NOVARTIS

Clinical Development

OMB157/Ofatumumab

COMB157G1301 / NCT03249714

A 24-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy, safety and pharmacokinetics of ofatumumab in patients with relapsing multiple sclerosis followed by an extended treatment of at least 24 weeks with open-label ofatumumab

Statistical Analysis Plan (SAP)

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Document type:	SAP Documentation
Document status:	Final v1.0 for final analysis
Release date:	4-September-2020
Number of pages:	61

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
09-Mar-2018	Prior to FPFV	Creation of final version	N/A - First version	NA
13-Dec-2019	Prior to DBL	Amendment 1	The variable “Gd-enhanced T1 lesion” was renamed “Gd-enhanced lesion”.	Overall except “1 Introduction” and “3 Sample size calculation”
			Overall rules on Cut-off 1 and Cut-off 2/EOS analyses are additionally mentioned.	2.1 Data analysis general information
			Documentation was updated to define “1 month”.	2.1.1 General definition
			It was clarified that visit windows are based on study days relative to Core part Day 1.	2.1.2 Visit windows for data analysis
			Extension FAS was defined for efficacy analysis including Extension part.	2.2 Analysis sets
			Analysis plan on medical history was documented independently.	2.3.4 Medical history
			Analysis plan on smoking/alcohol history was documented independently.	2.3.5 Smoking
			Definition of time-at-risk was updated for AE analysis.	2.4.1 Study treatment / compliance
			Analyses plans were added for impact assessment on potential unblinding issue.	2.7.3 Impact assessment of potential unblinding
				2.8.1 Adverse events (AE)
			It was clarified which safety analysis to repeat for Cut-off 2/EOS analysis	2.8.1 Adverse events (AE)
				2.8.3 Laboratory data
				2.8.4.2 Vital signs.

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
				2.8.4.3 Suicidality evaluations
			Analyses of AE leading to study drug interruption, AE by onset period, subgroup analyses of AE, and analysis of drug-related CDS risks were added.	2.8.1 Adverse events (AE)
			Documentation on liver and renal events was updated	2.8.3 Laboratory data
			Analysis plan for suicidality evaluation was updated.	2.8.4.3 Suicidality evaluations
			[redacted]	[redacted]
			Section “Analysis for Japan CTD” was removed, and relevant analysis plans were moved to the section for adverse events Also, box plots of lab parameters were cancelled.	N/A
			The imputation rule was updated for relapse.	5.1 Imputation rules.
			CTCAE grade is displayed in the document	5.3.4 CTCAE grades for laboratory parameters
			PD “INCL01A” was added.	5.6 Rule of exclusion criteria of analysis sets
			“Randomization despite screen failure” was added to non-PD criteria.	5.6 Rule of exclusion criteria of analysis sets
20-Jul-2020	Prior to W48 DBL	Amendment 2 for Cut-off 2 analysis	The visit windows for Cut-off 2 analysis were updated.	2.1.2 Visit windows for data analysis
			Definitions of Extension FAS was updated.	2.2 Analysis sets
			Extension safety set was additionally defined	2.2 Analysis sets
			Description on summary of PD was added.	2.3.1 Patient disposition

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Data handling on the baseline data was updated.	2.3 Patient disposition, demographics and other baseline characteristics
			Summary on pre-post ofatumumab treatment was added.	2.4.2 Prior, concomitant and post therapies
			Summary on MS relapse characteristics was added.	2.7 Analysis of secondary efficacy objective(s)
			The analysis plan for AE by onset period was refined.	2.8.1 Adverse events
			Efficacy analysis for Cut-off 2 were additionally documented.	2.15 Analysis on the Extension part not mentioned in the previous sections
			Abnormality criteria was added on AST.	5.3.2 Newly occurring liver enzyme abnormalities.
4-Sep-2020	Prior to final DBL	For final analysis	Analysis sets for patient disposition and baseline data were updated to FAS	2.3 Patient disposition, demographics and other baseline characteristics
			“Gd-enhanced/enhancing lesions” was updated to “Gd-enhanced/enhancing T1 lesions” to align with study protocol and for consistency within this document.	Overall, wherever applicable

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List of abbreviations

AE	Adverse event
ADA	Anti-drug-antibody
ALP	Alkaline Phosphate
ALT	Alanine Aminotransferase
ARR	Annualized Relapse Rate
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
BIL	Bilirubin
BMI	Body Mass Index
C-CASA	Columbia Classification Algorithm for Suicide Assessment
[redacted]	[redacted]
[redacted]	[redacted]
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
(e)CSSRS	(electronic) Columbia Suicide Severity Rating Scale
DMC	Data Monitoring Committee
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
(e)EDSS	(electronic) Expanded Disability Status Scale
EOS	End of Study
FAS	Full Analysis Set
FDA	Food Drug Association
FU	Follow up
Gd	Gadolinium
GGT	Gamma-Glutamyltransferase
INR	International Normalized Ratio
ITT	Intention to treat
IRR	Injection related reaction
KM	Kaplan-Meier
LLN	Lower limit of Normal
M	Month
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MRI	Magnetic Resonance Image
MS	Multiple Sclerosis
NCI	National Cancer Institute
[redacted]	[redacted]
o.d.	Once Daily
OS	Overall Survival
PD	Pharmacodynamics
PDS	Programming Datasets Specification

PFS	Progression-Free Survival
PH	Proportional Hazard
PK	Pharmacokinetics
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
PT	Preferred term
qd	Qua'que di'e / once a day
QoL	Quality of Life
RAP	Report and Analysis Process
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
[redacted]	[redacted]
SOC	System Organ Class
TBIL	Total Bilirubin
TEAE	Treatment Emergent AE
TFLs	Tables, Figures, Listings
ULN	Upper Limit of Normal
WHO	World Health Organization

1 Introduction

The purpose of Statistical Analysis Plan (SAP) is to describe the implementation of the statistical analysis planned in the protocol of study COMB157G1301. Protocol version 01 has been referenced at the time of finalization of the SAP.

1.1 Study design

The study is designed, in conjunction with the global Phase 3 studies (COMB157G2301 and COMB157G2302), to provide the necessary data to support registration of ofatumumab for the treatment of relapsing MS in Japan.

The study will provide efficacy, safety, tolerability and pharmacokinetics data for ofatumumab 20 mg subcutaneous injections every 4 weeks compared with placebo for 24 weeks in patients from Japan (neither Caucasian nor African) and the other countries (mainly Caucasian, not East Asian) and also provide the extended efficacy, safety, tolerability and pharmacokinetics data.

This study has 2 parts: A randomized, double-blind, placebo controlled Core part, and an Extension part in which all patients receive open-label ofatumumab.

- Core part: A 24-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy, safety and tolerability and PK of ofatumumab in patients with relapsing MS.
- Extension part: The Core part is followed by an Extension part in which all patients receive open-label ofatumumab. In the Extension part, patients are treated for at least 24 weeks and no longer than 48 weeks. Patients who complete the Extension part will be given the option to transfer into a planned open label ofatumumab umbrella extension study (under separate protocol).

All patients who prematurely discontinue study treatment or who do not enter the separate umbrella extension study, will be followed for a total of at least 36 weeks after study drug discontinuation in the Safety Follow-up (FU) period.

It is planned that a total of 60 patients will be randomized in a 2:1 ratio to ofatumumab or placebo in the Core part; approximately half of the study patients will be from Japan (neither Caucasian nor African) and the other half from the other countries (mainly Caucasian, not East Asian). Randomization will be stratified by region (Japan or other countries) and baseline number of Gd-enhanced T1 weighted lesions (0 or ≥ 1).

The Core part consists of 2 periods; **Screening period** and **Double-blind treatment period** (Figure 1-1).

The **Screening period** can last up to 45 days and consists of 2 sections; Screening section and Baseline section. The Baseline section can last up to the point of first study drug administration (Day −7 to Day 1). Patient eligibility will be determined based on the Screening and Baseline assessments.

The **Double-blind treatment period** will start on Day 1 with randomization of the patient. Patients will be randomly assigned in a 2:1 ratio to receive either ofatumumab 20 mg sc or matching placebo sc in a double-blind fashion. Injectable study treatments (ofatumumab or

placebo) will be administered on Day 1, Day 7, Day 14, Week 4 and every 4 weeks thereafter. The Double-blind treatment period will continue until the completion of all assessments required for the Core part at Week 24.

Patients who prematurely discontinue double-blind study medication will have their end of Study (EOS) visit as soon as possible and will be followed up for safety in the Safety FU period for a minimum of 36 weeks**.**

The Extension part consists of 2 periods; **Double-blind loading dose period** and **Open-label treatment period**.

The **Double-blind loading dose period** will be applicable for patients who complete the Double-blind treatment period. All patients will receive ofatumumab 20 mg sc at Week 24; the Extension part starts with the injection of the Week 24. Patients randomized to ofatumumab in the Double-blind treatment period will receive the matching placebo sc at Week 25 and 26. Patients randomized to placebo in the Double-blind treatment period will receive ofatumumab 20 mg sc at Week 25 and 26. All patients will receive the study drug in a double-blind manner at Week 25 and 26.

The **Open-label treatment period** will begin at Week 28 and all patients will receive open-label ofatumumab 20 mg sc every 4 weeks in this period. This period will continue until the last patient is transferred to a planned umbrella extension study (under separate protocol requiring another informed consent).

Patients who prematurely discontinue study treatment will have their EOS visits as soon as possible and will be followed up for safety in the Safety FU period for a minimum of 36 weeks. After study drug discontinuation, during Core or Extension parts, patients may initiate alternative MS therapy according to local standard of care if clinically indicated.

The **Safety FU period** will be applicable for the following patients:

- Patients who complete this study and do not enter the planned umbrella long-term extension study
- Patients who prematurely discontinue study treatment in Core or Extension part

All Safety FU visits must be scheduled relative to the date of EOS visit.

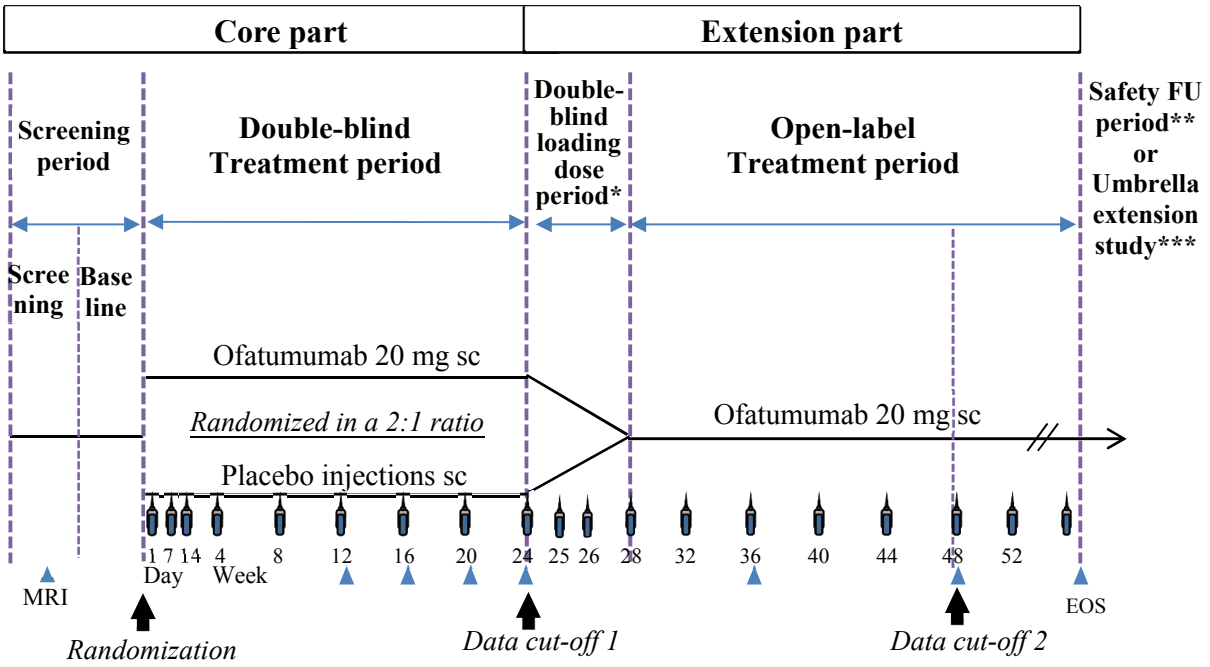
These patients will be followed for a total of at least 36 weeks after study drug discontinuation (by 36 weeks the majority of patients are expected to have repleted their circulating B-cells, see Protocol Section 3.3).

