

Clinical Development

OMB157/Ofatumumab

COMB157G2102 / NCT03560739

**A 12 week randomized open label parallel group
multicenter study to evaluate bioequivalence of 20 mg
subcutaneous ofatumumab injected by pre-filled syringe or
autoinjector in adult RMS patients**

Statistical Analysis Plan (SAP)

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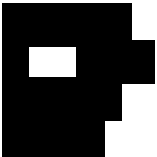
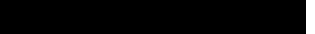





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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
12-Sep-2018	FPFV	Creation of final version	N/A - First version	NA
07-Jun-2019	Prior to DBL	FDA feedback on submission; Align with submission planning and update for corrections and clarity	Amendment 1	<p>Section 2.3.5: Smoking and Alcohol history (removed summary tables as they are not needed)</p> <p>Section 2.8.1: AEs (updated common AEs as $\geq 2\%$ per FDA feedback)</p> <p>Section 2.8.2: Deaths (removed table summary as death is expected to be rare in this study)</p> <p>Section 2.8.3: presentation of shift table for lab parameters are updated.</p> <p>Section 2.8.3.2: Other lab parameters (added T-cell and minor corrections). </p> <p>Figure presentation for B-cell are updated.</p> <p>Section 2.8.5: CSSRS (Added texts for “complete suicide” data collection per update of standard MAP); added data handling rules for all prior history and recent history if multiple assessments collected prior to first dose.</p> <p>Section 2.4.2.1: Concomitant medication (added rules for cases with both missing start date and end date)</p> <p>Section 2.4.2.3: Injection related premedication time window update</p>

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
18-Sep-2019	Prior to DBL	Align with submission planning and update for corrections and clarity	Amendment 2	Section 2.4.1: Add condition of analysis cut-off date for time at risk definition. Section 2.1.2.1: [REDACTED] [REDACTED] to account for some assessments occurring outside the original definitions Sections 2.1.2.1, 2.8.3.2, 5.3.1: Remove left-over reference to T-cell assessment (T-cell analysis was already removed from previous amendment, due to panel unavailable at the study start) Section 2.3.5: Remove entirely (smoking and alcohol history information not needed in listings) Section 2.5.1: Clarify exclusion of concentrations / patients from BE analysis due to missing concentration value or dose missed due to reasons that are not protocol deviations (missed dose leads to the exclusion of two patients at the time of amendment). [REDACTED] Section 2.8.6: Final naming decision for Registration and Final CSR.

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
21- Oct- 2019	After DBL	Correct inaccurate reference to PD ID INCL01 and 	Addendum 1	<p data-bbox="940 383 1398 461">Section 4:  </p> <p data-bbox="940 472 1398 577">Other minor corrections or clarifications made in the document.</p> <p data-bbox="940 600 1398 663">Section 2.8.3.4: Other special lab results</p> <p data-bbox="940 685 1398 790">Updates are made in order to provide more accurate information on </p>  <p data-bbox="940 1216 1398 1249">2) correct the data cutoff for </p>  <p data-bbox="940 1709 1398 1814">Same section: correction of error in explanation of notably low IgM/IgG criteria.</p> <p data-bbox="940 1836 1398 1906">Section 5.6: Rule of exclusion criteria of analysis sets</p>

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
				<p>Removed reference to protocol deviation ID INCL01 to prevent inappropriate exclusion of patients with this PD ID from analyses: At the time of writing of the SAP it was assumed that INCL01 would be assigned to PD “Informed consent obtained = 'No' or missing”, however, in the database no code was assigned to this deviation (and no patients affected), while INCL01 was in fact assigned to “Incorrect ICF procedure” as per Edit Check Specifications – which does not justify exclusion of patients from analysis. Impact: Change allows inclusion of data from two patients who consented, but were affected by incorrect ICF procedure in all analyses.</p> <p>Document history: Correct date of amendment 2 to release date 18 Sep 2019 as provided on title page.</p>
8- May- 2020	After DBL	Adapt plan for reporting of SFU patients to very low sample size	Addendum 2	<p>Section 2.1.2.1: Updated visit window definition for data after study drug discontinuation (replaced EOS date with Last dose date as starting point for visit window definitions).</p> <p>Section 2.8.6.2: Clarify that only patients that did not roll over to the extension study or prematurely stopped treatment should be included in SFU analyses, to avoid contributions from patients not in SFU, who had unscheduled assessments shortly after the regular EOS/Week 12 visit.</p>




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List of abbreviations

ABE	Average bioequivalence
ADA	Anti-drug antibodies
AE	Adverse event
AI	Autoinjector
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
AUC	Area under the curve
BE	Bioequivalence
CI	Confidence interval
CRF	Case Report/Record Form (paper or electronic)
CSR	Clinical Study report
CTCAE	Common Terminology Criteria for Adverse Events
CTC	Common Toxicity Criteria
CV	Coefficient of variation
DBL	Database lock
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCSSRS	Electronic Columbia Suicide Severity Rating Scale
EDSS	Expanded Disability Status scale
EOS	End of Study
FDA	Food and Drug Administration
FU	Follow up
GMR	Geometric mean ratio
HDL	Hepatitis C Virus
HIV	human immunodeficiency virus
Ig	Immunoglobulins
LDL	low density lipoprotein
LLN	lower limit of normal
MedDRA	Medical dictionary for regulatory activities
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NCA	Non- Compartmental Analysis
█	█
PD	pharmacodynamic(s)
PFS	prefilled syringe
PK	pharmacokinetic(s)
PML	Progressive Multifocal Leukoencephalopathy
PRO	Patient-reported Outcomes

QTcF	QT correction formula
RBC	Red blood cells
RRMS	Relapsing-remitting Multiple Sclerosis
RSABE	Reference scaled average bioequivalence
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sc	Subcutaneous
	
SIB	Suicidal ideation and behavior
SOC	System Organ Class
SPMS	Secondary progressive Multiple Sclerosis
TOST	Test one sided test
ULN	upper limit of normal
WBC	white blood cell(s)
WHO	World Health Organization

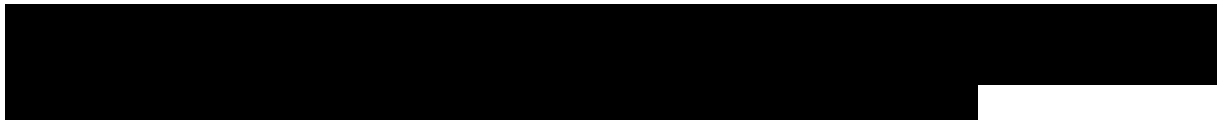
Pharmacokinetic definitions and symbols

AUC _{0-t}	The area under the plasma (or serum or blood) concentration-time curve from time zero to time 't' where t is a defined time point after administration (mass x time/volume)
AUC _{last}	The area under the plasma (or serum or blood) concentration-time curve from time zero to the time of the last quantifiable concentration (mass x time/volume)
AUC _{tau}	The area under the plasma (or serum or blood) concentration-time curve from time zero to the end of the dosing interval tau (mass x time/volume)
C _{max}	The observed maximum plasma (or serum or blood) concentration following drug administration (mass/volume)
T _{max}	The time to reach the maximum concentration after drug administration (time)

1 Introduction

The purpose of this Statistical Analysis Plan (SAP) is to describe the implementation of the statistical analysis planned in the protocol for study OMB157G2102 (G2102). The corresponding clinical study report (CSR) will include results from this SAP.

