NOVARTIS

Clinical Development

OMB157/ Ofatumumab/Kesimpta®

COMB157G2402 / NCT05199571

A 12-month, open-label, prospective, multicenter, interventional, single-arm study assessing the efficacy and safety of ofatumumab 20mg s.c. injection in relapsing multiple sclerosis (RMS) patients in China

Statistical Analysis Plan (SAP)

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26-Feb-2025	Prior to DB lock	Creation of Amendment 1	• Remove analyses on new or enlarged T2 lesions during onset period; • Remove exposure adjusted incidence rates for TEAEs and serious TEAEs; • [redacted] • Revise lab parameters in Table 5-3 that are not applicable in this study	• Section 2.6.2 Statistical hypothesis, model, and method of analysis • Section 2.7.1 Adverse events (AEs), Section 5.4.3 Exposure adjusted incidence rate for TEAEs removed • [redacted] • Section 5.3.3 CTCAE grades for laboratory parameters

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List of abbreviations

[redacted]	[redacted]
AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ARR	Annualized relapse rate
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DMT	Disease modifying therapy
eCRS	Electronic Case Retrieval Sheet
EDSS	Expanded Disability Status Scale
EOS	End of Study
FAS	Full Analysis Set
FS	Functional System
Gd	Gadolinium
IA	Interim Analyses
IgG	Immunoglobulin G
IgM	Immunoglobulin M
KM	Kaplan-Meier
LDD	Last dose date
LLN	Lower limit of normal
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MRI	Magnetic Resonance Imaging
MS	Multiple sclerosis
NB	Negative binomial
NMPA	National Medical Products Administration
PD	Pharmacodynamic(s)
PDS	Programming datasets specifications
PK	Pharmacokinetics
PT	Preferred term
RAP	Reporting & Analysis Process
RMS	Relapsing MS
SAE	Serious AE
SAF	Safety Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SCR	Screened subjects set
SOC	System Organ Class
TBL	Total Bilirubin
TEAE	Treatment emergent AE
TFLs	Tables, Figures, Listings

ULN	Upper Limit of Normal
WHO	World Health Organization

1 Introduction

The purpose of this Statistical Analysis Plan (SAP) is to describe the implementation of the statistical analysis planned in the protocol for study COMB157G2402.

There will be one report resulting from this SAP: the clinical study report (CSR) of the G2402 study. This report will be generated once and referred to as final CSR. The final CSR will be completed after the final database lock.

This document is consistent with the current study protocols (version 00 original protocol).

1.1 Study design

This is a 12-month, open-label, prospective, multi-center, single-arm, interventional study to evaluate the efficacy and safety of ofatumumab (OMB157) in approximately 100 adult participants with RMS in China.

The study consists of three periods (see Figure 1-1): Screening, Treatment, and Post-treatment Follow-up.

Screening (up to 30 days):

After signing the informed consent, participants will enter the Screening period to determine eligibility according to the inclusion and exclusion criteria. The Investigator must ensure that participants meet all the inclusion and none of the exclusion criteria to be eligible for the study. If a participant is declared a screen failure, he/she may be re-screened and all assessments must be repeated, with the possible exception of the MRI (if the initial screening MRI was completed within the last 3 months). For details, refer to [Protocol Section 8.1].

Treatment (12 months):

During the Treatment period, all eligible participants will receive initial dosing with ofatumumab 20 mg s.c. injection at Baseline/Week 0 (BL/W0), W1 and W2, followed by subsequent monthly dosing starting at W4 (Month 1/M1; a study month is defined as 28 days). The first s.c. injection at W0 will be administered [redacted]

All participants will have an End of Study (EOS) visit at the end of the Treatment period, when a participant has reached the maximum of 12-month treatment, or at the time a participant prematurely discontinues study treatment. After study treatment discontinuation, participants may initiate alternative MS therapy according to local standard of care if clinically indicated (refer to [Protocol Section 9.3]).

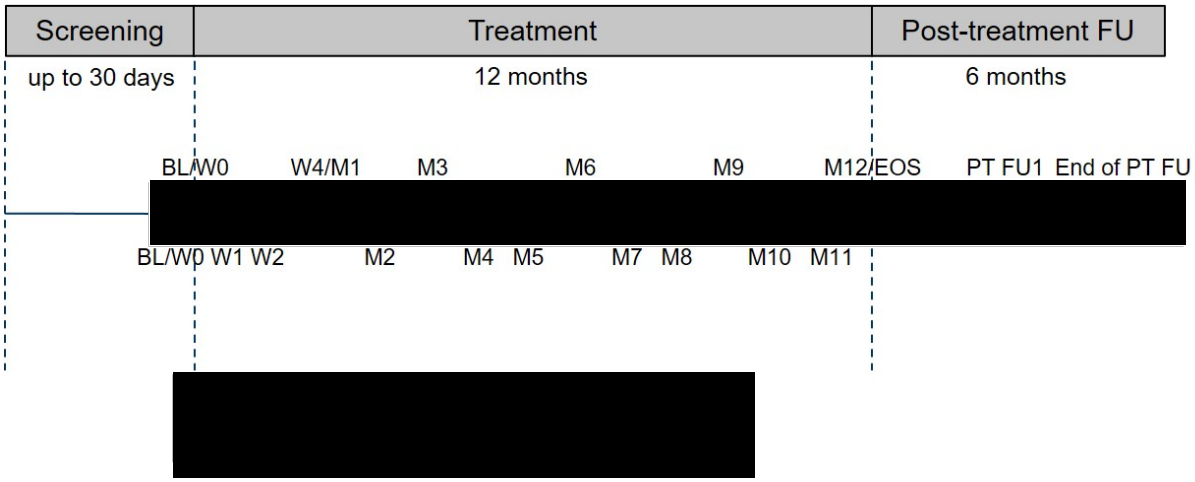
Post-treatment Follow-up (6 months):

All participants, except for completers who decide to continue with commercially available ofatumumab treatment, will be followed up in the Post-treatment Follow-up period for 6 months

after last study drug dose ([Protocol Table 8-2]). The Post-treatment Follow-up visits should be scheduled relative to the EOS visit and will occur at EOS+3 months and EOS+6 months (End of Post-treatment Follow-up). If a participant prematurely discontinues from Post-treatment Follow-up, the End of Post-treatment Follow-up visit should be arranged as soon as possible. Investigators may continue to follow participants outside of this study at his/her discretion (for example, if participants have not repleted their B-cells at the end of Post-treatment Follow-up).

Throughout the study periods, participants may have unscheduled visits due to a suspected MS relapse, an acute illness of undetermined cause, for other reasons, or at the discretion of the Investigator (refer to [Protocol Section 8.3.1]).

Figure 1-1 Study Design



1.2 Study objectives, endpoints and estimands

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To evaluate the effect of ofatumumab 20 mg monthly s.c. on annualized relapse rate (ARR) in participants with RMS	• Annualized relapse rate (ARR, based on frequencies of confirmed relapses)
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the safety and tolerability of ofatumumab 20 mg monthly s.c. in participants with RMS	• Adverse events, including injection-related reactions; • Laboratory data and vital signs.
• To evaluate the effect of ofatumumab 20 mg monthly s.c. on MRI lesions in participants with RMS	• Number of Gd-enhancing T1 lesions per MRI scan ; • Number of new/enlarging T2 lesion per year (annualized T2 lesion rate); • Change in T2 lesion volume compared to baseline.
[redacted]	

[redacted]

1.2.1 Primary estimand(s)

Not applicable.

