NOVARTIS

Clinical Development

# OMB157G/Ofatumumab

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

# Statistical Analysis Plan (SAP)

| | |
|---|---|
| Document type: | SAP Documentation |
| Document status: | Final 2.0, Amendment 1 |
| Release date: | 28-Jun-2023 |
| Number of pages: | 32 |

## Document History – Changes compared to previous final version of SAP

| Date | Time point | Reason for update | Outcome for update | Section and title impacted (Current) |
|---|---|---|---|---|
| 28-May-2021 | Prior to clinical DB lock | Creation of final version | NA - first version | NA |
| 28-Jun-2023 | Prior to clinical DB lock | Creation of Amendment 1 | 1. Updated to align with protocol version 01 (amended protocol) dated 29-Sep-2021: added 3 new cohorts; increased sample size; included participants who are fully vaccinated; increased number of interim analyses; addressed inconsistencies and made clarifications<br>2. Updated list of abbreviations<br>3. Clarified primary analysis time point for Cohorts 4-6 as Visit 2<br>[redacted]<br>5. Updated definition of immune conversion to account for participants with serum unavailable prior to vaccine but who have not received a booster (Cohorts 4 and 5)<br>6. Indicated that 95% CIs for point estimates of mean or proportion will be provided<br>7. Clarified that summarization of data will be done via cohort groupings: Cohort 1, Cohorts 2 and 4, Cohorts 3 and 5, and Cohort 6<br>8. Changed baseline to pre-vaccination and post-baseline to post-vaccination<br>9. Modified definition of safety analysis set to include participants who signed | 1. Section 1 Introduction; Section 1.1 Study design; Section 1.2 Study objectives, endpoints and estimands; Section 1.2.1 Primary estimand(s); Section 2.1.1 General definitions; Section 2.5.1 Primary endpoint(s); Section 2.13 Interim analysis; Section 3 Sample size calculation<br>2. List of abbreviations table<br>3. Section 1.1 Study design<br>[redacted]<br>5. Section 1.2 Study objectives, endpoints and estimands; Section 2.6.1 Secondary endpoint(s)<br>6. Section 2.1 Data analysis general information<br>7. Section 2.1 Data analysis general information<br>8. Section 1.2 Study objectives, endpoints and estimands; Section 2.1.1 General definitions; Section 2.6.1 Secondary endpoint(s)<br>9. Section 2.2 Analysis sets<br>10. Section 2.3.1 Patient disposition<br>11. Section 2.3.3 MS history |

| Date | Time point | Reason for update | Outcome for update | Section and title impacted (Current) |
|---|---|---|---|---|
| | | | informed consent and met all entry criteria<br>10. Removed disposition event of Safety follow-up<br>11. Added section to address summarization of MS history<br>12. Clarified that medical history will be summarized with frequency counts and percentages<br>13. Added variables for time between points of interest; indicated that MS treatment compliance will be listed<br>14. Made updates to visit windows based on protocol amendment and review of data<br>15. Clarified that non-drug therapies/procedures will be coded per MedDRA terminology and summarized by primary SOC and PT; indicated that prior MS DMTs will be summarized by PT<br>16. Clarified that the primary analysis will be conducted using the safety analysis set<br>17. Added supplemental analysis in which primary analysis is repeated using data from Cohort 6 participants and any participants in Cohorts 1-5 who received a booster during the study<br>18. Added supplemental analysis in which analysis of secondary endpoints is repeated using data from Cohort 6 participants and any participants in Cohorts 1-5 who received a booster during the study<br>19. Removed reference to CTC AE grades<br>20. Added descriptive summary of laboratory assessments | 12. Section 2.3.4 Medical history<br>13. Section 2.4.1 Study treatment / compliance<br>14. Section 2.4.1.1 Visit windows<br>15. Section 2.4.2 Prior, concomitant and post therapies<br>16. Section 2.5 Analysis supporting primary objective(s)<br>17. Section 2.5.6 Supplementary analyses<br>18. Section 2.6.6 Supplementary analyses<br>19. Section 2.7.1 Adverse events (AEs)<br>20. Section 2.7.3 Laboratory data<br>21. Section 2.7.4.1 MS relapse<br>[redacted]<br>24. Section 5.1.2 AE date imputation; Section 5.1.3 Concomitant medication date imputation<br>25. Section 5.1.3.3 Other imputations |

| Date | Time point | Reason for update | Outcome for update | Section and title impacted (Current) |
|---|---|---|---|---|
| | | | 21. Modified the categories for summary of number of relapses [redacted]<br>24. Replaced AE and medication partial date imputation rules with [redacted] standard rules<br>25. Added imputation rule for partial relapse start dates | |

## Table of contents

## List of abbreviations

| | |
|---|---|
| AE | Adverse Event |
| ATC | Anatomical Therapeutic Chemical |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| CDBL | Clinical Database Lock |
| CI | Confidence Interval |
| COVID-19 | Coronavirus 2019 |
| CRO | Contract Research Organization |
| CSP | Clinical Study Protocol |
| CSR | Clinical Study Report |
| EOS | End of Study |
| HBV | Hepatitis B Virus |
| IA | Interim Analysis |
| [redacted] | [redacted] |
| IgG | Immunoglobulin G |
| LS | Least Squares |
| MedDRA | Medical Dictionary for Drug Regulatory Activities |
| mRNA | Messenger Ribonucleic Acid |
| MS | Multiple Sclerosis |
| NRI | Non-Response Imputation |
| PD | Pharmacodynamic |
| PK | Pharmacokinetic |
| PT | Preferred Term |
| SAE | Serious Adverse Event |
| SAF | Safety Analysis Set |
| SAP | Statistical Analysis Plan |
| SARS-CoV-2 | Severe Acute Respiratory Syndrome Coronavirus 2 |
| s.c. | Subcutaneous |
| SOC | System Organ Class |
| [redacted] | [redacted] |
| WHO | World Health Organization |

# 1 Introduction

The purpose of this Statistical Analysis Plan (SAP) is to describe the statistical methods planned in Section 12 of the Clinical Study Protocol (CSP) version 01 (dated 29-Sep-2021) for the clinical trial COMB157GUS16 and any additional analyses, specifications or deviations from this planned protocol before clinical database lock (CDBL).

This SAP will be used to draft the Clinical Study Report (CSR) Section 9.7: Statistical methods.

## 1.1 Study design

This is a 6-cohort, multicenter prospective study in up to 88 participants with relapsing multiple sclerosis (MS). 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 (2 doses) of a non-live coronavirus 2019 (COVID-19) messenger ribonucleic acid (mRNA) (Pfizer or Moderna) vaccine. Participants also must meet inclusion criteria and not meet exclusion criteria.

The study consists of 2 periods as outlined below.

### Screening period

Participants will enter a screening period of up to 7 days to assess eligibility requirements. Participants in Cohorts 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 to be drawn. Participants with 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.