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



1.1 Study design

This is a randomized, open-label, multi-center, parallel group 12-week study to evaluate the pharmacokinetic bioequivalence of ofatumumab injected by PFS or AI devices. The study design includes four parallel groups of RMS patients. Assessment of the primary and secondary endpoints are performed based on data collected through the dosing interval between Week 8 and Week 12 where approximate steady-state pharmacokinetics are anticipated.

Randomization: A total of approximately 150 eligible patients will receive open-label ofatumumab 20 mg sc every 4 weeks (after an initial loading regimen of three weekly 20 mg doses in the first 14 days). Patients will be randomized in a 5:5:1:1 ratio into the following 4 groups dependent on what type of injection device they will use and the location of their injection (62 subjects for groups 1 and 2, and 13 subjects for groups 3 and 4). Randomization will be stratified by body weight (< 60 kg, 60-90 kg, and > 90 kg) to ensure a balance between covariates with potential impact on the primary endpoint. Randomization will not be blinded as the endpoints of the study are primarily related to pharmacokinetics and all patients will be receiving active treatment at identical dosing regimens.

- Group 1: PFS, abdomen
- Group 2: AI, abdomen
- Group 3: PFS, thigh
- Group 4: AI, thigh

Interim analyses: The study will feature one interim analysis that will be conducted when approximately 36 patients have completed Week 12 ([Section 2.14](#)).

The study has 3 Parts:

- Part 1 – Screening
- Part 2 - Treatment
- Part 3 - Safety follow-up

Part 1 – Screening

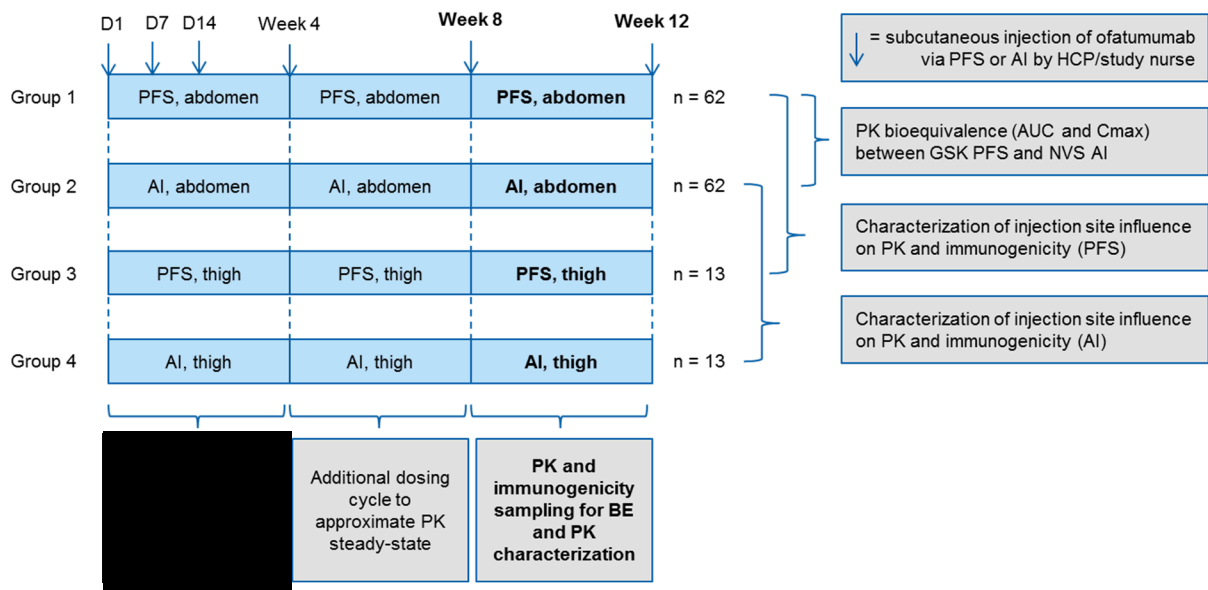
- The Screening period can last up to 30 days and consists of Screening and Baseline assessments. Patient eligibility will be determined based on the Screening and/or Baseline assessments.

- Patients may be rescreened if they do not initially meet eligibility criteria. All assessments must be repeated, [REDACTED]

Part 2 – Treatment

Graphical outline of Part 2, Treatment period study design with four parallel groups. Evaluation of primary and secondary end-points are performed between Week 8 and Week 12.

Figure 1-1 Study design – Part 2



The study Part 2 Treatment period will consist of an initial induction phase (Week 0 to Week 4) and a pharmacokinetics phase (Week 8 to Week 12) at approximate steady-state conditions. Week 4 to Week 8 ensures that approximate steady-state conditions are reached prior to the pharmacokinetics phase. A schematic presentation of the study design is provided in [Figure 1-1](#).



The pharmacokinetics will be assessed for primary objectives during Week 8 to Week 12 at approximate steady-state conditions. The rationale for this is to avoid the expected larger inter-individual variation in exposure at treatment initiation due to the potentially different levels of

target expression between patients. This would result in high variability in the pharmacokinetics parameter leading to an increased sample size of the study. Further, the approximate steady-state condition is a clinically relevant situation as full target depletion would be expected in contrast to the situation after administration of a single dose typically used for bioequivalence assessment. During the study, ofatumumab will be administered to the respective groups of patients by a health care provider and according to specified instructions.

No clinically significant difference in ofatumumab exposure is expected between the two administration sites (abdomen vs thigh) (Xu et al 2010). Groups 3 and 4 will enable an assessment of the pharmacokinetics of ofatumumab injected to the thigh which can then be compared to abdominal administration using the PFS and AI, respectively. The aim of assessment of the injection site influence on ofatumumab pharmacokinetics is not to demonstrate bioequivalence but to enable an evaluation of the potential clinical significance of differences in pharmacokinetic parameters. Potentially, the absorption rate may vary between different injection sites for subcutaneous single dose administration of ofatumumab possibly resulting in different T_{max} and C_{max} values. However, under steady-state conditions and with the primary target being depletion of CD20-positive B-cells, the comparison of AUCs over the dosing period would be the most relevant parameter to evaluate. In order for patients to obtain a clinical benefit from participation in the study, continued treatment with ofatumumab will be offered to the eligible patients through enrollment into the umbrella open-label Phase 3 extension study (COMB157G2399). Patients waiting for open label extension study to open can continue to receive study drug. Patients should return every 12 weeks and complete assessments per assessment schedule.

