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OMB157G/Ofatumumab

COMB157GUS12 / NCT04667117

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

Statistical Analysis Plan (SAP)

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List of abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
BMI	Body Mass Index
CDBL	Clinical Database Lock
CRF	Case Report Form
CRO	Contract Research Organization
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DMS	Document Management System
EMA	European Medicines Agency
EOS	End of Study
FAS	Full Analysis Set
GPS	Global Statistical and Programming Environment
HI	Hemagluttination Inhibition
IA	Interim Analyses
MS	Multiple Sclerosis
MedDRA	Medical Dictionary for Drug Regulatory Affairs
NRI	Non-responder Imputation
PK	Pharmacokinetics
PRO	Patient-reported Outcomes
PT	Preferred Term
QIV	Quadrivalent inactivated influenza vaccine
RAP	Reporting & Analysis Process
RMS	Relapsing Multiple Sclerosis
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
sc	Subcutaneous
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Events
TFLs	Tables, Figures, Listings
iDMT	Injectable Disease Modifying Therapy

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 00 (release date 10 November 2020) for the clinical trial COMB157GUS12 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 and IA plans.

1.1 Study design

This is a three-cohort, multicenter prospective study in up to 66 participants with relapsing multiple sclerosis (RMS).

Cohorts 1 and 2 will include up to 44 participants who will either begin treatment with ofatumumab (Cohort 1) or who are already treated with commercial ofatumumab (Cohort 2). Participants in **Cohort 1** will receive the inactivated influenza vaccine two weeks prior to starting treatment with ofatumumab, while participants in **Cohort 2** will receive the inactivated influenza vaccine after at least 4 weeks of commercial ofatumumab treatment.

Cohort 3 will include the remaining 22 participants who are already treated with commercial injectable disease modifying therapy (iDMT) and who will receive the inactivated influenza vaccine after at least 4 weeks of commercial iDMT treatment.

The study consists of three periods:

- Screening Period (1 week);
- Investigational Period (4 weeks);
- Optional, 6-month open-label Extension Period

Screening Period

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

Investigational Period

All participants will receive the inactivated influenza vaccine before or during the Week 0 visit, but within 9 calendar days after their screening visit.

- Participants in **Cohort 1**: Loading doses of ofatumumab will be administered at Week 2, 3 and 4.
- Participants in **Cohort 2** will continue taking their prescribed ofatumumab as per their dosing schedule throughout the investigational period.
- Participants in **Cohort 3** will continue administration of their prescribed iDMT as per their dosing schedule throughout the investigational period.

Optional, 6-month open-label Extension Period

- Participants in **Cohort 1** will administer their first dose of ofatumumab in the open-label Extension Period at Week 6. Thereinafter, they will continue monthly dosing until the final dose at Week 26. Novartis will supply ofatumumab to participants in Cohort 1 for the Extension Period.
- Participants in **Cohort 2** will continue to administer ofatumumab monthly until the final dose at Week 28. Novartis will supply ofatumumab to participants in Cohort 2 for the open-label Extension Period.
- Participants in **Cohort 3** will not have the option to enter this Extension Period.

Study completion

For participants completing the trial, the total duration of the trial will be a minimum of 5 weeks. This accounts for the mandatory 1 week Screening Period and 4 week Investigational Period starting at Week 0. Upon completing the Investigational Period, participants in Cohorts 1 and 2 will have the option to enter a 6 month open-label Extension Period, where they will continue monthly dosing of ofatumumab. Participants in cohort 3 will not enter the Extension Period.

Cohort 1 and 2 participants who prematurely discontinue the study while in the Investigational Period should be scheduled for the End of Study (EOS1) visit within 7 days. Cohort 3 participants who prematurely discontinue the study while in the Investigational Period should be scheduled for the End of Study (EOS) visit within 7 days. Cohort 1 and 2 participants who prematurely discontinue the study while in the Extension Period should be scheduled for the final visit of the extension period (EOS2) within 7 days. All EOS assessments should be performed except study drug administration.

Study design schematics for Cohorts 1, 2 and 3 are shown in Figure 1-1, Figure 1-2 and Figure 1-3 and respectively.

Primary analysis time point

The primary analysis time point will be Week 4.

Interim analysis

An interim analysis (IA) will be performed after all participants complete the Investigational Period or discontinue the Investigational Period prematurely, or on/around March 29, 2021, whichever comes first.