2 Statistical methods

2.1 Data analysis general information

The Novartis statistical and programming teams will conduct the CSR analysis as planned in this SAP, unless otherwise specified.

The Statistical Analysis System (SAS) 9.4 and/or R 3.6.1 or higher versions will be used.

Unless otherwise stated, summary tables/figures/listings will be on all subjects in the respective analysis sets. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviations, median, 25th and 75th percentiles (optional), minimum and maximum will be presented.

For efficacy analyses other than MRI related analysis, all available data until the end of the Treatment Period, i.e. excluding the data collected during the Post-treatment Follow-up period, will be considered and no other cut-offs will be applied. For MRI related analysis, all available data from scheduled scans will be included, i.e. also including the ones taken in Post-treatment Follow-up period for the prematurely discontinued participants.

For safety analyses, unless otherwise specified, only data up to and including the safety cut-off of 100 days after the last administration of study treatment will be considered. Therefore, observations obtained beyond safety cut-off will be excluded from such analyses. Nevertheless, all serious adverse events (SAE) and all deaths, regardless of the safety cut-off will be summarized.

2.1.1 General definitions

Below summarize some general definitions to be used in the rest of the document.

Table 2-1 General definitions

Study treatment/Study drug	The investigational drug (ofatumumab) will be referred as study treatment or study drug.
Date of first administration of study drug/first dose date	The first dose date of active study drug (ofatumumab) administration.
Date of last administration of study drug/last dose date	The last dose date of active study drug (ofatumumab) administration.

Study Day 1 or Day 1	The date of first administration of study drug/first dose date.
Study Day	All other study days will be labeled relative to Day 1. For events with dates on or after Day 1, study day for the event is calculated as (event start date – first dose date + 1). For events with dates before Day 1, study day for the event is calculated as (event start date – first dose date). Day 0 will not be used.
Duration of an event	Duration of an event is calculated as (event end date – event start date +1).
1 month	30 days; to be used in defining 3-month confirmed disability progression.
4 weeks	28 days; to be used in determining target days of scheduled visits. It is based on the scheduled injection frequency for ofatumumab (during the maintenance phase).
Day post-study drug discontinuation	Day post-study drug discontinuation for a particular event is calculated as (event start date – study drug discontinuation date).
Baseline	Baseline is the last assessment with non-missing value obtained prior to the first administration of study drug. No visit windows will be needed for the identification of baseline assessment. For pulse and blood pressure vital sign values, if 3 measurements were taken on the last visit prior to the first administration of study drug, then the baseline is the average of the non-missing values of them.
On-treatment period	For participants received ofatumumab, on-treatment period includes days from the first injection date until 30 days after the last injection date. The on-treatment definition applies to efficacy analyses and B-cell summaries only. For calculation of compliance to study drug administration, similar definition of on-treatment period will be used.
Safety cutoff (off-treatment)	The safety cutoff is defined as 100 days after the last dose administration of study drug (or EOS for participants continue with commercial ofatumumab immediately after EOS, or min (last dose of study medication + 100 days, date of switching to another DMT - 1) for participants who have such switch in the Post-treatment Follow-up period). Unless

	explicitly otherwise stated, only data up to and including the safety cut-off will be included in the analysis and data beyond this time point for a given subject will be excluded. The safety cutoff applies to safety analyses only.
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.
End of Study (EOS)	EOS, used in the context of individual participants, refers to EOS visit.
End of treatment period date	This date is the date of discontinuation/study phase completion as recorded in the Study disposition eCRF page.
Last assessment on drug	It is the last assessment with non-missing value taken before or on the date of last administration of study drug. No visit windows will be needed for the identification of the last assessment on drug evaluation.

2.1.2 Visit windows

2.1.2.1 Visit windows for treatment period

Visit-windows will be used for both efficacy and safety data summaries by visit. Visit windows define a time period "around" the targeted visit date as defined in the evaluation schedule of the clinical study protocol. Visit-windows are non-overlapping and defined without gaps between consecutive visit windows. The width of visit windows may vary over the course of the study period.

Baseline assessments are defined in Section 2.1.1 and do not require a visit window.

The purpose of visit windows is to analyze data based on the actual study days (rather than "nominal" visits). E.g., if a subject's Month 1 visit is delayed; it is possible that the Month 1 data be re-aligned to visit-window Month 2 and be summarized under Month 2.

- For **efficacy analyses** all nominal visits (i.e. excluding unscheduled visits) will be mapped into one of the defined visit-windows. Note: for the derivation of disability progression all visits (scheduled and unscheduled) need to be considered before the progression can be confirmed (see Section 2.12.1).

-For **safety analyses** all visits (scheduled and unscheduled) will be mapped to visit windows.

It is possible that more than one assessment of a subject fall into a particular visit-window. Section 2.1.2.3 deals with the statistical approaches to handle multiple visits in a given visit-window.

Tables displaying summary statistics "by visit" will also use the term *visit-window* as column header; this is to remind the reviewer that multiple assessments of a subject might be summarized. Below tables provide visit-windows definitions for applicable parameters.

[redacted]

Table 2-3 Visit-windows for MRI

Visit-window	Start day	Target Day	End day
Month 3	1	84	210
Month 12	211	336	462

Table 2-4 Visit-windows for routine laboratory values

Visit-window	Start day	Target Day	End day
Month 1	1	28	56
Month 3	57	84	126
Month 6	127	168	210
Month 9	211	252	294
Month 12	295	336	378
Month 15	379	420	462

Table 2-5 Visit-windows for vital signs*

Visit-window	Start day	Target Day	End day
Month 1	1	28	56
Month 3	57	84	126
Month 6	127	168	210
Month 9	211	252	294
Month 12	295	336	378
Month 15	379	420	462

*Data collected from Day 1 protocol scheduled visit will not be mapped to the visit windows due to different data collection on those visits.

Table 2-6 Visit-windows for B-cell counts

Visit-window	Start day	Target Day	End day
Month 1	1	28	56
Month 3	57	84	126

Month 6	127	168	252
Month 12	253	336	420

Table 2-7 Visit-windows for IgG and IgM

Visit-window	Start day	Target Day	End day
Month 6	1	168	252
Month 12	253	336	420

2.1.2.2 Visit windows after study drug discontinuation

For summaries of data collected after study drug discontinuation, data from both Treatment period and Post-treatment Follow-up period will be considered. All reporting will be done based on visit windows defined relative to the last administration of study drug.

The visit window definitions are provided in Table 2-8 where the Start day and End day are relative to the date of last administration of study drug. For the "Last assessment on drug", the last assessment with non-missing value taken before or on the date of last administration of study drug will be summarized (no visit window applies). For the "Month 3 after LDD (last dose date)" visit-window, assessments taken at least 1 day after but no more than 126 days after the date of last administration of study drug will be considered. LDD stands for last dose date and will be footnoted in applicable output(s).

Table 2-8 Visit-windows after study drug discontinuation

Visit-window	Start day	Target Day	End day
Last assessment on drug	NA	NA	NA (see above or Section 2.1.1)
Month 3 after LDD	2	84	126
Month 6 after LDD	127	168	210
Month 9 after LDD	211	252	294
Month 12 after LDD	295	336	378
Month 15 after LDD	379	420	462

2.1.2.3 Multiple assessments within visit windows

It is possible that multiple assessments of a subject fall into the same visit-window (e.g. due to unscheduled visits). All results (scheduled and unscheduled) will be displayed in listings, but only one value (observed or derived) will be selected for summary statistics by visit-window. If multiple unscheduled visits within visit window are allocated to the same missed scheduled visit:

For **quantitative variables**, the unscheduled assessment closest to the target day will be selected. If more than one assessment is at the same distance to the target day, the later one will be selected. For tables displaying the worst case scenario, such as notable abnormalities, all assessments within a visit window will be used to identify the worst (e.g. the maximum or the

minimum depending on parameter). Where applicable it will be defined for each parameter what the worst case is.

