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Novartis Research and Development

OMB157G/Ofatumumab

Synopsis/Clinical Trial Protocol COMB157GUS16 / NCT04878211

An open-label multicenter study to assess response to COVID-19 vaccine in participants with multiple sclerosis treated with ofatumumab 20 mg subcutaneously

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List of abbreviations

AE	Adverse Event
COVID-19	Coronavirus 2019
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CTC	Common Terminology Criteria
EDC	Electronic Data Capture
EOS	End of Study
[redacted]	[redacted]
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBV	Hepatitis B Virus
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
iDMT	Injectable Disease Modifying Therapy
[redacted]	[redacted]
IN	Investigator Notification
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	Interactive Response Technology
mg	milligram(s)
ml	milliliter(s)
mAb	monoclonal antibody
QMS	Quality Management System
s.c.	subcutaneous
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction

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
Mis-enrolled participants	Mis-enrolled participants are those who were not qualified for enrollment and who did not take study treatment, but have been inadvertently enrolled into the study
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly-diagnosed disease
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
Participant number	A unique identifier assigned to each screened participant
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 2

Amendment Rationale

This protocol has been amended to allow participants with a known diagnosis of COVID-19 prior to starting in the study to be enrolled. In this amendment we have also addressed inconsistencies and sought to make clarifications at certain points.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 1

Amendment Rationale

This protocol has been amended to add 3 new cohorts comprised of participants who have completed a full course (two doses) of a COVID-19 mRNA vaccine. Also, the sample size of the study is increased to enroll a reasonable number of participants in all six cohorts. Given the decline in the US vaccination rate, the decision to include participants who are fully vaccinated was made to increase the rate in which participants are enrolled and to capture additional data related to mounting an immune response. The number of interim analysis is increased from one to three. In this amendment we have also addressed inconsistencies and sought to make clarifications at certain points.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Protocol summary

<table>
<tr><td>Protocol number</td><td>COMB157GUS16</td></tr>
<tr><td>Full Title</td><td>An open-label multicenter study to assess response to COVID-19 vaccine in participants with multiple sclerosis treated with ofatumumab 20 mg subcutaneously</td></tr>
<tr><td>Brief title</td><td>A multicenter study to assess response to COVID-19 vaccine in multiple sclerosis participants treated with ofatumumab</td></tr>
<tr><td>Sponsor and Clinical Phase</td><td>Novartis
Clinical phase IV</td></tr>
<tr><td>Investigation type</td><td>Biological/Vaccine</td></tr>
<tr><td>Study type</td><td>Interventional, 6-cohort</td></tr>
<tr><td>Purpose and rationale</td><td>The objective of this study is to assess whether participants treated with ofatumumab 20 mg subcutaneous (s.c.) administered once monthly can mount an adequate immune response to non-live COVID-19 mRNA vaccine as measured by humoral responses compared to participants on an interferon or glatiramer acetate.</td></tr>
<tr><td>Primary Objective(s)</td><td>To assess immune response to non-live mRNA COVID-19 vaccine in ofatumumab treated subjects</td></tr>
<tr><td>Secondary Objectives</td><td>• To assess immune conversion to non-live mRNA COVID-19 vaccine in ofatumumab treated subjects
• To assess adverse events and serious adverse events</td></tr>
<tr><td>Study design</td><td>This is a 6-cohort, multicenter, prospective study of up to 88 relapsing MS participants.
<table>
<tr><td>Cohort</td><td>Brief Description</td></tr>
<tr><td>1</td><td>Vaccine naive, planning to start OMB</td></tr>
<tr><td>2</td><td>Vaccine naive, currently on OMB for ≥ 4 weeks</td></tr>
<tr><td>3</td><td>Vaccine naive, on interferon or glatiramer acetate for ≥ 4 weeks</td></tr>
<tr><td>4</td><td>Fully vaccinated, currently on OMB for ≥ 4 weeks</td></tr>
<tr><td>5</td><td>Fully vaccinated, on interferon or glatiramer acetate for ≥ 4 weeks, +/- booster</td></tr>
<tr><td>6</td><td>Fully vaccinated, currently on OMB for ≥ 4 weeks, + booster</td></tr>
</table>
All groups will undergo serologic testing.
Participants will obtain the COVID-19 mRNA vaccine from their HCP (private insurance) or appropriate federal, state or local program.</td></tr>
<tr><td>Study population</td><td>Adult (ages 18-55) relapsing MS participants</td></tr>
<tr><td>Key Inclusion criteria</td><td>Patients eligible for inclusion in Cohort 1 of this study must fulfill the following criteria:
1. Signed informed consent must be obtained prior to participation in the study
2. Age 18-55 years old inclusive at Screening
3. Diagnosis of relapsing MS by 2017 revised McDonald criteria
4. Must be willing to comply with the study schedule</td></tr>
</table>

	5. Will be receiving an mRNA COVID-19 vaccine (Pfizer or Moderna vaccine) 6. Eligible to receive and plan to be started on Ofatumumab according to the approved labeling 7. Pre-ofatumumab serologies with Hepatitis B testing not indicative of active or latent infection 8. Total serum immunoglobulin IgG ≥ 400 mg/dl at Screening Patients eligible for inclusion in Cohort 2 of this study must fulfill the following criteria: 1. Signed informed consent must be obtained prior to participation in the study 2. Age 18-55 years old at Screening 3. Diagnosis of relapsing MS by 2017 revised McDonald criteria 4. Must be willing to comply with the study schedule 5. Currently on commercially prescribed ofatumumab for ≥ 4 weeks for the treatment of RMS 6. Will be receiving an mRNA COVID-19 vaccine (Pfizer or Moderna vaccine) 7. Pre-ofatumumab serologies with Hepatitis B testing not indicative of active or latent infection 8. Total serum immunoglobulin IgG ≥ 400 mg/dl at Screening Patients eligible for inclusion in Cohort 3 of this study must fulfill the following criteria: 1. Signed informed consent must be obtained prior to participation in the study 2. Age 18-55 years old at Screening 3. Diagnosis of relapsing MS by 2017 revised McDonald criteria 4. Must be willing to comply with the study schedule 5. Currently on commercially prescribed interferon or glatiramer acetate for ≥ 4 weeks for the treatment of RMS 6. Will be receiving an mRNA COVID-19 vaccine (Pfizer or Moderna vaccine) 7. Total serum immunoglobulin IgG ≥ 400 mg/dl at Screening Patients eligible for inclusion in Cohort 4 of this study must fulfill the following criteria: 1. Signed informed consent must be obtained prior to participation in the study 2. Age 18-55 years old at Screening 3. Diagnosis of relapsing MS by 2017 revised McDonald criteria 4. Must be willing to comply with the study schedule 5. Completed a full course (two doses) of a COVID-19 mRNA vaccine at least ≥ 4 weeks after start of commercially prescribed ofatumumab for the treatment of RMS 6. Currently on commercially prescribed ofatumumab for ≥ 4 weeks for the treatment of RMS 7. Received two dose mRNA COVID-19 vaccine (Pfizer or Moderna vaccine) ≥ 2 weeks ago 8. Pre-ofatumumab serologies with Hepatitis B testing not indicative of active or latent infection 9. Total serum immunoglobulin IgG ≥ 400 mg/dl at Screening Patients eligible for inclusion in Cohort 5 of this study must fulfill the following criteria: 1. Signed informed consent must be obtained prior to participation in the study 2. Age 18-55 years old at Screening 3. Diagnosis of relapsing MS by 2017 revised McDonald criteria 4. Must be willing to comply with the study schedule 5. Currently on commercially prescribed interferon or glatiramer acetate for ≥ 4 weeks for the treatment of RMS

	6. Completed a full course (two doses) of a COVID-19 mRNA vaccine after start of glatiramer acetate or interferon 7. Received two dose mRNA COVID-19 vaccine (Pfizer or Moderna vaccine) ≥ 2 weeks ago 8. If the patient has received the mRNA booster, then the mRNA booster should be ≥ 2 weeks prior to enrollment 9. Total serum immunoglobulin IgG ≥ 400 mg/dl at Screening Patients eligible for inclusion in Cohort 6 of this study must fulfill the following criteria: 1. Signed informed consent must be obtained prior to participation in the study 2. Age 18-55 years old at Screening 3. Diagnosis of relapsing MS by 2017 revised McDonald criteria 4. Must be willing to comply with the study schedule 5. Currently on commercially prescribed ofatumumab 6. Completed a full course (two doses) of a COVID-19 mRNA vaccine at least ≥ 4 weeks after start of commercially prescribed ofatumumab for the treatment of RMS 7. Received two dose mRNA COVID-19 vaccine (Pfizer or Moderna vaccine) ≥ 2 weeks ago 8. Pre-ofatumumab serologies with Hepatitis B testing not indicative of active or latent infection 9. Total serum immunoglobulin IgG ≥ 400 mg/dl at Screening 10. Has received an mRNA booster ≥ 2 weeks prior to enrollment
Key Exclusion criteria	1. Already has received the J&J vaccine. 2. Has a contraindication to receiving an mRNA COVID-19 vaccine 3. Has an immediate allergic reaction to a past vaccine or injection 4. Any safety finding including low immunoglobulin IgG and/or low immunoglobulin IgM levels requiring an ofatumumab treatment interruption within the 12 weeks immediately prior to vaccination as determined by the HCP 5. Any major episode of infection requiring hospitalization or treatment with intravenous antibiotics within 4 weeks prior to the first vaccination visit or oral antibiotics within two weeks prior to the first vaccination visit 6. Prior treatment with B-cell targeted therapies (e.g., rituximab or ocrelizumab), alemtuzumab, anti-CD4, cladribine, cyclophosphamide, mitoxantrone, azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, total body irradiation, or bone marrow transplantation 7. Prior treatment with S1P agent within 2 months at Screening 8. Prior treatment with natalizumab within 6 months of study enrollment/Visit 2 9. Since commercially prescribed ofatumumab is being used in the study, contraindications as per the USPI will be adhered to which include active infection hepatitis B infection, progressive multifocal leukoencephalopathy and pregnancy 10. Participation in another interventional clinical trial within 14 days before enrollment
Study treatment	Participants in Cohort 1 (Pfizer vaccine): The first of three 20 mg sc ofatumumab loading doses will be administered on Day 36 or 2 weeks after receiving a full course (two doses) of COVID-19 vaccine. The 2nd and 3rd loading doses should be administered on Day 43 and Day 50 or 7 and 14 days respectively after the 1st loading dose. Subsequent dosing includes 20 mg sc administered monthly starting at Day 64.

	Participants in Cohort 1 (Moderna vaccine): The first of three 20 mg sc ofatumumab loading doses will be administered on Day 43 or 2 weeks after receiving a full course (two doses) of COVID-19 vaccine. The 2nd and 3rd loading doses should be administered on Day 50 and Day 57 or 7 and 14 days respectively after the 1st loading dose. Subsequent dosing includes 20 mg sc administered monthly starting at Day 71. Participants in Cohort 2: Will continue to take prescribed ofatumumab as per their current dosing schedule. Participants in Cohort 3: Will continue to take interferon or glatiramer acetate as per their current dosing schedule. Participants in Cohort 4: Will continue to take prescribed ofatumumab as per their current dosing schedule. Participants in Cohort 5: Will continue to take prescribed glatiramer acetate or interferon as per their current dosing schedule. Participants in Cohort 6: Will continue to take prescribed ofatumumab as per their current dosing schedule.
Treatment of interest	COVID-19 mRNA vaccine
Efficacy assessments	None
Key safety assessments	• SARS-CoV-2 qualitative/quantitative IgG antibody assay • Adverse events/serious adverse events [redacted]
Data analysis	The primary endpoint is achieving immune response as defined by a positive SARS-CoV-2 qualitative IgG antibody assay 14 days after full course (two doses) vaccination (yes/no). The sample size of 20 participants per individual or combined cohort is selected based on budget and need for early availability of results. The sample size of 20 participants will provide estimates with margin of error (half-width of a 95% confidence interval) of 20.1%, 19%, and 17.5% corresponding to immune response rates of 70%, 75%, and 80%, respectively. Adjusting for 10% drop-out, 22 participants will be enrolled in Cohort 1. In combination, 22 participants will be enrolled in Cohorts 2 and 4. In combination, 22 patients will be enrolled in Cohorts 3 and 5. In Cohort 6, 22 participants will be enrolled. The number and percentage of responders will be presented. The 95% confidence interval for the proportion of responders will be calculated by using exact method.
Key words	COVID-19, vaccine, ofatumumab, SARS-coV2, antibody, [redacted] open-label

1 Introduction

1.1 Background

Multiple sclerosis (MS) is a common cause of neurologic disability in young adults. In this disease, damage is caused by an autoimmune attack of the central nervous system. Recent phase 3 trials have demonstrated that antibodies that bind and cause CD20 B cells apoptosis have a powerful anti-inflammatory effect as measured by relapse and MRI activity, and leave participants with less disability than active comparators (Hauser et al 2020 and Hauser et al 2017).