A longer than 36 weeks of post-treatment Safety FU period will be required for patients who have not repleted their B-cells (i.e. B-cells not back to baseline value or to lower limit of normal (LLN) whichever comes first as determined by central lab) at 36 weeks.

These patients will continue to be followed with assessments every 12 weeks until their B-cell counts have repleted. To protect the study blind, the assessment of B-cell counts will be performed centrally and the Investigators and Sponsor study team will only be informed of whether or not continued follow-up is necessary.

Patients who have initiated therapy with another disease modifying/immunosuppressive therapy before the end of the 36-week follow-up will not be monitored beyond 36 weeks.

Figure 1-1 Study design



* Patients randomized to placebo in the Double-blind treatment period will receive ofatumumab 20 mg sc at Week 24, 25 and 26 as loading dose regimen. Patients randomized to ofatumumab in the Double-blind treatment period will receive ofatumumab 20 mg sc at Week 24 and the matching placebo sc at Week 25 and 26. In all patients, the extension part starts with the Week 24 injection.

** Patients who prematurely discontinue study drug or patients who do not enter the umbrella extension study will enter the Safety FU period following their EOS visits.

*** Umbrella extension study (planned) will be conducted under separate protocol.

Data cut-off 1 is defined as the date the last patient completes all the assessments for Week 24.

Data cut-off 2 is defined as the date the last patient completes all the assessments for Week 48.

Three types of analyses to be conducted are described in the SAP. They will be referred to in this document as Cut-off 1 analysis, Cut-off 2 analysis, and EOS analysis:

1. The Cut-off 1 analysis will be conducted for the Core part. Data up to the Week 24 (cut-off 1) will be used. Data from the safety FU period for patients who prematurely discontinued from study treatment before Week 24 will also be included. The analysis will be performed when the last patient has completed the double-blind loading dose period at Week 28. This analysis will be used in support of the registration of ofatumumab in Japan.
2. The Cut-off 2 analysis will be conducted when the last patient completes all assessments up to the Week 48 visit. The analysis will also include assessments of maintenance of efficacy and extended safety during the extension part and data from the Safety FU period for patients who prematurely discontinued from study treatment before the cut-off 2. Any between treatment comparison will be based on treatment assignment in the core part. The analysis will also be used in support of the registration of ofatumumab in Japan.
3. The final analysis will be conducted when the last patient completes the EOS visit or Safety FU period.

1.2 Study objectives and endpoints

Primary objective

The primary objective of the study is to demonstrate that ofatumumab is superior to placebo in reducing the cumulative number of Gd-enhanced T1 lesions across 4 MRI scans at Week 12, 16, 20 and 24 in patients with relapsing MS. The primary objective will be assessed during the core part. (Section 2.5)

Secondary objectives

The secondary objectives are described separately for the core part and the extension part:

Core part

Assess the consistency of the efficacy of ofatumumab versus placebo across regions (Japan vs other countries) in the cumulative number of Gd-enhanced T1 lesions on MRI scans at Week 12, 16, 20 and 24. (Section 2.5.4)

Assess the efficacy of ofatumumab versus placebo in the number of new or enlarging T2 lesions on MRI scans. (Section 2.7)

Assess the efficacy of ofatumumab versus placebo in annualized relapse rate (ARR) and time to first relapse. (Section 2.7)

Assess the safety and tolerability of ofatumumab versus placebo. (Section 2.8)

Assess the similarity of the pharmacokinetics (PK) and B-cell count following the treatment with ofatumumab across regions (Japan vs other countries). (Section 2.9, Section 2.10, Section 2.8)

Extension part (additional to objectives for Core part)

Assess extended safety and tolerability of ofatumumab. (Section 2.8)

Assess extended efficacy of ofatumumab in:

- Number of Gd-enhanced T1 lesions (Section 2.5)
- Number of new or enlarging T2 lesions (Section 2.7)
- Annualized relapse rate (Section 2.7)
- Time to first relapse (Section 2.7)

Assess the PK and B-cell count following the extended treatment with ofatumumab. (Section 2.9, Section 2.10, Section 2.8)

[redacted]

2 Statistical methods

2.1 Data analysis general information

Data will be analyzed by Novartis statistical and programming team according to the data analysis Section 9 of the study protocol which is available in Appendix 16.1.1 of the CSR. Important information is given in the following sections and details are provided, as applicable, in Appendix 16.1.9 of the CSR.

SAS (version 9.4 or higher) will be used for generating study outputs used for clinical reports.

Unless otherwise stated, summary tables/figures/listings will be on all subjects included in the population under consideration. Data will be summarized with respect to demographic and baseline disease characteristics, efficacy, and safety assessments.

The three analysis conducted at:

- Cut-off 1 (Core part data up to Week 24 visit),
- Cut-off 2 (all data obtained until the last patient completes all assessments up to Week 48 visit),
- Final, when the last patient completes the EOS visit or Safety FU period.

Each analysis will be conducted on all subject data available at the corresponding cut-off. Cut-off 2 and final *safety* analysis will include only each patient's assessments under ofatumumab treatment or during Safety FU.

In these analyses, data from Safety FU period will be analyzed separately if necessary.

The stratification factors, which are the number of Gd-enhanced T1 weighted lesions at baseline (0 or >=1) and region (Japan or non-Japan), will be included in subgroup analysis where appropriate.

2.1.1 General definitions

Study drug/treatment refers to the investigational drug Ofatumumab and placebo.

"Date of Cut-off 2" is expected as the date the last patient completes all assessments at Week 48 visit. If the last patient discontinues from the study prior to Week 48 visit, "date of Cut-off 2" is the last patient's last visit.

Date of first administration of study drug/treatment, or first date of study drug/treatment, is defined depending on the analysis purposes.

- For Cut-off 1 analysis and Cut-off 2 and final *efficacy* analysis, it refers to the date when the first dose of randomized treatment is administered.
- For Cut-off 2 and final *safety* analysis, it refers to the date when the first dose of ofatumumab is administered.

Date of last administration of study drug/treatment, or last date of study drug/treatment is defined by analysis time point.

- For Cut-off 1 analysis, it refers to the date when the last dose of randomized treatment is administered up to Week 24 visit.
- For Cut-off 2 analysis, it refers to the date when the last dose of treatment is administered up to the date of Cut-off 2.
- For final analysis, it refers to the date when the last dose of treatment is administered up to EOS visit.

Study day is defined as: if after first date of study drug, then (Study Day) = (Date) – (first date of study drug) +1; if before first date of study drug, then (Study Day) = (Date) – (first date of study drug); Study Day 1 is defined as the date of the first administration of study drug; there is no Study Day 0.

Duration of an event is calculated as (event end date) – (event start date) +1.

1 month is counted as 30 days unless otherwise specified.

Baseline is defined for each cut-off analysis.

- For Cut-off 1 analysis, and Cut-off 2 and final *efficacy* analysis, baseline is defined as the last non-missing result before or on the first date of study drug.
- For Cut-off 2 and final *safety* analysis, definition of baseline depends on each patient's treatment course in the study
  - For a patient continuously having ofatumumab across Core and Extension parts, baseline is defined as the last non-missing result before or on the first date of study drug.
  - For a patient switching the treatment from placebo to ofatumumab when entering the Extension part, baseline is defined as the dose date of ofatumumab at Week 24. *For analysis on vital signs*, the baseline is defined as *the pre-dose measurement* at Week 24.

On-treatment period is defined as the one between the first date of study drug and 30 days after the last date of study drug. The on-treatment definition applies to efficacy analyses only.

"Safety cut-off" is defined as 100 days after the last dosing date of the study drug.

2.1.2 Visit windows for data analysis

Visit windows for data analysis will be used in 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 window is to analyze data based on the actual study days (rather than the nominal visits). E.g., if a patient's Week 4 visit is delayed, then it is possible that the Week 4 data be re-aligned to visit window of Week 8 and be summarized under Week 8.

For efficacy analyses, all nominal visits excluding unscheduled visits will be mapped into one of the defined visit windows. [redacted]

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 patient 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 use the term "Visit-window" as column header; this is to remind the reviewer that multiple assessments of a patient might be summarized for one visit. Below tables provide visit windows definitions for applicable parameters. Visit windows will be defined relative to the date of first administration of study treatment assigned in the Core part, or date of first administration of ofatumumab, depending on analysis variables and cut-off time points.

2.1.2.1 Visit windows during core and extension treatment periods

Table 2-1 Visit windows for MRI

Visit-window	Start day	Target day	End day
Week 12	1	84	98
Week 16	99	112	126
Week 20	127	140	154
Week 24 (Cut-off 1)	155	168	182
Week 36	183	252	294
Week 48	295	336	378

Day counts are relative to the first date of study drug in the Core part.

Table 2-2 Visit windows for [redacted] EDSS

Visit-window	Start day	Target day	End day
Week 12	1	84	126
Week 24 (Cut-off 1)	127	168	210
Week 36	211	252	294
Week 48	295	336	378
Week 60	379	420	462

Visit-window	Start day	Target day	End day
Week 72	463	504	546
Week x*	x*7-42+1	x*7	x*7+42

*if study goes beyond Week 72, every 12 weeks the same assessments on Week 60 and Week 72 will be performed. X will be a multiple of 12 weeks from Week 84 and beyond.
Day counts are relative to the first date of study drug in the Core part.

Table 2-3 Visit windows for routine lab (including urine), ADA, and Total IgM, IgG levels

Visit-window	Start day	Target day	End day
Week 4	1	28	56
Week 12	57	84	126
Week 24 (Cut-off 1)	127	168	182
Week 28	183	196	224
Week 36	225	252	294
Week 48	295	336	378
Week 60	379	420	462
Week 72	463	504	546
Week x*	x*7-42+1	x*7	x*7+42

*if study goes beyond Week 72, every 12 weeks the same assessments on Week 60 and Week 72 will be performed. X will be a multiple of 12 weeks from Week 84 and beyond.
Day counts are relative to the first date of study drug in the Core part for Cut-off 1 analysis, or the first date of ofatumumab for Cut-off 2 and final analysis.

Table 2-5 Visit windows for B-cell counts and T-cell counts: Cut-off 1 analysis

Visit-window	Start day	Target day	End day
Day 2	--	2	--
Day 5	3	5	--
Day 7	6	7	10
Day 14	11	14	21

Visit-window	Start day	Target day	End day
Week 4	22	28	56
Week 12	57	84	126
Week 24 (Cut-off 1)	127	168	182

Day counts are relative to the first date of study drug in the Core part.

Table 2-6 Visit windows for B-cell and T-cell counts: Cut-off 2 and final analysis

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 x*	x * 7 - 42 + 1	x * 7	x * 7 + 42

*if study goes beyond Week 72, every 12 weeks the same assessments on Week 60 and Week 72 will be performed. X will be a multiple of 12 weeks from Week 84 and beyond.

Day counts are relative to the first date of ofatumumab.

Table 2-7 Visit windows for vital signs: Cut-off 1 analysis

Visit-window	Start day	Target day	End day
Week 8	1	56	70
Week 12	71	84	98
Week 16	99	112	126
Week 20	127	140	168

*if study goes beyond Week 72, every 12 weeks the same assessments on Week 60 and Week 72 will be performed. X will be a multiple of 12 weeks from Week 84 and beyond.

Data collected from Day 1, Day 7, Day 14, Week 4, and Week 24 are collected differently and not re-mapped.

Day counts are relative to the first date of study drug in the Core part.