Part 3 – Safety follow-up/Extension study

- The Safety FU period will be applicable for the following patients:
 - a. Patients who complete the Treatment period on study drug and do not enter the planned Extension study
 - b. Patients who prematurely discontinue study treatment
- All Safety FU visits must be scheduled relative to the EOS Visit.
- All patients will be followed for a total of at least 9 months after study drug discontinuation (by 9 months the vast majority of patients are expected to have repleted their circulating B-cells).

A longer than 9 months of post-treatment follow up in the Safety FU period will be required for patients who have not repleted their B-cells (ie B-cells not back to baseline value or to lower limit of normal (LLN) whichever comes first as determined by central lab) at 9 months. These patients will continue to be followed with 3-monthly assessments until their B-cell counts have repleted. Patients who have initiated therapy with another disease modifying/immunosuppressive therapy before the end of the 9-month follow up will not be monitored beyond 9 months.

1.2 Study objectives and endpoints

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s)	Endpoint(s) for primary objective(s)
To demonstrate pharmacokinetic bioequivalence of 20 mg ofatumumab injected by the PFS or AI devices	AUCtau Cmax
Secondary Objective(s)	Endpoint(s) for secondary objective(s)
To characterize the pharmacokinetics following subcutaneous administration of ofatumumab to either the abdominal region or the thigh	AUCtau Cmax
Assessment of immunogenicity	Proportion of patients with anti-ofatumumab antibodies
Assess the safety and tolerability of ofatumumab	Adverse events including injection related reaction, lab, vital signs, ECG, and eCSSRS

2 Statistical methods

2.1 Data analysis general information

Novartis statistical and programming team will be performing the final CSR analysis as planned in this document unless otherwise specified. The Statistical Analysis System (SAS) 9.4 and/or R 15.2.1 or higher versions will be used.

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

The Week 12 CSR analysis cut-off date will be the Week 12 visit date or EOS date if patients drop out of the study prematurely. All data up to this date will be included in the Week 12 CSR. A complete analysis of the post-treatment safety follow-up will be provided in the Final CSR when all patients have completed Safety FU period.

For analyses of adverse events, only data up to and including the safety cutoff of 100 days (5 x 20 days takes the long half-life of ofatumumab into account) after last administration of study drug or the subject entered the Study G2399 will be considered. Therefore, observations obtained more than 100 days after last administration of study drug will be excluded from the

analyses. Nevertheless, all serious adverse events (SAE) and all deaths, regardless of the safety cut-off will be summarized.

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

Table 2-1 provides an overview on all planned reporting.

Table 2-1 Analyses for Week 12 registration vs. Final CSR

	Week 12 registration CSR	Final CSR
PK + immunogenicity	Complete	Complete
Tables + figures of planned safety assessments ¹	Complete up to Week 12 / EOS, no reporting of assessments during safety follow-up	Complete, including all assessments during safety follow-up
Listings of planned safety assessments ²	Complete up to 12 week DBL date	Complete, including all assessments during safety follow-up
Adverse events	Up to and including the safety cutoff of 100 days after last administration of study drug or the subject entered the Study G2399 or 12 week DBL date, whatever comes first	Up to and including the safety cutoff of 100 days after last administration of study drug or the subject entered the Study G2399, whatever comes first
Serious adverse events and deaths	Up to 12 week DBL date or subject entered the study G2399, whatever comes first	Up to final DBL date or subject entered the study G2399, whatever comes first

¹ These include also B-cells, total IgG, total IgM.

² These include also B-cells, total IgG, total IgM [REDACTED].

2.1.1 General definitions

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

Table 2-2 General definitions

Study treatment/Study drug	The investigational drug ofatumumab injected by PFS or AI devices will be referred as study treatment or study drug.
Date of first administration of study drug/first dose date	The first injection date of ofatumumab.
Date of last administration of study drug/last dose date	The last injection date of ofatumumab.
Study Day 1 or Day 1	The date of first administration of study drug/first dose date.

Study Day	<p>All other study days will be labeled relative to Day 1. For events with dates on or after Day 1, study day for the event is calculated as (event start date – first dose date + 1). For events with dates before Day 1, study day for the event is calculated as (event start date – first dose date).</p> <p>Day 0 will not be used.</p>
Duration of an event	Duration of an event is calculated as (event end date – event start date +1).
1 month	30 days; to be used in defining 3-month or 6-month confirmed disability worsening or improvement.
4 weeks	28 days; to be used in determining target days of scheduled visits. It is based on the scheduled injection frequency for ofatumumab (during the maintenance phase).
Day post-study drug discontinuation	Day post-study drug discontinuation for a particular event is calculated as (event start date – study drug discontinuation date).
Baseline	<p>Baseline is the last assessment obtained prior to the first administration of study drug. No visit windows will be needed for the identification of baseline assessment.</p> <p>For pulse and blood pressure vital sign values, the baseline is the average of the non-missing values of the 3 measurements taken on the last visit prior to the first administration of study drug. The pre-injection assessment values on Day 1 vital sign CRF page will not be used for baseline derivations.</p>
On-treatment period	On-treatment period includes days from the first injection date until 30 days after the last injection date; This definition considers patients are scheduled to inject every 28 +/- 3 days. The on-treatment definition applies to efficacy analyses only.
Safety cutoff (off-treatment)	Safety cutoff: Unless explicitly otherwise stated (e.g. SAEs and deaths), data up to and including the safety cutoff of 100 days after permanent study drug discontinuation will be included in the analysis and data beyond this time point for a given patient will be excluded from the safety analysis. The safety cutoff of 100 days (5x20 days) takes the long half-life of the investigational drug into account. The safety cutoff applies to safety analyses only.

Nominal visits	Nominal visits are defined as all scheduled visits as per the clinical study protocol including the EOS visits. The definition of nominal visit excludes unscheduled visits.
End of Study (EOS)	EOS, used in the context of individual patients, refers to EOS visit. EOS, used in the context of the entire study, refers to completion of Week 12 visit for all patients.
Last assessment on drug	It is the last assessment with non-missing value taken before or on the date of last administration of study drug. No visit windows will be needed for the identification of the last assessment on drug evaluation.

2.1.2 Visit windows

2.1.2.1 Visit windows definition

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

Baseline assessments are defined in [Section 2.1.1](#) and do not require a visit window.

