.1: Background

- Typo was corrected

Section 1.2: Purpose

- specification that SARS-CoV-2 vaccines can be the initial vaccination or a booster vaccine
- patients will be monitored for up to 18 months after initial vaccination (Amendment1)

Section 2: Objectives and endpoints

- Primary objective and endpoint were adjusted to updated study design
- New subcohorts were included in all secondary objectives and endpoints
- New secondary endpoint to investigate T-cell levels
- [redacted]

Section 2.1: Primary estimands

- specification that SARS-CoV-2 vaccines can be the initial vaccination or a booster vaccine
- explanation was added for how the new cohorts 1b and 2b answer the primary question of the study
- “developing” was replaced by “having developed” to adjust for new study design
- population was adjusted to reflect new study design (integration of cohort 1b and 2b)
- variable was updated to reflect new study design (integration of cohort 1b and 2b)

- intercurrent events were updated with conditions for the new subcohorts 1b and 2b

Section 3: Study design

- specification that SARS-CoV-2 vaccines can be the initial vaccination or a booster vaccine
- Description of the new subcohorts 1b and 2b were added
- Figure 3-1 was adjusted to reflect new study design (one figure each for cohort 1a/2a and cohort 1b/2b)
- Sentences were added to specify that remote phone calls 1 week, 2 weeks and 4 weeks after first ofatumumab dosing should be used to ensure that the application of the first ofatumumab doses are performed according to SmPC
- Baseline visit in cohort 2 should be approx. one week before the first vaccination and not “at least” one week
- Specification that “1 month” equivalates 4 weeks.
- Description of run-in period and study period was updated and now describes procedure for all subcohorts
- Typos were corrected

Section 4.1: Rationale for study design

- Specification that SARS-CoV-2 vaccines can be the initial vaccination or a booster vaccine

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

- Start of ofatumumab treatment for all subcohorts was specified

Section 4.4: Purpose and timing of interim analyses/design adaptations

- Section was adjusted to the new primary endpoint.
- Additional interim analysis was added.

Section 4.5: Risks and benefits

- Specification that SARS-CoV-2 vaccines can be the initial vaccination or a booster vaccine

Section 4.5.1: Blood sample volume

- Reference to new assessment tables was added

Section 5.1: Inclusion criteria

- As ofatumumab SmPC is final, the expected date was deleted
- SARS-CoV-2 vaccines (initial vaccination cycle and booster shots) should be done according to respective SmPC and local regulations

Section 5.2: Exclusion criteria

- Addition of new criterion that no previous non-modRNA SARS-CoV-2 vaccines are allowed

Section 6.1: Study treatment

- Specification that SARS-CoV-2 vaccines can be the initial vaccination or a booster vaccine

Section 6.1.3: Treatment arms/group

- Specification that SARS-CoV-2 vaccines can be the initial vaccination or a booster vaccine

Section 6.3.2: Treatment assignment, randomization

- Description of subcohorts was added

Section 8: Visit schedule and assessments

- Visit schedules for cohort 1b (Table 8-2) and cohort 2b (Table 8-4) were added
- Visit schedules for cohort 1a (Table 8-1) and cohort 2a (Table 8-3) were updated to reflect new optional booster vaccine and a corresponding additional visit.

Section 8.1: Screening

- Specification that SARS-CoV-2 vaccines can be the initial vaccination or a booster vaccine

Section 8.: Efficacy

- Reference to assessment schedules was updated
- “Pharmacodynamic samples” was replaced with “blood samples”

Section 8.3.1: Efficacy assessment 1

- Text was updated to reflect new primary endpoint

Section 8.3.2: Efficacy assessment 2

- Complement of efficacy assessments, which have already been added by amendment 1
- Endpoints of cohorts 1b and 2b were added to existing endpoints

Section 8.3.3: Appropriateness of efficacy assessments

- Text was adapted to reflect new primary endpoint

Section 8.4: Laboratory evaluatins

- Reference to assessment schedules was updated

Section 9.1.1: Replacement policy

- Patients with a confirmed COVID-19 disease after screening do not have to be excluded from the study and replaced.
- Specification that SARS-CoV-2 vaccines can be the initial vaccination or a booster vaccine
-

Section 9.1.2: Withdrawal of informed consent

- Sentence was adjusted to reflect that after withdrawal of consent, patients can decide if their stored and not yet analyzed blood samples should be destroyed or can still be used by Novartis.

Section 9.1.4: Early study termination by the sponsor

- Typo was corrected

Section 10.1.3: SAE Reporting

- SAE follow-up information need to be submitted immediately, without undue delay, and under no circumstances later than within 24 hours of the investigator receiving the follow-up information

Section 12.1: Analysis set

- The efficacy analysis set was adapted to new visit schedule.

Section 12.2: Population demographics and other baseline characteristics

- Update of cohorts to new study design
- Specification that SARS-CoV-2 vaccines can be the initial vaccination or a booster vaccine

Section 12.4: Analysis of the primary endpoint(s)/estimand(s)

- Specification that SARS-CoV-2 vaccines can be the initial vaccination or a booster vaccine

Section 12.4.1: Definitin of primary endpoint(s)/estimand(s)

- Primary endpoint was adjusted to include patients from new cohorts (1b and 2b). In order to have comparable date between new and old cohorts, “one month” was chosen as best timepoint.

Section 12.4.3: Handling of remaining intercurrent events of primary estimand

- Addition of an intercurrent event in new cohorts 1b and 2b.

Section 12.4.3: Supportive analyses

- Addition of an sentence that patients receiving their initial vaccine vs. patients receiving booster vaccines will also be described separately.

Section 12.7: Interim analysis

- Definition of second interim analysis

Table 2.1: Objectives

- Typos were corrected

Table 6-1

- New cohorts were added to table

Table 8.1/8.2/8.3/8.4: Treatment schedule

- Cohort 1a and cohort 2a: a new optional remote visit was added in case patients in this cohort receive booster vaccinations. In that case, an additional visit (A2) should be performed 1 month after the booster (including blood sampling) in order to assess the immune reaction towards booster vaccines.
- Table 8.2 and 8.4 were added to describe treatment schedule for cohort 1b and cohort 2b. Patients will follow a similar schedule as patients in cohort 1a and 2a. The main difference is that patients in cohort 1b and 2b receive booster vaccines instead of their initial SARS-CoV-2 vaccines. The immune response towards the booster will be measured 1, 6 and 12 months after the booster.
- Footnotes were added to specify that remote phone calls 1 week, 2 weeks and 4 weeks after first ofatumumab dosing should be used to ensure that the application of the first ofatumumab doses are performed according to SmPC
- Wording for timing of baseline visit in cohort 2 was specified: visit should be approx. one week before vaccination.

Amendment 1

Amendment Summary:

Main changes in this amendment include the inclusion of an additional interim analysis as well as prolongation of the study period in order to investigate sustainability of SARS-CoV-2 vaccination induced immune reaction and reaction towards possible additional booster shots. [redacted]

Prolongation of study period: Maintenance of the immune response after SARS-CoV-2 vaccination should be evaluated for at least 6 months after vaccination. As evidence grows for the possibility to sustained immunity beyond 6 months post-vaccination and a third booster shot for patients with immunocompromising treatments after 1 year is currently discussed in multiple countries, the investigational phase of this study should in total comprise 18 months after the initial vaccination cycle to ensure an at least 6-months follow-up after a possible booster vaccination. Patients in this study therefore will be specifically allowed to receive additional SARS-CoV-2 vaccines (either as additional booster or as yearly refresher) if suggested by local regulations and according to the physician's discretion.

[redacted]

Interim analysis: An additional interim analysis will be performed once at least five patients have completed the primary endpoint or on September 1st 2021, whichever comes first, as proof of concept for the study.

Changes to the protocol:

Section 1.1: Background

- Insertion of sentence that additional SARS-CoV-2 vaccines will be allowed within the study if suggested by local regulations.

Section 3: Study design

- Follow up phase will be replaced by extended study phase
- Additional visits during study phase were added
- Sentence was added that during the study, additional SARS-CoV-2 vaccines can be received according to physician’s discretion if suggested by local regulations

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

- Description of vaccination was amended to specify that vaccines will be received according to respective SmPC or following local regulations provided e.g. by German health authorities and additional SARS-CoV-2 vaccines can be received if suggested by local regulations.