MS disease modifying treatments target the immune system and in so doing may diminish vaccine efficacy (Farez et al 2019). Questions have arisen whether therapies that affect B cells might also abrogate vaccine response. Though other medications also impact B cells, anti-CD20 antibodies have the most selective and potent impact on B cells. These antibodies impact memory B cells which are believed to be an important component in maintaining immunologic memory but also preserve immunoglobulin secreting plasma cells which function to recognize and remove pathogens. Research with an anti-CD20 B cell agent, ocrelizumab, indicates that an immune response can occur after vaccination but that the proportion of participants with an adequate response is diminished relative to a control group (Bar-Or et al 2020).

Ofatumumab is a subcutaneously administered anti-CD20 therapy that received FDA approval for treatment of relapsing forms of MS in August 2020. Data is currently lacking regarding whether MS participants on ofatumumab can mount an appropriate immune response to vaccines, including the COVID-19 vaccine. In this study, MS participants will receive the COVID-19 vaccination and follow-up assays to assess whether they are able to mount a response to the vaccine. A reference cohort of participants on injectable disease modifying treatments (interferon or glatiramer acetate) is included. In a prior study, interferon and glatiramer acetate did not diminish vaccine response (Olberg et al 2018).

1.2 Purpose

An important safety concern for health care providers and patients is whether an MS disease modifying agent might compromise vaccine efficacy. Ofatumumab is a human anti-CD20 monoclonal antibody (mAb) that induces B-cell depletion. An increased risk of infections has been observed with other anti-CD20 B-cell depleting therapies. Ofatumumab has the potential for an increased risk of infections, including serious bacterial, fungal, and new or reactivated viral infections; some of these infections have been fatal in patients treated with other anti-CD20 antibodies. As such, participants on ofatumumab may have an increased risk of morbidity and mortality should they contract COVID-19. Therefore, it is important to assess if participants treated with ofatumumab are able to mount protective immune responses against the COVID-19 vaccine.

This study will aim to address the following:

1. To define COVID vaccine response in patients receiving a full course mRNA vaccination and how treatment with ofatumumab effects response.
2. To determine the impact of a booster dose on immune response.

2 Objectives, endpoints and estimands

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objectives	**Endpoint(s) for primary objective(s)**
• To assess immune response to non-live mRNA COVID-19 vaccine in ofatumumab treated participants	• Achieving immune response as defined by positive SARS-CoV-2 qualitative IgG antibody assay ≥ 14 days after vaccination (yes/no)
Secondary Objectives	**Endpoint(s) for secondary objective(s)**
• To assess sustained immune response to non-live mRNA COVID-19 vaccine in ofatumumab treated participants	• Achieve immune response at other assessment time points (yes/no)
• To assess immune conversion to non-live mRNA COVID-19 vaccine in ofatumumab treated participants	• Immune conversion to non-live mRNA COVID-19 vaccine (yes/no) defined as : • For patients with serum available prior to vaccine: o Baseline absence of SARS-CoV-2 spike IgG with post-vaccination SARS-CoV-2 positive qualitative antibody assay ≥ 14 days after full course (two doses) vaccination (yes/no) or o Baseline serum presence of SARS-CoV-2 quantitative IgG antibody with post-vaccination ≥ 4-fold increase in SARS-CoV-2 quantitative antibody titer as determined by dilution assay ≥ 14 days after vaccination (yes/no) • For patients with serum unavailable prior to vaccine but who have not received a booster (Cohorts 4 and 5): o Initial negative SARS-CoV-2 nucleocapsid antibody with post-vaccination SARS-CoV-2 positive qualitative antibody assay ≥ 14 days after full course (two doses) vaccination (yes/no)
• To assess adverse events and serious adverse events	• Adverse events/serious adverse events

[redacted]

[redacted]

2.1 Primary estimands

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during the trial conduct which could impact the interpretation of the trial results (e.g., premature discontinuation of treatment).

The primary clinical question of interest is: Do relapsing MS participants who receive ofatumumab treatment mount an immune response to non-live mRNA COVID-19 vaccine?

The justification for the primary estimand is that it will capture whether ofatumumab treated participants generate antibodies to mRNA COVID-19 vaccines.

The primary estimand is described by the following attributes:

- **Population:** Defined through appropriate inclusion/exclusion criteria to reflect the targeted population. Relapsing MS participants subdivided into 6 cohorts. (1) Will receive a full course (two doses) of a COVID-19 mRNA vaccine two weeks prior to starting ofatumumab 20 mg subcutaneous treatment; (2) Will receive a full course (two doses) of a COVID-19 mRNA vaccine after at least 4 weeks of commercial ofatumumab 20 mg subcutaneous treatment (3) Will receive a full course (two doses) of a COVID-19 mRNA vaccine after at least 4 weeks of interferon or glatiramer acetate treatment (4) Completed a full course (two doses) of a COVID-19 mRNA vaccine after at least 4 weeks of commercial ofatumumab 20 mg subcutaneous treatment but has not yet received a COVID-19 mRNA booster (5) Completed a full course (two doses) of a COVID-19 mRNA vaccine after at least 4 weeks of interferon or glatiramer acetate (may or may not have received at least 1 COVID-19 mRNA booster) (6) Completed a full course (two doses) of a COVID-19 mRNA vaccine after at least 4 weeks of commercial ofatumumab 20 mg subcutaneous treatment and received at least 1 additional booster vaccine ≥ 14 days prior to Screening.
- **Variable:** Achieving immune response as defined by a positive SARS-CoV-2 qualitative IgG antibody assay ≥ 14 days after full course (two doses) vaccination (yes/no)
- **Treatment of interest**: Non-live COVID-19 mRNA vaccine either two weeks prior to ofatumumab start or at least 4 weeks after ofatumumab start or while on interferon or glatiramer acetate
- **Intercurrent event:** Discontinuation of treatment/study, or death
- **Summary measure:** Proportion of participants achieving immune response

2.2 Secondary estimands

Not applicable.

3 Study design

This is a 6-cohort, multicenter prospective study in up to 88 participants with relapsing multiple sclerosis. Up to 66 of the participants will begin treatment with ofatumumab or already be on commercial ofatumumab, the remaining 22 participants will remain on interferon or glatiramer acetate.

In this study, participants must intend to receive or have received a full course of a non-live COVID-19 mRNA (Pfizer or Moderna) vaccine. Participants also must meet inclusion criteria and not meet exclusion criteria.

1. Screening Period:

Participants will enter a Screening Period of up to 7 days to assess eligibility requirements. Participants in Cohort 1, 2, 4 and 6 without Hepatitis B virus (HBV) and total serum immunoglobulin results within the past 6 months prior to screening will require central labs drawn. Participants with Hepatitis B virus (HBV) and total serum immunoglobulin results within the specified inclusion range the past 6 months prior to screening will not require the labs to be drawn.

Participants in Cohort 3 and 5 without total serum immunoglobulin results within the past 6 months prior to screening will require central labs drawn. Participants with total serum immunoglobulin results within the specified inclusion range the past 6 months prior to screening will not require the labs to be drawn.

1. Treatment Period:

Participants will obtain the mRNA vaccine through their HCP (private insurance) or appropriate federal, state or local program. Participants should be instructed to provide documentation of vaccine administration to the Study Doctor at the next scheduled on-site study visit.

Cohort 1:

For participants who receive the Pfizer vaccine, the first of three 20 mg s.c ofatumumab loading doses will be administered on Day 36 or 2 weeks after receiving a full course (two doses) of a COVID-19 vaccine. The 2nd and 3rd loading doses should be administered on Day 43 and Day 50 or 7 and 14 days respectively after the 1st loading dose. Subsequent dosing includes 20 mg s.c. administered monthly starting at Day 64.

For participants who receive the Moderna vaccine, the first of three 20 mg s.c ofatumumab loading doses will be administered on Day 43 or 2 weeks after receiving a full course (two doses) of a COVID-19 vaccine. The 2nd and 3rd loading doses should be administered on Day 50 and Day 57 or 7 and 14 days respectively after the 1st loading dose. Subsequent dosing includes 20 mg s.c administered monthly starting at Day 71.

Cohort 2: Will continue taking their prescribed ofatumumab as per their current dosing schedule.

Cohort 3: Will continue administration of their prescribed interferon or glatiramer acetate as per their current dosing schedule.

Cohort 4: Will continue taking their prescribed ofatumumab as per their current dosing schedule and should adhere to the visit schedule as shown in either Table 8-5 (Pfizer) or Table 8-6 (Moderna).

Cohort 5: Will continue taking their prescribed glatiramer acetate or interferon as per their current dosing schedule and should adhere to the visit schedule as shown in either Table 8-5 (Pfizer) or Table 8-6 (Moderna).

Cohort 6: Will continue taking their prescribed ofatumumab as per their current dosing schedule and should adhere to the visit schedule as shown in either Table 8-5 (Pfizer) or Table 8-6 (Moderna).

Study design schematics for Cohorts 1, 2 and 3 are shown in Figure 3-1, Figure 3-2, Figure 3-3, and Figure 3-4. Study design schemas for Cohorts 4, 5, and 6 are shown in Figure 3-5 and Figure 3-6.

Figure 3-1 Study Design (Cohort 1, Pfizer)

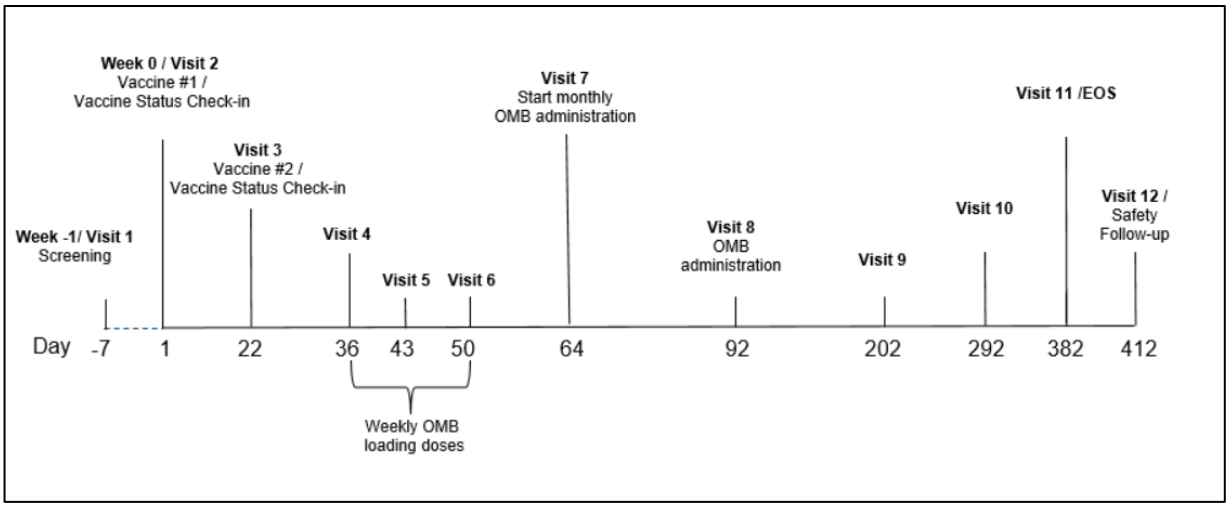


Figure 3-2 Study Design (Cohort 1, Moderna)