Figure 1-1 Study Design (Cohort 1)

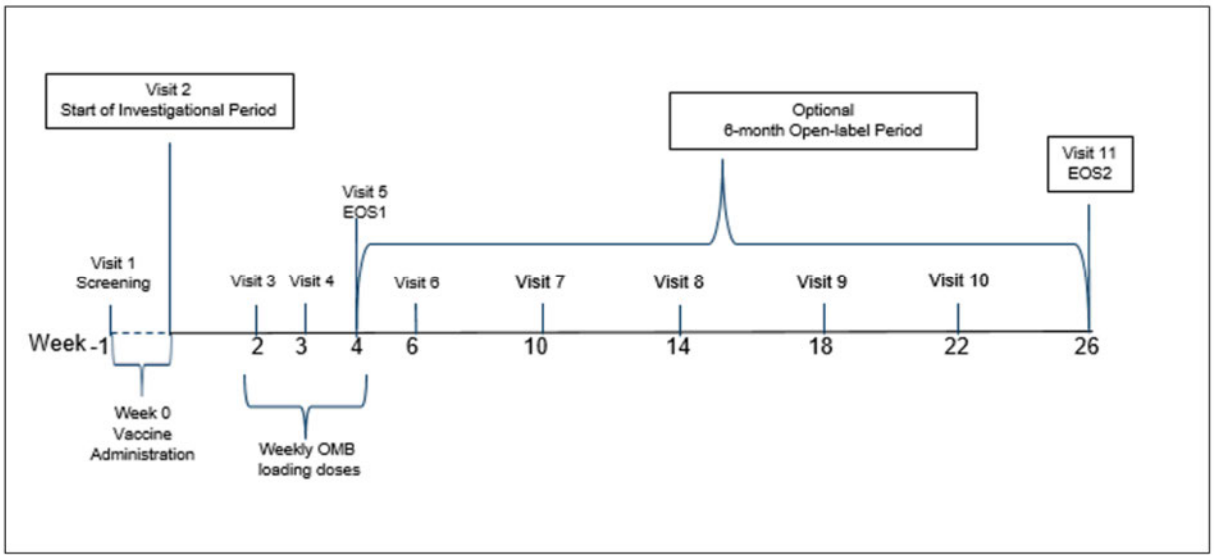


Figure 1-2 Study Design (Cohort 2)

