NOVARTIS

Clinical Development

OMB157/Ofatumumab®

COMB157G23101 / NCT04353492

A single-arm, prospective, multicentre, open-label study to evaluate ofatumumab treatment effectiveness and patient-reported outcomes in patients with relapsing multiple sclerosis (RMS) transitioning from fumarate-based RMS approved therapies or fingolimod

Statistical Analysis Plan (SAP)

Document type:	SAP Amendment Documentation
Document status:	Amendment 4
Release date:	4-Apr-2025
Number of pages:	45

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
4-Apr-2025	Prior to DBL	Creation of SAP amendment 4	Add a sensitivity analysis for all relapses	Section 2.5.5
			Add text to describe how to deal with data which is greater than the upper range for lab data	Section 2.9.3
			Add details about how to deal with non-convergence issue and a summary table for Gd-enhancing T1 lesions	Section 2.14.4
			Add details about how to deal with non-convergence issue and a summary table for new or enlarging T2 lesions	Section 2.14.5
			Modify the analysis methods for T2 lesion volume	Section 2.14.6
			Add by prior DMT analysis for proportion of subjects without MRI activity	Section 2.14.8
			Modify the analysis methods for NfL	Section 2.14.10
			Add clarification for imputation rules of study drug	Section 5.1
			Modify sample SAS codes that were previously provided	Section 5.4.4
			Remove contents of T-cells since T-cell will not be presented in CSR	Section 2.9.3
12-Dec-2024	Prior to IA	Creation of SAP amendment 3	Update efficacy cutoff definition and use same safety cutoff for AE and SAE	Section 2.1
			Add definition of last assessment on drug and delete time at risk for SAE	Table 2-1 and 2-2, Section 2.4.1
			Change MRI visit-window	Table 2-4
			Add subgroup of baseline NfL and subgroup analysis of last prior DMT and duration of washout	Section 2.2.1
			Add text to distinguish study and treatment disposition	Section 2.3.1
			Add by last prior DMT analysis	Section 2.3.2, 2.3.3
			For the primary objective, specify the new efficacy cutoff and the order of dropping covariates if encountering model convergence issues, delete “onset of action” analysis (≤ 8 weeks vs. > 8 weeks) and subject/time-based ARR by last prior DMT analysis, add ARR by year analysis	Section 2.5
			For safety analysis, align text of safety cutoff with text in the previous section, add most common TEAEs by PT (> 2%) and last prior DMT, add a listing of relapse as SAE, add two additional analyses for B-cell and IgG/IgM	Section 2.9

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			For the exploratory analyses, delete KM plot and modify event rate analysis for 6mCCD, add by last prior DMT analysis for EDSS, add the analyses of T1/T2 lesions by visit using negative binomial GEE model, add by last prior DMT and duration of washout analyses for T1/T2 lesions, add analysis of T2 lesion volume and NfL by visit using MMRM model, remove logistic regression analysis from NEDA-3 and add NEDA-3 by year as well as by last prior DMT analysis, add each NEDA-3 component by year analysis, add a figure of change from baseline CCI remove CCI from CSR	Section 2.14 Section 2.15 Section 4
			Add text of the second interim analysis	
			For change to protocol specified analysis, add baseline NfL as a subgroup, add text of removing CCI from CSR	Section 5.4
			Remove details of piecewise negative binomial models and SAS codes, add sample SAS codes for ARR by year analysis, negative binomial GEE model and MMRM model	
13-Sep-2024	Prior to dry-run	Creation of SAP amendment 2	Align study languages with the latest protocol	All sections
			Re-define study cut-off, including efficacy and safety cut-off	Section 2.1
			Delete EOT definition and modify the definition of key terms according to the latest protocol	Table 2-1 and 2-2
			Modify analytic windows according to the latest protocol	Table 2-3 to 2-10 Table 2-11
			Add visit windows after study drug discontinuation	Section 2.2.1
			Add subgroups of interest for both efficacy and safety analyses	Section 2.3.3
			Add IgG, IgM, B-cell, lymphocytes and neutrophils into MS baseline disease characteristics	Section 2.4.2.4
			Add previous MS disease modifying treatment output	Section 2.5
			For primary objectives, add ARR by yearly interval, add a section of handling of intercurrent event, remove sensitivity analyses of excluding subjects with > 9 consecutive missed doses, remove supplementary analysis and pandemic impact analysis, add subgroup analysis by last prior DMT and duration of washout	Section 2.9
			For safety analysis, add more separate summaries of TEAEs, add infection as another AESI, keep same IRR analyses as compared to ASCLEPIOS, add IgG, IgM, lymphocyte and neutrophils analyses by last prior DMT, add treatment discontinuation or interruption by IgG and IgM ≥LLN vs. < LLN	Section 2.12 and 2.14
			Exclude PROs and digital endpoints from CSR	

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			For exploratory analyses, add 6mCDW and also by last prior DMT, add 6mCCD, add T1 and T2 lesions by last prior DMT, add NEDA-3 and also by last prior DMT, add proportion of subjects without MRI activity, add [redacted] and also by last prior DMT, add T25FW, 9HPT and LCVA, add NfL and also by last prior DMT.	Section 2.15
			Add a section of Interim analysis	Section 2.16
			Update the latest calculation of sample size, aligning with the latest protocol and sample size document	Section 3
			Specify the change to protocol specified analyses	Section 4
			Document the PD which causes data/sample to be excluded from final analyses	Section 5.5
8-July-2020	Prior to DB lock	Creation of final version	N/A - First version	NA
29-Apr-2021	SAP amendment	Protocol amendment	Updated safety follow up details based on protocol amendment; safety follow up post study drug discontinuation is reduced to 6 months instead of 9 months	Section 1.1 Study design
		Protocol amendment	1. Changed NEDA-4 to NEDA-3 2. Removed endpoint percentage change from baseline in brain volume	Section 1.2 Study objectives and endpoints Table 2-2 Section 2.3.3 Section 2.14 Other exploratory analyses
		Protocol amendment	Added summary of missed doses	Section 2.4
		Protocol amendment	Added pandemic impact analysis for efficacy; Added analysis to assess impact of missed doses on primary endpoint	Section 2.5.4 Sensitivity / supplementary analyses
		Protocol amendment	Added pandemic impact analysis for safety	Section 2.9 Safety analyses
		Protocol amendment	Added bar plot for injection related reactions and symptoms	Section 2.9.1.1.1 Injection reaction related AEs
		Protocol amendment	Added analysis to assess impact of missed doses on special labs parameters	Section 2.9.3.1
		Protocol amendment	Removed this section as this will be not used for CSR	Section 2.9.5 Safety evaluation during safety follow up
		To support primary and secondary results	a. Added exploratory endpoints analysis as part of CSR 1. Change from baseline in EDSS 2. Number of T1 lesions per scan	Section 2.14 Other exploratory analyses

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			3. Number of T2 Gd-enhancing lesions per year 4. details on COVID-19 impact analysis	

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AE	Adverse event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphate
ALT	Alanine Aminotransferase
ARR	Annualized Relapse Rate
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
BMI	Body Mass Index
C-CASA	Columbia Classification Algorithm for Suicide Assessment
CCD	Confirmed Cognitive Decline
CDW	Confirmed Disability Worsening
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
eCRF	Electronic Case Report Form
eCRS	Case Retrieval Sheet
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTSD	Clinical Trial Safety Disclosure
DBP	Diastolic Blood Pressure
DMF	Dimethyl Fumarate
CCI	[redacted]
DMT	Disease Modifying Treatment
DRF	Diroximel Fumarate
eCSSRS	(electronic) Columbia Suicide Severity Rating Scale
ECG	Electrocardiogram
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
EOS	End of Study
FAS	Full Analysis Set
FDA	Food and Drug Administration
FS	Functional Score
CCI	[redacted]
FU	Follow-up
Gd	Gadolinium
CCI	[redacted]
9HPT	9-Hole Peg Test
CCI	[redacted]
HR	Heart Rate
IgG	Immunoglobulin G
IgM	Immunoglobulin M
CCI	[redacted]
IRR	Injection related reaction
KM	Kaplan-Meier
LCVA	Low Contrast Visual Acuity

LFT	Liver Function Test
LLN	Lower Limit of Normal
M	Month
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MH	Medical History
MMRM	Mixed Model for Repeated Measures
MRI	Magnetic Resonance Image
MS	Multiple Sclerosis
CCI	[redacted]
CCI	[redacted]
NB	Negative Binomial
NEDA	No evidence of disease activity
NfL	Neurofilament
PD	Pharmacodynamics/Protocol Deviation
PDS	Programming Dataset Specification
PK	Pharmacokinetics
PR	Pulse Rate
PRO	Patient-reported Outcomes
PSDS	Post Study Drug Supply
PT	Preferred Term
PTA	Post-Trial Access
RMS	Relapsing Multiple Sclerosis
CCI	[redacted]
RRMS	Relapsing-Remitting MS
SAE	Serious Adverse Events
SAF	Safety Analysis set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SBP	Systolic Blood Pressure
CCI	[redacted]
s.c.	Subcutaneous
CCI	[redacted]
SFU	Safety Follow-up
SIB	Self-Injurious Behavior
SOC	System Organ Class
SPMS	Secondary progressive MS
TEAE	Treatment Emergent AE
T25FW	Timed 25-foot Walk
TBIL	Total Bilirubin
CCI	[redacted]
ULN	Upper Limit of Normal
CCI	[redacted]
WHO	World Health Organization

1 Introduction

The purpose of this statistical analysis plan (SAP) is to describe the implementation of the statistical analysis planned in the protocol of study COMB157G23101.

