NOVARTIS

Clinical Development

OMB157G/Ofatumumab/Kesimpta®

COMB157GUS10 / NCT05084638

AGNOS: An 18-month, Open-label, Multi-Center Phase IV Study to Assess the Effect of Ofatumumab 20mg SC Monthly in Treatment Naïve, Very Early Relapsing Remitting Multiple Sclerosis Patients Benchmarked Against Healthy Controls on Select Outcomes

Statistical Analysis Plan (SAP)

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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
09-Nov-2021	Prior to clinical DB lock for Month 18 Interim Analysis	Creation of final version	NA - first version	NA
29-Oct-2024	Prior to clinical DB lock for Month 18 Interim Analysis	Creation of Amendment 1	1. Updated to align with protocol versions 02.01 and 03 dated 04-Mar-2022 and 14-Sep-2023, respectively: updated protocol title; [redacted]; updated study design figure; changed method for calculating confidence interval from normal approximation to exact for primary and select secondary endpoints 2. Specified Clopper-Pearson as exact method used for calculating confidence interval for primary endpoint and select secondary [redacted] endpoints 3. Clarified that smoking status will be summarized by type of substance, as well as for any type of substance 4. Specified formulas for calculating time from onset of most recent relapse to first dose of ofatumumab and time from RRMS diagnosis to first dose of ofatumumab 5. Changed FAS to SAF for summarizing MS history and medical history 6. Added 'Other' as a race subcategory within 'Asian specify' category 7. Added cohort-based approach for calculating annualized new/enlarging T2 lesion rate and annualized relapse rate 8. Clarified that brain volume parameters will be assessed via percent change (not absolute change) 9. Removed C-SSRS from visit window Table 3 10. Defined change and percent change from Month 6 re-baseline 11. Updated approach for summarizing C-SSRS 12. Changed primary clinical question of interest in primary estimand section to be focused on NEDA-3 at 18 months 13. Changed definition of intercurrent event for primary estimand	1. Cover page; Section 1.2 Study objectives, endpoints and estimands; [redacted] Section 1.1 Study design; Section 2.5.2 Statistical hypothesis, model, and method of analysis; Section 2.5.6 Supplemental analyses; Section 2.6.2 Statistical hypothesis, model, and method of analysis 2. Section 2.5.2 Statistical hypothesis, model, and method of analysis; Section 2.5.6 Supplemental analyses; Section 2.6.2 Statistical hypothesis, model, and method of analysis; Section 2.12 [redacted]; Section 6 Reference 3. Section 2.3.2 Demographics and other baseline characteristics; Section 2.7.4.2 Smoking status 4. Section 2.3.3 MS history 5. Section 2.3.3 MS history; Section 2.3.4 Medical history 6. Section 2.3.2 Demographics and other baseline characteristics 7. Section 2.6.2 Statistical hypothesis, model, and method of analysis 8. Section 2.6.1 Secondary endpoint(s) 9. Section 2.4.1.1 Visit windows 10. Section 2.1.1 General definitions 11. Section 2.7.4.3 Columbia-Suicide Severity Rating Scale (C-SSRS) 12. Section 1.2.1 Primary estimand(s) 13. Section 1.2.1 Primary estimand(s); Section 2.5.1 Primary endpoint(s)

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			14. Defined new analysis set, modified FAS (mFAS), to be used for NEDA-3, NEDA clinical and NEDA radiological efficacy analyses 15. Defined a new analysis set, per-protocol set (PPS), to be used for supplemental efficacy analysis of NEDA-3 16. Changed handling of intercurrent events for primary estimand to reflect a composite variable strategy for handling of treatment discontinuations 17. Changed handling of missing values not related to intercurrent event for primary estimand to clarify that, if treatment discontinuation is due to reasons other than lack of efficacy or death, participants who had NEDA-3 before early discontinuations will be excluded from mFAS for all NEDA-3 and associated endpoints efficacy analyses and thusly out of scope for intercurrent events handling 18. Added supplemental analyses of primary endpoint using a non-response imputation approach, using the PPS, using an MRI-activity free component of NEDA-3 that is based on no new or enlarging T2 lesions, and using a 6-month clinical disability progression-free component of NEDA-3 19. Changed 'BVL' references to 'brain volume parameters' or 'brain volume assessment' as appropriate 20. Included steps for calculating percent change from Month 6 re-baseline to post-Month 6 time points in brain volume parameters 21. Indicated that percent change from baseline and percent change from Month 6 re-baseline will be evaluated for lesion volume and brain volume parameters 22. For NEDA clinical and NEDA radiological, changed approach for handling of intercurrent events and missing values not related to intercurrent events to match that for NEDA-3 23. Documented changes from protocol specified analyses 24. Updated rule of exclusion criteria of analysis sets to reference mFAS and PPS	14. Section 2.2 Analysis sets; Section 2.5.2 Statistical hypothesis, model, and method of analysis; Section 2.6.2 Statistical hypothesis, model, and method of analysis 15. Sections 2.2 Analysis sets; Section 2.5.6 Supplementary analyses 16. Section 2.5.3 Handling of intercurrent events 17. Section 2.5.4 Handling of missing values not related to intercurrent event 18. Section 2.5.6 Supplementary analyses 19. Section 2.6.1 Secondary endpoint(s); Section 2.6.2 Statistical hypothesis, model, and method of analysis; Section 1.2 Study objectives, endpoints and estimands 20. Section 2.6.2 Statistical hypothesis, model, and method of analysis 21. Section 2.6.1 Secondary endpoint(s) 22. Section 2.6.3 Handling of intercurrent events; Section 2.6.4 Handling of missing values not related to intercurrent event 23. Section 4 Change to protocol specified analyses 24. Section 5.5 Rule of exclusion criteria of analysis sets 25. [redacted] 26. [redacted] 27. Section 2.10 Patient-reported outcomes 28. Section 2.6.1 Secondary endpoint(s) 29. Section 1.2 Study objectives, endpoints and estimands 30. Section 1.2 Study objectives, endpoints and estimands 31. Section 2.6.1 Secondary endpoint(s); Section 2.6.2 Statistical hypothesis, model, and method of analysis 32. Section 5.1.3.3 Other imputations

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			25. [redacted] 26. [redacted] 27. For NeuroQOL indicated that derivation of total raw scores and conversion to T scores will be done as per the NeuroQOL scoring manual version 5.0 dated September 2022; total raw scores and T-scores will not be derived for urinary and bowel custom 14-item short form 28. Specified two derivations of secondary endpoint MRI activity-free, one for ofatumumab-treated participants only and the other for all participants 29. Clarified secondary endpoint as 'Number of confirmed relapses' 30. Clarified that secondary endpoints 'Number of confirmed relapses' and '3-month disability worsening-free' are derived in Months 6 to 18 31. Clarified MRI parameters that are assessed via changes (percent changes) by time point versus those that are assessed via values by time point 32. Added partial date imputation rules for most recent relapse onset and RRMS diagnosis 33. Added MRI parameter 'new/enlarging T2 lesion volume' to list of conventional MRI metrics 34. Revised Month 18 interim analysis data cut-off to allow for window of +7 days relative to date of Month 18 visit 35. Added MS relapse data handling rules	33. Section 1.2 Study objectives, endpoints and estimands; Section 2.6.1 Secondary endpoint(s) 34. Section 2.1.1 General definitions 35. Section 5.1.3.4
22-Apr-2025	Prior to clinical DB lock for Month 18 Interim Analysis	Creation of Amendment 2	1. Clarified assignment of protocol deviations to open-label treatment phase vs. open-label extension period 2. Updated definition of mFAS 3. Removed per-protocol analysis set 4. Clarified definition of time from onset of most recent relapse to first dose of ofatumumab; added definition of variable for time from first MS symptoms to first dose of ofatumumab; added baseline EDSS score	1. Section 2.1.1 General definitions 2. Section 2.2 Analysis sets 3. Section 2.2 Analysis sets 4. Section 2.3.3 MS history 5. Section 2.4.1 Study treatment / compliance; Section 5.6 Ofatumumab dose dates during open-label treatment phase and open-label extension period 6. Section 2.4.1 Study treatment / compliance 7. Section 2.4.1.1 Visit windows