### 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.

**<u>Cohort 1</u>: Relapsing MS participants receiving a full course (2 doses) of a non-live COVID-19 mRNA vaccine ≥2 weeks prior to ofatumumab start.**

For participants who receive the Pfizer vaccine, the first of three 20 mg subcutaneous (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 2$^{nd}$ and 3$^{rd}$ loading doses should be administered on Day 43 and Day 50 or 7 and 14 days respectively after the 1$^{st}$ 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 2$^{nd}$ and 3$^{rd}$ loading doses should be administered on Day 50 and Day 57 or 7 and 14 days respectively after the 1$^{st}$ loading dose. Subsequent dosing includes 20 mg s.c administered monthly starting at Day 71.

**Cohort 2: Relapsing MS participants receiving a full course (2 doses) of a non-live COVID-19 mRNA vaccine ≥4 weeks after ofatumumab start.**

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

**Cohort 3: Relapsing MS participants receiving a full course (2 doses) of a non-live COVID-19 mRNA vaccine ≥4 weeks after start of prescribed interferon or glatiramer acetate.**

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

**Cohort 4: Relapsing MS participants having completed a full course (2 doses) of a non-live COVID-19 mRNA vaccine ≥4 weeks after ofatumumab start.**

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

**Cohort 5: Relapsing MS participants having completed a full course (2 doses) of a non-live COVID-19 mRNA vaccine ≥4 weeks after glatiramer acetate or interferon start.**

Will continue taking their prescribed glatiramer acetate or interferon as per their current dosing schedule.

**Cohort 6: Relapsing MS 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.**

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

### Study completion

According to the protocol, study completion is defined as when the last participant completes the end of study (EOS) visit. 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. Where possible, they should return for the EOS visit.