Section 4.4: Interim analysis

- An additional interim analysis was added as proof of concept for the study

Section 4.5.1: Blood sample volume

- Time frame in which blood samples are collected was adapted from 9 to 23 months due to extension of study phase

Section 5: Study population

- Wording was updated due to addition of an earlier interim analysis

Section 8.3.1: Efficacy assessment 2

- The cell surface marker CD45R0 for immunophenotyping of SARS-CoV-2 reactive T-cells was replaced with CD27

Section 8.4: Safety

- Vital signs were added to the description of a full physical exam

Section 8.4.1: Laboratory assessments

- Paragraph about central laboratory was added
- ELISpot assays will be performed for IFN-γ and IL-2
- Inclusion of standard hematology tests
- Inclusion of B-cell count

Section 9.1.1.1: Replacement policy

- Vaccination was specified as mRNA vaccination
- Only patients with confirmed COVID-19 disease should be excluded and replaced

Section 10.1.1: Adverse events

- Adverse event monitoring should continue until 30 days after the last dose of study treatment

Section 10.1.3: SAE Reporting

- Specification that MS relapses will be reported in the MS relapse eCRF instead of SAE forms unless they are unusually severe or unexpected.

Section 12.1: Analysis sets

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

Section 12.5.1: Safety endpoints

- Treatment period was specified to last from first intake of study medication to 30 days after the last study visit.

Section 12.7: Interim analysis

- An additional interim analysis was added

Figure 3-1 Study design

- Figure was adapted to new study design with 18-months study phase
- Vaccination will be given according to respective SmPC or local regulations provided e.g. by German health authorities

[redacted]

Table 6-1: Study drug

- admin. route of mRNA vaccines was changed to i.m.

Table 8-1 and Table 8-2:

- For cohort 2, no blood analysis will be necessary at screening. Reference values for cellular and humoral immune responses will be measured at Baseline (visit 4).
- Two additional on site visits were added per cohort including blood sampling.
- Status of MS- and concomitant medication should be assessed at all onsite and remote visits
- A more detailed description of blood testing was included: standard hematology test and B-cell count
- Note was added to specify that MS relapses within the last two years should be recorded
- Note was added to amend that vaccination will be given according to respective SmPC or local regulations provided e.g. by German health authorities

Protocol summary

Protocol number	COMB157GDE01
Full Title	Tracking the immune response to SARS-CoV-2 modRNA vaccines in an open-label multicenter study in participants with relapsing multiple sclerosis treated with ofatumumab s.c. (KYRIOS)
Brief title	Study to assess SARS-CoV-2 vaccination response in ofatumumab treated RMS patients
Sponsor and Clinical Phase	Novartis / clinical phase IV
Investigation type	Drug (Ofatumumab (OMB157))
Study type	Low-intervention, 2 cohorts
Purpose and rationale	A major concern about B-cell depleting therapies in the context of vaccination is the potentially reduced immune response to vaccines. It has, however, been shown for the recently approved SARS-CoV-2 mRNA vaccines that they do not only induce a B-cell but also a functional T-cell response. For this purpose, we evaluate the proportion of patients that elicit humoral and specific T-cell responses upon vaccination with modRNA vaccines in patients receiving vaccination before initiation of ofatumumab treatment or at least 4 weeks after commencing ofatumumab treatment. The study will further follow the development of these immune responses for six months after vaccination.
Primary Objective(s)	To estimate the proportion of RMS patients having established SARS-CoV-2-specific T cells after receiving a modRNA vaccine (initial vaccination cycle or booster vaccine) either before or after starting ofatumumab treatment.
Secondary Objectives	• To estimate the proportion of RMS patients maintaining for up to 6 months SARS-CoV-2-specific T cells after receiving a modRNA vaccine either before or after starting ofatumumab treatment. • To estimate the proportion of RMS patients achieving seroconversion (i.e. having SARS-CoV-2 serum neutralizing antibodies) after receiving a modRNA vaccine either before or after starting ofatumumab treatment. • To estimate the proportion of RMS patients maintaining for up to 6 months quantifiable levels of SARS-CoV-2 serum functional antibodies after receiving a modRNA vaccine either before or after starting ofatumumab treatment. • Describing phenotypically the cellular response after receiving a modRNA vaccine either before or after starting ofatumumab treatment. • Describing safety and tolerability, incl. patients developing coronavirus disease 2019 (COVID-19) • To estimate the proportion of RMS patients with quantifiable SARS-CoV-2-specific T cells and functional antibodies after receiving an additional dose of modRNA vaccine (booster vaccine)
Study design	This is a two cohort, multicenter, open-label, prospective study of 40 (optionally up to 60) RMS patients.

	• The first cohort will be RMS patients receiving modRNA vaccine as part of clinical routine prior to starting ofatumumab treatment. • The second cohort will be participants receiving modRNA vaccine as part of clinical routine while already stable on ofatumumab treatment for at least 4 weeks (since first dose). Ofatumumab treatment initiation and maintenance will be performed as per approved SmPC. SARS-CoV-2 mRNA vaccination will be performed as part of clinical routine.
Study population	The study population will consist of females and males with relapsing MS.
Key Inclusion criteria	1. Signed informed consent must be obtained prior to participation in the study. 2. Patients eligible to start ofatumumab as per physician's discretion and approved SmPC (exp. April, 2021; for cohort 2, patients may already be on ofatumumab, but most patients will start ofatumumab as part of this study). 3. Patients willing and eligible to receive a modRNA vaccine against SARS-CoV-2 as part of clinical routine
Key Exclusion criteria	1. History of known COVID-19 infection (assessed based on patient statements and/or medical history) or current COVID-19 symptoms 2. Patients who previously received a BTK inhibitor or an antiCD20 therapy other than ofatumumab 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 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. No previous vaccination with a non-modRNA SARS-CoV-2 vaccine.
Study treatment	• **Cohort 1:** RNA vaccine will be received as part of clinical routine before starting Ofatumumab (OMB157) treatment o Cohort 1a: will receive their 1st and 2nd SARS-CoV-2 vaccines (and an optional booster vaccine) o Cohort 1b: will receive a booster vaccine • **Cohort 2:** RNA vaccine will be received as part of clinical routine while already stable on Ofatumumab (OMB157) treatment o Cohort 2a: will receive their 1st and 2nd SARS-CoV-2 vaccines (and an optional booster vaccine) o Cohort 2b: will receive a booster vaccine

Treatment of interest	Ofatumumab (OMB157) / *SARS-CoV-2 modRNA vaccine*
Efficacy assessments	• Detection of SARS-CoV-2 specific T-cells • Detection of SARS-CoV-2 serum functional antibodies
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, ofatumumab, relapsing remitting multiple sclerosis, SARS-CoV-2 booster

1 Introduction

1.1 Background

Since December 2019, coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has spread around the world and become a global pandemic. COVID-19 affects the health and social and economic life of millions of people. Especially the elderly and persons with preexisting conditions (e.g. asthma, diabetes, and heart disease) have an increased risk of a severe and potentially lethal course of the disease. With the nucleoside-modified RNA (modRNA) vaccine BNT162b2 (BioNTech SE/Pfizer), the first vaccine gained market authorization (e.g. in the UK, US, and EU) (Polack, Thomas et al. 2020). Similarly, mRNA-1273 (Moderna) has gained regulatory approval as SARS-CoV-2 vaccine, e.g. in UK, US, and EU. Most recently, Astra Zeneca's vaccine received approval in the UK. More approvals for these and other vaccines around the world are expected for 2021.

Multiple sclerosis (MS) is an autoimmune disease which causes demyelinisation and neuronal damage in the central nervous system. Worldwide, approximately 2.5 million people are affected by MS, most patients presenting with relapsing forms (RMS).

Between 2016 and 2019, two phase III clinical trials (ASCLEPIOS I & II) showed that monthly subcutaneous injections of ofatumumab can reduce the annual relapse rate and probability of confirmed disability progression compared to teriflunomide (Hauser, Bar-Or et al. 2020). Ofatumumab is a fully human anti-CD20 monoclonal antibody that selectively depletes CD20+ B- and T-cells, which prevent migration to the CNS and the formation of inflammatory lesions. Since August 2020, ofatumumab (Kesimpta) is available as treatment for RMS patients in the US and EMA approval is expected by Q2 2021.

A major concern about B-cell depleting therapies in the context of vaccination is the potentially reduced immune response to vaccines as seen e.g. in the VELOCE trial assessing the immune response in patients treated with the anti-CD20 monoclonal antibody ocrelizumab (Bar-Or, Calkwood et al. 2020). However, the average serum IgG levels in the ASCLEPIOS I and II trials remained well within the reference range over time and no association was observed between a decrease in immunoglobulin levels and the incidence of serious/non-serious infections in ofatumumab-treated patients (Wiendl 2020).

Although B-cells have been assumed to be the major drivers for establishment of immunity after vaccination, it has recently been shown that T-cells might be equally important for vaccine-induced immunity especially against intracellular infections like viruses (Ahmed and Akondy 2011). It has been observed for previous coronavirus-caused disease that T-cell responses were better markers for prior coronavirus infections than antibodies as some COVID-19 patients (especially with mild disease) don't undergo seroconversion and T-cell responses can be detected for a longer time period (Hellerstein 2020). Immunological memory to SARS-CoV-2 has been recently demonstrated for 8 months post infection (Dan, Mateus et al. 2021).