Table 2-8 Visit windows for vital signs: Cut-off 2 and final analysis

Visit-window	Start day	Target day	End day
Week 12	1	84	126
Week 36	211	252	294
Week 48	295	336	378
Week 60	379	420	462
Week 72	463	504	546
Week x*	x * 7 - 42 + 1	x * 7	x * 7 + 42

Visit-window	Start day	Target day	End day
*if study goes beyond Week 72, every 12 weeks the same assessments on Week 60 and Week 72 will be performed. X will be a multiple of 12 weeks from Week 84 and beyond. Data collected from Week 24 are not re-mapped, because they are collected at pre- and post-dose and will not be included in by-visit summary. Day counts are relative to the first date of ofatumumab.			

2.1.2.2 Visit windows for Safety Follow-up

For patients who prematurely discontinues treatment or do not enter the umbrella study after EOS, Safety Follow-up period should be entered. Visit windows are also defined.

The visit windows are defined in Table 2-9, where the start day, target day, and end day are relative to EOS visit.

Table 2-9 Visit windows for Safety Follow-up period

Visit-window	Start day	Target day	End day
Week 12 post EOS	2	84	126
Week 24 post EOS	127	168	210
Week 36 post EOS	211	252	294
Week x post EOS*	x * 7-42+1	x * 7	x * 7+42
*if study goes beyond Week 36, every 12 weeks the same assessments on Week 36 will be performed. X will be a multiple of 12 weeks from Week 48 and beyond. All days are relative to EOS visit. These visit windows will be applied only to assessments after the last date of study drug.			

2.1.2.3 Multiple assessments within visit windows

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).

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

2.1.3 Nominal visits for ECG analysis

By-visit summary of ECG measurement uses nominal visits.

For Cut-off 2 and final analysis, analysis visits will be based on the treatment course of patients in the study.

- For a patient having ofatumumab treatment across Core and Extension parts, assessments at study visits Week 24 and 48 will be included in the summary of corresponding visits.
- For a patient switching the treatment from placebo to ofatumumab at Week 24, assessments from Week 48 visit will be included *in the summary of Week 24 visit*

2.1.4 Treatment group for Cut-off 2 and final analysis

For analysis based on Extension FAS, the following treatment groups will be displayed:

- OMB 20mg: This will include patients randomized to ofatumumab treatment group and having at least one dose of ofatumumab in Extension part.
- Placebo – OMB 20mg: This will include patients randomized to placebo treatment group, and having at least one dose of ofatumumab in Extension part.

For safety analysis based on Extension SAF, the following treatment groups will be displayed:

- OMB 20mg: This will include patients treated with ofatumumab during Core part and having at least one dose of ofatumumab in Extension part.
- Placebo – OMB 20mg: This will include patients treated with placebo during Core part, and having at least one dose of ofatumumab in Extension part. For these patients, analysis will include only assessments on or after treatment at Week 24, and Safety FU period if necessary.

2.2 Analysis sets

Full analysis set (FAS): The FAS comprises all randomized subjects with assigned treatments. Subjects will be analyzed according to the randomized treatment assignment following the intention-to-treat (ITT) principle, even if they actually received no or a different treatment.

The FAS will be used for the summary of demography and baseline characteristics and all efficacy analyses.

Extension FAS (EFAS): The EFAS will include all FAS subjects who received at least one dose of ofatumumab during Extension part. Analyses on EFAS will include *all* available efficacy assessments of the Core and Extension parts.

Per-protocol set (PPS): The PPS is a subset of FAS, consists of all randomized subjects who take at least one dose of study medication and have no major protocol deviations that could confound the interpretation of analyses conducted on the FAS. Major protocol deviations will be determined according to the pre-defined protocol deviation criteria before treatment unblinding (e.g. non-compliance for a large proportion of the time in study). For analyses performed on the PPS, only on-treatment assessments will be used.

The PPS will primarily be used for the supportive analyses of the primary efficacy variable.

Safety set (SAF): The SAF set includes all subjects who received at least one dose of study medication. Subjects will be analyzed according to the actual treatment received. The Safety Set will be used for all safety analyses for Cut-off 1 analysis.

Extension Safety set (ESAF): The ESAF set includes all subjects who received at least one dose of ofatumumab during Extension part. Subjects will be analyzed according to the actual treatment received. The Extension Safety Set will be used for all Cut-off 2 and final safety analyses. Analyses on ESAF will include safety assessments *only under ofatumumab treatment during the Core and Extension parts*.

2.2.1 Subgroups of interest

Subgroup analyses by stratification factors (Japan vs non-Japan, Gd-enhanced T1 weighted lesions 0 or >=1). (Section 2.1).

Subgroup analysis by age group, weight, and gender will be included for Safety analyses as stated in the applicable sections. The subgroup categories are:

Age group (< 40, >= 40);

Weight (< Median, >= Median);

Gender (Male, female).

In addition, for Cut-off 2 analysis, subgroup of home injection will be defined on basis of whether each patient had at least one home injection during the Extension part.

2.3 Patient disposition, demographics and other baseline characteristics

Patient disposition, background and demographic characteristics, and MS baseline disease characteristics will be summarized by treatment group for Cut-off 1 and final analysis based on FAS, and for Cut-off 2 analysis based on EFAS.

For final analysis, analyses will focus on patient disposition and demographics.

2.3.1 Patient disposition

The number and percentage of patients who are screened but do not enter treatment period will be presented. The summary will be on all screened patients. This summary will be included in Cut-off 1 analysis.

For Cut-off 1 analysis, the number and percentage of patients who complete the core part or prematurely discontinue study drug will be presented, along with the primary reason for discontinuation. Data collected on the end of double blind treatment period CRF page will be used to summarize this information. Similarly, the number and percentage of patients who complete the open label treatment period of the extension part or prematurely discontinue the study drug will be summarized and will be included in Cut-off 2 and final analysis.

Then number and percentage of patients who enter and complete the Safety FU period as well as the number of patients who prematurely discontinue the Safety FU period (along with the primary reason for discontinuation) will be presented. Data collected on the end of Safety FU period CRF page will be used to summarize this information. For patients who join the separate umbrella extension study an additional line will be added in the summary. The summary will be based on the patients who enter Safety FU period or the umbrella extension study and will be included in Cut-off 2 and final analysis, if needed.

The numbers of patients in each analysis set will be presented by treatment group. Protocol deviations will be summarized by deviation categories and treatment. In addition, protocol deviations that led to exclusion from the analysis set will be summarized by deviation category, deviation terms and treatment groups. Summary on protocol deviations will be based on FAS for Cut-off 1 analysis, and EFAS for Cut-off 2 or final analysis

2.3.2 Background and demographic characteristics

Demographic and background characteristics (age, gender, race, and ethnicity as collected on the Demography CRF), and prior/concomitant medications at screening visit, height, body weight, derived BMI, and employment status at baseline will be summarized by treatment group using frequency distributions (for categorical variables) and descriptive statistics of mean, standard deviation, minimum, median, and maximum (for continuous variables).

2.3.3 MS baseline disease characteristics

MS disease history, MRI baseline characteristics, and MS medication history will be summarized by treatment group.

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, time since onset of most recent relapse (months) prior to screening, type of MS at study entry, and time since onset of SPMS (years).

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

Duration of MS since diagnosis (years) will be derived as [(first dose date of the assigned treatment – MS diagnosis start date +1)/365.25]; duration of MS since first symptom (years) will be derived as [(first dose date of the assigned treatment – first MS symptom 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.

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

2.3.4 Medical history

Medical history will be summarized by treatment group. 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), preferred term (PT) and treatment group.

2.3.5 Smoking history and alcohol history

Data collected on smoking history and alcohol history CRF pages will be listed as appropriate.

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

2.4.1 Study treatment / compliance

Analyses detailed in this section will be performed for Cut-off 1 analysis, Cut-off 2 and final analysis.

For the core part and the extension part, duration of exposure to study drug is defined as (last dose date) – (first dose date) + 31 – sum[(j+1)-th injection date – j-th injection date - 31], where j and j+1 refer to consecutive injections with injection dates more than 31 days apart (as patients are scheduled to take the subcutaneous injections every 28+/- 3 days).
Duration of exposure to study drug of core part and extension part will be summarized by treatment with number and percentage of patients and by duration category (i.e., >= 1 week, >= 2 weeks, >= 3 weeks, >= 4 weeks, >= 8 weeks, >= 12 weeks, >= 24 weeks, >= 36 weeks, >= 48 weeks, >= 60 weeks, >= 72 weeks, until end of the study). The number of patient years of exposure is calculated as (the sum of the number of days of exposure for all

patients in the group)/365.25 and will be summarized for each treatment arm, and by stratification factor Japan vs non-Japan.

Time at risk is the censoring time used for estimating exposure adjusted incidence rate of SAEs or AEs in patients who did not experience the event of interest. For patients who have experienced the event of interest, the actual date of the SAE, or AE onset will be used. Time at risk corresponds to the time window used for adverse event reporting and can serve as a denominator to certain safety analyses (e.g. in exposure-adjusted incidence rates).

Table 2-10 includes definition of time at risk for AE and SAE for Cut-off 1 analysis. It will determine the "end date of the Core part" when all randomized patients completed their assessment during the Core part.

Table 2-10 Time at risk for AE and SAE: Cut-off 1 analysis

Category	For those who completed Week 24 visit	For those discontinued the study prior to Week 24 visit
Time at risk for AE	Number of days in the study from first date of study drug to Week 24 visit date	Number of days in the study from first date of study drug to the earlier date of the following: - Safety cut-off - "End date of the Core part"*
Time at risk for SAE		Number of days in the study from first date of study drug to "end date of the Core part"

*: "End date of the Core part" will denote the date when all randomized patients complete Week 24 visit or discontinue study drug prior to Week 24 visit. This date is going to be declared by the study team, but not derived from any data.

Table 2-11 includes definition of time at risk for AE and SAE for Cut-off 2 and final analysis. It will determine the "date of Cut-off 2" when all patients entering the Extension part completed their assessment up to Week 48, or EOS visit following premature study drug discontinuation.

Table 2-11 Time at risk for AE and SAE: Cut-off 2 and final analysis

Category	Definition for Cut-off 2 analysis	Definition for final analysis
Time at risk for AE	Number of days in the study from first date of *ofatumumab* treatment to the earlier date of the following: - Safety cut-off - "Date of Cut-off 2"*	Number of days in the study from first date of *ofatumumab* treatment to safety cut-off.
Time at risk for SAE	Number of days in the study from first date of *ofatumumab* treatment to "date of Cut-off 2"*	Number of days in the study from first date of *ofatumumab* treatment to the last visit date, including Safety FU period.

*: "Date of Cut-off 2" is defined in section 2.1.1

Time-at-risk for AE and time at risk for SAE will be summarized in a similar way to exposure to investigational study medication.

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 patient 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 by treatment group. In addition, compliance will be summarized with cumulative number and percentage of patients in each compliance category (i.e., >= 20%, >= 30%, >= 40%, >= 50%, >= 60%, >= 70%, >= 80%, >= 90%, >= 95%, >= 98%, = 100%)

2.4.2 Prior, concomitant and post therapies

Analyses described in this section will be performed on the SAF for Cut-off 1 analysis, and on ESAF for Cut-off 2 analysis.

2.4.2.1 Concomitant medication

Records on the Prior and Concomitant Medication 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 started prior to first dose and continued into the treatment period).
- Post-study drug discontinuation medications will be drugs started after the discontinuation of randomized study medication.

For Cut-off 2 analysis, medications will be also classified by whether they are taken prior to or on or after start of ofatumumab treatment.

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 in PDS).

Medications in each of these 3 categories will be summarized separately by treatment group, ATC code and preferred term. ATC level 1 and level 3 will be used.

Data collected from the Previous MS disease modifying treatment pages will not be included in this summary (See Section 2.3.3).

2.4.2.2 Surgical and medical procedures

Records on the surgical and medical 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. Surgical and medical procedures in each of these 3 categories will be summarized separately by system organ class, preferred term and treatment group.

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 dataset. Injection related premedication will also be summarized separately for each injection as well as cumulatively for all injections by each cut-off.

For Day 1 injection summary, the injection related premedication with start date on the same day as the first injection date will be included and summarized for each of the three protocol specified types (type 1: steroids, type 2: antihistamines and type 3: acetaminophen) and for the combination of the specified types (type 1 + type 2 + type 3 and type 2 + type 3). The steroids (type 1) will be identified by category “Steroid”. The antihistamine (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 types, the number and proportion of patients who took any combination of types of injection related premedication at specified injection will be provided.

