NOVARTIS

Clinical Development

OMB157/Ofatumumab

COMB157GUS07 / NCT04486716

A single-arm, prospective, multi-center study to explore maintained efficacy with ofatumumab therapy in patients with relapsing Multiple Sclerosis who discontinue intravenously delivered anti-CD20 monoclonal antibody (aCD20 mAb) therapy (OLIKOS)

Statistical Analysis Plan (SAP)

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04-Jul-2023	*Prior to DB lock*	*Incorporate protocol amendment, and dry run changes.*	*Amendment 1.0 approved in the documentation management system*	*Section 1 Figure 1-1. Replaced with new study design as per protocol amendment.* [redacted] *Section 2.1. Site 1003 removed from analysis due to investigator disqualification.* *Section 2.1.1.7. Added detail for the definition of the safety follow-up period.* *Section 2.1.1.11. Added section for "discontinuation from study treatment".* *Section 2.1.1.12. Added section for "discontinuation from study".* [redacted] *Section 2.4.2.1. Updated the visit windows.*

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				Section 2.8.1. Definition of treatment emergent adverse event updated. *Section 2.8.1.3. Updated to include summary of all deaths.* *Section 2.8.2.1. Additional summary of historical change of IgG/IgM added.* *Clarification added for baseline derivation of IgG/IgM.* [redacted] *Section 2.14. Data cut-off details for interim analysis added.* *Section 4 Table 4-1. Update change to protocol specified analyses to not applicable.* *Section 5.1.3.3. Details of time imputation derivation added.* *Section 5.5. Added rule to exclude site 1003 from the analysis sets.*

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
				General. [redacted]
13-Nov-2023	*Prior to DB lock*	*Incorporate changes from CSR dry run review*	*Amendment 2.0 approved in the documentation management system*	*Section 2.1. Added detail to clarify the definition of core and post-treatment phases.* *Section 2.1.1.7. Removed criteria in definition of the safety follow-up period.* *Section 2.1.1.9. Updated the definition of the safety analysis cut-off.* *Section 2.3.3. Tests added to summary of MS baseline characteristics.* *Section 2.4.2. Added text clarifying presentation of by visit outputs. Simplified the definition of the visit windows.* *Section 2.4.2.2. Changed to make similar to 2301 study.* *Section 2.5.4.1. Details of supplementary analyses provided.* *Section 2.8.8.3. Removed vital signs analyses of pre-injection to post-injection.* [redacted]

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
				[redacted] *Section 5.1.3. Further details added to imputation rules for concomitant medications.* [redacted] *Section 5.5. Added SAS code for the MMRM analyses.*
29-Jan-2024	*Prior to DB lock*	*Incorporate changes from CSR dry run review*	*Amendment 3.0 approved in the documentation management system*	*Section 2.1. Added text detailing post-treatment safety follow analysis.* *Section 2.4.2.1. Added serology.* *Section 2.4.2.2 Added Table 2-4 detailing the visit windows for morphology.* *Section 2.5.2. Added details of other intercurrent events to align with the protocol. Added detail for the use of non-responder imputation.* *Section 2.5.2, 2.5.4. Added clarification that assessments after the cut-off are not considered for the analysis.* [redacted]

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
				[redacted] *Section 5.5. Added details to the description for site/investigator disqualification. Included new reason of exclusion based on prohibited medication.*
23-Feb-2024	*Prior to DB lock*	*Incorporate detail, and DQT meeting action.*	*Amendment 4.0 approved in the documentation management system*	*Section 5.4.2. Added detail to TSQM-9 scoring.* *Section 5.5. Included new reason of exclusion from analyses based on assessments performed after withdrawal of consent.*

Table of contents

List of abbreviations

AE	Adverse event
AESI	Adverse events of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
[redacted]	[redacted]
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Classification
BMI	Body mass index
CDBL	Clinical database lock
CMD	Concomitant medication
CRF	Case Report Form
CSR	Clinical Study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTT	Clinical Trial Team
DMT	Disease Modifying Therapy
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eCRS	Electronic Case Retrieval Sheet
[redacted]	[redacted]
EOS	End of study
FACS	Fluorescence activated cell sorting
FAS	Full analysis set
FDA	Food and Drug Administration
FU	Follow-up
GdE	Gadolinium enhancing lesion
[redacted]	[redacted]
GPS	Global Programming and Statistical Environment
LLN	Lower limit of normal
LPLV	Last patient last visit
mAb	Monoclonal Antibody
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NBS	Novartis Business Services
[redacted]	[redacted]
[redacted]	[redacted]
NRI	Non-responder imputation
PD	Protocol deviation
[redacted]	[redacted]
PK	Pharmacokinetics

[redacted]	[redacted]
PT	Preferred term
RAP	Report and Analysis Process
RMS	Relapsing Multiple Sclerosis
RRMS	Relapsing-remitting Multiple Sclerosis
SAE	Serious adverse event
SAF	Safety set
SAP	Statistical Analysis Plan
SOC	System Organ Class
SPMS	Secondary Progressive Multiple Sclerosis
TEAE	Treatment emergent adverse event
TSQM-9	Treatment Satisfaction Questionnaire for Medication
WHO	World Health Organization
WHODD	WHO Drug Dictionary

1 Introduction

The purpose of this Statistical Analysis Plan (SAP) is to describe the statistical methods planned in Section 12 of the clinical study protocol version 02 (release date 28 June 2022) for the clinical trial COMB157GUS07 and any additional analyses, specifications or deviations from this protocol planned before clinical database lock (CDBL).

The SAP will be used to draft the Clinical Study Report (CSR) Section 9.7: Statistical methods and IA plans.

1.1 Study design

This is a single-arm, multi-center, prospective study in patients with relapsing multiple sclerosis (RMS) who have been previously treated with anti-CD20 (aCD20) monoclonal antibody (mAb) therapy and have received at least 2 consecutive courses of intravenously administered ocrelizumab or rituximab every 6 months and the last dose is within 4 to 9 months before Baseline/Day 1.

In this study, participants may enroll only if discontinuing aCD20 therapy for reasons other than lack of efficacy or due to certain treatment-emergent adverse events. Reasons for switching may include but are not limited to physician/participant preference, access to commercial drug (e.g., insurance coverage issues) or for other logistical reasons (such as geographical relocation, travel, etc.).

A total of approximately 100 eligible participants will be enrolled as part of this study. Participants will receive open label ofatumumab 20 mg subcutaneous once monthly for 12 months following initial loading regimen of 20 mg subcutaneous doses on Days 1, 7 and 14.

For participants completing the trial, the total duration of the trial will be a minimum of 14 months. This accounts for the:

- 28 day screening period
- 12 month treatment period
- 30 day telephone safety follow-up

Participants are considered as having completed the study after completing the 12 month treatment period and attending the End of Study (EOS) visit. For participants who discontinue study treatment prematurely for any reason before the end of the 12 month treatment period, an EOS visit will be performed within 7 days of study discontinuation.