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			5. Added logic for determining last dose of ofatumumab during open-label treatment phase and first dose of ofatumumab during open-label extension period 6. Added definition of variable for open-label treatment phase duration 7. Removed multiple assessments rule for baseline and post-baseline based on lowest CRF visit number 8. Updated logic for determining prior and concomitant medications and non-drug therapies/procedures 9. Updated definition of MRI activity-free 10. Removed text regarding analysis of NEDA-3 being conducted only in participants followed-up from Months 6 to 18 11. Updated approach to the handling of intercurrent events and missing values not related to intercurrent events 12. Clarified participants included in observed case approach analysis 13. Removed analysis using the per-protocol set 14. Removed analysis of percent change from baseline and Month 6 re-baseline in lesion volume parameters 15. Clarified determination of number of new/enlarging T2 lesions for derivation of annualized new/enlarging T2 lesion rate 16. Removed observed case approach for summarization of participants with confirmed relapses 17. Added summaries for treatment-related SAEs and AEs occurring with frequency >5% 18. Added details regarding summarization of AEs needed for ClinicalTrials.gov and EudraCT 19. Removed summary of infection-related AEs 20. Clarified that only total raw score for NeuroQOL Communication short form domain will be summarized 21. Indicated that analysis of NfL values will not occur for the Month 18 interim analysis; NfL values will be analyzed at the time of the final analysis for the study 22. [redacted]	8. Section 2.4.2 Prior, concomitant and post therapies 9. Section 2.5.1 Primary endpoint(s); Section 2.5.6 Supplementary analyses; Section 2.6.1 Secondary endpoint(s) 10. Section 2.5.1 Primary endpoint(s) 11. Section 2.5.3 Handling of intercurrent events; Section 2.5.4 Handling of missing values not related to intercurrent event 12. Section 2.5.6 Supplementary analyses 13. Section 2.5.6 Supplementary analyses 14. Section 2.6.1 Secondary endpoint(s) 15. Section 2.6.2 Statistical hypothesis, model, and method of analysis 16. Section 2.6.2 Statistical hypothesis, model, and method of analysis 17. Section 2.7.1 Adverse events (AEs) 18. Section 2.7.1 Adverse events (AEs) 19. Section 2.7.1.1 Adverse events of special interest / grouping of AEs 20. Section 2.10 Patient-reported outcomes 21. [redacted] 22. [redacted] 23. [redacted] 24. [redacted] 25. Section 4 Change to protocol specified analyses 26. Section 5.1.3.3 Other imputations 27. Section 5.1.3.4 Data handling for relapses within 30 days of onset of previous relapses or relapses with duration beyond 90 days 28. Section 5.3 Laboratory parameters derivations 29. Section 5.5 Rule of exclusion criteria of analysis sets 30. Section 6 Reference

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			23. Removed analysis of [redacted] adverse events over the course of the study 24. Updated derivations for PDC and MPR 25. Indicted removal of analysis of [redacted] adverse events over the course of the study 26. Clarified MS history date imputation rules 27. Removed severity determination of "linked" relapses 28. Added rules for conversion of character to numeric continuous laboratory values 29. Removed reference to per-protocol set 30. Added Brookmeyer and Crowley reference	

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AE	Adverse Event
ARR	Annualized Relapse Rate
ATC	Anatomical Therapeutic Chemical
BDNF	Brain-Derived Neurotrophic Factor
BMI	Body Mass Index
[redacted]	[redacted]
CD19	Cluster of Differentiation 19
CDBL	Clinical Database Lock
[redacted]	[redacted]
CI	Confidence Interval
CNS	Central Nervous System
CRO	Contract Research Organization
[redacted]	[redacted]
CSP	Clinical Study Protocol
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
[redacted]	[redacted]
DMT	Disease Modifying Therapy
EDSS	Expanded Disability Status Scale
EOS	End of Study
FAS	Full Analysis Set
Gd	Gadolinium
[redacted]	[redacted]
HCAS	Healthy Control Analysis Set
IA	Interim Analysis
[redacted]	[redacted]
[redacted]	[redacted]
MCP1	Monocyte Chemoattractant Protein
MedDRA	Medical Dictionary for Drug Regulatory Activities
mFAS	Modified Full Analysis Set
MPR	Medication Possession Ratio
[redacted]	[redacted]
[redacted]	[redacted]
MS	Multiple Sclerosis
NBV	Normalized Brian Volume
NEDA	No Evidence of Disease Activity

NeuroQOL™	Quality of Life in Neurological Disorders
NfL	Neurofilament Light
[redacted]	[redacted]
NRI	Non-Response Imputation
PBVC	Percentage Brain Volume Change
PD	Pharmacodynamic
PDC	Proportion of Days Covered
PDDS	Patient Determined Disease Steps
PK	Pharmacokinetic
PRO	Patient Reported Outcome
PT	Preferred Term
RRMS	Relapsing-Remitting Multiple Sclerosis
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
[redacted]	[redacted]
SOC	System Organ Class
[redacted]	[redacted]
TFL	Tables, Figures and Listings
UBC	United BioSource LLC
USPI	United States Prescribing Information
WHO	World Health Organization

1 Introduction

The purpose of this Statistical Analysis Plan (SAP) is to describe the data analysis and statistical methods planned in Section 12 of the Clinical Study Protocol (CSP) version 03 (dated 14-Sep-2023) for the clinical trial COMB157GUS10 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. It will also be used to draft the statistical methods section of the Interim Analysis Report.

1.1 Study design

This study is an open-label, multi-center, prospective eighteen-month study in a minimum of 118 multiple sclerosis (MS) patients with early relapsing-remitting MS (RRMS) (defined as within 6 months of diagnosis of clinically definite RRMS) and who are disease modifying therapy (DMT) treatment naïve. RRMS patients will be benchmarked against age- and sex-matched healthy controls (n=50) for select secondary [redacted] outcomes.

The study consists of 3 main periods/phases as outlined below. In addition, a safety follow-up period applies to participants who meet specific criteria as described below.

Screening period

Participants will enter a screening period of up to 4 weeks to assess eligibility requirements.

Open-label treatment phase

Eligible participants with RRMS will receive ofatumumab 20 mg subcutaneous doses during the open-label treatment phase at Baseline/Week 0 (Day 1), followed by Week 1 (Day 7), Week 2 (Day 14) and then every month thereafter, beginning at Week 4 (Month 1) until Month 18 (see Figure 1). Ofatumumab will be administered according to the United States Prescribing Information (USPI). RRMS patients must remain on ofatumumab monotherapy to remain in the trial, with no DMT switching or combination DMT therapy allowed.

Healthy control participants will not be given a therapy.

Optional open-label extension period

Additional efficacy and safety assessments will be evaluated during the optional open-label extension period to further elucidate the long-term clinical and radiological effects of ofatumumab (see Figure 1). Of note, magnetic resonance imaging (MRI) data will be re-baselined at Month 6 to account for treatment-related pseudo atrophy.

Safety follow-up period

The safety follow-up period applies to the following participants:

- Participants who complete the open-label treatment phase on study drug and do not continue on any MS DMT.
- Participants who prematurely discontinue study drug and study participation, and do not continue on any MS DMT.

All safety follow-up period visits are scheduled relative to the End of Study (EOS) visit.

All participants who elect to not be included in the 12-month extension will be followed for an additional 100 days following the EOS timing for that individual participant. A shorter follow-up time is acceptable if participants select a different approved MS DMT (injectable, infusion or oral) treatment during this period. Participants who do not have access to commercial drug within one day of the EOS visit must continue into the safety follow-up period until they are able to access commercial drug or decline DMT treatment moving forward (up to 100 days maximum).

Healthy control participants will not have a safety evaluation post end of study.