For **qualitative variables**, the worst record is selected; it is noted that in the relevant data subsection, worst case is always well defined.

Note that "Last assessment on study drug" is the last observation while the subject is on study drug. Therefore, the above multiple assessment rules do not apply.

2.2 Analysis sets

The Full Analysis Set (FAS) comprises all participants who have signed the Informed Consent and who have received at least one dose of study treatment. The FAS will be used for the summary of demography and baseline characteristics as well as for all efficacy analyses.

The Safety Set (SAF) is identical to FAS in this study. The Safety Set will be used for all safety analyses.

The screened subjects (SCR) set comprises all subjects who have signed the Informed Consent and were screened.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

The number and percentage of subjects who were screened but did not continue into the Treatment Period will be presented, along with the reason for discontinuation being "Screen Failure". Data collected on the Disposition CRF page will be used to summarize this information. The summary will be on the SCR set.

The number and percentage of subjects who completed the study (i.e. the Treatment Period) or prematurely discontinued the study prior to the end of the treatment period will be presented, along with the primary reason for discontinuation. Data collected on the Study disposition CRF page will be used to summarize this information. The summary will be on the FAS. Subjects who prematurely discontinue the study will also be listed along with the reason for discontinuation. Similar summary will also be provided for the Post-treatment Follow-up period based on the FAS and data collected on the Post treatment follow-up disposition CRF.

Protocol deviations will be summarized by deviation categories for the FAS. In addition, protocol deviations that led to exclusion from the analysis set will be listed.

2.3.2 Demographics and other baseline characteristics

2.3.2.1 Background and demographic characteristics

All analyses in this section will be presented on FAS.

Background characteristics include subject demographic characteristics (sex, race and ethnicity collected on the Demography CRF), age at screening, height, body weight and BMI at baseline.

Age, baseline height, body weight and derived BMI will be presented. These variables will be summarized for the FAS using frequency distributions (for categorical variables) and descriptive statistics of mean, standard deviation, minimum, median and maximum (for continuous variables).

2.3.2.2 MS baseline disease characteristics

All analyses in this section will be presented on FAS.

MS baseline characteristics, MS disease history and MS medication history will be summarized for the FAS.

MS baseline characteristics include baseline EDSS and key MRI parameters (e.g., number of Gd-enhancing T1 lesions and T2 lesion volume).

MS disease history includes duration of MS since diagnosis (years), duration of MS since first symptom (years), number of relapses in the last 12 months prior to screening, number of relapses in the 12 to 24 months prior to screening, and time since onset of most recent relapse (months) prior to screening.

Duration of MS since diagnosis (years) will be derived as [(first dose date − MS diagnosis start date + 1) / 365.25]. Duration of MS since first symptom (years) will be derived as [(first dose date − first MS symptom date + 1) / 365.25]. Time since onset of most recent relapse (months) will be derived as [(first dose date − most recent relapse onset date + 1) / (365.25 / 12)]. In these calculations, partial dates (if any) will be imputed according to the rules specified in Section 5.1.4.1.

MS medication history of previous disease-modifying drugs (coded by World Health Organization (WHO) drug dictionary) will be summarized by preferred term (PT). The number and proportion of treatment-naïve subjects (i.e. subjects who have not been treated with any disease- modifying drug before study enrollment) will also be presented.

2.3.2.3 Medical history

Medical history will be summarized on the FAS. Any condition entered on the Medical History CRF will be coded using the Medical Dictionary for Drug Regulatory Affairs (MedDRA) dictionary. The medical history will be summarized by primary system organ class (SOC) and preferred term.

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

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

2.4.1 Study treatment / compliance

The summary of exposure and time-at-risk will be based on the SAF.

Duration of exposure to study drug expressed in days is defined as the number of days spent on study treatment. Intermediate treatment interruptions will be subtracted from drug exposure, i.e. the duration of exposure to study treatment (in days) will be calculated as (last injection date – first injection date + 31 – Σ [$(j+1)^{th}$ injection date – j^{th} injection date -31]), where j and j+1 refer to consecutive injections with injection dates more than 31 days apart.

Exposure to investigational study drug will be summarized with number and percentage of subjects by time category, and with summary statistics of the number of patient years of exposure.

Duration of exposure to study treatment will be summarized descriptively by duration category (i.e. ≥ 1 month, ≥ 3 months, ≥ 6 months, ≥ 9 months, ≥ 12 months). Descriptive statistics of duration in days will also be provided. The number of patient years is calculated as the sum of the duration of exposure for all subjects in the group.

Time at risk is the censoring time used for participants who did not experience the event of interest. For participants who have experienced the event of interest, the actual date of the SAE, or AE onset will be used.

- **Time at risk for AE** is defined as the number of days spent in the study, from first to last administration of study drug, plus the safety data cut-off of 100 days (or until EOS for participants continue with commercial ofatumumab immediately after EOS, or until last dose of study medication plus 100 days or one day before switching to another DMT, whichever comes earlier, for participants who have such switch in the PT FU). Time at risk for AE will be used for tables reporting AEs (including both SAE and non-SAE).
- **Time at risk for SAE** is defined as the number of days spent in the study from the day of first administration of study drug to the end of Post-treatment Follow-up period if the participant does not continue with commercial ofatumumab immediately after EOS. Time at risk for SAE will be used only for tables reporting SAEs.

Time at risk for AE and time at risk for SAE will be summarized in a similar way to duration of exposure to study drug.

Compliance to the study treatment administration schedule will be calculated as duration of exposure to study treatment in (days) / duration of on-treatment period (as defined in Table 2-1) (in days) × 100%. This rule means that compliance will be measured during the time interval the subject took study treatment, i.e. premature discontinuation from study treatment will not be considered non-compliance. Compliance to study treatment administration will be summarized descriptively on the SAF. In addition, compliance will be summarized with cumulative number and percentage of subjects in each compliance category (i.e. ≥ 20%, ≥ 30%, ≥ 40%, ≥ 50%, ≥ 60%, ≥ 70%, ≥ 80%, ≥ 90%, ≥ 95%, ≥ 98%, = 100%).

2.4.2 Prior, concomitant and post therapies

Analyses described in this section will be performed on the SAF.

2.4.2.1 Prior and Concomitant medication

Records on the Concomitant Medications CRF page will be coded using the WHO drug dictionary. All medications will be classified as prior, concomitant or post study treatment discontinuation medication as follows:

- Prior medications are defined as drugs taken and stopped prior to first dose of study medication.
- Concomitant medications are defined as drugs taken at least once between the first and last dose of study medication (including those which were started prior to first dose and continued into the treatment period).
- Post-study treatment discontinuation medications are defined as drugs started after the discontinuation of study medication.

Medications will be categorized into one (and only one) of the above classes based on recorded or imputed start and end dates. When incomplete or missing, dates will be imputed according to Novartis standards (details will be given in programming datasets specifications (PDS) document). If both the start date and the end date are completely missing and medication has not been collected on the "Previous MS Disease Modifying Treatment" page, the medication will be classified into concomitant medication category.

