STATISTICAL ANALYSIS PLAN

Study: MG0002

Product: UCB7665

A MULTICENTER, RANDOMIZED, INVESTIGATOR- AND SUBJECT-BLIND, PLACEBO-CONTROLLED, TREATMENT SEQUENCE STUDY EVALUATING THE SAFETY, TOLERABILITY, AND EFFICACY OF UCB7665 IN SUBJECTS WITH MODERATE TO SEVERE MYASTHENIA GRAVIS

SAP/Amendment Number	Date
Final SAP	20 Dec 2017
Final SAP amendment 1	20 Jun 2018

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LIST OF ABBREVIATIONS

ACP	above cut-point
[redacted]	[redacted]
ADaM	Analysis Data Model
AE	adverse event
ALC	absolute lymphocyte count
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANT	absolute neutrophil count
aPTT	activated partial thromboplastin time
ALQ	above the limit of quantification
ANCOVA	analysis of covariance
[redacted]	[redacted]
[redacted]	[redacted]
AST	aspartate aminotransferase
BAFF	B-cell activating factor
BCP	below cut-point
BLQ	below the limit of quantification
BMI	body mass index
BUN	blood urea nitrogen
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CP	confirmed positive
CRO	Contract Research Organization

CSF	cerebral spinal fluid
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DEM	Data Evaluation Meeting
ES	Enrolled Set
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full Analysis Set
FDA	Food and Drug Administration
geoCV	geometric coefficient of variation
geoMean	geometric mean
GGT	gamma-glutamyltransferase
GI	gastrointestinal
HbA1c	glycosylated hemoglobin
HBsAG	hepatitis B surface Antigen
HCV Ab	hepatitis C virus antibody
HDL	high density lipoprotein
HIV	human immunodeficiency virus
HLT	high level term
hsCRP	high sensitivity C-reactive protein
ICH	International Council for Harmonisation
Ig	immunoglobulin

IgA	immunoglobulin A
IgE	immunoglobulin E
IgG	immunoglobulin G
IgM	immunoglobulin M
IGRA	interferon-gamma release assay
IMP	investigational medicinal product
IPD	important protocol deviation
IPI	interpotential interval
LDH	low density lipoprotein
LLOQ	lower limit of quantification
LOCF	last observation carried forward
LP	lumbar puncture
LS	least squares
MCD	mean consecutive difference
MedDRA	Medical Dictionary for Regulatory Activities
MG	myasthenia gravis
MGADL	myasthenia gravis-Activities of Daily Living
MGFA	Myasthenia Gravis Foundation of America
MGII	Myasthenia Gravis Impairment Index
MMRM	mixed model repeated measures
MRI	magnetic resonance imaging
NCP	not confirmed positive
PCS	potentially clinically significant
PD	pharmacodynamic(s)

PDILI	potential drug-induced liver injury
PD-PPS	Pharmacodynamic Per-Protocol-Set
PEOT	Premature End of Treatment Visit
PK	pharmacokinetic(s)
PK-PPS	Pharmacokinetic Per Protocol Set
PPS	Per Protocol Set
PRO	Patient Reported Outcome
PT	preferred term
QMG	quantitative myasthenia gravis
QTcB	QT corrected for heart rate using Bazett's formula
QTcF	QT corrected for heart rate using Fridericia's formula
RBC	red blood cell
RS	Randomized Set
SAP	Statistical Analysis Plan
sc	subcutaneous
SD	Standard Deviation
SFEMG	single fiber electromyography
SS	Safety Set
SOC	system organ class
TFL	Tables, figures and listings
TEAE	treatment-emergent adverse event
TEMA	treatment-emergent markedly abnormal
ULN	upper limit of normal
WBC	white blood cell

WHODD	World Health Organization Drug Dictionary

LIST OF TABLES

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide all information that is necessary to perform the required statistical analysis of MG0002. It also defines the summary tables, figures and listings (TFLs) to be included in the final Clinical Study Report (CSR) according to the protocol.

This SAP is based upon, and assumes familiarity, with the following study documents:

1. Final Protocol: 21 Oct 2016
2. Protocol Amendment 1: 07 Feb 2017
3. Protocol Amendment 2: 15 Sep 2017

Unless specified below, the study will be analyzed as described in the most recent version of the protocol/amendment (European Union Drug Regulating Authorities Clinical Trials [EudraCT]-Number: 2016-002698-36).

If a future protocol amendment necessitates a substantial change to the statistical analysis of the study data, this SAP will be amended accordingly. If, after database lock, additional analyses are required to supplement the planned analyses described in this SAP, those unplanned analyses will not be described in an amended SAP but they will be described in a separate statistical analysis plan. However, if analysis definitions have to be modified or updated, a SAP amendment will be required. The content of this SAP is compatible with the International Council for Harmonisation (ICH)/ Food and Drug Administration (FDA) E9 Guidance documents. UCB is the sponsor and PAREXEL International is the Contract Research Organization (CRO) for this study.

2 PROTOCOL SUMMARY

2.1 Study objectives

2.1.1 Primary objective

The primary objective of the study is:

- To evaluate the clinical efficacy of UCB7665 as a chronic-intermittent treatment in subjects with generalized myasthenia gravis (MG) who are classified as moderate to severe

2.1.2 Secondary objectives

The secondary objectives of the study are:

- To gather data for future study planning, whether for chronic-intermittent treatment or a longer therapy option by evaluating the general concept that UCB7665 has a clinical effect in patients with generalized MG
- To evaluate the safety and tolerability of UCB7665 administered by subcutaneous (sc) infusion in subjects with MG
- To assess the effect of UCB7665 as measured by total Immunoglobulin G (IgG) concentrations in serum

2.1.3 Exploratory Objectives

The exploratory objectives are:

- To assess the effect of UCB7665 on MG-specific autoantibodies ([redacted] levels in serum
- To evaluate the effects of UCB7665 on the concentration of IgG subclasses, immunoglobulin M (IgM), immunoglobulin A (IgA), and immunoglobulin E (IgE), and serum and plasma complement levels
- To evaluate the effect of UCB7665 on B-cell activating factor (BAFF) and on cytokines (in all subjects)
- To evaluate the effect of UCB7665 on cytokines in subjects experiencing infusion reactions
- To evaluate the emergence of [redacted] with respect to immunogenicity and Pharmacokinetics/Pharmacodynamics (PK/PD)
- To evaluate the effect of UCB7665 on clinical electrophysiological parameters of neuromuscular transmission in a subset of subjects
- To assess the plasma concentrations of UCB7665 administered by sc infusion
- To evaluate the effects of UCB7665 on blood biomarkers for safety (including, but not limited to [redacted]) only in subjects with severe headache and/or moderate to severe gastrointestinal (GI) disturbance
- The effects of UCB7665 on [redacted] antibodies
- To evaluate peripheral blood biomarkers in relation to disease etiology, progression and treatment outcome
- To evaluate the genomic components of MG to understand the molecular etiology, progression, and treatment of the disease, applicable only for subjects consenting to participate in the optional genomic analyses substudy

2.2 Study variables

2.2.1 Efficacy variables

2.2.1.1 Primary efficacy variable

The primary efficacy variable is:

- Change from Baseline in quantitative myasthenia gravis (QMG) score to Visit 9 (Day 29)

2.2.1.2 Secondary efficacy variables

The secondary efficacy variables are:

- Change from Baseline in MG-Composite score to Visit 9 (Day 29)
- Change from Baseline in myasthenia gravis-Activities of Daily Living (MGADL) score to Visit 9 (Day 29)

2.2.1.3 Other efficacy variables

The other efficacy variables are:

- Value and change from Baseline in QMG at each scheduled assessment during Treatment and Observation Periods
- QMG responder (≥3.0 point improvement from Baseline) at each scheduled assessment during Treatment and Observation Periods
- Value and change from Baseline in MG-Composite score at each scheduled assessment during Treatment and Observation Periods
- MG-Composite responder (≥3.0 point improvement from Baseline) at each scheduled assessment during Treatment and Observation Periods
- Value and change from Baseline in MGADL at each scheduled assessment during Treatment and Observation Periods
- MGADL responder (≥3.0 point improvement from Baseline) at each scheduled assessment during Treatment and Observation Periods
- Myasthenia Gravis Foundation of America (MGFA) classification at each scheduled assessment during Treatment and Observation Periods
- Value and change from Baseline in MG muscle weakness and fatigability at each scheduled assessment during Treatment and Observation Periods
- Value and change from Baseline in fatigue at each scheduled assessment during Treatment and Observation Periods
- Value and change from Baseline in Myasthenia Gravis Impairment Index (MGII) scores at each scheduled assessment during Treatment and Observation Periods
- Value and change from Baseline in MGII ocular sub-scores at each scheduled assessment during Treatment and Observation Periods
- Value and change from Baseline in MGII generalized domain sub-scores at each scheduled assessment during Treatment and Observation Periods
- Change in the percentage of normal fiber pairs in jitter [single fiber electromyography (SFEMG)] studies from Baseline to Visit 9 for the subjects consenting to this measurement at the participating sites
- Change in mean consecutive difference (MCD) of the interpotential interval (IPI) in jitter (SFEMG) studies from Baseline to Visit 9 for the subjects consenting to this measurement at the participating sites
- A reduction in MCD of ≥9µs in jitter (SFEMG) studies will define clinically meaningful improvement

2.2.2 Other and exploratory variables

2.2.2.1 Safety variables

The safety variables are the following:

- Occurrence of treatment-emergent adverse events (TEAEs)
- Vital sign values and changes from Baseline (systolic and diastolic BP, temperature, pulse rate, respiratory rate, and body weight) at each scheduled assessment during Treatment and Observation Periods
- 12-lead ECG values and change from Baseline at each scheduled assessment during Treatment and Observation Periods
- Laboratory values and changes from Baseline at each scheduled assessment during Treatment and Observation Periods (hematology, clinical chemistry, and urinalysis)
- Change from Baseline in exploratory safety biomarkers (may include but not limited to [redacted]) in subjects with severe headache and/or moderate to severe GI disturbance
- TEAEs leading to withdrawal of investigational medicinal product (IMP)

The clinical safety laboratory tests are detailed in Table 11–1.

2.2.2.2 Pharmacokinetic variable

The PK variable is the following:

- Plasma concentration of UCB7665 at each scheduled assessment during Treatment and Observation Periods

2.2.2.3 Pharmacodynamic variables

The PD variables are the following:

- Minimum value and maximum (absolute and percentage) decrease from Baseline in total serum IgG concentration during the study
- Value and change (absolute and percentage) from Baseline in total serum IgG concentrations at each scheduled assessment during Treatment and Observation Periods
- Value and change (absolute and percentage) from Baseline in serum IgG subclass concentrations at each scheduled assessment during Treatment and Observation Periods
- Change in MG-specific autoantibody [redacted] levels in serum from Baseline at each scheduled assessment during Treatment and Observation Periods

2.2.2.4 Immunological variables

The other immunological variables are the following:

- Change from Baseline in serum immunoglobulin (Ig) concentrations (total IgA, IgE, and IgM) at each scheduled assessment during Treatment and Observation Periods
- Change from Baseline in serum complement levels (C3 and C4) and plasma complement levels (C3a and C5a) predose at Visit 2 and 4 hours postdose at each scheduled assessment during Treatment and Observation Periods
- [redacted] ([redacted]) status (negative or confirmed positive) and either change from Baseline in relative mass units at each scheduled assessment during Treatment and Observation Periods or titre for those confirmed positive

- Change from Baseline in serum BAFF levels
- Change from Baseline in cytokines pre- and postdose (postdose - in subjects experiencing infusion reactions) at assessments during Treatment and Observation Periods
- Change from Baseline in [redacted] antibodies
- Change from Baseline in exploratory biomarkers relating to mechanism of action, disease activity, treatment response, and clinical outcome

2.3 Study design and conduct

This is a Phase 2a, multicenter, randomized, investigator- and subject-blind, placebo controlled, 2-arm, repeat dose, treatment sequence study evaluating the safety and efficacy of UCB7665 as a chronic-intermittent treatment for subjects with moderate to severe generalized MG.