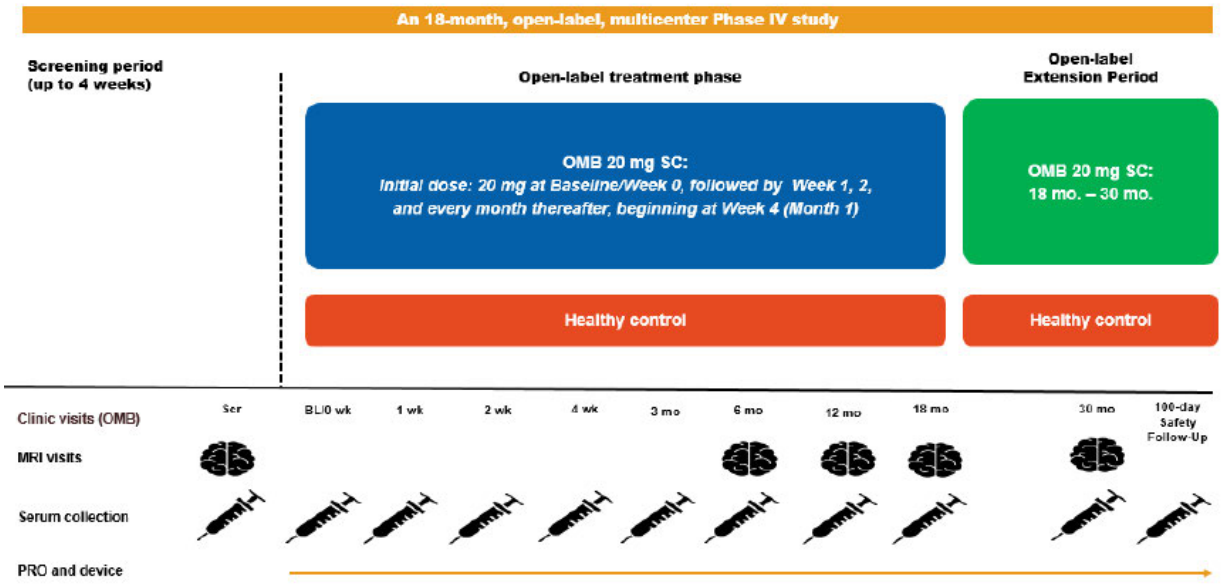
Study completion

According to the protocol, study completion is defined as when the last participant finishes their Study Completion or EOS visit and any repeat assessments associated with this EOS visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

For participants who discontinue study treatment and study participation prematurely for any reason before the end of the open-label treatment phase, an EOS visit must be performed within 7 days of study discontinuation.

The study design schematic is shown in Figure 1.

Figure 1 Study design



Primary analysis time point

The primary analysis time point will be Month 18.

Interim analysis

There will be one interim analysis (IA) after the last participant completes his/her Month 18 (primary analysis time point) visit.

1.2 Study objectives, endpoints and estimands

Study objectives and associated endpoints are shown in Table 1.

Table 1 Study objectives and endpoints

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
• The primary objective is to explore the impact of ofatumumab on the ability to achieve No Evidence of Disease Activity (NEDA-3) status in treatment-naïve, very early RRMS participants over an 18 month, open-label study period after a re-baseline of MRI at 6 months	• NEDA-3 (relapse-free, 3-month clinical disability progression-free, MRI activity-free) in Months 6 to 18 (yes/no)
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
• Evaluate the effect of ofatumumab on various clinical (NEDA, disability, relapse) metrics at 18 months	• Number of confirmed relapses in Months 6 to 18 • 3-month disability worsening-free in Months 6 to 18 (yes/no) • NEDA clinical in Months 6 to 18 (yes/no) • NEDA radiological in Months 6 to 18 (yes/no)
• Evaluate the effect of ofatumumab on conventional MRI metrics, with MRIs at Baseline and Months 6, 12, 18, 30 (T1 gadolinium (Gd) @ Baseline, Month 6, 18 and T1/T2 @ every timepoint)	• Change from baseline in conventional MRI metrics (Gd+ lesion number, new Gd+ lesion number, Gd+ lesion volume, T2 lesion number (Baseline), new/enlarging T2 lesion number (post-Baseline), T2 lesion volume, new/enlarging T2 lesion volume, new unenhancing T1 lesion number, T1 unenhancing lesion volume)
• Evaluate the effect of ofatumumab on patient reported outcomes (PROs) (Quality of Life in Neurological Disorders [NeuroQOLTM], Patient Determined Disease Steps [PDDS])	• Change from baseline in PROs (NeuroQOLTM, PDDS) (also obtained in healthy controls)
• Evaluate the effect of ofatumumab vs healthy controls on 1) whole brain and regional atrophy measured at Month 18/30 after re-baseline at 6 months; and 2) regional atrophy measured 18/30 months from Baseline	• Brain volume assessment (whole brain and regional) (also obtained in healthy controls)
• Evaluate the safety and tolerability of ofatumumab	• Adverse events, laboratory data, physical examination, and vital signs (also obtained in healthy controls)
[redacted]	

1.2.1 Primary estimand(s)

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

The primary clinical question of interest is: will treatment with ofatumumab allow young and very early RRMS patients to achieve NEDA-3 at 18 months?

The justification for the primary estimand is that it will capture the effect of ofatumumab on shutting down MS inflammatory and associated clinical disease activity within the central nervous system (CNS) in a RRMS population that is at first diagnosis.

The primary estimand is described by the following attributes:

- **Population:** Defined through appropriate inclusion/exclusion criteria to reflect the targeted population. Young adult and very early RRMS (defined as within 6 months of diagnosis of clinically definite RRMS) patients that are DMT treatment naïve.
- **Variable:** NEDA-3 (relapse-free, clinical disability progression-free, MRI activity-free) in Months 6 to 18 (yes/no)
- **Treatment of interest:** An initial dose regimen consisting of doses administered at Baseline/Week 0 (Day 1), followed by Week 1 (Day 7), Week 2 (Day 14), and then every month thereafter, beginning at Week 4 (Month 1) until Month 18 (see Figure 1). All doses of ofatumumab will be given subcutaneously via an auto-injector at a dose of 20 mg. Healthy controls will be used for comparison purposes and will not receive study treatment.
- **Intercurrent event:** Treatment discontinuation due to lack of efficacy or death

- **Summary measure:** Proportion of participants achieving NEDA-3 in Months 6 to 18

1.2.2 Secondary estimand(s)

There are no secondary estimands specified for this study.

2 Statistical methods

2.1 Data analysis general information

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

The primary analysis will be based on Month 18 data, i.e., all data up to and including Month 18. This analysis will be performed after all participants have completed their Month 18 visit, discontinued study treatment prior to Month 18 (ofatumumab-treated participants) or discontinued the study prior to Month 18 (healthy control participants) (see Section 2.1.1 and Section 2.13 for additional details). The final analysis will include all data through Month 30.

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

In general, data summaries will be presented for ofatumumab-treated participants in the relevant analysis set. In instances where data are collected for both ofatumumab-treated participants and healthy control participants, data summaries will be presented **by Cohort** (ofatumumab-treated participants or healthy control participants) and on all participants in the respective analysis set.

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

2.1.1 General definitions

Investigational treatment

The investigational treatment (study treatment) will refer to the administration of ofatumumab provided by Novartis in an auto-injector pen containing 20 mg ofatumumab (20 mg/0.4 ml) for subcutaneous administration to participants as per the assessment schedule.

Study day 1, study day and event duration

Study Day 1 is defined as the date of the first dose of ofatumumab for ofatumumab-treated participants and the date of the Week 0 visit for healthy control participants.

For assessment/event dates on or after Study Day 1, the **study day of the assessment/event** will be calculated as follows:

- [(date of assessment/event − date of first dose of ofatumumab) + 1] for ofatumumab-treated participants
- [(date of assessment/event − date of Week 0 visit) + 1] for healthy control participants

For assessment/event dates prior to Study Day 1, the **study day of the assessment/event** will be calculated as follows:

- (date of assessment/event − date of first dose of ofatumumab) for ofatumumab-treated participants
- (date of assessment/event − date of Week 0 visit) for healthy control participants

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

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

Screening

Screening refers to any procedures (e.g., checking inclusion and exclusion criteria) performed prior to the first dose of ofatumumab for ofatumumab-treated participants or prior to the Week 0 visit for healthy control participants. Per protocol, participant informed consent must be obtained prior to performing any study related activity. The date of signing of informed consent is the start date of the screening period. Any assessment obtained during the screening period will be labelled as a screening assessment.

Baseline

Unless otherwise specified, baseline will be derived as follows:

- For ofatumumab-treated participants, baseline is the last non-missing assessment, including unscheduled assessments, obtained prior to or on the date of the first dose of ofatumumab.
- For healthy control participants, baseline is the last non-missing assessment, including unscheduled assessments, obtained prior to or on the date of the Week 0 visit.

Unless otherwise specified, all assessments obtained after the date of the first dose of ofatumumab for ofatumumab-treated participants, or after the date of the Week 0 visit for healthy control participants, are considered post-baseline assessments.

Nominal visits

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

Month 18 interim analysis data cut-off

As noted in Section 2.1, the primary analysis will be based on Month 18 data (i.e., all data up to and including Month 18) and performed after all participants have completed their Month 18 visit, discontinued study treatment prior to Month 18 (ofatumumab-treated participants) or discontinued the study prior to Month 18 (healthy control participants). The data cut-off for the Month 18 interim analysis is defined for different participant scenarios in Table 2. Note that visits are assumed to be nominal visits.