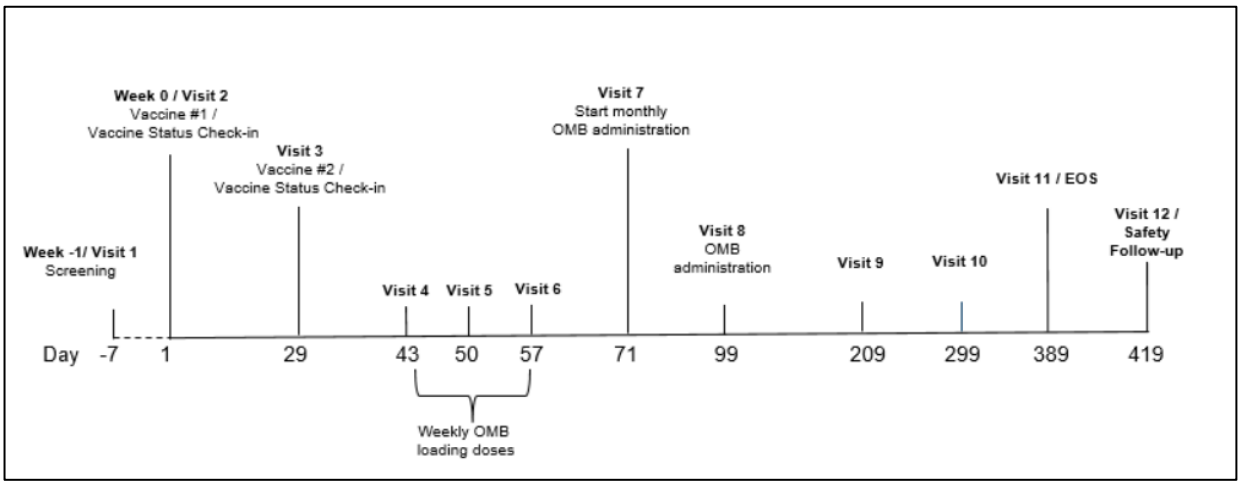


Figure 3-3 Study Design (Cohorts 2 and 3, Pfizer)

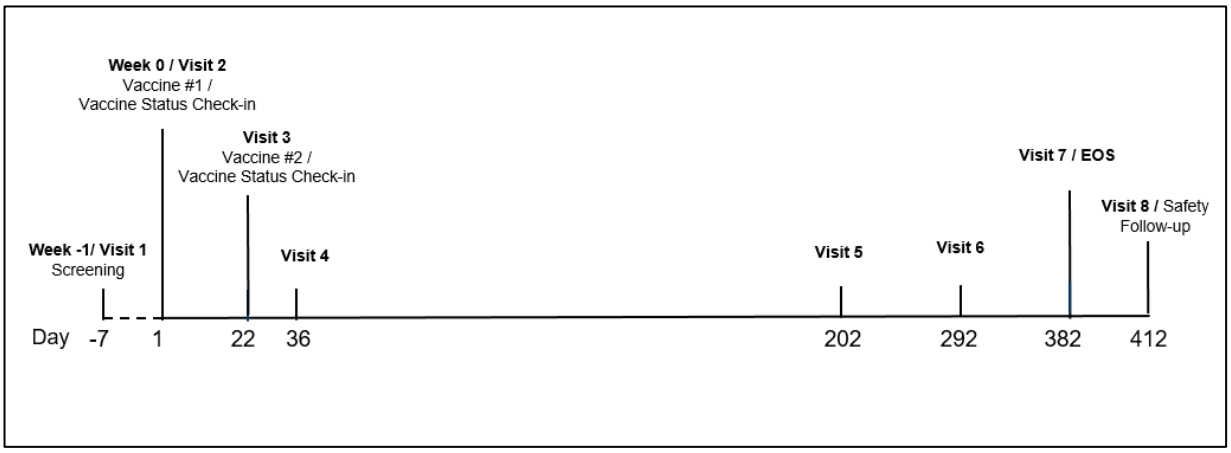


Figure 3-4 Study Design (Cohorts 2 and 3, Moderna)

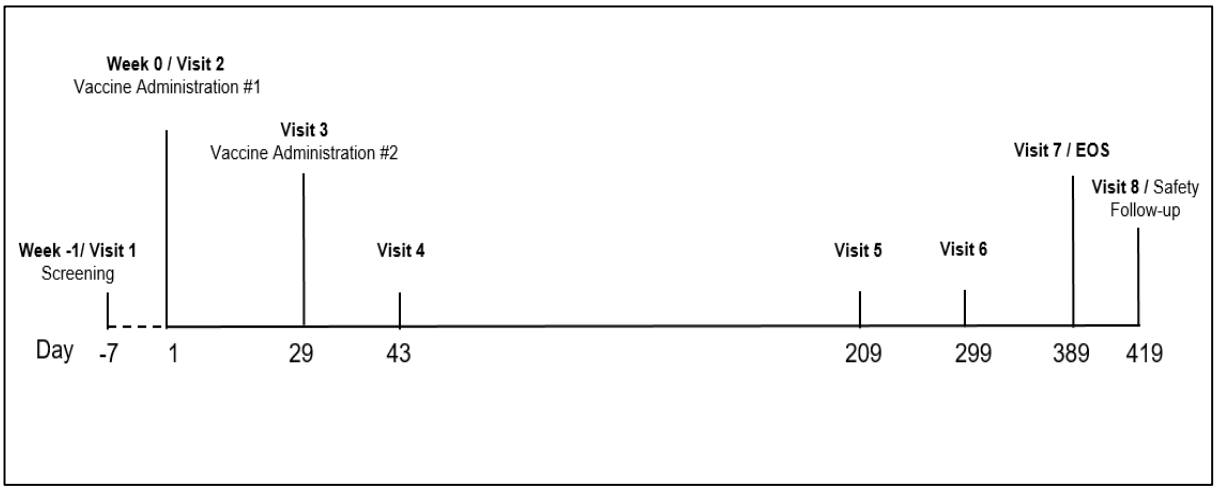


Figure 3-5 Study Design (Cohorts 4, 5, and 6, Pfizer)

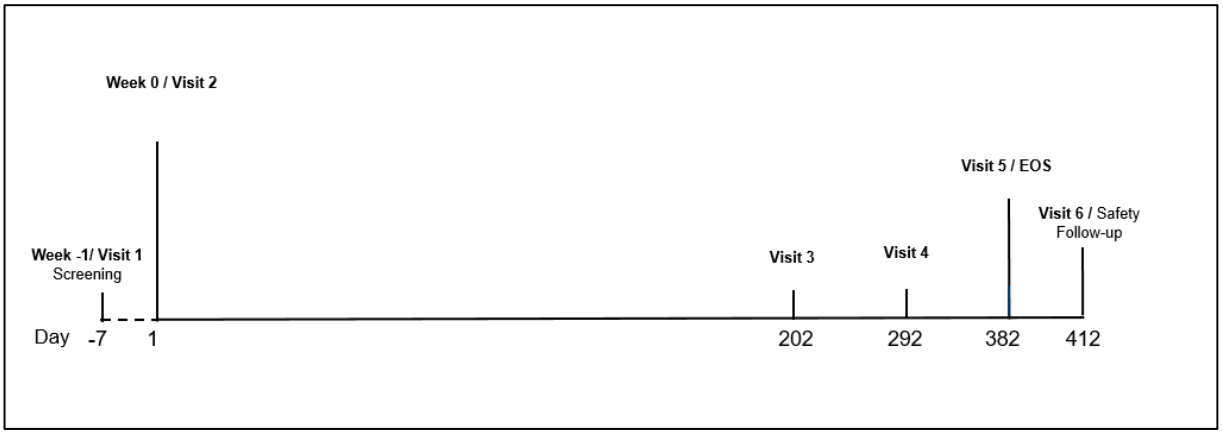


Figure 3-6 Study Design (Cohorts 4, 5, and 6, Moderna)

Remote procedures

At the investigator's direction and based on benefit-risk considerations of the participant's clinical condition, qualifying participants may be offered the option to have certain clinical trial procedures according to the assessment schedules in Table 8-1, Table 8-2, Table 8-3, Table 8-4, Table 8-5 and Table 8-6 performed from within their home.

Such procedures will be performed remotely under the oversight of the Investigator, who retains accountability for the oversight and all efficacy and safety decisions with delegation of tasks to an off-site healthcare professional. Off-site healthcare professionals will be provided by a third-party vendor sourced by Novartis or an agent for Novartis.

In addition to procedures performed by the off-site healthcare professional, the on-site staff may perform certain procedures remotely using tele-visits.

4 Rationale

4.1 Rationale for study design

A multicenter, 6-cohort, open-label, comparator design has been selected in order to render feasible recruitment given the study's expedited schedule based on the importance of this dataset. The study will address two questions:

1. Can participants treated with ofatumumab develop an immune response if receiving a COVID-19 mRNA vaccine two weeks prior to ofatumumab start?
2. If receiving COVID-19 mRNA vaccine after introduction of ofatumumab treatment, can participants develop an immune response?

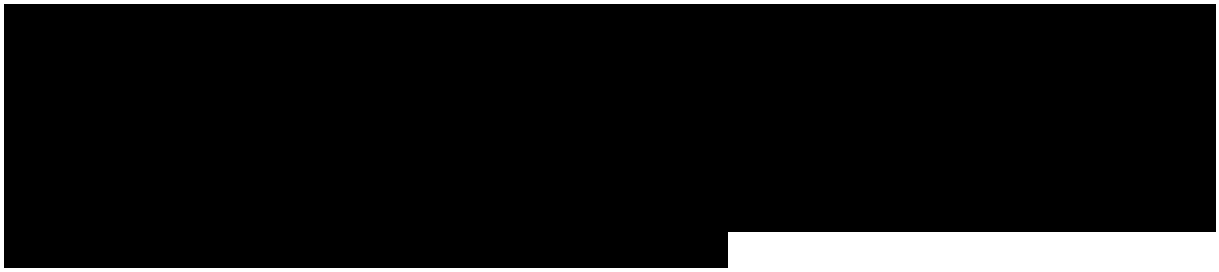
Participant Cohorts 3 and 5 on interferon or glatiramer acetate are included as a comparator.

Rationale of study population:

The included population is selected to be consistent with the ofatumumab phase 3 trial program and within the parameters of use specified by FDA approval and United States Prescribing Information (USPI). Screening participants will be excluded if they possess contraindications to either receiving ofatumumab per prescribing information or they possess contraindications to receiving a COVID-19 mRNA vaccine. Participants will also be excluded if there is clinical or serologic evidence, they have already contracted COVID-19. This is appropriate because the aim of the study is to assess whether a non-vaccinated ofatumumab treated individual can mount a response after COVID-19 mRNA vaccine.

Rationale of chosen endpoints:

Whether or not participants develop an immune response to the mRNA COVID-19 vaccine they receive will be determined by serum immune measures of humoral and cell mediated responses. Currently there is no consensus on which assays, and values would indicate seroprotection or seroconversion. Notwithstanding this, testing is available to consider both arms of the immune response. Here we propose to use a serum qualitative IgG SARS coV2 antibody assay to measure the humoral response. The qualitative IgG SARS CoV2 assay has received an emergency use approval from the FDA.



4.2 Rationale for dose/regimen and duration of treatment

Ofatumumab dose

The dose regimen for ofatumumab in this study is consistent with the FDA approved regimen in the prescribing information.

Duration of treatment:

The treatment duration is 382 days for those receiving the Pfizer mRNA vaccine and 389 days for those receiving the Moderna mRNA vaccine. This duration is chosen to provide long term information regarding vaccine response and safety outcomes.

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

A reference cohort of participants on Injectable Disease Modifying Therapy (iDMT)) is included. Permitted iDMTs include interferon or glatiramer acetate. In a prior study, interferon and glatiramer acetate have been found to preserve vaccine responses (Olberg et al 2018).

4.4 Purpose and timing of interim analyses

For the purpose of early dissemination of results, an interim analysis will be performed once Cohorts 2 and 4 in combination have at least 10 patients enrolled that have had their serum drawn ≥ 14 days after full vaccination (two dose) course.

A second interim analysis will be performed once Cohort 6 has at least 10 participants. A third interim analysis will be performed once Cohorts 2-5 have full enrollment with blood drawn ≥ 14 days after full course (two doses) vaccination.