The content of this SAP is based on protocol OMB157G23101 version 03.

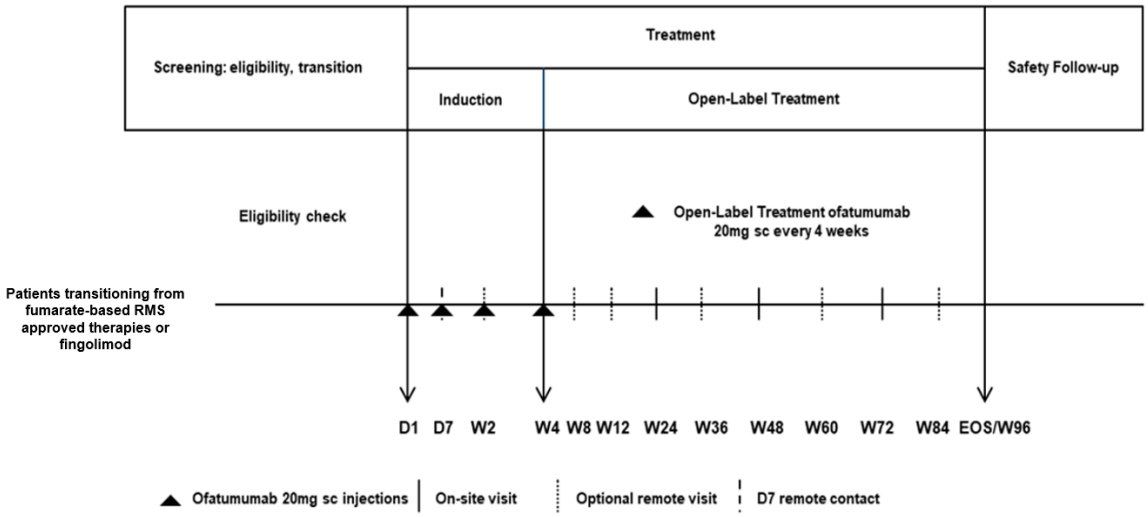
Data will be analyzed by Novartis or a contracted contract research organization (CRO) according to the data analysis section 12 of the study protocol. Important information is given in the following sections and details will be provided, as applicable, in Appendix 16.1.9 of the CSR.

1.1 Study design

This is a single arm, prospective, multicentre and open-label, 96-week study to evaluate the treatment effectiveness of ofatumumab (OMB157) in subjects with relapsing MS transitioning from any fumarate-based RMS approved therapy, such as DMF or DRF, or fingolimod due to breakthrough disease activity. A total of approximately 555 eligible subjects will receive open-label ofatumumab 20 mg s.c. every 4 weeks (after an initial loading regimen of three weekly 20 mg doses in the first 14 days).

The study is divided into three parts: Part 1 - Screening period, Part 2 - Treatment period, Part 3 - Safety follow-up.

Figure 1-1 Study Design



Transition period is described in protocol Section 6.6.1.

Part 1 - Screening (and transition) period

The Screening period can last up to 60 days and consists of two sections; namely Screening section and Baseline section. The Screening period will include the transition period (see

protocol Section 6.6.1 for details around subjects transitioning from either a fumarate therapy or fingolimod as per clinical practice). Baseline section can last up to the point of first study drug administration (Day -7 to Day 1). Participant eligibility will be determined based on the Screening and Baseline assessments.

Part 2 - Treatment period

Treatment period will consist of an initial induction phase (Week 1 to Week 4) with 20 mg s.c. ofatumumab during visits at Day 1, Day 7 and Day 14 followed by a monthly maintenance dose regimen of 20 mg s.c. ofatumumab every 4 weeks starting at Week 4. During the treatment period, the subjects will have the assessments as per Table 8-1 in the protocol. All visits should be performed in the morning whenever possible to reduce the impact of fatigue on the scheduled assessments.

Part 3 - Safety follow-up period

Safety follow-up:

- The Safety follow-up (FU) period will be applicable for the following subjects:
  - Subjects who complete the Treatment period on the study drug and do not continue ofatumumab treatment (either commercial ofatumumab via prescription or via Post-Trial Access mechanisms*)
  - Subjects who prematurely discontinue study drug
- All Safety FU visits must be scheduled relative to the End of Study (EOS) Visit.

***Post-Trial Access**

In the countries where ofatumumab is not approved by Health Authorities, not launched or reimbursed, subjects participating in the current study with a clinical benefit in the opinion of the Investigator at the completion of the Treatment period may continue to receive ofatumumab via a Post-Trial Access (PTA) mechanism until ofatumumab becomes commercially available and it is reimbursed in the particular country or until the PTA program ends, whichever occurs first. Reimbursement refers to country level and not individual reimbursement, if there are multiple reimbursement channels in a country the date of reimbursement is when the first major reimbursement is in place. Post Study Drug Supply (PSDS) is the first option for PTA. If PSDS cannot be implemented in a country due to the local legislation, the clinical trial team will work with the Investigator to assess other PTA possibilities.

All participants continuing ofatumumab after the study completion (either commercial ofatumumab via prescription or via Post-Trial Access mechanisms), must complete the EOS visit of this study first.

1.2 Study objectives and endpoints

Table 1-1 Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• Demonstrate the effectiveness of ofatumumab 20 mg s.c. administered every 4 weeks in subjects with relapsing forms of MS who had breakthrough disease on fumarates or fingolimod	• Annual relapse rate (ARR, based on confirmed relapses) measured over the 96 weeks
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• Evaluate the safety of ofatumumab 20 mg s.c. administrated every 4 weeks in subjects with relapsing forms of MS who had breakthrough disease on fumarates or fingolimod	• Proportion of subjects with adverse events, including injection related reactions • Proportion of subjects with laboratory or vital signs results meeting abnormal criteria • The proportion of subjects discontinuing treatment due to insufficient effectiveness (lack of efficacy) or tolerability/safety reasons
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**

• Demonstrate effectiveness of ofatumumab 20 mg s.c. administered every 4 weeks	• Change from Baseline during the treatment period, of the following Assessments:
	  • EDSS
	  • Timed 25-Foot Walk (T25FW)
	  • Nine-Hole Peg Test (9HPT)
	  • CCI [redacted]
	  • Low Contrast Visual Acuity (LCVA)
	  • T2 lesion volume
	• Time to 6-month Confirmed Disability Worsening (6mCDW) based on EDSS
	• Time to a 6-month confirmed cognitive decline (6mCCD), defined as a 4-point worsening on CCI [redacted]
	• Number of T1 Gd+ lesions per scan
	• Number of new or enlarging T2 lesions on MRI per year (annualized T2 lesion rate)
	• Proportion of patients without MRI activity
	• Proportion of subjects with No Evidence of Disease Activity (NEDA-3) as per protocol defined events during a 96-week period

• Explore patient reported outcomes in subjects treated with ofatumumab 20 mg s.c. administered every 4 weeks	• Change from Baseline during the treatment period of the following Assessments:
	  • The impact of MS disease as measured by the CCI [redacted]
	  • CCI [redacted]
	  • CCI [redacted]
	  • CCI [redacted]

• Explore Neurofilament (NfL) light chain as a biomarker for MS in terms of prognosis and disease activity monitoring	• Change from baseline in serum NfL light chain concentration

Objective(s)	Endpoint(s)

• Explore the utility of CCI using the CCI application	• Adherence to CCI assessments quantified as compliance level (%), which will be measured in terms of CCI
	• Correlation between CCI assessments and other assessments performed in the study
	• CCI includes the following:
	  • CCI
	  • CCI
	  • CCI
	  • CCI
	  • CCI
	  • CCI
	  • CCI
	  • CCI
	  • CCI
	  • CCI

• Explore daily activity and sleep patterns via CCI	• Change from Baseline in CCI derived metrics

2 Statistical methods

2.1 Data analysis general information

Novartis statistical and programming team will be performing the final CSR analysis unless otherwise specified. The Statistical Analysis System (SAS) 9.4 and/or R 3.6.1 or higher versions will be used.