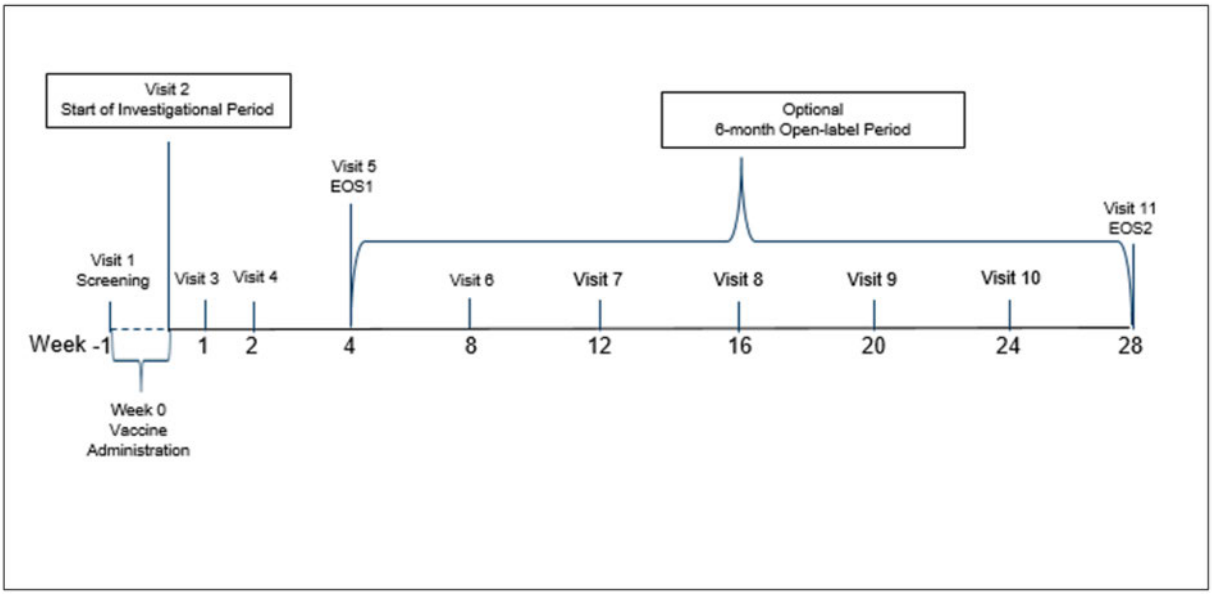
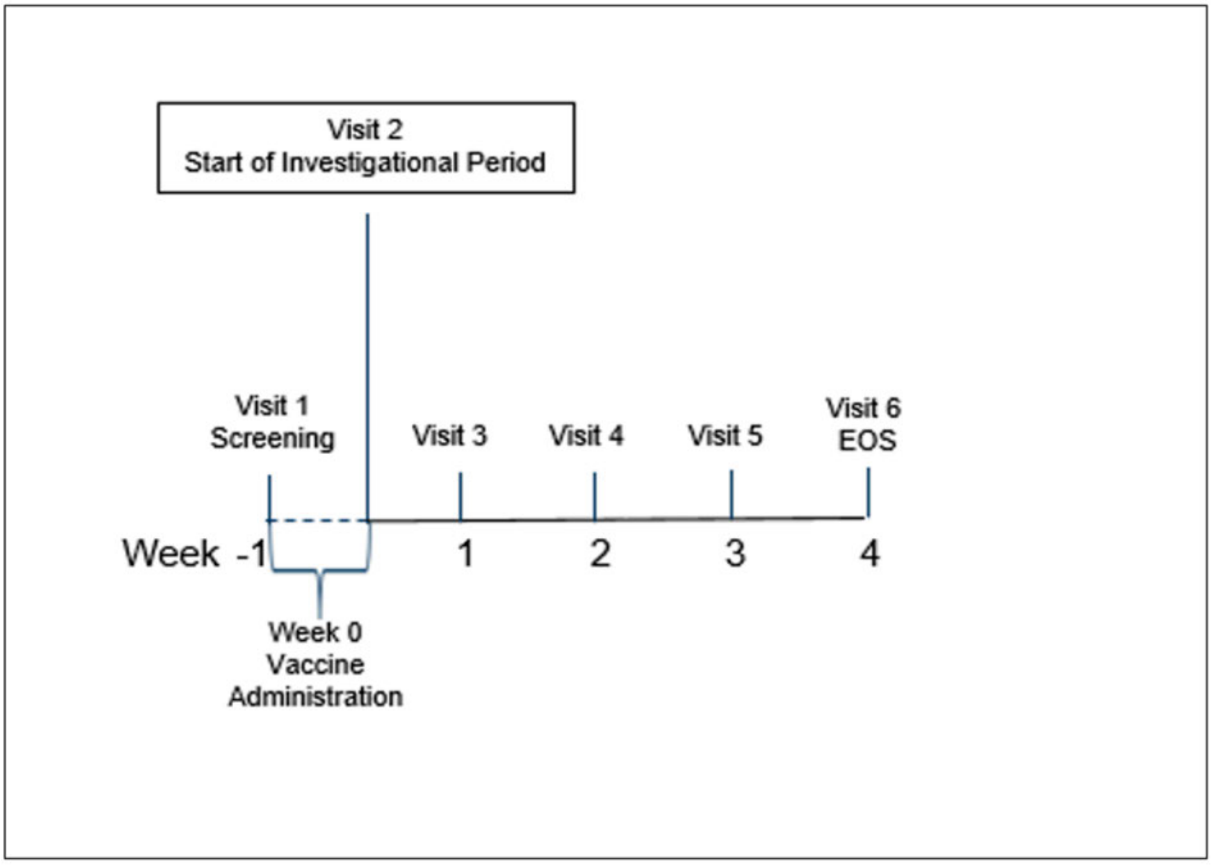


Figure 1-3 Study Design (Cohort 3)



1.2 Study objectives and endpoints

Study objectives and associated endpoints are shown in Table 1-1.

Table 1-1 Study objectives and endpoints

Objective(s)	Endpoint(s)
Primary objectives(s) • To characterize those achieving seroprotection after receiving the 2020-2021 seasonal quadrivalent influenza vaccine in participants treated with ofatumumab 20 mg sc once every 4 weeks	**Endpoint(s) for primary objective(s)** • Achieving seroprotection as defined by a post-vaccination antibody titer ≥40 at Week 4 (yes/no)
Secondary objective(s) • To characterize those achieving seroconversion after receiving the 2020-2021 seasonal quadrivalent influenza vaccine in participants treated with ofatumumab 20 mg sc once every 4 weeks • Safety	**Endpoint(s) for secondary objective(s)** • Achieving seroconversion at Week 4 as defined by either: a. a ≥4-fold increase in HI titers after vaccination (in participants with pre-vaccination HI titers ≥10) or

Objective(s)	Endpoint(s)
	b. post-vaccination HI titers ≥40 (in participants with pre-vaccination HI titers <10) (yes/no) • Change in HI titers • AEs, SAEs, AEs leading to discontinuation

2 Statistical methods

2.1 Data analysis general information

The statistical analysis outlined in this SAP will be performed by Novartis or a designated Contract Research Organization (CRO), using SAS® version 9.4 or higher and stored in the Novartis Global Programming and Statistical Environment (GPS).