4.5 Risks and benefits

There is no benefit expected for participants in this study. Their participation will help contribute to a better understanding of the immune response that occurs when participants receiving ofatumumab are given a COVID-19 mRNA vaccine.

The risk to participants in this trial may be minimized by compliance with the eligibility criteria and study procedures, close clinical monitoring, avoidance of prohibited treatments and adherence to investigator guidance regarding specific safety areas. For further details about ofatumumab, please refer to the Investigator's Brochure (IB) and USPI.

Ofatumumab is approved for the treatment of RMS in several countries. Over 1500 RMS participants have been exposed to ofatumumab across phase 2 and phase 3 studies. In the

pivotal Phase 3 studies COMB157G2301 and COMB157G2302, treatment with ofatumumab significantly lowered the annualized relapse rate (ARR; primary endpoint) compared to the active comparator teriflunomide by >50%. Ofatumumab also significantly reduced the risk of disability progression by >30% and showed significant suppression of both gadolinium (Gd)-enhancing T1 lesions (>90%) and new/enlarging T2 lesions (>80%) on brain MRI compared to teriflunomide.

The data from the ofatumumab program in MS indicates ofatumumab to have an acceptable safety profile and to be well tolerated at the recommended subcutaneous dose of 20 mg. Adverse reactions in the MS population included upper respiratory tract infections, decreased immunoglobulin M, injection site reaction, and injection related reactions. For further details about ofatumumab, please refer to the IB and USPI.

Overall, the balance of benefit and risk supports the proposed clinical study to evaluate the potential of ofatumumab s.c as an effective and safe therapy to address the unmet medical need of participants with RMS.

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

Novartis will supply participants in Cohort 1 with ofatumumab treatment as per the assessment schedules in Table 8-1 and Table 8-2.

In the context of the COVID-19 pandemic, additional risks for participants taking part in any clinical trial cannot be excluded. Eligibility criteria for the study requires the Investigator to evaluate infections and exclude participants with ongoing infection. Additionally, this protocol includes home visits (Cohort 1 only) to minimize unnecessary risk that would be associated with on-site visits. Other options like home nursing visits conducted by an off-site healthcare professional and shipment of IMP directly to participants' home may be considered on a case-by-case basis.

4.5.1 Blood sample volume

Timings of blood sample collection are outlined in the assessment schedules (Table 8-1, Table 8-2, Table 8-3, Table 8-4, Table 8-5 and Table 8-6).

4.6 Rationale for Public Health Emergency mitigation procedures

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

5 Study Population

The study population will consist of male and female participants, ≥ 18 years of age to 55 years of age inclusive, with a diagnosis of relapsing MS.

The study aims to enroll up to 88 participants at up to 30 centers in the United States. Since a 25% screen failure rate is expected, approximately 117 participants will be screened. 22 participants will be enrolled in Cohort 1. In combination, 22 participants will be enrolled in Cohorts 2 and 4. In combination, 22 patients will be enrolled in Cohorts 3 and 5. In Cohort 6, 22 participants will be enrolled.

5.1 Inclusion criteria

Participants eligible for inclusion in Cohort 1 of this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study
2. Age 18-55 years old inclusive at Screening
3. Diagnosis of relapsing MS by 2017 revised McDonald criteria
4. Must be willing to comply with the study schedule
5. Will be receiving an mRNA COVID-19 vaccine (Pfizer or Moderna vaccine) at least two weeks prior to starting ofatumumab
6. Eligible to receive and plan to be started on ofatumumab according to the approved labeling
7. Pre-ofatumumab serology with Hepatitis B testing not indicative of active or latent infection
8. Total serum immunoglobulin IgG ≥ 400 mg/dl at Screening

Participants eligible for inclusion in Cohort 2 of this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study
2. Age 18-55 years old inclusive at Screening
3. Diagnosis of relapsing MS by 2017 revised McDonald criteria
4. Must be willing to comply with the study schedule
5. Will be receiving an mRNA COVID-19 vaccine (Pfizer or Moderna vaccine)
6. Currently on commercially prescribed ofatumumab for ≥ 4 weeks for the treatment of RMS
7. Pre-ofatumumab serology with Hepatitis B testing not indicative of active or latent infection
8. Total serum immunoglobulin IgG ≥ 400mg/dl at Screening

Participants eligible for inclusion in Cohort 3 of this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study
2. Age 18-55 years old inclusive at Screening
3. Diagnosis of relapsing MS by 2017 revised McDonald criteria

4. Must be willing to comply with the study schedule
5. Will be receiving an mRNA COVID-19 vaccine (Pfizer or Moderna vaccine)
6. Currently on commercially prescribed interferon or glatiramer acetate for ≥ 4 weeks for the treatment of RMS
7. Total serum immunoglobulin IgG ≥ 400mg/dl at Screening

Participants eligible for inclusion in Cohort 4 of this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study
2. Age 18-55 years old at Screening
3. Diagnosis of relapsing MS by 2017 revised McDonald criteria
4. Must be willing to comply with the study schedule
5. Completed a full course (two doses) of a COVID-19 mRNA vaccine at least ≥ 4 weeks after start of commercially prescribed ofatumumab for the treatment of RMS
6. Currently on commercially prescribed ofatumumab for ≥ 4 weeks for the treatment of RMS
7. Received two dose mRNA COVID-19 vaccine (Pfizer or Moderna vaccine) ≥ 2 weeks ago
8. Pre-ofatumumab serologies with Hepatitis B testing not indicative of active or latent infection
9. Total serum immunoglobulin IgG ≥ 400 mg/dl at Screening

Patients eligible for inclusion in Cohort 5 of this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study
2. Age 18-55 years old at Screening
3. Diagnosis of relapsing MS by 2017 revised McDonald criteria
4. Must be willing to comply with the study schedule
5. Currently on commercially prescribed interferon or glatiramer acetate for ≥ 4 weeks for the treatment of RMS
6. Completed a full course (two doses) of a COVID-19 mRNA vaccine after start of glatiramer acetate or interferon
7. Received two dose mRNA COVID-19 vaccine (Pfizer or Moderna vaccine) ≥ 2 weeks ago
8. If the patient has received the mRNA booster, then the mRNA booster should be ≥ 2 weeks prior to enrollment.
9. Total serum immunoglobulin IgG ≥ 400 mg/dl at Screening

Patients eligible for inclusion in Cohort 6 of this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study
2. Age 18-55 years old at Screening
3. Diagnosis of relapsing MS by 2017 revised McDonald criteria
4. Must be willing to comply with the study schedule
5. Currently on commercially prescribed ofatumumab for ≥ 4 weeks for the treatment of RMS

6. Completed a full course (two doses) of a COVID-19 mRNA vaccine at least ≥ 4 weeks after start of commercially prescribed ofatumumab for the treatment of RMS
7. Received two dose mRNA COVID-19 vaccine (Pfizer or Moderna vaccine) ≥ 2 weeks ago
8. Pre-ofatumumab serologies with Hepatitis B testing not indicative of active or latent infection
9. Total serum immunoglobulin IgG ≥ 400 mg/dl at Screening
10. Has received an mRNA booster ≥ 2 weeks prior to enrollment

5.2 Exclusion criteria

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

1. Already has received the J&J vaccine.
2. Has a contraindication to receiving an mRNA COVID-19 vaccine
3. Has an immediate allergic reaction to past vaccine or injection
4. Any safety finding including low immunoglobulin IgG and/or low immunoglobulin IgM levels requiring an ofatumumab treatment interruption within the 12 weeks immediately prior to vaccination as determined by the HCP
5. Any major episode of infection requiring hospitalization or treatment with intravenous antibiotics within 4 weeks prior to the first vaccination visit or oral antibiotics within two weeks prior to the first vaccination visit
6. Prior treatment with B-cell targeted therapies (e.g., rituximab or ocrelizumab), alemtuzumab, anti-CD4, cladribine, cyclophosphamide, mitoxantrone, azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, total body irradiation, or bone marrow transplantation
7. Prior treatment with S1P agent within 2 months at Screening
8. Prior treatment with natalizumab within 6 months of study enrollment
9. Since commercially prescribed ofatumumab is being used in the study, contraindications as per the USPI will be adhered to which include active infection hepatitis B infection, progressive multifocal leukoencephalopathy and pregnancy.
10. Participation in another interventional clinical trial within 14 days before enrollment.
11. Use of other investigational drugs at the time of enrollment (Screening) or within the prior 30 days, or five elimination half-lives, or until the expected pharmacodynamic effect has returned to baseline, whichever is longer.
12. History of hypersensitivity to any of the study treatments or its excipients or to drugs of similar chemical classes.
13. Have been treated with any of the medications listed below within the time specified:

Medication	**Exclusionary if used within the timeframe specified below**
Intravenous, oral, intra-articular or intramuscular corticosteroids, adrenocorticotropic hormone	30 days prior to Screening

Medication	**Exclusionary if used within the timeframe specified below**
Immunosuppressive, chemotherapeutic medications (e.g. mitoxantrone, cyclophosphamide, cladribine, S1P modulators)	2 months prior to first study drug administration
Natalizumab	Within 6 months of study enrollment/Visit 2
Mitoxantrone (with evidence of cardiotoxicity following treatment or cumulative life-time dose > 60mg/m2) Alemtuzumab Lymphoid irradiation; bone marrow transplantation Other strongly immunosuppressive treatments (with effects potentially lasting over 6 months) Ofatumumab aCD20+ monoclonal antibodies in development (e.g. ublituximab or obinutuzumab) Daclizumab	Anytime

14. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using effective methods of contraception while taking study treatment and for 6 months after stopping medication. Effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    - Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant
    - Use of oral, (estrogen and progesterone), injected, or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception.
    - Barrier methods of contraception: Condom or Occlusive cap (e.g. diaphragm or cervical/vault caps).

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

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

confirmed by follow up hormone level assessment is she considered not of childbearing potential.

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

6 Treatment

6.1 Study treatment

Novartis will supply the following study treatment:

- Cohort 1: Open-label ofatumumab in an auto-injector containing 20 mg s.c ofatumumab (20 mg/0.4ml) for subcutaneous administration as per the assessment schedules in Table 8-1 and Table 8-2.

Participants in Cohort 2 will continue on their commercially prescribed ofatumumab treatment.

Participants enrolled in Cohort 3 will continue on their commercially prescribed interferon or glatiramer acetate treatment.

Participants in Cohort 4 will continue on their commercially prescribed ofatumumab treatment.

Participants in Cohort 5 will continue on their commercially prescribed interferon or glatiramer acetate treatment.

Participants in Cohort 6 will continue on their commercially prescribed ofatumumab.

Participants will obtain a COVID-19 mRNA vaccine from their HCP (private insurance) or appropriate federal, state or local program.

6.1.1 Investigational and control drugs

Table 6-1 Investigational and control drug

Investigational/ Control Drug	Route of Administration	Supply Type	Supplied by
OMB157 20mg/0.4mL	Subcutaneous Use	Open-label auto-injectors (Cohort 1); commercially prescribed (Cohorts 2, 4 and 6)	Sponsor (Cohort 1) or commercially prescribed (Cohorts 2, 4 and 6)
Interferon or glatiramer acetate	Subcutaneous or intramuscular use	Commercially prescribed	Commercially prescribed
COVID-19 mRNA vaccine (Pfizer or Moderna)	Intramuscular	Commercially supplied	HCP/private insurance, or appropriate federal, state or local program

6.1.1.1 Decentralized Clinical Trial Model (US sites only)

The study medication and all required clinical study supplies may be distributed via direct-to-participant shipment utilizing an extension of the IND for compliance purposes.