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

**Figure 1 Study Design (Cohort 1, Pfizer)**

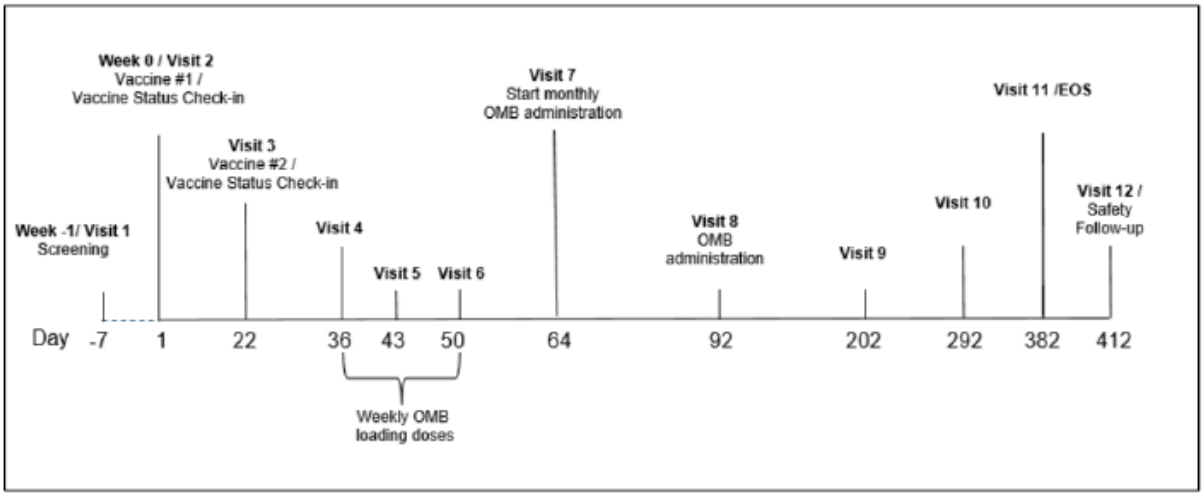



**Figure 2 Study Design (Cohort 1, Moderna)**

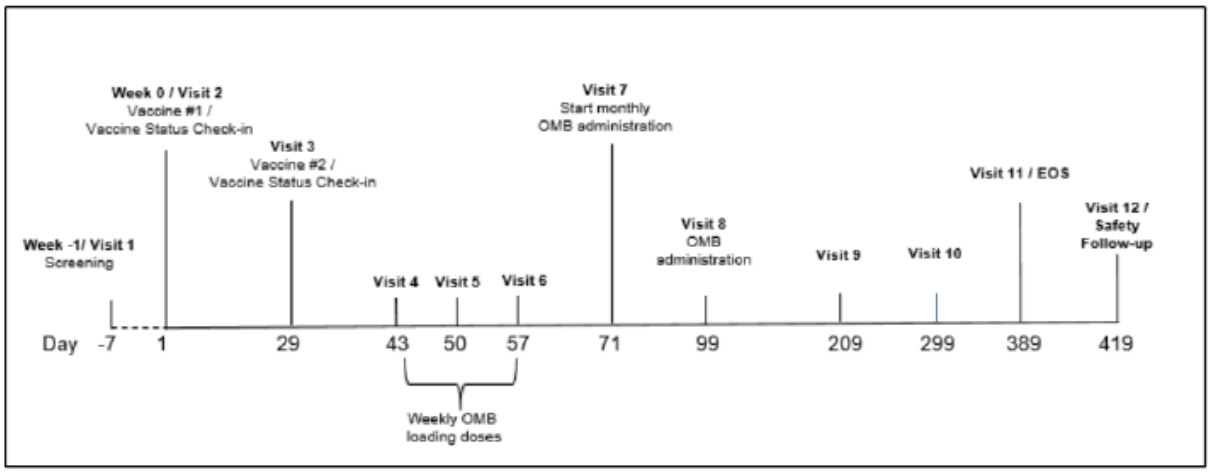



**Figure 3 Study Design (Cohorts 2 and 3, Pfizer)**

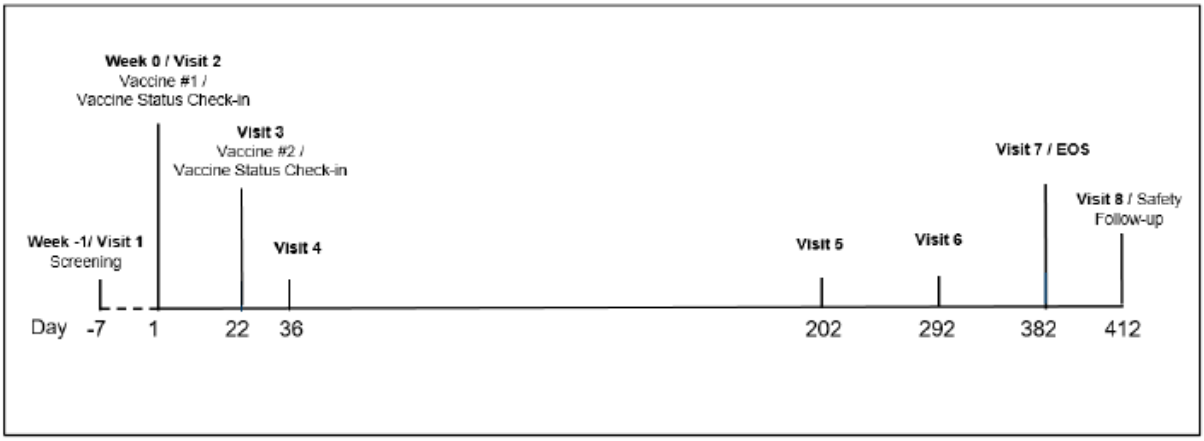


**Figure 4 Study Design (Cohorts 2 and 3, Moderna)**

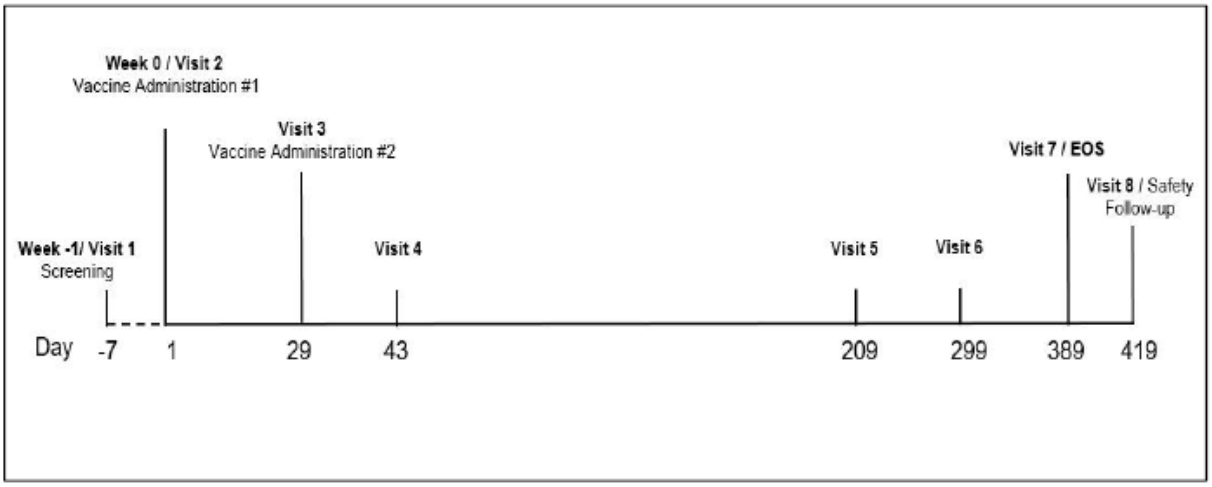



**Figure 5 Study Design (Cohorts 4, 5 and 6, Pfizer)**

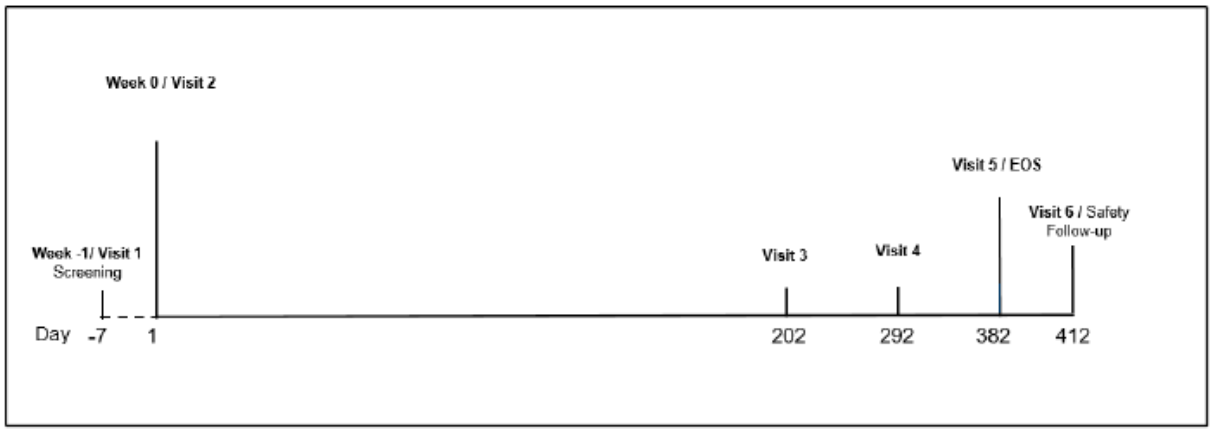
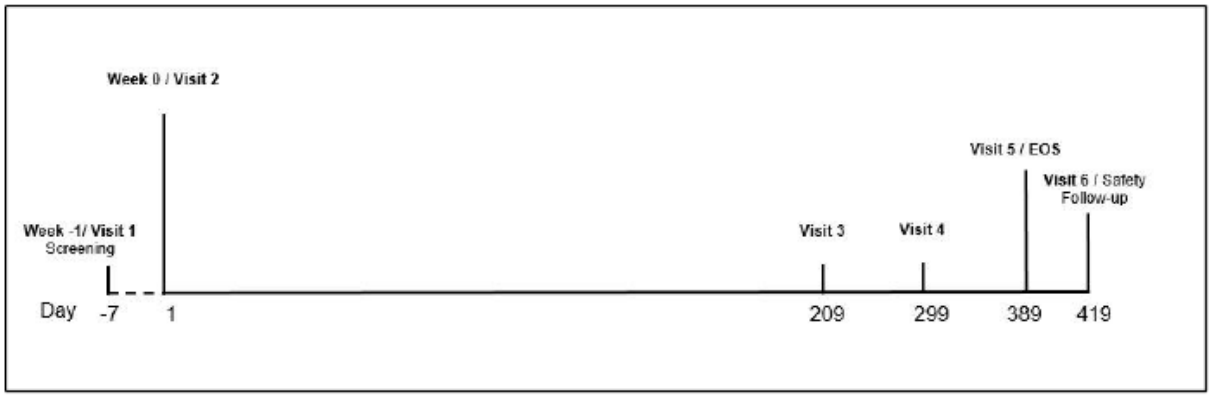



**Figure 6 Study Design (Cohorts 4, 5 and 6, Moderna)**




## Primary analysis time point

The primary analysis time point is Visit 4 for Cohorts 1, 2 and 3, and Visit 2 for Cohorts 4, 5 and 6.

### Interim analysis

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

A second IA will be performed once Cohort 6 has ≥10 participants.

A third IA will be performed once Cohorts 2 – 5 have full enrollment with blood drawn ≥14 days after full course (2 doses) vaccination.

## 1.2 Study objectives, endpoints and estimands

Study objectives and associated endpoints are shown in Table 1.