Table 2 Month 18 interim analysis data cut-off for different participant scenarios

Participant scenario	Cut-off	Participant data included in Month 18 interim analysis (primary analysis)
Completed Month 18 visit	Date of Month 18 visit + 7 days (inclusive)	All available data up to the date of the Month 18 visit + 7 days (inclusive)*
Did not complete Month 18 visit		
Discontinued study prior to Month 18 visit	None	All available data
Did not discontinue study prior to Month 18 visit	Date of next scheduled visit after Month 18 (exclusive)	All available data up to the date of the next scheduled visit (including home visit) after Month 18 (exclusive).** If the next scheduled visit after Month 18 has not been completed, all available data is used.

* Including data such as adverse events, medications, non-drug therapies/procedures, protocol deviations and relapses that started prior to or on the date of the Month 18 visit + 7 days.

** Including data such as adverse events, medications, non-drug therapies/procedures, protocol deviations and relapses that started prior to the date of the next scheduled visit (including home visit) after Month 18.

Open-label treatment phase/extension period

For summarization of data including, but not limited to, adverse events, medications, non-drug therapies/procedures, protocol deviations and relapses, data occurring from Study Day 1 through the Month 18 interim analysis data cut-off will be considered as part of the open-label treatment phase. Data occurring post Month 18 interim analysis data cut-off will be considered as part of the open-label extension period.

Change and percent change from baseline

Change from baseline will be calculated as follows:

- Post-baseline value – baseline value

Percent change from baseline will be calculated as follows:

- [(Post-baseline value – baseline value) / baseline value] × 100%

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

Change and percent change from Month 6 re-baseline will be calculated in a similar fashion using the above formulas where ‘baseline value’ is replaced with ‘Month 6 re-baseline value’ (i.e., Month 6 value) and ‘Post-baseline value’ is replaced with ‘Post-Month 6 value’.

2.2 Analysis sets

The Full Analysis Set (FAS) will include all enrolled participants that received any study drug.

The Safety Analysis Set (SAF) will be the same as the FAS.

The Healthy Control Analysis Set (HCAS) will include all enrolled healthy control participants. This analysis set will be used in the analysis of data collected from healthy control participants.

The modified FAS (mFAS) will include all participants in the FAS except for those who discontinued treatment prematurely prior to Month 18 for reasons other than lack of efficacy or death, or those who completed their Month 18 visit but missed relapse/EDSS/MRI (Gd+ or

new/enlarging T2 lesions) at Month 6, 12 or 18, unless they showed disease activity (i.e., MRI activity after Month 6 through 18 or relapse/3-month clinical disability progression between Months 6 and 18). The mFAS will be used for NEDA-3, NEDA clinical and NEDA radiological efficacy analyses.

2.2.1 Subgroup of interest

There is no subgroup analysis planned for this study.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

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

- Screening period
- Open-label treatment phase
- Open-label extension period
- Study

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

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

For each protocol deviation, the number and percentage of participants for whom the deviation applies will be summarized by Cohort for the open-label treatment phase, open-label extension period and overall using the FAS or HCAS, as appropriate.

2.3.2 Demographics and other baseline characteristics

The following demographic and baseline characteristic variables will be summarized descriptively by Cohort using the FAS or HCAS, as appropriate:

Continuous variables

- Age (years)
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m2) [weight (kg) / height (m2)]

Categorical variables

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

- Smoking status (Former, Current, Never) by type of substance (Tobacco, Marijuana, Vape); former smoker of any type of substance; current smoker of any type of substance

2.3.3 MS history

The number and percentage of participants with 0, 1, 2 or ≥3 relapses in the last 12 months prior to screening will be presented using the SAF. In addition, the number and percentage of participants with at least 1 relapse will be presented.

The following variables will be summarized descriptively as continuous variables using the SAF:

- Time (days) from onset of most recent relapse to first dose of ofatumumab [(date of first dose of ofatumumab – date of onset of most recent MS relapse) + 1]
- Time (years) from RRMS diagnosis to first dose of ofatumumab [(date of first dose of ofatumumab – date of RRMS diagnosis) + 1]/365.25
- Time (years) from first MS symptoms to first dose of ofatumumab [(date of first dose of ofatumumab – date of first MS symptoms) + 1]/365.25
- Baseline EDSS score

Partial most recent relapse onset dates, RRMS diagnosis dates and first MS symptoms dates will be imputed as outlined in Section 5.1.3.3.

2.3.4 Medical history

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

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

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

2.4.1 Study treatment / compliance

The duration of ofatumumab exposure in days for the open-label treatment phase, open-label extension period and overall will be summarized descriptively as a continuous variable using the SAF. The duration of ofatumumab exposure will be calculated within each phase/period and overall, as follows:

- (date of last dose of ofatumumab – date of first dose of ofatumumab) + 1

The date of the last dose of ofatumumab during the open-label treatment phase and the date of the first dose of ofatumumab during the open-label extension period will be determined as outlined in Section 5.6.

Adherence to and persistence on ofatumumab therapy will be evaluated through drug accountability and/or possession diary as outlined in Section 2.12.

Study duration

Study duration in days will be calculated as follows:

- [(date of last contact/EOS – date of first dose of ofatumumab) + 1] for ofatumumab-treated participants
- [(date of last contact/EOS – date of Week 0 visit) + 1] for heathy control participants

Open-label treatment phase duration

Open-label treatment phase duration in days will be calculated as follows:

- [(date of Month 18 interim analysis data cut-off – date of first dose of ofatumumab) + 1] for ofatumumab-treated participants
- [(date of Month 18 interim analysis data cut-off – date of Week 0 visit) + 1] for heathy control participants

For participants who do not complete the Month 18 visit, the date of last contact/EOS will be used.

Study duration and open-label treatment phase duration will be summarized descriptively as continuous variables by Cohort using the SAF or HCAS, as appropriate.

2.4.1.1 Visit windows

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

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

- The visit window associated with the previous assessment ends prior to the middle point; the visit window associated with the latter assessment begins after the middle point. In case the middle point is an exact study day, it will belong to the previous assessment.
- The visit window of the first post-baseline assessment starts with Study Day 2, unless otherwise indicated.

Tables 3, 4, 5 and 6 provide visit windows for applicable parameters.

Table 3 Visit windows for EDSS / Kurtzke Functional Systems Scores and Ambulation / NeuroQOLTM / PDDS / [redacted]

Analysis visit	Nominal time point	Scheduled visit day (target study day)	Visit window (study days)
Baseline/Week 0	BSL/Wk0	1	≤1
Week 1	Wk1	7	2 to 10
Week 2	Wk2	14	11 to 21
Week 4	Wk4	28	22 to 59
Month 3	M3	90	60 to 135
Month 6	M6	180	136 to 270
Month 12	M12	360	271 to 450
Month 18	M18	540	451 to cut-off day
Month 30	M30/EOS	900	≥cut-off day + 1

Note:
- Baseline is derived as outlined in Section 2.1.1.
- Cut-off day is the study day of the Month 18 interim analysis data cut-off described in Section 2.1.1.

Table 4 Visit windows for vital signs

Analysis visit	Nominal time point	Scheduled visit day (target study day)	Visit window (study days)
Baseline/Week 0	BSL/Wk0	1	≤1
60 Minutes Post-Injection*	60 Minutes Post-Injection	1	1 (post-injection)
Week 1	Wk1	7	2 to 10
Week 2	Wk2	14	11 to 21
Week 4	Wk4	28	22 to 59
Month 3	M3	90	60 to 135
Month 6	M6	180	136 to 270
Month 12	M12	360	271 to 450
Month 18	M18	540	451 to cut-off day
Month 30	M30/EOS	900	≥cut-off day + 1

* Only applicable to ofatumumab-treated participants.

Note:
- Baseline is derived as outlined in Section 2.1.1.
- Cut-off day is the study day of the Month 18 interim analysis data cut-off described in Section 2.1.1.

Table 5 Visit windows for [redacted] / hematology and chemistry labs / smoking status

Analysis visit	Nominal time point	Scheduled visit day (target study day)	Visit window (study days)
Baseline/Week 0	BSL/Wk0	1	≤1
Month 18	M18	540	2 to cut-off day
Month 30	M30/EOS	900	≥cut-off day + 1

Note:
- Baseline is derived as outlined in Section 2.1.1.
- Cut-off day is the study day of the Month 18 interim analysis data cut-off described in Section 2.1.1

Table 6 Visit windows for MRI

Analysis visit	Nominal time point	Scheduled visit day (target study day)	Visit window (study days)
Baseline/Week 0	BSL/Wk0	1	≤1
Month 6	M6	180	2 to 270
Month 12	M12	360	271 to 450
Month 18	M18	540	451 to cut-off day
Month 30	M30/EOS	900	≥cut-off day + 1

Note:
- Baseline is derived as outlined in Section 2.1.1.
- Cut-off day is the study day of the Month 18 interim analysis data cut-off described in Section 2.1.1.