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

For efficacy analyses on the full-analysis set (FAS), all available data collected in the database CCI

Safety analyses will be conducted using the safety (SAF) set. All safety analyses will be performed using all data collected in the database up to CCI

[redacted]

2.1.1 General definitions

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

Table 2-1 General Definitions

Study treatment/Study drug	The investigational drug (ofatumumab) will be referred as study treatment or study drug.
Date of first administration of study drug/first dose date	The first dose date of active study drug administration.
Date of last administration of study drug/last dose date	The last dose date of active study drug administration.
Study Day 1 or Day 1	The date of first administration of study drug/first dose date.
Study Day	All other study days will be labeled relative to Day 1. • For events with dates on or after Day 1, study day for the event is calculated as (event start date – first dose date + 1). • For events with dates before Day 1, study day for the event is calculated as (event start date – first dose date). Day 0 will not be used.
Duration of an event	Duration of an event is calculated as (event end date – event start date +1).
1 month	30 days; to be used in defining 6-month confirmed disability worsening or improvement.
4 weeks	28 days; to be used in determining target days of scheduled visits. It is based on the scheduled injection frequency for ofatumumab (during the maintenance phase).
Day post-study drug discontinuation	Day post-study drug discontinuation for a particular event is calculated as (event start date – study drug discontinuation date).
Baseline	Baseline is the last assessment obtained prior to the first administration of study drug. No visit windows will be needed for the identification of baseline assessment. For pulse and blood pressure vital sign values, 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. The pre-injection assessment values on Day 1 vital sign case report form (CRF) page will not be used for baseline derivations.

On-treatment period	On-treatment period includes days from the first injection date until 30 days after the last injection date. This definition considers subjects on ofatumumab are scheduled to inject every 28 +/- 3 days. For calculation of compliance to study drug administration, similar definition of on-treatment period will be used.
Nominal visits	Nominal visits are defined as all scheduled visits as per the clinical study protocol including the EOS visits. The definition of nominal visit excludes unscheduled visits. Only vital signs data collected on Day 1 protocol scheduled visit and ECG data collected on EOS visits will be summarized by nominal visit.
End of Study (EOS)	EOS, used in the context of individual subjects, refers to EOS visit. EOS, used in the context of the entire study, refers to completion of treatment epoch for all subjects.
End of treatment epoch date	This date is the date of discontinuation/study phase completion as recorded in the Study Phase Completion CRF page.
Last assessment on drug	It is the last assessment with non-missing value taken before or on the date of last administration of study drug. No visit windows will be needed for the identification of the last assessment on drug evaluation.

Table 2-2 Definition of time in key analyses

Time in study (ARR)	Time in study for ARR will be calculated as (efficacy cutoff date – first dose date+1)/365.25. The time in study by participant will be used as an offset variable to adjust for the various length participants have been observed and at risk of a confirmed MS relapse in the study. Definition of efficacy cutoff date is provided in Section 2.1.
Time from screening scan (MRI)	MRI lesions: The time from screening scan will be calculated as (date of last scheduled MRI scan with a non-missing value for the number of new or enlarging MRI lesions during the treatment epoch – date of screening scan +1)/365.25.
Time at risk for AE	Time at risk for AE is defined as the number of days spent in the study, from first to last administration of study drug, plus the safety data cut-off as in Section 2.1. Same definition is used for time at risk for SAE.

2.1.2 Visit Windows

2.1.2.1 Visit windows for treatment epoch

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

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

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

- For efficacy analyses all nominal visits (i.e. excluding unscheduled visits) will be mapped into one of the defined visit-windows. Note: for the derivation of disability worsening or improvement all visits (scheduled and unscheduled) need to be considered before the worsening or improvement can be confirmed. Similarly, for No Evidence of Disease Activity (NEDA-3), all visits (scheduled and unscheduled) need to be considered.
- For safety analyses all visits (scheduled and unscheduled) will be mapped to visit windows. Safety data from unscheduled visits may be reported separately if applicable.

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

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

Table 2-3 Visit-windows for EDSS / T25FW / 9HPT

Visit-window	Start day	Target day	End day
Week 24	1	168	252
Week 48	253	336	420
Week 72	421	504	588
Week 96	589	672	762

Table 2-4 MRI

Visit-window	Start day	Target day	End day
Week 24	2	168	252
Week 48	253	336	504
Week 96	505	672	762

Table 2-5 Visit-windows for vital signs*

Visit-window	Start day	Target day	End day
Week 4	1	28	98
Week 24	99	168	252
Week 48	253	336	420
Week 72	421	504	588
Week 96	589	672	762

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

Table 2-6 Visit-windows for routine laboratory values

Visit-window	Start day	Target day	End day
Week 4	1	28	56
Week 12	57	84	126

Week 24	127	168	252
Week 48	253	336	420
Week 72	421	504	588
Week 96	589	672	762

Table 2-7 Visit-windows for B-cell counts, IgG levels, IgM levels, PROs*

Visit-window	Start day	Target day	End day
Week 4	1	28	98
Week 24	99	168	252
Week 48	253	336	420
Week 72	421	504	588
Week 96	589	672	762

*Patient Reported Outcomes include CCI [redacted]

Table 2-8 CCI [redacted] LCVA, CCI [redacted]

Visit-window	Start day	Target day	End day
CCI [redacted]	[redacted]	[redacted]	504
Week 96	505	CCI [redacted]	762

Table 2-9 Visit-windows for biomarker data

Visit-window	Start day	Target day	End day
Week 4	1	28	56
Week 12	57	84	126
Week 24	127	168	210
Week 36	211	252	294
Week 48	295	336	378
Week 60	379	420	462
Week 72	463	504	546
Week 84	547	588	630
Week 96	631	672	762

Table 2-10 Visit-windows for eCSSRS

Visit-window	Start day	Target day	End day
Week 2	1	14	21
Week 4	22	28	42
Week 8	43	56	70
Week 12	71	84	126
Week 24	127	168	210
Week 36	211	252	294
Week 48	295	336	378
Week 60	379	420	462
Week 72	463	504	546
Week 84	547	588	630
Week 96	631	672	762

2.1.2.2 Visit windows after study drug discontinuation

For summaries of data collected after study drug discontinuation, data from both treatment epoch and safety follow-up epoch will be considered. Participants who prematurely discontinue the study drug will be required to have their EOS visit as soon as possible and enter into the SFU according to the assessment schedule in protocol Table 8-2. In the SFU, all assessments are relative to EOS visit. Day 1 will be the first day after EOS visit. The visit window definitions for SFU Visit 1 and Visit 2 are provided in Table 2-11. The SFU Visit 2 will be the last clinic visit and the end of SFU Visit will be performed by telephone contact. Additional SFU Visit will be required if participants have either IgG or IgM < screening or LLN, and they will be performed outside of the study.

Table 2-11 Visit-windows after study drug discontinuation

Visit-window	Start day	Target day	End day
SFU Visit 1	1	84	126
SFU Visit 2	127	168	210

2.1.2.3 Multiple assessments within visit windows

It is possible that multiple assessments of a participant 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). Where applicable it will be defined for each parameter what the worst case is.

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

2.2 Analysis sets

The Full Analysis Set (FAS) comprises all subjects to whom study drug has been assigned and who received at least one dose of study drug. The FAS will be used for the summary of demography and baseline characteristics as well as for all efficacy analyses except CCI

Modified Full Analysis Set (mFAS) : CCI

The Safety Set (SAF) includes all subjects who received at least one dose of study drug. The SAF will be used for all safety analyses.

Please refer to appendix Table 5-2 for subjects to be excluded from analysis.

2.2.1 Subgroup of interest

Subjects enrolled into the study are previously treated with either fumarate-based therapies or Fingolimod. The following efficacy subgroups will be analyzed as part of CSR:

- Last prior DMT (fumarate-based therapies vs. fingolimod)
- Duration of washout (<30 days vs. ≥30 days)
- Baseline NfL (<median of baseline NfL and ≥median of baseline NfL)

The primary endpoint analysis and part of exploratory endpoint analyses (MRI, NfL, 6mCDW, NEDA-3 and EDSS) will be repeated for last prior DMT subgroup. The primary endpoint will be repeated for duration of washout and baseline NfL subgroups separately. The primary endpoint and MRI endpoints (number of T1 Gd+ lesions and number of new or enlarging T2 lesions) will be analyzed by last prior DMT and duration of washout together.

The following safety subgroups will be analyzed as part of CSR:

- Last prior DMT (fumarate-based therapies vs. fingolimod)
- Duration of washout (<30 days vs. ≥30 days)
- Injection related premedication category

The analysis of injection related reaction (IRR) will be repeated for injection related premedication category subgroup. Details of premedication categories are specified in Section 2.4.2.3. TEAEs will be repeated by last prior DMT and duration of washout subgroups. Special lab results (IgG, IgM, lymphocyte and neutrophil) will be repeated by last prior DMT subgroup.