Medications in each of these three categories will be summarized separately, Anatomical Therapeutic Chemical (ATC) code and preferred term. ATC level 1 and level 3 (e.g. M [Musculo-skeletal system], M01A [anti-inflammatory and anti-rheumatic products, non-steroids], etc.) will be used.

Data collected from the Previous MS disease modifying treatment pages will not be included in this summary.

2.4.2.2 Surgical and medical procedures

Records on the Prior or Concomitant non-drug therapies/procedures CRF page will be coded using the MedDRA dictionary. All procedures will be classified as prior, concomitant or post-study treatment discontinuation procedure, in the same way as done for concomitant medications. Surgical and medical procedures in each of these three categories will be summarized separately by system organ class and preferred term (and/or listed, if appropriate).

Imputation rules for start and end dates will be the same as for the concomitant medications.

2.4.2.3 Injection related premedication

Injection related premedication will be identified by subcategory "Injection related premedication" in concomitant medication data set. Injection related premedication will also be summarized separately for each injection up to injection 5 and cumulatively for injections after injection 5 (i.e., injections 6 to last injection) as well as cumulatively for all injections.

For injection 1 summary, the injection related premedication with either start date or end date on the same day as the first injection date will be included and summarized for each of the three protocol specified types and for each combination of the specified types (type 1+ type 2, type 1+ type 3, type 2+ type 3, type 1+ type 2+ type 3). The three protocol specified types are steroids (type 1), antihistamines (type 2), and antipyretics/analgesics (type 3). The steroids (type 1) will be identified by category "Steroid". The antihistamines (type 2) will be identified by ATC level 3 "antihistamines for systemic use". The antipyretics/analgesics (type 3) will be identified by ATC level 3 "other analgesics and antipyretics" and "anti-inflammatory and anti-rheumatic products, non-steroids". In summaries for each combination of the specified types, the number and proportion of participants who took both or all 3 types of injection related premedication at specified injection will be provided.

Rest injection specific summaries or cumulatively summaries will be reported similarly.

2.4.2.4 Previous MS disease modifying treatment

MS medication history of previous disease-modifying drugs (coded by WHO drug dictionary) will be summarized by preferred term (PT) and treatment group. The number and proportion of treatment-naïve participants (i.e., participants who have not been treated with any disease-modifying drug before first dose of ofatumumab) will also be presented.

2.5 Analysis supporting primary objective(s)

All analyses for primary objective will be conducted using the FAS.

2.5.1 Primary endpoint(s)

The primary endpoint is the annualized relapse rate (ARR), which is defined as the average number of confirmed MS relapses in a year (i.e. the total number of confirmed relapses, divided by the total days in the study, multiplied by 365.25). In the primary analysis, the ARR is estimated in a negative binomial (NB) model by using individual confirmed relapse count as the response variable, with time in study as an offset variable.

Two variables are required for the calculation of the ARR (excluding covariates):

- The cumulative number of confirmed MS relapses by subject is the response variable in the negative binomial model. All confirmed relapses with a start date on or after the date of first administration of study drug and prior to or on the end of treatment period date will be included in the analysis. Additional details are provided in Section 5.1.4.
    - The definition of a confirmed MS relapse is one accompanied by a clinically relevant change in the EDSS assessment, i.e. an increase of at least 0.5 points on the EDSS (total) score, or an increase of at least 1 point on at least two Functional scores (FSs), or an increase of at least 2 points on at least one FS, excluding changes involving bowel/bladder or cerebral FS, compared to the last EDSS assessment taken in the absence of (confirmed or unconfirmed) relapse and prior to the current relapse. EDSS obtained on the date as indicated on the Summary of MS Relapse eCRF page will be used. If such EDSS assessment is missing or not meeting the criteria to confirm the relapse, all other EDSS assessments taken

within 30 days from the relapse start date (i.e., EDSS assessment date – relapse start date <=30) and before the relapse end date (EDSS assessment date < relapse end date) will be checked. If at least one of such available EDSS assessments meets the criteria, the relapse is a confirmed relapse. Otherwise, the relapse is considered an unconfirmed relapse.

- The time in study by subject will be used as an offset variable to adjust for the various length subjects have been observed (due to premature study discontinuation) and at-risk of a confirmed MS relapse in the study. Time in study for ARR will be calculated as (end of treatment period date – first dose date+1)/365.25.

2.5.2 Statistical hypothesis, model, and method of analysis

In the primary analysis, the ARR will be estimated by a negative binomial regression model with log-link function, the cumulative number of confirmed MS relapses per subject as the response variable, number of relapses in previous year, baseline EDSS, baseline number of T1 Gd-enhancing lesions and baseline age as continuous covariates. Natural log of time on study in years will be used as the offset variable to account for the varying lengths of subjects' time in the study. The adjusted ARR (i.e., model-based estimate adjusted for covariates) and the corresponding 95% confidence interval will be obtained.

In case of non-convergence, continuous covariates may be removed from the regression model in the order of: baseline EDSS, number of relapses in the previous year, baseline age.

2.5.3 Handling of missing values

For participants who withdraw early from the study, the number of relapses up to the study discontinuation will be used for the primary analysis. No imputation will be applied to the incomplete study duration.

The primary negative binomial regression model with an offset for the time in study adjusts for missing information (drop-out) under the assumption of non-informative drop-out, information is missing at random, and constant relapse rate over time.

2.5.4 Supportive analysis

The primary analysis will be repeated based on all reported MS relapses (confirmed and unconfirmed) for FAS population.

ARR time-based and ARR participant-based will be provided for confirmed relapses and then for all relapses (confirmed and unconfirmed). ARRs using a "time-based approach" are calculated by taking the total number of relapses observed for all subjects divided by the total number of days in study of all subjects and multiplied by 365.25 days. "Participant-based approach" is calculated in the way where individual ARRs are computed and summarized over all subjects.

Listings of relapses along with their confirmation status (confirmed or unconfirmed) will be presented.

2.6 Analysis supporting secondary objectives

All analyses for secondary efficacy objectives will be conducted using the FAS.

For MRI related analysis, all available data from scheduled scans will be included, i.e. also including the ones taken in Post-treatment Follow-up period for the prematurely discontinued participants.

2.6.1 Secondary endpoint(s)

Secondary efficacy endpoints include:

- To estimate the number of Gd-enhancing T1 lesions per scan, below variables will be derived:
    - The total number of Gd-enhancing T1 lesions will be derived by taking the sum of number of Gd-enhancing T1 lesions from all scheduled MRI scan with a non-missing value. Any Gd-enhanced T1 data obtained less than 30 days after the termination of steroid therapy which is used to treat MS relapses will not be included in analysis of Gd-enhancing T1 lesion related endpoint.
    - The number of MRI scans will be derived by counting the number of scheduled MRI scans with non-missing values for the number of Gd-enhancing T1 lesions (i.e., the number of scans contributed to the derivation of the total number of Gd-enhancing T1 lesions above). Scans obtained less than 30 days after the termination of steroid therapy which is used to treat MS relapses will not be included.
- To estimate annualized rate of new or enlarged T2 lesions, below variables will be derived:
    - The total number of new or enlarged T2 lesions will be derived by taking the number of new or enlarged T2 lesions from last available scheduled MRI scans (relative to the baseline scan) with a non-missing value.
    - The time (in years) from screening scan will be calculated as (date of last scheduled MRI scan with a non-missing value for the number of new or enlarging T2 lesions – date of screening scan +1)/365.25.
- Total T2 lesion volume. Change and % change from baseline will only be defined for subjects with both baseline and post-baseline values and will be calculated as:

  change from baseline = post-baseline value – baseline value;

  % change from baseline = change from baseline / baseline value*100.