**Table 1 Study objectives and endpoints**

| Objective(s) | Endpoint(s) |
|---|---|
| **Primary Objective(s)**<br>• To assess immune response to non-live mRNA COVID-19 vaccine in ofatumumab-treated participants | **Endpoint(s) for primary objective(s)**<br>• Achieving immune response as defined by positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) qualitative Immunoglobulin G (IgG) antibody assay ≥14 days after full course (2 doses) vaccination (yes/no) |
| **Secondary Objective(s)**<br>• To assess sustained immune response to non-live mRNA COVID-19 vaccine in ofatumumab-treated participants<br>• To assess immune conversion to non-live mRNA COVID-19 vaccine in ofatumumab-treated participants | **Endpoint(s) for secondary objective(s)**<br>• Achieving immune response at other assessment time points (yes/no)<br>• Immune conversion to non-live mRNA COVID-19 vaccine (yes/no) defined as:<br>• For participants with serum available prior to vaccination:<br>o Pre-vaccination absence of SARS-CoV-2 spike IgG with post-vaccination SARS-CoV-2 positive qualitative antibody assay ≥14 days after full course (2 doses) vaccination (yes/no) or<br>o Pre-vaccination 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 full course (2 doses) vaccination (yes/no)<br>• For participants with serum unavailable prior to vaccination and who have not received a booster (Cohorts 4 and 5):<br>o Initial negative SARS-CoV-2 nucleocapsid antibody with post-vaccination SARS-CoV-2 positive qualitative antibody assay ≥14 days after full course (2 doses) vaccination (yes/no) |

| Objective(s) | Endpoint(s) |
|---|---|
| • To assess adverse events and serious adverse events | • Adverse events/serious adverse events |
| [redacted] | |

### 1.2.1 Primary estimand(s)

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 (2 doses) of a COVID-19 mRNA vaccine ≥2 weeks prior to starting ofatumumab 20 mg s.c. treatment; (2) Will receive a full course (2 doses) of a COVID-19 mRNA vaccine after ≥4 weeks of commercial ofatumumab 20 mg s.c. treatment (3) Will receive a full course (2 doses) of a COVID-19 mRNA vaccine after ≥4 weeks of interferon or glatiramer acetate treatment (4) Completed a full course (2 doses) of a COVID-19 mRNA vaccine after ≥4 weeks of commercial ofatumumab 20 mg s.c. treatment but has not yet received a COVID-19 mRNA booster (5) Completed a full course (2 doses) of a COVID-19 mRNA vaccine after ≥4 weeks of interferon or glatiramer acetate (may or may not have received a COVID-19 mRNA booster) (6) Completed a full course (2 doses) of a COVID-19 mRNA vaccine after ≥4 weeks of commercial ofatumumab 20 mg s.c. treatment and received an 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 (2 doses) vaccination (yes/no)

- **Treatment of interest:** Non-live COVID-19 mRNA vaccine either ≥2 weeks prior to ofatumumab start or ≥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

### 1.2.2 Secondary estimand(s)

There are no secondary estimands specified for this study.

# 2 Statistical methods

## 2.1 Data analysis general information

The statistical analysis outlined in this SAP will be performed by [redacted], a Novartis-designated Contract Research Organization (CRO), using SAS® version 9.4 or higher.

For continuous variables, descriptive statistics will include number of participants (n), mean, standard deviation, minimum, maximum, median and 25th and 75th percentiles. For categorical variables, frequency counts and percentages will be reported. Where appropriate, 2-sided 95% confidence intervals (CIs) for point estimates of the mean or proportion will be provided.

Unless otherwise stated, all data summaries will be presented **by cohort group** (see below) and on all participants in the respective analysis set.

- Cohort 1
- Cohorts 2 and 4 combined
- Cohorts 3 and 5 combined
- Cohort 6

All data will be listed appropriately.

### 2.1.1 General definitions

#### Treatment of interest

The treatment of interest will refer to the administration of a COVID-19 mRNA vaccine (either Pfizer or Moderna) to participants in each of the 6 cohorts. Participants will obtain a COVID-19 mRNA vaccine from their HCP (private insurance) or appropriate federal, state or local program.

#### Additional treatment

- Ofatumumab provided by Novartis in an auto-injector containing 20 mg s.c. ofatumumab (20 mg/0.4ml) for s.c. administration to participants in **Cohort 1** as per the assessment schedule.
- Commercially prescribed ofatumumab treatment for participants in **Cohort 2** as per their current dosing schedule.

- Commercially prescribed interferon or glatiramer acetate treatment for participants in **Cohort 3** as per their current dosing schedule.
- Commercially prescribed ofatumumab treatment for participants in **Cohort 4** as per their current dosing schedule.
- Commercially prescribed interferon or glatiramer acetate treatment for participants in **Cohort 5** as per their current dosing schedule.
- Commercially prescribed ofatumumab treatment for participants in **Cohort 6** as per their current dosing schedule

### Study day, onset day, and event duration

The **study day** of an assessment will be derived relative to the date of Visit 2 (Study Day 1), primarily for use in the derivation of analysis visits using visit windows (see Section 2.4.1.1).

For data including but not limited to adverse events, medications, medical history, non-drug therapies/procedures and MS relapses, the **onset day** will be derived relative to the date of Visit 1 (Screening) as described below.

For event dates on or after the date of Visit 1, the day of the event will be calculated as follows:

- (date of event − date of Visit 1) + 1

For event dates prior to the date of Visit 1, the day of the event will be calculated as follows:

- (date of event − date of Visit 1)

The **duration of an event** in days will be calculated as follows:

- (event end date − event start date) + 1

### Screening

Screening refers to any procedures (e.g., checking inclusion and exclusion criteria) performed prior to Visit 2 (Study Day 1) unless otherwise specified. Per protocol, participant informed consent must be obtained prior to performing any study related activity. The date of signing of informed consent is the start date of the screening period. Any assessment obtained during the screening period will be labelled as a screening assessment.

### Pre-vaccination

Unless otherwise specified, pre-vaccination is the last non-missing assessment (including unscheduled assessments) obtained prior to the first dose of the COVID-19 vaccine. Pre-vaccination is only applicable to Cohorts 1, 2 and 3. All assessments obtained after the first dose of the COVID-19 vaccine are considered post-vaccination assessments unless otherwise specified.

### Nominal visits

Nominal visits are defined as all scheduled visits as per the clinical study protocol including the EOS visit. The definition of nominal visit excludes unscheduled visits.

## 2.2 Analysis sets

The Safety Analysis Set (SAF) comprises all participants who signed informed consent and met all entry criteria.

Unless otherwise specified the SAF will be used for all summary tables and listings.

### 2.2.1 Subgroup of interest

There is no subgroup analysis planned for this study.

## 2.3 Patient disposition, demographics and other baseline characteristics

### 2.3.1 Patient disposition

Participant disposition will be summarized for the following disposition events using all screened participants:

- Screening
- Treatment
- End of study

Participants who have discontinued from the study will be listed as appropriate along with the primary reason for discontinuation.

The number and percentage of screen failures and the reason for screen failure will be presented for all screened participants.

For each protocol deviation, the number and percentage of participants for whom the deviation applies will be summarized by cohort group.

### 2.3.2 Demographics and other baseline characteristics

The following demographic variables will be summarized descriptively by cohort group:

**Continuous variables**

- Age (years)

**Categorical variables**

- Sex (Male, Female)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown)
- Race (White, Black or African American, Asian [Chinese, Indian, Japanese, Korean, Vietnamese], Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, Multiple)

### 2.3.3 MS history

The number and percentage of participants with a relapse in the last 90 days prior to screening will be presented by cohort group.

The following variable will be summarized descriptively as a continuous variable by cohort group:

- Time (days) from onset of most recent relapse (in the last 90 days prior to screening) to Visit 1 (Screening), in participants with a relapse in the last 90 days prior to screening

### 2.3.4 Medical history

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The MedDRA version used for reporting the study will be indicated in a footnote on relevant outputs.