2.3 Subject disposition, demographics and other baseline characteristics

2.3.1 Subject disposition

The number and percentage of subjects who completed the study or study drug and prematurely discontinued study or study drug will be presented, along with the primary reason for discontinuation. Data collected on the study and treatment disposition CRF pages will be used to summarize this information. The summary will be on the FAS.

The number and percentage of subjects who completed the study (i.e., treatment epoch) or prematurely discontinued study prior to the end of the treatment epoch, as well as who entered the safety follow-up will be presented, along with the primary reason for discontinuation. Data collected on the disposition CRF page will be used to summarize this information. The summary will be on the FAS.

The number and percentage of subjects in each analysis set will be presented.

Protocol deviations will be summarized by deviation categories for the FAS. Protocol deviations leading to exclusion from analysis sets will be summarized.

In addition to the pre-defined standard PD terms, Novartis has also defined 6 new protocol deviations and the corresponding relationship (health status related vs. site lockdown, participant concerns, etc.) to the COVID-19 pandemic in line with “FDA Guidance on Conduct

of Clinical Trials of Medical Products during COVID-19 Public Health Emergency" (March 2020) and "Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic" (April 2020) from EMA as listed below. The following deviations related to the COVID-19 pandemic will be summarized.

- Missing visits
- Changes in procedures and assessments
- Planned visits not done at sites
- Changes in drug supply method
- Treatment not given
- Participant discontinuation due to COVID-19 situation

A cross-tabulation of COVID-19 related PD vs. corresponding relationship will also be produced.

In addition, COVID-19 related outcomes (e.g., COVID-19 AEs, discontinuation due to COVID-19, death due to COVID-19) will be descriptively summarized by country.

2.3.2 Background and demographic characteristics

Background characteristics include demographic characteristics (sex, race and ethnicity collected on the Demography CRF), age, height, body weight, BMI, employment status, alcohol and smoking history at baseline.

Age will be calculated from date of first administration of study drug and date of birth. Derived baseline height, body weight and BMI will be presented. These variables will be summarized for the FAS using frequency distributions (for categorical variables) and descriptive statistics of mean, standard deviation, minimum, median and maximum (for continuous variables).

Age categories: 18 to 30 years, 31 to 40 years, 41 to 55 years, >55 years

Subjects may be rescreened if they do not initially meet eligibility criteria. All assessments must be repeated, except for MRI (the original MRI may be used during rescreening if the rescreening occurs within 3 months of the original MR date). Demographic characteristics will also be summarized by last prior DMT.

2.3.3 MS baseline disease characteristics

MS baseline characteristics, MS disease history and MS medication history will be summarized for the FAS. MS baseline characteristics include baseline EDSS, 9HPT, T25FW, CCI LCVA, key MRI parameters (e.g., number of Gd-enhancing T1 lesions, number of T2 lesions, T2 lesion volume), Biomarkers such as NfL and IgG, IgM, CD-19 B-cell counts, Lymphocytes and neutrophils.

Baseline lymphocyte and neutrophil values should also be summarized, including reporting of lymphocyte and neutrophil abnormalities (Table 2-12).

Of note, laboratory values below limit of quantification (e.g. value coded as <x.xx) will be imputed to the lower limit of quantification/2. MS baseline disease characteristics will also be summarized by last prior DMT.

Table 2-12 Notable abnormalities for lymphocyte and neutrophil counts

Lymphocytes (10E9 /mL)	Decrease in lymphocytes counts: Gr1: <LLN - 0.8 x 10E9/L Gr2: <0.8 - 0.5 x 10E9/L Gr3: <0.5 - 0.2 x 10E9/L Gr4: <0.2 x 10E9/L
	Increase in lymphocytes counts: >4.0 - 20 x 10E9 /L (grade 2 lymphocytosis) >20 x 10E9 /L (grade 3 lymphocytosis)
Neutrophils (10E9 /mL)	Decrease in neutrophils counts: Gr1: <LLN – 1.5 x 10E9/L Gr2: <1.5- 1.0 x 10E9/L Gr3: <1.0 - 0.5 x 10E9/L Gr4: <0.5 x 10E9/L

MS disease history includes duration of MS since diagnosis (years), duration of MS since first symptom (years), number of relapses in the last 12 months prior to screening, number of relapses in the 12 to 24 months prior to screening, type of MS at study entry (i.e., RRMS or SPMS), time since onset of SPMS, time since onset of most recent relapse (months), and number of prior DMTs.

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

MS medication history of previous disease-modifying drugs (coded by WHO drug dictionary) will be summarized by preferred term (PT).

Consider following categories to summarize disease history variables:

- Duration of MS since diagnosis (years): 0-<1, 1-<2, 2-<5, 5-<10
- Duration of MS since first symptom (years): 0-<1, 1-<2, 2-<5, 5-<10, 10-<15, >=15
- Number of relapses in the last 12 months prior to screening: 0, 1, 2-3, 4-5, >5
- Number of relapses in the 12 to 24 months prior to screening: 0, 1, 2-3, 4-5, >5
- Type of MS at study entry: RRMS, SPMS
- Number of prior DMTs: 1, 2, 3

MS disease history will also be summarized by last prior DMT.

2.3.4 Medical history

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

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

2.4.1 Study treatment / compliance / time at risk

Duration of exposure to study drug will be derived as follows:

- For subjects on ofatumumab treatment, duration of exposure will be calculated as (last injection date – first injection date + 31 – Σ [(j+1)th injection date – jth injection date - 31]), where j and j+1 refer to consecutive injections with injection dates more than 31 days apart (as subjects are scheduled to take the subcutaneous injections every 28 +/- 3 days).

Duration of exposure to study drug will be summarized descriptively on SAF set by duration category (i.e., ≥ 1 week, ≥ 2 weeks, ≥ 4 weeks, ≥ 8 weeks, ≥ 12 weeks, ≥ 24 weeks, ≥ 36 weeks, ≥48 weeks, ≥ 60 weeks, ≥ 72 weeks, ≥ 84 weeks, ≥ 96 weeks). Descriptive statistics of duration in days will also be provided.

The number of subject-years is calculated as (the sum of the number of days of exposure for all subjects)/365.25 and will be summarized.

Compliance to the study drug administration schedule will be calculated as duration of exposure to study drug in (days)/duration of on-treatment period (as defined in Section 2.1.1) in (days) ×100%. This rule means that compliance will be measured during the time interval the subject took study medication: premature discontinuation from study drug will not be considered non-compliance. Compliance to study drug administration will be summarized descriptively on SAF. In addition, compliance will be summarized with cumulative number and percentage of subjects in each compliance category (i.e., ≥ 20%, ≥ 30%, ≥ 40%, ≥50%, ≥60%, ≥70%, ≥80%, ≥90%, ≥95%, ≥98%, =100%).

Time at risk: Time at risk for AE and time at risk for SAE will be summarized in a similar way to duration of exposure to study drug. Intermediate treatment interruptions will be included in time-at-risk calculations. It will be derived as follows:

Time at risk for AE is defined as the number of days spent in the study, from first to last administration of study drug, plus the safety data cut-off as described in Section 2.1. Same definition is used for time at risk for SAE.

Dose interruptions due to COVID-19 pandemic: Summary of at least one missed dose of ofatumumab due to non COVID-19 related reasons, COVID-19 related reasons and overall will be provided. Further frequency and percentage of subjects missed number of doses in the following category will be provided: 1-3, 4-6, 7-9, >9. Here subject may be counted in more than one category.

2.4.2 Prior, concomitant and post therapies

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

2.4.2.1 Concomitant medication

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

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

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

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

Data collected from the Previous MS disease modifying treatment pages or as "Injection related premedication" in the concomitant medication pages will not be included in this summary.

2.4.2.2 Non-drug therapies / procedures

Records on the prior and concomitant non-drug therapies/procedures CRF page will be coded using the MedDRA dictionary. All procedures will be classified as prior, concomitant or post-study drug discontinuation procedure, in the same way as done for concomitant medications. Non-drug therapies/procedures in each of these 3 categories will be summarized separately by system organ class and preferred term.

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

2.4.2.3 Injection related premedication

Injection related premedication will be identified by subcategory “Injection related premedication” in concomitant medication data set. Injection related premedication will also be summarized separately for each injection up to injection 9 and cumulatively for injections after injection 9 (i.e., injections 10 to last injection) as well as cumulatively for all injections.