6.1.2 Additional study treatments

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

6.1.3 Treatment cohorts

- Cohort 1: RMS participants receiving non-live COVID-19 mRNA vaccine at least two weeks prior to ofatumumab start.
- Cohort 2: RMS participants receiving non-live COVID-19 mRNA vaccine at least 4 weeks after ofatumumab start.
- Cohort 3: RMS participants receiving non-live COVID-19 mRNA vaccine at least 4 weeks after start of prescribed interferon or glatiramer acetate.
- Cohort 4: RMS participants having completed a full course (2 doses) of a non-live COVID-19 mRNA vaccine ≥ 4 weeks after ofatumumab start.
- Cohort 5: RMS participants having completed a full course (2 doses) of a non-live COVID-19 mRNA vaccine ≥ 4 weeks after glatiramer acetate or interferon start.
- Cohort 6: RMS participants having completed a full course (2 doses) of a non-live COVID-19 mRNA vaccine ≥ 4 weeks after ofatumumab start and having received a booster ≥ 14 days prior to screening

6.1.4 Post-Trial Access

Participants in Cohort 1 will be referred to the commercial participant services hub for post-trial continuity of treatment, where the benefit/risk is acceptable and discussed with the participant, investigator and if applicable, the participant's treating physician. Participants who do not complete the study or withdraw due to an ofatumumab related AE or SAE should follow-up with their treating physician for continued treatment options.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

The Investigator should instruct the participant to notify the study site about any new medications he/she takes after study enrollment. 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 electronic Case Report Forms (eCRFs).

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis Medical Director before randomizing a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study.

Premedication prior to subcutaneous injection

Premedication is not required. Premedication with acetaminophen and/or antihistamines (or equivalent) is optional and may be administered at the discretion of the Investigator. If Investigators choose to administer premedication, it should be administered 30 to 60 minutes prior to study drug injection.

Any administrations of premedication must be recorded in the appropriate eCRF.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis Medical Director before enrolling a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study.

6.2.2 Prohibited medication

Use of the treatments displayed in Table 6-2 is NOT allowed for any study cohort in combination with study drug, due to increased risk of immunosuppression and confounding of efficacy evaluations.

Exclusionary medications for study eligibility are listed in the exclusion criteria (Section 5.2). Use of excluded medications is not allowed for any study cohort while the participant is on study medication.

Table 6-2 Prohibited medication

Medication	Action taken
Immunosuppressive/chemotherapeutic medications (including herbal) or procedures, including but not limited to cyclosporine, azathioprine, leflunomide, methotrexate, cyclophosphamide, mitoxantrone, lymphoid irradiation and hematopoietic stem cell transplantation	Discontinue participant from study
Monoclonal antibodies targeting the immune system, including but not limited to natalizumab, alemtuzumab, daclizumab and B-cell depleting agents under investigation, such as but not limited to ublituximab and obinutuzumab	Discontinue participant from study
Any other immunomodulatory or disease modifying MS treatment, including but not limited to fingolimod, interferon beta, glatiramer acetate, dimethyl fumarate, intravenous immunoglobulin, plasmapheresis or systemic corticosteroids (except for when given for MS relapse treatment as defined in Section 6.2.3)	Discontinue participant from study.
Administration of any live or live attenuated vaccine (including for measles) is prohibited while participants are exposed to study drug	They may be administered when participants are no longer exposed to

Medication	Action taken
(long lasting effects of the study drugs should be taken into consideration)	study drug. Consider risk/benefit and follow local labels.

6.2.3 Recommended treatment of MS relapse

An MS relapse is defined as an appearance of a new neurological abnormality or worsening of previously stable or improving pre-existing neurological abnormality, separated by at least 30 days from onset of a preceding clinical demyelinating event (Polman et al 2011). The abnormality must have been present for at least 24 hours and occurred in the absence of fever (< 37.5°C) or a known infection.

The decision to treat MS relapses should be based on the Investigator's judgement and/or local clinical practice. Standard of care will be followed during treatment as per local clinical practice. Taper with oral steroids is not permitted. Plasmapheresis may be used only if participant does not respond to standard treatment with corticosteroids.

If MS relapses require treatment, the standard treatment should consist of a short course of corticosteroids of 3-5 days and up to 1000mg methylprednisolone/day or equivalent on an inpatient or outpatient basis. Standard of care will be followed during treatment as per local clinical practice.

Investigators should consider the added immunosuppressive effects of corticosteroid therapy and increase vigilance regarding infections during such treatment and in the weeks following administration. Use of steroids for treatment of MS attack/relapse must be recorded on the Concomitant Medications eCRF.

6.3 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section (Section 6.1.1).

A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits to dispense to the participant by contacting the Interactive Response Technology (IRT) and obtaining the medication number(s).

Special notes regarding dispensing treatment to Cohort 1

Participants have the option to take home multiple doses of study drug for administration at home between office visits or they may return to the study site between office visits for administration of study drug onsite. To facilitate this, Study Staff will have the option to either dispense multiple kits of study drug in IRT by selecting “home visit” or dispense 1 study drug kit for office administration by selecting “office visit”. Example:

- At Visit 4 (office visit), if “home visit” is selected in IRT, sufficient study drug will be dispensed for administration during the Visit 4 office visit plus sufficient study drug for at-home administrations until the participant returns for the Visit 8 office visit. If “office visit” is selected, the system will only dispense study drug for administration in the office during Visit 4. In this case, the patient will need to return to the site a week later to

receive their next scheduled dose at which time the Study Staff will need to contact IRT again to dispense treatment and select either “home visit” or “office visit”.

- At Visit 9 (office visit), participants will **not** receive a dose of study drug in the office but will receive sufficient study drug to cover monthly, at-home administrations of study drug until the Visit 10 office visit.
- At Visit 10 (office visit), participants will **not** receive a dose of study drug in the office but will receive sufficient study drug to cover the next 3 monthly, at-home administrations of study drug.

If a participant in Cohort 1 is unable to travel to the investigative site for their study visit, shipment of study treatment from the site to the participant’s home may be an option. As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, delivery of IMP directly to a participant's home may be permitted (if allowed by Local or Regional Health Authorities and Ethics Committees as appropriate) in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. The dispatch of IMP from the site to the participant’s home remains under the accountability of the Investigator. Regular phone calls or virtual contacts every month should occur between the site and the participant for instructional purposes, safety monitoring, investigation of any adverse events, ensuring participants continue to benefit from treatment, and discussion of the participant's health status until the participants can resume visits at the study site.

6.3.1 Handling of study treatment and other treatment

6.3.1.1 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 treatment 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.

Participants in Cohort 1 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.

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.

At the conclusion of the study, the site may destroy and document destruction of unused study treatment, drug labels and packaging as appropriate in compliance with site processes,

monitoring processes, and per local regulation/guidelines after approval from the Novartis Clinical Lead. Otherwise, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis or its agent.

The study treatment and all required clinical study supplies will be distributed direct to the participant utilizing an extension of the IND for compliance purposes.

6.3.2 Instruction for prescribing and taking study treatment

COVID-19 mRNA vaccine

The vaccine should be obtained through the HCP (private insurance) or appropriate federal, state or local program.

Participants in Cohort 1

Ofatumumab will be provided in an auto injector for subcutaneous administration containing 20 mg ofatumumab (20 mg/0.4 ml). Treatment should be administered after study assessments have been completed for the visit.

Cohort 1 should receive their first loading dose of ofatumumab at Visit 4 which should be held 2 weeks after receiving their 2nd COVID-19 vaccine dose.

Site staff should remove the study treatment from the refrigerator and allow the auto injector pen to reach room temperature in their unopened box (approximately 15-30 minutes) before self-injection by the participant. Used syringes should be disposed of immediately after use in a sharps container.

A different body site (front of thighs, lower abdomen) should be chosen each time a dose is administered to reduce the risk of an injection-site reaction; investigator/qualified site staff/caregiver can also inject the study treatment in the outer upper arms. Each new injection should be given at least one inch from the previously used site. If administration is in the abdomen, the 2-inch area around navel should be avoided. Study treatment should also not be injected into areas where the skin is tender, bruised, red, or hard, or where the participant has scars or stretch mark

As participants must self-administer ofatumumab, site personnel will provide training on the correct procedure for injection technique of the ofatumumab subcutaneous injections to enable the participant and/or a caregiver to administer from home in-between scheduled office visits. Documentation of the participant or caregiver understanding the correct administration procedure must be documented in the source document. Participants will be instructed to contact the investigator/site staff prior to self-administration at home if they are experiencing any AE/SAEs or have any concerns.

Site personnel will make remote contact with participants in Cohort 1 on/around the time of the 2nd loading dose to query about any new or worsening symptoms warranting an unscheduled visit, compliance with study treatment, injection reactions, and compliance with contraception requirements when applicable.

Additional remote contacts should be conducted on/around the time participants are due to administer treatment at home. The method of contact with each participant can be the personal

preference of the individual between telephone contacts, email contact or text messages, however, the site staff must be able to provide suitable source documentation of each contact regardless of the method of contact.

Participants will be asked to complete a participant diary to record doses of home administrations of ofatumumab.

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

Participants in Cohort 2

Upon enrollment, participants already receiving prescribed ofatumumab will continue to take prescribed treatment as per their current dosing schedule.

Participants will be asked to complete a participant diary to record doses of ofatumumab administered while in the study.

Participants in Cohort 3

Upon enrollment, participants in Cohort 3 will continue to take their interferon or glatiramer acetate as per their current dosing schedule.

Participants will be asked to complete a participant diary to record doses of their interferon or glatiramer acetate taken during the study.

Participants in Cohort 4

Upon enrollment, participants will continue to take prescribed ofatumumab treatment as per their current dosing schedule.

Participants will be asked to complete a participant diary to record doses of ofatumumab administered while in the study.

Participants in Cohort 5

Upon enrollment, participants will continue their prescribed interferon or glatiramer acetate treatment as per their current dosing schedule.

Participants will be asked to complete a participant diary to record doses of ofatumumab administered while in the study.

Participants in Cohort 6

Upon enrollment, participants will continue their prescribed ofatumumab treatment as per their current dosing schedule.

Participants will be asked to complete a participant diary to record doses of ofatumumab administered while in the study.

Table 6-3 Dose and treatment schedule

	Investigational Drug	Frequency and/or Regimen
Cohort 1	OMB157 20mg/0.4mL	Day 36, 43, 50, 64 and monthly thereafter for participants that receive the Pfizer vaccine. Day 43, 50, 57, 71 and monthly thereafter for participants that receive the Moderna vaccine.
Cohort 2	OMB157 20mg/0.4mL	Monthly as prescribed
Cohort 3	Interferon or glatiramer acetate	As prescribed
Cohort 4	OMB157 20mg/0.4mL	As prescribed
Cohort 5	Interferon or glatiramer acetate	As prescribed
Cohort 6	OMB157 20mg/0.4mL	As prescribed

6.4 Participant numbering, treatment assignment, randomization

6.4.1 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.

At the Screening Visit (Visit 1/Day -7), the Investigator or his/her staff will contact the Interactive Response Technology (IRT) system and provide the assigned participant study identification number along with the requested identifying information to register the participant into IRT. The site must use the eCRF with the matching participant number from the electronic data capture (EDC) system to enter data.

Once assigned to a participant, a participant number will not be reused. If a participant fails to be enrolled for any reason, the IRT system must be notified within 2 days and the reason for not being enrolled will be entered on the Screening Phase Disposition Form and the appropriate eCRF(s) pages should also be completed.

6.4.1.1 Treatment assignment, randomization

No randomization will be performed in this study. The assignment of a participant to a cohort will be determined by inclusion/exclusion criteria.

An IRT system will be used to track participant visits and status. IRT will also be used to dispense treatment to Cohort 1 as indicated in the assessment schedules in Table 8-1 and Table 8-2.

At dosing visits, the system will specify unique medication numbers that will correspond to open-label treatment to be dispensed.

6.5 Treatment blinding

Not applicable.

6.6 Dose escalation and dose modification

Dose adjustments and/or interruptions are not permitted.

6.7 Additional treatment guidance

Not applicable.

6.7.1 Treatment compliance

Participant compliance with treatment should be at least 80%. The Investigator and/or study personnel will counsel the participant if compliance is below 80%. 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 for Cohort 1 and in the eCRF for Cohorts 2, 3, 4, 5 and 6.

All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

6.7.2 Emergency breaking of assigned treatment code

Since this study is open-label, emergency breaking of assigned treatment codes is not applicable.

7 Informed consent procedures

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), IRB-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 E6 Good Clinical Practice (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/.