Concomitant with these findings, it has been shown that 100% of all COVID-19 patients showed specific $CD4^+$ and 70% showed specific $CD8^+$ T-cell responses (Grifoni, Weiskopf et al. 2020). Furthermore, it was observed that upon contact with a confirmed COVID-19 patient, multiple persons developed disease symptoms and a T-cell mediated response without

seroconversion suggesting the importance of T-cell activation even in the absence of SARS-CoV-2 neutralizing antibodies (Gallais, Velay et al. 2020).

When looking into the immune responses after vaccination with the two newly approved modRNA vaccines it was shown that both, BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna), not only induced an antibody-response against the SARS-CoV-2 spike protein but also functional $CD4^+$ and $CD8^+$ T-cell responses (Jackson, Anderson et al. 2020, Sahin, Muik et al. 2020).

Especially in the context of ofatumumab treatment and the imminent B-cell depletion, the activation of $CD4^+$ and $CD8^+$ T-cells plays an even more important role for the development of vaccine-induced immunity. It is therefore essential to understand the impact of concomitant ofatumumab treatment on

1) the cellular response, investigating the development of $CD4^+$ and $CD8^+$ T cell responses against the SARS-CoV-2 spike protein, which is necessary for infection of the target cell (Huang, Yang et al. 2020), and
2) the humoral immune response, investigating SARS-CoV-2 serum neutralizing antibody levels.

In recent publications describing SARS-COV-2 mRNA vaccines, functional T-cell responses were defined as interferon γ (IFNγ) secretion by T-cells measured by enzyme-linked immuno spot (ELISpot) assay after *in vitro* stimulation with a peptide mix resembling the SARS-CoV-2 spike protein (Jackson, Anderson et al. 2020, Sahin, Muik et al. 2020). In this study, we will perform ELISpot assays followed by detailed immunophenotyping to further characterize the developed T-cell response. Furthermore, 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). 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, immune response to SARS-CoV-2 mRNA vaccines will be analyzed in patients receiving the vaccine before starting ofatumumab treatment (cohort 1) or during stable ofatumumab treatment (cohort 2).

If suggested by local regulations, patients will be allowed to receive additional SARS-CoV-2 vaccines (either as additional booster or yearly refresher) during the study according to the physician's discretion and as part of the clinical routine.

Data gathered within AMA-VACC (CBAF312ADE03) will serve to describe differences to other DMTs. In AMA-VACC, humoral and cellular immune response is assessed at identical timepoints as within this study in MS patients treated with siponimod, platform therapies (i.e. interferons, glatiramer acetate, teriflunomide, dimethyl fumarate), or currently without DMT.

1.2 Purpose

B-cell depleting therapies have in the past been shown to impair the immune response to conventional vaccines. The objective of this study is to assess whether participants treated with monthly s.c. injections of ofatumumab (20 mg) can mount an adequate immune response to the new class of SARS-CoV-2 modRNA vaccines (initial or booster) as measured by humoral and cellular responses. The study will further investigate the maintenance of SARS-CoV-2 specific responses for up to 18 months after the initial vaccination.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s) • To estimate the proportion of RMS patients having established SARS-CoV-2-specific T cells after receiving a modRNA vaccine (initial vaccination or booster) either before or after starting ofatumumab treatment.	**Endpoint(s) for primary objective(s)** • Proportion of RMS patients having established SARS-CoV-2-specific T cells as defined by detection of SARS-CoV-2 reactive T-cells, measured by e.g. enzyme-linked immunosorbent spot (ELIspot) assay from T-cells that were stimulated with SARS-CoV-2 peptide mix, either one month after second dose of vaccine or one month after booster vaccine in participants who received the respective vaccine before or after starting ofatumumab treatment (yes/no)
Secondary Objective(s) • To estimate the proportion of RMS patients maintaining for up to 18 months SARS-CoV-2-specific T cells after receiving a modRNA vaccine either before or after starting ofatumumab treatment. • To estimate the increase in specific T-cells after receiving a modRNA booster vaccine either before or after starting ofatumumab treatment.	**Endpoint(s) for secondary objective(s)** • Proportion of RMS patients with detectable SARS-CoV-2 reactive T-cells one week, 6, 12 and 18 months after second dose of vaccine or 6 and 12 months after booster vaccine in participants who received the vaccine before or after starting ofatumumab treatment (yes/no) • Fold change of SARS-CoV-2 specific T-cell levels one week, 1 month, 6 months, 12 months and 18 months after the second dose of vaccine or 1 months, 6 months and 18 months after a booster vaccine compared to the last timepoint before the respective vaccine

Objective(s)	Endpoint(s)
• To estimate the proportion of RMS patients achieving seroconversion (i.e. having SARS-CoV-2 serum neutralizing antibodies) after receiving a modRNA vaccine either before or after starting ofatumumab treatment.	• Proportion of RMS patients achieving seroconversion (i.e. having SARS-CoV-2 serum neutralizing antibodies) after receiving a modRNA vaccine either before or after starting ofatumumab treatment (yes/no)
• To estimate the proportion of RMS patients maintaining for up to 18 months quantifiable levels of SARS-CoV-2 serum functional antibodies after receiving a modRNA vaccine either before or after starting ofatumumab treatment.	• Proportion of RMS patients with quantifiable levels of SARS-CoV-2 serum functional antibodies one week, 1, 6, 12 and 18 months after receiving the second dose of modRNA vaccine or 1, 6 and 12 months after a booster shot either before or after starting ofatumumab treatment (yes/no)
• Describing phenotypically the cellular response after receiving a modRNA vaccine either before or after starting ofatumumab treatment.	• Phenotypical characterization of peripheral blood mononuclear cells for CD45, CD3, CD4, CD8, CD62l, CD45RA, CD45R0, CCR7 • Immunophenotyping for naive, central memory, effector memory, and effector cells on $CD4^+$ and $CD8^+$ cells • Measuring cells positive for intracellular cytokine-staining for interferon-gamma and interleukin-4
• Describing safety and tolerability, incl. patients developing coronavirus disease 2019 (COVID-19)	• AEs, SAEs, incl. patients with clinical confirmed COVID-19

[redacted]

Objective(s)	Endpoint(s)
[redacted]	

2.1 Primary estimands

The primary clinical question of interest is: What is the proportion of RMS patients having developed a specific immune response after receiving a SARS-CoV-2 mRNA vaccine (initial vaccination or booster vaccine) either before or after starting ofatumumab treatment.

The justification for the primary estimand is that it will capture whether ofatumumab-treated patients will mount a specific T-cell response after receiving a SARS-CoV-2 mRNA vaccine assessed by enzyme-linked immunosorbent spot (ELISpot) assays from T-cells that were stimulated with SARS-CoV-2 peptide mix.

Patients will receive either their initial vaccination (1st and 2nd SARS-CoV-2 vaccines) or a booster vaccine before or after starting ofatumumab treatment. In both cases we want to assess if ofatumumab initiation negatively affects or prevents the immune response.

Since this is not a randomized trial, 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 primary estimand is described by the following attributes:

1. **Population**: Patients with relapsing MS (RMS) divided in two cohorts, each receiving a SARS-CoV-2 mRNA vaccine as part of clinical routine: (1) vaccination before start of ofatumumab treatment, (2) vaccination after having been on stable ofatumumab treatment for at least 4 weeks. The SARS-CoV-2 mRNA vaccine can be either the initial vaccination cycle (for patient that are exposed to the vaccine for the first time; cohort 1a and cohort 2a) or a booster vaccination (for patients that have already completed the initial vaccination cycle; cohort 1b and cohort 2b). Patients in cohort 1a or 2a who fail to receive

their second dose of vaccine for whatever reason will be included in the analysis as non-responders. Patients in cohort 1a and 2a who did receive their second dose of vaccine and patients in cohort 1b and 2b who received their booster shot and do not have a valid determination of specific T-cell response to SARS-CoV-2 for whatever reason will be excluded from the analysis of vaccine efficacy.