Medical history will be summarized with frequency counts and percentages by cohort group, primary system organ class (SOC) and preferred term (PT). Tables will show the overall number and percentage of participants with at least one reported medical history event in a particular primary SOC and at least one reported medical history event in a particular PT.

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

### 2.4.1 Study treatment / compliance

Participants in all cohorts must intend to receive or have received both doses of a COVID-19 mRNA vaccine.

The following variables will be summarized descriptively as continuous variables by cohort group unless otherwise specified:

- Time (days) from first dose of ofatumumab to last dose of ofatumumab for Cohort 1 participants
- Time (days) from first dose of earliest MS DMT to:
  - first dose of COVID-19 vaccine
  - primary analysis time point (see Section 1.1)
- Time (days) from first dose of most recent MS DMT to:
  - first dose of COVID-19 vaccine
  - primary analysis time point (see Section 1.1)

MS treatment compliance will be listed by individual cohort and participant.

#### Study duration

Study duration in days will be calculated as [(date of last contact/EOS – date of Visit 1) + 1] and summarized descriptively as a continuous variable by cohort group.

#### 2.4.1.1 Visit windows

Visit windows will be used for data that are summarized by visit; they are based on the study evaluation schedule and comprise a set of days around the nominal visit day. When visit windows are used, all visits, including unscheduled visits, will be re-aligned (i.e., they will be mapped into one of the visit windows). In the case of major deviations from the visit schedule, or due to unscheduled visits, several assessments for a participant may fall in a particular visit window (either scheduled or unscheduled). Approaches for handling multiple assessments in a visit window are outlined below.

The following steps are used to determine the cut-offs for visit windows:

- The visit window associated with the previous assessment ends prior to the middle point; the visit window associated with the latter assessment begins after the middle point. In case the middle point is an exact study day, it will belong to the previous assessment.
- The visit window of the first post-vaccination assessment starts the day after the second dose of the COVID-19 vaccine for Cohorts 1 – 5, and the day after the COVID-19 vaccine booster for Cohort 6, unless otherwise specified.

Tables 2 – 10 provide visit windows for applicable parameters.

**Table 2 Cohort 1 visit windows for SARS-CoV-2 qualitative antibody / CD19+ B cells / T cell**

| Analysis visit | Nominal time point | Scheduled visit day (target study day) | Visit window (study days) |
|---|---|---|---|
| **Pfizer vaccine:** | | | |
| Pre-vaccination | Day 1 | 1 | ≤1 |
| 14 days post-vaccination | Day 36 | 36 | (vaccine day + 1) to 64 |
| 70 days post-vaccination | Day 92 | 92 | 65 to 147 |
| 180 days post-vaccination | Day 202 | 202 | 148 to 247 |
| 270 days post-vaccination | Day 292 | 292 | 248 to 337 |
| 360 days post-vaccination | Day 382 | 382 | ≥338 |
| **Moderna vaccine:** | | | |
| Pre-vaccination | Day 1 | 1 | ≤1 |
| 14 days post-vaccination | Day 43 | 43 | (vaccine day + 1) to 71 |
| 70 days post-vaccination | Day 99 | 99 | 72 to 154 |
| 180 days post-vaccination | Day 209 | 209 | 155 to 254 |
| 270 days post-vaccination | Day 299 | 299 | 255 to 344 |
| 360 days post-vaccination | Day 389 | 389 | ≥345 |

Note:
- Pre-vaccination and study day are derived as outlined in Section 2.1.1.
- Vaccine day is the study day of the second dose of the COVID-19 vaccine.
- Assessments performed between the first and second doses of the COVID-19 vaccine are not assigned an analysis visit.

**Table 3 Cohort 1 visit windows for serum immunoglobulin (IgG, IgM)**

| Analysis visit | Nominal time point | Scheduled visit day (target study day) | Visit window (study days) |
|---|---|---|---|
| **Pfizer vaccine:** | | | |
| Pre-vaccination | Day 1 | 1 | ≤1 |
| 14 days post-vaccination | Day 36 | 36 | (vaccine day + 1) to 64 |
| 70 days post-vaccination | Day 92 | 92 | 65 to 147 |
| 180 days post-vaccination | Day 202 | 202 | 148 to 292 |
| 360 days post-vaccination | Day 382 | 382 | ≥293 |
| **Moderna vaccine:** | | | |
| Pre-vaccination | Day 1 | 1 | ≤1 |
| 14 days post-vaccination | Day 43 | 43 | (vaccine day + 1) to 71 |
| 70 days post-vaccination | Day 99 | 99 | 72 to 154 |
| 180 days post-vaccination | Day 209 | 209 | 155 to 299 |
| 360 days post-vaccination | Day 389 | 389 | ≥300 |

Note:
- Pre-vaccination and study day are derived as outlined in Section 2.1.1.
- Vaccine day is the study day of the second dose of the COVID-19 vaccine.
- Assessments performed between the first and second doses of the COVID-19 vaccine are not assigned an analysis visit.

**Table 5 Cohorts 2 and 3 visit windows for SARS-CoV-2 qualitative antibody / CD19+ B cells (Cohort 2 only) / T cell**

| Analysis visit | Nominal time point | Scheduled visit day (target study day) | Visit window (study days) |
|---|---|---|---|
| **Pfizer vaccine:** | | | |
| Pre-vaccination | Day 1 | 1 | ≤1 |
| 14 days post-vaccination | Day 36 | 36 | (vaccine day + 1) to 119 |
| 180 days post-vaccination | Day 202 | 202 | 120 to 247 |
| 270 days post-vaccination | Day 292 | 292 | 248 to 337 |
| 360 days post-vaccination | Day 382 | 382 | ≥338 |
| **Moderna vaccine:** | | | |
| Pre-vaccination | Day 1 | 1 | ≤1 |
| 14 days post-vaccination | Day 43 | 43 | (vaccine day + 1) to 126 |
| 180 days post-vaccination | Day 209 | 209 | 127 to 254 |
| 270 days post-vaccination | Day 299 | 299 | 255 to 344 |
| 360 days post-vaccination | Day 389 | 389 | ≥345 |

Note:
- Pre-vaccination and study day are derived as outlined in Section 2.1.1.
- Vaccine day is the study day of the second dose of the COVID-19 vaccine.
- Assessments performed between the first and second doses of the COVID-19 vaccine are not assigned an analysis visit.

**Table 6 Cohorts 2 and 3 visit windows for serum immunoglobulin (IgG, IgM)**

| Analysis visit | Nominal time point | Scheduled visit day (target study day) | Visit window (study days) |
|---|---|---|---|
| **Pfizer vaccine:** | | | |
| Pre-vaccination | Day 1 | 1 | ≤1 |
| 180 days post-vaccination | Day 202 | 202 | (vaccine day + 1) to 292 |
| 360 days post-vaccination | Day 382 | 382 | ≥293 |
| **Moderna vaccine:** | | | |
| Pre-vaccination | Day 1 | 1 | ≤1 |
| 180 days post-vaccination | Day 209 | 209 | (vaccine day + 1) to 299 |
| 360 days post-vaccination | Day 389 | 389 | ≥300 |

Note:
- Pre-vaccination and study day are derived as outlined in Section 2.1.1.
- Vaccine day is the study day of the second dose of the COVID-19 vaccine.
- Assessments performed between the first and second doses of the COVID-19 vaccine are not assigned an analysis visit.