Rest injection specified summaries or cumulative summaries will be reported similarly.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

The primary endpoint is the number of Gd enhanced T1 lesions per scan across 4 MRI scans at Week 12, 16, 20, and 24 during the core part.

2.5.2 Statistical hypothesis, model, and method of analysis

The null hypothesis is that there is no difference in the number of Gd-enhanced T1 lesions per scan between ofatumumab and placebo during the Core part (Cut-off 1 analysis). The alternative hypothesis is that there is a difference between the 2 treatment groups.

- Superiority of ofatumumab over placebo will be concluded if the mean number of Gd-enhanced T1 lesions per scan in patients treated with ofatumumab is lower compared with placebo and the observed p-value for the between-treatment comparison is less than the two-sided significance level of 0.05.

The null hypothesis will be tested on the FAS using a negative binomial regression model with log-link. Each patient's total number of Gd-enhanced T1 lesions during the Core part will be used as the response variable, and natural log of the number of MRI scans will serve as the offset variable to adjust for the different number of MRI scans between patients. The model will include treatment, region (Japan or other countries), and baseline number of Gd-enhanced T1 lesions (0 or ≥ 1) as factors.

The number of Gd-enhanced T1 lesions per scan will be estimated by treatment with 95% confidence interval. The between treatment effect will be calculated as rate-ratio (ofatumumab/placebo) with 95% confidence interval and p-value will be provided. In addition, the relative reduction in the number of Gd-enhanced T1 lesions per scan will be computed as one (1) minus the rate-ratio and expressed as a percentage.

The number of Gd-enhanced T1 lesions will be summarized descriptively by visit-window and treatment group.

Analyses on Gd-enhanced lesions will exclude MRI evaluation performed within 14 days after termination of systemic corticosteroids and/or adrenocorticotropic hormone.

The above summary analyses will be repeated with additional data from the extension part at the Cut-off 2 analysis (Section 2.14).

2.5.3 Handling of missing values/censoring/discontinuations

The primary negative binomial model with an offset for the number of MRI scans adjusts for missing information (dropout) under the assumption of non-informative dropout, information missing at random, and constant number of Gd-enhancing T1 lesions per scan within patient. Missing values will not be imputed. However, deviations from assumptions will be tested in sensitivity analyses.

2.5.4 Supportive analyses

Sensitivity analysis

The primary analysis will be repeated using the per-protocol set to provide an analysis of on-treatment data from subjects who have no major protocol violations. The analysis will be performed for Cut-off 1 analysis.

Additional sensitivity analyses may be defined in the analysis plan prior to database lock.

Consistency across regions

Consistency in efficacy across regions on the primary variable will be evaluated using a statistical model similar to the primary model, but with a treatment-by-region (Japan or other countries) interaction term added. The mean number of Gd-enhancing T1 weighted MRI lesions per scan will be provided by treatment and region. The rate-ratio will be presented for individual regions separately, together with 95% confidence intervals. The p-value of the treatment-by-region interaction will be displayed.

The estimates for individual regions will be displayed via a forest plot to visualize consistency.

The consistency across regions will be examined at Cut-off 1 analysis.

2.6 Analysis of the key secondary objective

There are no key secondary objectives.

2.7 Analysis of secondary efficacy objective(s)

All efficacy analyses will be done based on the FAS, unless explicitly stated otherwise.

2.7.1 Secondary endpoints

The secondary efficacy endpoints are:

Core part:

- Number of new or enlarging T2 lesions on MRI scans;
- Annualized relapse rate (ARR);
- Time to first relapse
- MS relapse characteristics

Extension part, including Core part: assess extended efficacy of ofatumumab in

- Number of Gd-enhanced T1 lesions
- Number of new or enlarging T2 lesions
- Annualized relapse rate (ARR)
- Time to first relapse
- MS relapse characteristics

2.7.2 Statistical hypothesis, model, and method of analysis

Number of new or enlarging T2 lesions on MRI scans

Analysis of the number of new or enlarging T2 lesions will be done based on the FAS using a negative binomial regression model with log-link. The number of new or enlarging T2 lesions on the last available MRI scan relative to baseline will be used as the response variable, and the natural log of the time (in years) of the MRI-assessment from the baseline/Screening scan will serve as the offset variable to adjust for the various lengths of follow-up times between patients in this study. The model will include treatment, region (Japan or other countries), baseline number of Gd-enhancing T1 lesions (0 or ≥ 1) as factors, and baseline volume of T2 lesions as continuous covariates.

The number of new or enlarging T2 lesions per year will be estimated by treatment with 95% confidence interval. The between treatment effect will be calculated as rate-ratio (ofatumumab/placebo) with 95% confidence interval and p-value. In addition, the relative reduction in the number of new or enlarging T2 lesions per year will be computed as one (1) minus the rate-ratio and expressed as a percentage.

The number of new or enlarging T2 lesions on MRI scans will be summarized descriptively by visit-window and treatment group.

The above summary analyses will be performed for both Cut-off 1 analysis and Cut-off 2 analysis (Section 2.14).

Annualized relapse rate (ARR)

Annualized relapse rate (ARR) is defined as the number of confirmed MS relapses in a year. Analysis of ARR will be done based on the FAS, using a negative binomial regression model with log-link. The model will include the number of confirmed relapses observed from each patient as the response variable, each patient's natural log of time in study (years) as the offset variable, and treatment, region (Japan or other countries), baseline number of Gd-enhancing T1 lesions (0 or ≥ 1) as factors, and number of relapses in previous year and baseline EDSS as covariates.

In the case where the above model does not converge or has other statistical limitations, a simpler model with only the offset variables, treatment and region (Japan or other countries) as factors will be fit to the data.

The adjusted ARR (i.e., model-based estimate adjusted for covariates) for each treatment and the corresponding 95% confidence interval, and ARR ratio (also expressed as percentage reduction relative to control group) along with the 95% confidence interval for the ARR ratio and the corresponding p-value will be obtained.

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 point 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 assessment 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 one. Otherwise, the relapse is considered an unconfirmed one.

The patient's time in study for ARR at each cutoff will be calculated as (Cutoff point – first dose date +1)/365.25.

The analysis will be performed at Cut-off 1 analysis. The adjusted ARR for each treatment and the corresponding 95% confidence interval will be provided also for Cut-off 2 analysis (Section 2.14).

Time to first confirmed relapse

Time to first confirmed relapse will be calculated as (start date of first confirmed relapse – date of first administration of study drug + 1). For patients without confirmed relapses at a cutoff point, they are censored with censoring time as time in study at the corresponding cutoff point.

Analysis of time to first relapse will be done based on the FAS, using a Cox proportional hazard model with treatment, region (Japan or other countries), and baseline number of Gd-enhancing T1 lesions (0 or ≥ 1) as factors, and number of relapses in previous year and baseline EDSS as covariates. The hazard ratio (also expressed as percentage reduction relative to control group) along with the 95% confidence interval for the hazard ratio and the corresponding p-value will be obtained. In the case where the above model does not converge or has other statistical limitations, a simpler model with only treatment and region (Japan or other countries) as factors will be fit to the data. The Cox model analysis will be done only for Cut-off 1 analysis.

In addition, Kaplan-Meier curves by treatment will be used to present the time-dependent cumulative frequency and percentage of subjects reaching the first relapse; by-treatment Kaplan-Meier estimates (with 95% confidence interval) at both cut-off 1 and Cut-off 2 analyses will be obtained (Section 2.14).

MS relapse characteristics

For MS relapse characteristics, summary statistics will be presented. The proportion of patients hospitalized for relapse and the proportion of patients with severe relapses will be compared between treatment groups using a Chi-square test. For Cut-off 2 analysis, summary statistics will be presented by study period (up to Week 24 or thereafter).

MS relapse characteristics include severity, recovery, hospitalization, and steroid treatment. The severity of MS relapses will be derived according to the criteria presented in **Table** 2-12. Severity will be derived for both types of relapses, confirmed and unconfirmed ones. It depends on the type of relapses which EDSS is used to derive severity:

- For confirmed relapses, the EDSS score used to confirm the relapse (as specified in Section 2.7.2) will be used to determine the severity.
- For unconfirmed relapses, all EDSS assessments taken within 30 days from the relapse start date and before the relapse end date will be checked among which the most severe case will

be selected to determine the severity. If no such EDSS assessment is available, the severity will be set to "missing EDSS". If none of such EDSS assessments meets the mild, moderate or severe conditions, the severity will be set to "no worsening in EDSS".

Table 2-12 Severity of MS relapse

Mild relapse	Moderate relapse	Severe relapse
EDSS increase of 0.5 point	EDSS increase of 1 or 2 points	Exceeding Moderate criteria
or	or	or
1 point FS change in one to three systems	2-point FS change in one or two systems	Exceeding Moderate criteria
	or	or
	1-point change in four or more systems	Exceeding Moderate criteria
Definition is based on the EDSS obtained to confirm the relapse as compared to the last EDSS (scheduled or unscheduled) taken in the absence of (confirmed or unconfirmed) relapse and prior to the current relapse. EDSS refers to total score; FS refers to functional score; all of the 7 functional scores are considered in this derivation.		

2.7.3 Impact assessment of potential unblinding

To assess impact of potential unblinding on evaluation of efficacy of ofatumumab on relapses, summary statistics of ARR (patient-based and time-based) will be displayed by subgroup defined by impact of potential unblinding and treatment group.

This analysis will be performed at Cut-off 1.

2.7.4 Handling of missing values/censoring/discontinuations

Missing data will not be imputed.

2.8 Safety analyses

Safety analyses during the study will be detailed below. All safety analyses will be based on the SAF for Cut-off 1 analysis and ESAF for Cut-off 2 and final analysis, unless explicitly stated otherwise.

Patients will be grouped by the actual treatment received. Safety data for the core part will be reported for the first time when the double-blind loading dose period has been completed by the last patient (Cut-off 1 analysis). Safety data for the extension part including Safety FU period

data will be reported for the first time when the last patient has finished 48 weeks of treatment (Cut-off 2 analysis). Safety data beyond the cut-off 2 will be reported separately.

Unless explicitly otherwise stated, for patients who entered Safety FU period, safety data will be reported up to and including the safety cut-off.

- For Cut-off 1 analysis, safety data reported up to safety cut-off, the latest visit date including Safety FU, or Week 24 visit date, whichever comes first.
- For Cut-off 2 and final analysis, safety data reported up to safety cut-off or the latest visit date including Safety FU, whichever comes first.

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.

2.8.1 Adverse events (AEs)

Treatment emergent adverse events (TEAE) is defined as any adverse event which start on or after the day of the first dose of study drug.

TEAEs will be reported if their onset days are no greater than “time at risk for AE”. Similarly, serious TEAEs will be reported if their onset days are no greater than “time at risk for SAE”.

TEAE will be coded by primary system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA). The MedDRA version used for reporting the study will be described in a footnote.

Incidence of TEAEs will be summarized (number and percentage of patients reporting any TEAE by primary SOC, preferred term, and treatment group. Serious TEAEs, drug related TEAEs, TEAEs leading to premature discontinuation from study drug, TEAE leading to study drug interruption, and most common TEAEs (>=5% in any of the treatment groups) will be presented in a similar format as adverse events. In addition, incidence of TEAEs will be summarized by SOC, preferred term, and maximum CTCAE grade. Missing CTCAE grade will not be imputed. The CTCAE version 5.0 will be used.

For Cut-off 1 analysis, odds ratios (investigational drug vs. control) with 95% confidence intervals will be presented along with the summary of any TEAEs and the summary of serious TEAEs. Details in calculations of odds ratios and their 95% confidence intervals are provided in Section 5.7.1. Incidence of any TEAEs will be plotted by SOC, along with the odds ratio (and corresponding 95% confidence interval) for TEAEs in each SOC. Odds ratios provide appropriate inferences for events that are likely to occur at certain times (e.g., injection related reactions) while no constant risk over time is expected.

If a patient reports more than one adverse event within the same primary SOC, the patient will be counted only once with the maximum CTCAE grade at the SOC level, where applicable.

All AEs will be presented in listings.