2. **Variable:** Receiving the second dose of mRNA vaccine (for cohort 1a and 2a) or a booster vaccination (cohort 1b and 2b) and mounting a specific T cell response one month after second dose of vaccine (cohort 1a and 2a) or booster vaccine (cohort 1b and 2b) defined by detection of SARS-CoV-2 specific T-cells by ELISpot assays after stimulation of T-cells with SARS-CoV-2 peptide mix (yes/no)
3. **Treatment of interest:** ofatumumab treatment, which is started either before or after receiving a SARS-CoV-2 mRNA vaccine (initial vaccination cycle or booster vaccine)
4. **Intercurrent events:**
    a. Vaccination with a non-mRNA vaccine: patients will be excluded from the study
    b. Failure to receive the second dose of vaccine (for cohort 1a and 2a): patients will be classified as non-responders
    c. Failure to initiate ofatumumab treatment within six weeks after completion of the vaccination cycle (cohort 1a) or of the booster vaccine (cohort 1b): patients will be excluded from the efficacy analyses
    d. Failure to complete ofatumumab initiation or interruption of ofatumumab treatment prior to first vaccination (cohort 2a) or prior to booster vaccination (cohort 2b): patents will be excluded from the study
    e. No valid detection of SARS-CoV-2 specific T-cells: patients will be excluded from the efficacy analyses if they received their second dose of vaccine (cohort 1a and 2a) or booster vaccine (cohort 1b and 2b) and further analyses will be performed to confirm methodical reasons
5. **Summary measure:** n.a., there will be no formal comparison between cohorts. Response rates will only be calculated within each cohort.

2.2 Secondary estimands

Not applicable

3 Study design

This is a two cohort, multicenter, open-label, prospective study of 20 RMS patients per treatment arm (optional increase to 30 depending on results of interim analysis) willing to start ofatumumab treatment and receive SARS-CoV-2 modRNA vaccination (initial vaccination or booster vaccine) as part of clinical routine.

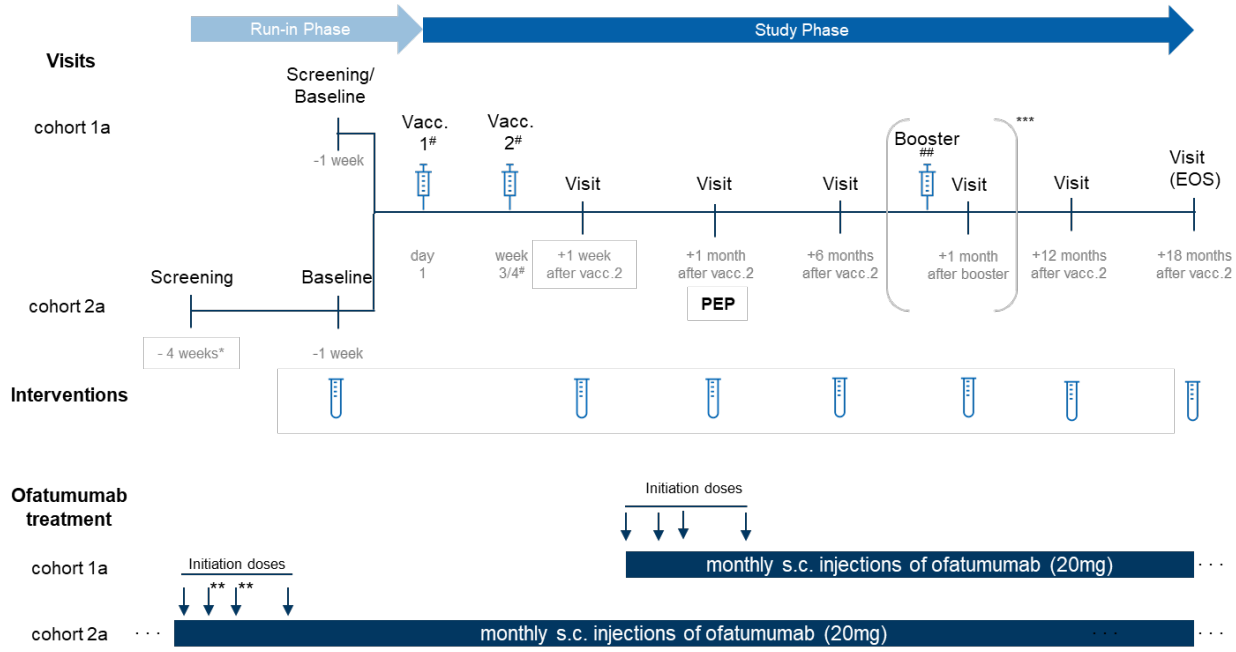
- The first cohort will be RMS patients receiving modRNA vaccine as part of clinical routine prior to starting ofatumumab treatment.
    - Cohort 1a will receive their initial SARS-CoV-2 mRNA vaccines (vaccination 1 and vaccination 2) before starting ofatumumab treatment
    - Cohort 1b will receive a booster vaccination before starting ofatumumab treatment

- The second cohort will be participants receiving modRNA vaccine as part of clinical routine while already stable on ofatumumab treatment for at least 4 weeks (since first dose).
    - Cohort 2a will receive their initial SARS-CoV-2 mRNA vaccines (vaccination 1 and vaccination 2) while being on stable ofatumumab treatment
    - Cohort 2b will receive a booster vaccination while being on stable ofatumumab treatment

Initiation and maintenance of ofatumumab treatment in this study will be performed according to the approved SmPC. Especially for cohort 1, possible effects of the previous MS treatment on vaccination efficacy should be kept in mind when scheduling SARS-CoV-2 vaccination. The interventional part of KYRIOS is limited to the collection of blood samples at specified time-points to analyze development of SARS-CoV-2 specific T-cells and neutralizing antibodies as response to the modRNA vaccination in clinical routine.

Figure 3-1 Study design

Cohort 1a and cohort 2a:



PEP: primary endpoint; Vacc.= vaccination with modRNA vaccine;

Vaccination as part of clinical routine; required number of vaccinations and interval depends on SmPC of respective modRNA vaccines or local regulations provided e.g. by German health authorities.

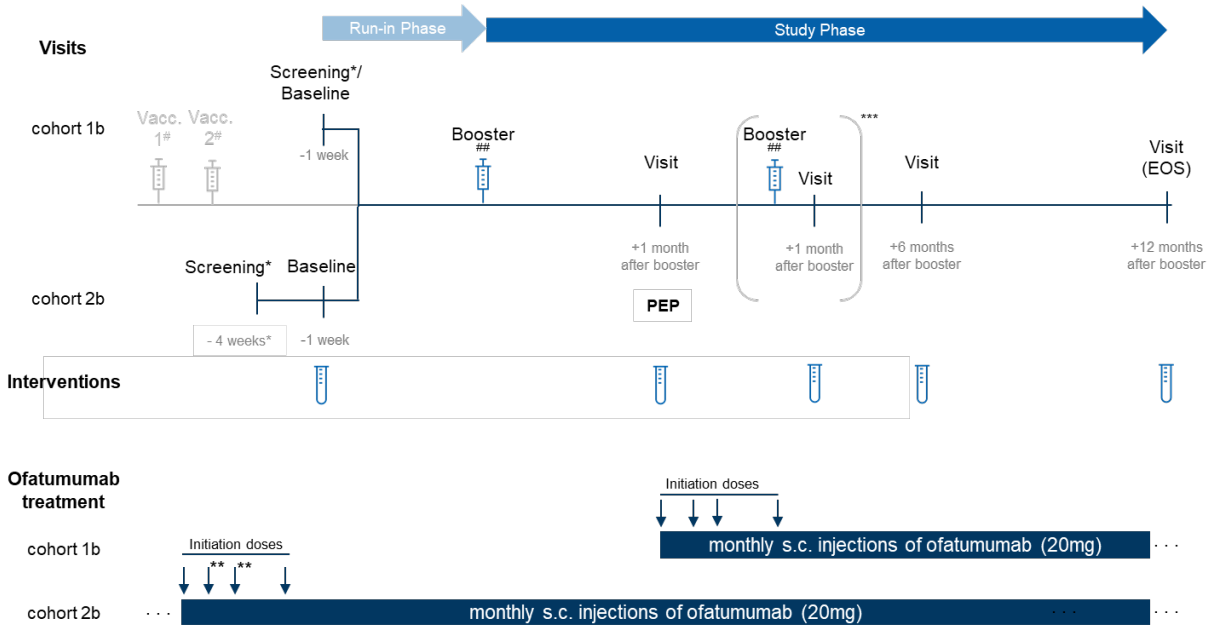
Booster vaccination as part of clinical routine e.g. if suggested by German health authorities and at the physician's discretion.

* Ofatumumab treatment has to be initiated at least 4 weeks before Vacc.1,

** Ofatumumab initiation doses can be omitted if patient already receives ofatumumab at the time of screening

***Booster vaccination is optional can be performed any time after vacc.2. If a booster vaccination is given, an additional unscheduled visit should be performed 1 month after the booster vaccination in order to assess the immune reaction. If this unscheduled visit would be within 2 weeks of the next scheduled visit, the next scheduled visit can be omitted. This only applies for the first and second booster, there won't be any additional visits for potential following boosters.

Cohort 1b and cohort 2b:



PEP: primary endpoint; Vacc.= vaccination with modRNA vaccine;

Vaccination as part of clinical routine and before the study; required number of vaccinations and interval depends on SmPC of respective modRNA vaccines or local regulations provided e.g. by German health authorities.