Information about common side effects already known about the investigational treatment can be found in the IB and USPI. This information will be included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or

an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

The following informed consents are included in this study:

- Main study consent, which also included:
  - A subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on data/samples collected during this study
- As applicable, Pregnancy Outcomes Reporting Consent for female participants or the female partners of any male participants who took study treatment

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

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

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local Health Authority. Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

8 Visit schedule and assessments

The below Assessment Schedules (Table 8-1, Table 8-2, Table 8-3, Table 8-4, Table 8-5 and Table 8-6) list all assessments with an X when they are performed. All data obtained from these assessments must be supported in the participant's source documentation. The "X" in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The "S" in the table denotes the assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.

Participants should be seen for all visits/assessments as outlined in the assessment schedules or as close to the designated day/time as possible. The Investigator should promote compliance by instructing the participant to attend the study visits as scheduled and by stating that compliance is necessary for the participant's safety and the validity of the study. Missed or rescheduled visits should not lead to automatic discontinuation. The participant should be instructed to contact the Investigator if he/she is unable for any reason to attend a study visit as scheduled or if he/she is unable for any reason to take the study treatment as prescribed.

Participants who prematurely discontinue the study should be scheduled for the End of Study (EOS) visit within 7 days. At this final visit, all the assessments mentioned under EOS visit should be performed, all dispensed investigational product should be reconciled, and the

adverse event and concomitant medications recorded on the CRF. Participants that prematurely discontinue should also have a remote follow-up safety visit performed 30 days after the EOS visit.

Special guidance regarding the scheduling of visits for Cohorts 1, 2 and 3

- The study site will need to perform Vaccine Status Check-ins (make remote contact with participant) to confirm when the 1st and 2nd COVID-19 vaccinations are scheduled in order to schedule Visit 4.
- The date of the 2nd COVID-19 vaccine dose will determine the date of Visit 4 and all other remaining study visits.
- Visits 2 and 3 should always occur prior to administration of the mRNA vaccine.
- The Visit 4 lab samples should be collected 14 days after a participant has received their 2nd COVID-19 vaccine dose.

Home study visits (Cohort 1)

Home (remote) study visits are planned at Visits 5, 6 and 7 for participants in Cohort 1. To facilitate this, at Visit 4, sufficient study drug can be supplied to the participant to cover all home administrations of study drug until the Visit 8 in-person, clinic visit. Refer to Section 6.7 for additional information.

Participants and/or caregivers trained to administer the ofatumumab subcutaneous injections will need to administer treatment at home study visits. Refer to Table 8-1 and Table 8-2.

The option for a participant to return to the clinic for administration of treatment at Visits 5, 6 and 7 is available if that is his/her preference.

Unscheduled visits

In addition to the scheduled visits, participants may have unscheduled visits due to a MS relapse, an acute illness of undetermined cause, for other reasons, or at the discretion of the Investigator. Data collected during unscheduled visits will be recorded in the unscheduled visits CRF.

Table 8-1 Assessment schedule for Cohort 1 (Pfizer vaccine)

Period	**Screening**	**Treatment**								**Follow-up**	
Visit Name	**Visit 1 Screening**	**Visit 2 (home visit)**	**Visit 3 (home visit)**	**Visit 4 (office visit)**	**Visit 5 Visit 6 Visit 7 (home visit)**	**Visit 8 (office visit)**	**Visit 9 (office visit)**	**Visit 10 (office visit)**	**Visit 11/ End of Study – EOS (office visit)**	**Visit 12 / Safety (remote contact)**	**Unscheduled**
Day/Week/Month	**Day -7**	**Day 1**	**Day 22**	**Day 36**	**Day 43 Day 50 Day 64**	**Day 92**	**Day 202**	**Day 292**	**Day 382**	**Day 412**	
Visit Window				+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	
Obtain informed consent	X										
Inclusion/exclusion criteria	X										
Demography	X										
Relevant medical history/current medical history	X										
Non-drug therapies and procedures	X	X	X	X	X	X	X	X	X	S	X
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	S	X
MS Relapse	X	X	X	X	X	X	X	X	X	S	X
Serum Pregnancy Test[1]	S								S		
Hepatitis B virus (HBV)[2]	X										

Period	**Screening**	**Treatment**								**Follow-up**	
Visit Name	**Visit 1 Screening**	**Visit 2 (home visit)**	**Visit 3 (home visit)**	**Visit 4 (office visit)**	**Visit 5 Visit 6 Visit 7 (home visit)**	**Visit 8 (office visit)**	**Visit 9 (office visit)**	**Visit 10 (office visit)**	**Visit 11/ End of Study – EOS (office visit)**	**Visit 12 / Safety (remote contact)**	**Unscheduled**
Day/Week/Month	**Day -7**	**Day 1**	**Day 22**	**Day 36**	**Day 43 Day 50 Day 64**	**Day 92**	**Day 202**	**Day 292**	**Day 382**	**Day 412**	
Visit Window				+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	
SARS CoV2 qualitative antibody	X			X		X	X	X	X		
[redacted]											
Serum Immunoglobulin[2]	X			X		X	X		X		
CD 19+ B cells	X			X		X	X	X	X		
[redacted]											
Biobanked serum sample[3]	X			X							
Biobanked whole blood sample[3]	X			X							
Vaccine Administration Form		X	X								
IRT Transaction	X	X	X	X	X	X	X	X	X		
Self-Injection Training				S							

Period	**Screening**	**Treatment**								**Follow-up**	
Visit Name	**Visit 1 Screening**	**Visit 2 (home visit)**	**Visit 3 (home visit)**	**Visit 4 (office visit)**	**Visit 5 Visit 6 Visit 7 (home visit)**	**Visit 8 (office visit)**	**Visit 9 (office visit)**	**Visit 10 (office visit)**	**Visit 11/ End of Study – EOS (office visit)**	**Visit 12 / Safety (remote contact)**	**Unscheduled**
Day/Week/Month	**Day -7**	**Day 1**	**Day 22**	**Day 36**	**Day 43 Day 50 Day 64**	**Day 92**	**Day 202**	**Day 292**	**Day 382**	**Day 412**	
Visit Window				+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	
Office administration of study drug				X		X					
Dispense study drug for future home administration				X		X	X	X			
Home administration of study drug					X						
Patient Diary/Drug Accountability				X	X	X	X	X	X		
Adverse Events / Serious Adverse Events	X	X	X	X	X	X	X	X	X	S	X
Subject disposition	X								X	S	
Vaccine check-in contacts[4]		S	S								
Remote check-in[5]					S					S	

X = assessment to be recorded in the clinical database or received electronically from a vendor
S = assessment to be recorded in the source documentation only
[1] Serum pregnancy should be performed locally for all sites except those unable to use a local lab. Sites unable to perform locally should send sample to the central lab.

[2] Participants with lab results within the past 6 months prior to screening will not require labs drawn at screening visit. Local labs should be documented in the source. Participants without lab results from the past 6 months prior to screening will require central labs drawn at the screening visit to be entered into the clinical database.
[3] Sample will be bio-banked for yet to be identified analyses.
[4] Vaccine check-ins (remote contacts) by site staff to confirm participant has received the COVID-19 vaccine and to collect any AEs/SAEs.
[5] Remote contact with participants by site staff. The contact should query about receipt any new AEs or SAEs, changes in con meds and compliance with current treatment. Method of contact can be via telephone, email or text message depending on the preference of each participant.

Table 8-2 Assessment schedule for Cohort 1 (Moderna vaccine)

Period	**Screening**	**Treatment**								**Follow-up**	
Visit Name	**Visit 1 Screening**	**Visit 2 (home visit)**	**Visit 3 (home visit)**	**Visit 4 (office visit)**	**Visit 5 Visit 6 Visit 7 (home visit)**	**Visit 8 (office visit)**	**Visit 9 (office visit)**	**Visit 10 (office visit)**	**Visit 11/ End of Study – EOS (office visit)**	**Visit 12 / Safety (remote contact)**	**Unscheduled**
Day/Week/Month	**Day -7**	**Day 1**	**Day 29**	**Day 43**	**Day 50 Day 57 Day 71**	**Day 99**	**Day 209**	**Day 299**	**Day 389**	**Day 419**	
Visit Window				+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	
Obtain informed consent	X										
Inclusion/exclusion criteria	X										
Demography	X										
Relevant medical history/current medical history	X										
Non-drug therapies and procedures	X	X	X	X	X	X	X	X	X	S	X
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	S	X
MS Relapse	X	X	X	X	X	X	X	X	X	S	X
Serum Pregnancy Test[1]	S								S		

Period	**Screening**	**Treatment**								**Follow-up**	
Visit Name	**Visit 1 Screening**	**Visit 2 (home visit)**	**Visit 3 (home visit)**	**Visit 4 (office visit)**	**Visit 5 Visit 6 Visit 7 (home visit)**	**Visit 8 (office visit)**	**Visit 9 (office visit)**	**Visit 10 (office visit)**	**Visit 11/ End of Study – EOS (office visit)**	**Visit 12 / Safety (remote contact)**	**Unscheduled**
Day/Week/Month	**Day -7**	**Day 1**	**Day 29**	**Day 43**	**Day 50 Day 57 Day 71**	**Day 99**	**Day 209**	**Day 299**	**Day 389**	**Day 419**	
Visit Window				+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	
Hepatitis B virus (HBV)[2]	X										
SARS CoV2 qualitative antibody	X			X		X	X	X	X		
[redacted]											
Serum Immunoglobulin[2]	X			X		X	X		X		
CD 19+ B cells	X			X		X	X	X	X		
[redacted]											
Biobanked serum sample[3]	X			X							
Biobanked whole blood sample[3]	X			X							
Vaccine Administration Form		X	X								
IRT Transaction	X	X	X	X	X	X	X	X	X		

Period	**Screening**	**Treatment**								**Follow-up**	
Visit Name	**Visit 1 Screening**	**Visit 2 (home visit)**	**Visit 3 (home visit)**	**Visit 4 (office visit)**	**Visit 5 Visit 6 Visit 7 (home visit)**	**Visit 8 (office visit)**	**Visit 9 (office visit)**	**Visit 10 (office visit)**	**Visit 11/ End of Study – EOS (office visit)**	**Visit 12 / Safety (remote contact)**	**Unscheduled**
Day/Week/Month	**Day -7**	**Day 1**	**Day 29**	**Day 43**	**Day 50 Day 57 Day 71**	**Day 99**	**Day 209**	**Day 299**	**Day 389**	**Day 419**	
Visit Window				+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	
Self-Injection Training				S							
Office administration of study drug				X		X					
Dispense study drug for future home administration				X		X	X	X			
Home administration of study drug					X						
Patient Diary/Drug Accountability				X	X	X	X	X	X		
Adverse Events / Serious Adverse Events	X	X	X	X	X	X	X	X	X	S	X
Subject disposition	X								X	S	
Vaccine check-in contacts[4]		S	S								
Remote check-in[5]					S					S	

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

S = assessment to be recorded in the source documentation only
[1] Serum pregnancy should be performed locally for all sites except those unable to use a local lab. Sites unable to perform locally should send sample to the central lab.
[2] Participants with lab results within the past 6 months prior to screening will not require labs drawn at screening visit. Local labs should be documented in the source. Participants without lab results from the past 6 months prior to screening will require central labs drawn at the screening visit to be entered into the clinical database.
[3] Sample will be bio-banked for yet to be identified analyses.
[4] Vaccine check-ins (remote contacts) by site staff to confirm participant has received the COVID-19 vaccine and to collect any AEs/SAEs.
[5] Remote contact with participants by site staff. The contact should query about receipt any new AEs or SAEs. Method of contact can be via telephone, email or text message depending on the preference of each participant.