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

- For **PK concentration** [REDACTED] nominal visits will be used for summaries by visit/time point. Due to the frequent sampling time points during week 8, conventional mapping to visit-windows are not considered appropriate, thus nominal visits are used in order to capture all data as intended.

-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 2.1.2.2](#) deals with the statistical approaches to handle multiple visits in a given visit-window.

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

Table 2-3 Visit-windows for ADA

Visit-window	Start day	Target Day	End day
Week 4	1	28	42

Week 8	43	56	70
Week 12	71	84	97

Table 2-4 Visit-windows for routine laboratory values and IgG and IgM

Visit-window	Start day	Target Day	End day
Week 4	1	28	56
Week 12	57	84	111

Table 2-6 Visit-windows* for [REDACTED] vital signs data after study drug discontinuation

Visit-window	Start day	Target Day	End day
Last assessment on drug	NA	NA	NA (see above or Section 2.1.1)
Week 12 after LDD	2	84	126
Week 24 after LDD	127	168	210
Week 36 after LDD	211	252	294

*The Start day, Target day, and End day are relative to the LDD date. For the “Last assessment on drug”, the last assessment with non-missing value taken before or on the date of last administration of study drug will be summarized (no visit window applies). For the “Week 12 after LDD” visit-window, assessments taken at least 1 day after but no more than 126 days after the LDD date will be considered. LDD stands for last dose date and will be footnoted in applicable outputs.

2.1.2.2 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 applicable 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.

2.2 Analysis sets

All screened patients (SCR): The SCR set comprises all patients who were screened.

BE analysis set: All patients randomized to PFS (Abdomen) or AI (Abdomen) treatment arms with PK data during dosing interval starting at Week 8. Patients will be grouped by the randomized treatment. Major deviation from the randomized treatment as defined in [Table 5-5](#) and [5.6](#) will result in exclusion of patients from the primary analysis.

PK analysis set: All patients randomized to PFS (Abdomen) or PFS (Thigh) or AI (Abdomen) or AI (Thigh) treatment arms with PK data during dose administrations. Patients will be grouped by the randomized treatment.

Safety set: All patients randomized and have taken at least one dose of study drug. Patients will be grouped by the actual treatment received. If patients received study treatment different from the randomized treatment accidentally during the study, they will be analyzed according to the treatment to which they were exposed longer in duration.

2.2.1 Subgroup of interest

None specified for the purpose of clinical study report.

2.3 Patient disposition, demographics and other baseline characteristics

Patient disposition, demographics, MS disease history, [REDACTED], and MS medication history will all be summarized by treatment group based on the safety set unless specified otherwise.

2.3.1 Patient disposition

The number and percentage of patients who completed the study or prematurely discontinued study will be presented, along with the primary reason for discontinuation. Data collected on the End of Study Disposition CRF page will be used to summarize this information.

The number and percentage of patients in each analysis set will be presented. Protocol deviations will be summarized by deviation categories.

Patients exclusion from BE analysis set will be listed for all patients with reasons for exclusion (i.e. including both protocol and non-protocol deviations).

2.3.2 Background and demographic characteristics

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

Derived baseline height, body weight and BMI will be presented. These variables will be summarized 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 baseline characteristics, MS disease history and MS medication history will be summarized.

MS baseline characteristics include baseline EDSS, [REDACTED]

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

Duration of MS since diagnosis (years) will be derived [(first dose date – MS diagnosis start date + 1)/365.25]; duration of MS since first symptom (years) will be derived as [(first dose date – first MS symptom date + 1)/365.25]; time since onset of SPMS (years) will be derived as [(first dose date – conversion to SPMS date + 1)/365.25]; and time since onset of most recent relapse (months) will be derived as [(first dose date – most recent relapse onset date + 1)/(365.25/12)]. In these calculations, partial dates if any will be imputed according to the rules specified in [Section 5.1.3.3](#).

MS medication history of previous disease-modifying drugs (coded by WHO drug dictionary) will be summarized by preferred term (PT). The number and proportion of treatment-naïve 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. Any condition entered on the Medical History (MH) CRF will be coded using the MedDRA dictionary. The medical history will be summarized by primary system organ class (SOC) and preferred term (PT).

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

All analyses in this section will be performed on the Safety set.

2.4.1 Study treatment

Patients are expected to take a total of 6 injections at Day 1, Day 7, Day 14, Day 28 (Week 4), Week 8 and Week 12. The number of injections actually taken will be summarized descriptively by treatment group.

Duration of exposure to study drug will be calculated as (last injection date – first injection date + 31 – $\sum [(j+1)^{\text{th}}$ 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 will be summarized descriptively by treatment group and duration category (i.e., number of patients exposed to study drug for at least 4 weeks, 8 weeks, and 12 weeks will be provided). Descriptive statistics of duration in days will also be provided by treatment group.

For each treatment group, the number of patient-years is calculated as (the sum of the number of days of exposure for all patients in the group)/365.25 and will be summarized.

Time at risk is defined as the number of days spent in the study, from first to last administration of study drug, plus the safety data cut-off of 100 days. Time at risk corresponds to the time period used for adverse event reporting on the safety set. If the corresponding last day of time at risk for AE is after the database lock date, then it will be truncated by the database lock date. Time at risk will be summarized in a similar way to duration of exposure to study drug.

2.4.2 Prior, concomitant and post therapies

2.4.2.1 Concomitant medication

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

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

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

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

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

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 medication data set. Injection related premedication will also be summarized separately for each injection as well as cumulatively for all injections.

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

The rest of the injection specific summaries or cumulatively summaries will be reported similarly.

2.4.2.4 Previous MS disease modifying treatment

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

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

The primary variables are pharmacokinetic endpoints, namely AUC_{tau} and C_{max} calculated from PK concentration data collected in the dosing interval after Week 8 dose administration in accordance with the assessment schedule.

All completed subjects in the BE analysis set (as defined in [Section 2.2](#)) will be included in the primary 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 potentially flagged for exclusion in data presentations and calculations. If values are missing

during the dosing interval after Week 8 dose administration having an impact to the validity of the PK assessment, the pharmacokinetic parameters of the affected patient may be excluded from the BE analysis. Furthermore, concentrations will be flagged and indicated in the data listing for exclusion from the BE analysis in case one or more doses were missed up to and including the Week 8 dose administration, which will also lead to exclusion of the pharmacokinetic parameters of the patient from the BE analysis. Pharmacokinetic parameters, expressed either as mean, SD, and CV, with any geometric means indicated, or as median and range of values, will be determined using non-compartmental method(s) with Phoenix WinNonlin (Version 6.2 or higher).