Additional post-treatment safety follow-up will be applicable for participants who:

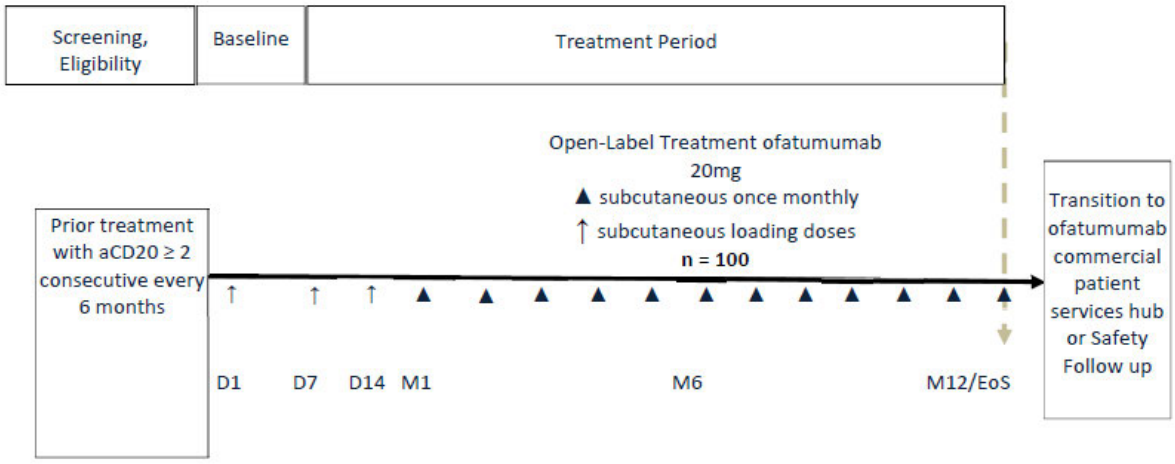
- Complete the Treatment period and do not continue on any MS disease modifying therapy (DMT)
- Do not continue into the ofatumumab commercial patient services hub within one month of the End of Study (EOS) visit, where the EOS visit is defined as the last patient's last visit (LPLV), which is the last patient's Month 12 visit, or the visit scheduled at the time of study discontinuation.
- Prematurely discontinue study drug and do not continue on an MS DMT.

The post-treatment safety FU period will consist of visits every 3 months post EOS. Assessments will include B cell monitoring until participants are able to start on commercial ofatumumab or until they switch to another therapy or until their B cells are repleted, where B cell repletion is defined as a B cell concentration greater than the individual participant's baseline value prior to starting the IV anti-CD20 mAb or greater than the lower limit of normal.

All post-treatment safety FU visits will be scheduled relative to the EOS visit.

The following Figure 1-1 describes the study design.

Figure 1-1 Study design



1.2 Study objectives and endpoints

Table 1-1 Study objectives and endpoints

Objectives(s)	Endpoint(s)
Primary objective(s) • Explore maintenance of efficacy of ofatumumab in participants with RMS transitioning from aCD20 therapy	**Endpoint(s) for primary objective(s)** • No change or a reduction from baseline in the number of gadolinium enhancing lesions observed by MRI at 12 months of ofatumumab treatment (yes, no)
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• Characterize participants retention, immune biomarkers, treatment satisfaction, and safety and tolerability at 6 and 12 months after transitioning to ofatumumab	• Retention on ofatumumab treatment from baseline to Month 6 and to Month 12 (Yes, No) • Change from baseline in lymphocytes, including total CD19+ B cell counts and CD20+CD3+ T cell counts, obtained by fluorescence activated cell sorting (FACS) at Months 6 and 12 • C-SSRS at Months 6 and 12

Objectives(s)	Endpoint(s)
	• Treatment Satisfaction Questionnaire for Medication (TSQM-9) scores (including domains) at baseline vs Month 6 and vs Month 12 • Treatment-emergent adverse events

2 Statistical methods

2.1 Data analysis general information

The statistical analysis outlined in this SAP will be performed by Novartis Business Services (NBS) CONEXTS, using SAS® version 9.4 or higher software, and stored in the Novartis Global Programming and Statistical Environment (GPS).

It is planned that the data from all centers that participate in this protocol will be used for analysis.

For continuous variables, summary statistics will include number of participants (n), mean, standard deviation, minimum, 25th percentile, median, 75th percentile, and maximum.

For categorical variables, frequency counts and percentages will be reported.

Unless otherwise specified, summary statistics tables will include change from baseline.

The study will be divided into two phases (the core and post-treatment safety FU phase) for the purpose of preparing the CSR.

- **Core phase:** The core phase will cover the on-treatment period up Month 12 visit date, or EOS date plus the 30 day Safety Telephone FU for participants who discontinue prematurely. The primary objective will be analyzed for the core phase and will be reported in the analysis CSR. All data up to this date will be reported in the analysis CSR.
- **Post-treatment phase:** The post-treatment phase will cover the post-treatment safety follow-up period which extends from the EOS (+ every 3 months) until the date of B cell repletion for study completers until the participant initiates a commercial MS disease modifying therapy or until the end of the safety follow-up for premature withdrawals. This overlaps with the 30 day Safety Telephone FU. All safety data from the EOS to 30 day Safety Telephone FU will be reported as part of the core phase. Post-treatment phase will be reported in the final CSR. Data collected during the post-treatment safety FU will be listed.

2.1.1 General definitions

2.1.1.1 Investigational treatment/investigational drug

The investigational treatment is open label ofatumumab 20 mg (20 mg/0.4 ml) provided in an auto injector for subcutaneous administration. The investigational drug will be supplied by Novartis. Throughout the remainder of this document the investigational treatment will be referred to as study treatment/study drug.

2.1.1.2 Date of first/last administration of study treatment

The date of first administration of study treatment is defined as the first date when a non-zero dose of study treatment is administered and recorded on the "Study Treatment - Injection" electronic Case Report Form (eCRF).

The date of last administration of study treatment is defined as the last date when a non-zero dose of the study treatment is recorded on the "Study Treatment - Injection" eCRF.

2.1.1.3 Study day

The first day of administration of study treatment (first dose) is defined as *Study Day 1* or *Day 1*. All other study days will be labeled relative to Day 1.

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

(Date of event − date of first dose) + 1

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

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

(Date of event − date of first dose)

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

The descriptor "Day 0" will not be used.

2.1.1.4 1 month

For reporting of event durations and determining target days of scheduled visits, 1 month will be considered as 365.25/12=30.4375 days.

Unless specified otherwise, study days will be reported to the nearest whole number.

2.1.1.5 Screening, baseline and post-baseline definitions

Screening refers to any procedures (e.g., checking inclusion and exclusion criteria) performed prior to the date of the first dose of study treatment. Per protocol, participant informed consent must be obtained prior to performing any study related activity. The date of signing of informed consent is the start date of the screening period. Any assessment obtained during the screening period will be labelled screening assessment.

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

For blood pressure **vital sign values**, the baseline is the average of the non-missing values of the 3 measurements taken on the last visit prior to the first administration of study drug.

2.1.1.6 On-treatment period (efficacy analyses)

The on-treatment period for efficacy analyses is defined as:

(Last study treatment administration date − first study treatment administration date) + 31.4375

The on-treatment period definition applies to efficacy analyses only. This definition considers that participants are scheduled to administer the study drug once monthly.

2.1.1.7 Post-treatment safety follow-up period

The post-treatment safety follow-up period is defined as:

(Date of B cell repletion – last actual study treatment administration date) + 1, for study completers

Or

(Date of initiation of a commercial MS disease modifying therapy – last actual study treatment administration date) + 1

2.1.1.8 Efficacy analysis cut-off

The efficacy analysis cut-off date is 30.4375 days after the date of last study treatment administration.

2.1.1.9 Safety analysis cut-off

The safety analysis cut-off is the same as the efficacy analysis cut-off. The safety analysis cut-off is 30 days after the treatment end date but for programming purposes 30.4375 days will be used.

2.1.1.10 Change from baseline

Change from baseline will be calculated as:

(Post-baseline value − baseline value)

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

2.1.1.11 Discontinuation from study treatment

Discontinuation of study drug for a participant occurs when study drug is permanently stopped for any reason (prior to the planned completion of study drug administration, if any), and can be initiated by either the participant or the Investigator.

2.1.1.12 Discontinuation from study

Discontinuation from study for a participant occurs when they permanently stop receiving the study treatment, and further protocol-required assessments or follow-up, for any reason.