For continuous variables, summary statistics will include number of participants (n), mean, standard deviation, minimum, maximum, median and 25th and 75th percentiles (optional). For categorical variables, frequency counts and percentages will be reported.

Unless otherwise stated, all data summaries will be presented by cohort and on all participants in the respective analysis set.

The CSR analysis cut-off date will be the EOS1/EOS visit for participants who do not continue to the Extension Period, or the EOS2 visit for participants who continue into the Extension Period. All data collected prior to this date will be used for analysis.

All data (collected or derived) will be listed appropriately.

2.1.1 General definitions

Treatment of interest

The investigational treatment or treatment of interest will refer to a once-off administration of the 2020-2021 quadrivalent inactivated influenza vaccine (QIV) via 0.5-mL single-dose prefilled syringe to participants in all three cohorts.

Additional treatment

- Ofatumumab provided by Novartis in an auto-injector containing 20 mg sc ofatumumab (20 mg/0.4ml) for subcutaneous administration to participants in Cohort 1 in the Investigational and optional Extension Periods and to participants in Cohort 2 entering the optional open-label extension period as per the assessment schedule.
- Ofatumumab as commercially prescribed in the course of medical practice for participants in **Cohort 2** for the Investigational Period.
- Any MS iDMT as commercially prescribed in the course of medical practice for participants in **Cohort 3**.

Study day

The day of Week 0 visit is defined as Study Day 1 or Day 1. All other study days will be labeled relative to Day 1.

For event dates **on or after Day 1**, study day for a particular event date is calculated as:

(Date of event − date Week 0 visit) + 1

I.e. Day 2, Day 3, etc., will be one day, two days, etc., after Day 1, respectively.

For dates **before Day 1**, study day for an event date is calculated as:

(Date of event − date Week 0 visit)

Duration of an event will be calculated as (event end date − event start date + 1).

The descriptor "Day 0" will not be used.

Screening, baseline and post-baseline definitions

Screening refers to any procedures (e.g., checking inclusion and exclusion criteria) performed prior to vaccination. 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 screening assessment.

Baseline is the last assessment (including unscheduled visits) obtained before the date of vaccination. No visit windows will be needed for the identification of baseline assessment. All assessments obtained after the date of vaccination are considered as **post-baseline** unless otherwise specified.

Nominal visits

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

Change from baseline

Change from baseline will be calculated as:

(Post-baseline value − baseline value)

Change from baseline will only be calculated and summarized for participants with both baseline and post-baseline values.

2.2 Analysis sets

Safety set

The Safety Set (SAF) comprises all participants who have received the 2020-2021 inactivated influenza vaccine.

Unless stated otherwise, 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

Patient disposition will be summarized for the following study periods: screening, treatment, extension treatment and treatment assigned.

Patient disposition for each period will be summarized for all participants who entered that period. Participants who have entered any study period but have discontinued from the study will be listed as appropriate along with the primary reason for discontinuation.

The number and percentage of screening failures and the reason for screening 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 tabulated.

2.3.2 Demographics

The following demographic variables will summarized descriptively by cohort:

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 Pacific Islander, American Indian or Alaska Native, Multiple)

2.3.3 Medical history

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

Medical histories will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The latest version of which will be used for the reporting activity.

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

2.4.1 Study treatment / compliance

Participants in all cohorts are expected to receive a single dose of the 2020-2021 quadrivalent inactivated influenza vaccine.

Participants in **Cohort 1** are expected to take a total of 3 ofatumumab 20 mg injections at Week 2, 3, 4 and once every 4 weeks starting at Week 6 if they chose to continue to the 6-month Extension Period.

Participants in **Cohort 2** are expected to continue on their commercially prescribed ofatumumab during the Investigational Period and take study supplied ofatumumab 20 mg injections once every 4 weeks thereafter if they chose to continue to the 6-month Extension Period.

Participants in **Cohort 3** are expected to continue on their commercially prescribed iDMT throughout the Investigational Period.