Table 8-3 Assessment schedule for Cohorts 2 and 3 (Pfizer vaccine)

Period	**Screening**	**Treatment**						**Follow-up**	
Visit Name	**Visit 1 Screening**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7/End of Study (EOS)**	**Visit 8 / Safety**	**Unscheduled**
Day/Week/Month	**Day -7**	**Day 1**	**Day 22**	**Day 36**	**Day 202**	**Day 292**	**Day 382**	**Day 412**	
Visit Window				**+3d**	**+/-3d**	**+/-3d**	**+/-3d**	**+/-3d**	
Obtain informed consent	X								
Inclusion/exclusion criteria	X								
Demography	X								
Relevant medical history/current medical history	X								
Non-drug therapies and procedures	X	X	X	X	X	X	X	S	X
Prior/Concomitant Medications	X	X	X	X	X	X	X	S	X
MS Relapse	X	X	X	X	X	X	X	S	X
Serum Pregnancy Test[1]	S						S		

Period	**Screening**	**Treatment**						**Follow-up**	
Visit Name	**Visit 1 Screening**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7/End of Study (EOS)**	**Visit 8 / Safety**	**Unscheduled**
Day/Week/Month	**Day -7**	**Day 1**	**Day 22**	**Day 36**	**Day 202**	**Day 292**	**Day 382**	**Day 412**	
Visit Window				**+3d**	**+/-3d**	**+/-3d**	**+/-3d**	**+/-3d**	
Hepatitis B virus (HBV) **(Cohort 2 only)**[2]	X								
SARS CoV2 qualitative antibody		X	X	X	X	X	X		
Serum Immunoglobulin [2]	X				X		X		
CD 19+ B cells **(Cohort 2 only)**	X	X	X	X	X	X	X		
Biobanked serum sample[3]	X			X					
Biobanked whole blood sample[3]	X			X					
Vaccine Administration Form		X	X						
IRT Transaction	X	X	X	X	X	X	X		
Drug Accountability		S	S	S	S	S	S		
Adverse Events / Serious Adverse Events	X	X	X	X	X	X	X	S	X
Subject disposition	X						X	S	

Period	**Screening**	**Treatment**						**Follow-up**	
Visit Name	**Visit 1 Screening**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7/End of Study (EOS)**	**Visit 8 / Safety**	**Unscheduled**
Day/Week/Month	**Day -7**	**Day 1**	**Day 22**	**Day 36**	**Day 202**	**Day 292**	**Day 382**	**Day 412**	
Visit Window				**+3d**	**+/-3d**	**+/-3d**	**+/-3d**	**+/-3d**	
Vaccine check-in contacts[4]		S	S						
Remote check-in[5]								S	

X = assessment to be recorded in the clinical database or received electronically from a vendor
S = assessment to be recorded in the source documentation only
[1] Serum pregnancy should be performed locally for all sites except those unable to use a local lab. Sites unable to perform locally should send sample to the central lab.
[2] Participants with lab results within the past 6 months prior to screening will not require labs drawn at screening visit. Local labs should be documented in the source. Participants without lab results from the past 6 months prior to screening will require central labs drawn at the screening visit to be entered into the clinical database.
[3] Sample will be bio-banked for yet to be identified analyses.
[4] Vaccine check-ins (remote contacts) by site staff to confirm participant has received the COVID-19 vaccine and to collect any AEs/SAEs.
[5] Remote contact with participants by site staff. The contact should query about receipt any new AEs or SAEs. Method of contact can be via telephone, email or text message depending on the preference of each participant.

Table 8-4 Assessment schedule for Cohorts 2 and 3 (Moderna vaccine)

Period	**Screening**	**Treatment**						**Follow-up**	
Visit Name	**Visit 1 Screening**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7/End of Study (EOS)**	**Visit 8 / Safety**	**Unscheduled**
Day/Week/Month	**Day -7**	**Day 1**	**Day 29**	**Day 43**	**Day 209**	**Day 299**	**Day 389**	**Day 419**	
Visit Window				**+3d**	**+/-3d**	**+/-3d**	**+/-3d**	**+/-3d**	
Obtain informed consent	X								
Inclusion/exclusion criteria	X								
Demography	X								
Relevant medical history/current medical history	X								

Period	**Screening**	**Treatment**						**Follow-up**	
Visit Name	**Visit 1 Screening**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7/End of Study (EOS)**	**Visit 8 / Safety**	**Unscheduled**
Day/Week/Month	**Day -7**	**Day 1**	**Day 29**	**Day 43**	**Day 209**	**Day 299**	**Day 389**	**Day 419**	
Visit Window				**+3d**	**+/-3d**	**+/-3d**	**+/-3d**	**+/-3d**	
Non-drug therapies and procedures	X	X	X	X	X	X	X	S	X
Prior/Concomitant Medications	X	X	X	X	X	X	X	S	X
MS Relapse	X	X	X	X	X	X	X	S	X
Serum Pregnancy Test[1]	S						S		
Hepatitis B virus (HBV) **(Cohort 2 only)**[2]	X								
SARS CoV2 qualitative antibody		X	X	X	X	X	X		
[redacted]									
Serum Immunoglobulin [2]	X				X		X		
CD 19+ B cells **(Cohort 2 only)**	X	X	X	X	X	X	X		
[redacted]									
Biobanked serum sample[3]	X			X					
Biobanked whole blood sample[3]	X			X					

Period	**Screening**	**Treatment**						**Follow-up**	
Visit Name	**Visit 1 Screening**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7/End of Study (EOS)**	**Visit 8 / Safety**	**Unscheduled**
Day/Week/Month	**Day -7**	**Day 1**	**Day 29**	**Day 43**	**Day 209**	**Day 299**	**Day 389**	**Day 419**	
Visit Window				**+3d**	**+/-3d**	**+/-3d**	**+/-3d**	**+/-3d**	
Vaccine Administration Form		X	X						
IRT Transaction	X	X	X	X	X	X	X		
Drug Accountability		S	S	S	S	S	S		
Adverse Events / Serious Adverse Events	X	X	X	X	X	X	X	S	X
Subject disposition	X						X	S	
Vaccine check-in contacts[4]		S	S						
Remote check-in[5]								S	

X = assessment to be recorded in the clinical database or received electronically from a vendor
S = assessment to be recorded in the source documentation only
[1] Serum pregnancy should be performed locally for all sites except those unable to use a local lab. Sites unable to perform locally should send sample to the central lab.
[2] Participants with lab results within the past 6 months prior to screening will not require labs drawn at screening visit. Local labs should be documented in the source. Participants without lab results from the past 6 months prior to screening will require central labs drawn at the screening visit to be entered into the clinical database.
[3] Sample will be bio-banked for yet to be identified analyses.
[4] Vaccine check-ins (remote contacts) by site staff to confirm participant has received the COVID-19 vaccine and to collect any AEs/SAEs.
[5] Remote contact with participants by site staff. The contact should query about receipt any new AEs or SAEs. Method of contact can be via telephone, email or text message depending on the preference of each participant.

Table 8-5 Assessment schedule for Cohorts 4, 5 and 6 (Pfizer vaccine)

Period	**Screening**	**Treatment**				**Follow-up**	
Visit Name	**Visit 1 Screening**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5/End of Study (EOS)**	**Visit 6 / Safety**	**Unscheduled**
Day/Week/Month	**Day -7**	**Day 1**	**Day 202**	**Day 292**	**Day 382**	**Day 412**	
Visit Window			**+/-3d**	**+/-3d**	**+/-3d**	**+/-3d**	
Obtain informed consent	X						
Inclusion/exclusion criteria	X						
Demography	X						
Relevant medical history/current medical history	X						
Non-drug therapies and procedures	X	X	X	X	X	S	X
Prior/Concomitant Medications	X	X	X	X	X	S	X
MS Relapse	X	X	X	X	X	S	X
Local Serum Pregnancy Test[1]	S				S		
Hepatitis B virus (HBV) **(Cohort 4 and 6 only)**[2]	X						
SARS CoV2 qualitative antibody		X	X	X	X		
SARS-CoV-2 nucleocapsid antibody		X					

Period	**Screening**	**Treatment**				**Follow-up**	
Visit Name	**Visit 1 Screening**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5/End of Study (EOS)**	**Visit 6 / Safety**	**Unscheduled**
Day/Week/Month	**Day -7**	**Day 1**	**Day 202**	**Day 292**	**Day 382**	**Day 412**	
Visit Window			**+/-3d**	**+/-3d**	**+/-3d**	**+/-3d**	
[redacted]							
Serum Immunoglobulin [2]	X		X		X		
CD 19+ B cells **(Cohort 4 and 6 only)**	X	X	X	X	X		
[redacted]							
Biobanked serum sample[3]	X						
Biobanked whole blood sample[3]	X						
Vaccine Administration Form	X						
IRT Transaction	X	X	X	X	X		
Drug Accountability		S	S	S	S		
Adverse Events / Serious Adverse Events	X	X	X	X	X	S	X
Subject disposition	X				X	S	
Remote check-in[4]						S	

X = assessment to be recorded in the clinical database or received electronically from a vendor
S = assessment to be recorded in the source documentation only
[1] Serum pregnancy should be performed locally for all sites except those unable to use a local lab. Sites unable to perform locally should send sample to the central lab.

[2] Participants with lab results within the past 6 months prior to screening will not require labs drawn at screening visit. Local labs should be documented in the source. Participants without lab results from the past 6 months prior to screening will require central labs drawn at the screening visit to be entered into the clinical database.
[3] Sample will be bio-banked for yet to be identified analyses.
[4]Remote contact with participants by site staff. The contact should query about receipt any new AEs or SAEs. Method of contact can be via telephone, email or text message depending on the preference of each participant.

Table 8-6 Assessment schedule for Cohorts 4, 5 and 6 (Moderna vaccine)

Period	**Screening**	**Treatment**				**Follow-up**	
Visit Name	**Visit 1 Screening**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5/End of Study (EOS)**	**Visit 6 / Safety**	**Unscheduled**
Day/Week/Month	**Day -7**	**Day 1**	**Day 209**	**Day 299**	**Day 389**	**Day 419**	
Visit Window			**+/-3d**	**+/-3d**	**+/-3d**	**+/-3d**	
Obtain informed consent	X						
Inclusion/exclusion criteria	X						
Demography	X						
Relevant medical history/current medical history	X						
Non-drug therapies and procedures	X	X	X	X	X	S	X
Prior/Concomitant Medications	X	X	X	X	X	S	X
MS Relapse	X	X	X	X	X	S	X
Local Serum Pregnancy Test[1]	S				S		
Hepatitis B virus (HBV) **(Cohort 4 and 6 only)**[2]	X						
SARS CoV2 qualitative antibody		X	X	X	X		
SARS-CoV-2 nucleocapsid antibody		X					

Period	**Screening**	**Treatment**				**Follow-up**	
Visit Name	**Visit 1 Screening**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5/End of Study (EOS)**	**Visit 6 / Safety**	**Unscheduled**
Day/Week/Month	**Day -7**	**Day 1**	**Day 209**	**Day 299**	**Day 389**	**Day 419**	
Visit Window			**+/-3d**	**+/-3d**	**+/-3d**	**+/-3d**	
[redacted]							
Serum Immunoglobulin [2]	X		X		X		
CD 19+ B cells **(Cohort 4 and 6 only)**	X	X	X	X	X		
[redacted]							
Biobanked serum sample[3]	X						
Biobanked whole blood sample[3]	X						
Vaccine Administration Form	X						
IRT Transaction	X	X	X	X	X		
Drug Accountability		S	S	S	S		
Adverse Events / Serious Adverse Events	X	X	X	X	X	S	X
Subject disposition	X				X	S	
Remote check-in[4]						S	

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

S = assessment to be recorded in the source documentation only
[1] Serum pregnancy should be performed locally for all sites except those unable to use a local lab. Sites unable to perform locally should send sample to the central lab.
[2] Participants with lab results within the past 6 months prior to screening will not require labs drawn at screening visit. Local labs should be documented in the source. Participants without lab results from the past 6 months prior to screening will require central labs drawn at the screening visit to be entered into the clinical database.
[3] Sample will be bio-banked for yet to be identified analyses.
[4]Remote contact with participants by site staff. The contact should query about receipt any new AEs or SAEs. Method of contact can be via telephone, email or text message depending on the preference of each participant.

8.1 Screening

Rescreening is not permitted.

8.1.1 Eligibility screening

8.1.1.1 Hepatitis screen

Hepatitis B virus (HBV) will be performed at Visit 1/Screening for participants in Cohort 1, 2, 4 and 6 that do not have test results in their medical history within 6 months prior to the Screening Visit/Day -7.

8.1.1.2 Serum Immunoglobulins

Total serum immunoglobulins will be performed at Visit 1/Screening for all participants that do not have test results in their medical history within 6 months prior to the Screening Visit/Day -7.

8.1.2 Information to be collected on screening failures

Participants who sign an informed consent form and subsequently found to be ineligible prior to enrollment will be considered a screen failure. The reason for screen failure should be recorded on the appropriate Case Report Form. The demographic information, informed consent, cohort, Protocol Amendment log 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). If the participant fails to be enrolled, the IRT must be notified within 2 days of the screen fail that the participant was not enrolled.