First booster vaccination as part of clinical routine according to SmPC of respective vaccine or local regulations, e.g. German health authorities. Additional boosters can be performed any time during the study.

* Screening can be performed any time after completion of the initial vaccination cycle (vacc.2). For cohort 2b, ofatumumab treatment has to be initiated at or after screening but at least 4 weeks before booster vaccination

** Ofatumumab initiation doses can be omitted if patient already receives ofatumumab at the time of screening

*** Additional booster vaccination is optional can be performed any time after the first booster. If a second booster vaccination is given, an unscheduled visit should be performed 1 month after the second booster vaccination in order to assess the immune reaction. If this unscheduled visit would be within 2 weeks of the next scheduled visit, the next scheduled visit can be omitted. This only applies for the second booster, there won't be any additional visits for potential following boosters.

The study consists of 2 periods: run-in period and study period.

The **run-in period** comprises the time from screening to vaccination, including the baseline visit (approx. one week before the first vaccination). Patient eligibility will be determined based on the screening and baseline assessments.

- For cohort 1a, screening and baseline can be performed on the same day, and have to be performed before the first vaccination. Possible effects of the previous MS treatment on vaccination efficacy should be kept in mind when scheduling SARS-CoV-2 vaccination. For cohort 1b, screening and baseline can be performed any time after completion of the initial vaccination cycle and should be approx. 1 week before the first SARS-CoV-2 booster vaccine. Possible effects of the previous MS treatment on booster vaccine efficacy should be kept in mind when scheduling SARS-CoV-2 booster vaccination.

- For cohort 2a and 2b, the run-in period includes initiation of ofatumumab treatment as per approved SmPC and lasts for at least 4 weeks after the first ofatumumab dosing. For cohort 2a and 2b, additional visits during the run-in period will be necessary: one visit to start ofatumumab treatment (can be performed at screening), three remote visits (e.g. phone calls) 1, 2 and 4 weeks after the first ofatumumab dose to ensure the application of the first ofatumumab doses according to SmPC, and the baseline visit approx. 1 week
    - before the first vaccine (cohort 2a).
    - before the first booster vaccination (cohort 2b)

  Patients that have already been on stable ofatumumab treatment for at least 4 weeks before the screening visit will follow the run-in period assessment schedule for cohort 1: no additional visits except screening/baseline will be needed. Assessments during the study period will be performed as defined for cohort 2.

The **study period** starts for cohorts 1a and 2a with the first SARS-CoV-2 modRNA vaccination and ends 18 months after the second vaccination (EOS). All patients will return to the study site 1 week, 1 month, 3 months, 6 months, 12 months and 18 months after the second vaccination for study visits. During the study, patients are allowed to receive additional SARS-CoV-2 vaccines (as booster shot or yearly refresher) if suggested by local regulations and as per physician's discretion.

For cohorts 1b and 2b, the study period starts with the first booster vaccination and patients will return to the study site 1 month (equivalates 4 weeks), 3 months, 6 months and 12 months (EOS) after the booster vaccine.

- For cohort 1a, ofatumumab treatment will be initiated as per approved SmPC during visit 2 (4 weeks after receiving the second SARS-CoV-2 modRNA vaccine). Ofatumumab treatment can be started earlier if medically indicated but at the earliest two weeks after the second mRNA vaccine. If ofatumumab treatment can't be started 4 weeks after the second vaccine, the Novartis Medical Advisor should be contacted to discuss further proceeding.
- For cohort 1b, ofatumumab treatment will be initiated as per approved SmPC during visit 1 (4 weeks after receiving the first SARS-CoV-2 modRNA booster vaccine). Ofatumumab treatment can be started earlier if medically indicated but at the earliest

two weeks after the booster vaccine. If ofatumumab treatment can't be started 4 weeks after the booster vaccine, the Novartis Medical Advisor should be contacted to discuss further proceeding.

Cohort 1a and 1b will have three additional remote visits (e.g. phone contact) 1 week, 2 weeks and 4 weeks after the initial ofatumumab dosing in order to ensure application of the first ofatumumab doses according to SmPC.

- Cohort 2a will receive both initial vaccinations while continuing on stable ofatumumab treatment.
- Cohort 2b will receive first booster vaccination while continuing on stable ofatumumab treatment.

4 Rationale

4.1 Rationale for study design

A two-cohort, multicenter, open-label, prospective design has been selected to generate data in a timely manner in order to provide a guidance for physicians and patients on the timing of initial and booster SARS-CoV-2 vaccination and the start of ofatumumab treatment in RMS patients. The study will assess two main questions:

a) Can patients mount an immune response towards SARS-CoV-2 modRNA vaccines (initial vaccination or booster) when starting ofatumumab treatment after vaccination?

b) Can patients mount an immune response towards SARS-CoV-2 modRNA vaccines (initial vaccination or booster) when receiving the vaccination while on stable ofatumumab treatment (for at least 4 weeks after the first ofatumumab dosing)?

A non-randomized design has been chosen to enable feasible recruitment as the patient's wish as well as the physician's discretion have to be taken into consideration when deciding on the timing of the vaccine and start of ofatumumab treatment.

Rationale for study population

Initiation and maintenance of ofatumumab treatment in this study will be performed as per approved SmPC. No inclusion/ exclusion criteria regarding age or disease severity were implemented in this study in order to reflect the clinical routine of ofatumumab patients in Germany as closely as possible. Therefore, all patients eligible for ofatumumab treatment and a SARS-CoV-2 modRNA vaccine may be suitable for KYRIOS as long as all other inclusion/exclusion criteria are met. In order to assess whether ofatumumab patients can mount an immune response after vaccination, patients with previous known COVID-19 disease will be excluded from the study.

Rationale for chosen endpoints

Recent publications about the immune responses after vaccination with the new SARS-CoV-2 modRNA vaccines show that both, BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna), not only induced an antibody-response against the SARS-CoV-2 spike protein but also functional $CD4^+$ and $CD8^+$ T-cell responses (Jackson, Anderson et al. 2020, Sahin, Muik et al. 2020).

Especially in the context of ofatumumab treatment and the imminent B-cell depletion, the activation of $CD4^+$ and $CD8^+$ T-cells plays a very important role for the development of vaccine-induced immunity. The primary endpoint in this study was therefore chosen in analogy to the recently completed trials and in-depth analyses of the modRNA vaccines BNT162b2 (ClinicalTrials.gov Identifier: NCT04368728, (Sahin, Muik et al. 2020, Walsh, Frenck et al. 2020)) and mRNA-1273 (ClinicalTrials.gov Identifier: NCT04283461, (Jackson, Anderson et al. 2020)).

4.2 Rationale for dose/regimen and duration of treatment

Ofatumumab

All patients in this study will be treated with ofatumumab (20 mg s.c.) according to approved SmPC to be as close to the clinical routine as possible. Cohort 1 will start ofatumumab treatment four weeks after the second SARS-CoV-2 modRNA vaccination (1a) or four weeks after SARS-CoV-2 booster vaccination (1b), cohort 2 will already have been on stable ofatumumab treatment at the start of the study or will start ofatumumab treatment at least 4 weeks before the first vaccination (2a) or before booster vaccination (2b) and will remain on stable treatment until completion of the study.

Vaccination

In this study, patients will receive a modRNA vaccine at the discretion of the treating physician as part of the clinical routine and according to the respective SmPC or local regulations provided e.g. by German health authorities. If suggested by local regulations, patients are allowed to receive additional SARS-CoV-2 vaccines (as booster or yearly refresher) as per physician's discretion.

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Not applicable

4.4 Purpose and timing of interim analyses/design adaptations

The first interim analysis is planned when at least five patients per cohort have completed the study visit one week after the second SARS-CoV-2 modRNA vaccination or on September 1st 2021, whichever comes first. The data gathered at this time point will be examined as a preliminary evaluation of proof of concept.

The second interim analysis is planned when at least 10 patients that were vaccinated during stable ofatumumab-treatment have passed the primary endpoint, 1 month after the 2nd vaccination or after booster or on January 10th 2022, whichever comes first. The data gathered at this time point will be examined as a preliminary evaluation of proof of concept for the new study design.

An additional interim analysis is planned after all participants have completed the study visit 1 month after the second SARS-CoV-2 modRNA vaccination or one month after the booster vaccine, respectively. The data gathered at this time point will be the basis for the primary endpoint of this study.

Additional interim analyses may be conducted to support decision making concerning the current clinical study including an increase in participants (from 40 to 60), 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 with ofatumumab or SARS-CoV-2 vaccinations. The only intervention is the blood sampling at specific time-points in the course of this trial.

As blood draw is also regularly performed in the clinical routine, the procedure of additional drawings of blood (venous puncture) within this study for antibody- and T-cell response measurements only bear minimal risk for the patient.