The number of injections of either ofatumumab 20 mg, ofatumumab as prescribed or iDMT as prescribed actually taken will be summarized descriptively by cohort and period (i.e. Investigational Period and Extension Period).

The summaries by cohort will be performed by the actual treatment received (as follows).

Treatment sequence:

- QIV + OMB 20mg
- QIV + OMB as prescribed
- QIV + iDMT as prescribed

Study duration

Study duration will be summarized by cohort and duration category (i.e. ≥1 week, ≥2 weeks, ≥3 weeks, ≥4 weeks, ≥8 weeks, ≥12 weeks, ≥24 weeks).

2.4.1.1 Visit windows

Visit windows will be used for the data that is summarized by visit; they are based on the study evaluation schedule and comprise a set of days around the nominal visit day. For any assessment, there are the protocol defined scheduled visits around which visit windows are created to cover the complete range of days within the study.

The visit windows for Cohorts 1, 2 and 3 are shown in Table 2-2, Table 2-2 and Table 2-3 respectively. These windows apply to measurements taken at every visit. For assessments collected less often different visit windows will be applied as detailed below.

When visit windows are used, all 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 of a participant may fall in a particular visit window (either

scheduled or unscheduled). Statistical approaches to handle multiple assessments in a given visit window are specified below.

As a rule, the following steps are followed to determine the cut-offs for post-baseline time windows:

- Transform all scheduled assessment time points into study days, assuming 1 month is equal to 30.4375 days. Middle points of scheduled assessments are determined.
- The time window associated with the previous assessment ends prior to the middle point; the time 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 time window of first post-baseline assessment starts with Study Day 2, unless otherwise indicated.
- For parameters, which are not collected at every visit, visit windows will be combined. For example, if a parameter is measured at Week 2 and Week 4 only, Week 2 visit window will extend from Week 2 to Week 4 (combining Week 2 and Week 4 visit windows).

Table 2-1 Visit windows for Cohort 1

Analysis visit	Time point	Scheduled visit day (study days)	Visit window (study days)
Visit 2/Baseline	Week 0	1	-7 to 1*
Visit 3	Week 2	14	2 to 17
Visit 4	Week 3	21	18 to 24
Visit 5/EOS1	Week 4	28	25 to 35
Visit 6	Week 6	42	36 to 56
Visit 7	Week 10	70	57 to 84
Visit 8	Week 14	98	85 to 112
Visit 9	Week 18	126	113 to 140
Visit 10	Week 22	154	141 to 168
Visit 11/EOS2	Week 26	182	169 to 196

*Baseline measurement before vaccine administration for safety assessments.

Table 2-2 Visit windows for Cohort 2

Analysis visit	Time point	Scheduled visit day (study days)	Visit window (study days)
Visit 2/Baseline	Week 0	1	-7 to 1*
Visit 3	Week 1	7	2 to 10
Visit 4	Week 2	14	11 to 21
Visit 5/EOS1	Week 4	28	22 to 42
Visit 6	Week 8	56	43 to 70
Visit 7	Week 12	84	71 to 98
Visit 8	Week 16	112	99 to 126
Visit 9	Week 20	140	127 to 154
Visit 10	Week 24	168	155 to 182
Visit 11/EOS2	Week 28	196	183 to 210

* Baseline measurement before vaccine administration for safety assessments.

Table 2-3 Visit windows for Cohort 3

Analysis visit	Time point	Scheduled visit day (study days)	Visit windows (study days)
Visit 2/Baseline	Week 0	1	-7 to 1*
Visit 3	Week 1	7	2 to 10
Visit 4	Week 2	14	11 to 17
Visit 5	Week 3	21	18 to 24
Visit 6/EOS	Week 4	28	25 to 31

* Baseline measurement before vaccine administration for safety assessments.

Multiple assessments

When there are *multiple assessments* in a particular visit window, the following rules are applied to select one value "representing" the participant in summary statistics in a visit window

- **Baseline:** The last non-missing measurement made prior to or on the date of administration of vaccine administration (the reference start date / Day 1). Only date part is considered if just one assessment on Day 1. If there are multiple assessments on Day 1, the following rules will apply:
  a. If assessment time exists,
     - select the last available measurement prior to reference start date/time considering time;
     - If no measurement prior to reference start date/time considering time, select the earliest measurement post reference start date/time considering time.

  b. If assessment time does not exist, select the available measurement from the lowest CRF visit number.
- **Post-baseline:** The measurement closest to the target day will be used. In the event two measurements are taken equally apart (e.g., 1 day before target date and 1 day after), the earlier one will be used. Cases where the same parameter is recorded more than once on the same date will be handled as follows:
  a. If time of completion exists, the earliest measurement will be used;
  b. If time does not exist, the measurement from the lowest CRF visit number will be used.