2.6.2 Statistical hypothesis, model, and method of analysis

Methods of analyses for efficacy endpoints defined in Section 2.6.1 are described below.

- The number of Gd-enhancing T1 lesions per scan will be estimated by a negative binomial regression model with log-link function, the total number of Gd-enhancing T1 lesions during (per subject) as the response variable. Natural log of the number of MRI scans will be used as the offset. The model will include baseline age and number of Gd-enhancing T1 lesions at baseline as continuous covariates. The estimated number of Gd-enhancing T1 lesions per scan will be obtained together with the corresponding 95% confidence interval.

  In case of non-convergence, continuous covariates may be removed from the regression model in the order of number of Gd-enhancing T1 lesions at baseline and baseline age.

  Supportive analyses: descriptive summary statistics (mean, median, standard deviation, min, max) for the number of Gd-enhancing T1 lesions per scan will be provided by visit. Number and percentage of subjects free of Gd-enhancing T1 lesions will also be provided.

- The annualized rate of new or enlarged T2 lesions will be estimated by a negative binomial regression model with log-link function, the total number of new or enlarged T2 lesions (relative to baseline scan, per subject) as the response variable. Natural log of time from screening scan in years will be used as the offset. The model will include baseline age and baseline volume of T2 lesions as continuous covariates. The estimated number of new or enlarged T2 lesions will be obtained together with the corresponding 95% confidence interval.

  In case of non-convergence, continuous covariates may be removed from the regression model in the order of baseline volume of T2 lesions and baseline age.

  Supportive analyses: descriptive summary statistics (mean, median, standard deviation, min, max) for the number of new or enlarged T2 lesions will be provided by visit. Number and percentage of subjects free of new or enlarged T2 lesions will also be provided.

  Above analyses will also be repeated to assess new or enlarged T2 lesions after onset period (EOS scan relative to Month 3 scan).

  Note: new or enlarged T2 lesions after onset period (EOS scan relative to Month 3 scan) will be derived as the new or enlarged T2 lesions at EOS scan (relative to baseline scan) subtracting that at Month 3 scan (relative to baseline scan). If a negative value is obtained, then 0 will be used. i.e.

$$neT2_{EOS\ rel\ M3} = \max(neT2_{EOS\ rel\ BL} - neT2_{M3\ rel\ BL}, 0)$$

- Descriptive summary statistics (mean, median, standard deviation, min, max) will be provided by visit for the change and % change in total volume of T2 lesion.

2.6.3 Handling of missing values

As a general rule, missing data will not be imputed in any secondary endpoint analyses.

2.6.4 Supportive analyses

See supportive analyses defined in Section 2.6.2.

2.7 Safety analyses

All safety analyses will be conducted using the SAF. The safety cutoff is defined as 100 days after the last dose administration of study drug (or EOS for participants continue with commercial ofatumumab immediately after EOS, or min(last dose of study medication + 100 days, date of switching to another DMT - 1) for participants who have such switch in the Post-treatment Follow-up period). Unless explicitly otherwise stated, only data up to and including the safety cut-off will be included in the analysis and data beyond this time point for a given subject will be excluded from the safety analysis.

The assessment of safety will be primarily based on the frequency of adverse events (including death and non-fatal serious adverse events). Additional safety assessments include laboratory tests and vital sign measures. Clinically significant findings in these additional safety assessments and other will be reported as adverse events and analyzed as such.

2.7.1 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 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 treatment emergent adverse event (TEAE), defined as any adverse event which started on or after the day of first dose of study medication or events present prior to the start of treatment but increased in severity based on preferred term.

Except for serious TEAEs and death, only TEAEs up to and including safety cut-off will be included in the analyses. All serious TEAEs and death will be included, regardless of safety cut-off.

AEs will be reported by primary system organ class (SOC) and preferred term (PT) according to the most recent Medical Dictionary for Regulatory Activities (MedDRA). The MedDRA version used for reporting the study will be described in a footnote.

The number and percentage of participants reporting any TEAEs (referred to as incidence of any TEAEs later) will be summarized by primary SOC and PT. Separate summaries (if applicable) will be provided for serious TEAEs, drug related TEAEs, TEAEs leading to permanent discontinuation of study drug, TEAEs causing study drug interruption. Additionally, incidence of any TEAEs will also be summarized by SOC, PT, and maximum CTCAE grade. Missing CTCAE grade will not be imputed.

If a participant reported more than one adverse event within the same primary system organ class, the participant will be counted only once with the maximum CTCAE grade at the system organ class level, where applicable.

All AEs will be presented in listings.

2.7.1.1 Adverse events of special interest / grouping of AEs

Selected tables will be produced for Adverse Events of Special Interest (AESI) (i.e. risks), which will be defined in the electronic case retrieval sheet (eCRS) at the time of analysis implementation (i.e. study database lock). Specifically, incidence of TEAEs that fulfill the risk search terms as defined in eCRS will be summarized, risk name and preferred term. Similarly, separate summaries will be provided for serious TEAEs that fulfill the risk search terms as defined in the eCRS. Additionally, incidence of any TEAEs that fulfill the search terms as defined in the eCRS will also be summarized by risk name, preferred term and maximum severity.

2.7.1.1.1 Injection reaction related AEs

Incidence of injection site reaction AEs and injection systemic reaction AEs as collected in the relevant CRF pages will be reported as part of the AE summary tables as two preferred terms respectively. For summaries of injection systemic reaction AEs specified in this section, reaction/symptom start date and time will be compared with the injection date and time. Only reactions/symptoms within 24 hours after injections will be included (i.e., time to onset of reaction <= 24 hours). The time to onset of reaction will be derived as (reaction start date/time – injection date/time) and rounded to the closest integer in hours.

Symptoms listed in the injection site reaction or injection systemic reaction CRF pages will be summarized by providing the number and percentage of participants with each of the symptoms and pre-specified grouping of symptoms as well as overall. These summaries will be provided for each injection up to injection 5 and cumulatively for all injections.

For the injection site reaction, no grouping of symptoms will be specified. For the injection systemic reaction, symptoms will be grouped under 6 categories as defined below and the number and percentage of participants with at least one symptom reported under the category will be provided for each category.

- Skin/mucosal tissue symptoms: Rash, Urticaria, Pruritus general, Flushing
- Respiratory compromise: Dyspnea, Bronchospasm, Chest discomfort, Cough
- Related to change in vital signs: Hypotension, Hypertension, Dizziness, Tachycardia
- Gastrointestinal symptoms: Nausea, Vomiting, Abdominal pain, Diarrhea
- Musculoskeletal/connective tissue symptoms: Arthralgia, Myalgia, Back pain
- Other manifestations: Fever, Headache, Chills, Asthenia, Fatigue, and Other

A table of injection-related reactions reported separately for each injection up to a maximum injection 5 as well as overall for all injections by category of premedication (none, any steroid and non-steroid only) will be provided. A table with incidence rate of Injection-related reactions by maximum CTCAE grade for all injections as well as by injection (up to a maximum of injection 5) will also be given.

2.7.2 Deaths

Detailed listing for deaths will also be provided. All deaths as recorded in the final database (i.e. up to the final database lock) will be included.