2.5.2 Statistical hypothesis, model, and method of analysis

To address the primary objective of testing bioequivalence between PFS and AI, the primary analysis involves the two groups (PFS (abdomen) and AI (abdomen)). In the following, the PFS (abdomen) group will be referred to as the Reference (or R) group and the AI (abdomen) group as the Test group (or T).

The null hypothesis is that “Mean difference in $\ln(\text{AUC}_{\text{tau}})$ and/or $\ln(\text{C}_{\text{max}})$ greater than allowed-difference between these 2 groups” ($H_0: |\mu_T - \mu_R| > \Delta$). The alternative hypothesis is that “Mean difference in $\ln(\text{AUC}_{\text{tau}})$ and $\ln(\text{C}_{\text{max}})$ less than allowed-difference between these 2 groups” ($H_a: |\mu_T - \mu_R| \leq \Delta$). \ln refers to the natural log function. The testing procedure is described below.

As the testing for Average Bioequivalence (ABE) will be based on a between-groups comparison, the variabilities of the R and T groups are expected to be high, with a coefficient of variation (CV) greater than 0.3. Hence, the FDA recommended, reference-scaled ABE (RSABE) bioequivalence approach for highly variable drugs is proposed.

As there is no FDA guidance for using RSABE in a parallel groups design, the current guidance for cross-over trials (see [\[Draft Guidance on Bioequivalence, 2001\]](#), [\[Draft Guidance on Progesterone, 2011\]](#)), has been modified for application in a parallel groups design.

The between-subject variability for the R group will take the place of the within-subject variability for R.

A mixed scaling approach will be used: (1) if the standard deviation of the R group data (on the log scale) exceeds 0.294, the traditional ABE limits of $\ln(0.8)$ and $\ln(1.25)$ will be scaled by the between-subject variability for the R group, (2) otherwise the standard TOST (two one-sided tests) approach for (unscaled) ABE will be used. The regulatory constant used in the linearised criterion for the RSABE approach will be set to $\sigma_0 = 0.25$ (as in the recommended RSABE approach for cross-over trials).

The steps in the analysis will therefore be:

1. Calculate s_R the standard deviation of the R group subjects' data on the log-scale (for AUC_{tau} or C_{max}).
2. If $s_R < 0.294$ then apply the standard ABE criteria, i.e., determine if the 90% confidence interval for the mean difference between T and R on the log-scale, $(\mu_T - \mu_R)$, lies within $[-\ln(1.25), \ln(1.25)]$.

3. If $s_R \geq 0.294$ then apply the reference scaled ABE criteria, i.e., determine if, $-\theta_s \leq \frac{(\mu_T - \mu_R)}{s_R} \leq \theta_s$ where $\theta_s = \frac{\ln(1.25)}{\sigma_0}$, and $\sigma_0 = 0.25$. This is done by calculating an approximate 95% upper confidence bound for the linearised criterion, $(\mu_T - \mu_R)^2 - \theta_s^2 \sigma_R^2$. If this upper bound is less than or equal to zero and the point estimate of the T/R geometric mean ratio (GMR) falls within (0.8, 1.25), then ABE is declared (i.e., the null hypothesis is rejected).

Testing will be performed as above for AUCtau and Cmax separately on the BE analysis set.

2.5.3 Handling of missing values/censoring/discontinuations

Missing data will not be imputed in general for any analyses. Only patients with non-missing data will be included in the relevant analyses.

2.5.4 Supportive analyses

No additional analysis is planned for the primary objective.

2.6 Analysis of the key secondary objective

There is no key secondary objective.

2.7 Analysis of secondary objective(s)

2.7.1 Secondary endpoints

Secondary endpoints include:

- PK endpoints (i.e., concentration by time point, AUCtau, and Cmax at week 8 dosing interval)
- Positive ADA by time point

2.7.2 Statistical hypothesis, model, and method of analysis

Analysis of secondary endpoints include:

- Summary statistics of concentration by time point will be provided for each of the four treatment groups on the PK analysis set. Descriptive summary will also be provided for AUCtau and Cmax at week 8 dosing interval.
- Proportion of patients with positive ADA will be provided by time point and overall for each of the four treatment groups on the safety set. The proportion will be based on patients with non-missing ADA results at the evaluation time point. A listing by patient will also be provided.

2.7.3 Handling of missing values/censoring/discontinuations

Not applicable.

2.8 Safety analyses

Safety analyses will be conducted using the safety (SAF) set. Patients will be grouped by the actual treatment received. If patients received study treatment different from the randomized treatment accidentally during the study, they will be analyzed according to the treatment to which they were exposed longer in duration. Unless explicitly stated otherwise, only data up to and including the safety cut-off of 100 days after last administration of study drug will be included in the analysis and data beyond this time point for a given patient will be excluded from the safety analysis. The safety cut-off of 100 days (5 x 20 days) takes the long half-life of the investigational drug into account.

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)

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

Except for serious TEAEs and death, only TEAEs up to and including safety cut-off of 100 days after last administration of study drug will be included in the analyses. All serious TEAEs and death will be included, regardless of safety cut-off.

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

The number and percentage of patients reporting any TEAEs (referred to as incidence of any TEAEs later) will be summarized by primary SOC, preferred term and treatment. Separate summaries will be provided for serious TEAEs, drug related TEAEs, TEAEs leading to permanent discontinuation of study drug and most common TEAEs ($\geq 2\%$ in any of the treatment groups). Additionally, incidence of any TEAEs will also be summarized by SOC, preferred term, and maximum CTCAE grade. Missing CTCAE grade will not be imputed.

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

All AEs will be presented in listings.

2.8.1.1 Adverse events of special interest / grouping of AEs

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

2.8.1.1.1 Injection reaction related AEs

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

Additionally, incidence of injection site reaction AEs and injection systemic reaction AEs will be reported separately for each injection.

For summaries of injection systemic reaction AEs specified in this section, reaction/symptom start date and time will be compared with the injection date and time. Only reactions/symptoms within 24 hours after injections will be included (i.e., time to onset of reaction \leq 24 hours). The time to onset of reaction will be derived as (reaction start date/time – injection date/time).

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 for each injection as well as 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.

- 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 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 as well as 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 numbers (injections 1, 2, 3, 4, 5, 6 etc.).

For the first 3 injections, additional summaries will be provided by category of injection related premedication. 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 injection sequence number 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.

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.

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 Other analyses

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment emergent adverse events which are not serious adverse events with an incidence greater than 5% and on treatment emergent serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

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

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

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

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

2.8.2 Deaths

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

2.8.3 Laboratory data

Data summaries will be provided in SI units. The summary of laboratory evaluations will be presented for three groups of laboratory tests: Hematology, Chemistry and Urinalysis. On presenting summary statistics, laboratory data will be grouped and displayed in an alphabetical order within the Hematology and Chemistry groups and subgroups. Refer to [Section 5.3.1](#) for subgroup definitions.