2.2 Analysis sets

Full analysis set

The Full Analysis Set (FAS) comprises all participants who have received at least one dose of the investigational drug.

Safety set

The Safety Set (SAF) is identical to the FAS in this study.

2.2.1 Subgroup of interest

There is no subgroup analysis planned for this study.

2.3 Patient disposition, demographics and other baseline characteristics

Unless stated otherwise, all patient disposition, demographics, medical history and baseline characteristics data will be listed and summarized descriptively for the FAS.

2.3.1 Patient disposition

Participant disposition will be summarized for the following study periods: screening, baseline, study and 30 day Telephone follow-up.

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

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

For each protocol deviation, the number and percentage of participants for whom the deviation applies will be tabulated.

2.3.2 Demographics

The following demographic variables will be listed and summarized descriptively:

Continuous variables

- Age (years)
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2) = (weight in kg)/(height in meters)^2

Weight and height will be reported as captured in the "Vital signs" eCRF page at baseline. If there is no weight recorded prior to taking of study treatment, BMI will be missing.

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), Native Hawaiian or Pacific Islander, American Indian or Alaska Native, Multiple)

2.3.3 Baseline characteristics

Baseline disease characteristics will be summarized for the following variables:

- **MS baseline characteristics:**
  - [redacted]
  - Baseline lymphocyte value, including reporting of lymphocyte abnormalities (CTCAE grade).
  - [redacted] Immunoglobulin G (IgG) and Immunoglobulin M (IgM) value.
  - MRI parameters including:
    - Number of GdE enhancing T1 lesions
    - Number of GdE enhancing T1 upper cervical cord lesions
    - [redacted]
    - [redacted]

- **MS disease history:**
  - Duration of Multiple Sclerosis (MS) since diagnosis (years) defined as: (first study treatment administration date − date of MS diagnosis + 1)/365.25
  - Duration of MS since first symptom (years) defined as: (first study treatment administration date − first MS symptom date + 1)/365.25
  - Number of relapses in the last 12 months prior to screening
  - Number of relapses in the 12 to 24 months prior to screening
  - Type of MS at study entry (Relapsing-remitting MS (RRMS), Secondary progressive MS (SPMS))
  - Time since onset of most recent relapse (months) prior to screening defined as: (first study treatment administration date − most recent relapse onset date + 1)/(365.25/12)
- **Participants' employment status** (part-time, full-time, not employed)

2.3.4 Medical history

Relevant medical histories and current medical conditions at baseline (i.e., prior to the first dose of the study treatment) will be summarized by system organ class (SOC) and preferred term (PT) for the SAF.

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

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

Unless otherwise stated, the SAF will be used for all treatment summaries.

2.4.1 Study treatment / compliance

Exposure to study treatment

Duration of exposure to the study treatment will be calculated as

(date of last administration of study drug – date of first administration of study drug + 1 + 30.4375 – Σ [$(j + 1)^{th}$ administration date – j^{th} administration date – 33.4375]).

Where j and j + 1 refer to consecutive study drug administration dates more than 33.4375 days apart (as participants are scheduled to receive the study drug once monthly ± 3 days).

The duration of exposure will include any periods of temporary dose interruption.

Duration of exposure to the study drug will be summarized by duration category (i.e., ≥1 week, ≥2 weeks, ≥3 weeks, ≥4 weeks, ≥8 weeks, ≥12, weeks, ≥24 weeks, ≥36 weeks, and ≥48 weeks, >=52 weeks).

A listing of the drug doses administered will be provided.

Treatment compliance

Compliance to the study drug administration schedule will be calculated as:

(Duration of exposure to study drug in (days)/duration of on-treatment period in (days)) × 100%

This rule means that compliance will be measured during the time interval the participant took study drug: premature discontinuation from study drug will not be considered non-compliance. Compliance to study drug administration will be summarized descriptively for the SAF. In addition, compliance will be summarized with cumulative number and percentage of participants in each compliance category (i.e., ≥ 20%, ≥ 30%, ≥ 40%, ≥50%, ≥60%, ≥70%, ≥80%, ≥90%, ≥95%, ≥98%, =100%).

2.4.2 Visit windows

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

The visit windows for the on-treatment period are shown in Table 2-1. In this table, the days are counted since the first dose of study treatment (study days) for safety and efficacy assessments. These windows apply to measurements taken at every visit. For assessments collected less often different visit windows will be applied as detailed below. Similarly, visit windows for the post-treatment safety follow-up period are shown in Table 2-2. Unless specified otherwise these windows will be applied for all assessments.

When visit windows are used, all visits will be re-aligned, i.e., they will be mapped into one of the visit windows. E.g., if the Visit 4 visit of a participant is delayed and occurs on Day 62 instead of on Day 30, say, it will be re-aligned to visit window Visit 5. In the case of major deviations from the visit schedule, or due to unscheduled visits, several assessments of a participant may fall in a particular visit window (either scheduled or unscheduled). Statistical approaches to handle multiple assessments in a given visit window are specified below.

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 patient might be summarized.

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

- Transform all scheduled assessment time points into study days, assuming 1 month is equal to 30.4375 days. Middle points of scheduled assessments are determined.
- The time window associated with the previous assessment ends prior to the middle point; the time window associated with the latter assessment begins after the middle point. In case the middle point is an exact study day, it will belong to the previous assessment.
- The time window of first post-baseline assessment starts with Study Day 2, unless otherwise indicated.

- For parameters, which are not collected at every visit, visit windows will be combined. For example, if a parameter is measured at Month 2 and Month 12 only, Month 2 visit window will extend from Month 2 to Month 12 (combining Month 2 and Month 12 visit windows).

Table 2-1 Visit windows for the on-treatment period

Analysis visit	Time point	Scheduled visit day (study days)	Visit window (study days)
Baseline	Day 1	1	-28 to 1*
Visit 2	Day 7	7	2 to 10
Visit 3	Day 14	14	11 to 22
Visit 4	Month 1	31	23 to 46
Visit 5	Month 2	62	47 to 77
Visit 6	Month 3	92	78 to 107
Visit 7	Month 4	123	108 to 138
Visit 8	Month 5	153	139 to 168
Visit 9	Month 6	184	169 to 199
Visit 10	Month 7	214	200 to 229
Visit 11	Month 8	245	230 to 260
Visit 12	Month 9	275	261 to 290
Visit 13	Month 10	305	291 to 320
Visit 14	Month 11	336	321 to 351
EOS (Visit 15)	Month 12	366	352 to 381
30-day tel. safety FU	Month 13	396	382 to 427

*Baseline measurement before the first study drug administration for safety and efficacy assessments.

Table 2-2 Visit windows for the post-treatment safety follow-up period

Analysis visit	Time point	Scheduled visit day (study days)	Visit window (study days)
Safety FU visit 1	EOS + 3 months	458	428 to 503
Safety FU visit 2	EOS + 6 months	549	504 to 594
Safety FU visit 3	EOS + 9 months	640	595 to 685
Safety FU visit n (n>3)	EOS + n*3 months	640+91*(n-3)	595+91*(n-3) to 685+91*(n-3)

2.4.2.1 Vital signs, laboratory, biomarker and questionnaire

Chemistry , Hematology, Sample for CD+19 B-cells & CD20+CD3+ T-cells, LBCAT=Immunophenotyping, Total IgG and IgM levels, Urinalysis, serology (only measured at baseline visit), vital signs, [redacted], and questionnaires ([redacted]) are to be carried out at Screening, Baseline Day 1, Month 1, Month 6, Month 12 (EOS) and any unplanned visits. These are measured at EOS + 3 Months, EOS + 6 Months, and if required, at every 3 months after the 6 Month follow up for the patients requiring prolonged B-cell plasma level monitoring. Weight is not measured at unplanned visits, and height is only measured at the baseline visit. C-SSRS, TSQM-9, [redacted] are not measured at post-treatment Safety FU, [redacted].