Approximately 42 randomized subjects will be enrolled at approximately 30 sites from Europe, United States of America (USA), and Canada to achieve the targeted number of 40 evaluable subjects.

The maximum duration of the study per subject is approximately 18 weeks, consisting of a Screening Period (1 to 28 days), Treatment Period (6 weeks), and an Observation Period (8 Weeks).

Screening Period: The purpose of the Screening Period is to evaluate and confirm the subject's eligibility. The Screening Period should not exceed 28 days in total.

Treatment Period: The Treatment Period will consist of Dosing Period 1 followed by Dosing Period 2. Subjects will receive 3 doses of IMP at weekly intervals during each Dosing Period as follows.

- Dosing Period 1 will be 4 weeks, with 2 parallel Treatment Groups (UCB7665 7mg/kg or placebo).
- Dosing Period 2 will be 2 weeks, with 2 parallel Treatment Groups (UCB7665 7mg/kg or UCB7665 4mg/kg).

Prior to receiving an infusion with IMP, subjects will be assessed for efficacy measurements at each visit in the Treatment Period. All safety and efficacy measurements must follow the order specified in the Study Procedures Manual.

Dosing Period 1: Dosing Period 1 will last for approximately 4 weeks (Day 1 to Day 28) and includes Visits 2, 3, 4, 5, 6, 7, and 8. Following completion of the Screening Period, eligible subjects will check-in at the clinic/hospital for the Randomization Visit (Visit 2). Subjects who continue to meet eligibility requirements will be randomized 1:1 to receive 7mg/kg of UCB7665 or placebo, administered by an approximately 30 minute sc infusion at weekly intervals for 3 weeks (Visits 2, 4, and 6) followed by an assessment visit at Week 4 (Visit 8). At Visits 2, 4, and 6 in Dosing Period 1, subjects will be required to remain in the clinic/hospital for at least 4 hours for safety monitoring after the infusion. Subjects may leave the clinic/hospital once the safety monitoring postdose period is over and the investigator or designee has no safety concerns. A follow-up telephone call will be conducted 24 hours postdose to assess the status of the subject (Visits 3, 5, and 7). Subjects will return to the clinic/hospital at Visit 8 for safety and efficacy assessments. The primary efficacy endpoint, change from Baseline in the QMG score, will be

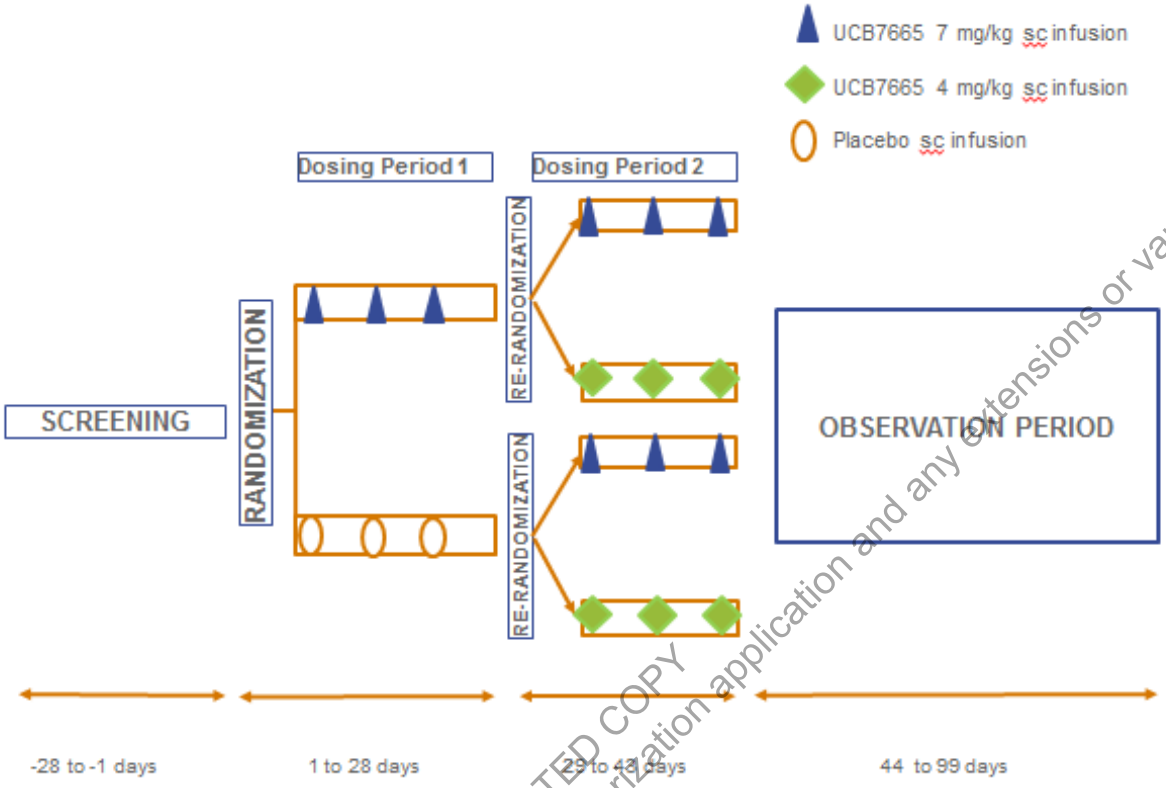
assessed at the beginning of Dosing Period 2 at Visit 9 (Day 29) prior to rerandomization . The efficacy assessments that are performed at Visit 9 will therefore occur 2 weeks after the final dose of study drug in Dosing Period 1.

Dosing Period 2: Dosing Period 2 will last for approximately 2 weeks (Day 29 to Day 43) and includes Visit 9, 10, 11, 12, 13, and 14. Subjects will return to the clinic for Visit 9, 11, and 13 for safety and efficacy assessments. At Visit 9, following the administration of safety and efficacy assessments, subjects initially randomized at Baseline to placebo or to 7mg/kg of UCB7665 will be rerandomized 1:1 to receive either 3 doses of 7mg/kg or 3 doses of 4mg/kg administered by a 30 minute sc infusion at weekly intervals (Visit 9, 11, and 13). The interactive response technology (IRT) will stratify the rerandomization based on the treatment received in Dosing Period 1. At each weekly clinic visit in Dosing Period 2 (Visits 9, 11, and 13), subjects will be required to remain in the clinic/hospital for at least 4 hours safety monitoring postdose period as determined. Subjects may leave the clinic/hospital once the safety monitoring postdose period is over and the investigator or designee has no safety concerns. A follow-up telephone call will be conducted 24 hours post dose to assess the status of the subject (Visits 10, 12, and 14).

Observation Period: All subjects must be followed for 8 weeks after the final dose of IMP is administered. Subjects will return to the clinic for Visits 15, 16, and 18 for efficacy and for safety assessments. Subjects will either return to the clinic/hospital, or, if possible and agreed by investigator and subject, have home visits conducted by certified healthcare professionals, for Visits 17, 19, and 20. The Observation Period begins the day after the final dose of IMP (ie, Visit 13, Day 43); Visit 15 (Day 50) is the first visit in the Observation Period.

Figure 2–1 presents a schematic diagram of the study design.

Figure 2–1: Schematic diagram



2.4 Determination of sample size

The primary efficacy endpoint of this study is change in QMG score from Baseline to Visit 9 (Day 29).

The sample size calculation use a 1-sided [redacted] significance level, an estimate (based on a [redacted] Confidence Interval [CI]) of the Standard Deviation (SD) for change in QMG of [redacted] and an anticipated treatment effect of [redacted] (Zinman et al, 2007).

Assuming a treatment difference of [redacted] points in the mean change from Baseline in QMG at Visit 9 between the placebo and UCB7665 treatment arm with SD equal to [redacted], a sample size of [redacted] subjects ([redacted] for each treatment group) provides >90% power to detect a treatment difference. Further it will be assumed that [redacted] of the randomized subjects cannot be utilized for the Full Analysis Set (FAS) and, hence [redacted] subjects will be randomized.

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

Statistical evaluation will be performed by PAREXEL. Analysis Data will adhere to CDISC (Clinical Data Interchange Standards Consortium) guidance documents for Analysis Data Model (ADaM) and follow their UCB interpretation.

All analyses will be performed using SAS version 9.3 or higher (SAS Institute, Cary, North Carolina, USA). Continuous variables will be summarized by visit (where applicable) including number of subjects (n), mean, SD, median, minimum and maximum. Geometric coefficient of

variation (geoCV), geometric mean (geoMean) and 95% CI for the geoMean will also be presented in the descriptive statistics for the PK and PD concentration data. Categorical variables will be summarized by visit (where applicable) with frequency counts and percentages.

When reporting relative frequencies or other percentage values, the following rules apply:

- For values where all subjects fulfill certain criteria, the percentage value will be displayed as 100
- For values where the absolute frequency is zero, there will be no percentage displayed at all
- All other percentage displays will use 1 decimal place

Percentages displayed based on continuous data (eg, percentage changes from baseline) will be displayed to 1 decimal place.

When reporting descriptive statistics, the following rules will apply in general:

- n will be an integer
- Mean (arithmetic and geometric), SD and median will use 1 decimal place more than the original data
- geoCV will be reported as a percentage to 1 decimal place
- Minimum and maximum will be reported using the same number of decimal places as the original value
- Correlations will use 3 decimal places
- If no subjects have data at a given time point, for example, then only n=0 will be presented. If n<3, then only n, minimum and maximum will be presented. If n=3, then only n, mean, median, minimum and maximum will be presented. The other descriptive statistics will be left blank.

Analyses will be performed by treatment group and for all subjects where stated. The treatment groups for Dosing Period 1 will be as follows and will be displayed as such in the TFLs:

- Placebo
- UCB7665 7mg/kg

For Dosing Period 2 and the Observation Period the following treatment groups will be considered for analysis and will be displayed as such in the TFLs (the first two groups will only be utilized, for observation period, in case patients do not receive any dosing in period 2):

- Placebo
- UCB7665 7mg/kg
- Placebo - UCB7665 7mg/kg
- Placebo - UCB7665 4mg/kg
- UCB7665 7mg/kg - UCB7665 7mg/kg
- UCB7665 7mg/kg - UCB7665 4mg/kg

These treatment groups will be used for all safety and efficacy analyses.

Unless stated otherwise, all statistical tests will be 1-sided and conducted at 0.05 alpha levels. For Dosing Period 2, only descriptive analyses will be performed.

Data listings containing all documented data and all derived data will be generated.

3.2 General study level definitions

3.2.1 Analysis time points

3.2.1.1 Relative day

Relative day for an event will be derived with the date of the first sc infusion of study drug as reference.

Relative days for an event of measurement occurring before the date of first sc infusion are calculated as follows:

Relative Day = [(Event Date – Date of First Infusion)]

The relative day for an event or measurement occurring on or after the reference date to the date of the last infusion is calculated as follows:

Relative Day = [(Event Date - Date of First Infusion) + 1]

For events or measurements occurring after the date of the last sc infusion, relative day will be prefixed with '+' in the data listings and will be calculated as follows:

Relative Day = + [(Event Date – Date of Last Infusion)]

There is no relative Day 0. Relative day is not calculated for partial dates in cases where relative day is shown in a subject data listing. In such cases, relative day should be presented as '- -' in the subject data listings.