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

$$\text{change from baseline} = \text{post baseline value} - \text{baseline value}$$

In addition, shift tables will be provided for all parameters to compare a patient's baseline laboratory evaluation relative to the post-baseline values. For the shift tables, the grade level based on CTC grade (as defined by CTCAE as listed in [Section 5.3.3](#)) will be used to evaluate whether a particular laboratory test value was Grade 0, 1, 2, 3, or 4 relative to whether or not the baseline value was Grade 0, 1, 2, 3 or 4. These summaries will be presented by laboratory test and treatment group. Shift table will also be provided for urinalysis results to compare baseline to post-baseline extreme values (negative, +, 2+, 3+, or 4+).

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

Number of patients with newly occurring liver enzymes abnormalities will be summarized. Newly occurring liver enzymes abnormalities are defined in [Section 5.3.2](#).

Liver function tests 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 CTC 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.

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

2.8.3.1 Serology at screening

Collected data of laboratory serology to determine patient's eligibility includes parameters with respect to hepatitis and HIV viruses. Parameters with respect to hepatitis include 1) anti-hepatitis A virus IgM; 2) hepatitis B surface antigen and anti-hepatitis B core antigen IgM/IgG; 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 (refer to as B-cell counts), total IgG, total IgM, [REDACTED]

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

[REDACTED]

[REDACTED]

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 (i.e. equal to or less than 80% of the LLN) and a notably low IgM level is defined as a level 10% below the LLN (i.e. equal to or less than 90% of the LLN).

2.8.4 Other safety data

2.8.4.1 ECG data

ECG data will be collected at screening/baseline visit and EOS visit. Clinically significant findings from ECG evaluations will be reported as AEs and included in the analysis of AEs. ECG parameters include max heart rate, mean PR duration, mean QT duration, mean QRS duration, and QT corrected using Fridericia's correction formula (all as collected on the ECG CRF). Descriptive statistics of each ECG parameter will be provided by treatment group for baseline and the EOS visits.

The number and percentage of patients meeting the criteria defined in [Table 2-7](#) will be provided for each criterion by treatment group for baseline and the EOS visits.

Table 2-7 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 include sitting systolic and diastolic blood pressures, sitting pulse, body temperature, height and body weight. Three sitting measurements of blood pressure (SBP and DBP) and pulse will be taken at each vital sign assessment.

For post-baseline assessments, the blood pressure and pulse values will be the average of the non-missing values of the 3 measurements. Derivation of baselines for blood pressure and pulse are provided in [Section 2.1.1](#).

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

Change from baseline to EOS visit in vital sign measurements will be summarized using descriptive summary statistics (mean, median, standard deviation, min, max). 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 and will be calculated as:

$$\text{change from baseline} = \text{post-baseline value} - \text{baseline value}$$

For vital signs data collected on Day 1, Day 7, Day 14, Week 4, and Week 8 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.

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](#).

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

2.8.5 Suicidality ideation and behavior

The Columbia Suicide Severity Rating Scale (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 phone interview because, e.g. the subject was hospitalized and unable to conduct the interview or the subject refused to conduct the interview/withdrew from the study and external information on suicidal ideation and behavior (SIB) is required. In such cases, SIB information will still be collected from external parties (spouse, caregiver, nurse, investigator, etc.) through means of this CRF page. Further, for deaths due to suicide, the site should fill out the Supplemental Data CRF (“completed suicide” tickbox) to ensure accurate reporting of such cases. When reporting the SIB data, data from both sources (IVR eC-SSRS and Supplemental CRF) will be used in a pooled manner and no distinction will be made between the two.

Table 2-8 Standard SIB events as categorized by C-SSRS

Category number	C-SSRS category
Suicidal Ideation	
1	Wish to be dead
2	Non-specific active suicidal thoughts
3	Active suicidal ideation with any methods (not plan) without intent to act
4	Active suicidal ideation with some intent to act, without specific plan
5	Active suicidal ideation with specific plan and intent
Suicidal behavior	
6	Preparatory acts or behavior
7	Aborted attempt
8	Interrupted attempt
9	Actual attempt
10	Completed suicide
Self-injurious behavior, without suicidal intent	
11	Non-suicidal self-injurious behavior

Definition of ‘all prior history’ and ‘recent history’

SIB will be collected once before randomization, either at screening or at baseline visits. 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 *pre-defined period (i.e., past 6 months or 24 months)* assessment of the screening or baseline visit. If there are multiple assessments prior to first dose, the worst case value will be used for *All prior history*, and *recent history* respectively. Worst case is defined by answer ‘yes’ to the SIB category.

Data summaries

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 14 events will be included in the summary table:

- Each of the 11 categories listed in [Table 2-8](#), 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](#)):

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).

2.8.6 Safety evaluation during the Safety follow-up

Safety data collected after last administration of study drug includes adverse events, vital signs, routine laboratory parameters, laboratory assessments to measure total IgG, total IgM, B-cell repletion, and eCSSRS. No safety cutoff date will be applied in the analyses defined in this section. As stated in [Section 2.1](#), the Week 12 Registration CSR will contain only partial data

collected from the Safety FU. A complete analysis of the post-treatment safety follow-up will be provided in the Final CSR when all patients have completed the Safety FU.

2.8.6.1 Analysis in the Week 12 registration CSR

In CSR, due to the small number of patients expected to have data and only partial data after study drug discontinuation, such data will only be included in respective listings as applicable.

2.8.6.2 Analysis in the Final CSR

The number and percentage of patients with at least one TEAEs that started after the date of last administration of study drug will be reported by SOC, preferred term, and treatment group. The subset of patients in SAF who had data reported after the date of last administration of study drug will be included in the analysis and the number of patients in this subset will be the denominator in calculating the percentage.

The vital signs data collected after study drug discontinuation will be summarized as summary statistics of the vital sign measures and of the change from baseline in the vital sign measures by treatment group for each visit-window after study drug discontinuation (as defined in [Section 2.1.2.1](#)). The analysis will be limited to the subset of patients in SAF who either completed the treatment period on study drug and do not enter the extension study or prematurely discontinued study treatment.

The B-cell counts and its change from baseline values will be summarized by treatment group for each visit-window after study drug discontinuation. The analysis will be limited to the subset of patients in SAF who had B-cell count data after the date of last administration of study drug and either completed the treatment period on study drug and do not enter the extension study or prematurely discontinued study treatment; the number of patients in this subset will be the denominator in calculating the percentage.

2.9 Pharmacokinetic endpoints

Analysis of PK endpoints are included in primary and secondary analysis sections ([Section 2.5](#) and [Section 2.7](#)) as they are considered primary and secondary endpoints in this study.