The following summaries will be repeated for Cut-off 2 and final analysis:

- Overall TEAE
- TEAE by CTCAE grade
- Serious TEAE
- Drug-related TEAE
- TEAE causing study drug discontinuation
- TEAE leading to study drug interruption
- Serious TEAE causing study drug discontinuation
- Most common TEAE
- Infections and infestations TEAE

2.8.1.1 Adverse events of special interest / grouping of AEs

Incidence of adverse events of special interest as defined in the latest version of case retrieval sheet (eCRS) at the time of each cut-off will be summarized by risk name, level, and treatment group. For Cut-off 1 analysis, odds ratios and 95% confidence intervals presented. The exposure-adjusted incidence rate of TEAEs that fulfill the risk search terms as defined in eCRS will also be summarized by risk name, preferred term and treatment group. For Cut-off 1 analysis, incidence rate ratios and 95% confidence intervals presented. Similarly, separate summaries will be provided for serious TEAEs that fulfill the risk search terms as defined in eCRS. Additionally, incidence or any TEAEs that fulfill the search terms as defined in eCRS will also be summarized by risk name, level, and maximum CTCAE grade.

2.8.1.1.1 Injection reaction related AEs

Incidence of injection site reaction AEs and injection systemic AEs as collected in the relevant CRF pages will be reported as part of the AE summary tables as two preferred terms respectively.

Additionally, incidence of injection site reaction AEs and injection systemic reaction AEs will be reported separately for each injection and cumulatively for all injections at each cutoff.

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

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

- 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 above summaries, 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).

For the injection systemic reaction, time to onset of the first symptoms after each injection will be summarized by cumulative hour intervals (i.e., 0 to 1, 0 to 2, 0 to 3, etc. until 0 to 24 hours). These summaries will be provided for each injection and cumulatively for all injections.

The proportion of patients with injection site reactions and the proportion of patients with injection systemic reactions will be plotted by treatment group against the injection sequence labeled by the visit weeks of the corresponding injection.

Patients with injection site reactions and the corresponding category of the combination of the 3 types (type 1: steroid, type 2: antihistamine, type 3: antipyretics/analgesics) will be listed by treatment. Specifically, 9 categories are defined as 1) no injection related premedication, 2) type 1, 3) type 2, 4) type 3, 5) type 1+ type 2, 6) type 1+ type 3, 7) type 2+ type 3, 8) type 1+ type 2+ type 3, 9) Any injection related premedication. The types 1 to 3 refer to protocol specified three types of injection related premedication as stated in Section 2.4.2.3.

A separate listing for injection site reaction AEs and injection systemic reaction AEs will be provided where all reported injection related reactions (IRR) (regardless of timing) will be listed along with the corresponding visit with injection and time to onset from the most recent injection as well as from Day 1. The listing will be sorted by injection of first occurrence of symptoms. Specifically, under the first injection, patients whose first IRR was associated with the first injection will be listed; within a patient all IRRs to all injections will be listed chronologically. Under the second injection, patients whose first IRR was associated with the second injection will be listed; similarly, within a patient all IRRs to all injections will be listed chronologically. The listing will continue with subsequent injections until all patients with IRRs are included in the listing.

The following analyses will be repeated for Cut-off 2 analysis:

- Line plots for proportions of injection-related symptoms
- Proportion of patients with injection systemic reactions
- Proportion of patients with injection site reactions

2.8.1.1.2 Liver safety related AEs

Standardized MedDRA Queries (SMQs) are groupings of terms from one or more MedDRA SOCs that relate to a defined medical condition or area of interest. They are intended to aid in case identification.

Standardised MedDRA Queries (SMQ) and preferred terms searches for drug-related hepatic disorders will be conducted. Results of these searches will be analyzed and presented in a similar format as other adverse events. In case of liver events, detailed listings will be provided.

SMQ Table: The number and percentage of patients experiencing adverse events categorized under the SMQ module drug-related hepatic disorders – comprehensive search (SMQ code 20000006, broad search) and its SMQ sub-modules will be reported.

SMQ-PT Table: The more detailed SMQ-PT table including the respective preferred term frequencies falling under the SMQ drug-related hepatic disorders – comprehensive search (SMQ code 20000006, broad search) and its SMQ sub-modules will be provided.

2.8.1.1.3 Drug-related adverse events for Japan package insert

For display in the Japan package insert, incidence rate of drug-related adverse events will be displayed.

2.8.1.2 Adverse events by onset period

Incidence of TEAE will be displayed by first onset period. The following periods will be displayed:

- Day 1 – Month 3 (Day 1 – Day 90)
- Month 3 – Month 6 (Day 91 – Day 180)
- Month 6 – Month 9 (Day 181 – Day 270)
- Month 9 – Month 12 (Day 271 – Day 360)
- Month 12 or later (Day 361 or later).

For each period, incidence of an AE will be the proportion of patients with the AE among patients "at risk". As seen section 2.4.1, "time at risk" will be defined in two ways for overall AE and SAE. Then two types of summary will be provided:

- Incidence of overall AE by first onset period: This will be based on time at risk for AE. Then *no SAE will be counted if it is reported after safety cut-off* in this analysis.
- Incidence of SAE by first onset period: This will be based on time at risk for SAE.

This analysis will be performed only for Cut-off 2 analysis.

2.8.1.3 Adverse events by subgroup

Incidences of TEAE will be displayed by the following subgroup.

- Age (< 40 or >= 40)
- Gender
- Region (Japan or non-Japan)

This analysis will be performed for Cut-off 1 and Cut-off 2 analyses.

In addition, for Cut-off 2 analysis only, the following subgroup analyses will be provided:

- Incidence of TEAE by region and CTCAE grade
- Incidence of TEAE will be displayed by subgroup defined on basis of whether each patient had home-injection during the treatment period.

2.8.1.4 Impact assessment of potential unblinding

Incidence of the TEAEs will be summarized by subgroup defined by impact of potential unblinding.

This analysis will be performed only for Cut-off 1 analysis.

2.8.2 Deaths

Death, if any, will be listed by treatment group. All deaths as recorded in the database will be included at each analysis cut-off.

2.8.3 Laboratory data

Data summaries will be provided in SI units. The summary of laboratory evaluations will be presented for 3 groups of laboratory tests: Hematology, Chemistry and Urinalysis. Subgroup analyses as specified in Section 2.2.1 will be performed as needed.

Laboratory data will be summarized by presenting summary statistics (mean, median, standard deviation, Min and Max) of raw data and change from baseline values to each study visit-window by treatment group, and by presenting shift tables using clinically notable ranges (baseline to most extreme post-baseline value) by treatment group. Change from baseline (i.e. post baseline value – baseline value) will only be summarized for patients with both baseline and post baseline values. Laboratory data, and specifically liver enzymes, will also be summarized by maximum change from baseline.

The number and percentage of patients with new or worsening laboratory abnormalities based on CTCAE grade (Section 5.3.4) in each visit-window and at any time post baseline will be presented. Patients with specific laboratory abnormalities (defined by CTCAE grade 3 and 4) will be listed.

For liver enzymes, the number of subjects with newly occurring liver enzymes abnormalities will be summarized by treatment group. Newly occurring liver enzymes abnormalities are defined relative to the upper limit of normal (Section 5.3.2.

Liver function test will also be presented graphically as matrix plots of each of the parameters (ALT, AST, TBIL, ALP) maximum post-baseline/ULN normalized.

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

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

Regarding renal function, the overall frequency of events and percentage of patients with renal events during the treatment period will be summarized and detailed listings provided. Renal events will be defined in section 5.3.3.

The following analyses will be repeated for Cut-off 2 analysis:

- New or worsening abnormalities based on CTCAE grade

- New or worsening liver enzyme abnormalities at any time post-baseline
- Shift table
- Renal events
- Summary statistics

2.8.3.1 Serology at screening

Laboratory serology to determine patient's eligibility includes parameters with respect to hepatitis and HIV viruses, syphilis (RPR), and tuberculosis. Parameters with respect to hepatitis include 1) anti-hepatitis A virus IgM; 2) hepatitis B surface antigen and anti-hepatitis B core IgM/IgG antibody; 3) anti-hepatitis C virus IgG; 4) anti-hepatitis E virus IgM.

The result of each serology parameter is a categorical value. The number and percentage of patients with values in each of the categories will be provided by treatment group for all above-mentioned parameters. Serology test should be performed once at screening. For patients with multiple assessments, the latest result will be used in the summary. Additional serology data with numerical values may be collected but will not be reported.

2.8.3.2 Other special lab results

Other non-routine laboratory data include pregnancy test results, $CD19^{+}$B-cell counts, $CD3^{+}$, $CD20^{+}$T-cell counts, total IgG, total IgM, [redacted] All data will be listed appropriately.

The B-cell counts, T-cell counts, total IgG, total IgM, [redacted] will be summarized using descriptive statistics by treatment group and visit-window.

In addition, number and percentage of patients with B-cells < the lower limit of normal (LLN) will be presented by treatment group and visit-window. Graphic presentation of B-cell counts distribution via box-plots will also be provided by treatment group and visit-window.

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

The following analyses will be repeated for Cut-off 2 analysis:

- Number and percentage of patients with B-cells < LLN by visit window
- Number and percentage of patients meeting the notable low level criteria in IgG and IgM
- Summary statistics

2.8.4 Other safety data

2.8.4.1 ECG

ECG data will be collected at baseline visit, Week 24 visit, Week 48 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 by treatment group for baseline and for the 3 nominal visits (i.e., Week 24, Week 48, and EOS visits).

The number and percentage of patients meeting the criteria defined in Table 2-13 will be provided for each criterion by treatment group for baseline and for the 2 nominal visits.

Table 2-13 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	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)	

2.8.4.2 Vital signs

Vital sign measurements and their change from baseline will be summarized with descriptive (mean, median, standard deviation, min, max) by visit window. The number and percentage of subjects with clinically notable vital signs will be presented.

Vital sign measurements include sitting systolic and diastolic blood pressure, 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 (Section 2.1.2) the blood pressure/pulse value will be the average of all assessments. 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, Day 7, Day 14, Week 4 and Week 24) 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 and treatment group. Change from baseline will only be summarized for patients with both baseline and post-baseline values.

The number and percentage of patients with clinically notable vital signs will be presented. For clinical notable vital signs values, refer to Section 5.4. This analysis will be repeated for Cut-off 2 analysis.

For vital signs data collected on Day 1, Day 7, Day 14, Week 4, and Week 24 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. This analysis will be performed for Cut-off 1 analysis only.

2.8.4.3 Suicidality evaluations

In this study, the C-SSRS questionnaire will be administered electronically (eC-SSRS), via an interactive voice response (IVR) system. 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 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 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" tickbox) 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.

Definition of all prior history and recent history

SIB assessments obtained before the first dose of study drug will be defined by two components: *all prior history* and *recent history*.

All prior history will be defined as the SIB results obtained from the *lifetime* assessment, and *recent history* will be defined as the SIB results obtained from the assessment in past 6 months or past 24 months of the screening or baseline visit.

In case multiple assessments collected before first dose of study drug, results should be derived as the worst case value per the reporting timeframe. Worst case is defined by an answer 'yes' to the SIB category.

Data summary

SIB data will be summarized for the Safety Set. The number and percentage of subjects with suicidal ideation, suicidal behavior and self-injurious behavior without suicidal intent will be presented by analysis-period (recent history, all prior history and any time post-baseline) and treatment group. The following 4 types of events will be included in the summary table:

- Each of the 11 categories listed in Table 2-14 separately
- Any suicidal ideation or behavior (a 'yes' answer to at least one of the 10 suicidal ideation and behavior questions in analysis-period of interest)
- Any suicidal ideation (answered 'yes' to at least one of the 5 suicidal ideation questions in analysis-period of interest)

- Any suicidal behavior (answered ‘yes’ to at least one of the 5 suicidal behavior questions in analysis-period of interest).