3.2.2 Study periods

The maximum duration of the study per subject will be approximately 18 weeks, consisting of the following 3 periods:

- Screening Period: 1 to 28 days
- Treatment Period: 6 weeks
  - Dosing Period 1 of 4 weeks. This period will start at the first actual dosing of Period 1.
  - Dosing Period 2 of 2 weeks. This period will start at the first actual dosing of Period 2.
- Observation Period: 8 weeks

The end of the study is defined as the date of the final clinic/hospital visit of the final subject in the study.

In the case a subject does not receive dosing in Dosing Period 2, the rule for entering the Observation Period given in Section 2.3 will be generalized such that the subject will enter the Observation Period the day after the last dosing of Dosing Period 1. All data up to the missed dose will be treated according to plan, including data planned on the dosing day prior to the actual dosing.

The following definitions for starting and entering the study periods will be applied:

- Started period 1 is defined as all subjects in the safety set. Completed period 1 includes those subjects who have completed assessments prior to the first study treatment of Period 2 (Day 29).
- Started period 2 is defined as having received treatment on Period 2 Day 29. Completed period 2 includes those subjects who have completed assessments on Observation Period Day 50.
- Started Observation Period is defined as having assessments on Observation Period Day 50. Completed observation period includes those subjects who have a completed status in the study termination case report form

3.2.3 Mapping of assessments performed at Premature End of Treatment Visit

Efficacy and safety assessments at a Premature End of Treatment Visit (PEOT) that correspond to a scheduled visit will be summarized at the next scheduled visit.

In particular, clinical laboratory parameters, vital signs, ECG and exploratory safety biomarkers are assessed at all Treatment Period visits, and so all assessments of these variables at PEOT corresponding to a scheduled visit will be mapped to the corresponding scheduled visit.

3.3 Definition of Baseline values

Baseline will be the last available predose value prior to the first infusion of study drug in Dosing Period 1, or if missing, the Screening values. Scheduled or unscheduled measurements can be used as the Baseline value. Expected measurement-specific Baseline time points are presented in Table 3–1. If an unscheduled measurement occurs after the planned baseline measurement time point but before dosing, then the unscheduled measurement will be used.

Table 3–1: Expected Baseline Visits

Measurement	Baseline
Safety data • Clinical Chemistry • Hematology • Urinalysis • ECG • Vital signs • [redacted] • Body weight	• Clinical chemistry, Hematology, Urinalysis, ECG and Vital signs: Predose Day 1 or if missing the Screening value • [redacted]: Predose Day 1 • Body weight: screening visit

Table 3–1: Expected Baseline Visits

Measurement	Baseline
Pharmacodynamic data • Total serum IgG • Serum IgG subclass concentrations • MG specific antibodies ([redacted])	• Total serum IgG and Serum IgG subclass: Predose Day 1 or if missing the Screening value • Mg-specific autoantibodies: Predose Day 1
Immunological data: • IgM, IgE, IgA • Serum complement levels (C3 and C4) and plasma complement levels (C3a and C5a) • [redacted] • Serum BAFF levels • Cytokines • [redacted] specific IgG antibodies • Exploratory biomarkers relating to mechanism of action, disease activity, treatment response, and clinical outcome	• IgM, IgE, IgA, C3, C4, C3a, C5a, [redacted] BAFF, cytokines: Predose Day 1 • [redacted] antibodies: Screening • Exploratory biomarkers: Predose Day 1
Efficacy data: • QMG scale • MG-composite scale • MGADL • MGFA scale • MG muscle weakness • Fatigue • MGII • SFEMG	• QMG, MG composite scale and MFGA: Predose Day 1 or if missing the Screening value • MGADL, Muscle weakness, Fatigue scale, MGII, SFEMG: Predose Day 1.

[redacted] BAFF=B-cell activating factor ; Ig=immunoglobin; MGADL=myasthenia gravis-Activities of Daily Living; MGFA=Myasthenia Gravis Foundation of America; MGII= Myasthenia Gravis Impairment Index; SFEMG=single fiber electromyography; QMG=quantitative myasthenia gravis

3.4 Protocol deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on study conduct or on the primary efficacy, key safety, or PK/PD outcomes (if applicable) for an individual subject. The criteria for identifying important protocol deviations will be defined within the appropriate protocol-specific document. Important protocol deviations will be reviewed as part of the ongoing data cleaning process and data evaluation. All important deviations will be identified and documented prior to unblinding to confirm exclusion from analysis sets.

3.5 Analysis sets

3.5.1 Enrolled Set

The Enrolled Set (ES) will consist of all subjects who have given informed consent.

3.5.2 Randomized Set

The Randomized Set (RS) will consist of all subjects randomized into the study at the first randomization visit.

3.5.3 Safety Set

The Safety Set (SS) will consist of all subjects in the RS, who have received at least 1 dose of IMP.

Safety and immunological variables will be analyzed using the SS.

It is expected that subjects will receive treatment as randomized and hence safety analyses will be based on the randomized treatment group. However, if after unblinding it is determined that a subject has received the incorrect treatment based on the randomization schedule, then for safety analyses the subject will be allocated to the actual treatment they received in the respective Dosing Period.

3.5.4 Full Analysis Set

The FAS will consist of all subjects in the SS, who have a Baseline and least 1 post-Baseline QMG measurement during Dosing Period 1 (up to and including Visit 9, ie, Day 29).

The FAS is the primary analysis set for efficacy analyses. As for the SS, in the case of mistreatment, subjects will be primarily analyzed as treated. However, if applicable, sensitivity analysis will also be performed according to the randomized treatment group.

3.5.5 Per Protocol Set

The Per-Protocol Set (PPS) is a subset of the FAS, consisting of those subjects who had no important protocol deviations affecting the primary efficacy variable, as confirmed during a pre-analysis data review meeting conducted prior to study unblinding. Post-Baseline deviations will not necessarily lead to total exclusion of a subject from the PPS but may lead to exclusion of specific data. In the case of mistreatment the subject will be analyzed as randomized.

Analysis of the primary efficacy variable will be repeated using the PPS.

3.5.6 Pharmacokinetic Per-Protocol Set:

The PK-PPS is a subset of the FAS, consisting of those subjects who had no important protocol deviations affecting the plasma concentration of UCB7665.

3.5.7 Pharmacodynamic Per-Protocol Set:

The PD-PPS is a subset of the FAS, consisting of those subjects who had no important protocol deviation affecting the serum concentrations of total serum IgG or IgG subclasses. As for the SS, in the case of mistreatment, subjects will be primarily analyzed as treated.

3.6 Treatment assignment and treatment groups

Safety, PK, PD and efficacy analyses will be assigned treatment as described in Section 3.5.

Analyses will be performed by treatment group and for all subjects (if applicable) as described in Section 3.1.

The Treatment Groups for Dosing Period 1 will be as follows:

- Placebo
- UCB7665 7mg/kg

For Dosing Period 2 and the Observation Period the following treatment groups will be considered for analysis and will be displayed as such in the TFLs (the first two groups will only be utilized for observation period in case patients do not receive any dosing in period 2):

- Placebo
- UCB7665 7mg/kg
- Placebo - UCB7665 7mg/kg
- Placebo - UCB7665 4mg/kg
- UCB7665 7mg/kg - UCB7665 7mg/kg
- UCB7665 7mg/kg - UCB7665 4mg/kg

These Treatment Groups will be used for all analyses.

3.7 Center pooling strategy

It is planned to recruit subjects in USA, Canada, and Europe in this study, with possible extension to other regions and countries. The data from different sites will be pooled for all analyses.

3.8 Coding dictionaries

All AEs and medical history will be coded for analysis according to the Medical Dictionary for Regulatory Activities (MedDRA)® coding dictionary, using the latest version available. Prior and concomitant medications will be coded for analysis using the latest version of the World Health Organization Drug dictionary (WHO-DD). Medical procedures will not be coded.

3.9 Changes to protocol-defined analyses

In protocol section 14.3.2, it is described that the secondary variable change from baseline in at Visit 9 will be analyzed utilizing similarly to the approach used for QMG. However, since MGADL is measured only at Visit 2 and Visit 9, it is not possible to use the repeated measures model and a simpler model will be used, see Section 8.2.2.

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

In the analysis of the efficacy variables, the Baseline value of the QMG, MG-composite score, MGADL score or MGII score will be used as a covariate in the analysis of the respective variable.

4.2 Handling of dropouts or missing data

In general, there will be no imputation of missing data unless stated otherwise below.

4.2.1 Efficacy data

The rules for handling missing data of single items in the calculation of the overall QMG, MGADL or MGII scores at a certain visit are described in Section 14.1, Section 14.3 and Section 14.5, respectively. Missing overall scores at a certain visit will not be imputed.

4.2.2 Safety laboratory data

Measurements below the limit of quantification (BLQ) will be imputed with half of the lower limit of quantification (LLOQ) for the purpose of calculating change from Baseline. Measurements above the limit of quantification (ALQ), if applicable, will be imputed to the upper limit of quantification. These rules will be applied to all safety laboratory data including clinical chemistry and urinalysis.

Descriptive statistics will be calculated if at most 33% of the individual data points at a time point are missing or are either not quantifiable (<LLOQ) or ALQ.

4.2.3 Pharmacodynamic data

Measurements BLQ are not anticipated for the serum total serum IgG data. In the event that any measurements BLQ are received, these will be regarded as missing for the calculation of descriptive statistics and changes from Baseline.

Descriptive statistics will be calculated if at most 33% of the individual data points at a time point are missing or are either not quantifiable (<LLOQ) or ALQ as described in Section 4.2.2.

For the MG-specific autoantibodies and IgG subclasses, measurements BLQ will be imputed with LLOQ/2 for the purpose of calculating change from Baseline. Measurements ALQ, if applicable, will be imputed to the upper quantification limit.

4.2.4 Immunological data

The rules for handling BLQ or ALQ measurements for all immunological data will be as described in Section 4.2.2.

Descriptive statistics will be calculated if at most 33% of the individual data points at a time point are missing or are either not quantifiable (<LLOQ) or ALQ as described in Section 4.2.2.

4.2.5 UCB7665 concentration data

Measurements that are BLQ will be imputed with half of the LLOQ for the purpose of calculating the geoMean and its 95% CI, the geoCV, the arithmetic mean, and SD for summaries and figures. If any summary value (geoMean, arithmetic mean, lower CI level or minimum) is lower than LLOQ, then 'BLQ' will be displayed.

For the individual figures, any concentrations that are BLQ will be regarded as missing, with the exception of predose measurements BLQ on Day 1, which will be imputed with zero for linear scale plots.

Additional rules for PK data summaries are provided in Section 9.1.

4.2.6 Electrocardiogram data

For the ECG data, all calculations of changes from Baseline and descriptive statistics will be based on the mean of the triplicate assessments at each time point. In the event that there are not 3 available measurements at a given time point, the mean will be calculated based on the number of measurements for which data is provided.