Multiple assessments

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

- **Baseline:** The last non-missing assessment, including unscheduled assessments, obtained prior to or on the date of the first dose of ofatumumab for ofatumumab-treated participants (Study Day 1), or prior to or on the date of the Week 0 visit for healthy control participants (Study Day 1). If there are multiple assessments on Study Day 1, the following rules apply:
  a. If a complete assessment time exists:
     - The latest assessment prior to the time of the first dose of ofatumumab will be used for ofatumumab-treated participants.
     - If there is no assessment prior to the time of the first dose of ofatumumab, the earliest assessment post time of first dose of ofatumumab will be used for ofatumumab-treated participants.
- **Post-baseline:** For post-baseline visit windows, the following rules apply (unless otherwise specified):
  a. For *continuous variables*, the assessment with the study day that is closest to the target study day is selected. If two assessments are equidistant from the target study day, the earlier assessment is selected (if one of the two equidistant assessments is an unscheduled assessment, it should be excluded from consideration).
  b. For *categorical variables*, the assessment with the worst result is selected.

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

In situations where the same assessment is performed more than once on the same date, the following applies:

a. If a complete assessment time exists, the earliest assessment will be used.

2.4.2 Prior, concomitant and post therapies

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

Medications will be classified as prior or concomitant as follows:

- Prior medications are defined as medications taken and stopped prior to the date of the first dose of ofatumumab for ofatumumab-treated participants, or prior to the date of the Week 0 visit for healthy control participants.
- Concomitant medications are defined as medications that started on or after the date of the first dose and within 30 days (inclusive) following the date of the last dose of ofatumumab for ofatumumab-treated participants, or on or after the date of the Week 0 visit for healthy control participants. Note the 30-day window post last dose of ofatumumab is not applicable to ofatumumab-treated participants who are ongoing in the study at the time of the Month 18 interim analysis.
    - For ofatumumab-treated participants, this includes medications that started prior to the date of the first dose and ended on or after the date of the first dose (and within 30 days [inclusive] following the date of the last dose) or are indicated as ongoing.
    - For healthy control participants, this includes medications that started prior to the date of the Week 0 visit and ended on or after the date of the Week 0 visit or are indicated as ongoing.

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

Prior and concomitant medications will be summarized with frequency counts and percentages by Cohort, Anatomical Therapeutic Chemical (ATC) class and PT using the SAF or HCAS, as appropriate. Concomitant medications will be summarized for the open-label treatment phase, open-label extension period and overall. Tables will show the overall number and percentage of participants receiving at least one medication of a particular ATC class and at least one medication of a particular PT.

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

Prior and concomitant non-drug therapies/procedures will be summarized by Cohort, primary SOC and PT using the SAF or HCAS, as appropriate. Concomitant non-drug therapies/procedures will be summarized for the open-label treatment phase, open-label extension period and overall. Tables will show the overall number and percentage of participants

with at least one non-drug therapy/procedure of a particular primary SOC and at least one non-drug therapy/procedure of a particular PT.

2.5 Analysis supporting primary objective(s)

The primary objective is to explore the impact of ofatumumab on the ability to achieve NEDA-3 status in treatment-naïve, very early RRMS patients over an 18 month, open-label study period after a re-baseline of MRI at 6 months.

2.5.1 Primary endpoint(s)

The primary endpoint is NEDA-3 (relapse-free, 3-month clinical disability progression-free, MRI activity-free) in Months 6 to 18 (yes/no). The 3 components of the primary endpoint are defined as follows:

- Relapse-free is defined as no confirmed relapses. Partial relapse start and end dates will be imputed as outlined in Section 5.1.3.3. Criteria for the linking/combining of individual relapses is outlined in Section 5.1.3.4.
- 3-month clinical disability progression-free is defined as no clinical disability progression as measured by EDSS (global assessment scale), where 3-month confirmed clinical disability progression is defined as an increase from Month 6 in EDSS (global assessment scale) sustained for at least 3 months. That is, after a scheduled or unscheduled visit at which the participant fulfills the clinical disability progression criteria as outlined in Table 7, all EDSS assessments (scheduled or unscheduled) need to also fulfill the clinical disability progression criteria until the progression can be confirmed at the first scheduled visit that occurs in the absence of relapse (confirmed or unconfirmed) 3 months after the onset of the progression, or later. If a participant fulfills the clinical disability progression criteria based on the single EDSS assessment at Month 18, it will be considered a confirmed clinical disability progression (sustainment for at least 3 months will not be required). If a participant dies due to MS (i.e., EDSS = 10 at any time), it will be considered a confirmed clinical disability progression regardless of the Month 6 EDSS or change in EDSS.

Table 7 Criteria for clinical disability progression based on change from Month 6 in EDSS (global assessment scale)

EDSS at Month 6	Clinical disability progression criterion
0	≥ +1.5
1 to 5	≥ +1
≥5.5	≥ +0.5

- MRI activity-free is defined as no Gd+ lesions on any MRI scan (scheduled or unscheduled) after Month 6, or new/enlarging T2 lesions compared to Month 6 on any MRI scan (scheduled or unscheduled) after Month 6.

The primary estimand is described by the following attributes:

- **Population:** Defined through appropriate inclusion/exclusion criteria to reflect the targeted population. Young adult and very early RRMS (defined as within 6 months of diagnosis of clinically definite RRMS) patients that are DMT treatment naïve.

- **Variable:** NEDA-3 (relapse-free, clinical disability progression-free, MRI activity-free) in Months 6 to 18 (yes/no)
- **Treatment of interest:** An initial dose regimen consisting of doses administered at Baseline/Week 0 (Day 1), followed by Week 1 (Day 7), Week 2 (Day 14), and then every month thereafter, beginning at Week 4 (Month 1) until Month 18. All doses of ofatumumab will be given subcutaneously via an auto-injector at a dose of 20 mg. Healthy controls will be used for comparison purposes and will not receive study treatment.
- **Intercurrent event:** Treatment discontinuation due to lack of efficacy or death
- **Summary measure:** Proportion of participants achieving NEDA-3 in Months 6 to 18

2.5.2 Statistical hypothesis, model, and method of analysis

The number and percentage of participants achieving NEDA-3 in Months 6 to 18 will be presented using the mFAS. The 2-sided 95% CI for the proportion of participants achieving NEDA-3 in Months 6 to 18 will be calculated using an exact method (Clopper and Pearson, 1934).

2.5.3 Handling of intercurrent events

Handling of treatment discontinuations will follow composite variable strategy. For treatment discontinuation prior to Month 18 due to lack of efficacy or death, NEDA-3 and associated endpoints will be considered as “non-response”; if treatment discontinuation prior to Month 18 is due to reasons other than lack of efficacy or death, or if the Month 18 visit was completed but relapse/EDSS/MRI (Gd+ or new/enlarging T2 lesions) was missed at Month 6, 12 or 18, and disease activity was not shown (i.e., MRI activity after Month 6 through 18 or relapse/3-month clinical disability progression between Months 6 and 18), the participant will be excluded from mFAS for all NEDA-3 and associated endpoints efficacy analyses and thusly out of scope for intercurrent events handling; the rest of the participants had disease activities in Months 6 to 18, and NEDA-3 and associated endpoints for those participants will be considered as “non-response”.

2.5.4 Handling of missing values not related to intercurrent event

If treatment discontinuation prior to Month 18 is due to reasons other than lack of efficacy or death, or if the Month 18 visit was completed but relapse/EDSS/MRI (Gd+ or new/enlarging T2 lesions) was missed at Month 6, 12 or 18, and disease activity was not shown (i.e., MRI activity after Month 6 through 18 or relapse/3-month clinical disability progression between Months 6 and 18), the participant will be excluded from mFAS for all NEDA-3 and associated endpoints efficacy analyses and thusly out of scope for intercurrent events handling.

2.5.5 Sensitivity analyses

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

2.5.6 Supplementary analyses

The following supplemental analyses of the primary endpoint will be performed:

- An analysis using an observed case approach (completers) using the FAS based on participants who completed their Month 6 and Month 18 visits.