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

Table 2-14 Standard SIB events

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

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)

- Worsening suicidal ideation compared to recent history: An increase in the maximum suicidal ideation category at any time post-baseline from the maximum suicidal ideation category during pre-treatment recent history.
- Worsening serious suicidal ideation compared to recent history: An increase in the maximum suicidal ideation category to 4 or 5 at any time post-baseline from not having serious suicidal ideation (categories of 0-3) during pre-treatment recent history.
- Emergence of serious suicidal ideation compared to recent history: A maximum suicidal ideation category of 4 or 5 at any time post-baseline from no suicidal ideation (category 0) during pre-treatment recent history.
- Improvement in suicidal ideation at last on-treatment measurement compared to recent history: A decrease in suicidal ideation score at last on-treatment measurement from pre-treatment recent history.
- Emergence of suicidal behavior compared to all prior history: The occurrence of suicidal behavior (Categories 6-10) at any time post-baseline from not having suicidal behavior (Categories 6-10) prior to treatment (includes "lifetime" and any other assessments prior to treatment taken prior to treatment).

For those analyses, each subject can only be counted once for each event. However, a subject 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 subjects 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 subject 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).

This analysis will be repeated for Cut-off 2 analysis with focusing on post-baseline.

2.8.4.4 Safety evaluation during the Safety follow-up

Safety data collected during the Safety Follow-up period includes adverse events, laboratory assessments (hematology, chemistry, urinalysis, B-cells, T-cells and Immunoglobulins) and eCSSRs. All safety assessments after study drug discontinuation will be analyzed, summarized or listed.

Safety data collected during the Safety Follow-up period will be reported separately. These analyses will include laboratory assessments including B-cell repletion, adverse events, vital signs, and eCSSRS. MS relapses and change in EDSS will also be collected. For all patients change is defined relative to the End of Study visit (EOS). Since post-treatment safety follow-up in the Safety Follow-up period may continue for up to 36 weeks (or longer if criteria for longer follow-up are met) after completion of the Treatment period study, the study report for the Core part (Screening and Double-blind treatment period) will be completed based on the completed core part i.e. based on all patients who have completed the Double-blind treatment period, and the partial data from the Safety Follow-up period available at that time. A complete analysis of the post-treatment safety follow-up will be provided in an addendum to the study report when all patients who entered the Safety Follow-up period have completed this period.

2.9 Pharmacokinetic endpoints

All completed subjects will be included in the pharmacokinetic (PK) data analysis. Concentrations will be given in mass per volume units. Missing values or those below the limit of quantification (LOQ) will be indicated in the data listings and treated as zero in data presentations and calculations. Pharmacokinetic parameters, expressed as mean, SD, and CV, with geometric means will be summarized.

2.10 PD and PK/PD analyses

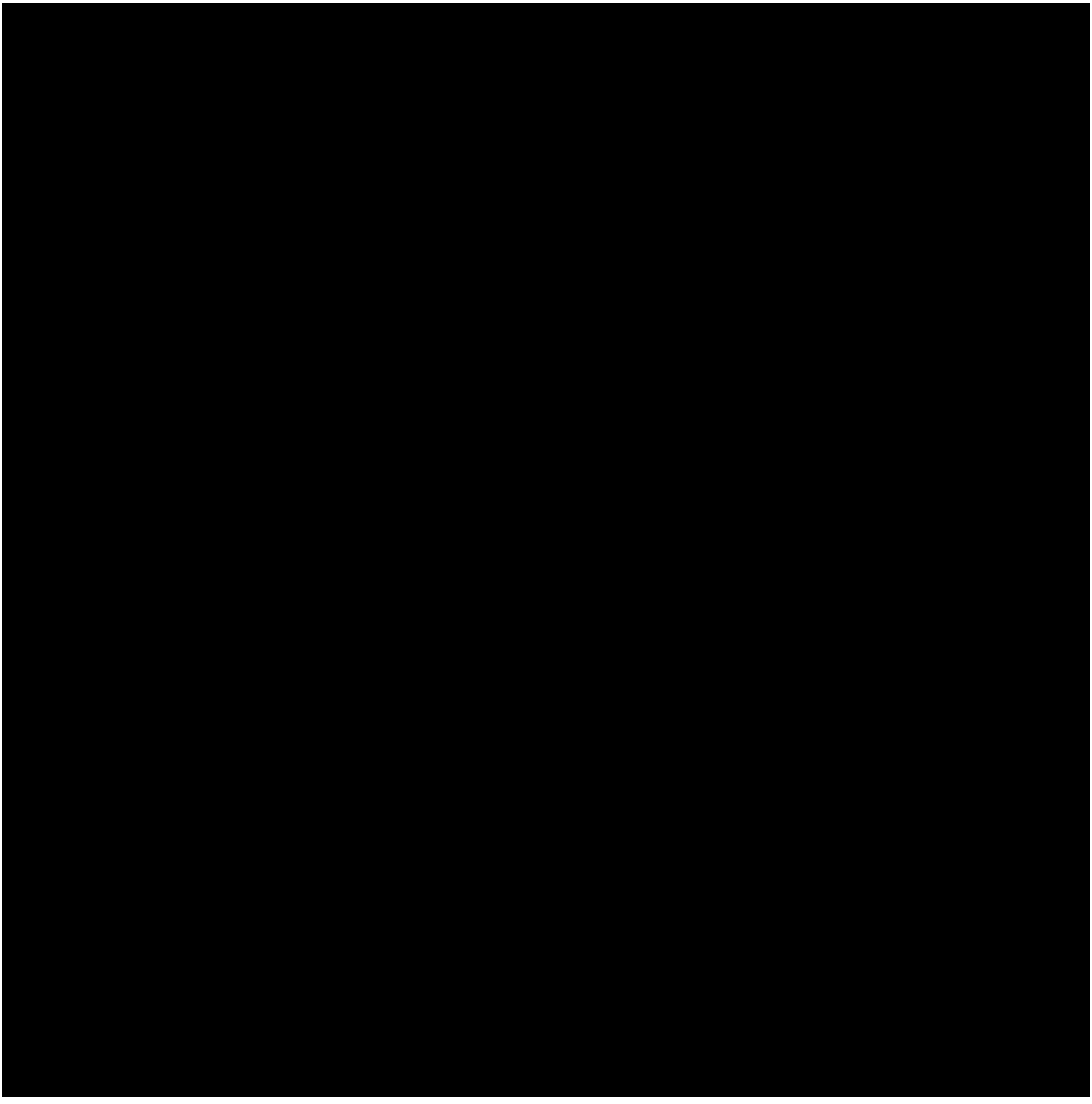
PK concentration and B-cell count data will be summarized by visit for the overall population, and separately by region (Japan or non-Japan) and provided together with by-patient listings in the study report. All patients in FAS with non-missing values will be included in these analyses.

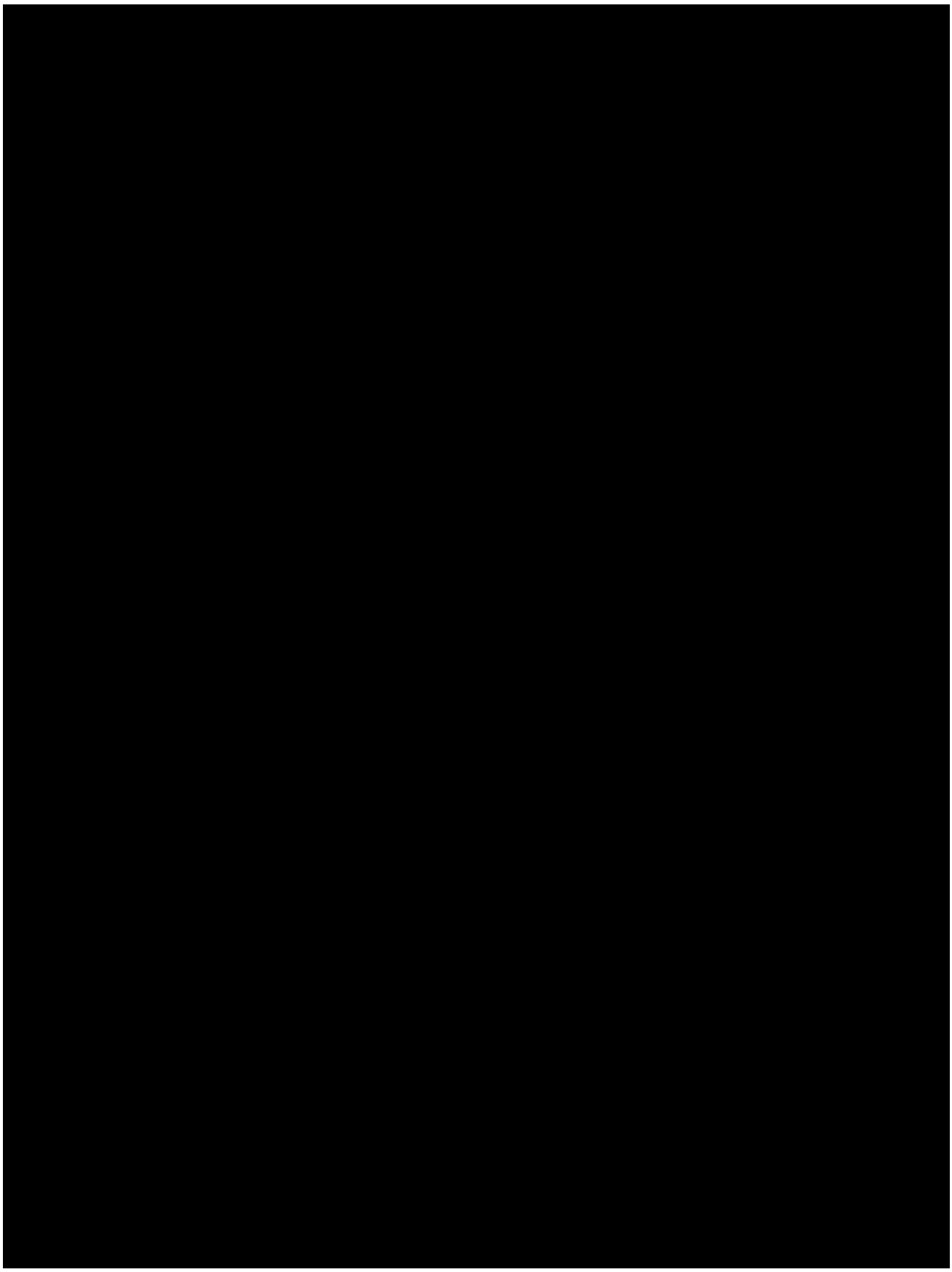
2.11 Immunogenicity assessment

Samples will be analyzed for the presence of human anti-drug antibodies (ADA). The proportion of patients with ADA will be summarized by visit window and overall (i.e. proportion of patients with ADA) as an assessment of the immunogenicity potential of ofatumumab. A listing by patient will also be provided. All patients in FAS with non-missing values will be included.

2.12 Patient-reported outcomes

Not applicable.





2.15 Analysis on the Extension part not mentioned in the previous sections

Switch effect from placebo to ofatumumab on the number of Gd-enhancing T1 lesions

Mean numbers of Gd-enhancing T1 lesions per scan, defined as

(total number of Gd-enhancing T1 lesions) / (total number of scans),

will be calculated by treatment and study period (up to Week 24, or thereafter).

Also, mean numbers of Gd-enhancing T1 lesions per scan will be summarized by region and study period.

In addition, mean numbers of Gd-enhancing T1 lesions per scan will be summarized by subgroup of home injection and study period.

Switch effect from placebo to ofatumumab on the number of new or enlarging T2 lesions

Annualized rate of new or enlarging T2 lesions, defined as

(total number of new or enlarging T2 lesions) / (total time of MRI assessment),

will be calculated by treatment and study period (up to Week 24, or thereafter).

For this calculation, each patient's number of new or enlarging T2 lesions will be relative to Week 24. In addition, definition of time of MRI assessment will depend on the study part:

- For the period up to Week 24, the time of MRI assessment will be defined as (Week 24 visit date) – (first dose date in the Core part) + 1 divided by 365.25.
- For the period after Week 24, the time of MRI assessment will be defined as (Week 48 visit date) – (Week 24 visit date) divided by 365.25. If Week 48 visit is not available, the time of MRI assessment will be defined as (last visit date up to Week 48) – (Week 24 visit date) divided by 365.25.

Switch effect from placebo to ofatumumab on the annualized relapse rate (ARR)

ARR (time-based and patient-based) will be summarized by study period (up to Week 24 or thereafter).