4.2.7 Dates and times

Partial dates may be imputed for the following reasons:

- Classification of Adverse events (AEs) as treatment-emergent
- Classification of medications as prior or concomitant

The following rules will be applied for partial start dates/times:

- If only start month and year are specified and not the same as month and year of first dosing then use the 1st of the month, or the date of screening if this is later (if the latter imputation results in an end date that is earlier than the start date, then use the 1st of the month). If time is missing this will be imputed as 00:00 h;
- If only the month and year are specified and the month and year of first dosing is the same as the month and year of the start date, then use the date of first dosing. If this results in an imputed start date that is after the specified end date, then use the 1st of the start month, or the date of screening if this is later (if the latter imputation results in an end date that is earlier than the start date, then use the 1st of the month). If the imputed date is the date of first dosing then time will be imputed as the start time of the infusion (ie, event will be regarded as treatment-emergent);
- If only the year is specified, and the year of dosing is not the same as the year of the start date then use January 01 of the year of the start date. If time is missing this will be imputed as 00:00 h;
- If only the year is specified, and the year of dosing is the same as the year of the start date, then use the date of first dosing. If this results in an imputed start date that is after the specified end date, then use January 01 of the year of the start date, or the date of screening if this is later (if the latter imputation results in an end date that is earlier than the start date, then use January 01). If the imputed date is the date of first dosing then time will be imputed as the start time of the infusion (ie, event will be regarded as treatment-emergent);

- If the start date is completely unknown, then use the date of first dosing. If this results in an imputed start date that is after the specified end date, then use January 01 of the year of the end date, or the date of screening if this is later (if the latter imputation results in an end date that is earlier than the start date, then use January 01). If the imputed date is the date of first dosing then time will be imputed as the start time of the infusion (ie, event will be regarded as treatment-emergent).

Start and end time is not recorded for concomitant medications, thus no imputations for missing times will be performed. Any medication with a start date on the first dosing date, will be assumed to be concomitant.

The following rules will be applied for partial stop dates:

- If only the month and year are specified, then use the last day of the month;
- If only the year is specified, then use December 31 of the known year;
- If the stop date is completely unknown, do not impute the stop date

Missing or partially missing date and/or times will be imputed as described in Table 4–1 for the calculation of duration of each AE. Adverse event duration is computed in and reported in day and time format: xx d hh:mm.

Table 4–1: Calculation rules for duration of AEs

Data availability	Onset date/time	Outcome date/time	Calculation rules
Complete data	D1/T1	D2/T2	Duration = [(D2 – D1)*24 + (T2 – T1)]/24 d
End time missing	D1/T1	D2/--	End time is substituted by time 23:59h (=23.98 in decimal format) Duration = <[(D2 – D1)*24 + (23.98 – T1)]/24 d
Start time missing	D1/--	D2/T2	Onset time is substituted by time 00:00h.
Start and end time missing	D1/--	D2/--	Duration = <D2 – D1 + 1
Start day and time missing	-/--	D2/T2	Duration = <[(D2 – D0)*24 + (T2 – T0)]/24 d For a subject in the SS, D0 and T0 are the date and time of first administration of UCB7665 and for screen failures, D0 is the date of the screening visit and T0 = 00:00h

Table 4–1: Calculation rules for duration of AEs

Data availability	Onset date/time	Outcome date/time	Calculation rules
End day and time missing	D1/T1	--/--	For ongoing AE: Duration = >Discharge day – D1 d OR For resolved AE: Duration = <Discharge day – D1 d OR Where discharge refers to the date of the end of study visit for completed subjects or the date of discontinuation for subjects that were withdrawn. For any AEs with known start date/time after the date of discontinuation, the date of last contact will be used as the discharge day.
Start and end date missing	--/--	--/--	For ongoing AE: Duration = >Discharge day – D0 d OR For resolved AE: Duration = <Discharge day – D0 d OR For a subject in the SS, D0 and T0 are the date and time of first administration of UCB7665 and for screen failures, D0 is the date of the screening visit and T0 = 00:00h. Discharge refers to the date of the end of study visit or the date of discontinuation for subjects that were withdrawn. For any AEs with known start date/time after the date of discontinuation, the date of last contact will be used as the discharge day.

4.3 Handling of repeated and unscheduled measurements

All repeated and unscheduled measurements will be presented in the listings. The following general rules will apply to all repeated and unscheduled measurements:

- For repeated measurements obtained prior to the first dose of IMP the latest value (which may be scheduled or unscheduled) will be used in the calculation of descriptive statistics
- For repeated measurements obtained at the designated Baseline visit, the latest value (which may be scheduled or unscheduled) will be defined as the Baseline provided that this occurred prior to the first dose of IMP. Repeated measurements designated Baseline will be used in descriptive statistics rather than the planned measurement they replace
- For repeated measurements obtained at any time point after the first dose of IMP, the first value of any repeated measurements will be used in the calculation of changes from Baseline and for the descriptive statistics. Unscheduled and repeated measurements will not be included in the descriptive statistics at time points after the first dose of IMP

The above rules also apply to triplicate measurements obtained for the ECG data, both for repetitions of the whole triplicate or when single measurements of the triplicate are repeated.

4.4 Interim analyses and data monitoring

At least three interim analyses will be performed. The first interim analysis for futility will be performed once approximately 20 subjects have attended Visit 9, the first visit of the second Dosing Period (ie, Day 29). Futility of UCB7665 will be assessed based on QMG score, MG-Composite score, and MGADL data. In case of futility, the study will be stopped or amended. The decision rules for futility will be described in the data monitoring committee (DMC) charter. The second interim analysis will be conducted after approximately 20 subjects (receiving 6 sc infusions) have had Visit 16 (Day 57). Based on this unblinded analysis the safety of UCB7665 will be assessed by the DMC. The safety variables to be used and the potential outcomes of the analysis will be specified in the DMC charter. During this review recruitment will not be stopped. The third interim analysis will be performed once all subjects have attended Visit 9 (Day 29), the first visit of the second Dosing Period (ie, Day 29). This interim analysis will provide the results for the primary variable 'change from Baseline to Visit 9 (Day 29) in the QMG score', and secondary variables 'change from Baseline to Visit 9 (Day 29) in MG-Composite score' and 'change from Baseline to Visit 9 (Day 29) in the MGADL score'. For the third interim analysis the DMC will not be utilized.

The analyses will be described in a separate Interim SAP. The first interim analysis will utilize all efficacy data (as specified in the DMC charter), which will be available at the time the 20th subject attended Visit 9. The second interim analysis will utilize all safety data (as specified in the DMC charter), which will be available at the time the 20th subject attended Visit 16. For all interim analyses, the data subject to analysis should be as clean as possible; however, the database will not be locked and a snapshot will be taken.

4.5 Multicenter studies

Individual center results will not be displayed.

4.6 Multiple comparisons/multiplicity

Not applicable

4.7 Use of an efficacy subset of subjects

Not applicable

4.8 Active-control studies intended to show equivalence

Not applicable

4.9 Examination of subgroups

Not applicable

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject disposition

The number of subjects who were enrolled, dosed, subjects included in each analysis set, and subjects who completed or prematurely discontinued the study/the period, as well as the reason

for discontinuation, discontinuation due to AEs, will be presented by dose arm and overall. Screen failure reasons will be summarized, based on the ES.

In addition the following listings will be presented by dose arm:

- Subject disposition (ES)
- Study discontinuation (ES)
- Visit dates (RS)
- Subject analysis sets (ES)

Subject disposition will be listed by treatment group based on the ES, and will include the date of informed consent, presence of informed consent for SFEMB with date, date of randomization for Dosing Period 1 and Dosing Period 2, date and time of first and last dose of IMP, date of premature termination and primary reason, and date of final contact.

The listing of study discontinuation will include the reason for discontinuation, period of discontinuation, with dose and number of days on that dose and the total number of days on study medication.

The number of days on IMP will be calculated as follows:

Number of days on IMP=[(Date of Last Dose Received)-(Date of First Dose Received)]+1

5.2 Protocol deviations

Important protocol deviations (IPDs) will be identified and classified by the deviation types identified in the IPD document. A listing of all IPDs identified at the Data evaluation meetings (DEMs) will be presented for all subjects in the SS, and will include the deviation type and description. The number and percentage of subjects in the SS with IPDs will be summarized overall if appropriate. The denominator for percentages will be the number of subjects in the SS.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

6.1 Demographics

A by-subject listing of Baseline demographics will be presented by treatment group for the ES. This will include the day, month and year of birth (if available), age (in years), sex, race, ethnicity, height (in cm), weight (in kg) and body mass index (BMI). The age will be directly entered into the study database and will not be re-calculated for the statistical analysis. Childbearing potential will be listed for the ES.

All demographic characteristics obtained at the Screening visit will be summarized for the RS (apart from the date of birth).

Body mass index in kg/m^2 is calculated based on the height (in m) and the weight (in kg) using the following formula:

BMI (kg/m^2) = weight (kg)/[height (m)]^2

The BMI will be reported to 1 decimal place.

The demographic characteristics listing will include a flag for BMI values identified as TEMA/PCS as defined by the criteria outlined in Table 14-7.

For the EudraCT reporting, the age categories will include

- 18 to <65 years
- 65 to <85 years
- ≥85 years

For the clinicaltrials.gov reporting, the age categories will include:

- ≤18 years
- 19 to <65 years
- ≥65 years

6.2 Other Baseline characteristics

MG medication (medication where indication is MG), MGFA disease class and thymectomy (yes/no) at baseline will be listed and summarized by treatment group for the RS.

6.3 Medical history and concomitant diseases

Medical history will be listed and summarized for the RS by treatment group, and will include the MedDRA system organ class (SOC), high level term (HLT) and preferred term (PT). Procedure history and concomitant medical procedure will be listed separately from the medical history based on the RS.

History of MG will be listed for the RS.

6.4 Past, prior and concomitant medications

Past, prior and concomitant medications will be listed and summarized, separately, for the RS by treatment group and for all subjects by WHODD Anatomical Main Group [Level 1], Therapeutic Subgroup [Level 3], preferred term (PT) and reported term (listing only). The listing will also include the dose per intake and unit, frequency, formulation, route of administration, indication, category (three categories: prior, concomitant and prior and concomitant), study period (Dosing Period 1, Dosing Period 2 and/or Observation Period) and both start and end date (or ongoing, if applicable).

Separate tabulations will be presented for the following:

- Past medications
- Prior and concomitant medications
- Concomitant medications

All medications will be listed and will include coding information, reported term, dose per intake and unit, frequency, formulation, route of administration, indication, category (past/prior and concomitant/concomitant) and start and end date (or ongoing, if applicable).

6.4.1 Past medication definition

Past medications will include any medications that started and stopped prior to the first IMP administration.

6.4.2 Prior medication definition

Prior medications will include any medications that started prior to the first administration of IMP. This includes any medications that started and stopped prior to dosing (past medications) as well as those which started prior to dosing and continued after (classified as prior and concomitant medications).

6.4.3 Concomitant medication definition

Concomitant medications will include any medication that has been taken at least once (after the first administration of IMP) during the Dosing Periods and/or the Observation Period.

Any medication that started prior to the first administration of IMP and continued after dosing will be classified as prior and concomitant. Any medication that started after the first administration of IMP in Dosing Period 1 will be classified as concomitant only.

Any medications with missing dates and/or times will be handled as described in Section 4.2.7 in order to classify them as prior or concomitant.

6.4.4 Assignment of medications to study period

The following rules will be used to assign a concomitant medication to a study period:

- Dosing Period 1: a medication will be assigned to Dosing Period 1 if it has been taken at least once between the first administration of IMP on Day 1 and the first administration of IMP in Dosing Period 2 (Day 29). This includes medications that started prior to Dosing Period 1 and those that continued into Dosing Period 2.
- Dosing Period 2: a medication will be assigned to Dosing Period 2 if it has been taken at least once between the first administration of IMP in Dosing Period 2 (Day 29 and 7 days after the last dose of IMP in Dosing Period 2 [Day 50]). This includes medications that started prior to Dosing Period 2 and those that continued into the Observation Period.
- Observation Period: a medication will be assigned to the Observation Period if it has been taken at least once between Day 50 (or 7 days after the last dose of IMP) and the final visit. This includes medications that started prior to the Observation Period.