Based on this criteria, for the above information, the visit windows are shown in Table 2-3. The window is based on the visit day for the scheduled visit +/- the additional days based on the half mark between the next/previous scheduled visit.

Table 2-3 Visit windows for vital signs, laboratory, biomarker and questionnaire

Analysis Visit	Time Point	Scheduled visit day (study days)	Visit window (study days)
Baseline	Day 1	1	-28 to 1
Visit 4	Month 1	31	2 to 107
Visit 9	Month 6	184	108 to 275
(EOS) Visit 15	Month 12	366	276 to 427
Safety FU visit 1	EOS + 3 months	458	428 to 503
Safety FU visit 2	EOS + 6 months	549	504 to 594
Safety FU visit n (n>2)	EOS + n*3 months	549+91*(n-2)	504+91*(n-2) to 594+91*(n-2)

2.4.2.2 Morphology

Morphology i.e. MRI assessments are to be carried out at Screening, Month 6, and Month 12 (EOS). However, the final assessment of subjects who discontinue early is recorded as Month 12 (EOS). Based on this criteria, the visit windows for morphology are shown in Table 2-4.

Table 2-4 Visit windows for morphology

Analysis Visit	Time Point	Scheduled visit day (study days)	Visit window (study days)
Baseline	-28 days	-28	-28 to 1
Visit 9	Month 5 - 7	184	139 to 229
(EOS) Visit 15	Month 11 – 13	366	321 to 427

2.4.2.3 Treatment exposure and Electrocardiogram (ECG)

Treatment exposure and ECG data will be presented according to the visit schedule, no visit windows will be applied.

Multiple assessments

It is possible that multiple assessments of a patient 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.

For quantitative variables, the 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 shift tables or 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).

- **Baseline:** The last non-missing measurement made prior to or on the date of administration of the first dose of study treatment (the reference start date / Day 1). Only date part is considered if just one assessment on Day 1. If there are multiple assessments on Day 1, the following rules will apply:
  a. If assessment time exists,
     - select the last available measurement prior to reference start date/time considering time;

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

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

2.4.3 Prior, concomitant and post therapies

Prior and concomitant medications will be summarized in separate tables for the SAF. Medications will be coded using the WHO Drug Dictionary (WHODD). The latest version of which (at the time of the data cut-off) will be used for the reporting activity.

Medications will be classified as prior, or concomitant as follows:

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

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

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

Non-drug therapies/procedures

Records on the concomitant non-drug therapies/procedures eCRF page will be coded using the MedDRA dictionary. All procedures will be classified as prior or concomitant in the same way as done for medications above. Non-drug therapies/procedures in each of these 2 categories will be summarized separately by primary SOC and MedDRA PT.

Prior MS medication

Previous aCD20 therapy (ocrelizumab or rituximab) and reason for discontinuation/switching will be summarized.

Injection-related premedication

Injection related premedication will be identified by subcategory "Injection related premedication" in concomitant medication dataset. Injection related premedication will be summarized separately.

2.5 Analysis of the primary objective

The primary objective of this study is to explore the maintenance of efficacy of ofatumumab in participants with RMS transitioning from aCD20 mAb therapy, as assessed by no change or reduction in the number of gadolinium enhancing (GdE) lesions observed by MRI.

The primary efficacy analysis will be conducted when all participants complete the 12 month on-treatment period or discontinue from the study.

2.5.1 Primary endpoint

The primary efficacy variable is no change or a reduction from baseline in the number of GdE T1 lesions observed by MRI at 12 months of treatment (Yes, No).

2.5.2 Statistical hypothesis, model, and method of analysis

The primary analysis to address the primary objective will be based on the following estimand:

- Treatment of interest: Following a loading dose regimen consisting of once daily doses on days 1, 7 and 14, ofatumumab is given once monthly starting at Month 1. All doses of ofatumumab will be given subcutaneously via an auto injector at a dose of 20mg.
- Population: Relapsing MS participants currently treated with an infused aCD20 mAb, specifically ocrelizumab or rituximab, that have received at least 2 courses of therapy that are switching due to reasons other than safety or efficacy. Further defined through the appropriate inclusion/exclusion criteria to reflect the target population.
- Variable: Reduction or no change from baseline in the number of GdE lesions as observed by MRI (Yes, No).
- Other intercurrent events: Death or treatment/study discontinuation.
- Summary measure: Proportion of participants with no change or a reduction in the number of GdE T1 lesions at Month 12 and corresponding 95% confidence interval.

The 95% CI for the primary endpoint will be calculated using a normal approximation method. In addition, the change from baseline in the number of GdE T1 lesions will also be summarized descriptively by time point and graphically using a longitudinal plot.

Both non-responder imputation (NRI) for missing data and observed data approaches will be applied.

NRI is a conservative imputation method for dichotomous variables. NRI assumes that a participant is a treatment failure, i.e. non-responder, if they do not have a valid month 12 MRI assessment, or if they discontinue the study prematurely and do not have a valid month 12 MRI assessment. Hence, for missing data the primary variable outcome will be imputed to "No". MRI assessments occurring after the efficacy cut-off will not be included in the analysis.

The primary analysis of the primary efficacy variable will be based on the FAS.

2.5.3 Handling of missing values/censoring/discontinuations

For participants with missing number of GdE T1 lesions at Month 6 and Month 12, NRI method will be used.

2.5.4 Sensitivity analyses

The primary analysis will be repeated to analyze no change or a reduction from baseline in the number of GdE T1 lesions observed by MRI at 12 months of treatment (Yes, No), based on observed data. MRI assessments occurring after the efficacy cut-off will not be included in the analysis.

2.5.4.1 Supplementary analysis:

The primary analysis will be repeated to analyze no change or a reduction from baseline in the number of GdE T1 lesions observed by MRI at 12 months of treatment (Yes, No), including any assessments after the efficacy analysis cut-off. Both NRI for missing data and observed data approaches will be applied.

2.6 Analysis of the key secondary objective

There is no key secondary objective for this study.

2.7 Analysis of secondary objective

Refer to Table 1-1 of Section 1.2 for the list of secondary objectives.

The secondary efficacy analysis will be conducted after all participants complete the 12 month on-treatment period or discontinue from the study.

2.7.1 Secondary endpoints

The secondary endpoints are as follows:

1. Retention on study treatment from baseline to Month 6, and to Month 12 (Yes, No)

2. Change from baseline in lymphocytes, including total CD19+ B cell counts and CD20+CD3+ T cell counts, obtained by fluorescence activated cell sorting (FACS) at Months 6 and 12
3. The Columbia Suicide Severity Rating Scale (C-SSRS) at Months 6 and 12
4. Treatment Satisfaction Questionnaire for Medication (TSQM-9) scores (including domains) at baseline vs Month 6 and vs Month 12
5. Treatment-emergent adverse events (TEAEs)

2.7.2 Statistical hypothesis, model, and method of analysis

The following statistical analyses are planned for the secondary endpoints:

1. Retention on study treatment from baseline to Month 6, and to Month 12 (Yes, No) will be summarized using frequency counts and percentages for the FAS. Retention will be based on the number of study drug discontinuations.
2. Biomarker analysis – See Section 2.12.1
3. C-SSRS analysis – See Section 2.8.3.1
4. TSQM-9 analysis – See Section 2.11.1
5. TEAEs analysis – See Section 2.8.1

2.8 Safety analyses

Unless stated otherwise, all safety analyses will be summarized for the SAF. Only data captured prior to the safety cut-off will be used for safety analyses.