Here definition of time in study will depend on the study part:

- For the period up to Week 24, the time in study will be defined as (Week 24 visit date) – (first dose date in the Core part) + 1 divided by 365.25.
- For the period after Week 24, the time in study will be defined as (last visit date up to date of Cut-off 2) – (Week 24 visit date) divided by 365.25.

2.16 Interim analysis

No interim analysis will be conducted.

3 Sample size calculation

A total sample size of 60 patients, randomized 2:1 to ofatumumab and placebo, will provide more than **90% power** for a statistical test of superiority of ofatumumab compared with placebo at a one-sided alpha level 0.025. The power was calculated based on a negative binomial model under the assumption of 1.0 Gd-enhancing T1 lesions per scan for placebo and a 92% relative reduction with ofatumumab (i.e. 0.08 Gd-enhancing T1 lesions per scan for ofatumumab), and a dispersion parameter $\kappa = 4.5$ (as observed in the combined Phase 3 placebo-controlled studies of fingolimod, namely FREEDOMS and FREEDOMS II studies for the same parameter, data on file). The sample size allows for a dropout rate of 10%.

Sample size calculation was done in EAST 6, version 6.3, Cytel Inc.

3.1 Evaluation of consistency in the treatment effect on the primary variable across regions

As a secondary objective the effect of ofatumumab on Gd-enhancing T1 lesion compared with placebo will be estimated for individual regions (Japan and other countries). It is planned to include 30 patients from Japan out of 60 in total.

The randomization will be stratified by region (Japan or other countries), and by Gd-lesion status on the screening scan (0 Gd-enhancing T1 lesions or ≥ 1 Gd-enhancing T1 lesions). Under the protocol assumptions for placebo, it is expected that approximately 2/3 of the patients will be free of Gd-enhancing T1 lesions at baseline.

A simulation was performed to evaluate the consistency in efficacy on the primary variable across regions. Consistency is defined as a rate ratio < 1 in both Japan and other countries. For the simulation the following assumptions apply:

- The assumptions for the primary variable are the same for Japan and other countries and identical to those for the primary endpoint (i.e. 1 Gd-enhancing T1 lesion per scan, a rate-ratio of 0.08 between ofatumumab and placebo, dispersion 4.5)

- In addition, it was assumed that the study would include 30 patients from Japan and 30 from other countries, and that patients would be randomized 2:1 to ofatumumab or placebo group in each region.

The probability to observe a consistent treatment effect between Japan and other countries was estimated to be higher than 99% under these settings.

Furthermore, we estimated the probability to observe a difference in treatment effect (percentage lesion reduction between ofatumumab and placebo) between Japan and other countries under the same assumptions. The probability to observe a difference of 20% or more (one-sided) in treatment effect between Japan and other countries was estimated to be < 3% (Table 3-1).

Table 3-1 Probability to observe a difference in Gd-lesion reduction across regions of more than delta

Delta*	Probability of a difference in percentage lesion reduction > Delta
5%	13.7%
10%	6.1%
20%	2.3%
30%	1.3%

*Delta=Percentage lesion reduction for other countries - percentage lesion reduction for Japan

3.2 Numerical comparison of annualized relapse rate (ARR)

As a secondary objective the ARR will be compared between patients treated with ofatumumab or placebo. We evaluated the probability to observe a treatment effect in favor of ofatumumab, as defined by an ARR-ratio (ofatumumab/placebo) less than 1 in the overall population. The following assumptions were made for this evaluation:

- 60 subjects in total are randomized 2:1 to ofatumumab or placebo.
- The true ARRs are 0.4 in the placebo arm, and 0.16 in the ofatumumab arm.
- The dispersion parameter, k, is 0.1.
- The follow-up period is 6 months.

Under these settings, the probability to observe a lower ARR in patients treated with ofatumumab compared with placebo is > 80%.

4 Changes to protocol specified analyses

Below changes to protocol specified analyses are included in this document:

1. Cut-off 2 analysis will be conducted when the last patient completes all assessments up to the Week 48 visit, which includes all data from the Safety FU period obtained up to the date of Cut-off 2 as defined above.
2. Final analysis will be conducted when all patients completed the EOS visit or Safety FU period.

3. Used 100 days for Safety cut-off instead of 30 days based on the half life of the compound.
4. Removed Time to first confirmed relapse from the sensitivity analyses section.
5. Defined a simpler negative binomial model with only treatment and region (Japan or other countries) as factors as a fallback option on the ARR analysis and time to first confirmed relapse analysis, in case the model specified in the protocol do not converge or has other statistical limitations.

[redacted]

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Missing or partial dates are not allowed in completing the study drug administration CRF pages. The end date of study drug will be the last end date or last injection date for patients randomized to ofatumumab or placebo, respectively.

5.1.2 AE date imputation

For the start and end dates of the adverse event records, when incomplete or missing, dates will be imputed according to Novartis standards (details will be given in PDS document).

5.1.3 Concomitant medication date imputation

For the start and end dates of the concomitant medication records, when incomplete or missing, dates will be imputed according to Novartis standards (details will be given in PDS document).

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 Relapse date imputation

Missing or partial dates are not allowed for completing the start date of relapses on the MS relapses CRF pages. Sites are required to provide best estimate if patients don't have the exact date. In the rare cases when partial date (unknown day with month and year available) exist in the final database, the following rule will apply:

- A partial start date will be imputed by the first day of the month or the first dose date if it occurs in the same month as the first dose date.
- A partial end date will be imputed by the last day of the month or truncated to have a duration of maximally 90 days.

5.1.5 Other imputations

For the calculation of duration or time since relevant history events as specified in section 2.3.3 (MS disease baseline characteristics), partial dates will be imputed for the MS diagnosis start date, the first MS symptom date, the most recent relapse onset date via below imputation rules.

- If the year is missing or impossible (e.g. 12-Jan-1911), then the date will be imputed as missing.
- If the year is not missing and possible, but the month is impossible or missing (e.g. 17-XXX-2010), then the year will be kept and date will be imputed as July 1st (e.g., 1-July-2010).
- If the year and the month are not missing and possible, but the day is impossible or missing (e.g., 31-FEB-2009), then the year and month will be kept, and date will be imputed as 15th (e.g., 15-FEB-2009).
- The imputed dates should be prior to the screening visit date. That is, if imputed dates are on or after the screening visit date, the dates will be imputed to be one day before the screening visit date.

5.1.5.1 Data manipulation 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.

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). 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 CRF page.

5.3 Laboratory parameters derivations

For each patient, the estimated creatinine clearance values (without collecting urine) will be calculated using the Cockcroft-Gault formula (as specified in Table 5-1). In these calculations, the body weight is the last measurement collected on or before the day when the patient takes the laboratory test and age should also be calculated based on the time when the patient takes the laboratory test.

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

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

Table 5-1 Creatinine clearance calculation

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

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

5.3.1 Laboratory test groups and subgroups

On presenting lab results, grouping parameters by family will ease the review. Table below shows a possible set of lab parameters and their corresponding classification.

Table 5-2 Laboratory tests

Order	Laboratory Group Subgroups	Tests [SI unit]
1	Hematology	
	Red Blood Cells	Hematocrit [%] Hemoglobin [mmol/L] Platelets [10E9/L] Red cell count [10E12/L]
	White Blood Cell Differential	Absolute Basophils [10E9/L] Absolute Eosinophils [10E9/L] Absolute Lymphocytes [10E9/L] Absolute Monocytes [10E9/L] Basophils [%] Eosinophils [%] Lymphocytes [%] Monocytes [%] Neutrophils [%] White Cell Count [10E9/L]
	B-cells	CD19+ B-cell counts [cells/ μ l]
	T-cells	CD3+ CD20+ T-cell counts [cells/ μ l]
	[redacted]	[redacted]
	Immunoglobulin	Total IgG [g/L] Total IgM [g/L]
2	Chemistry	
	Renal Function	Creatinine [umol/L] Blood urea nitrogen [mmol/L]
	Liver Function Test	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]

Order	Laboratory Group Subgroups	Tests [SI unit]
	Other Enzymes	Amylase [U/L]
	Lipids	Cholesterol HDL [mmol/L] Cholesterol LDL [mmol/L] Triglycerides [mmol/L] Total Cholesterol [mmol/L]
	Other	Random glucose [mmol/L] C-Reactive protein CRP [mg/L]
	Electrolytes / Metabolism Tests	Bicarbonate [mmol/L] Calcium [mmol/L] Chloride [mmol/L] Magnesium [mmol/L] Phosphate [mmol/L] Potassium [mmol/L] Sodium [mmol/L]
3	Urinalysis	Blood Glucose Specific gravity Albumin Protein

5.3.2 Newly occurring liver enzymes abnormalities

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

- ALT > 3, 5, 10, 20x ULN
- ALT or AST > 3, 5, 8, 10, 20x ULN
- 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 & TBIL > 2x ULN

- ALT or AST > 3x ULN & TBIL > 2x ULN & ALP ≤ 2x 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, section: Safety parameters for special liver event analyses.

5.3.3 Newly occurring renal events

Below lists the criteria for newly occurring renal events:

- SCr increase >= 25% and <50% from baseline
- SCr increase >=50% from baseline
- New onset dipstick proteinuria (confirmed) (≥ 1+)
- New onset dipstick glycosuria (≥ 1+)
- New onset dipstick hematuria (≥ 1+)

5.3.4 CTCAE grades for laboratory parameters

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

		Grade			
Abnormality	**Lab parameter**	**1**	**2**	**3**	**4**
Hematology					
Anemia	Hemoglobin (g/L)	<LLN - 100 g/L	<100 - 80 g/L	<80 g/L transfusion indicated	
Platelet count decreased	Platelets (thrombocytes) (10^9/L)	<LLN-75.0 x 10^9/L	<75.0 - 50.0 x 10^9/L	<50.0 - 25.0 x 10^9/L	<25.0 x 10^9/L
White blood cell decreased	Leukocytes (WBCs) (10^9/L)	<LLN - 3.0 x 10^9/L	<3.0 - 2.0 x10^9/L	<2.0 - 1.0 x 10^9/L	<1.0 x 10^9/L
Neutrophil count decreased	Absolute neutrophil count (10^9/L)	<LLN - 1.5 x10^9/L	<1.5 - 1.0 x10^9/L	<1.0 - 0.5 x10^9/L	<0.5 x10^9/L
Lymphocyte count decreased	Absolute lymphocyte count (10^9/L)	<LLN x 0.8 - 10^9/L	<0.8 - 0.5 x 10^9/L	<0.5 - 0.2 x 10^9/L	<0.2 x 10^9/L
Lymphocyte count increased	Absolute lymphocyte count (10^9/L)		>4 - 20 x 10^9/L	> 20 x 10^9/L	
Chemistry					

		Grade			
Liver function					
Alanine aminotransferase increased	ALT (SGPT) (U/L)	>ULN - 3.0 x ULN if baseline was normal; >1.5 – 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 – 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 – 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Aspartate aminotransferase increased	AST (SGOT) (U/L)	>ULN - 3.0 x ULN if baseline was normal; 1.5 – 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 – 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 – 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Blood bilirubin increased	Bilirubin (µmol/L)	>ULN - 1.5 x ULN if baseline was normal; >1.0 – 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 – 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 – 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
GGT increased	Gamma-glutamyl transferase (GGT) (U/L)	>ULN - 2.5 x ULN if baseline was normal; 2.0 – 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 – 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 – 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Alkaline phosphatase increased	Alkaline Phosphatase (U/L)	>ULN - 2.5 x ULN if baseline was normal; 2.0 – 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 – 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 – 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Renal function Note: A semi-colon (;) indicates 'or' within the description of the grade.					
Creatinine increased*	Creatinine (µmol/L)	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0x ULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN
Other enzymes					
Serum amylase increased	Amylase (U/L)	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 - 5.0 x ULN with signs or symptoms; >5.0 x ULN and asymptomatic	>5.0 x ULNand with signs or symptoms
Serum amylase** increased	Amylase (U/L)	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN;	>2.0 - 5.0 x ULN	>5.0 x ULN
Lipids					
Cholesterol high	Cholesterol Total (mmol/L)	>ULN- 7.75 mmol/L	>7.75-10.34 mmol/L	>10.34-12.92 mmol/L	>12.92 mmol/L
Hypertriglyceridemia	Triglycerides (mmol/L)	1.71 - 3.42 mmol/L	>3.42 - 5.7 mmol/L	>5.7 - 11.4 mmol/L	>11.4 mmol/L

	Grade

*Highest grade will be assigned if more than one grade criteria are met for an observed value of a patient.
**CTCAE 4.03 definition. For reporting in CSR, the grade definition per CTCAE 4.03 will be used for this parameter only.