Participation in this study might delay initiation of ofatumumab treatment (for patients in cohort 1) or SARS-CoV-2 vaccination (for patients in cohort 2). Duration of the delay depends on multiple parameters:

- For cohort 1, the delay of ofatumumab initiation depends on a) time between screening and appointment for vaccination (1-12 weeks), b) type of vaccination and resulting interval between vaccination one and two (e.g. 3 weeks for BioNTech/Pfizer or 4 weeks for Moderna) and c) on the physician's discretion on how long to wait between last vaccination and ofatumumab initiation (2-4 weeks). In total, the delay will be a minimum of six weeks.
- For cohort 2, the delay of SARS-CoV-2 vaccination will be 4-12 weeks after screening/ofatumumab initiation depending on the physician's discretion.

The overall risks associated with this study are therefore comparable to those in usual clinical practice. Patients will most likely not have a direct benefit from participating in this study except

receiving information about whether SARS-CoV-2 specific antibodies and T-cells can be detected after vaccination.

The results of this study will, however, contribute to a better understanding of the immune responses to modRNA vaccines (initial vaccination and booster) in ofatumumab treated RMS patients. Findings may also provide guidance for the timing of modRNA vaccines and the start of ofatumumab treatment and inform patients and physicians if risk management might be needed.

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 23 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, 8-2, 8-3 and Table 8-4).

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 or confirmed.

5 Study Population

The study population will consist of 40 female and male RMS patients that are planned to be treated in clinical routine with Ofatumumab as per approved SmPC. There is an optional increase to 60 patients after the interim analyses.

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. Patients eligible to start ofatumumab as per physician's discretion and approved SmPC (for cohort 2, patients may already be on ofatumumab, but most patients will start ofatumumab as part of this study).
3. Patients willing and eligible to receive a modRNA (according to respective SmPC and local regulations) vaccine against SARS-CoV-2 (initial vaccination cycle or booster shot) 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 known COVID-19 infection (assessed based on patient statement and/or medical history) or current COVID-19 symptoms.
2. Participants who previously received a BTK inhibitor or an antiCD20 therapy other than ofatumumab
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
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. No previous vaccination with a non-modRNA SARS-CoV-2 vaccine.

6 Treatment

6.1 Study treatment

The SARS-CoV-2 modRNA vaccine (initial vaccination or booster) will be received as part of clinical routine. Ofatumumab initiation and treatment in this study will be performed as per approved SmPC to resemble clinical routine as closely as possible.

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.

Table 6-1 Investigational and control drug

Treatment Arm	Type of Study Drug	Compound	Min Dose	Max Dose	Frequency	Admin. Route
Cohort 1a, 1b, 2a and 2b	investigational	modRNA	Clinical routine	Clinical routine	Clinical routine	i.m.
	investigational	ofatumumab	20 mg	20 mg	monthly	sc

6.1.2 Supply of study treatment

Ofatumumab is supplied during the study while modRNA vaccines are part of clinical routine and there will be no supply.

6.1.3 Treatment arms/group

Participants will be assigned at screening to one of the following "2" treatment arms in a ratio of "1:1" at the discretion of the physician. There is no randomization within the trial.

- The first treatment arm will be RMS patients receiving modRNA vaccine (either initial vaccination cycle or a booster) as part of clinical routine prior to starting ofatumumab treatment.
- The second treatment arm will be participants receiving modRNA vaccine (either initial vaccination cycle or a booster) as part of clinical routine while already stable on ofatumumab treatment for at least 4 weeks (since first dose).

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.

6.2.2 Prohibited medication

The use of non-mRNA SARS-CoV-2 vaccines is prohibited in this study.

Further prohibited medication applies according to approved Ofatumumab SmPC.

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. A new Participant No. will be assigned at every subsequent enrollment if the participant is re-screened. The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis 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.

Cohort 1: will be RMS patients receiving modRNA vaccine as part of the clinical routine prior to starting ofatumumab treatment (Cohort 1a: patients that receive their first SARS-CoV-2 vaccination within the study and cohort 1b: patients that have already completed their initial vaccination cycle and will receive a booster vaccine within the study)

Cohort 2: will be participants receiving modRNA vaccine as part of clinical routine while already stable on ofatumumab treatment for at least 4 weeks (since the first dose) (Cohort 2a: patients that receive their first SARS-CoV-2 vaccination within the study and cohort 2b: patients that have already completed their initial vaccination cycle and will receive a booster vaccine within the study).

6.4 Treatment blinding

Not applicable.

6.5 Dose escalation and dose modification

Investigational or other study treatment dose adjustments and/or interruptions are not permitted.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

The investigator must promote compliance by instructing the participant to take the study treatment exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study. The participant must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed. Compliance will be assessed by the investigator and/or study personnel at each visit using information provided by the participant. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

6.7 Preparation and dispensation

Each study site will be supplied with ofatumumab in packaging as described under investigational and control drugs section.

SARS-CoV-2 modRNA vaccines will be received as part of clinical routine and will not be provided.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the participant except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Participants will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

7 Informed consent procedures

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), 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 (cohort 1a: Table 8-1 and cohort 1b: Table 8-2, cohort 2a; Table 8-3 and cohort 2b: Table 8-4) 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 (cohort 1a: Table 8-1, cohort 1b: Table 8-2, cohort 2a: Table 8-3 and cohort 2b: Table 8-4) 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, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

Table 8-1 Assessment schedule cohort 1a

Period	**Run-in**	**Investigational**													
Visit	Screening/ Baseline	Vaccination 1[#]	Vaccination 2[#]	1 On site	A1** (onsite, only if medically indicated)	2 On site	3 remote	4 remote	5 remote	6 On site	Booster vacc. **** remote	A2**** (onsite, only if booster vacc.)	7 On site	8 On site	9 On site **(end of study)**
Day/Week/ Month	1-12 weeks before vacc.1	Day 1	Day 22/29*	+1 week after vacc. 2	2-4 weeks after vacc. 2	+4 weeks after vacc. 2	+5 weeks after vacc.2	+6 weeks after vacc.2	+8 weeks after vacc.2	+3 months after vacc. 2	after vacc.2	+1 month after booster	+6 months after vacc.2	+12 months after vacc.2	+ 18 months after vacc.2
Obtain informed consent	X														
Inclusion/exclusion criteria	X														
Anamnesis, Demography, Relevant medical and MS history	X														
Physical exam	F			S	S	S						S	S	S	F
Blood sampling [3]	X			X		X						X	X	X	X
MS relapse[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Status MS and concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Local urine and	X				X	X***									

pregnancy test [1]															
Administration of study drug at site					X	X***									
Self-injection training [1]					X	X***									
Study drug dispension					X	X***				X			X	X	
Contact after modRNA vaccination [2]		X	X								X				
Documentation SARS-CoV-2 vaccination		X	X								X				
Telephone contact							X	X	X						
AE/SAE	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

White color: timing of visits depends on vaccination date

Light grey color: optional visits

Dark grey color: Timing of visits depends on start of ofatumumab treatment and timelines have to be adjusted if ofatumumab treatment is initiated at visit A1 instead of visit 2. Visit 3: 1 week after start of ofatumumab treatment, visit 4: two weeks after start of ofatumumab treatment and visit 5: 4 weeks after start of ofatumumab treatment. Remote visits should be used to ensure that the first ofatumumab doses are applied according to SmPC.

A = additional visit; vacc. = Vaccination with modRNA vaccine,

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

F = full assessment, S = short medical exam

modRNA vaccination independent of study site at designated vaccination centers as part of clinical routine and depending on federal regulations

* Number of required vaccinations and interval depends on the SmPC of the respective modRNA vaccination and on local guidelines provided e.g. by the responsible health authorities

** If medically indicated, ofatumumab treatment might be started at an additional visit (A1) before visit 2 but at the earliest two weeks after the last vaccination.

*** Assessments don't have to be performed on visit 2 if ofatumumab treatment has already been initiated at visit A1.

**** Patients are allowed to receive SARS-CoV-2 booster vaccines any time after vacc. 2 according to respective SmPCs or local regulations, as part of clinical routine and at the physician's discretion. If patients receive a booster vaccination, additional visit 2 (A2) should be performed 1 month (4 weeks) after the booster vaccination to collect a blood sample and assess immune response. If the next scheduled visit falls within two weeks of visit A2, the scheduled visit can be omitted. This only applies for the first and second booster. All potential following boosters should be documented but there won't be any additional visits afterwards.

[1] According to approved SmPC requirements

[2] Contact can be on site, virtual or via phone according to physician's choice.

[3] Laboratory test includes a standard hematology set, B-cell count, detection and characterization of SARS-CoV-2 specific T cells and neutralizing antibodies; if no SARS-CoV-2 specific T-cells can be detected, HLA-haplotyping will be considered to exclude methodical reasons. Blood samples will be stored.