For injection 1 summary, the injection related premedication with either start date or end date on the same day as the first injection date will be included and summarized for each of the three protocol specified types and for each combination of the specified types (type 1+ type 2, type 1+ type 3, type 2+ type 3, type 1+ type 2+ type 3). The three protocol specified types are steroids (type 1), antihistamines (type 2) , and antipyretics/analgesics (type 3). The steroids (type 1) will

be identified by category "Steroid". The antihistamines (type 2) will be identified by ATC level 3 "antihistamines for systemic use". The antipyretics/analgesics (type 3) will be identified by ATC level 3 "other analgesics and antipyretics" and "anti-inflammatory and anti-rheumatic products, non-steroids". In summaries for each combination of the specified types, the number and proportion of subjects who took both (or all 3) types of injection related premedication at specified injection will be provided. In addition to this, summary of subjects with no premedication will also be provided.

2.4.2.4 Previous MS disease modifying treatment

Data collected from the previous MS disease modifying treatment pages will be summarized separately.

2.5 Analysis of the primary objective

The primary objective of the study is to determine the effectiveness of ofatumumab 20 mg s.c. administered every 4 weeks in subjects with relapsing forms of MS who have breakthrough treatment response on fumarate-based RMS approved therapies or fingolimod as evaluated by the annualized relapse rate (ARR, based on confirmed relapses) in participants with relapsing MS.

2.5.1 Primary endpoint

The primary endpoint of the study is the annualized relapse rate (ARR, based on confirmed relapses), which is defined as the number of confirmed MS relapses in a year. In the primary analysis, the ARR is estimated based on the FAS using individual relapse count as the response variable with natural log of time in study in years as an offset variable.

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

- The cumulative number of confirmed MS relapses by subject based on EDSS will be derived. All confirmed relapses with a start date on or after the date of first administration of study drug and prior to the efficacy cutoff date will be included in the analysis. Additional details are provided in Section 5.1.4 and Section 5.4.1.
    - The definition of a confirmed MS relapse is one accompanied by a clinically relevant change in the EDSS assessment, i.e. an increase of at least 0.5 points on the EDSS (total) score, or an increase of at least 1 point on at least two Functional scores (FSs), or an increase of at least 2 points on at least one FS, excluding changes involving bowel/bladder or cerebral FS, compared to the last EDSS assessment taken in the absence of (confirmed or unconfirmed) relapse and prior to the current relapse. EDSS obtained on the date as indicated on the Summary of MS Relapse eCRF page will be used. If such EDSS assessment is missing or not meeting the criteria to confirm the relapse, all other EDSS assessments taken within 30 days from the relapse start date (i.e., EDSS assessment date – relapse start date <=30) and before the relapse end date (EDSS assessment date < relapse end date) will be checked. If at least one of such available EDSS assessments meets the criteria, the relapse is a confirmed relapse. Otherwise, the relapse is considered an unconfirmed relapse.

- The time-in-study by subject will be used as an offset variable to adjust for the various length subjects have been observed and at-risk of a confirmed MS relapse in the study. Time in study for ARR will be calculated as (end of efficacy cutoff date – first dose date+1)/365.25. Definition of efficacy cutoff date is provided in Section 2.1.

2.5.2 Statistical hypothesis, model, and method of analysis

The primary analysis will describe the test for null hypothesis (H0):ARR >=0.18 versus alternative hypothesis (H1): ARR<0.18.

In the analysis, the response variable is the number of confirmed relapses observed from each participant and the participant's time in study (natural log of time in years) is used as an offset variable to adjust for the varying lengths of participant's time in the study. The adjusted ARR (i.e., model-based estimate adjusted for covariates) along with the corresponding one-sided 95% confidence interval and one-sided p-value for hypothesis testing will be obtained.

A negative binomial model with log-link and subject's time in study (as natural log of time in years) will be used as an offset with number of relapses in previous year, baseline EDSS, baseline number of T1 Gd-enhancing lesions, the participant's age at baseline and prior MS therapies (fumarates or fingolimod) as covariates. CCI [redacted] In addition, ARR time-based and subject-based will also be summarized based on only confirmed relapses. Below are the definitions time-based and subject-based ARR:

- ARR (time-based) is calculated by taking the total number of relapses observed for all subjects, divided by the total number of days in study of all subjects and multiplied by 365.25 days.
- ARR (subject-based) is the individual subject ARR which is calculated by taking the total number of relapses observed for a subject divided by the total number of days in study of that subject and multiplied by 365.25.

2.5.3 CCI [redacted]

[redacted]

2.5.4 CCI [redacted]

[redacted] informative drop-out, information is missing at random, and constant relapse rate over time.

2.5.5 CCI [redacted]

[redacted]

cCCI [redacted]

2.5.6 CCI [redacted]

[redacted]

2.6 Analysis of the key secondary objective

There is no key secondary objective defined for this study.

2.7 Analysis of secondary efficacy objective(s)

No other secondary efficacy objectives were analyzed.

2.8 Analysis of secondary objective(s)

The secondary objective is to evaluate the safety of ofatumumab 20 mg s.c. administrated every 4 weeks in subjects with relapsing forms of MS who had breakthrough disease on fumarates or fingolimod.

Below are the secondary endpoints defined to evaluate secondary objective.

- Proportion of subjects with adverse events, including injection related reactions
- Proportion of subjects with laboratory or vital signs results meeting abnormal criteria
- The proportion of subjects discontinuing treatment due to insufficient effectiveness (lack of efficacy) or tolerability/safety reasons

Since these objectives are related to safety, details on analysis is provided in safety Section 2.9.

2.9 Safety analyses

Safety analyses will be conducted using the safety (SAF) set. Unless explicity stated otherwise, all safety analyses will be performed using all data collected in the database up to CCI [redacted]

[redacted]

The assessment of safety will be primarily based on the frequency of adverse events (including death and non-fatal serious adverse events). Additional safety assessments include laboratory tests, physical examination (including examination of skin), vital sign measures, ECG evaluations and assessment of suicidality. Clinically significant findings in these additional safety assessments will be reported as adverse events and analyzed as such. In addition all safety assessments will be summarized or listed as appropriate.

2.9.1 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 subject or clinical investigation of a subject after providing written informed consent for participation in the study. That means that a subject can report AEs before having started study medication. For reporting purposes, the main focus will be on treatment emergent adverse event (TEAE), defined as any adverse event which started on or after the day of first dose of study medication.

TEAEs and serious TEAEs up to and including safety cut-off date will be included in the analyses (see detailed explanation in Section 2.9 for safety cut off date).

AEs will be reported by primary system organ class (SOC) and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA). The MedDRA version is 27.0.

The number and percentage of subjects reporting any TEAEs (referred to as incidence of any TEAEs later) will be summarized by primary SOC and preferred term.

Separate summaries will be provided for:

- overview of TEAEs,TEAEs by primary SOC,most common TEAEs by preferred term (≥ 2%), most common TEAEs by preferred term (≥ 2%) and last prior DMT, TEAE by last prior DMT, TEAE by duration of washout
- serious TEAEs by primary SOC and preferred term, serious TEAEs by last prior DMT, serious TEAEs by duration of washout, deaths by primary SOC and preferred term,
- drug related TEAEs by primary SOC and preferred term,
- TEAEs leading to treatment interruption and permanent discontinuation of study drug by primary SOC and preferred term, TEAEs leading to treatment interruption and permanent discontinuation of study drug by last prior DMT, TEAEs leading to treatment interruption and permanent discontinuation of study drug by duration of washout, any TEAEs will also be summarized by primary SOC, preferred term, and maximum Common Terminology Criteria for Adverse Events (CTCAE) grade. Missing CTCAE grade will not be imputed.

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

2.9.1.1 Adverse events of special interest / grouping of AEs

Selected tables will be produced for Adverse Events of Special Interest (AESI) (i.e., risks) defined in the latest version of case retrieval sheet (eCRS) at the time of analysis implementation (i.e., study database lock). Specifically, incidence of TEAEs that fulfill the risk search terms as defined in eCRS will be summarized by risk name and level.

2.9.1.1.1 Injection reaction related AEs

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

Symptoms listed in the injection site reaction or injection systemic reaction CRF pages will be summarized by providing the number and percentage of subjects with each of the symptoms and pre-specified grouping of symptoms as well as overall. These summaries will be provided for each injection up to injection 9 and cumulatively for injections after injection 9 (i.e., injections 10 to last injection) as well as cumulatively for all injections. The proportion of subjects with injection site reactions and the proportion of subjects with injection systemic reactions will be plotted against the injection sequence numbers (injections 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10+).

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

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

For both injection site and systemic reaction, symptoms will be summarized by injection and injection related premedication category. Details about injection related premedication category are given in Section 2.4.2.3. Injection systemic reaction will be summarized by none, any premedication and all combinations of three types of premedication. A listing of injection related reactions by injection of first occurrence, subjects and event start date will be provided.

2.9.1.1.2 Clinical Trial Safety Disclosure (CTSD) reports

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on nonserious treatment emergent adverse events with an incidence greater than 5% and on treatment emergent serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

If for a same subject, 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 AE's 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. Relapse as SAE will be listed separately with timing, last previous DMT and washout period. All serious adverse events (SAE), regardless of the safety cut-off, will be summarized.