**Table 8 Cohorts 4, 5 and 6 visit windows for SARS-CoV-2 qualitative antibody / CD19+ B cells (Cohorts 4 and 6 only) / T cell**

| Analysis visit | Nominal time point | Scheduled visit day (target study day) | Visit window (study days) |
|---|---|---|---|
| **Pfizer vaccine:** | | | |
| 14 days post-vaccination | Day 1 | 1 | (vaccine day + 1) to 1 |
| 180 days post-vaccination | Day 202 | 202 | 2 to 247 |
| 270 days post-vaccination | Day 292 | 292 | 248 to 337 |
| 360 days post-vaccination | Day 382 | 382 | ≥338 |
| **Moderna vaccine:** | | | |
| 14 days post-vaccination | Day 1 | 1 | (vaccine day + 1) to 1 |
| 180 days post-vaccination | Day 209 | 209 | 2 to 254 |
| 270 days post-vaccination | Day 299 | 299 | 255 to 344 |
| 360 days post-vaccination | Day 389 | 389 | ≥345 |

Note:
- Study day is derived as outlined in Section 2.1.1.
- Vaccine day is the study day of the second dose of the COVID-19 vaccine for Cohorts 4 and 5, and the study day of the COVID-19 vaccine booster for Cohort 6.

**Table 9 Cohorts 4, 5 and 6 visit windows for serum immunoglobulin (IgG, IgM)**

| Analysis visit | Nominal time point | Scheduled visit day (target study day) | Visit window (study days) |
|---|---|---|---|
| **Pfizer vaccine:** | | | |
| 14 days post-vaccination | Day 1 | 1 | (vaccine day + 1) to 1 |
| 180 days post-vaccination | Day 202 | 202 | 2 to 292 |
| 360 days post-vaccination | Day 382 | 382 | ≥293 |
| **Moderna vaccine:** | | | |
| 14 days post-vaccination | Day 1 | 1 | (vaccine day + 1) to 1 |
| 180 days post-vaccination | Day 209 | 209 | 2 to 299 |
| 360 days post-vaccination | Day 389 | 389 | ≥300 |

Note:
- Study day is derived as outlined in Section 2.1.1.
- Vaccine day is the study day of the second dose of the COVID-19 vaccine for Cohorts 4 and 5, and the study day of the COVID-19 vaccine booster for Cohort 6.

## Multiple assessments

When there are multiple assessments in a particular visit window, the rules outlined below are applied to select one value "representing" the participant in summary statistics for that visit window. All assessments will be displayed in listings.

- **Pre-vaccination (only applicable to Cohorts 1, 2 and 3):** Pre-vaccination is derived as outlined in Section 2.1.1. In situations where the same assessment is performed more than once on Study Day 1 the repeated assessment will be used.
- **Post-vaccination:** For post-vaccination visit windows, the following rules apply (unless otherwise specified):
  - For *continuous variables*, the assessment with the study day that is closest to the target study day is selected. If two assessments are equidistant from the target study

day, the earlier assessment is selected (if one of the two equidistant assessments is an unscheduled assessment, it should be excluded from consideration).

- For *categorical variables*, the assessment with the worst result is selected.

If categorical variables are based on continuous variables, the analysis visit will be assigned to the continuous variable, and this analysis visit will be used for the derived categorical variable.

In situations where the same assessment is performed more than once on the same date the repeated assessment will be used.

### 2.4.2 Prior, concomitant and post therapies

Medications will be coded using the World Health Organization (WHO) Drug Dictionary. The WHO Drug Dictionary version used for reporting the study will be indicated in a footnote on relevant outputs.

Medications will be classified as prior or concomitant as follows:

- Prior medications are defined as medications taken prior to the date of Visit 1 (Screening).
- Concomitant medications are defined as medications taken on or after the date of Visit 1 (Screening).

Medications will be categorized into the above classes based on recorded or imputed start and end dates (see Section 5.1.3).

Prior and concomitant medications will be summarized with frequency counts and percentages by cohort group, Anatomical Therapeutic Chemical (ATC) class and PT. Tables will show the overall number and percentage of participants receiving at least one medication of a particular ATC class and at least one medication of a particular PT. A separate summary of prior MS DMTs by PT will be provided.

Non-drug therapies/procedures will be coded using MedDRA terminology. The MedDRA version used for reporting the study will be indicated in a footnote on relevant outputs. Non-drug therapies/procedures will be classified as prior or concomitant based on recorded or imputed start and end dates as outlined above for medications.

Prior and concomitant non-drug therapies/procedures will be summarized by cohort group, primary SOC and PT. Tables will show the overall number and percentage of participants with at least one non-drug therapy/procedure of a particular primary SOC and at least one non-drug therapy/procedure of a particular PT.

## 2.5 Analysis supporting primary objective(s)

The primary objective of this study is to characterize those achieving immune response after receiving a full course (2 doses) vaccination with a non-live mRNA COVID-19 vaccine (Pfizer or Moderna vaccine) in participants treated with ofatumumab 20 mg s.c. once monthly. This will be achieved by estimating the immune response rate using the SAF.

An immune responder is a participant achieving immune response as defined by a positive SARS-CoV-2 qualitative IgG antibody assay after full course (2 doses) vaccination.

### 2.5.1 Primary endpoint(s)

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

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 (2 doses) of a COVID-19 mRNA vaccine ≥2 weeks prior to starting ofatumumab 20 mg s.c. treatment; (2) Will receive a full course (2 doses) of a COVID-19 mRNA vaccine after ≥4 weeks of commercial ofatumumab 20 mg s.c. treatment (3) Will receive a full course (2 doses) of a COVID-19 mRNA vaccine after ≥4 weeks of interferon or glatiramer acetate treatment (4) Completed a full course (2 doses) of a COVID-19 mRNA vaccine after ≥4 weeks of commercial ofatumumab 20 mg s.c. treatment but has not yet received a COVID-19 mRNA booster (5) Completed a full course (2 doses) of a COVID-19 mRNA vaccine after ≥4 weeks of interferon or glatiramer acetate (may or may not have received a COVID-19 mRNA booster) (6) Completed a full course (2 doses) of a COVID-19 mRNA vaccine after ≥4 weeks of commercial ofatumumab 20 mg s.c. treatment and received an 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 (2 doses) vaccination (yes/no)
- **Treatment of interest:** Non-live COVID-19 mRNA vaccine either ≥2 weeks prior to ofatumumab start or ≥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

### 2.5.2 Statistical hypothesis, model, and method of analysis

The number and percentage of responders will be presented by cohort group and overall. The 2-sided 95% CI for the proportion of responders will be calculated using an exact method (Clopper and Pearson, 1934).

### 2.5.3 Handling of intercurrent events

Non-response imputation (NRI) approach will be applied to missing post-vaccination antibody assay regardless of intercurrent events.