[4] MS relapses within the last two years should be reported

Table 8-2 Assessment schedule cohort 1b

Period	**Run-in**		**Investigational**									
Visit	Screening On site	Booster vacc. #	A1* (onsite, only if medically indicated)	1 On site	2 remote	3 remote	4 remote	Booster vacc. *** remote	A2*** (onsite, only if booster vacc.)	5 On site	6 On site	7 On site **(end of study)**
Day/Week/ Month	Approx. 1 week before booster	Day 1	2-4 weeks after booster	+1 month after booster	+5 weeks after booster	+6 weeks after booster	+8 weeks after booster	any time	+1 month after booster	+3 months after booster	+6 months after booster	+12 months after booster
Obtain informed consent	X											
Inclusion/exclusion criteria	X											
Anamnesis, Demography, Relevant medical and MS history	X											
Physical exam	F		S	S					S		S	F
Blood sampling [3]	X			X					X		X	X
MS relapse[4]	X	X	X	X	X	X	X	X	X	X	X	X
Status MS and	X	X	X	X	X	X	X	X	X	X	X	X

concomitant medication												
Local urine and pregnancy test [1]	X		X	X**								
Administration of study drug at site			X	X**								
Self-injection training [1]			X	X**								
Study drug dispension			X	X**						X	X	
Contact after modRNA vaccination [2]		X						X				
Documentation on SARS-CoV-2 vaccination	X	X						X				
Telephone contact					X	X	X					
AE/SAE	X	X	X	X	X	X	X	X	X	X	X	X

White color: timing of visits depends on vaccination date

Grey color: Timing of visits depends on start of ofatumumab treatment and timelines have to be adjusted if ofatumumab treatment is initiated at visit A1 instead of visit 1. Visit 2: 1 week after start of ofatumumab treatment, visit 3: two weeks after start of ofatumumab treatment and visit 4: 4 weeks after start of ofatumumab treatment. Remote visits should be used to ensure that the first ofatumumab doses are applied according to SmPC.

A = additional visit; vacc. = Vaccination with modRNA vaccine,

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

F = full assessment, S = short medical exam

First booster vaccination; can be performed any time after termination of the initial SARS-CoV-2 vaccination cycle (vacc.2) as part of clinical routine independent of the study, e.g. at designated vaccination centers according to respective SmPCs or local/federal regulations and at the physician's discretion. Additional booster shots can be performed any time during the study and should be documented, however, there won't be any additional visits afterwards.

* If medically indicated, ofatumumab treatment might be started at an additional visit (A1) before visit 1 but at the earliest two weeks after the booster vaccination.

** Assessments don't have to be performed on visit 1 if ofatumumab treatment has already been initiated at visit A1.

*** Patients are allowed to receive additional SARS-CoV-2 booster vaccines any time after their first booster according to respective SmPCs or local regulations, as part of clinical routine and at the physician's discretion. If patients receive a second booster vaccination, additional visit 2 (A2) should be performed 1 month (4 weeks) after the second booster vaccination to collect a blood sample and assess immune response. If the next scheduled visit falls within two weeks of visit A2, the scheduled visit can be omitted. This only applies for the second booster. All potential following boosters should be documented but there won't be any additional visits afterwards.

[1] According to approved SmPC requirements

[2] Contact can be on site, virtual or via phone according to physician's choice.

[3] Laboratory test includes a standard hematology set, B-cell count, detection and characterization of SARS-CoV-2 specific T cells and neutralizing antibodies; if no SARS-CoV-2 specific T-cells can be detected, HLA-haplotyping will be considered to exclude methodical reasons. Blood samples will be stored.

[4] MS relapses within the last two years should be reported

Table 8-3 Assessment schedule cohort 2a

Phase	**Run-in phase**					**Investigational phase**									
Visit	**Screening** on site	**1*** remote	**2*** remote	**3*** remote	**4 Baseline** on site	**Vacc. 1#**	**Vacc. 2#**	**5** on site	**6** on site	Booster vacc. ***	A1*** (onsite, only if booster vacc.)	**7** on site	**8** on site	**9 on site**	**10 On site (end of study)**
Time of Visit	4-12 weeks before vacc. 1	+ 1 week after screening	+ 2 weeks after screening	+ 4 weeks after screening	approx. 1 week before vacc. 1	day 1	day 22/29**	+ 1 week after vacc. 2	+ 1 month after vacc. 2	after vacc.2	+ 1 month after booster	+ 3 months after vacc. 2	+ 6 months after vacc. 2	+ 12 months after vacc. 2	+ 18 months after vacc.2
Inclusion/Exclusion criteria	X														
Information & Informed consent	X														
Anamnesis, demographics, MS history	X														
MS relapse [4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Status MS and concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Physical exam	F				S			S	S		S		S	S	F
Blood sample [3]					X			X	X		X		X	X	X
Local urine pregnancy test	X														
Administration of study drug at site* [1]	X														
Self-injection training* [1]	X														
Study drug dispension	X				X				X			X	X	X	
Contact after modRNA vaccination [2]						X	X			X					
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Phone contact		X	X	X											

White color: timing of visits depends on vaccination date

Light grey color: optional visits

Dark grey color: timing of visits depends on start of ofatumumab treatment. Remote visits should be used to ensure that the first ofatumumab doses are applied according to SmPC

Vacc. = Vaccination with modRNA vaccine

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

F = full assessment, S = short medical exam

modRNA vaccination independent of study site at designated vaccination centers as part of clinical routine and depending on federal regulations.

***** If patient is already on stable ofatumumab treatment at the time of screening, the marked assessments as well as visits 1, 2 and 3 are not necessary. In that case, screening and baseline visit can be performed at the same day approx. one week before the first vaccination (similar to cohort 1).

****** Number of required vaccinations and interval depends on the SmPC of the respective modRNA vaccination and on local guidelines provided e.g. by the responsible health authorities

******* Patients are allowed to receive SARS-CoV-2 booster vaccines any time after vacc.2. If patients receive a booster vaccination, an additional visit (A1) should be performed 1 month (4 weeks) after the booster vaccination to collect a blood sample and measure immune response. If the next scheduled visit falls within two weeks of visit A1, the scheduled visit can be omitted. This only applies for the first and second booster. All potential following boosters should be documented but there won't be any additional visits afterwards.

[†] Phone contact to follow up on the occurrence of COVID-19 cases

[1] According to approved SmPC requirements

[2] Contact can be on site, virtual or via phone according to physician's choice.

[3] Laboratory test includes a standard hematology set, B-cell count, detection and characterization of SARS-CoV-2 specific T cells and neutralizing antibodies; if no SARS-CoV-2 specific T-cells can be detected, HLA-haplotyping will be considered to exclude methodical reasons. Blood samples will be stored. [4] MS relapses within the last two years should be reported

Table 8-4 Assessment schedule cohort 2b

Period	**Run-in**					**Investigational**						
Visit	Screening On site	1* remote	2* remote	3* remote	Baseline* On site	Booster vacc. #	4 On site	Booster vacc. **	A1** (onsite, only if booster vacc.)	5 On site	6 On site	7 On site **(end of study)**
Day/Week/Month	min. 4 weeks before booster	+ 1 week after screening	+ 2 weeks after screening	+ 4 weeks after screening	Approx. 1 week before booster	Day 1	+1 month after booster	after vacc.2	+ 1 month after booster	+3 months after booster	+6 months after booster	+12 months after booster
Obtain informed consent	X											
Inclusion/exclusion criteria	X											
Anamnesis, Demography, Relevant medical and MS history	X											
Physical exam	F				S		S		S		S	F
Blood sampling [3]					X		X		X		X	X
MS relapse[4]	X	X	X	X	X	X	X	X	X	X	X	X
Status MS and concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
Local urine and pregnancy test [1]	X											
Administration of study drug at site *	X											
Self-injection training * [1]	X											

Study drug dispension	X				X					X	X	
Contact after modRNA vaccination [2]						X		X				
Documentation SARS-CoV-2 vaccination	X					X		X				
Telephone contact		X	X	X								
AE/SAE	X	X	X	X	X	X	X	X	X	X	X	X

White color: timing of visits depends on vaccination date

Grey color: Timing of visits depends on start of ofatumumab treatment. Remote visits should be used to ensure that the first ofatumumab doses are applied according to SmPC.

A = additional visit; vacc. = Vaccination with modRNA vaccine,

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

F = full assessment, S = short medical exam

First booster vaccination; can be performed any time after termination of the initial SARS-CoV-2 vaccination cycle (vacc.2) as part of clinical routine independent of the study, e.g. at designated vaccination centers according to respective SmPCs or local/federal regulations and at the physician's discretion. Additional booster shots can be performed any time during the study and should be documented, however, there won't be any additional visits afterwards.

* If patient is already on stable ofatumumab treatment at the time of screening, the marked assessments as well as visits 1, 2 and 3 are not necessary. In that case, screening and baseline visit can be performed at the same day approx. one week before the booster vaccine (similar to cohort 1b).