2.9.1.1.3 Infection

Infection adverse event will be summarized by:

- COVID-19 related infection vs. non COVID-19 related infection
- COVID-19 related serious infection vs. non COVID-19 related serious infection
- Within COVID-19 related infection: serious infection vs. non serious infection
- COVID-19 related infection by CTCAE grade
- Non COVID-19 related infection by CTCAE grade
- Serious COVID-19 related infection by CTCAE grade
- Non serious COVID-19 related infection by CTCAE grade

Number of subjects with at least one infection AE will also be provided. AEs related to malignancies will also be summarized.

2.9.2 Deaths

Death, if meaningful number of cases reported (i.e., 5 or more cases), will be summarized by providing the number and percentage of subjects, otherwise only listing will be provided. All deaths as recorded in the final database (i.e., up to database lock) will be included.

2.9.3 Laboratory data

Data summaries will be provided in SI units. The summary of laboratory evaluations will be presented for three groups of laboratory tests: Hematology, Chemistry and Urinalysis. On presenting summary statistics, laboratory data will be grouped and displayed in an alphabetical order within the Hematology and Chemistry groups.

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

change from baseline = post baseline value – baseline value

The number and percentage of subjects with new or worsening laboratory abnormalities based on CTC grade (CTCAE version 5.0) in each visit-window (grade 1/2, grade 3/4) and at any time

post baseline will be presented. Subjects with specific laboratory abnormalities based on CTC grades >=3 will be listed.

Number of subjects with newly occurring liver enzymes abnormalities will be summarized. Newly occurring liver enzymes abnormalities are defined in Section 5.3.1.

For continuous variables databased as < lower limit, these will be imputed as being half of the lower limit. For continuous variables databased as > upper limit, there will be imputed as equal to the upper limit,

All above summaries include only data up to and including safety cut off date (see Section 2.9 for safety cut off date).

2.9.3.1 Other special lab results

Other non-routine laboratory data include B-cell counts, total IgG, total IgM, and other biomarkers such as neurofilaments. All data will be listed appropriately.

The B-cell counts, total IgG, total IgM, neurofilaments, lymphocytes and neutrophils will be summarized using descriptive statistics by visit-window. IgG, IgM, lymphocytes and neutrophils will also be summarized by visit-window and last prior DMT.

In addition, number and percentage of subjects with B-cells < the lower limit of normal (LLN) or < their baseline value (i.e., B-cell depleted) will be presented by visit window. For subjects who entered the safety follow-up, number and percentage of subjects with B-cell recovery (above LLN) will be summarized by SFU visit-window.

Number and percentage of subjects with IgG and IgM below LLN and meet the notable low level criteria in IgG or IgM by visit window will be provided. IgG and IgM will also be summarized by visit window and last prior DMT. A notably low IgG level is defined as a level that is ≤ 4.5 g/L (20% below LLN) and ≤0.36 g/L (10% below LLN) for IgM. LLN is 5.65 g/L for IgG and 0.4 g/L for IgM. For subjects who had IgG or IgM below LLN at the time of entering SFU, number and percentage of subjects with IgG or IgM recovery (above LLN) will be summarized by SFU visit-window.

Number and percentage of subjects with lymphocytes and neutrophils below LLN and meet the notable abnormalities by visit window will be provided. Lymphocytes and neutrophils will also be summarized by visit window and last prior DMT. Notable abnormalities for lymphocytes and neutrophils are listed in Table 2-12.

2.9.4 Other safety data

2.9.4.1 ECG and cardiac imaging data

ECG data will be collected at baseline visit and EOS visit. Clinically significant findings from ECG evaluations will be reported as AEs and included in the analysis of AEs. ECG parameters include max heart rate, mean PR duration, mean QT duration, mean QRS duration, and QT corrected using Fridericia's correction formula (all as collected on the ECG CRF). Descriptive statistics of each ECG parameter will be provided for baseline and for the nominal visit (i.e., EOS visit). The number and percentage of subjects meeting the criteria defined in Table 2-13. Criteria for relevant ECG absolute or change from baseline values will be provided

for each criterion for baseline and for the nominal visit. A listing based on clinically significant findings will be provided.

Table 2-13 Criteria for relevant ECG absolute or change from baseline values

Absolute values criteria	Changes from baseline criteria
Heart rate: HR <50 or HR > 120 beats/min	QRS complex : increase > 25% compared to baseline
Pulse rate: PR <110 or PR >200 msec	QTcF > 500 msec and QTcF increase > 60 msec
QRS complex: < 70 msec or > 120 msec	
QTcF < 350 or > 450 msec (males)	
QTcF <360 or > 460 msec (females)	

2.9.4.2 Vital signs

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

Three sitting measurements of blood pressure (SBP and DBP) and pulse will be taken at each vital sign assessment.

For post-baseline assessments, the blood pressure and pulse values will be the average of the non-missing values of the 3 measurements. If more than one blood pressure/pulse assessment (scheduled or unscheduled) exists in a particular visit-window (as defined in Section 2.1.2.1), derivation should follow the rules as defined in Section 2.1.2.3. Derivation of baselines for blood pressure and pulse are provided in Section 2.1.1.

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

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

change from baseline = post-baseline value – baseline value

The number and percentage of subjects with clinically notable vital signs will be presented. For clinical notable vital signs values, refer to Table 2-14.

For vital signs data collected on Day 1 protocol scheduled visit, pre and post-injection vital signs data including temperature, pulse rate and blood pressure are collected. Change from pre-injection to post-injection in these 3 parameters will be summarized by nominal visit.

All above summaries include only data up to and including safety cut off. A listing of subjects with clinically notable vital signs values will be provided.

Table 2-14 Vital signs clinically notable values

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

2.9.4.3 Treatment discontinuation or interruption due to lack of efficacy or tolerability

The proportion of subjects discontinuing treatment or having treatment interruption due to insufficient effectiveness (lack of efficacy) or tolerability/safety reasons will be provided. On treatment disposition CRF page, reason for discontinuation "Lack of efficacy" and "Adverse events" will be selected to provide this summary. In addition, treatment discontinuation or interruption due to lack of efficacy or safety will also be summarized by participants who have IgG < LLN at any point post-baseline vs participants who have IgG ≥ LLN at any point post-baseline. Same analysis will be repeated by IgM.

2.9.4.4 Suicidality evaluations

The eCSSRS data will be mapped to Columbia Classification Algorithm for Suicide assessment (C-CASA) as per FDA guidance on suicidality. The proportion of subjects who have completed suicide, suicide attempt, and preparatory actions toward imminent suicidal behavior, suicidal ideation, and self-injurious behavior without suicidal intent as per the C-CASA scale during the study (safety data cutoff applies) at any time post baseline will be summarized.

The Columbia Suicide Severity Rating Scale (C-SSRS) questionnaire will be administered via electronic device (eC-SSRS). However, as per internal Novartis guidelines, a CRF page 'Supplemental Data for Suicidal Ideation and Behavior Categories' is also used as an unplanned/unscheduled visit for those cases when the subject did not conduct the phone interview because, e.g. the subject was hospitalized and unable to conduct the interview or the subject refused to conduct the interview/withdrew from the study and external information on suicidal ideation and behavior (SIB) is required. In such cases, SIB information will still be collected from external parties (spouse, caregiver, nurse, investigator, etc.) through means of this CRF page. Further, for deaths due to suicide, the site should fill out the Supplemental Data CRF ("completed suicide" tick box) to ensure accurate reporting of such cases. When reporting the SIB data, data from both sources (eC-SSRS and Supplemental CRF) will be used in a pooled manner and no distinction will be made between the two.

Table 2-15 Standard SIB events as categorized by C-SSRS

Category number	C-SSRS category
Suicidal Ideation	
1	Wish to be dead
2	Non-specific active suicidal thoughts
3	Active suicidal ideation with any methods (not plan) without intent to act

4	Active suicidal ideation with some intent to act, without specific plan
5	Active suicidal ideation with specific plan and intent
Suicidal behavior	
6	Preparatory acts or behavior
7	Aborted attempt
8	Interrupted attempt
9	Actual attempt
10	Completed suicide
Self-injurious behavior, without suicidal intent	
11	Non-suicidal self-injurious behavior

2.10 Pharmacokinetic endpoints

Not Applicable.

2.11 PD and PK/PD analyses

Not Applicable.

2.12 Patient-reported outcomes

All the Patient-reported outcomes CCI [redacted] will be analyzed as part of exploratory endpoints outside of CSR separately.

2.13 Digital endpoints

All digital endpoints CCI [redacted] will be analyzed as part of exploratory endpoints outside of CSR separately.

2.14 Other Exploratory analyses

Following exploratory endpoints will be analyzed as part of CSR based on FAS population.