- An analysis using a non-response imputation (NRI) approach using the FAS. NRI will be applied to missing data regardless of intercurrent events. NRI is a conservative imputation method for dichotomous variables. For missing data, the primary endpoint will be imputed as "No". Refer to Section 5.1.3.3.
- An analysis using the mFAS in which the MRI activity-free component of NEDA-3 is defined as no new/enlarging T2 lesions compared to Month 6 on any MRI scan (scheduled or unscheduled) after Month 6
- An analysis using the mFAS in which the clinical disability progression-free component of NEDA-3 is based on 6-month clinical disability progression-free

For each of the supplemental analyses described above the number and percentage of participants achieving NEDA-3 in Months 6 to 18 will be presented. The 2-sided 95% CI for the proportion of participants achieving NEDA-3 in Months 6 to 18 will be calculated using an exact method (Clopper and Pearson, 1934).

2.6 Analysis supporting secondary objectives

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

Analysis of safety and PRO endpoints supporting secondary objectives is described in Section 2.7 and Section 2.10, respectively.

2.6.1 Secondary endpoint(s)

Secondary efficacy endpoints include the following:

- Number of confirmed relapses in Months 6 to 18
- 3-month disability worsening-free in Months 6 to 18 (yes/no)
- NEDA clinical (relapse-free, 3-month clinical disability progression-free) in Months 6 to 18 (yes/no)
- NEDA radiological (MRI activity-free) in Months 6 to 18 (yes/no) for ofatumumab-treated participants, where MRI activity-free is defined as no Gd+ lesions on any MRI scan (scheduled or unscheduled) after Month 6, or new/enlarging T2 lesions compared to Month 6 on any MRI scan (scheduled or unscheduled) after Month 6
- NEDA radiological (MRI activity-free) in Months 6 to 18 (yes/no) for ofatumumab-treated and healthy control participants, where MRI activity-free is defined as no new/enlarging T2 lesions compared to Month 6 on any MRI scan (scheduled or unscheduled) after Month 6
- Change from baseline, as well as change from Month 6 re-baseline, in the following conventional MRI metrics by time point: Gd+ lesion number, Gd+ lesion volume, T2 lesion volume and T1 unenhancing lesion volume
- Values of the following conventional MRI metrics by time point (baseline or post-baseline, as appropriate): new Gd+ lesion number, T2 lesion number, new/enlarging T2 lesion number, new unenhancing T1 lesion number and new/enlarging T2 lesion volume

- Percent change from baseline and percent change from Month 6 re-baseline in brain volume parameters (whole brain and regional) by time point (also obtained in healthy control participants for normalization purposes)

Note that Gd will not be given to healthy control participants and Gd enhanced T1 MRI imaging will not be conducted in healthy control participants.

2.6.2 Statistical hypothesis, model, and method of analysis

Values, changes from baseline and percent changes from baseline (brain volume parameters only) in the following endpoints will be summarized by Cohort and time point with descriptive statistics using the FAS or HCAS, as appropriate:

- Conventional MRI metrics including Gd+ lesion number, Gd+ lesion volume, T2 lesion volume and T1 unenhancing lesion volume
- Brain volume parameters (whole brain and regional)

In addition, changes and percent changes (for applicable endpoints) from Month 6 re-baseline to post-Month 6 time points will be summarized in a similar fashion.

Percent change from Month 6 re-baseline to post-Month 6 time points in brain volume parameters will be calculated via the following steps:

1. Calculate normalized brain volume (NBV) at post-baseline time points as follows (note that NBV at baseline and percentage brain volume change [PBVC] at post-baseline time points are provided by the MRI vendor):
   NBV at post-baseline time point = [(PBVC at post-baseline time point/100) x NBV at baseline] + (NBV at baseline)
2. Calculate the percent change from Month 6 re-baseline to post-Month 6 time points using the NBVs at Month 6 re-baseline and Months 12, 18 and 30 from Step 1 according to the formula provided in Section 2.1.1.

Values of the following endpoints will be summarized by Cohort and time point (baseline or post-baseline, as appropriate) with descriptive statistics using the FAS or HCAS, as appropriate:

- Conventional MRI metrics including new Gd+ lesion number, T2 lesion number, new/enlarging T2 lesion number, new unenhancing T1 lesion number and new/enlarging T2 lesion volume

The annualized new/enlarging T2 lesion rate will be calculated using a participant-based approach and a cohort-based approach as follows:

- Participant-based approach: [(number of new/enlarging T2 lesions in Months 6 to 18 for a given participant) / (number of days in Months 6 to 18 for a given participant)] × 365.25
- Cohort-based approach: [(total number of new/enlarging T2 lesions in Months 6 to 18 for all participants within a cohort) / (total number of days in Months 6 to 18 for all participants within a cohort)] × 365.25

The number of new/enlarging T2 lesions in Months 6 to 18 for each participant = Month 12 value (i.e., Month 12 scan relative to Month 6 scan) + Month 18 value (i.e., Month 18 scan relative to Month 12 scan). Participants are excluded from this calculation if the Month 6 value

(i.e., Month 6 scan relative to baseline scan) is missing. Only participants with a Month 6 value and at least one of the Month 12 or Month 18 values are included in this calculation.

The annualized new/enlarging T2 lesion rate (participant-based) will be summarized descriptively as a continuous variable by Cohort using the FAS or HCAS, as appropriate. The annualized new/enlarging T2 lesion rate (cohort-based), along with its components (i.e., numerator and denominator), will be reported by Cohort using the FAS or HCAS, as appropriate.

The annualized relapse rate (ARR) will be calculated using a participant-based approach and a cohort-based approach as follows:

- Participant-based approach: [(number of confirmed relapses in Months 6 to 18 for a given ofatumumab-treated participant) / (number of days in Months 6 to 18 for a given ofatumumab-treated participant)] × 365.25
- Cohort-based approach: [(total number of confirmed relapses in Months 6 to 18 for all participants within the ofatumumab-treated cohort) / (total number of days in Months 6 to 18 for all participants within the ofatumumab-treated cohort)] × 365.25

The ARR (participant-based) will be summarized descriptively as a continuous variable using the FAS. The ARR (cohort-based), along with its components (i.e., numerator and denominator), will be reported using the FAS. The ARR (both participant- and cohort-based) will also be derived though Month 18 and summarized descriptively using the FAS.

The number and percentage of participants with 0, 1, 2 or ≥3 confirmed relapses in Months 6 to 18 will be presented using the FAS. In addition, the number and percentage of participants with at least 1 confirmed relapse in Months 6 to 18 will be presented using the FAS. Participants with confirmed relapses through Month 18 will be summarized in a similar manner using the FAS.

The number and percentage of participants achieving 3-month disability worsening-free in Months 6 to 18 will be presented using an observed case approach (completers) using the FAS. The number and percentage of participants achieving NEDA clinical in Months 6 to 18 and NEDA radiological in Months 6 to 18 using the ofatumumab-treated participants derivation described in Section 2.6.1 will be presented using the mFAS. In addition, the number and percentage of participants achieving NEDA radiological in Months 6 to 18 using the ofatumumab-treated and healthy control participants derivation described in Section 2.6.1 will be presented using the mFAS or HCAS, as appropriate. The 2-sided 95% CI for the proportion of participants achieving each of these endpoints will be calculated using an exact method (Clopper and Pearson, 1934).

2.6.3 Handling of intercurrent events

For NEDA clinical in Months 6 to 18 and NEDA radiological in Months 6 to 18, the same approach outlined for NEDA-3 in Section 2.5.3 will be followed. For all other secondary endpoints, there is no imputation of missing data planned for this study.

2.6.4 Handling of missing values not related to intercurrent event

For NEDA clinical in Months 6 to 18 and NEDA radiological in Months 6 to 18, the same approach outlined for NEDA-3 in Section 2.5.4 will be followed. For all other secondary endpoints, there is no imputation of missing data planned for this study.

2.6.5 Sensitivity analyses

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

2.6.6 Supplementary analyses

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

2.7 Safety analyses

Analysis of safety endpoints supports secondary objectives.