*** Patients are allowed to receive SARS-CoV-2 booster vaccines any time after their first booster. If patients receive a second booster vaccination, an additional visit (A1) should be performed 1 month (4 weeks) after the second booster vaccination to collect a blood sample and measure immune response. If the next scheduled visit falls within two weeks of visit A1, the scheduled visit can be omitted. This only applies for the second booster. All potential following boosters should be documented but there won't be any additional visits afterwards.

[1] According to approved SmPC requirements

[2] Contact can be on site, virtual or via phone according to physician's choice.

[3] Laboratory test includes a standard hematology set, B-cell count, detection and characterization of SARS-CoV-2 specific T cells and neutralizing antibodies; if no SARS-CoV-2 specific T-cells can be detected, HLA-haplotyping will be considered to exclude methodical reasons. Blood samples will be stored.

[4] MS relapses within the last two years should be reported

8.1 Screening

Re-screening is permitted if the patient is not eligible for SARS-CoV-2 vaccination (initial vaccination or booster vaccine) by local regulation within 12 weeks after screening. In this case the Novartis Medical Advisor should be contacted to discuss further proceeding.

8.1.1 Eligibility screening

At screening, patients will be asked about previous COVID-19 disease. If a patient has had COVID-19 disease before screening, the patient is not eligible to further participate in the study.

8.1.2 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).

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 Efficacy

Blood samples will be collected at the timepoints defined in the Assessment Schedule (cohort 1a: Table 8-1, cohort 1b: Table 8-2, cohort 2a: Table 8-3, cohort 2b: Table 8-4). Follow instructions outlined in the Laboratory manual regarding sample collection, numbering, processing, and shipment.

8.3.1 Efficacy assessment 1

SARS-CoV-2 vaccination efficacy is defined as detection of SARS-CoV-2 specific T-cells one month after completion of the initial vaccination cycle or 1 month after a booster vaccination.

8.3.2 Efficacy assessment 2

Additional efficacy assessments are:

- Longitudinal follow-up of SARS-CoV-2 specific T-cells one week, one month, six months, 12 months and 18 months after second dose of vaccine as well as 6 months and 12 months after booster vaccine
- Longitudinal follow-up of SARS-CoV-2 serum functional antibody levels one week, one month, six months, 12 months and 18 months after second dose of vaccine as well as 6 months and 12 months after booster vaccine
- Phenotypical characterization of peripheral blood mononuclear cells for CD45, CD3, CD4, CD8, CD62l, CD45RA, CD27, CCR7
- Immunophenotyping for naive, central memory, effector memory, and effector cells on $CD4^+$ and $CD8^+$ cells
- Measuring cells positive for intracellular cytokine-staining for interferon-gamma and interleukin-4

[redacted]

8.3.3 Appropriateness of efficacy assessments

Efficacy assessments in KYRIOS 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 BNT162b2 (Sahin, Muik et al. 2020). This study reports SARS-CoV-2 specific T-cell responses one week after completion of the vaccination cycle measured by ex vivo IFNγ ELISPOT assay. Sahin et al. further characterized the T cells involved in the T cell response with regards to surface markers and Th1/Th2 polarization and reported stable IgG levels from one week after the second vaccine for up to 60 days. Comparable results were also reported for mRNA-1273 by Jackson et al, 2020.

The detection of SARS-CoV-2 reactive T-cells one month after completion of the vaccination cycle was chosen as a primary endpoint in this study to assess efficacy.

Further characterization of the T-cell response as well as measurement of IgG antibodies as reported by Sahin et al. will be performed as secondary assessments.

8.4 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), general appearance, height, weight, 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). 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.

8.4.1 Laboratory evaluations

A central laboratory will be used for analysis of all safety specimens collected. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in the central laboratory manual.

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 clinically significant.

Special clinical laboratory evaluations

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 and IL-2 enzyme-linked immunosorbent spot (ELISpot)
Hematology	Blood samples will be collected according to the schedule in Table 8-1, 8-2, 8-3 and Table 8-4. Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)
B cell count	CD19+/CD20+ B-cell counts. Samples will be collected according to the schedule in Table 8-1, Table 8-2, Table 8-3 and Table 8-4.

8.4.2 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

8.5 Additional assessments

No additional tests will be performed on participants entered into this study.

9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

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
- Any situation in which study participation might result in a safety risk to the participant

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the participant’s premature discontinuation of study treatment and record this information.

Participants who discontinue study treatment or 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.

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments
- Adverse Events / Serious Adverse Events (including COVID-19 disease)

9.1.1.1 Replacement policy

Patients successfully screened who do not receive a SARS-CoV-2 mRNA vaccination or a booster vaccine within 3 months after screening will be excluded from the study and be 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.

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.

The patient can decide if Novartis is allowed to retain and use all research results (data) that have already been collected for the study evaluation or if stored blood samples need to be destroyed.

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 or until the end of the study.

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.

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 dose of study treatment.

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 within 24 hours of learning of its occurrence. MS relapses are exempt from SAE reporting although they may meet the SAE definition on the basis that they are considered medically significant and are frequently associated with hospitalization. These events will be reported on the MS relapse eCRF instead of the SAE form. However, if in the judgement of the Investigator, a MS relapse is unusually severe or unexpected and warrants specific notification, then an SAE form must be completed and submitted according to SAE reporting procedures outlined above. 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, and under no circumstances 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.

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.

Any SAEs experienced after the 30 day period should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

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 study treatment any 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.

10.2 Additional Safety Monitoring

Not applicable.

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 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, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/delegated CRO/CRA organization. Additionally,

a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each 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,six months, 12 months and 18 months after the second SARS-CoV-2 vaccine and 1, 6 and 12 months after a booster vaccine, respectively, will include all participants who have a valid determination of SARS-CoV-2 reactive T-cells 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 and 2) 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 time between second vaccination (cohort 1a) or booster vaccination (cohort 1b) and start of ofatumumab treatment will be presented. For Cohort 2, the time from first ofatumumab dose to first vaccination (cohort 2a) or booster vaccination (cohort 2b) will be summarized. For both cohorts, continuous ofatumumab intake will be presented.

12.3 Treatments

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, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure in days to Ofatumumab will be summarized by means of descriptive statistics using the safety set.

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.

12.4 Analysis of the primary endpoint(s)/estimand(s)

The primary clinical question of this study is to estimate the proportion of RMS patients mounting an immune response after receiving a modRNA vaccine (initial vaccination or booster) either before or after starting ofatumumab treatment.

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

The primary endpoint of this study is the proportion of RMS patients having established SARS-CoV-2-specific T cells as defined by detection of SARS-CoV-2 reactive T-cells, measured by e.g. enzyme-linked immunosorbent spot (ELISpot) assay from T-cells that were stimulated with SARS-CoV-2 peptide mix, one month after second dose of vaccine or one month after booster vaccine in participants who received the respective vaccine before or after starting ofatumumab treatment (yes/no).

12.4.2 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 with detectable SARS-CoV-2 reactive T-cells within each cohort will be calculated. It will be augmented by a (descriptive) 95% confidence interval (exact Clopper-Pearson).

12.4.3 Handling of remaining intercurrent events of primary estimand

Cohort 1a and cohort 2a: 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 reactive T-cells to SARS-CoV-2 for whatever reason will be excluded from the analysis of vaccine efficacy.

Patients in cohort 1b and 2b who did receive a booster vaccine and do not have a valid determination of reactive T-cells to SARS-CoV-2 for whatever reason will be excluded from the analysis of vaccine efficacy.

12.4.4 Supportive analyses

Patient demographics and baseline characteristics among both cohorts will be compared in the data analysis. Additionally, patients receiving their initial vaccination (cohorts 1a and 2a) vs. a booster shot (cohort 1b and 2b) will be analyzed separately. If patients received a non-mRNA vaccine as booster, this would be reflected in the analysis.

12.5 Analysis of secondary endpoints/estimands

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.

12.5.1 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 with the exception of baseline data 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 last study visit.

Adverse events

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

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.
- by treatment, Standardized MedDRA Query (SMQ) and preferred term.

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 and 2), participant, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

[redacted]

12.7 Interim analyses

The first interim analysis will be performed when at least 5 participants per cohort have completed the study visit one week after a complete SARS-CoV-2 vaccination cycle or on September 1st 2021, whichever comes first.

The second interim analysis will be performed when at least 10 patients in cohort 2 have completed the primary endpoint, 1 month (4 weeks) after the second vaccine (2a) or the booster vaccine (2b) or on January 10th 2022, whichever comes first.

An additional 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 and whenever deemed necessary. As all analyses in this study are purely descriptive, there is no need for any statistical adjustments.

12.8 Sample size calculation

12.8.1 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. 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.

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