For post-baseline visit windows, the following applies (unless otherwise specified):

- For *continuous variables*, the closest to the target study day is chosen (if two assessments have the same distance, than the earlier one will be chosen).
- For *categorical variables,* identifying notable abnormalities, the record with the worst result is selected. It is noted that in the analyses performed, the worst case is clearly defined.

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

2.4.2 Prior, concomitant and post therapies

Prior and concomitant medications will be summarized separately by cohort.

Medications will be classified as prior or concomitant as follows:

- Prior medications are defined as drugs taken and stopped prior to the Week 0 visit.
- Concomitant medications are defined as drugs taken at least once between Week 0 visit and the date of study completion (including those which were started prior to the Week 0 visit and continued into the Investigational Period).

Medications will be categorized into one (and only one) of above classes based on recorded or imputed start and end dates.

Medications will be presented in alphabetical order, by Anatomical Therapeutic Classification (ATC) codes and grouped by anatomical main group. Tables will show the overall number and percentage of participants receiving at least one treatment of a particular ATC code and at least one treatment in a particular anatomical main group.

2.5 Analysis of the primary objective

The primary objective of this study is to characterize those achieving seroprotection after receiving the 2020-2021 inactivated influenza vaccine in participants in all three cohorts. This will be achieved by estimating the seroprotection response rate.

A seroprotection responder is a participant achieving seroprotection as defined by a post-vaccination hemagluttination inhibition (HI) titer ≥40.

The seroprotection response rate is defined as the proportion of participants with seroprotection.

2.5.1 Primary endpoint

The primary endpoint variable is achieving seroprotection as defined by a post vaccination HI titer ≥40 (Yes/No) at Week 4.

The primary estimand is described by the following attributes:

- Treatment: 2020-2021 inactivated influenza vaccine in participants treated with ofatumumab 20 mg (Cohort 1), ofatumumab as commercially prescribed (Cohort 2) or iDMT as commercially prescribed (Cohort 3).
- Population: Relapsing MS participants subdivided into three cohorts as defined in Section 1.1
- Variable: Achieving seroprotection as defined by a post-vaccination HI titer ≥40 (Yes/No)
- Other intercurrent events: None
- Population-level summary: Proportion of participants who achieve seroprotection at Week 4

2.5.2 Statistical hypothesis, model, and method of analysis

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

2.5.3 Handling of missing values/censoring/discontinuations

Non-responder imputation (NRI) for missing data will be applied. NRI is a conservative imputation method for dichotomous variables. NRI assumes that a participant is a treatment

failure if they discontinue the study prematurely. Hence, for missing data the primary variable outcome will be imputed to "No". Please refer to Appendix Section 5.1.3.3.

2.5.4 Supportive analyses

No supportive analyses are planned.

2.6 Analysis of the key secondary objective

There is not key secondary objective for this study.

2.7 Analysis of secondary objective(s)

The secondary objective of this study is to characterize those achieving seroconversion after receiving the 2020-2021 inactivated influenza vaccine in participants in all three cohorts where seroconversion is defined as:

- a ≥4-fold increase in HI titers after vaccination (in participants with pre vaccination HI titers ≥10) **OR**
- post vaccination HI titers ≥40 (in participants with pre vaccination HI titers <10)

The seroconversion response rate is defined as the proportion of participants with seroconversion.

To meet European Medicines Agency (EMA) guidelines for cohort protection, at least one of the following criteria has to be met:

- Seroprotection rate is better than 70%;
- Seroconversion rate is higher than 40%;
- Mean geometric increase of post- to pre-vaccination HI titers ≥ 2.5.

2.7.1 Secondary endpoints

The secondary endpoint variable is achieving seroconversion as defined in Section 2.7 above (Yes/No) at Week 4.

2.7.2 Statistical hypothesis, model, and method of analysis

The number and percentage of responders will be presented. A 95% confidence interval for the proportion of responders will be calculated using an exact method. To assess the change in HI titers, geometric means will be calculated and summarized for pre- and post-vaccination HI titers.

2.7.3 Handling of missing values/censoring/discontinuations

Both NRI for missing data and observed data approaches will be applied. Result based on NRI will be used to meet the secondary endpoint. Other observed data approaches will be applied as sensitivity analyses.