NRI is a conservative imputation method for dichotomous variables. NRI assumes that a participant is a treatment failure if the participant discontinues the study prematurely. Hence, for missing data the primary endpoint will be imputed as “No”. Refer to Section 5.1.3.3.

### 2.5.4 Handling of missing values not related to intercurrent event

NRI approach will be applied to missing post-vaccination antibody assay.

### 2.5.5 Sensitivity analyses

There are no sensitivity analyses of the primary endpoint planned for this study.

### 2.5.6 Supplementary analyses

A supplemental analysis of the primary endpoint will be performed using an observed case approach (completers) by using valid assessments of antibody assay without imputation of missing data.

In addition, the primary analysis will be repeated using data from Cohort 6 participants and any participants in Cohorts 1 – 5 who received an mRNA booster during the study. Missing post-vaccination antibody assay will be handled according to the NRI approach.

For each supplemental analysis the number and percentage of responders will be presented by cohort group and overall. The 2-sided 95% CI for the proportion of responders will be calculated using an exact method (Clopper and Pearson, 1934).

## 2.6 Analysis supporting secondary objectives

Analysis of endpoints supporting secondary objectives is described in Sections 2.6.1 – 2.6.6 below.

### 2.6.1 Secondary endpoint(s)

Secondary endpoints include the following:

- Achieving immune response (responder) as defined by a positive SARS-CoV-2 qualitative IgG antibody assay at other assessment time points ≥14 days after full course (2 doses) vaccination (yes/no).
- Immune conversion (yes/no) which is defined as:
  - Pre-vaccination absence of SARS-CoV-2 qualitative IgG antibody with post-vaccination positive SARS-CoV-2 qualitative IgG antibody assay at any assessment time point ≥14 days after full course (2 doses) vaccination (yes/no); or
  - Pre-vaccination serum presence of SARS-CoV-2 quantitative IG antibody with post-vaccination ≥4-fold increase in SARS-CoV-2 quantitative antibody titer as determined by dilution assay at any assessment time point ≥14 days after full course (2 doses) vaccination (yes/no); or
  - Initial negative SARS-CoV-2 nucleocapsid antibody at Visit 2 (Day 1) with post-vaccination positive SARS-CoV-2 qualitative IgG antibody assay at any post-Visit 2 (Day 1) assessment time point ≥14 days after full course (2 doses) vaccination (yes/no) (Applicable to Cohorts 4 and 5.)

### 2.6.2 Statistical hypothesis, model, and method of analysis

The number and percentage of responders will be presented by cohort group (and overall) and time point (where appropriate). The 2-sided 95% CI for the proportion of responders will be calculated using an exact method (Clopper and Pearson, 1934). Participants achieving immune conversion will be summarized in a similar fashion.

### 2.6.3 Handling of intercurrent events

NRI approach will be applied to missing antibody assay regardless of intercurrent events.

### 2.6.4 Handling of missing values not related to intercurrent event

NRI approach will be applied to missing antibody assay.

### 2.6.5 Sensitivity analyses

There are no sensitivity analyses of secondary endpoints planned for this study.

### 2.6.6 Supplementary analyses

A supplemental analysis of each secondary endpoint will be performed using an observed case approach (completers) by using valid assessments of antibody assay without imputation of missing data.

In addition, analysis of secondary endpoints will be repeated using data from Cohort 6 participants and any participants in Cohorts 1 – 5 who received an mRNA booster during the study. Missing antibody assay will be handled according to the NRI approach.

The number and percentage of responders will be presented by cohort group and overall. The 2-sided 95% CI for the proportion of responders will be calculated using an exact method (Clopper and Pearson, 1934). Participants achieving immune conversion will be summarized in a similar fashion.

## 2.7 Safety analyses

### 2.7.1 Adverse events (AEs)

Adverse events (AEs) will be coded using MedDRA terminology. The MedDRA version used for reporting the study will be indicated in a footnote on relevant outputs.

For reporting purposes, summary tables for AEs will summarize only on-study events, which started or worsened on or after the date of Visit 1 (Screening).

The number and percentage of participants with on-study AEs will be summarized in the following ways:

- by cohort group, primary SOC and PT
- by cohort group, primary SOC, PT and maximum severity
- by cohort group and PT

Separate summaries will be provided for MS treatment-related AEs (MS treatment includes ofatumumab, interferon and glatiramer acetate), serious adverse events (SAEs) and other significant AEs leading to discontinuation.

If a participant reported more than one AE with the same PT, the AE with the greatest severity/grade will be presented. A participant with multiple AEs within a primary SOC is only counted once towards the total of the primary SOC.

#### 2.7.1.1 Adverse events of special interest / grouping of AEs

There are no AEs of special interest defined for this study.

### 2.7.2 Deaths

All deaths will be listed.

### 2.7.3 Laboratory data

Values and changes from pre-vaccination (where appropriate) in laboratory assessments will be summarized by cohort group and time point with descriptive statistics.

### 2.7.4 Other safety data

#### 2.7.4.1 MS relapse

The number and percentage of participants with 0, 1, 2 or ≥3 confirmed relapses during the study will be presented by cohort group. In addition, the number and percentage of participants with at least 1 confirmed relapse during the study will be presented by cohort group.

## 2.8 Pharmacokinetic endpoints

There are no pharmacokinetic (PK) endpoints defined for this study.

## 2.9 PD and PK/PD analyses

There are no pharmacodynamic (PD) or PK/PD analyses planned for this study.