2.7.3 Laboratory data

The summary of laboratory evaluations will be presented for two groups of laboratory tests: Hematology and Chemistry. On presenting summary statistics, laboratory data will be grouped and displayed in an alphabetical order within the Hematology and Chemistry groups.

Descriptive summary statistics (mean, median, standard deviation, Min and Max) of the change from baseline in the laboratory result to each study visit-window will be presented. Change from baseline will only be summarized for participants with both baseline and post baseline values and will be calculated as:

change from baseline = post baseline value – baseline value

In addition, shift tables will be provided for all parameters to compare a participant's baseline laboratory evaluation relative to the post-baseline values. For the shift tables, the grade level based on CTC grade (as defined by CTCAE as listed in Section 5.3.3) will be used to evaluate whether a particular laboratory test value was Grade 0, 1, 2, 3, or 4 relative to whether or not the baseline value was Grade 0, 1, 2, 3 or 4. These summaries will be presented by laboratory test.

The number and percentage of participants with new or worsening laboratory abnormalities based on CTC grade (as defined by CTCAE as listed in Section 5.3.3) in each visit-window and at any time post baseline will be presented. Participants with specific laboratory abnormalities (defined by CTC grade 3 and 4) will be listed.

Number of participants with newly occurring liver enzymes abnormalities will be summarized. Newly occurring liver enzymes abnormalities are defined in Section 5.3.2.

For the shift tables and abnormalities based on CTC grades tables, all applicable post-baseline values will be checked against the respective criteria and the rules for handling multiple laboratory assessments within visit windows will not be applied.

For continuous variables databased as <lower limit, these will be imputed as being half of the lower limit.

All above summaries include only data up to and including safety cut off.

2.7.3.1 Other special lab results

Non-routine laboratory data include pregnancy test results, B-cell counts, total IgG and total IgM. All data will be listed appropriately.

The B-cell counts, total IgG and total IgM will be summarized using descriptive statistics by visit-window.

In addition, number and percentage of participants with B-cells < the lower limit of normal (LLN) value (i.e. B-cell depleted) will be presented by visit-window. All B-cell summaries defined in this section will include data up to last dose date + 30.

Number and percentage of participants meeting the notable low level criteria in IgG or IgM at least once will be provided. A notably low IgG level is defined as a level that is 20% below the LLN and a notably low IgM level is defined as a level 10% below the LLN.

2.7.4 Other safety data

2.7.4.1 Vital signs

Vital sign measurements include sitting systolic and diastolic blood pressures, sitting pulse, body temperature, height and body weight.

Three sitting measurements of blood pressure (SBP and DBP) and pulse may be taken for some vital sign assessment of some subjects. For post-baseline assessments, if 3 measurements are collected then the blood pressure and pulse values will be the average of the non-missing values of them. If more than one blood pressure/pulse assessment (scheduled or unscheduled) exists in a particular visit-window (as defined in Section 2.1.2), derivation should follow the rules as defined in Section 2.1.2. Derivation of baselines for blood pressure and pulse are provided in Section 2.1.1.

Height will be collected at screening visit only and will be summarized in demographics.

Analyses of vital sign measurements (excluding data collected on Day 1 protocol scheduled visit) using descriptive summary statistics (mean, median, standard deviation, min, max) for the change from baseline for each post-baseline visit-window will be performed. These descriptive summaries will be presented by vital sign parameter. Change from baseline will only be summarized for participants with both baseline and post-baseline values and will be calculated as:

change from baseline = post-baseline value − baseline value

The number and percentage of participants with clinically notable vital signs will be presented. Clinical notable vital signs values are defined in the table below.

Table 2-9 Vital signs clinically notable values

Vital Sign	Notable criteria
Pulse (beats/min, bpm)	>120 bpm Or <50 bpm
Systolic Blood Pressure (mmHg)	≥160 mmHg Or <90 mmHg
Diastolic Blood Pressure (mmHg)	≥100 mmHg Or <50 mmHg
Temperature (°C)	>38.3 °C (>101 °F)
Body weight (kg)	≥7% from baseline weight

All above summaries include only data up to and including safety cut-off.

2.7.5 Safety evaluation after last administration of study treatment

The SAF will be used for analyses in this section.

Safety data collected after last administration of study treatment includes adverse events, vital signs, routine laboratory parameters, and laboratory assessments to measure total IgG, total IgM and B-cell repletion. No safety cutoff date will be applied in the analyses defined in this section. Safety data within the safety cutoff date but after last administration of study treatment will also be included. Only subjects who prematurely discontinue the study treatment will be included.

TEAEs beyond safety cutoff will be listed.

Spaghetti plots of time to B-cell repletion after study drug discontinuation will be presented with median value per timepoint overlaid.

In addition, subjects with notable lab abnormalities or clinically notable vital signs will be listed.

2.8 Pharmacokinetic endpoints

Not applicable.

2.9 PD and PK/PD analyses

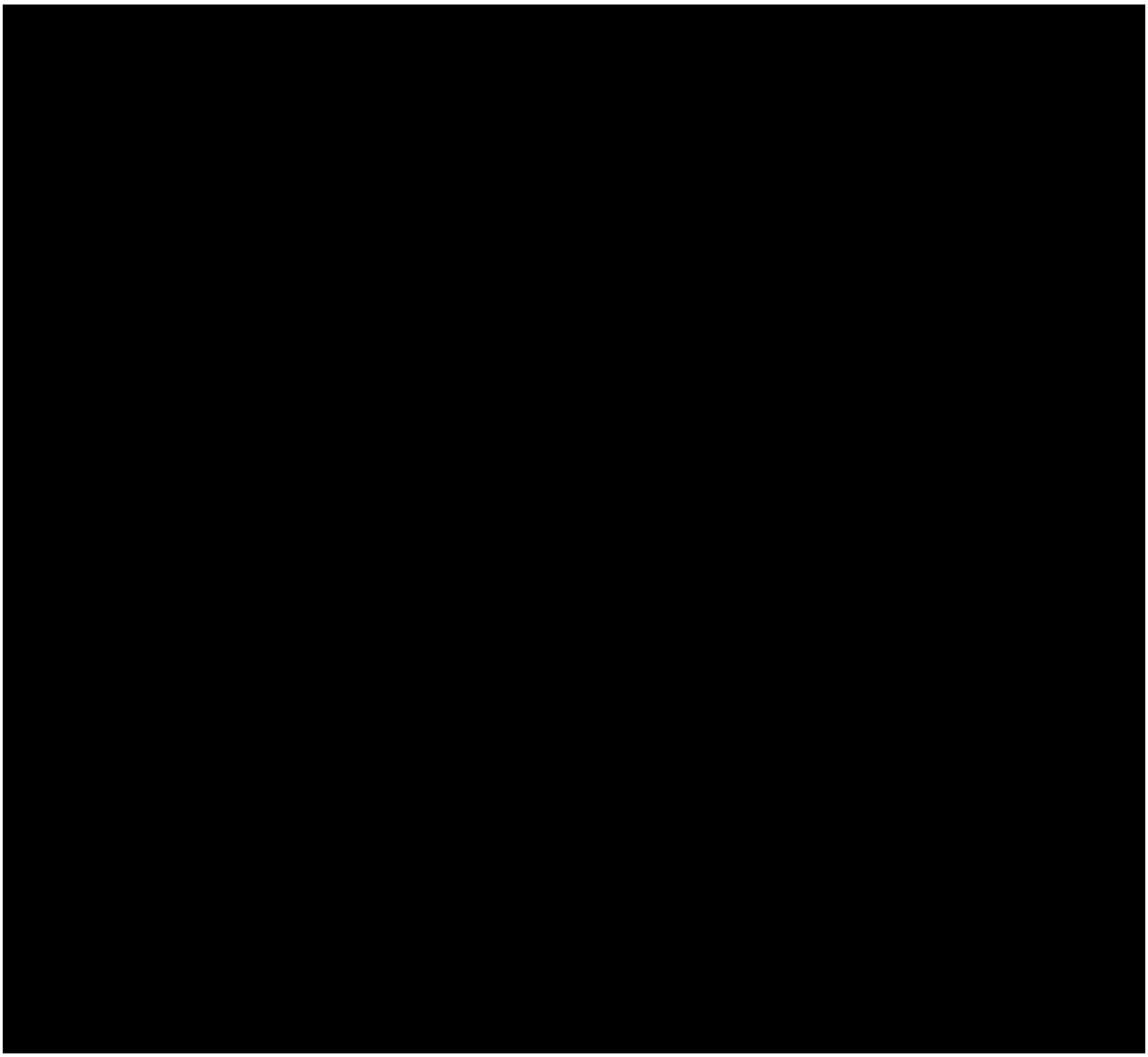
Not applicable.