Participants who are enrolled and fail to start treatment, e.g. participants enrolled in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate Case Report Form.

8.2 Participant demographics/other baseline characteristics

Participant demographic data and baseline characteristics to be collected on the participants include: age, sex, race and ethnicity. Relevant medical history/current medical condition data includes data collected up to the point in which informed consent is signed. Where possible, diagnoses, and not symptoms will be recorded. Investigators will have the discretion to record abnormal test findings on the CRF capturing medical history whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

8.3 Efficacy

Not applicable.

8.4 Safety

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

8.4.1 Laboratory evaluations

Clinically significant abnormalities must be recorded as either medical history/current medical conditions or adverse events as appropriate.

A central laboratory will be used for analysis of all specimen collected listed below with the exception of the serum pregnancy test. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in the central laboratory manual.

In the case where a laboratory range is not specified by the protocol, but a value is outside the reference range for the laboratory at screening and/or initial baseline, a decision regarding whether the result is of clinical significance or not shall be made by the Investigator (in consultation with the sponsor) and shall be based, in part, upon the nature and degree of the observed abnormality. The assessment may be repeated once prior to enrollment/Visit 2.

In all cases, the Investigator must document in the source documents, the clinical considerations (i.e., result was/was not clinically significant and/or medically relevant) in allowing or disallowing the participant to continue in the study.

Follow instructions outlined in the laboratory manual regarding sample collection, numbering, processing, and shipment.

8.4.2 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing. A serum pregnancy test will be performed for all women of child-bearing potential at Screening Visit/Day -7 and the End of Study Visit. Serum pregnancy should be performed locally for all sites except those unable to use a local lab. Sites unable to perform locally should send sample to the central lab.

Additional pregnancy testing might be performed if requested by local requirements.

Assessments of fertility

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

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

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

8.5 Additional assessments

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

8.5.1 Use of residual biological samples

[redacted]

8.5.2 Serum Immunoglobulins

In Cohort 1, total serum immunoglobulin IgG will be obtained 14 days, 70 days, 180 days, and 360 days after full course (second) vaccination. In Cohort 2, total serum immunoglobulin IgG will be obtained 180 days and 360 days after full course (second) vaccination. In Cohorts 4 and 6, total serum immunoglobulin IgG will be obtained ≥ 180 days and ≥ 360 days after full course (second) vaccination. If serum immunoglobulin IgG obtained is below 400mg/dl the patient will be withdrawn from the study.

8.5.3 Bio-banked samples

As new and relevant assays are validated during this study and after its completion, (1) whole blood and (1) serum sample will be collected at Screening and Visit 4 for Cohorts 1, 2 and 3 to be bio-banked for yet to be identified analyses. For Cohorts 4, 5, and 6, (1) whole blood and (1) serum sample will be collected at Screening Visit/Visit 1 only.

9 Discontinuation and completion

9.1 Discontinuation from study treatment and from study

9.1.1 Discontinuation from study treatment

Discontinuation of study treatment for a participant occurs when study treatment is permanently stopped for any reason (prior to the planned completion of study drug administration, if any) 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.

Discontinuation from study treatment is required under the following circumstances:

- Participant/guardian decision
- Pregnancy
- Total serum immunoglobulin IgG < 400mg/dl after Visit 2
- Use of prohibited treatment as per recommendations as per the USPI
- Any situation in which study participation might result in a safety risk to the participant
- Diagnosis of PML
- Participants with active serious infections or reactivation

- Skin and/or mucosal reactions which raise the suspicion of severe generalized major skin reactions (Stevens-Johnson syndrome, or toxic epidermal necrolysis-Lyell's syndrome)
- Hypersensitivity to ofatumumab
- Protocol violation that results in a significant risk to the participant's safety
- Emergence of certain adverse events, such as malignancy (except successfully treated basal cell carcinoma, *in situ* squamous cell carcinoma and *in situ* carcinoma of cervix of uterus), liver failure or serious chronic infection (such as human immunodeficiency virus (HIV))
- Severe hyperproteinemia
- Non-compliance with study drug or study procedures

If discontinuation from study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the participant's discontinuation from 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 EOS Visit**. At EOS visits all dispensed study drug to participants in Cohort 1 should be reconciled and the adverse event and concomitant medications should be recorded on the CRF (for participants in both cohorts). 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 discontinuation from study treatment, 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

The investigator must also contact the IRT to register the participant's discontinuation from study treatment.

9.1.2 Discontinuation from study

Discontinuation from study is when the participant permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason.

Participants must be discontinued from the study under the following circumstances:

- Failure to receive a complete COVID-19 mRNA (Pfizer or Moderna) vaccination course (2 doses)
- IgG $\leq$ 400mg/dl

If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table under the End of Study Visit (refer to Section 8).

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 from study treatment or discontinue from study or withdraw consent/oppose to the use of their data/biological samples, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed.

9.2 Withdrawal of informed consent/Opposition to use data/biological samples

Withdrawal of consent/opposition to use data/biological samples occurs when a participant:

- Explicitly requests to stop use of their biological samples and/or data (opposition to use participant's data and biological samples)

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts)

This request should be in writing (depending on local regulations) and recorded in the source documentation.

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 their consent/opposition to use data/biological samples and record this information.

Where consent to the use of Personal and Coded Data is not required in a certain country's legal framework, the participant therefore cannot withdraw consent. However, they still retain the right to object to the further collection or use of their 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.

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/opposition to use data/biological samples should be made as detailed in the assessment table under the EOS Visit (refer to Section 8).

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation, including processing of biological samples that has already started at time of consent withdrawal/opposition. No new Personal Data (including biological samples) will be collected following withdrawal of consent/opposition.

9.3 Study stopping rules

Not applicable.

9.4 Study completion and post-study treatment

Study completion is defined as when the last participant completes the EOS Visit.

9.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination may include:

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Practical reasons
- Regulatory or medical reasons

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 for an End of Study Visit within 7 calendar days 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 of the early termination of the trial.

10 Safety monitoring, reporting and committees

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 (1-5)
    - 1 = mild: usually transient in nature and generally not interfering with normal activities
    - 2 = moderate: sufficiently discomforting to interfere with normal activities
    - 3 = severe: prevents normal activities
    - 4 = life threatening
    - 5 = death
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 ongoing) and the outcome 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/permanently discontinued

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 IB or USPI.

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

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
    - 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 and the malignant neoplasm is not a disease progression of the study indication.

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 as per Section 10.1.5.

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. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE to each specific component of study treatment, (if study treatment consists of several components) complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signature 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 within 24 hours of the investigator receiving the follow-up information using the Serious Adverse Event Report Form. 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 IB or USPI (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 European Union (EU) Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30 day period after the last study visit 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 pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the investigator to collect and report information regarding the 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 any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.

Reporting of study treatment errors including misuse/abuse

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 (Section 10.1).

10.2 Additional Safety Monitoring

Not applicable.

11 Data Collection and Database management

11.1 Data collection

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

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

The investigator/designee is responsible for assuring that the data (recorded on 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 Contract Research Organization (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, non-drug therapies/procedures and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Dates of study visits, screen failures and study completion, as well as treatment codes and data about all study treatment (s) dispensed to participants in Cohort 1 will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis at specific timelines.

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

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for analysis. Any changes to the

database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. 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 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

The analysis will be conducted on all participant data at the time the trial ends. Any data analysis carried out independently by the investigator should be submitted to Novartis prior to publication or presentation.

Categorical variables will be presented as counts and percentages. For continuous variable, mean, standard deviation, minimum, 25th percentile, median, 75th percentile, and maximum will be presented. All summaries will be presented for Cohort 1, Cohorts 2 and 4, Cohorts 3 and 5, and Cohort 6.

12.1 Analysis sets

The Safety Set comprises all participants who signed informed consent and met all entry criteria.

The Safety Set will be used for the summary of demographic and baseline characteristics as well as for all safety analyses.

12.2 Participant demographics and other baseline characteristics

Demographics and other baseline characteristics will be summarized descriptively.

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

12.3 Treatments

The duration of study in days will be summarized descriptively.

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 (if applicable) and preferred term.

12.4 Analysis supporting primary objectives

The primary objective of this study is to characterize those achieving immune response after receiving vaccination of non-live mRNA COVID-19 vaccine (Pfizer or Moderna vaccine) in subjects treated with ofatumumab 20 mg s.c. once monthly. This will be achieved by estimating the immune response rate using the Safety Set.

An immune responder is a participant achieving immune response as defined by a positive SARS-CoV-2 qualitative antibody assay after vaccination.

12.4.1 Definition of primary endpoint(s)

The primary endpoint is achieving immune response as defined by a positive SARS-CoV-2 qualitative antibody assay 14 days after vaccination (yes/no).

12.4.2 Statistical model, hypothesis, and method of analysis

The number and percentage of responders will be presented. The 95% confidence interval for the proportion of responders will be calculated by using exact method.

12.4.3 Handling of intercurrent events of primary estimand

Non-responder imputation approach will be applied to missing postvaccination antibody assay regardless of intercurrent events.

12.4.4 Handling of missing values not related to intercurrent event

Non-responder imputation approach will be applied to missing postvaccination antibody assay.

12.4.5 Sensitivity analyses

Not applicable.

12.4.6 Supplementary analysis

Similar analyses will be performed by using valid assessments of antibody assay without imputation of missing data.

12.5 Analysis supporting secondary objectives

In addition to assess immune response at other than ≥14 days after full course, the following variables will also be evaluated.

- Immune conversion is defined as:
  - Baseline absence of SARS-CoV-2 qualitative IgG antibody with post-vaccination SARS-CoV-2 qualitative IgG antibody assay 14 days after full course (two doses) vaccination (yes/no); or
  - Baseline serum presence of SARS-CoV-2 quantitative antibody with post-vaccination ≥ 4-fold increase in SARS-CoV-2 quantitative antibody titer as determined by dilution assay 14 days after full course (two doses) vaccination (yes/no).
  - Initial negative SARS-CoV-2 nucleocapsid antibody with post-vaccination SARS-CoV-2 positive qualitative antibody assay ≥ 14 days after vaccination (yes/no) (Applicable to Cohorts 4 and 5.)

Those variables will be summarized by frequency count and percentage together with the 95% confidence intervals for the proportion of responders obtained using exact method.

Both non-responder imputation of missing data and observed case approach (no imputation for missing data) will be used in the above analyses.

Participants may be enrolled after receiving at least 1 or more mRNA booster or may receive a booster during the trial. This group will be segregated for further analysis.

12.5.1 Safety endpoints

All listings and tables will be presented by cohort.

In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, which started or worsened during the on-treatment period (treatment-emergent AEs).

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 will be summarized in the following ways:

- by cohort, primary system organ class and preferred term.
- by cohort, primary system organ class, preferred term and maximum severity.
- by cohort, preferred term in descending order

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

In addition, a separate listing of death including on treatment and post treatment deaths will be provided.

Clinical laboratory evaluations

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

12.7 Interim analyses

For the purpose of early dissemination of results, an interim analysis will be performed once Cohorts 2 and 4 in combination have at least 10 patients enrolled that have had their serum drawn ≥ 14 days after full vaccination (two dose) course.

A second interim analysis will be performed once Cohort 6 has at least 10 participants.

The third interim analysis will be performed once Cohorts 2-5 have full enrollment with blood drawn ≥ 14 days after full course (two doses) vaccination.

The following variables (but not limited to) will be summarized for each interim analysis mentioned above:

- Demographics
- Baseline characteristics
- Immune response related variables
- AE, SAE, AEs leading to study discontinuation and death

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

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

The sample size of 20 participants per cohort is selected based on budget and need for early availability of results. This sample size of 20 participants will provide estimates of proportion of responders 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 participants will be enrolled in Cohort 1. In combination, 22 participants will be enrolled in Cohorts 2 and 4. In combination, 22 patients will be enrolled in Cohorts 3 and 5. In Cohort 6, 22 participants will be enrolled.

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

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board (IRB) 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, IRBss, 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 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 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 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 at the study site should be informed according to local regulations.

15 References

References are available upon request.

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