Thus, a medication taken from the time of the first drug administration in Dosing Period 1 to the end of the study will be assigned to Dosing Period 1, Dosing Period 2 and the Observation Period.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

The study medication will be administered and monitored by the investigator or designee. The measured plasma concentrations will provide information regarding compliance. Any dosing deviations (eg, incomplete infusion volume administered, infusion temporarily interrupted, infusion discontinued) will be discussed at the DEM and any actions taken regarding the analyses will be documented accordingly and discussed in the CSR.

There will be no specific analysis of compliance. Exposure to UCB7665 will be presented as described in Section 11.1.

8 EFFICACY ANALYSES

8.1 Statistical analysis of the primary efficacy variable

The primary efficacy variable is the change from Baseline in QMG score to Visit 9 (Day 29) prior to the first infusion of IMP in Dosing Period 2.

8.1.1 Derivations of primary efficacy variable

The QMG scale comprises 13 items, including ocular and facial movement, swallowing, speech, limb strength and forced vital capacity. Scoring for each item ranges from no weakness (0) to severe weakness (3), with an overall score range from 0 to 39, ie, a higher scores indicates more severe disease. A 3-point change in the overall score is considered to be clinically relevant.

The complete list of items and scores are provided in Table 14–1. The items of QMG scale will be displayed in a glossary. A total score after single item imputation will be calculated according to the rules set down in Section 14.1. All individual item results will be listed. The total score after single item imputation will be listed and used to calculate change from baseline, in descriptive summaries and for efficacy analysis. Total score will be used to determine responder state, which will be flagged in the listing and descriptively summarized.

8.1.2 Primary analysis of the primary efficacy variable

A 1-sided hypothesis test will be performed to test the primary hypothesis of superiority of UCB7665 7mg/kg vs placebo at Visit 9. The null hypothesis is that the mean change from Baseline in QMG score is larger or equal in the UCB7665 7mg/kg group than the placebo group. The alternative hypothesis is that the mean change from Baseline in QMG score is smaller in the UCB7665 7mg/kg group than the placebo group.

The primary analysis of the primary variable will be analyzed for the FAS using a mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) that includes terms for week (as categorical effect), treatment group, the Baseline QMG score, and the interaction between treatment group and week. The model will define subject as a random effect and utilize an unstructured covariance pattern. Least Squares (LS) Means for changes from Baseline at Visit 9 (Day 29) for each treatment group will be presented together with LS mean differences (UCB7665 - 7mg/kg vs placebo), p-value and 1 sided 95% CI.

For subjects who prematurely withdraw for any reason before Visit 9 (Day 29), data collected during the PEOT Visit will be used to impute QMG scores at the next consecutive visit.

8.1.3 Supportive and sensitivity analyses of the primary efficacy variable

Different sensitivity analyses to evaluate the effect of missing observations on the primary analysis findings will be done. The first sensitivity analysis will be performed in the same way as the primary analysis but will use PPS instead. A further analysis will utilize the Last Observation Carried Forward (LOCF) approach and the FAS; missing values will be replaced by the last observed post-Baseline value of the variable and the analysis will be performed on the resulting dataset.

8.2 Statistical analysis of the secondary efficacy variables

The secondary efficacy variables are the changes from Baseline in MG-Composite and MGADL scores to Visit 9 (Day 29) prior to the first infusion of IMP in Dosing Period 2.

The MG-composite score comprises 10 items, each of which is weighted differently in the calculation of the overall score. The overall score ranges from 0 to 50, with a higher score indicating more severe disease. The items of MG-composite score will be displayed in a glossary. All individual item results will be listed. The total score will be listed and used to calculate change from baseline and used in descriptive summaries and for efficacy analysis. Total score will be used to determine responder state, which will be flagged in the listing and descriptively summarized.

The complete list of items and scores are provided in Table 14–2 .

The MGADL score comprises of 8 items, each with a score of 0 to 3. The items of MGADL will be displayed in a glossary. The total MGADL score ranges from 0 to 24 with a higher score indicating more disability. The complete list of items and scores are provided in Table 14–3. The total score will be calculated according to the rules set down in Section 14.3 All individual item results will be listed. The MGADL listing will contain total score for an interpolated visit at Day 57, where the total score is derived based on interpolation of Day 50 and 64. If total score on either day 50 or day 64 is not available no interpolated score will be derived. The total score after single item imputation will be listed and used to calculate change from baseline and used in descriptive summaries and for efficacy analysis, interpolated data from Day 57 will be part of the descriptive summary. Total score will be used to determine responder state, which will be flagged in the listing and descriptively summarized.

A comparison summary of MGADL showing absolute scores of Visit 9 (day 29), interpolated Day 57 and their differences will be presented by treatment group of second treatment period (Placebo - UCB7665 7mg/kg, Placebo - UCB7665 4mg/kg, UCB7665 7mg/kg - UCB7665 7mg/kg, UCB7665 7mg/kg - UCB7665 4mg/kg).

8.2.1 MG-composite score

The MG-composite score will be analyzed utilizing the MMRM ANCOVA. A 1-sided hypothesis test will be performed to test the hypothesis of superiority of UCB7665 7mg/kg vs placebo at Visit 9. The null hypothesis is that the mean change from Baseline in MG-composite score is larger or equal in the UCB7665 7mg/kg group than the placebo group. The alternative hypothesis is that the mean change from Baseline in MG-composite score is smaller in the UCB7665 7mg/kg group than the placebo group.

The change from baseline of the MG-composite score will be analyzed for the FAS using a MMRM ANCOVA that includes terms for week (as categorical effect), treatment group, the Baseline MG-composite score, and the interaction between treatment group and week. The model will define subject as a random effect and utilize an unstructured covariance pattern. Least Squares (LS) Means for changes from Baseline at Visit 9 (Day 29) for each treatment group will be presented together with LS mean differences (UCB7665 - 7mg/kg vs placebo), p-value and 1 sided 95% CI.

For subjects who prematurely withdraw for any reason before Visit 9 (Day 29), data collected during the PEOT Visit will be used to impute MG-composite scores at the next consecutive

visit.. There will be no sensitivity analysis for the MG-composite score. Subjects without baseline value will not be analyzed.

8.2.2 MG activities of daily living

Since the MGADL does not have repeated observations per subject, the MGADL score will be analyzed via a simplified version of the model. The change from baseline MGADL will be analyzed for the FAS using a ANCOVA that includes terms for treatment group and the Baseline score. Least Squares (LS) Means for changes from Baseline at Visit 9 for each treatment group will be presented together with LS mean differences (UCB7665 - 7mg/kg vs placebo), p-value and 1 sided 95% CI. Subjects without baseline or Visit 9 observations will not be analyzed. There will be no sensitivity analysis for MGADL.

8.3 Analysis of other efficacy variables

8.3.1 Summaries of efficacy variables

Values and change from Baseline in QMG, MG-Composite and MGADL at each scheduled visit will be descriptively summarized at each scheduled assessment during Treatment and Observation Periods. MGFA classification will be summarized during Treatment and Observation Periods.

8.3.2 Muscle weakness severity and fatigability scale

The Muscle weakness severity and fatigability scale is displayed in Section 14.4. It consists of a domain for muscle weakness on a total scale from 0 to 90 and a domain for fatigability on a total scale from 0 to 36. The total scale ranges from 0 to 126 with a higher score indicating more disability. The items of the muscle weakness and fatigability scale will be displayed in a glossary. All individual item results will be listed per time point, including total per domain and total. The total score will be used to calculate change from baseline and used in descriptive summaries and for efficacy analysis. Total score will be descriptively summarized by treatment and time point.

Muscle weakness severity and fatigability scale at each assessed post-Randomization Visit (during Dosing Period 1 including Visit 9) will also be analyzed utilizing the MMRM approach.

A 1-sided hypothesis test will be performed to test the hypothesis of superiority of UCB7665 7mg/kg vs placebo at Visit 9. The null hypothesis is that the mean change from Baseline in muscle weakness score is larger or equal in the UCB7665 7mg/kg group than the placebo group. The alternative hypothesis is that the mean change from Baseline in muscle weakness score is smaller in the UCB7665 7mg/kg group than the placebo group.

The change from baseline of the muscle weakness score will be analyzed for the FAS using a MMRM ANCOVA that includes terms for week (as categorical effect), treatment group, the Baseline muscle weakness score, and the interaction between treatment group and week. The model will define subject as a random effect and utilize an unstructured covariance pattern. Least Squares (LS) Means for changes from Baseline at Visit 9 (Day 29) for each treatment group will be presented together with LS mean differences (UCB7665 - 7mg/kg vs placebo), p-value and 1 sided 95% CI.

For subjects who prematurely withdraw for any reason before Visit 9 (Day 29), data collected during the PEOT Visit will be used to impute muscle weakness scores at the next consecutive visit.

The complete lists of items and scores are provided in Table 14–4 and Table 14–5.

8.3.3 Fatigue Instrument

The fatigue instrument consists of 55 items across 3 domains: 16 physical domain items (with a scale of 16 to 80), 18 mental domain items (with a scale of 18 to 90), and 21 fatigability domain items (with a scale of 21 to 105). The subject will be asked to score each item based on how frequently she/he experienced the item during the past 7 days using a 5-point Likert scale ("none of the time" to "all of the time"). The items of the fatigue instrument will be displayed in a glossary. The overall score ranges from 55 to 275, with a higher result indicating more severe fatigue. All individual item results will be listed per time point including overall score. Change from baseline will be calculated for the overall score and both overall score and change from baseline will be used in descriptive summaries and for efficacy analysis. Overall score will be descriptively summarized by treatment and time point.

Fatigue scale at each assessed post-Randomization Visit (during Dosing Period 1 including Visit 9) will also be analyzed utilizing the MMRM approach. A 1-sided hypothesis test will be performed to test the hypothesis of superiority of UCB7665 7mg/kg vs placebo at Visit 9. The null hypothesis is that the mean change from Baseline in fatigue instrument score is larger or equal in the UCB7665 7mg/kg group than the placebo group. The alternative hypothesis is that the mean change from Baseline in fatigue instrument score is smaller in the UCB7665 7mg/kg group than the placebo group.

The change from baseline of the fatigue instrument score will be analyzed for the FAS using a MMRM ANCOVA that includes terms for week (as categorical effect), treatment group, the Baseline muscle weakness score, and the interaction between treatment group and week. The model will define subject as a random effect and utilize an unstructured covariance pattern. Least Squares (LS) Means for changes from Baseline at Visit 9 (Day 29) for each treatment group will be presented together with LS mean differences (UCB7665 - 7mg/kg vs placebo), p-value and 1 sided 95% CI.

For subjects who prematurely withdraw for any reason before Visit 9 (Day 29), data collected during the PEOT Visit will be used to impute fatigue instrument scores at the next consecutive visit.

8.3.4 MGFA Clinical Classification

The MGFA Clinical Classification is a 5 stage classification (I to V), with a higher class indicating more severe disease. Results of MGFA Clinical Classification will be listed.

The percentage of subjects with each MGFA classification at each scheduled assessment during Treatment and Observation Periods will be calculated and descriptively summarized for the FAS.