2.10 Patient-reported outcomes

Not applicable.

2.11 Biomarkers

Descriptive summaries of IgM/IgG and B-cell counts will be provided as part of the safety analyses (see Section 2.7.3.1).



2.13 Interim analysis

Not applicable because no interim analysis will be conducted.

3 Sample size calculation

3.1 Primary endpoint(s)

The ARR of Chinese RMS participants treated with ofatumumab is assumed based on the pivotal studies, COMB157G2301 and COMB157G2302. Since the participants are treated up to 12 months in the current study, the cumulative ARR from Month 0 to Month 12 from the pivotal studies is adopted:

	Ofatumumab 20mg	Teriflunomide 14mg

Cumulative ARR from Month 0 to Month 12 in COMB157G2301 & COMB157G2302	0.145	0.307

Under the assumption of a negative binomial distribution (~ NB(μ, k)) for the ARR, where μ is the true ARR which we assume to be 0.15 based on the reference above, and k is the dispersion parameter which we assume to be 0.82 based on historical trial data in MS. For different sample sizes, the following can be calculated using normal approximation: the 95% lower and upper ranges of the estimated ARR (point estimate), and the probability of showing the ARR on ofatumumab is significantly lower than 0.30 (i.e. lower than the historical reference value for the ARR in participants treated with teriflunomide based on the COMB157G2301 & COMB157G2302 trial data)). Note that this probability is equivalent to the probability that the upper limit of 95% CI is lower than 0.3. The results are showed below.

μ (true ARR)	k	Sample size	95% lower range of estimated ARR	95% upper range of estimated ARR	Probability that the upper limit of 95% CI is lower than 0.30
0.15	0.82	60	0.05	0.25	80.8%
0.15	0.82	65	0.05	0.25	83.8%
0.15	0.82	70	0.05	0.25	86.4%
0.15	0.82	75	0.06	0.24	88.6%
0.15	0.82	80	0.06	0.24	90.5%
0.15	0.82	85	0.06	0.24	92.1%
0.15	0.82	90	0.07	0.23	93.4%

Based on the calculation, a sample with 85 participants will provide an estimated ARR in [0.06, 0.24] with 95% probability. In addition, with a probability of 92.1%, a sample with this size will also provide a 95% CI with upper limit lower than 0.30, i.e. it would be strongly suggestive of a higher efficacy of ofatumumab compared with the historical teriflunomide data. Therefore, a sample size of 85 completers is considered adequate. Allowing for a dropout rate of 15% (dropout rate was 10.3% in COMB157G2301 and 17.3% in COMB157G2302), the sample size for this study will be approximately 100 participants.

Sample size calculation was performed in nQuery 8, Version 8.4.1.0, Statistical Solutions Ltd.

4 Change to protocol specified analyses

Not applicable.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Missing or partial dates are not allowed in completing the Study treatment CRF pages. The end date of study drug will be the last injection date.

5.1.2 AE date imputation

Incomplete or missing start and end dates of AE records will be imputed according to Novartis standards (details will be given in programming data sets specifications (PDS) document).

5.1.3 Concomitant medication date imputation

Incomplete or missing start and end dates of concomitant medication records will be imputed according to Novartis standards (details will be given in programming data sets specifications (PDS) document).

5.1.3.1 Prior therapies date imputation

Same handling as for concomitant medications.

5.1.3.2 Post therapies date imputation

Same handling as for concomitant medications.

5.1.4 Other imputations

5.1.4.1 MS disease baseline characteristics

For the calculation of duration or time since relevant history events (MS disease baseline characteristics), partial dates will be imputed for the MS diagnosis start date, the first MS symptom date, and the most recent relapse onset date via below imputation rules:

- If the year is missing or impossible (e.g. 12-Jan-1911), then the date will be imputed as "missing".
- If the year is not missing and possible, but the month is impossible or missing (e.g. 17-XXX-2010), then the year will be kept and date will be imputed as July 1st (e.g. 1-July-2010).
- If the year and the month are not missing and possible, but the day is impossible or missing (e.g. 31-FEB-2009), then the year and month will be kept, and date will be imputed as 15th (e.g. 15-FEB-2009).
- The imputed dates should be prior to the screening visit date. That is, if imputed dates are on or after the screening visit date, the dates will be imputed to be one day before the screening visit date.
- To guarantee the first MS symptom date is earlier than the MS diagnosis start date, and most recent relapse onset date is not earlier than the first MS symptom date after the imputation. If, after imputation, MS diagnosis date is before first MS symptom date, then the imputed first MS symptom date will be set to MS diagnosis date; or if, after imputation, most recent relapse onset date is before the first MS symptom date, then the imputed relapsed onset date should be set to the first MS symptom date.

5.1.4.2 Relapse date imputation

Missing or partial dates are not expected for the start and end dates of relapses on the Summary of MS relapse CRF pages. In case partial dates (unknown day with month and year available) exist in the final database, the following rules will apply:

- The start date will be imputed as the first day of the month or the first dose date if it occurs in the same month as the first dose date.
- The end date will be imputed as the last day of the month or truncated to have a duration of maximally 90 days (whatever comes first).

5.1.4.3 Data handling for relapses within 30 days of onset of previous relapses or relapses with duration beyond 90 days

According to the protocol definition of MS relapses, the start date of a new relapse has to be at least 30 days after the start date of a previous relapse (i.e. start date of a new relapse – start date of a previous relapse ≥ 30). If a relapse is recorded with a start date < 30 days after the start date of a previous relapse, the below data manipulation will be done to combine them into a single relapse by creating a new relapse record with the following information:

- Start date: Take the earliest start date.
- End date: Take the latest end date. If one of the end dates is missing, set it to missing.
- Date of EDSS intended to confirm the relapse:
  - Take the date of EDSS by which the relapse can be confirmed.
  - If more than one EDSS assessments meet the above criterion, take the date of the EDSS from which the worst severity value is derived.
  - If no EDSS assessment meets the above criterion, take the earliest date of EDSS as captured on the Summary of MS Relapse CRF page.
- Severity: Take the value representing the worst case (severe > moderate > mild > missing) (as specified in Table 5-1)
- "Hospitalization?", "Steroid used?", "Recovery status": For each of these characteristics, take the value representing the worst case (yes > no for the first 2 questions; no > partial > complete recovery for the last question).