2.14.1 6-month Confirmed Disability Worsening (6mCDW)

A 6-month confirmed disability worsening (6mCDW) is defined as an increase from baseline in EDSS sustained for at least 6 months. This means that after a scheduled or unscheduled visit at which the participant fulfills the disability worsening criterion as defined in Table 2-16, all EDSS assessments (scheduled or unscheduled) need to also fulfill the worsening criteria until the worsening ("the event") can be confirmed at the first scheduled visit that occurs in the absence of (confirmed or unconfirmed) relapse 6 months/166 days after the onset of the worsening, or later.

In the time to event (6mCDW) analysis, time will be calculated as (the date of EDSS assessment at onset of the event – date of first administration of study drug+1) for patients with the events. Censoring occurs in those participants who did not experience an event up to the analysis cutoff date (i.e. end of treatment epoch date), this includes participants who had a "tentative" disability worsening that could not be confirmed due to an early discontinuation or any another reason.

The censoring time is calculated as (the date of last EDSS assessment up to analysis cutoff date – date of first administration of study drug+1). Additional details are provided in footnote of Table 2-16.

Table 2-16 Criterion for disability worsening based on change in EDSS score

Total EDSS at baseline*	"Disability worsening" criterion
0	≥ +1.5
0.5 to 5	≥ +1
≥5.5	≥ +0.5
A 6-month confirmed disability worsening can have an onset at any scheduled or unscheduled visit if the disability worsening criterion is met. A disability worsening event can only be confirmed at a scheduled visit in the absence of (confirmed or unconfirmed) relapse if, over a period of 6 months (≥166 days=6*30-14 [visit window]) time interval, all assessments meet the worsening criterion. If a participant dies due to MS (EDSS=10 at any time), it will be considered a confirmed disability worsening regardless of the baseline EDSS or the change in EDSS. The time will be calculated as (date of EDSS assessment at a tentative onset of the event – date of first administration of study drug+1) or (date of death – date of first administration of study drug + 1) if a tentative onset date does not exist. Note: Death for other reasons than MS (i.e. not EDSS=10) will not be considered a disability worsening. *Baseline EDSS is defined as the last EDSS assessment prior to the first dose of study medication (protocol inclusion criterion is EDSS 0-4 at screening)	

For statistical analysis, Kaplan-Meier curves (and/or cumulative incidence plots) will be provided to present the time-dependent cumulative probability of participants reaching 6mCDW. Kaplan-Meier (KM) estimates will be calculated for the study with 95% confidence intervals. Separate Kaplan-Meier curves and estimates will also be calculated with 95% confidence intervals for last prior DMT subgroup (fumarates vs. fingolimod).

2.14.2 6-month Confirmed Cognitive Decline (6mCCD)

A 6-month confirmed cognitive decline (6mCCD) is defined as at least a 4-point worsening on CCI score sustained for at least 6 months. Event rate by time interval (0-12 months, 12-24 months) will be provided to participants reaching 6mCCD. Cumulative event rate will be calculated with 95% confidence intervals.

2.14.3 EDSS

The change from baseline in EDSS will be summarized descriptively by visit window, as well as by visit window and last prior DMT.

2.14.4 Number of T1 Gd-enhancing lesions per scan

Number of Gd-enhancing lesions will be obtained from each MRI scan per protocol assessment schedule. To estimate the number of Gd-enhancing lesions per scan, below variables will be derived.

- The total number of Gd-enhancing lesions will be derived by taking the sum of numbers of Gd-enhancing lesions from all scheduled MRI scans. MRI scans taken within 14 days after the termination of steroid therapy will not be included in analysis of Gd lesion related endpoint.
- The number of MRI scans will be derived by counting the number of scheduled MRI scans with non-missing values for the number of Gd-enhancing lesions.

The mean number of T1 Gd-enhancing lesions per scan and corresponding 95% CI will be estimated using a negative binomial model with log-link with number of relapses in previous year, baseline EDSS, baseline number of T1 Gd-enhancing lesions, the participant's age at baseline and prior MS therapies (fumarates and Fingolimod) as covariates. In addition, separate estimates of T1 lesions and corresponding 95% CIs for last prior DMT (fumarates and fingolimod) and for last prior DMT and duration of washout will be given. In case model has convergence issues, covariates will be dropped with the following order: 1) Number of relapses in previous year; 2) Baseline EDSS; 3) Age. Time-based and subject-based T1 Gd-enhancing lesions will also be summarized.

The reduction rate of mean number of T1 Gd-enhancing lesions per scan over time vs baseline will be estimated using a Generalized Estimating Equation (GEE) for a negative binomial model with log-link and natural log the number of MRI-scans with evaluable Gd-enhancing lesions at each visit as an offset variable, and with number of relapses in previous year, baseline EDSS, the patient's age at baseline and prior MS therapies as covariates. In this analysis, outcome will also include number of T1 Gd-enhancing lesions at baseline, the reduction rate vs baseline will be derived using contrast. The negative binomial model will also be performed by prior MS therapy subgroups. In this analysis, separate models will be implemented for each subgroupDetails of negative binomial GEE models and SAS codes are given in Section 5.4.3.

2.14.5 Number of new or enlarging T2 lesions on MRI per year (annualized T2 lesion rate)

The number of new or enlarging T2 lesions as compared to the previous MRI scan will be obtained from each MRI scan per protocol assessment schedule. To estimate the annualized rate of new or enlarging T2 lesions, below variables will be derived:

- The total number of new or enlarging T2 lesions will be derived by taking the number of new or enlarging T2 lesions from the last scheduled MRI scan with a non-missing value.
- The time (in years) from previous MRI scan will be calculated as (date of last scheduled MRI scan with a non-missing value for the number of new or enlarging T2 lesions– date of previous MRI scan +1) / 365.25.

The mean number of new or enlarging T2 lesions on MRI per year and corresponding 95% CI will be estimated using a negative binomial model with log-link and time from previous MRI scan (as natural log of time in years) will be used as an offset with number of relapses in previous year, baseline EDSS, baseline T2 lesion volume, the participant's age at baseline and prior MS therapies (fumarates and Fingolimod) as covariates. In addition, separate estimates of T2 lesions and corresponding 95% CIs for last prior DMT (fumarates and fingolimod) and for last prior DMT and duration of washout will be given. In case model has convergence issues, covariates will be dropped with the following order: 1) Number of relapses in previous year; 2) Baseline EDSS; 3) Age. Time-based and subject-based new or enlarging T2 lesions will also be summarized.

The reduction rate of mean annulized rate of new or enlarging T2 lesions over time vs baseline will be estimated using a Generalized Estimating Equation (GEE) for a negative binomial model with log-link and natural log of the time from previous MRI scan as an offset variable, and with baseline T2 lesion volume, baseline EDSS, the patient's age at baseline and prior MS therapies

as covariates. The negative binomial model will also be performed by prior MS therapy subgroups. In this analysis, separate models will be implemented for each subgroup. Details of negative binomial GEE models and SAS codes are given in Section 5.4.3.

2.14.6 Change from baseline in T2 lesion volume

Raw T2 lesion volume and change from baseline in T2 lesion volume will be summarized by visit window. The mixed model for repeated measures (MMRM) model will be fitted, using log-transformed change from baseline T2 lesion volume as the outcome, adjusting for last prior DMT and visit as factors, log-transformed baseline T2 lesion volume, baseline EDSS and subject's age at baseline as continue covariates. Unstructured correlation matrix will be specified within the model. Estimates for each visit window, as well as 95% CI and p-values will be given. This analysis will also be repeated by last prior DMT. In case model has convergence issues, the following actions will be taken: 1) Drop age; 2) Change the covariance structure from unstructured to Autoregreesive(1). Details of MMRM model and SAS codes will be provided in Section 5.4.4.

2.14.7 Proportion of subjects with No Evidence of Disease Activity (NEDA-3)

NEDA-3 is a composite of three related measures of disease activity: (i) no relapses; (ii) no 6-month confirmed disability worsening (6mCDW); (iii) no MRI activity (new of enlarging T2 lesions or Gd-enhancing lesion).

NEDA-3 will be set to "No" if at least one of the following conditions is met; otherwise NEDA-3 will be set to "Yes".

- 6mCDW event
- Confirmed relapse
- ≥1 Gd-enhancing T1 lesions
- ≥1 new/enlarging T2 lesions
- Discontinued from study drug due to either "death" or "lack of efficacy"

Proportions of subjects after 96 weeks that meet the criteria of NEDA-3 will be summarized descriptively by last prior DMT (fumarates vs. fingolimod), along with 95% CI.

NEDA-3 will also be summarized by year (use Day 365.25 as the cut-off of Year 1 and Year 2), as well as by year and by last prior DMT, along with corresponding 95% CI. In addition, each NEDA-3 components (Gd-enhancing T1 lesions, new and enlarging T2 lesions, MRI lesion activity, confirmed relapses, 6mCDW, discontinued from study drug due to either death or lack of efficacy) will be summarized by year.