8.3.5 MG Impairment Index

The MGII consists of a 22 items patient questionnaire and an 8 item examination. It is divided in two sub-scores reflecting an ocular and a generalized domain. The ocular score is calculated by summing 8 items reflecting ocular impairments. These items are: patient questionnaire items 1 to

6 and examination items 1 and 2. The generalized score is calculated by adding items 7 to 22 from the patient questionnaire and items 3 to 6 from the examination. The complete list of items is given in Table 14–6. The items of MGII will be displayed in a glossary. All individual item results will be listed per time point including overall score. Change from baseline will be calculated for the overall score and sub-scores (ocular and generalized domain). The overall score, two sub-scores and their change from baseline will be used in descriptive summaries and for efficacy analysis. For overall score and sub-scores, missing items will be imputed according to the rules set in Section 14.5. Descriptive summaries will be by treatment and time point.

The change from baseline MGII scale at each assessed post-Randomization Visit (during Dosing Period 1 including Visit 9) will also be analyzed utilizing the MMRM approach. A 1-sided hypothesis test will be performed to test the hypothesis of superiority of UCB7665 7mg/kg vs placebo at Visit 9. The null hypothesis is that the mean change from Baseline in MGII score is larger or equal in the UCB7665 7mg/kg group than the placebo group. The alternative hypothesis is that the mean change from Baseline in MGII score is smaller in the UCB7665 7mg/kg group than the placebo group.

The change from baseline of the MGII score will be analyzed for the FAS using a MMRM ANCOVA that includes terms for week (as categorical effect), treatment group, the Baseline muscle weakness score, and the interaction between treatment group and week. The model will define subject as a random effect and utilize an unstructured covariance pattern. Least Squares (LS) Means for changes from Baseline at Visit 9 (Day 29) for each treatment group will be presented together with LS mean differences (UCB7665 - 7mg/kg vs placebo), p-value and 1 sided 95% CI.

For subjects who prematurely withdraw for any reason before Visit 9 (Day 29), data collected during the PEOT Visit will be used to impute MGII scores at the next consecutive visit.

8.3.6 Responder rates

QMG, MG-Composite, and MGADL responder rates will be summarized at each assessed post-Randomization Visit (during Dosing Period 1) and compared between the 2 Treatment Groups utilizing Fisher's exact test for each visit for the FAS.

The frequency of attained point improvement will be plotted against treatment for Visit 9 (Week 8). For each point improvement the test result will be displayed in a table and in the plot.

8.3.7 Single Fiber Electromyogram

Jitter (SFEMG) results will be listed, including change from Baseline.

Three variables will be further analyzed; MCD of the IPI accepted after external review, % Normals accepted after external review and % Blocking accepted after external review. For these variables the listing will include change from baseline. In addition, for these variables observed values and change from baseline will be summarized using descriptive statistics, by treatment group and visit, including changes from Baseline for the FAS.

Change from baseline line MCD accepted after external review will be plotted against change from baseline in efficacy variables, QMB, MG-composite and MGADL.

Clinically meaningful improvement in jitter (SFEMG) will be calculated upon MCD of the IPI accepted after external review. Clinically meaningful improvement, defined as a reduction in

MCD of at least 9us, will be flagged in the listing. Contingency tables will be created of jitter (SFEMG) clinically meaningful improvement against QMG, MG-composite and MGADL responders by treatment.

8.3.8 Correlation analysis

Pearson correlation of patient reported outcomes (PROs) with IgG levels and association using Spearman's correlation with [redacted], [redacted] and [redacted] status will be displayed by visit. In addition Pearson correlation of the clinical assessment of disease activity (variables QMG and MG composite), disease severity (MGFA) and patients' assessment on impact on daily life (MG-ADL) will be displayed for each visit. This analysis will be repeated using baseline corrected values of the PROs and the variables QMG, MG composite, MGFA and MG-ADL.

Further association between PROs will also be investigated using Pearson correlation.

8.3.9 Psychometric analyses

The Psychometric analyses of the newly developed measures MG muscle weakness severity and fatigability and fatigue scales will be performed blinded from treatment arms. This psychometric analysis of the MG muscle weakness severity and fatigability scale and fatigue scale will be performed by a vendor using Rasch analysis and will be reported separately from the CSR. For these analyses a separate psychometric analysis plan will be written. Subsequently, the data will be further analysed using Rasch models, with the aim to decrease the number of items and develop a scoring algorithm, this is not described in this SAP and will not reported in the CSR.

9 PHARMACOKINETICS AND PHARMACODYNAMICS

9.1 Pharmacokinetics

The PK variable is the plasma concentration of UCB7665. Pharmacokinetic parameters such as Cmax and area under the curve will not be derived (eg, by non-compartmental analysis) due to the limited sampling performed at each visit.

Individual concentrations of UCB7665 will be listed for the SS and summarized for the PK-PPS at each scheduled time point. In the listing relative and absolute time will be displayed. Relative time of pre-dose samples will be relative to start of infusion and display pre-dose for samples prior to dosing and display actual relative time for samples not prior to dosing. Relative time of post-dose samples will be relative to end of infusion. Descriptive statistics of concentrations will be calculated only if at least two thirds of the individual data points are quantifiable (≥LLOQ). Summaries will include the number of available observations, mean, median, SD, minimum, maximum, geometric mean, and geometric coefficient of variation (assuming log-normally distributed data). Values below the LLOQ will be reported with a clear sign indicating that they were below the LLOQ. Individual concentrations of UCB7665 will also be displayed graphically on a linear and on a semi-log scale. UCB7665 concentrations also be displayed in a spaghetti plot by treatment group on a linear and on a semi-log scale. In the spaghetti plot, time will

9.2 Pharmacodynamics

The analysis of the PD data will be performed on the FAS with the exception of the total serum IgG and IgG subclasses results, which will be analyzed on the PD-PPS. All listings will be presented for the SS.

Any values that are BLQ or ALQ will be handled as described in Section 4.2.2.

All analyses described in this section will be performed on the PD-PPS.

9.2.1 Total serum IgG and IgG subclasses

Total serum IgG concentrations and IgG subclasses will be listed by treatment and time point including changes from Baseline and percentage changes from Baseline. Descriptive summaries (including n, arithmetic mean, median, SD, minimum and maximum) will be presented by treatment group and time point for absolute values, changes from Baseline and percentage changes from Baseline. The maximum decrease from Baseline in total serum IgG (absolute and percentage decrease) will be reported in the listing and summarized for each treatment.

In the event that a decrease from Baseline in total serum IgG is not observed in a given subject, the maximum decrease will be reported as the smallest increase from Baseline. Mean and mean percentage change from Baseline values in total serum IgG will be plotted over time by treatment and period with all treatments overlaid on the same plot.

9.2.2 MG-specific autoantibodies

MG-specific autoantibodies [redacted] will be listed by treatment and time point including changes from Baseline and percentage changes from Baseline. Descriptive summaries (including n, arithmetic mean, median, SD, minimum and maximum) will be presented by treatment group and time point for absolute values, changes from Baseline and percentage changes from Baseline.

Mean and mean percentage change from Baseline values in MG-Specific autoantibodies will be plotted over time by treatment and period with all treatments overlaid on the same plot.

10 IMMUNOLOGICAL ANALYSES

All analyses described in this section will be based on the SS.

10.1 Immunoglobulins

Immunoglobulins (IgE, IgA and IgM) will be listed by treatment group and time point including changes from Baseline. Descriptive summaries will be presented by treatment group and time point for both absolute values and changes from Baseline.

Individual figures over time (absolute value) will be presented by subject, with all variables overlaid on the same plot and separate plots each subject.

Any values that are BLQ or ALQ will be handled as described in Section 4.2.4.

10.2 [redacted]

Immunological variables will be analyzed for all subjects in the SS. [redacted] data will be summarized at each scheduled visit, and the rate of [redacted] positive subjects will be calculated.

Dependent on availability the intention is to use a [redacted] screening assay without a calibrator. A cut point will be determined by the bioanalytical laboratory that will be used to determine the status of [redacted] as above the cut point (ACP) or below the cut point (BCP). A calibrator screening assay currently in place to measure [redacted] as relative mass units (RMU) in units/mL will be used in the event that the newer screening assay is unavailable.

A cut point will be determined by the bioanalytical laboratory that will be used to determine the status of [redacted] as above the cut point (ACP) or below the cut point (BCP). For any [redacted] levels that are ACP, a further confirmatory assay will be performed, the results of which will be determined as either 'confirmed positive' (CP) or 'not confirmed positive' (NCP). In the case of the newer screening assay; for samples that are CP a further titre assay will be performed and the [redacted] titre reported. In lieu of the newer screening assay, the RMU result from the calibrator screening assay will be used to report [redacted] levels.

The results for the [redacted] measurements will be listed by treatment group and time point based on the SS, including the screening assay, confirmatory assay and either the titre or level in units/mL (as applicable).

The following definitions will be applied:

- An [redacted] status of positive will be concluded for any subject with an [redacted] level that is ACP and CP at any time point
- An [redacted] status of negative will be concluded for any subject with an [redacted] level that is either BCP or ACP and NCP at any time point
- A subject will be classified as having [redacted] positivity at Baseline if the Day 1, predose result is ACP and CP
- A subject will be classified as having treatment-induced [redacted] positivity when meeting one of the following criteria:
  - The Baseline result is either BCP or ACP and NCP, and at least one post-Baseline time point is ACP and CP
  - The Baseline result is positive (ACP and CP) and at least one post-Baseline measurement shows a pre-defined fold increase in titre or units/mL (as applicable) from the Baseline value (the fold increase from Baseline required to meet this criteria will be defined with the development of the assay and will be included in the TFLs)
- A subject will be classified as overall positive if at least one post-Baseline measurement is ACP and CP (this includes subject who have negative results at Baseline)
- A subject will be classified as overall negative if at all post-Baseline visits the [redacted] status is negative (this includes subjects who have positive [ACP and CP] results at Baseline)

The [redacted] status (positive/negative) will be summarized as a categorical endpoint (number and percentage of subjects) for all time points and overall, based on the SS.

In addition, the first occurrence of treatment-induced [redacted] positivity (based on the definitions above) will be summarized (number and percentage of subjects) at each post-Baseline visit, based on the SS. This tabulation will count the number of subjects at each post-Baseline visit who fulfill at least one of the above defined criteria for treatment-induced positivity; subjects will be counted in the numerator based on the earliest visit at which one of these criteria is fulfilled. At other visits, subjects will be counted in the denominator (assuming a measurement is available). For all tabulations, percentages will be based on the number of observations at each visit.

A separate listing will be presented (based on the SS) showing the UCB7665 concentrations and [redacted] measurements in the same output in adjacent columns. The listing will include the UCB7665 concentration, [redacted] status (ACP or BCP) and confirmatory assay results if applicable (NCP or CP), together with the titre or units/mL (as applicable) for results that are CP. In addition the time since the previous administration of IMP will be reported (in days).

Finally, individual subject plots (based on the SS) will be presented displaying the [redacted] titre or units/mL (as applicable) and UCB7665 concentrations overlaid on the same figure. The figure will also show the timing and dose of each administration of UCB7665 received during the study. The [redacted] titre data will be plotted using a semi-logarithmic scale.

The rules for handling values that are BLQ in the UCB7665 concentration data are described in Section 4.2.5 For the [redacted] data, any negative results for which there are no titres or units/mL (as applicable) available at a specific visit will be substituted with 0.001 for the purpose of the figure.

10.3 Serum complement levels and plasma complement levels

Serum (C3 and C4) and plasma (C3a and C5a) complement variables will be listed by treatment group and time point including changes from Baseline. Descriptive summaries (including n, arithmetic mean, median, SD, minimum and maximum) will be presented by treatment group and time point for both absolute values and changes from Baseline.

Any values are that BLQ or ALQ will be handled as described in Section 4.2.4.