2.7.1 Adverse events (AEs)

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

For reporting purposes, summary tables for AEs will summarize only the following events for ofatumumab-treated participants and healthy control participants:

- On-treatment events (treatment-emergent AEs), which started or worsened on or after the date of the first dose of ofatumumab for ofatumumab-treated participants
- On-study events, which started or worsened on or after the date of the date of Week 0 visit for healthy control participants

The number and percentage of participants with treatment-emergent/on-study AEs will be summarized for the open-label treatment phase, open-label extension period and overall, in the following ways using the SAF or HCAS, as appropriate:

- by Cohort, primary SOC and PT
- by Cohort, primary SOC, PT and maximum severity
- by Cohort and PT

Separate summaries will be provided using the SAF or HCAS, as appropriate, for treatment-emergent/on-study AEs occurring with a frequency of >5% in either Cohort, treatment-related AEs (only applicable to ofatumumab-treated participants), AEs leading to study drug interruptions (only applicable to ofatumumab-treated participants), serious adverse events (SAEs), treatment-related SAEs (only applicable to ofatumumab-treated participants) and other significant AEs leading to discontinuation.

In addition, an overview of treatment-emergent/on-study AEs will be summarized for the open-label treatment phase, open-label extension period and overall, presenting the number and percentage of participants having at least one AE for each of the categories described above.

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.

Partial AE start and end dates will be imputed as outlined in Section 5.1.2.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on on-treatment/treatment-emergent AEs which are not SAEs with an incidence greater than 5% and

on on-treatment/treatment-emergent SAEs and SAEs suspected to be related to study treatment will be provided by SOC and PT on the SAF.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- A single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- More than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE/SAE suspected to be related to study treatment/non-SAE has to be checked in a block e.g., among AEs in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.7.1.1 Adverse events of special interest / grouping of AEs

The number and percentage of participants with at least one treatment-emergent AE in each of the following categories will be presented for the open-label treatment phase, open-label extension period and overall using the SAF:

- Injection site reaction
- Injection systemic reaction

2.7.2 Deaths

All deaths, including on-treatment and post-treatment deaths for ofatumumab-treated participants, will be listed.

2.7.3 Laboratory data

Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value for hematology and chemistry parameters using the SAF. In particular, the number and percentage of participants with laboratory values will be presented by low/normal/high/ (low and high) classifications to compare baseline to worst on-treatment value for the open-label treatment phase, open-label extension period and overall. Unscheduled assessments will be considered.

Values and changes from baseline in hematology and chemistry parameters will be summarized by time point with descriptive statistics using the SAF.

Laboratory abnormalities will be flagged in listings.

2.7.4 Other safety data

2.7.4.1 Vital signs

Values and changes from baseline in the following vital signs will be summarized by Cohort and time point with descriptive statistics using the SAF or HCAS, as appropriate:

- Sitting systolic blood pressure (mmHg), sitting diastolic blood pressure (mmHg), pulse rate (beats per minute) and body temperature (°C)

2.7.4.2 Smoking status

The number and percentage of participants in each smoking status category (Former, Current, Never) will be presented by Cohort, time point and type of substance (Tobacco, Marijuana, Vape, Other substance) using the SAF or HCAS, as appropriate. In addition, at each time point the number and percentage of participants who are former or current smokers of any type of substance will be presented separately by Cohort using the SAF or HCAS, as appropriate

2.7.4.3 Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a questionnaire that prospectively assesses suicidal ideation and suicidal behavior. The number and percentage of participants in the following categories will be presented by analysis period/study phase (all prior history, recent history, open-label treatment phase, open-label extension period and overall) using the SAF.

- Each of the 10 individual suicidal ideation and behavior categories (during the analysis period/study phase of interest)
- Any suicidal ideation (answer of 'yes' to at least 1 of the 5 suicidal ideation questions during the analysis period/study phase of interest)
- Any suicidal behavior (answer of 'yes' to at least 1 of the 5 suicidal behavior questions during the analysis period/study phase of interest)
- Any suicidal ideation or behavior (answer of 'yes' to at least 1 of the 10 suicidal ideation and behavior questions during the analysis period/study phase of interest)
- Non-suicidal self-injurious behavior (during the analysis period/study phase of interest)

The analysis period 'All prior history' includes data from the Lifetime assessment obtained at Screening or Baseline/Week 0. The analysis period 'Recent history' includes data from the Past 6 Months assessment obtained at Screening or Baseline/Week 0. If there are multiple assessments within an analysis period/study phase, results will be derived as the worst-case value (i.e., an answer of 'yes' for the category) for that analysis period/study phase.

In addition, the number and percentage of participants with the following post-baseline events will be presented (Nilsson et al., 2013) by study phase (open-label treatment phase and open-label extension period) using the SAF. Note: In these definitions, a category of 0 is assigned to a participant without suicidal ideation (i.e., a 'no' answer to all suicidal ideation categories).

- Worsening suicidal ideation compared to recent history: An increase in the maximum suicidal ideation category at any time post-baseline from the maximum suicidal ideation category during pre-treatment recent history.
- Worsening serious suicidal ideation compared to recent history: An increase in the maximum suicidal ideation category to 4 or 5 at any time post-baseline from not having serious suicidal ideation (categories of 0-3) during pre-treatment recent history.
- Emergence of serious suicidal ideation compared to recent history: A maximum suicidal ideation category of 4 or 5 at any time post-baseline from no suicidal ideation (category 0) during pre-treatment recent history.

- Improvement in suicidal ideation at last on-treatment measurement compared to recent history: A decrease in suicidal ideation score at last on-treatment measurement from pre-treatment recent history.
- Emergence of suicidal behavior compared to all prior history: The occurrence of suicidal behavior (categories 6-10) at any time post-baseline from not having suicidal behavior (categories 6-10) prior to treatment (includes "lifetime" and any other assessments prior to treatment taken prior to treatment).

A participant can only be counted once within a given category; however, a participant can be counted in more than one category. Suicidal ideation and behavior data will be listed. Detailed answers to C-SSRS items will be listed separately for participants with any suicidal ideation at any time post-baseline (i.e., a 'yes' answer to at least one of the five suicidal ideation questions at any time post-baseline) and for participants with any suicidal behavior at any time post-baseline (i.e., a 'yes' answer to at least one of the five suicidal behavior questions at any time post-baseline). Additional details are provided in the TFL Shells document.

2.8 Pharmacokinetic endpoints

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

2.9 PD and PK/PD analyses

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

2.10 Patient-reported outcomes

PRO measures included in this study are the NeuroQOL™ and the PDDS. Analysis of these PRO measures supports secondary objectives.

The NeuroQOL™ is a measurement system that evaluates and monitors the physical, mental, and social effects experienced by adults and children living with neurological conditions (://.healthmeasures.net/explore-measurement-systems/neuro-qol; Miller et al., 2016). The following domains will be measured:

- Physical Health: Fatigue, Sleep disturbance, Lower Extremity function (mobility), Upper Extremity Function (Fine motor, ADL), Urinary/Bladder Function and Bowel Function (custom 14-item short form)
- Mental Health: Anxiety, Depression, Cognitive Function, Communication, Positive Affect and Well-Being
- Social Health: Ability to Participate in Social Role and Activities

The PDDS is a standardized rating scale developed by Hohol et al. 1995, which is a self-assessment scale of functional disability in multiple sclerosis patients primarily based on ambulation. The questionnaire contains 1 question which is scored ranging from 0 (normal) to 8 (bedridden) (://.nationalmssociety.org/For-Professionals/Researchers/Resourcesfor-Researchers/Clinical-Study-Measures/Disease-Steps-(DS)). A score of 0 to 2 indicates mild disability; a score of 3 to 5 indicates moderate disability; a score of 6 to 8 indicates severe disability (Hohol et al., 1995).

Values and changes from baseline in NeuroQOL™ short form domain T-scores, and the PDDS score, will be summarized by Cohort and time point with descriptive statistics using the FAS or HCAS, as appropriate. In addition, changes from Month 6 to post-Month 6 time points will be summarized in a similar fashion.

Details on the derivation of total raw scores and the conversion of those total raw scores to T-scores for the NeuroQOL™ short form domains are provided in the TFL Shells document; they are based on NeuroQOL™ Scoring Manual version 5.0 dated September 2022. Note that total raw scores and T-scores will not be derived for the urinary and bowel custom 14-item short form. In addition, only the total raw score for the communication short form domain will be summarized; no T-score is determined since this short form domain is comprised of uncalibrated items.

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2.13 Interim analysis

There will be one interim analysis after the last participant completes his/her Month 18 (primary analysis time point) visit.

The presentation of tables, listings, and figures will include data up to participants' date of Month 18 visit (inclusive). All available data for participants discontinuing the study prior to Month 18 will be included in the interim analysis.

This interim analysis will be the primary analysis. There will be neither hypothesis testing nor estimation at Month 30. Therefore, no statistical adjustment will be made at Month 18.