2.8.1 Adverse events (AEs)

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a participant or clinical investigation of a participant after providing written informed consent for participation in the study. That means that a participant can report AEs before having started study medication. For reporting purposes, the main focus will be on treatment emergent adverse event (TEAE), defined as any adverse event which started on or after the day of first dose of study drug, or before 30 days after treatment end date, if severity at baseline if missing or if post baseline severity is greater than baseline severity.

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

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

Separate summaries will be provided for:

- study drug related TEAEs
- serious adverse events (SAEs)
- TEAEs leading to permanent study drug discontinuation
- TEAEs leading to study drug interruption

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

All AEs will be listed.

2.8.1.1 Adverse events of special interest / grouping of AEs

Selected AEs will be considered under the heading of adverse events of special interest (AESI) and described in the electronic Case Retrieval Sheet (eCRS). The eCRS that is current at the time of the database lock will be used and AESIs will be identified where the flag Core safety topic risk (SP) = 'Y'. The search criteria for the AESI will be included in the TFL shell document.

AESI will be summarized by category and preferred term for the SAF, and will also be listed.

2.8.1.2 Other adverse events analyses

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on TEAEs which are not SAEs with an incidence greater than 5% and on treatment emergent SAEs and SAEs suspected to be related to study treatment will be provided by primary SOC and PT.

If for the same participant, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same primary 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.

2.8.1.3 Deaths

All deaths including on-treatment and post-treatment deaths will be summarized by MedDRA SOC and PT. All deaths will be listed. Deaths occurring after the on-treatment period will be highlighted in the listing.

2.8.2 Laboratory data

The summary of laboratory evaluations will be presented for three groups of laboratory tests: hematology, chemistry and urinalysis. Each group will be further subdivided into subgroups and presented as per Table 5-1. Summary statistics for the change from baseline to each time point will be tabulated for each laboratory parameter. Data summaries will be provided in SI units.

In addition, shift tables based on normal ranges will be provided for all parameters in Table 5-1 to compare participants' baseline laboratory evaluation relative to the visit's observed value and to the worst post-baseline value.

Number of participants with newly occurring liver enzyme abnormalities at any time post baseline will be summarized. Newly occurring liver enzyme abnormalities are defined in Section 5.3.2.

All laboratory data will be listed by participant and visit/time point and if normal ranges are available, abnormalities will be flagged.

2.8.2.1 Other special laboratory results

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 lower limit of normal (LLN) and a notably low IgM level is defined as a level 10% below the LLN. A summary of IgG and IgM less than LLN will be provided. Historical change of IgG and IgM will be summarized. Historical IgG and IgM will not be considered for baseline calculations.

2.8.3 Other safety data

2.8.3.1 Suicidality evaluations

The Columbia-Suicide Severity Rating Scale (C-SSRS data) will be mapped into 11 levels (see Section 5.4.1 of the Appendix for details) using the Columbia Classification Algorithm for Suicide assessment (C-CASA) as outlined in Food and Drug Administration (FDA) guidance on suicidality (FDA, 2012).

Definition of 'all prior history' and 'recent history'

Suicidality evaluations will be collected once pre-treatment, either at screening or at baseline visits. These assessments will be defined by two components: all prior history and recent history.

All prior history will be defined as the assessment result obtained from the *lifetime* assessment, and **recent history** will be defined as the assessment result obtained from the *recent past period* assessment.

Data summaries

The number and percentage of participants with suicidal ideation, suicidal behavior and self-injurious behavior without suicidal intent will be presented. The following 14 events will be included in the summary table:

- Each of the 11 categories listed in Table 5-2.
- Any suicidal ideation or behavior (a 'yes' answer to at least one of the 10 suicidal ideation and behavior questions).
- Any suicidal ideation (answered 'yes' to at least one of the 5 suicidal ideation questions).
- Any suicidal behavior (answered 'yes' to at least one of the 5 suicidal behavior questions).

In addition, the number and percentage of participants with the following post-baseline events will be presented (Nilsson et al. 2013):

- 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 baseline: 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).

Note: in these definitions, a category of 0 is assigned to a subject without suicidal ideation (i.e., a ‘no’ answer to all suicidal ideation categories).

For those analyses, each participant can only be counted once for each event. However, a participant can be counted in several different events.

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 a participant 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).

2.8.3.2 ECG and cardiac imaging data

ECG data will be collected at screening visit, Day 1 and EOS visit. Clinically significant findings from ECG evaluations will be reported as AEs and included in the analysis of AEs. ECG parameters include: mean heart rate, pulse rate (PR) interval aggregate, QRS duration, QT duration and QT corrected using Fridericia’s correction formula (QTcF).

Descriptive statistics including change from baseline of each ECG parameter will be provided by time point. In addition, the number and percentage of participants meeting the criteria defined in Table 2-9 will be summarized by time point.

Table 2-9 Criteria for relevant ECG absolute or change from baseline values

Absolute values criteria	Changes from baseline criteria
Heart rate: HR <40 or HR >120 beats/min	NA
Pulse rate: PR <110 or PR >200 msec	NA
QRS duration: <70 msec or >120 msec	QRS duration: increase >25% compared to baseline
QTcF <350 or >450 msec (males) QTcF <360 or >460 msec (females)	QTcF >500 msec and QTcF increase >60 msec

There will be no cardiac imaging data collected for this study.

2.8.3.3 Vital signs

All vital signs data will be listed by participant and time point (including pre and post injection data points as applicable), and if reference ranges are available, abnormalities will be flagged.

For vital signs data collected at Month 6 and Month 12, summary statistics for change from baseline will be provided.

Pre-injection vital sign assessments will be defined as the assessment result obtained 30-60 (+/- 10 min) minutes pre-injection of the study drug, and **post-injection** vital sign assessments will be defined as the assessment result obtained 60 minutes post-injection of the study drug.

Height will be collected at screening visit only and will be summarized in the baseline characteristics summary only.

Notable vital sign abnormalities will be summarized. Notable vital sign abnormalities are defined in Table 2-10.

Table 2-10 Criteria for notable vital sign abnormalities

Vital sign	Criteria for notable abnormality
Pulse (bpm)	<50 or >120 bpm
Systolic blood pressure (BP) (mmHg)	<90 or >180 mmHg
Diastolic BP (mmHg)	<50 or >205 mmHg
Temperature (°C)	<35 or >40 °C
Body weight (kg)	<30 or >180 kg

2.9 Pharmacokinetic endpoints

There are no pharmacokinetic endpoints planned for this study.

2.10 PD and PK/PD analyses

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

2.11 Patient-reported outcomes

2.11.1 Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9)

The Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9) is a 9-item general instrument that measures the major dimensions of satisfaction with a medication (Bharmal et al. 2009). Scores will be calculated for the effectiveness (Items 1-3), convenience (Items 4-6) and global satisfaction scale (Items 7-9). See Appendix Section 5.4.2 for the scoring algorithm. Scores on the TSQM scale range from 0 (indicating poor satisfaction) to 100 (indicating perfect satisfaction).

Change from baseline in TSQM-9 scores for all 3 domains (effectiveness, convenience and global satisfaction) to Month 6 and 12 will be summarized for the FAS.