2.10 PD and PK/PD analyses

The arithmetic and geometric mean of PK concentration at each time point will be calculated for each treatment group. Graphic presentation will also be provided by treatment group.

2.11 Patient-reported outcomes

Not applicable for this study.

2.14 Interim analysis

As this is an open-label study with primary objective of pharmacokinetic endpoints and no interim analyses on which statistical comparisons will be made is planned, there is no relevance on blinding or alpha-adjustment.

Periodic interim safety analyses to support regulatory updates and interim reports may be warranted.

An interim analysis will be conducted to assess the variability of data as measured by coefficient of variation (CV) when approximately 36 patients total randomized in the PFS (abdomen) and AI (abdomen) treatment groups have completed Week 12. The purpose of this interim analysis is to provide an opportunity to increase the sample size so that sufficient power for the bioequivalence testing can still be achieved in case the estimated CV is larger than the assumed value of 85% at design stage. If deemed necessary, the sample size for the bioequivalence testing can be increased from 120 to a maximum of 250 completed patients.

3 Sample size calculation

The grand total sample size of this study is estimated by sum of the estimated sample size in all 4 treatment groups.

Section 3.1 provides sample size calculation for groups 1 and 2, which are used to address our primary objective. This sample size may be increased by the results of the interim analysis.

Section 3.2 provides sample size calculation for groups 3 and 4. This sample size will not be impacted by the results of the interim analysis.

3.1 Sample size calculation for PFS (abdomen) and AI (abdomen)

A total of 120 patients (60 per arm) will be required to achieve 90% power in the testing of bioequivalence between these two groups assuming their geometric mean ratio (GMR) = 1 and the coefficient of variation (CV) = 85%, which are considered reasonable and conservative assumptions according to previous experience with the variability of drug concentration pharmacokinetic parameters. To account for 3% dropout, a total of 124 patients (62 per arm)

will be randomized. The dropout rate assumption is based on data observed in the on-going phase III studies.

Due to limited PK data in the existing databases, CV can't be assessed accurately. Therefore, an interim analysis is planned to re-assess the CV of C_{max} and AUC_{tau}. Details are as described in [Section 2.14](#). If deemed necessary, the sample size for the BE testing can be increased to a maximum of 250 (125 per arm), in which case, the total number of patients to be randomized will be 258 (129 per arm) accounting for 3% dropout. The maximum sample size will provide approximately 80% power if the true CV is as high as 240%.

The sample size calculation is based on simulation for the testing procedure via a mixed scaling approach as described in [Section 2.5.2](#). Specifically, for a given CV on the natural scale, which is assumed to be the same for the two groups, and an assumed value of the GMR, 10,000 parallel groups trials with a given total sample size n are simulated and the proportion of trials that lead to a decision to declare ABE are recorded. If this value of n does not give a power greater than or equal to 0.9 then the n is increased in steps of 2, until a power of 0.9 is first achieved or exceeded. This n is then taken as the sample size that gives 90% power for the chosen values of CV and GMR. The estimated sample sizes for a range of values of CV and three values assumed for the GMR are given in below table.

Total sample sizes to achieve 90% power for testing for RSABE in a two-group parallel groups design

(with $\sigma_0 = 0.25$ and $\theta = \left(\frac{\ln(1.25)}{\sigma_0}\right)$)

CV	GMR=0.95	GMR=1.00	GMR=1.05
0.30	84	66	82
0.35	78	66	78
0.40	74	66	74
0.45	72	66	72
0.50	74	66	72
0.55	76	68	76
0.60	82	72	82
0.65	92	80	90
0.70	102	88	100
0.75	114	98	112
0.80	126	108	126
0.85	138	120	136

As a comparison, the sample sizes required to achieve a power of 0.9, when the standard test (TOST) for ABE is used with a parallel groups design, are given in below table.

Total sample sizes to achieve 90% power for testing for standard ABE in a two-group parallel groups design with equivalence limits $(-\ln(1.25), \ln(1.25))$

CV	GMR=0.95	GMR=1.00	GMR=1.05
0.30	102	78	100
0.35	138	102	134
0.40	176	132	170
0.45	218	162	212
0.50	262	196	256
0.55	310	232	302
0.60	360	270	352
0.65	414	308	402
0.70	468	350	454
0.75	522	390	508
0.80	578	432	564
0.85	636	476	620

For true CV values larger than 0.30, the Type I error rate is controlled at true mean difference values equal to the FDA implied limits $[\pm (\log(1.25)/0.25) * \sigma]$ on the log-transformed scale (see [Draft Guidance on Bioequivalence, 2001], [Draft Guidance on Progesterone, 2011]), where $CV = \sqrt{e^{\sigma^2} - 1}$.

3.2 Sample size calculation for PFS (thigh) and AI (thigh)

Sample size requirement is based on a conventional size of studies for an evaluation of pharmacokinetic endpoints in treatment groups with different administration sites (i.e., comparing PFS (abdomen) vs. PFS (thigh) or comparing AI (abdomen) vs. AI (thigh)). No formal statistical testing is planned.

A total of 24 patients (12 per arm) will be required for PFS (thigh) and AI (thigh) groups. This is in alignment with sample size often applied to standard pharmacokinetic studies.

For an estimation of mean difference in the two groups of different administration sites (abdomen (n=60) vs. thigh (n=12)), the width of 90% CI will be 0.78 assuming the CV is 85%.

To account for 3% dropout, a total of 26 patients (13 per arm) will be randomized.

4 Change to protocol specified analyses

Plots of median instead of mean B-cell counts by treatment group against time point, for consistency with outputs for Phase III studies.

The current study protocol (version 00) stated the use of CTCAE version 4.03. As the latest CTCAE version 5 is available, Section 5.3.3 includes CTCAE grade definitions based on version 5.

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 injection date.

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 programming datasets specifications (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 programming datasets specifications (PDS) document).

5.1.3.1 Prior therapies date imputation

Same as above.

5.1.3.2 Post therapies date imputation

Same as above.

5.1.3.3 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 conversion to SPMS date, and the most recent relapse onset date via below imputation rules.

- If the year is missing or impossible (e.g. 12-Jan-1911), then the date will be imputed as missing.
- If the year is not missing and possible, but the month is impossible or missing (e.g. 17-XXX-2010), then the year will be kept and date will be imputed as July 1st (e.g., 1-July-2010).
- If the year and the month are not missing and possible, but the day is impossible or missing (e.g. 31-FEB-2009), then the year and month will be kept, and date will be imputed as 15th (e.g., 15-FEB-2009).

The imputed dates should be prior to the screening visit date. That is, if imputed dates are on or after the screening visit date, the dates will be imputed to be one day before the screening visit date.

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).

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 (e)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 collected at baseline will be used as the study is only 3 months in duration.