2.14.8 Proportion of subjects without MRI activity

The proportion of subjects free of Gd-enhanced T1 lesions (in this scan) at Week 24, Week 48 and Week 96 will be summarized.

The proportion of subjects free of Gd-enhanced T1 lesion (all post-baseline scan) will be summarized. This analysis should only include subjects with MRI results at Week 24, Week 48 and Week 96.

The proportion of subjects free of new or enlarging T2 lesion (in this scan relative to previous scan) at Week 24, Week 48 and Week 96 will be summarized.

The proportion of subjects free of new or enlarging T2 lesion (all post-baseline scan) will be summarized. This analysis should only include subjects with MRI results at Week 24, Week 48 and Week 96.

MRI scans conducted while on steroid should be kept in this analysis. Above analyses will be repeated by last prior DMT.

2.14.9 Other efficacy endpoints

Change from baseline of CCI will be summarized by last prior DMT (fumarates vs. fingolimod) and visit window. A figure of change from baseline of CCI by last prior DMT will also be given.

T25FW, 9HPT and LCVA will be summarized descriptively by visit.

2.14.10 Biomarkers (NfL)

Serum Neurofilament (NfL) concentration will be explored related to biomarker for MS. Change in NfL concentration will be summarized by visit descriptively using FAS. The arithmetic mean, arithmetic standard deviation, the mean, median, min, max, Geometric-mean, the coefficient of variation of arithmetic mean (%) and the coefficient of variation of the Geometric-mean (%), will be reported in descriptive summaries. In addition, NfL will also be summarized by visit and last prior DMT (fumarates vs. fingolimod). The mixed model for repeated measures (MMRM) on log-transformed change from baseline NfL will also be fitted, with last prior DMT and time points as factors, baseline age and the log-transformed NfL baseline concentration as continuous covariates. Unstructured correlation matrix will be specified within the model. Estimates for each time point, as well as 95% CI and p-values will be given. This analysis will also be repeated by last prior DMT. In case model has convergence issues, the following actions will be taken: 1) Drop age; 2) Change the covariance structure from unstructured to Autoregreesive(1). Details of MMRM model and SAS codes will be given in Section 5.4.4.

Serum CCI will be analyzed separately outside of CSR.

2.15 Interim analysis

CCI

CCI [redacted]

3 Sample size calculation

The primary analysis (ARR) will use a negative binomial regression model with log-link and time-in-study as offset. The ARR in Phase 3 ofatumumab studies was 0.10 and 0.11 (Hauser et al 2019). In the targeted population of patients with breakthrough activity on either fumarates or fingolimod, an ARR of 0.16 on ofatumumab is assumed (Hauser et al 2015; Kappos et al 2011). CCI [redacted]

[redacted] The study population consists of subjects transitioning from fingolimod or fumarates to ofatumumab. Thus, the sample size of CCI [redacted] is reasonable in order

- to make conclusion on disease control in the overall trial
- to be able to separately analyze effectiveness and safety of ofatumumab in subjects coming from fumarates or fingolimod.

4 Change to protocol specified analyses

Changes to protocol specified analyses are listed below:

CCI [redacted]

CCI

5 Appendix

5.1 CCI

5.1.1 CCI

CCI

5.1.2 CCI

CCI

5.1.3 CCI

CCI

5.1.3.1 CCI

CCI

5.1.3.2 CCI

CCI

5.1.4 CCI

CCI

5.1.4.1 CCI

CCI

5.1.4.2 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, below data manipulation will be done to combine them into a single relapse by creating a new relapse record with the following information.

- Start date: take the earliest start date.
- End date: take the latest end date. If one of the end dates is missing, set it to missing.
- Date of EDSS intended to confirm the relapse:
  - Take the date of EDSS by which the relapse can be confirmed.
  - If more than one EDSS assessments meet the above 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.
- Severity: take the value representing the worst case (severe>moderate>mild>missing)
- "Did the relapse affect daily activities?", "Hospitalization?", "Steroid used?", "Recovery status": for each of these characteristics, take the value representing the worst case (yes>no for first 3 questions; no>partial>complete recovery for last question).

According to CRF completion guidelines, 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 above procedure. Missing end date of relapse is not allowed. In the rare cases that missing end date exist in the final database, it will be imputed so that the duration of relapse is exactly 90 days.

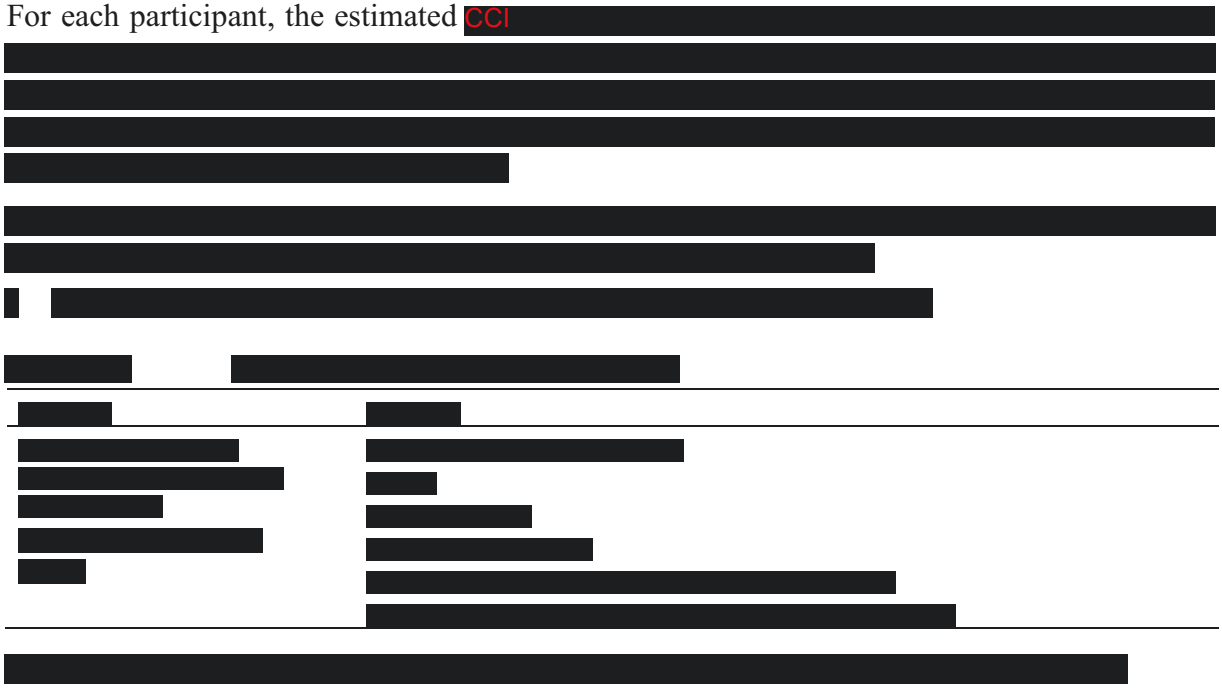
5.2 AEs coding/grading

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

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. 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).

5.3 Laboratory parameters derivations

For each participant, the estimated CCI



5.3.1 Newly occurring liver enzymes abnormalities

CCI

- CCI [redacted]

[redacted]

5.4 Statistical models

5.4.1 Primary analysis

The primary analysis will describe the test for null hypothesis (H0):ARR >=0.18 versus alternative hypothesis (H1): ARR<0.18. The ofatumumab treatment effect will be estimated for the entire duration by a negative binomial model with log-link and subject's time in study (as natural log of time in years) will be used as an offset with number of relapses in previous year, baseline EDSS, baseline number of T1 Gd-enhancing lesions, the participant's age at baseline and prior MS therapies as covariates.

CCI [redacted]

5.4.2 Supplementary analysis for primary endpoint

CCI [redacted]

5.4.3 Negative binomiel GEE model—Sample SAS code

CCI

5.4.4 Mixed model for repeated measures—Sample SAS code

CCI

5.5 Rule of exclusion criteria of analysis sets

CCI

6 Reference

Novartis: Philippe Close (2011): Hepatotoxicity: Clinical Development Safety Guideline.

ASCLEPIOS 1 and 2 study protocol CREDI links:

/CREDI Projects/O/OMB157G/CREDI Studies/OMB157G2301-Migrated to ARONDA/CSP (Clinical Study Protocol) - COMB157G2301 protocol version 02 clean

/CREDI Projects/O/OMB157G/CREDI Studies/OMB157G2302/CSP (Clinical Study Protocol) - COMB157G2302 protocol version 02 clean

ARTIOS interim analysis SAP CREDI link:

/CREDI Projects/O/OMB157G/CREDI Studies/OMB157G23101/Administrative Files (study level)/RAP or RAMP Meeting - COMB157G23101_SAP_IA_amendment_2