5.4 Clinical notable vital signs

Clinically notable vital sign values to be used for this study are listed below.

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)	>38.3oC (>101 oF)
Body weight (kg)	>=7% from baseline weight

5.5 Statistical models

5.5.1 Primary analysis

The null hypothesis is that there is no difference in the number of Gd-enhanced T1 lesions per scan between ofatumumab and placebo during the core part. The alternative hypothesis is that there is a difference between the 2 treatment groups.

The null hypothesis will be tested using a negative binomial regression model with log-link, each patient's total number of Gd-enhanced lesions during the Core part as the response variable, and natural log of the number of MRI scans as the offset variable to adjust for the different number of MRI scans between patients. The model will include treatment, region (Japan or other countries), and baseline number of Gd-enhanced lesions (0 or ≥ 1) as factors.

The SAS procedure GENMOD will be used to conduct the analysis. In GENMOD, the log of the dispersion parameter will be used (lognb) as an option in model statement. The natural log of number of MRI scans is used as an offset by specifying offset option in the model statement.

5.5.2 Key secondary analysis

For the secondary endpoints Number of new or enlarging T2 lesions on MRI scans and Annualized Relapse Rate (ARR), statistical model is similar with that of the primary endpoints (Section 5.5.1), in that a negative binominal model is used.

For the secondary endpoint Time to relapse, a Cox proportional hazard model with treatment, region (Japan or other countries), and baseline number of Gd enhancing lesions (0 or ≥ 1) as factors, and number of relapses in previous year and baseline EDSS as covariates will be used to test H0: $\lambda o/\lambda t = 1$ vs. Ha: $\lambda o/\lambda t < 1$. Where λo and λt are hazard of relapse in ofatumumab and placebo groups respectively.

The SAS procedure PHREG will be used to conduct the Cox PH analysis. The SAS procedure LIFETEST will be used to conduct the KM analysis.

5.6 Rule of exclusion criteria of analysis sets

Patient classification in the analysis sets is entirely based on protocol deviation and non-protocol deviation criteria. Details are provided in Table 5-4 and Table 5-5.

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

Deviation ID	Description of Deviation	Exclusion in Analyses
EXCL01	Patients with primary progressive MS or SPMS without disease activity	Excluded from PPS
EXCL02	Patients meeting criteria for neuromyelitis optica	Excluded from PPS
EXCL06	Patients with an active chronic disease (or stable but treated) of the immune system other than MS or with a known immunodeficiency syndrome	Excluded from PPS
EXCL11	Systemic steroid or adrenocorticotropic hormone treatment within 30 days prior to Screening MRI	Excluded from PPS
EXCL12	Dimethyl fumarate within 1 month prior to randomization	Excluded from PPS
EXCL13	Fingolimod taken within 2 months prior to randomization	Excluded from PPS
EXCL15	Daclizumab within 4 months prior to randomization	Excluded from PPS
EXCL16	Natalizumab treatment within 6 months prior to randomization	Excluded from PPS
EXCL17	Teriflunomide within 3.5 months prior to randomization or 1 month prior to randomization following accelerated elimination procedure and documented teriflunomide plasma level below 0.02 mg/L	Excluded from PPS
EXCL18	Mild to moderately Immunosuppressive / chemotherapeutic medications (e.g. azathioprine, methotrexate) within 6 months prior to randomization	Excluded from PPS
EXCL19	Highly immunosuppressive/chemotherapeutic medications(Mitoxantrone, cyclophosphamide, cladribine)or any B-cell targeted therapy(rituximab, ocrelizumab)or laquinimod within 2 years before randomization	Excluded from PPS
EXCL20	Mitoxantrone with evidence of cardiotoxicity following treatment or a cumulative life-time dose of more than 60 mg/m2, at any time prior to randomization	Excluded from PPS
EXCL21	Lymphoid irradiation; bone marrow transplantation; other strongly immunosuppressive treatments (with effects potentially lasting over 6 months), at any time prior to randomization	Excluded from PPS
EXCL22	Ofatumumab or alemtuzumab use at any time	Excluded from PPS
EXCL23	Use of other investigational drugs at screening or within the prior 30 days, or five elimination half-lives, or until the expected pharmacodynamics effect has returned to baseline, whichever is longer	Excluded from PPS
EXCL24	History of malignancy of any organ system within the past 5 years, regardless of evidence of local recurrence or metastases.	Excluded from PPS
EXCL46	History of clinically significant CNS disease (e.g. stroke, traumatic brain or spinal injury, history or presence of myelopathy) or neurological disorders which may mimic MS	Excluded from PPS

Deviation ID	Description of Deviation	Exclusion in Analyses
EXCL47	Patients with neurological findings consistent with Progressive Multifocal Leukoencephalopathy (PML) or confirmed PML at Screening	Excluded from PPS
EXCL48	Patients unable or unwilling to undergo MRI scans	Excluded from PPS
EXCL49	History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes	Excluded from PPS
INCL01	Study Informed consent Date = missing	Excluded from All analysis sets
INCL01A	Incorrect ICF procedure	Excluded from All analysis sets
INCL03	No diagnosis of MS as defined by 2010 revised McDonald criteria	Excluded from PPS
INCL05	No appearance of new neurological abnormality or worsening of pre-existing neurological abnormality during the previous 2 years prior to Screening	Excluded from PPS
INCL06	No appearane of MRI activity, namely no appearance of Gd-enhanced T1 lesions or new/enlarging T2 lesions in brain during the previous 1 year prior to randomization	Excluded from PPS
INCL07	Neurologically Unstable (i.e. Clinical relapse) within 1 month prior to randomization	Excluded from PPS
WITH09	Patient withdraws consent but study treatment was not discontinued	Excluded from PPS
WITH11	Patient diagnosed with PML and study treatment was not discontinued	Excluded from PPS
TRT01	Patient recieved incorrect study drug	Excluded from PPS
TRT02	Patient recieved damaged or expired study drug	Excluded from PPS
COMD01	Immunosuppressive medicines such as cyclosporine, azathioprine, methotrexate, cyclophosphamide, mitoxantrone or lymphoid irradiation, hematopoietic stem cell transplantation on study treatment	Excluded from PPS
COMD02	Monoclonal antibodies targeting the immune system such as natalizumab, alemtuzumab, daclizumab and B-cell depleting agents such as rituximab, ocrelizumab and obinutuzumab on study treatment	Excluded from PPS
COMD03	Any other immunomodulatory treatment such as fingolimod, interferon beta, glatiramer acetate, dimethyl fumarate, IVIG, plasmapheresis or chronic corticosteroids on study treatment	Excluded from PPS
COMD04	Leflunomide or teriflunomide while taking study treatment	Excluded from PPS
OTH01	EDSS rater acted as a treating physician or treating physician acted as EDSS rater	Excluded from PPS
OTH02	Not following per protocol blinding procedures such that the integrity of the study is compromised	Excluded from PPS

Table 5-5 Patient Classification

Analysis Set	PD ID that cause patients to be excluded	Non-PD criteria that cause patients to be excluded
FAS	INCL01 INCL01A	Not assigned a valid randomization number; Randomization despite screen failure
PPS	As listed in Table 5-4	Not in FAS; Compliance to study drug administration < 80% EDSS baseline value >=7.0
SAF	INCL01, INCL01A	No double-blind study drug taken

5.7 Statistical method details for TEAEs

5.7.1 Odds ratios and 95% confidence interval

For an investigational drug group with n_1 patients at risk, independent from the control group with n_0 patients at risk, of whom x_1 and x_0 experience a certain event with probability π_1 and π_0 respectively, the odds ratio (OR) is estimated as

$$\frac{p_1/(1-p_1)}{p_0/(1-p_0)} \text{ with } p_1 = x_1/n_1 \text{ and } p_0 = x_0/n_0, \text{ simplifying to } \frac{x_1 \times (n_0 - x_0)}{x_0 \times (n_1 - x_1)}.$$

The OR and a conditional exact 95% confidence interval will be obtained by using the SAS procedure PROC FREQ with statement EXACT OR. The data set will include a patient level response variable indicating whether a patient has at least one AE of a specific type (1=yes, 0=no).

By default SAS sets the OR to missing if the odds for one of the treatments cannot be calculated (no infinity in SAS). This is problematic as infrequent but very serious adverse events that happen exclusively on active treatment can easily be missed if the OR for such highly imbalanced advents is set to missing and sorted last. To ensure that potentially important imbalances appear at the top of a table if it is sorted by OR, the following additional rules are applied (considering the numerator and the denominator of the OR that would lead to divisions by zero):

- NO CASE CLAUSE [0/0]: If (x_1=0 and x_0=0) or (x_1=n_1 and x_0=n_0), i.e. there are either no events in both treatment groups, or all patients in both treatment groups had the event, then the OR cannot be estimated. The OR can be left missing for the sorting, but should be displayed on the output as “N.E.” indicating not estimable (if it has to be shown on the table, in this case it needs to be explained in the footnote).
- SAFETY CLAUSE[~/0]: If (x_0=0 and x_1≠0) or (x_0≠n_0 and x_1=n_1), i.e. there are no events on control, but some on investigational drug, or everyone on investigational drug experienced the event, but not everyone on control, then OR will be imputed as 100000

for the sorting (so that it comes up top if sorted by the OR). On the output present the OR as ">100".

- EFFICACY CLAUSE[0/~]: If (x_1=0 and $x_0 \neq 0$) or ($x_1 \neq n_1$ and $x_0 = n_0$), i.e. there are no events on investigational drug, but some on control, or, everyone on control experienced the event, but not everyone on investigational drug, then OR will be imputed as 1/100000 for the sorting (so that it comes prior to the missing ones). On the output present the OR as "<1/100".

5.7.2 Exposure adjusted incidence rate and 95% confidence interval

It will be assumed that for each of n patients in a clinical trial the time t_j (j=1,...,n) to the first incidence of a certain event is observed, or if the event was not experienced, the time is censored at the end of the observation period. The sequence of first occurrences of an event will be modeled to follow approximately a Poisson process θ with constant intensity λ. The rate parameter λ will be estimated by $\hat{\lambda} = \frac{D}{T}$, where $T = \sum_{j=1}^{n} t_j$ and D is the number of patients with at least one event. Conditionally on T, an exact 95% confidence interval for a Poisson variable with parameter θT and observed value D can be obtained based on (Garwood, 1936), from which an exact 95% confidence interval for $\hat{\lambda} = \frac{D}{T}$ will be derived as follows (Sahai, 1993; Ulm, 1990):

Lower confidence limit $L = \frac{0.5 c_{\alpha/2,2D}}{T}$ for D>0, 0 otherwise,

Upper confidence limit $U = \frac{0.5 c_{1-\alpha/2,2D+2}}{T}$

where $c_{\alpha,k}$ is the α^{th} quantile of the Chi-square distribution with k degrees of freedom.

The SAS procedure GENMOD will be used to fit a Poisson regression model with only treatment as factor, the log-link and natural logarithm of time as the offset variable. The incidence rate (and 95% confidence intervals) are obtained as the exponentiated estimates by treatment (e.g. obtained by statement LSMEANS with option EXP). The data set will include a patient level response variable indicating whether the patient experienced at least one event of a specific type (1=yes, 0=no) and a patient level time variable which is derived as follows:

- For patients who had at least one event of that type: time is calculated as (start day of the first event - date of first administration of study drug+1).
- For patients who did not have an event of that type: time at risk as defined inSection 2.4.1will be used.

The time will be divided by 365.25 before taking the logarithm transformation as offset variable so that the estimated incidence rate corresponds to an annualized rate.

6 Reference

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