[redacted]

[redacted]

[redacted]

2.12 Biomarkers

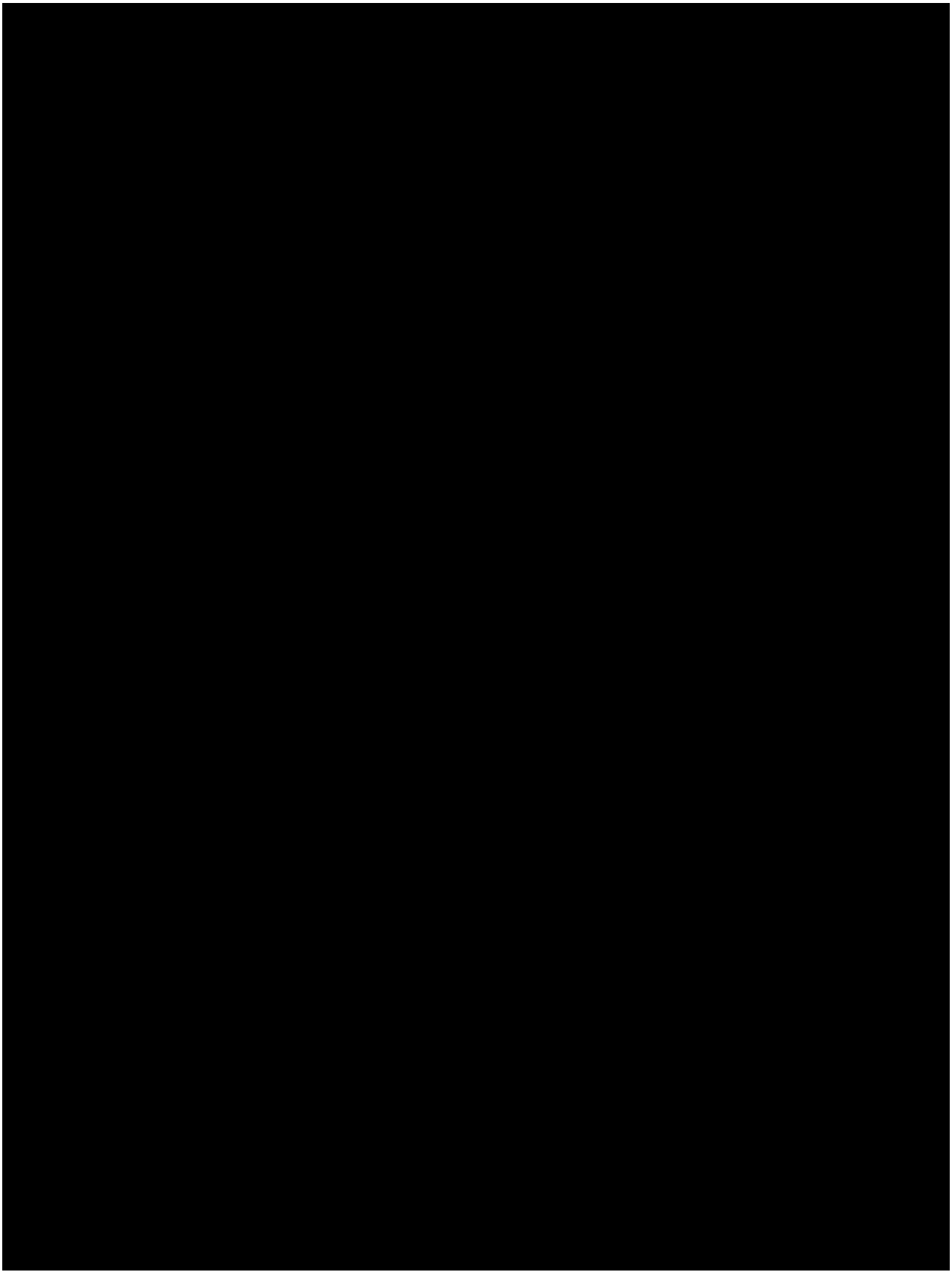
2.12.1 B and T cell counts

Change from baseline in lymphocytes, including total CD19+ B cell counts and CD20+CD3+ T cell counts, obtained by FACS will be summarized descriptively by time point for the SAF.

Both absolute and percentage counts will be presented.

In addition, number and percentage of participants with B cells < the lower limit of normal (LLN) or < their baseline value (i.e., B cell depleted) will be presented by time point.

[redacted]



2.14 Interim analysis

For the purpose of earlier dissemination of results, an interim analysis will be performed after all enrolled participants have either met the criteria of at least 6 months treatment or discontinued treatment prematurely. For this analysis, only primary variables, demographics, baseline characteristics, adverse events and serious adverse events will be summarized. The cut-off for the interim analysis will be the Month 6 visit date. Data up to the cut-off date will be presented.

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

3 Sample size calculation

Sample size calculations were based on the proportion of participants with no change or a reduction from baseline in the number of GdE MRI lesions 12 months after initiating ofatumumab therapy. Three precision estimates were considered for this study:

The sample size of 100 participants is selected based on budget and early availability of interim analysis results. This sample size of 100 participants will provide us with an 8.5% precision (half-width of 95% confidence interval), a 7.8% precision, or a 7.0% precision corresponding to estimated proportions of 75%, 80%, and 85% of participants achieving the primary endpoint.

4 Change to protocol specified analyses

Please see Table 4-1 Change to protocol specified analyses below for a list of changes to protocol specified analyses are tabulated below.

Table 4-1 Change to protocol specified analyses

Section(s) of the protocol	Change
No changes	Not Applicable

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

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

5.1.2 AE date imputation

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

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

The following matrix explains the logic behind the imputation.

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

The following table is the legend to the logic matrix.

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

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

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

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

5.1.3 Concomitant medication date imputation

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

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

The following the logic behind the imputation of CM end date.

1. If CM end day is missing and CM month and year are non-missing then CM end day was imputed as the minimum of treatment end date and the last day of the month
2. If CM end day and month are missing and CM end year is non-missing then CM end day was imputed as the minimum of treatment end date and the end of the year (31DECYYYY).
3. Missing CM end dates was not imputed.
4. If the imputed CM end date is less than CM start date then impute CM end date as CM start date.
5. Additional condition for Prior MS modifying therapies (CMSCAT = 'OTHER MULTIPLE SCLEROSIS DISEASE MODIFYING THERAPY'): If imputed date after treatment start date TRTSDT, impute as TRTSDT – 1.

The following matrix explains the logic behind the imputation of start date.

	MON MISSING	MON<TRTM	MON=TRTM	MON>TRTM
YYYY MISSING	(1) Uncertain	(1) Uncertain	(1) Uncertain	(1) Uncertain
YYYY < TRTY	(2.a) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start
YYYY = TRTY	(4.a) Uncertain	(4.b) Before Treatment Start	(4.b) Uncertain	(4.c) After Treatment Start
YYYY > TRTY	(3.a) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start

1. If the CM start date year value is missing, the imputed CM start date was set to missing.
2. If the CM start date year value is less than the treatment start date year value, the CM started before treatment. Therefore:
   a. If the CM month is missing, the imputed CM start date was set to the mid-year point (01JulYYYY).
   b. Else if the CM month is not missing, the imputed CM start date was set to the mid-month point (15MONYYYY).
3. If the CM start date year value is greater than the treatment start date year value, the CM started after treatment. Therefore:
   a. If the CM month is missing, the imputed CM start date was set to the year start point(01JanYYYY).
   b. Else if the CM month is not missing, the imputed CM start date was set to the month start point (01MONYYYY).
4. If the CM start date year value is equal to the treatment start date year value:

a. And the CM month is missing or the CM month is equal to the treatment start date month, then the imputed CM start date was set to one day prior treatment start date.
b. Else if the CM month is less than the treatment start date month, the imputed CM start date was set to the mid-month point (15MONYYYY).
c. Else if the CM month is greater than the treatment start date month, the imputed CM start date was set to the month start point (01MONYYYY).

5. If the imputed CM start date is after CM end date then impute CM start date as CM end date.

Concomitant Medication Date Flag
If not a complete date then

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

5.1.3.1 Prior therapies date imputation

Same as above.

5.1.3.2 Post therapies date imputation

Same as above.