10.4 Serum BAFF levels

Serum BAFF levels will be listed by treatment group and time point including changes from Baseline. Descriptive summaries (including n, arithmetic mean, median, SD, minimum and maximum) will be presented by treatment group and time point for both absolute values and changes from Baseline.

Any values are that BLQ or ALQ will be handled as described in Section 4.2.4.

10.5 Cytokines

Cytokines will be listed by treatment group and time point, changes from Baseline will be added to the listing. Descriptive summaries (including n, arithmetic mean, median, SD, minimum and maximum) will be presented by treatment group and time point for both absolute values and changes from Baseline, both for all subjects and for subjects experiencing infusion reactions.

Any values are that BLQ or ALQ will be handled as described in Section 4.2.4.

10.6 [redacted]

[redacted] will be listed by treatment group and time point. I subjects experiencing infusion reactions changes from Baseline will be added to the listing. For subjects experiencing infusion reactions, descriptive summaries (including n, arithmetic mean, median, SD, minimum and maximum) will be presented by treatment group and time point for both absolute values and changes from Baseline.

Any values are that BLQ or ALQ will be handled as described in Section 4.2.4.

11 SAFETY ANALYSES

All safety analyses will be presented using the SS. Listings will be presented by Dosing Period, treatment group and subject; tabulations will be presented by Dosing Period and treatment group in the following order:

Dosing Period 1:

- Placebo
- UCB7665 7mg/kg

For Dosing Period 2 and the Observation Period the following treatment groups will be considered for analysis and will be displayed as such in the TFLs (the first two groups will only be utilized for observation period in case patients do not receive any dosing in period 2):

- Placebo
- UCB7665 7mg/kg
- Placebo - UCB7665 7mg/kg
- Placebo - UCB7665 4mg/kg
- UCB7665 7mg/kg - UCB7665 7mg/kg
- UCB7665 7mg/kg - UCB7665 4mg/kg

11.1 Extent of exposure

All drug administration details (including date, start and stop time of infusion, location of infusion site, interruptions, discontinuations, body weight, dose, volume delivered, percent of planned dose) will be listed using the SS. The reasons for any interruptions or discontinuations will be included in the listing. The duration of the infusion, in minutes, will also be calculated.

The percent of planned dose administered will be calculated based on the actual volume delivered as follows:

Percent of planned dose (%) = (Actual volume/Planned volume)*100

For all subjects the planned volume is 10mL.

In Dosing Period 1 subjects will be randomized (1:1) to receive one of the following treatments:

- 3 sc doses of UCB7665 7mg/kg at 1 week intervals
- 3 sc doses of placebo at 1 week intervals

In Dosing Period 2 subjects will be rerandomized (1:1) to receive one of the following treatments:

- 3 sc doses of UCB7665 7mg/kg at 1 week intervals
- 3 sc doses of UCB7665 4mg/kg at 1 week intervals

The randomization in Dosing Period 2 will be stratified by the treatment received in Dosing Period 1.

11.2 Adverse events

Adverse events will be recorded from the time of informed consent until study completion. All AEs will be coded (Section 3.8) and categorized by relationship to UCB7665.

In addition, AEs will be classified according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 for severity. For any AEs where it is not possible to provide a CTCAE grading, the events will be assessed using a standard intensity classification (mild, moderate and severe).

A TEAE is defined as any event that was not present prior the first administration of IMP or any unresolved event already present before the first administration of IMP that worsens in intensity following exposure to treatment. Adverse events starting before the first administration of IMP or after 8 weeks following the final dose of IMP will not be considered TEAEs. Thus AEs before first dosing and AEs after 8 weeks following the final dose will be combined in one category. Such events will be listed only.

Where dates are missing or partially missing, AEs will be assumed to be treatment-emergent. Handling of missing dates/times for classification of AEs as TEAEs is described in Section 4.2.7.

The following rules will be used to assign a TEAE to a study period:

- Dosing Period 1: a TEAE will be assigned to Dosing Period 1 for the tabulations if the start date/time of the event is at the time of or after the first administration of IMP on Day 1, up to the time of actual first administration of IMP in Dosing Period 2 (planned for Day 29)
- Dosing Period 2 or Observation Period: a TEAE will be assigned to 'Dosing Period 2 or Observation Period' for the tabulations if the start date/time of the event is at the time of or after the first administration of IMP (planned for Day 29), until 8 weeks following the final dose; events starting later than 8 weeks following the final dose of IMP are not considered TEAEs

In the case of early withdrawal in either Dosing Period 1 or 2, a TEAE will be assigned to the respective Dosing Period based on the last received infusion.

The number and percentage of subjects who experience TEAEs will be summarized for each Dosing Period and treatment group. In all tabulations, TEAEs occurring during the Observation Period will be presented as part of Dosing Period 2. In addition summaries for total active and all treatments will be created. The following summaries will be presented:

- Incidence of TEAEs (overview including number and percentage of subjects with any TEAEs, serious TEAEs, discontinuations due to TEAEs, related TEAEs, TEAEs with CTCAE Grade 3 and above [or rated as 'severe' for events with no CTCAE classification], and deaths; event counts will also be included)
- Incidence of TEAEs by SOC, HLT and PT
- Incidence of TEAEs during the Dosing Period by SOC, HLT and PT
- Incidence of serious TEAEs by SOC, HLT and PT
- Incidence of non-serious TEAEs by SOC, HLT and PT
- Incidence of AEs of special interest by SOC, HLT and PT

- Incidence of AEs of interest by SOC, HLT and PT
- Incidence of TEAEs by relationship, SOC, HLT and PT
- Incidence of serious TEAEs by relationship, SOC, HLT and PT
- Incidence of non-serious TEAEs by relationship, SOC, HLT and PT
- Incidence of fatal TEAEs by relationship, SOC, HLT and PT
- Incidence of TEAEs by maximum relationship, SOC, HLT and PT
- Incidence of TEAEs by maximum intensity (mild, moderate and severe), SOC, HLT and PT
- Incidence of non-serious TEAEs above threshold of 5% of subjects by SOC and PT
- Incidence of non-serious TEAEs above threshold of 5% of subjects by relationship, SOC and PT
- Discontinuation due to AEs

Summary tables will contain counts of subjects, percentages of subjects in parentheses and the number of events. A subject who has multiple events in the same SOC, HLT and PT will be counted only once in the subject counts but all events will be included.

In the TEAEs above threshold of 5% only those AEs will be included which are present at 5% of the subjects within a treatment group.

Adverse event summaries will be ordered by alphabetical SOC, alphabetical HLT within SOC and decreasing frequency of PT in the 'Period 2 UCB7665 7mg/kg - UCB7665 7mg/kg' column for tables.

A listing will be presented by treatment group and subject for all AEs. This will include the onset date/time and outcome date/time of the event (including relative days), the AE duration, days since first dose of IMP, days since most recent dose of IMP, pattern of event, severity/intensity, relationship, action taken and outcome. In addition the listing will flag AEs that led to discontinuation, TEAEs, serious adverse events (SAEs), AEs of interest, AEs of special interest and infusion reactions.

AEs of interest are:

- Severe headache
- Moderate to severe diarrhea
- Moderate to severe abdominal pain
- Moderate to severe vomiting

AEs of special interest are Potential Hy's Law, defined as ≥3x upper limit of normal (ULN) Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN alkaline phosphatase (ALP), with no alternative explanation for the biochemical abnormality.

11.3 Clinical laboratory evaluations

Laboratory data (chemistry, hematology and urinalysis) and changes from Baseline (if applicable) for numeric variables will be summarized by treatment group and time point. Any laboratory measurements that are BLQ or ALQ will be handled as described in Section 4.2.2. Values outside the reference range for the numeric variables will be flagged in the listings. The reference ranges will also be reported in the listings. In addition, the listings will include a flag for values identified as treatment-emergent markedly abnormal (TEMA)/potentially clinically significant (PCS) as defined by the criteria outlined in Table 14-7.

Chemistry, hematology and coagulation parameters will be summarized by treatment group at each time point, for both absolute values and changes from Baseline.

The laboratory variables are presented in Table 11–1. For selected laboratory variables that are identified in Table 11–1, the change in category from Baseline will be presented in shift tables at each post-Baseline assessment.

Table 11–1: Clinical laboratory measurements

Category	Panel	Variable
Hematology	Red blood cell	RBC count, hemoglobin, hematocrit, HbA1c
	Platelet	Platelet count[a]
	White blood cell	WBC count
	White blood cell differential	Absolute counts: ANC, basophils, eosinophils, ALC, monocytes Percentages: neutrophils/leukocytes, basophils/leukocytes, eosinophils/leukocytes, lymphocytes/leukocytes, monocytes/leukocytes
Chemistry	Electrolytes	Sodium, chloride, potassium, calcium, phosphate, magnesium
	Enzymes	Amylase, Creatine kinase
	Hormones	procalcitonin
	Kidney function	Urea-N, creatinine[a]
	Proteins	Total protein, albumin[a], alpha- and beta- globulins, hsCRP[a]
	Liver function	AST[a], ALT[a], GGT, ALP, LDH, total bilirubin, direct bilirubin (if indicated)

Table 11–1: Clinical laboratory measurements

Category	Panel	Variable
	Lipids	Total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides
Urinalysis	Dipstick	pH, protein, glucose, ketones, urobilinogen, bilirubin, blood, nitrite, leucocytes
	Quantitative	Albumin, creatinine, protein
	Sediment	Leukocytes

[a] Shift table will be created for these variables
ALC=absolute lymphocyte count; ALP=alkaline phosphatase; ALT=alanine aminotransferase; ANC=absolute neutrophil count; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; GGT=gamma-glutamyltransferase; HbA1c=glycosylated hemoglobin; HBsAG=hepatitis B surface Antigen; HCV Ab=hepatitis C virus antibody; HDL=high density lipoprotein; hsCRP=high sensitivity C-reactive protein; LDH=lactate dehydrogenase; LDL=low density lipoprotein; RBC=red blood cell; WBC=white blood cell.

11.3.1 Potential drug-induced liver injury

A separate listing will present subjects who meet one or more of the following potential drug-induced liver injury (PDILI) criteria at any visit:

- Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) ≥5x Upper limit of normal (ULN)
- ALT or AST increase ≥3x ULN and Total bilirubin ≥2x ULN
- ALT or AST ≥3x ULN who exhibit temporally associated symptoms of hepatitis or hypersensitivity
- ALT or AST ≥3xULN (and ≥2x Baseline) and <5xULN, total bilirubin <2xULN, and no eosinophilia (i.e., ≤5%), with no fever, rash, or symptoms of hepatitis.

The listing will display only visits for which at least one of the above criteria was fulfilled for a given subject, and will display all results obtained at that visit for the specified parameters.

A summary of subjects who met the criteria for PDILI will be presented together with any additional relevant data collected, if applicable.

11.4 Vital signs, physical findings, and other observations related to safety

11.4.1 Vital signs

The following vital signs measurements will be obtained:

- Pulse rate
- Systolic and diastolic blood pressure
- Temperature (oral preferred, ear or axillary permitted)

- Respiratory rate

A by-subject listing of all vital sign measurements and change from Baseline will be presented by treatment group and time point. The listing will include a flag for values identified as TEMA/PCS as defined by the criteria outlined in Table 14-7.

Descriptive statistics will be reported for all vital sign measurements. Measured values and changes from Baseline will be summarized by vital signs variables and time point for each treatment group. Summarization will be as treated, subjects who missed treatments will not be summarized.

Repeated and unscheduled measurements will be handled as described in Section 4.3.