2.8 Safety analyses

2.8.1 Adverse events (AEs)

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a participant or clinical investigation of a participant after providing written informed consent for participation in the study. That means that a participant can report AEs before having started study medication. For reporting purposes, the main focus will be on any adverse event which started on or after the Week 0 visit.

The number (and percentage) of participants with AEs will be summarized by cohort in the following ways:

- by primary SOC and PT
- by primary SOC, PT and maximum severity
- by Standardized MedDRA Query (SMQ) and PT

Separate summaries will be provided for:

- serious adverse events (SAEs)
- AEs leading study discontinuation

Separate summaries will be presented for data collected during the Extension Period.

The MedDRA version used for reporting the study will be described in a footnote. If a particular Missing CTCAE grade will not be imputed. If a participant reported more than one AE with the same PT, the AE with the greatest severity will be presented. A participant with multiple AEs within a primary SOC is only counted once towards the total of the primary SOC.

All AEs will be listed by cohort.

2.8.2 Deaths

If a meaningful number of cases of death is reported (i.e., 5 or more cases), deaths will be summarized. All deaths will be listed. Deaths occurring during the Extension Period will be flagged.

2.8.3 Laboratory data

For participants in Cohort 1 that do not have relevant laboratory test results in their medical history within 6 months prior to the Screening Visit, all laboratory data collected will be listed by participant and if normal ranges are available, abnormalities will be flagged.

2.8.4 Other safety data

2.8.4.1 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.

If a meaningful number of cases of MS relapse is reported (i.e., 5 or more cases), MS relapse during the study will be summarized by cohort. All occurrence of MS relapse will be listed. Incidence of MS relapse during the Extension Period will be flagged.

2.9 Pharmacokinetic endpoints

There are no pharmacokinetic endpoints planned for this study.

2.10 PD and PK/PD analyses

There are no PD and PK/PD analyses planned for this study.

2.11 Patient-reported outcomes

There are no patient-reported outcome analyses planned for this study.

2.12 Biomarkers

There are no biomarker analyses planned for this study.

2.13 Other analyses

No other analyses are planned for this study.

2.14 Interim analysis

For the purpose of earlier dissemination of results, an interim analysis will be performed after:

- all enrolled participants have completed the Investigational Period or discontinued the Investigational Period prematurely OR
- On/around March 29, 2021, whichever comes first.

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

3 Sample size calculation

Sample size calculations were based on the proportion of participants who responded to influenza vaccination.

The sample size of 20 participants per arm is selected based on budget and need for early availability of results. The sample size of 20 subjects will provide estimates with margin of error (half-width of a 95% confidence interval) of 20.1%, 19%, and 17.5% corresponding to response rates of 70%, 75%, and 80%, respectively. Adjusting for 10% drop-out, 22 subjects will be enrolled in each arm.

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 table explains the notation used in the logic matrix. Please note that missing start dates will not be imputed.

	Day	Month	Year
Partial Adverse Event Start Date	Not used	MON	YYYY
Treatment Start Date (TRTSTD)	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSIN	MON<TRTM	MON=TRTM	MON>TRTM
YYYY MISSIN	NC Uncertain	NC	NC	NC
YYYY < TRTY	(D) Before Treatment Start	(C)	(C)	(C)
YYYY = TRTY	(B) Uncertain	(C) Before Treatment	(A) Uncertain	(A) After Treatment
YYYY > TRTY	(E) After Treatment Start	(A) After Treatment	(A) After Treatment	(A) After Treatment

The following table is the legend to the logic matrix.

If AE end date is complete and AE end date < Treatment start date or AE end date is partial and AE imputed end date < Treatment start date, then AE start reference = min (informed consent date, earliest visit date from SV) Else if AE end date is partial, AE end date > = Treatment start date or AE is ongoing, then AE start reference = treatment start date.

Relationship	
Before AE start reference	Partial date indicates AE start date prior to AE start
After AE start reference	Partial date indicates AE start date after AE start

Uncertain	Partial date insufficient to determine relationship of AE start date to AE start
Imputation Calculation	
NC/Blank	No convention
(A)	MAX(01MONYYYY, AE start reference+1 day)
(B)	AE start reference+1
(C)	15MONYYYY
(D)	01JULYYYY
(E)	01JANYYYY
Complete date	No date imputation

Adverse Event End Date Imputation
Imputed date = date part of original date, if complete date
Imputed date = min (completion/discontinuation visit date, DEC 31, date of death), if month is missing
Imputed date = min (completion/discontinuation visit date, last day of the month, date of death), if day is missing

Imputed Date Flag
If year of the imputed date is not equal to YYYY then date flag = Y
else if month of the imputed date is not equal to MON then date flag = M
else if day of the imputed date is not equal to day of original date then date_flag = D
else date flag = null.