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

- $\text{mg/dL} = 88.4 \mu\text{mol/L}$ (e.g., creatinine = 2.0 mg/dL = 176.8 $\mu\text{mol/L}$).

Table 5-1 Creatinine clearance calculation

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

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

5.3.1 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	<p>Hematology</p> <p>Red Blood Cells</p> <p>White Blood Cell Differential</p> <p>B-cells</p> <p>Other</p>	<p>Hematocrit [%] Hemoglobin [g/L] Platelets [10E9/L] Red cell count [10E12/L]</p> <p>Absolute Basophils [10E9/L] Absolute Eosinophils [10E9/L] Absolute Lymphocytes [10E9/L] Absolute Monocytes [10E9/L] Absolute Neutrophils [10E9/L] Basophils [%] Eosinophils [%] Lymphocytes [%] Monocytes [%] Neutrophils [%] White Cell Count [10E9/L]</p> <p>CD19+ B-cell counts[cells/μL]</p> <p>Prothrombin Time (s) International Normalized Ratio (INR)</p>
2	<p>Chemistry</p> <p>Renal Function</p> <p>Liver Function Tests</p> <p>Other Enzymes</p> <p>Lipids</p>	<p>Creatinine [umol/L] Blood urea nitrogen [mmol/L]</p> <p>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]</p> <p>Amylase [U/L]</p> <p>Cholesterol HDL [mmol/L] Cholesterol LDL [mmol/L] Triglycerides [mmol/L] Total Cholesterol [mmol/L]</p>

Order	Laboratory Group Subgroups	Tests [SI unit]
	Other Electrolytes / Metabolism Tests Immunoglobulin	Random glucose [mmol/L] C-Reactive protein (CRP) [mg/L] Bicarbonate [mmol/L] Calcium [mmol/L] Chloride [mmol/L] Magnesium [mmol/L] Phosphate [mmol/L] Potassium [mmol/L] Sodium [mmol/L] Total IgG [g/L] Total IgM [g/L]
3	Urinalysis	Blood Glucose Specific gravity 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
- AST > 3, 5, 8, 10, 20x ULN
- ALT or AST > 3, 5, 8, 10, 20x ULN
- ALT or AST > 3x ULN & TBIL > 1.5x ULN
- ALT or AST > 3x ULN & TBIL > 2x ULN
- ALP > 1.5, 2, 5x ULN
- TBIL > 1, 1.5, 2x ULN
- ALP > 3, 5x ULN & TBL > 2x ULN
- ALT or AST > 3x ULN & TBIL > 2x ULN & ALP ≤ 2x ULN

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

The “events” are defined in the Novartis safety guideline on hepatotoxicity ([Novartis: Philippe Close 2011](#)), section: Safety parameters for special liver event analyses.

5.3.3 CTCAE grades for laboratory parameters

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

		Grade			
Abnormality	Lab parameter	1	2	3	4
Hematology					
Anemia	Hemoglobin (g/L)	<LLN - 100 g/L	<100 - 80 g/L	<80 g/L transfusion indicated	
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 x 10 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 x 10 ⁹ /L	<1.5 - 1.0 x 10 ⁹ /L	<1.0 - 0.5 x 10 ⁹ /L	<0.5 x 10 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					
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

		Grade			
Abnormality	Lab parameter	1	2	3	4
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 ULN and 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
Metabolism					
Hyperglycemia	Fasting glucose (mmol/L)	>ULN - 8.9 mmol/L	>8.9 - 13.9 mmol/L	>13.9 - 27.8 mmol/L	>27.8 mmol/L
<p>*Highest grade will be assigned if more than one grade criteria are met for an observed value of a patient.</p> <p>**CTCAE 5.0 definition. For reporting in the CSR, this definition will not be used for this parameter, but the grade definition per CTCAE 4.03 will be used instead (see next row).</p> <p>***CTCAE 4.03 definition. For reporting in CSR, the grade definition per CTCAE 4.03 will be used for this parameter only.</p>					

5.4 Clinical notable vital signs

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

Table 5-4 Vital signs clinically notable values

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

5.5 Statistical models

5.5.1 Primary analysis

Details have been provided in [Section 2.5.2](#).

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 5-5](#) and [Table 5-6](#).

Table 5-5 Protocol deviations that cause patients to be excluded

Deviation ID	Description of Deviation	Exclusion in Analysis sets
	Informed consent obtained = 'No' or missing[#]	Excluded from all analysis sets
TRT04	Administration of study drug to wrong site of body at week 8	Excluded from BE analysis set
TRT05	Administration of study drug using incorrect device at week 8	Excluded from BE analysis set
TRT06	Patient missed injection at any visit in the treatment phase	Excluded from BE analysis set

[#] No deviation ID was assigned in the database to this event

Table 5-6 Patient Classification

Analysis Set	PD ID that cause patients to be excluded	Non-PD criteria that cause patients to be excluded
SCR	NA	NA

Analysis Set	PD ID that cause patients to be excluded	Non-PD criteria that cause patients to be excluded
BE	Informed consent obtained = 'No' or missing, TRT04; TRT05, TRT06	Not assigned a valid randomization number
PK	Informed consent obtained = 'No' or missing	Not assigned a valid randomization number
SAF	Informed consent obtained = 'No' or missing	No study drug taken

6 Reference

Cockcroft DW, Gault MJ (1976) Prediction of creatinine clearance from serum creatinine. *Nephron*; 16:31-41

FDA Draft Guidance on Progesterone (2011)

https://www.accessdata.fda.gov/drugsatfda_docs/psg/Progesterone_caps_19781_RC02-11.pdf

FDA Guidance for Industry (2001) Statistical Approaches to Establishing Bioequivalence. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/statistical-approaches-establishing-bioequivalence>

Garwood F. (1936) Fiducial Limits for the Poisson Distribution. *Biometrika* 28, 437-442.

Keene ON, Jones MRK, Lane PW, Anderson J. (2007) Analysis of exacerbation rates in asthma and chronic obstructive pulmonary disease: example from the TRISTAN study. *Pharmaceutical Statistics*; 6: 89-97

Nilsson M. et al. (2013) Columbia-Suicide Severity Rating Scale. Scoring and data analysis guide.

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

Sahai H, Khurshid A (1993). Confidence intervals for the ratio of two Poisson means. *The Mathematical Scientist*, 18, 43–50.

Ulm K (1990). A simple method to calculate the confidence interval of a standardized mortality ratio. *American Journal of Epidemiology* 1990;131(2):373-375.

Xu, Z, Wang Q, Zhuang Y, et al Subcutaneous Bioavailability of Golimumab at 3 Different Injection Sites in Healthy Subjects. *The Journal of Clinical Pharmacology*, 50: 276–284. doi:10.1177/0091270009340782