Table 5-1 Severity of MS relapses (Panitch et al 2002)

Mild relapse	Moderate relapse	Severe relapse
EDSS increase of 0.5 point	EDSS increase of 1 or 2 points	Exceeding moderate criteria
or	or	Or
1-point FS change in one to three systems	2-point FS change in one or two systems	Exceeding moderate criteria
	or	Or

	1-point change in four or more systems	Exceeding moderate criteria
Definition is based on the EDSS obtained to confirm the relapse as compared to the last EDSS (scheduled or unscheduled) taken in the absence of (confirmed or unconfirmed) relapse and prior to the current relapse. EDSS refers to total score; FS refers to functional score; all of the 7 functional scores are considered in this derivation.		

According to the protocol definition of MS relapses, the maximum duration of a relapse is furthermore limited to 90 days. If a relapse is recorded with a duration longer than 90 days, the end date will be truncated to have a duration of exactly 90 days. This applies also to the artificial records created by the above procedure. Missing end date of relapse is not allowed. In the rare cases that missing end date exists in the final database, it will be imputed so that the duration of relapse is exactly 90 days.

5.2 AEs coding/grading

AEs are coded using the Medical dictionary for regulatory activities (MedDRA) terminology. The latest MedDRA version will be used and will be described in the footnote of relevant outputs.

5.3 Laboratory parameters derivations

5.3.1 Creatinine clearance values

For each subject, the estimated creatinine clearance values (without collecting urine) will be calculated using the Cockcroft-Gault formula (as specified in Table 5-2). In these calculations, the body weight is the last measurement collected on or before the day when the subject takes the laboratory test and age should also be calculated based on the time when the subject takes the laboratory test.

If the creatinine value is collected in the unit *µmol/L* (SI unit), it will be converted to *mg/dL* in order to use the formulas. The conversion is via the equation below:

- mg/dL = 88.4 µmol/L (e.g. creatinine = 2.0 mg/dL = 176.8 µmol/L).

Table 5-2 Creatinine clearance calculation

Variable	Formula
Creatinine clearance [mL/min] using Cockcroft-Gault formula (Cockcroft and Gault 1976)	$= (140 - A) \times W \ / \ (72 \times C) \times G$ Where A is age [years] W is body weight [kg] C is the serum concentration of creatinine [mg/dL] G is a constant: G=1 for males and G=0.85 for females.

The estimated creatinine clearance will be included as one of the laboratory parameters.

5.3.2 Newly occurring liver enzymes abnormalities

Below lists the criteria for "events" of newly occurring liver enzymes abnormalities:

- ALT > 3, 5, 10, 20 × ULN
- ALT or AST > 3, 5, 8, 10, 20 × ULN
- ALT or AST > 3 × ULN & TBL > 1.5 × ULN
- ALT or AST > 3 × ULN & TBL > 2 × ULN
- ALP > 1.5, 2, 5 × ULN
- TBL > 1, 1.5, 2, 3 × ULN
- ALP > 3, 5 × ULN & TBL > 2 × ULN
- ALT or AST > 3 × ULN & TBL > 2 × ULN & ALP ≤ 2 × ULN (Potential Hy's Law)

When a criterion contains multiple laboratory parameters (e.g. ALT > 3 × ULN & TBL > 2 × ULN), unless otherwise requested by the project clinical team/Global Program Safety Lead (GPSL), the criterion should be only considered to be met when the elevation in both parameters occurs on the same sample day (as evidenced by the same date that the lab samples were taken).

The "events" are defined in the Novartis safety guideline on hepatotoxicity (Novartis: Kullak-Ublick et al 2019).

5.3.3 CTCAE grades for laboratory parameters

Table 5-3 CTCAE grades for laboratory parameters (CTCAE Version 5)

		Grade			
Abnormality	**Lab parameter**	**1**	**2**	**3**	**4**
Hematology					
Anemia	Hemoglobin (g/L)	<LLN - 100 g/L	<100 - 80 g/L	<80 g/L transfusion indicated	
Hemoglobin Increased#	Hemoglobin (g/L)	>ULN - ULN+20 g/L	>ULN+20 - ULN+40 g/L	>ULN+40 g/L	
Platelet count decreased	Platelets (thrombocytes) (10^9/L)	<LLN-75.0 x 10^9/L	<75.0 - 50.0 x 10^9/L	<50.0 - 25.0 x 10^9/L	<25.0 x 10^9/L
White blood cell decreased	Leukocytes (WBCs) (10^9/L)	<LLN - 3.0 x 10^9/L	<3.0 - 2.0 x10^9/L	<2.0 - 1.0 x 10^9/L	<1.0 x 10^9/L
Neutrophil count decreased#	Absolute neutrophil count (10^9/L)	<2 - 1.5 x10^9/L	<1.5 - 1.0 x10^9/L	<1.0 - 0.5 x10^9/L	<0.5 x10^9/L

		Grade			
Abnormality	**Lab parameter**	**1**	**2**	**3**	**4**
Lymphocyte count decreased[#]	Absolute lymphocyte count (10^9/L)	<1.5 - 0.8 10^9/L	<0.8 - 0.5 x 10^9/L	<0.5 - 0.2 x 10^9/L	<0.2 x 10^9/L
Lymphocyte count increased	Absolute lymphocyte count (10^9/L)		>4 – 20 x 10^9/L	> 20 x 10^9/L	
Chemistry					
Liver function					
Alanine aminotransferase increased[#]	ALT (SGPT) (U/L)	>ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
Aspartate aminotransferase increased[#]	AST (SGOT) (U/L)	>ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
Blood bilirubin increased[#]	Bilirubin (µmol/L)	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN
GGT increased[#]	Gamma-glutamyl transferase (GGT) (U/L)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
Alkaline phosphatase increased[#]	Alkaline Phosphatase (U/L)	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Renal function Note: A semi-colon (;) indicates 'or' within the description of the grade.					
Creatinine increased* [#]	Creatinine (µmol/L)	>ULN - 1.5 x ULN	>1.5 - 3.0x ULN	>3.0 - 6.0 x ULN	>6.0 x ULN

*Highest grade will be assigned if more than one grade criteria are met for an observed value of a participant.

**For reporting in CSR, CTCAE grades based on lab results alone will be applied programmatically, clinical assessments (in *italic font*) will not be considered.

[#]Reference: Novartis Internal Guidance on CTC Grading of Lab Parameters (ver. 1.0 effective on 27-Nov-2023).

5.4 Statistical models

5.4.1 Analysis supporting primary objective(s)

The SAS procedure GENMOD will be used to conduct the analysis on the negative binomial regression model. In GENMOD, the log of the dispersion parameter will be used (lognb) as an option in model statement. The natural log of time in year is used as an offset by specifying offset option in the model statement.

5.4.2 Analysis supporting secondary objective(s)

Details to conduct the analysis on the negative binomial regression model are the same as that in the primary objective.

5.5 Rule of exclusion criteria of analysis sets

Subject classification in the analysis sets is entirely based on protocol deviation (PD) and non-protocol deviation (non-PD) criteria. Details are provided in tables below.

Table 5-4 Protocol deviations that cause subjects to be excluded

Deviation ID	Description of Deviation	Exclusion in Analysis sets
INCL01	Written informed consent was never obtained	Excluded from all analysis sets

Table 5-5 Subject Classification

Analysis Set	PD ID that cause subjects to be excluded	Non-PD criteria that cause subjects to be excluded
FAS	INCL01	No study treatment taken
SAF	INCL01	No study treatment taken

6 Reference

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