3 Sample size calculation

3.1 Primary endpoint(s)

Ofatumumab sample size calculations were based on the proportion of participants with NEDA-3 in Months 6 to 18.

A sample size of 100 participants will provide a 7.8% precision (half-width of 95% CI), or a 7.0% precision corresponding to estimated proportions of 80% and 85% of participants achieving NEDA-3. Adjusting for a 15% drop out rate, 118 participants will be enrolled in the study.

3.2 Secondary endpoint(s)

A sample size of 50 age- and sex-matched healthy controls with no diagnosis of neurologic disease will be enrolled.

4 Change to protocol specified analyses

Changes to analyses specified in CSP version 03 dated 14-Sep-2023 at the time of SAP amendment 1 finalization on 29-Oct-2024 are as follows (relevant SAP section[s] are indicated in parentheses):

- Changed the primary clinical question of interest in primary estimand section to be focused on NEDA-3 at 18 months (Section 1.2.1)
- Changed the definition of intercurrent event for primary estimand to be treatment discontinuation due to lack of efficacy or death (Section 1.2.1 and Section 2.5.1)
- Updated the definition of the HCAS to remove the requirement for having at least one valid assessment of variables of interest (Section 2.2)
- Defined a new analysis set, the modified FAS (mFAS), to be used for NEDA-3, NEDA clinical and NEDA radiological efficacy analyses (Section 2.2 and Section 2.6.2)
- Defined a new analysis set, the per-protocol set (PPS), to be used for a supplemental efficacy analysis of NEDA-3 (Section 2.2 and Section 2.5.6)
- Changed the handling of intercurrent events for the primary estimand to reflect a composite variable strategy for the handling of treatment discontinuations (Section 2.5.3)

- Changed the handling of missing values not related to intercurrent events for the primary estimand to clarify that, if treatment discontinuation is due to reasons other than lack of efficacy or death, participants who had NEDA-3 before early discontinuations will be excluded from mFAS for all NEDA-3 and associated endpoints efficacy analyses and thusly out of scope for intercurrent events handling (Section 2.5.4)
- Specified supplemental analyses of the primary endpoint (Section 2.5.6):
  - Using an observed case approach (completers) using the FAS
  - Using the PPS
  - Using the mFAS in which the MRI-activity free component of NEDA-3 is defined as no new or enlarging T2 lesions
  - Using the mFAS in which the clinical disability progression-free component of NEDA-3 is based on 6-month clinical disability progression-free
- Clarified that secondary endpoints 'Number of confirmed relapses' and '3-month disability worsening-free' are derived in Months 6 to 18 (Section 1.2 and Section 2.6.1)
- Indicated that change and percent change (lesion volume and brain volume parameters) from Month 6 re-baseline to post-Month 6 time points in conventional MRI metrics will be evaluated (Section 2.6.1 and Section 2.6.2); clarified 'brain volume loss assessment' as 'brain volume assessment' (Section 1.2)
- [redacted]
- [redacted]

Changes to analyses specified in CSP version 03 dated 14-Sep-2023 at the time of SAP amendment 2 finalization on 22-Apr-2025 are as follows (relevant SAP section[s] are indicated in parentheses):

- [redacted]

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

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

5.1.2 AE date imputation

The following algorithm will be used to estimate AE start dates for which only partial information is known. Note that "index date" refers to the date of the first dose of ofatumumab for ofatumumab-treated participants and the date of the Week 0 visit for healthy control participants.

Missing day and month:

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

Missing month only:

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

Missing day only:

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

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

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

Missing year:

- Date left missing.

Missing month:

- Impute 'December'.

Missing day:

- Impute 'last date of that month'.

5.1.3 Concomitant medication date imputation

The following algorithm will be used to estimate medication start dates for which only partial information is known. Note that "index date" refers to the date of the first dose of ofatumumab for ofatumumab-treated participants and the date of the Week 0 visit for healthy control participants.

Missing day and month:

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

Missing month only:

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

Missing day only:

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

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

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

Missing year:

- Date left missing.

Missing month:

- Impute 'December'.

Missing day:

- Impute 'last date of that month'.

5.1.3.1 Prior therapies date imputation

Same as for medications above.

5.1.3.2 Post therapies date imputation

Same as for medications above.

5.1.3.3 Other imputations

Non-response imputation

NRI assumes that a participant is a non-responder (treatment failure) if the participant does not have a complete set of valid response assessments (relapse, disability [EDSS] and MRI) in Months 6 to 18 after receiving at least one dose of ofatumumab. Hence, for missing data the primary endpoint of NEDA-3 in Months 6 to 18 (yes/no) will be imputed as "No".

MS relapse date imputation

Missing or partial MS relapse start and end dates are not expected.

The following algorithm will be used to estimate MS relapse start dates for which only partial information is known (i.e., month and year are available but day is missing). Note that "index date" refers to the date of the first dose of ofatumumab.

Missing day only:

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

The following algorithm will be used to estimate MS relapse stop dates for which only partial information is known (i.e., month and year are available but day is missing). Note that "index date" refers to the date of the first dose of ofatumumab.

Missing day only:

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

MS history date imputation

For the derivation of "time from onset of most recent relapse to first dose of ofatumumab", "time from RRMS diagnosis to first dose of ofatumumab" and "time from first MS symptoms to first dose of ofatumumab" (see Section 2.3.3), the following algorithm will be used to estimate most recent relapse onset dates, RRMS diagnosis dates and first MS symptoms dates for which only partial information is known.

Year is missing or impossible (e.g., 12-Jan-1911):

- Date will be imputed as missing.

Missing day and month:

- July 1 will be assigned to the missing day and month.

Missing day only:

- The 15th of the month will be assigned to the missing day.

The imputed date should be prior to the date of the Screening visit. However, if the imputed date is on or after the date of the Screening visit, it will be reset to be one day prior to the Screening visit date.

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

According to 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 less than 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 assessment meets the above criteria, take the date of EDSS by which the worst severity value is derived.
  - If no EDSS assessment meets the above criteria, take the earliest date of EDSS as captured on the relapse CRF page.
- "Affects daily activities?", "Was the participant hospitalized for this MS relapse?", "Was corticosteroid treatment taken for this MS relapse?", "Recovery from MS relapse": for each of these characteristics, take the value representing the worst case (i.e., yes > no for first 3 questions; no > partial > complete recovery for last question).

The maximum duration of a relapse is 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 record created by the above procedure. A missing end date of relapse is not allowed. In the rare case that a 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

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

5.3 Laboratory parameters derivations

The following derivations will be performed for continuous laboratory variables:

- If variables are databased as <lower limit, these will be imputed as being half of the lower limit. For example, Brain-Derived Neurotrophic Factor with a value of <.013000000 will be imputed to be 0.0065.
- If variables are databased as >upper limit, these values will be excluded from the analysis.

5.4 Statistical models

5.4.1 Analysis supporting primary objective(s)

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

5.4.2 Analysis supporting secondary objective(s)

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

5.5 Rule of exclusion criteria of analysis sets

Deviation ID	Description of deviation	Exclusion in analyses
I01	Participant's signed informed consent was not obtained prior to participation in the study	Exclude from all analysis sets (FAS, mFAS, SAF and HCAS)

Analysis set	PD ID(s) that cause participants to be excluded	Non-PD criteria that cause participants to be excluded
FAS	I01	Not enrolled; Did not take any study drug
mFAS	I01	Not in FAS; See mFAS definition in Section 2.2 for additional exclusion criteria
SAF	I01	Did not take any study drug
HCAS	I01	Not applicable

5.6 Ofatumumab dose dates during open-label treatment phase and open-label extension period

The date of the last dose of ofatumumab during the open-label treatment phase and the date of the first dose of ofatumumab during the open-label extension period will be determined according to the following three participant scenarios.

1. Completed Month 18 visit and continued into open-label extension period
   a. Last dose date of ofatumumab during open-label treatment phase is last dose date < Month 18 visit date
   b. First dose date of ofatumumab during open-label extension period is first dose date ≥ Month 18 visit date
2. Completed Month 18 visit and did not continue into open-label extension period
   a Last dose date of ofatumumab during open-label treatment phase is last dose date ≤ Month 18 visit date
3. Did not complete Month 18 visit
   a. Last dose date of ofatumumab during open-label treatment phase is last dose date ≤ Month 18 interim analysis data cut-off date
   b. First dose date of ofatumumab during open-label extension period is first dose date > Month 18 interim analysis data cut-off date

6 Reference

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