5.1.4 Other imputations

5.1.4.1 Time

If it is a start date or date/time of test done and date is not missing, then;

1. If seconds component is missing then seconds component is imputed as 00.
2. If minutes and seconds component is missing then minutes and seconds component are imputed as 00 and 00 respectively.
3. If whole time component is missing then Time component is imputed as 00:00:00.

If it is an end date and date is not missing, then;

1. If seconds component is missing then seconds component is imputed as 59.
2. If minutes and seconds component is missing then minutes and seconds component are imputed as 59 and 59 respectively.
3. If whole time component is missing then Time component is imputed as 23:59:59.

5.1.4.2 Medical History

For the calculation of duration or time since relevant history events in Section 2.3.3 (Baseline Characteristics), partial dates will be imputed for the MS diagnosis start data, the first MS symptom date, and the most recent relapse onset date via the 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 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.

When the onset date of most recent relapse is missing, then the date of diagnosis is considered as Onset Date of Most Recent Relapse.

5.2 AEs coding/grading

Adverse events will be 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.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE). The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1). The CTCAE grade of 5 (death) is not used; rather, 'fatal' is collected as AE outcome and death information is also collected on a separate eCRF page.

5.3 Laboratory parameters derivations

Laboratory results in the form AVAL = "< X", where X is a positive number, and the numeric form is not available, will be derived as AVAL=AVALC/2. If it is a valid decimal number then AVAL will be numeric value of AVALC. If AVALC is in any other form, it will be kept as missing.

5.3.1 Laboratory test groups and subgroups

Laboratory test groups and subgroups are tabulated in Table 5-1.

Table 5-1 Laboratory test groups and subgroups with SI units

Order	Laboratory Group Subgroups	Tests (SI unit)
1	**Hematology**	
	Red blood cells	Hematocrit (ratio) Hemoglobin (g/L) Platelets (10E9/L) Erythrocytes (Red cell count) (10E12/L)
	White blood cell differential	Basophils (10E9/L) Eosinophils (10E9/L) Lymphocytes (10E9/L) Monocytes (10E9/L) Neutrophils (10E9/L) Basophils/Leukocytes (%) Eosinophils/Leukocytes (%) Lymphocytes/Leukocytes (%) Monocytes/Leukocytes (%) Neutrophils/Leukocytes (%) Leukocytes (White cell count)(10E9/L)
	B cells	CD19+ B cell counts (10E6/L)
2	**Chemistry**	
	Renal function	Creatinine (umol/L) Blood urea nitrogen (mmol/L)
	Liver function	ALT (U/L) Albumin (g/L) Alkaline phosphatase (U/L) AST (U/L) Bilirubin (direct/conjugated) (umol/L) GGT (U/L) Total bilirubin (umol/L) Total protein (g/L)
	Other enzymes	Amylase (U/L)
	Lipids	Cholesterol HDL (mmol/L) Cholesterol LDL (mmol/L) Triglycerides (mmol/L) Total cholesterol (mmol/L)

Order	Laboratory Group Subgroups	Tests (SI unit)
	Other	Random glucose (mmol/L) C-reactive protein (CRP) (mg/L)
	Electrolytes/Metabolism	Bicarbonate (mmol/L) Calcium (mmol/L) Chloride (mmol/L) Magnesium (mmol/L) Phosphate (mmol/L) Potassium (mmol/L) Sodium (mmol/L)
	Immunoglobulin	Total IgG (g/L) Total IgM (g/L)
3	**Urinalysis**	Erythrocytes (Blood) Specific gravity Specific gravity (Ratio) Albumin Protein pH Leukocytes (White blood count)
4	**Immunophenotyping** T cells	CD3+CD20+ T cell counts (10E6/L)

5.3.2 Newly occurring liver enzyme abnormalities

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

- ALT > 3, 5, 10, 20x ULN
- AST > 3, 5, 10, 20x ULN
- ALT or AST > 3, 5, 8, 10, 20x ULN
- ALT or AST > 3x ULN & TBIL > 1.5x ULN
- ALT or AST > 3x ULN & TBIL > 2x ULN
- ALP > 1.5, 2, 5x ULN
- TBIL > 1, 1.5, 2x ULN
- ALP > 3, 5x ULN & TBL > 2x ULN
- ALT or AST > 3x ULN & TBIL > 2x ULN & ALP ≤ 2x ULNALT or AST > 3x ULN

When a criterion contains multiple laboratory parameters (e.g., ALT > 3xULN & TBL > 2xULN), unless otherwise requested by the project clinical team/Brand Safety Leader (BSL), 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: Philippe Close 2011), section: Safety parameters for special liver event analyses.

5.3.2.1 Definition of characteristics for liver event overview summary

Characteristics: Liver events are categorized based on ALT and ALP measurements using the closest lab assessment +/- 7 days from the onset of the liver event into the following characteristics 'Hepatocellular' (ALT > 2xULN or ALT/ULN:ALP/ULN > 5), 'Cholestatic' (ALP > 2xULN or ALT/ULN:ALP/ULN ≤ 2), 'Mixed' (ALT > 2xULN and ALP > ULN and 2 < ALT/ULN:ALP/ULN ≤ 5), 'None' (if none of the three above qualifies), and 'Unknown' (in case of a missing ALT or ALP values). Note that the categories are not mutually exclusive. The definition is consistent with Novartis safety guideline on hepatotoxicity.

5.4 Other derivations

5.4.1 The Columbia-Suicide Severity Rating Scale (C-SSRS)

The Columbia-Suicide Severity Rating Scale (C-SSRS) includes 11 levels considered as standard for classifying suicidal ideation and behavior events.

These include five levels of suicidal ideation, five levels of suicidal behavior, and the category self-injurious behavior, no suicidal intent.

These categories and levels are defined in Table 5-2:

Table 5-2 Suicidal ideation and behavior categories and definitions

Category number	C-SSRS category	Definition
Suicidal ideation		
1	Wish to be dead	Patient has thoughts about a wish to be dead or not alive anymore or wish to fall asleep and not wake up.
2	Non-specific active suicidal thoughts	General nonspecific thoughts of wanting to end one's life or commit suicide (e.g., "I've thought about killing myself") without general thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
3	Active suicidal ideation with any methods (not plan) without intent to act	Patient has thoughts of suicide and has thought of at least one method during the assessment period. This situation is different than a specific plan with time, place, or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, "I thought about taking an overdose but I never made a specific plan as to when, where, or how I would actually do it . . . and I would never go through with it."
4	Active suicidal ideation with some intent to act, without specific plan	Active suicidal thoughts of killing oneself, and patient reports having some intent to act on such thoughts, as opposed to "I have the thoughts but I definitely will not do anything about them."

5	Active suicidal ideation with specific plan and intent	Thoughts of killing oneself with details of plan fully or partially worked out and patient has some intent to carry it out (i.e., some degree of intent is implicit in the concept of plan).
Suicidal behavior		
6	Completed suicide	A self-injurious behavior that resulted in fatality and was associated with at least some intent to die as a result of the act. Evidence that the individual intended to kill him- or herself, at least to some degree, can be explicit or inferred from the behavior or circumstance.
7	Suicide attempt	A potentially self-injurious behavior, associated with at least some intent to die as a result of the act. Evidence that the individual intended to kill him- or herself, at least to some degree, can be explicit or inferred from the behavior or circumstance. A suicide attempt may or may not result in actual injury.
8	Interrupted suicide attempt	When the person is interrupted (by an outside circumstance) from starting a potentially self-injurious act (if not for that, actual attempt would have occurred).
9	Aborted suicide attempt	When person begins to take steps toward making a suicide attempt, but stops before actually engaging in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops before being stopped by something else.
10	Preparatory acts toward imminent suicidal behaviors	This category can include anything beyond a verbalization or thought, but it stops short of a suicide attempt, an interrupted suicide attempt, or an aborted suicide attempt. This might include behaviors related to assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note).
Self-Injurious Behavior Without Suicidal Intent		
11	Self-injurious behavior associated with no intent to die. The behavior is intended purely for other reasons, either to relieve distress (often referred to as self-mutilation (e.g., superficial cuts or scratches, hitting or banging, or burns)) or to effect change in others or the environment.	