5.1.3 Concomitant medication date imputation

This algorithm is used when *event* is the partial start date of the concomitant medication. The following table explains the notation used in the logic matrix. Please note that missing start dates will not be imputed.

	Day	Month	Year
Partial CM Start Date	Not used	MON	YYYY
Treatment Start Date (TRTSDT)	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON<TRTM	MON=TRTM	MON>TRTM
YYYY MISSING	(C2) Uncertain	(C1) Uncertain	(C1) Uncertain	(C1) Uncertain
YYYY < TRTY	(D) Before Treatment Start	(A) Before Treatment Start	(A) Before Treatment Start	(A) Before Treatment Start

YYYY = TRTY	(C2) Uncertain	(A) Before Treatment Start	(C1) Uncertain	(B) After Treatment Start
YYYY > TRTY	(E) After Treatment Start	(B) After Treatment Start	(B) After Treatment Start	(B) After Treatment Start

The following table is the legend to the logic matrix.

Relationship	
Before Treatment Start	Partial date indicates CMD start date **prior** to Treatment Start Date
After Treatment Start	Partial date indicates CMD start date **after** Treatment Start Date
Uncertain	Partial date **insufficient to determine** relationship of CMD start date relative to Treatment Start Date
Imputation Calculation	
(A)	15MONYYYY
(B)	01MONYYYY
(C1 or C2)	IF relative reference start = before treatment start THEN TRTSDT-1 ELSE IF relative reference start = ‘ ’ THEN TRTSDT+1
(D)	01JULYYYY
(E)	01JANYYYY

Concomitant Medication End Date Imputation
If not ongoing then
Imputed date = date part of CMENDTC, if complete date
Imputed date = min(completion/discontinuation visit date, DEC 31), if month is missing. (C2, D, E)
Imputed date = min(completion/discontinuation visit date, last day of the Month), if day is missing. (A, B, C1)

Concomitant Medication Date Flag
If not a complete date then

Y – If year of the imputed date is not equal to YYYY else M – If month of the imputed date is not equal to MON else D.

5.1.3.1 Prior therapies date imputation

Same as above.

5.1.3.2 Post therapies date imputation

Same as above.

5.1.3.3 Other imputations

Non-responder imputation

Non-responder imputation (NRI) assumes that a participant is a treatment failure if they discontinue the study prematurely. Hence, for missing data the primary variable outcome of achieving seroprotection as defined by a post vaccination HI titer ≥40 (Yes/No) at Week 4 will be imputed to "No".

5.2 AEs coding/grading

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) The latest MedDRA version will be used and will be described in the footnote of relevant outputs.

5.3 Laboratory parameters derivations

Not applicable.

5.4 Statistical models

Primary analysis

There is no hypothesis testing planned for this study.

Key secondary analysis

There is no key secondary analysis planned for this study.

Rule of exclusion criteria of analysis sets

Deviation ID	Description of deviation	Exclusion in analyses
INCL01A	No informed consent obtained or missing.	Exclude from the SAF.
INCL05	Not Planning to receive a 2020-2021 inactivated influenza vaccine	Exclude from the SAF
INCL06A	Not Planning to start treatment with ofatumumab for Cohort 1	Exclude from the SAF
INCL06B	Not already on commercially prescribed ofatumumab for Cohort 2 with minimum 4 weeks	Exclude from the SAF
INCL07	Currently not be receiving iDMT for Cohort 3	Exclude from the SAF

Analysis set	PD ID that cause participants to be excluded	Non-PD criteria that cause participants to be excluded
SAF	INCL01A	Influenza vaccine not taken
SAF	INCL05	Influenza vaccine not taken

Analysis set	PD ID that cause participants to be excluded	Non-PD criteria that cause participants to be excluded
SAF	INCL06A	Study treatment not taken
SAF	INCL06B	Study treatment not taken
SAF	INCL07	Study treatment not taken

6 Reference

Polman, C.H., Reingold, S.C., Banwell, B., Clanet, M., Cohen, J.A., Filippi, M., Fujihara, K., Havrdova, E., Hutchinson, M., Kappos, L., Lublin, F.D., Montalban, X., O'Connor, P., Sandberg‐Wollheim, M., Thompson, A.J., Waubant, E., Weinshenker, B. and Wolinsky, J.S. (2011), Diagnostic criteria for multiple sclerosis: 2010 Revisions to the McDonald criteria. Ann Neurol., 69: 292-302.