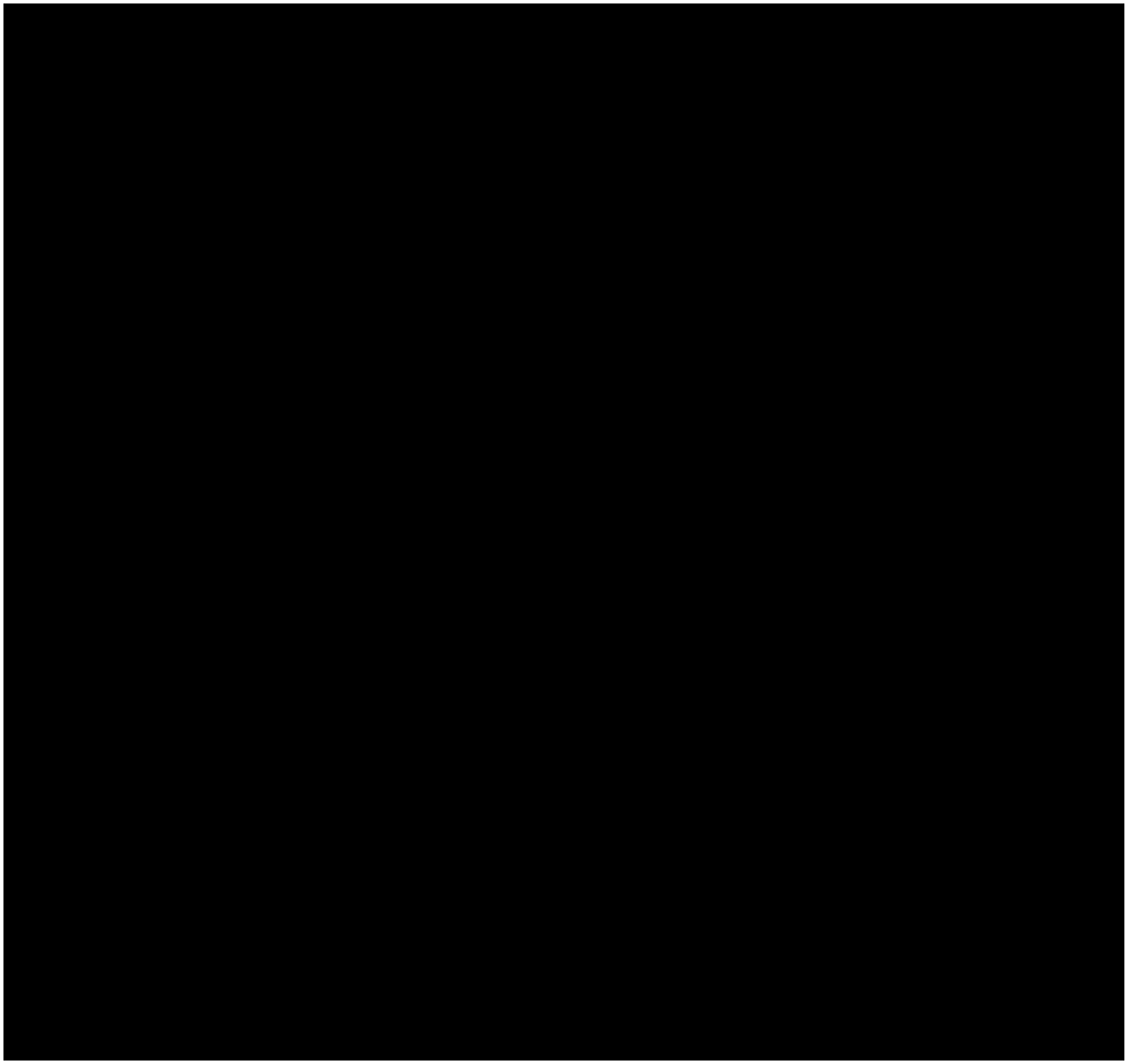
## 2.10 Patient-reported outcomes

There are no patient-reported outcome endpoints defined for this study.

## 2.11 Biomarkers

There are no biomarker endpoints defined for this study.

[redacted]



## 2.13 Interim analysis

For the purpose of early dissemination of results, an IA will be performed once Cohorts 2 and 4 in combination have ≥10 participants enrolled that have had their serum drawn ≥14 days after full course (2 doses) vaccination.

A second IA will be performed once Cohort 6 has ≥10 participants.

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

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

- Disposition
- Demographics

- Baseline characteristics
- Immune response-related variables
- AEs, SAEs and AEs leading to study discontinuation
- Deaths

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

# 3 Sample size calculation

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% CI) 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 participants will be enrolled in Cohorts 3 and 5. In Cohort 6, 22 participants will be enrolled.

# 4 Change to protocol specified analyses

There are no changes to protocol specified analyses.

# 5 Appendix

## 5.1 Imputation rules

### 5.1.1 Study drug

There will be no imputation rules for study drug detailed for this study.

### 5.1.2 AE date imputation

The following algorithm will be used to estimate AE start dates for which only partial information is known. Note that "index date" refers to the date of Visit 1 (Screening).

**Missing day and month:**

- If the year is the same as the year of the index date, then the day and month of the index date will be assigned to the missing fields.
- If the year is prior to the year of the index date, then December 31 will be assigned to the missing fields.
- If the year is after the year of the index date, then January 1 will be assigned to the missing fields.

**Missing month only:**

- Treat day as missing and replace both month and day according to the above procedure.

**Missing day only:**

- If the month and year are the same as the year and month of the index date, then the index date will be assigned to the missing day.
- If the month and year are before the year and month of the index date, then the last day of the month will be assigned to the missing day.
- If the month and year are after the year and month of the index date, then the first day of the month will be assigned to the missing day.

If the imputed start date result is after the stop date (and the stop date is complete), the imputed start date will be reset to the stop date.

The following algorithm will be used to estimate AE stop dates for which only partial information is known.

**Missing year:**

- Date left missing.

**Missing month:**

- Impute 'December'.

**Missing day:**

- Impute 'last date of that month'.

### 5.1.3 Concomitant medication date imputation

The following algorithm will be used to estimate medication start dates for which only partial information is known. Note that "index date" refers to the date of Visit 1 (Screening).

**Missing day and month:**

- If the year is the same as the year of the index date, then the day and month of the index date will be assigned to the missing fields.
- If the year is prior to the year of the index date, then December 31 will be assigned to the missing fields.
- If the year is after the year of the index date, then January 1 will be assigned to the missing fields.

**Missing month only:**

- Treat day as missing and replace both month and day according to the above procedure.

**Missing day only:**

- If the month and year are the same as the year and month of the index date, then the index date will be assigned to the missing day.
- If the month and year are before the year and month of the index date, then the last day of the month will be assigned to the missing day.

- If the month and year are after the year and month of the index date, then the first day of the month will be assigned to the missing day.

If the imputed start date result is after the stop date (and the stop date is complete), the imputed start date will be reset to the stop date.

The following algorithm will be used to estimate medication stop dates for which only partial information is known.

**Missing year:**

- Date left missing.

**Missing month:**

- Impute 'December'.

**Missing day:**

- Impute 'last date of that month'.

#### 5.1.3.1 Prior therapies date imputation

Same as for medications above.

#### 5.1.3.2 Post therapies date imputation

Same as for medications above.

#### 5.1.3.3 Other imputations

#### Non-response imputation

NRI assumes that a participant is a non-responder if there are no valid immune response assessments after receiving both doses of the vaccine. Hence, for missing data the primary endpoint of achieving immune response as defined by a positive SARS-CoV-2 qualitative IgG antibody assay ≥14 days after full course (2 doses) vaccination (yes/no) will be imputed as "No".

#### MS relapse date imputation

The following algorithm will be used to estimate relapse start dates for which only partial information is known. Note that "index date" refers to the date of Visit 1 (Screening).

**Missing day only:**

- The first day of the month will be assigned to the missing day. In case the relapse start date occurs in the same month as the index date, the relapse start date will be imputed as the index date.

The following algorithm will be used to estimate relapse stop dates for which only partial information is known.

**Missing day only:**

- The last day of the month will be assigned to the missing day or truncated to have a maximum duration of 90 days.

## 5.2 AEs coding/grading

Adverse events will be coded using the MedDRA terminology. The MedDRA version used for reporting the study will be indicated in a footnote on relevant outputs.

## 5.3 Laboratory parameters derivations

There are no laboratory parameter derivations for this study.

## 5.4 Statistical models

### 5.4.1 Analysis supporting primary objective(s)

There is no hypothesis testing planned for the analysis supporting the primary objective of this study.

### 5.4.2 Analysis supporting secondary objective(s)

There is no hypothesis testing planned for the analyses supporting the secondary objectives of this study.

## 5.5 Rule of exclusion criteria of analysis sets

There are no rules of exclusion criteria of analysis sets for this study.

# 6 Reference

Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934; 26:404-413.