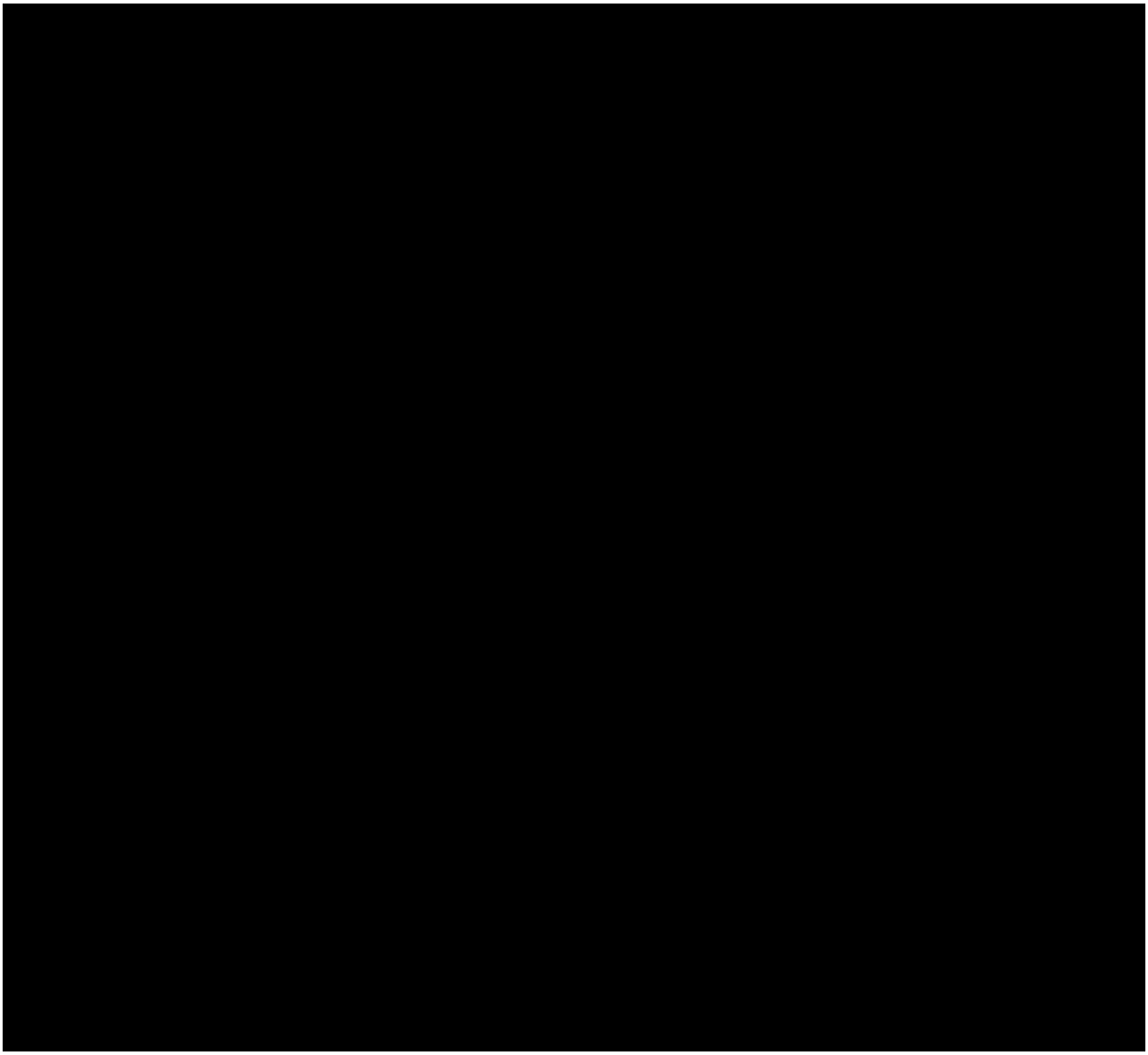
5.4.2 TSQM-9 scoring

TSQM-9 scale scores range from 0 to 100 and no computed score should be lower or higher than these limits. If more than 1 item score is missing, the scale score should not be computed, and set to missing. The TSQM-9 scale scoring algorithm as described by Atkinson et al. is tabulated in Table 5-3:

Table 5-3 TSQM-9 scale scoring algorithm

Domain	Scale score

Effectiveness	[(Item 1 + Item 2 + Item 3 – 3) / 18] × 100. If one item is missing then [sum(available items)-2/12]*100
Convenience	[(Item 4 + Item 5 + Item 6 - 3) / 18] × 100. If one item is missing then [sum(available items)-2/12]*100
Global satisfaction	First recode create Item 9_R: Item 9_R = (Item 9 - 1) × 4/6 + 1 Then the global satisfaction scale score is [(Item 7 + Item 8 + Item 9_R - 3) / 12] × 100. If one item is missing then [sum(available items)-2/8]*100



5.5 Statistical models

Primary analysis

Type is no hypothesis testing planned for this study.

Key secondary analysis

There is no key secondary analysis planned for this study.

Mixed model with repeated measures (MMRM) with baseline value retained in the outcome – Sample SAS code

The OM option is to ensure that the distribution of categorical variable is according to population included in analysis.

```
PROC MIXED DATA = dsn;
   CLASS avisitn usubjid &listCatCovar;
   MODEL aval = avisitn &listCovar/s ddfm =kr;
   LSMEANS avisitn/diff cl E OM;
   LSMESTIMATE avisitn 'chg from baseline at Week 24' -1 1 0 /OM;
   LSMESTIMATE avisitn 'chg from baseline at Week 48' -1 0 1 /OM;
   REPEATED avisitn/TYPE = UN subject = usubjid;
RUN;
```

Rule of exclusion criteria of analysis sets

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

Deviation ID	Description of deviation	Exclusion in analyses
INCL01A	No informed consent obtained or missing	Exclude from Safety set and FAS

Table 5-5 Other reasons for exclusion from analysis

Reason	Description	Exclusion in analyses
Site/Investigator disqualification	Due to breaches of ethical or regulatory standards, a site/investigator may be disqualified, and all data from the disqualified site will be excluded from the analysis. All data from the following site(s) will be excluded, 1003.	Exclude from Safety set and FAS
Prohibited medication (COMD02)	Data up to date of PD will be included.	Exclude from primary analyses.
Assessment performed after withdrawal of consent (WITH13)	Data up to date of PD will be included.	Exclude from applicable analyses.

Table 5-7 Participant classification

Analysis set	PD ID that cause participants to be excluded	Non-PD criteria that cause participants to be excluded
SAF	INCL01A	No study drug taken
	N/A	Site/investigator disqualification
FAS	INCL01A	No study drug taken
	N/A	Site/investigator disqualification

6 Reference

Atkinson, M.J., Sinha, A., Hass, S.L., Colman, S.S., Kumar, R.N., Brod, M., Rowland, C.R. (2004). Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. Health Qual Life Outcomes, 2 (12).

Bharmal, M., Payne, K., Atkinson, M.J., Desrosiers, M.P., Morisky, D.E., Gemmen, E. (2009). Validation of an abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) among patients on antihypertensive medications. Health Qual Life Outcomes, 7 (36).

Food and Drug Administration. Center for Drug Evaluation and Research. (2012). Guidance for Industry: Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials.

[redacted]

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[redacted]