11.4.2 Electrocardiograms

Standard 12-lead ECG recordings will be taken in triplicate with the subject resting in the supine position for at least 15 minutes and before obtaining any blood samples for assessments of laboratory variables. The following variables will be reported:

- Heart rate
- RR interval
- PQ/PR interval
- QRS duration
- QT interval
- QT corrected for heart rate using Bazett's formula ($QTcB = QT/RR^{1/2}$)
- QT corrected for heart rate using Fridericia's formula ($QTcF = QT/RR^{1/3}$)

The individual measurements and the mean of the triplicate measurements will be reported in the by-subject listings. The listing will include the change from Baseline (based on the mean of the triplicate measurements at each time point) and will be presented by treatment group and time point. The listing will also include a flag for values identified as TEMA/PCS TEMA/PCS as defined by the criteria outlined in Table 14-7.

Measured values and changes from Baseline will be summarized by treatment group at each time point and by ECG variable (based on the mean of the triplicate values at each time point). Summarization will be as treated, subjects who missed treatments will not be summarized.

Electrocardiogram findings for the individual triplicate measurements will be listed separately.

Frequency counts of normal vs abnormal findings will be presented by treatment group and time point.

Repeated and unscheduled measurements will be handled as described in Section 4.3.

In the event that the complete set of triplicate measurements is not available at a specified time point the data will be handled as described in Section 4.2.6.

11.4.3 Exploratory safety biomarkers

Serum biomarkers ([redacted], [redacted] only in subjects with severe headache and/or moderate to severe GI

disturbance) will be listed by treatment group and time point including changes from Baseline. Descriptive summaries (including n, arithmetic mean, median, SD, minimum and maximum) will be presented by treatment group and time point for both absolute values and changes from Baseline.

Mean and mean change from Baseline values will be plotted over time by treatment group with all treatment groups overlaid on the same plot and separate plots for each variable.

Any values that are BLQ or ALQ will be handled as described in Section 4.2.2.

11.4.4 Physical examination

Results of physical examination will be listed.

11.4.5 Other safety variable

Results of interferon-gamma release assay (IGRA) tuberculosis test will be listed.

Results of Serum pregnancy test will be listed.

Results of tuberculosis signs and symptoms questionnaire will be listed.

Results of serology testing for human immunodeficiency virus (HIV), Hepatitis B and Hepatitis C will be listed.

Suicidal ideation will be queried according to the scheduled in table 5.1 of the CSP. A full Columbia Suicide Severity Rating Scale (C-SSRS) assessment will be performed only when subject has a positive response to the suicidal ideation query. Results of suicidal ideation and C-SSRS will be listed.

Full Neurological examination will be performed at screening and at Visit 9 (Day 29). Brief neurological examination will be performed at Visit 2 (Baseline) and Visit 9 (day 29). Results of the neurological examinations will be listed.

12 OTHER ANALYSES

Vaccination-specific antibody titres ([redacted] will be listed.

Subjects experiencing severe headache will complete the Headache Questionnaire and will complete the questionnaire daily until resolution (ie, if headache becomes moderate or mild, normal collection of AEs should apply); this assessment will be followed by a neurological assessment (including fundoscopy). Further workup will be performed (if indicated) at the discretion of the investigator and may include, eg, a computed tomography (CT) scan, magnetic resonance imaging (MRI) and/or a lumbar puncture (LP) for cerebral spinal fluid(CSF) collection. In addition assessment of exploratory safety biomarkers should be performed for subjects experiencing severe headache. These investigations will be performed in order to further understand the mechanism of headache in these subjects.

The results of the headache questionnaire, neurological examination and any additional tests performed (CT scan, fundoscopy and LP for CSF collection) will be listed for each subject. No summary tabulations will be provided for these assessments

Stool collection and analysis will be performed for subjects reporting moderate or severe diarrhea. Results of the analysis will be listed for each subject. No summary tabulation will be provided this assessment.

Subject's body weight will be listed and summarized over all treatment groups.

13 REFERENCES

The following information (eg, questionnaire) is copyrighted and UCB does not have permission to disclose the contents.

[redacted]

14.2 MG-composite score

The MG-composite score items and associated scores are provided in Table 14–2. The total score is obtained by summing the responses to each individual item. Thus the score ranges from 0 to 50.

In the event of missing data at a particular time point, the MG-composite score will not be calculated. Due to the different weighting applied to each item it is not possible to impute the missing data with the average score across the remaining items.

Table 14–2: MG-composite score items and scoring algorithm

Item	Result/Grade	Result/Grade	Result/Grade	Result/Grade
Ptosis, upward gaze (physician examination)	>45 seconds/0	11-45 seconds/1	1-10 seconds/2	Immediate/3
Double vision on lateral gaze, left or right (physician examination)	>45 seconds/0	11-45 seconds/1	1-10 seconds/3	Immediate/4
Eye closure (physician examination)	Normal/0	Mild weakness (can be forced open with effort)/0	Moderate weakness (can be forced open easily)/1	Severe weakness (unable to keep eyes closed)/2
Talking (patient history)	Normal/0	Intermittent slurring or nasal speech/2	Constant slurring or nasal but can be understood/4	Difficult to understand speech/6
Chewing (patient history)	Normal/0	Fatigue with solid food/2	Fatigue with soft food/4	Gastric tube/6
Swallowing (patient history)	Normal/0	Rare episode of choking or trouble swallowing/2	Frequent trouble swallowing eg, necessitating changes in diet/5	Gastric tube/6
Breathing (thought to be caused by MG)	Normal/0	Shortness of breath with exertion/2	Shortness of breath at rest/4	Ventilator dependence/9

Item	Result/Grade	Result/Grade	Result/Grade	Result/Grade
Neck flexion or extension (weakest) (physician examination)[a]	Normal/0	Mild weakness/1	Moderate weakness (ie, 50% weak, +/-15%)/3	Severe weakness/4
Shoulder abduction (physician examination) [a]	Normal/0	Mild weakness/2	Moderate weakness (ie, 50% weak, +/-15%)/4	Severe weakness/5
Hip flexion (physician examination) [a]	Normal/0	Mild weakness/2	Moderate weakness (ie, 50% weak, +/-15%)/4	Severe weakness/5

[a] Moderate weakness for head and neck items should be construed as weakness that equals roughly 50%+/-15% of expected normal strength. Any weakness milder than that would be mild and any weakness more severe than that would be classified as severe.

14.3 MG-Activities of Daily Living

The MGADL testing form is provided in Table 14–3. The total score is obtained by summing the responses to each individual item. Thus the score ranges from 0 to 24.

In the event of missing data the following rules will be applied:

- If 1 or 2 items are not answered, the overall score will be obtained by imputing the missing items with the average score across the remaining items at the specific visit. The imputed value will be rounded to one decimal place
- If more than 2 items are missing the overall score will not be calculated

The following information (eg, questionnaire) is copyrighted and UCB does not have permission to disclose the contents.

[redacted]

14.5 MG-Impairment Index

The MG-II is provided in Table 14–6. The MGII can be summarized as a total score and also as 2 sub-scores reflecting an Ocular and a Generalized domain.

The total score is the raw sum of all the items, including the clinical examination and the patient-reported questionnaire.

The ocular score is calculated by summing 8 items reflecting ocular impairments. These items are: patient questionnaire items 1 to 6 and examination items 1 and 2.

The generalized score is calculated by adding items 7 to 22 from the patient questionnaire and items 3 to 6 from the examination.

For missing answers, impute the average score for the other items in the same domain or region (ocular, or generalized). Only calculate the total sum-score when there are ≤ 3 items missing.

The following information (eg, questionnaire) is copyrighted and UCB does not have permission to disclose the contents.

14.6 TEMA/PCS criteria for Rozanolixizumab program

TEMA/PCS criteria for the clinical studies within the Rozanolixizumab clinical development program. These values are based on the CTCAE criteria version 4.03, grade 3 toxicity definitions and have been adapted to study needs.

Table 14-7: TEMA/PCS Values for Rozanolixizumab Clinical Development Program Based on CTCAE Grades

Domain	Term	Test	Criteria	Unit
Biochemistry	Hypoalbuminemia	Albumin	<2	g/dL
Biochemistry	Alkaline phosphatase increased	ALP	>5xULN	n/a
Biochemistry	Alanine aminotransferase increased	ALT	>5xULN	n/a
Biochemistry	Serum Amylase increased	Amylase	>2xULN	n/a
Biochemistry	Aspartate aminotransferase increased	AST	>5xULN	n/a
Biochemistry	Blood bilirubin increased	Bilirubin	>3 x ULN	n/a
Biochemistry	Hypercalcemia	Calcium	corrected >13.5 (>3.1); ionized (>1.8)	mg/dL (mmol/L)
Biochemistry	Hypocalcemia	Calcium	corrected <7 (<1.75); ionized (<0.9)	mg/dL (mmol/L)
Biochemistry	Cholesterol high	Cholesterol	>400 (>10.34)	mg/dL (mmol/L)
Biochemistry	Creatine phosphokinase increased	CK	>5xULN	n/a
Biochemistry	Creatinine increased	Creatinine	>3x baseline or >3 x ULN	n/a
Biochemistry	Acute kidney injury	Creatinine	>3x baseline or >4 x ULN	n/a
Biochemistry	Chronic kidney disease	eGFR or CrCl	<=29	ml/min/1.73 m^2
Biochemistry	GGT increased	GGT	>5xULN	n/a
Biochemistry	Hyperglycemia	Glucose	>250 (>13.9)	mg/dL (mmol/L)

Table 14-7: TEMA/PCS Values for Rozanolixizumab Clinical Development Program Based on CTCAE Grades

Domain	Term	Test	Criteria	Unit
Biochemistry	Hypoglycemia	Glucose	<40 (<2.2)	mg/dL (mmol/L)
Biochemistry	Hypermagnesemia	Magnesium	>3 (>1.23)	mg/dL (mmol/L)
Biochemistry	Hypomagnesemia	Magnesium	<0.9 (<0.4)	mg/dL (mmol/L)
Biochemistry	Hypophosphatemia	Phosphate	<2 (0.6)	mg/dL (mmol/L)
Biochemistry	Hyperkalemia	Potassium	>6	mmol/L
Biochemistry	Hypokalemia	Potassium	<3	mmol/L
Biochemistry	Hypernatremia	Sodium	>155	mmol/L
Biochemistry	Hyponatremia	Sodium	<130	mmol/L
Biochemistry	Hypertriglyceridemia	Triglycerides	>500 (>5.7)	mg/dL (mmol/L)
Biochemistry	Hyperuricemia	Uric acid	n/a	n/a
Body parameters	Obesity	BMI	>=30	kg/m^2
ECG	QT corrrected interval prolonged (Bazett)	QTcB	>=501 ms OR increase >=60 ms compared to Baseline	ms
ECG	QT corrrected interval prolonged (Fridericia)	QTcF	>=501 ms OR increase >=60 ms compared to Baseline	ms
ECG	PR prolongation	PR	>=210 ms AND >=10 ms change from Baseline	ms
Haematology	Anaemia	Hemoglobin	<8 (<4.9)	g/dL (mmol/L)
Haematology	Haemoglobin increased	Hemoglobin	increase >4 over ULN or increase >4 above Baseline (if Baseline is above ULN)	mg/dL
Haematology	Lymphocyte count decreased	Lymphocytes	<500 (<0.5)	$/mm^3$ (10^9/L)
Haematology	Lymphocyte count increased	Lymphocytes	>20,000 (>20)	$/mm^3$ (10^9/L)
Haematology	Neutrophil count decreased	Neutrophils	<1000 (<1)	$/mm^3$ (10^9/L)

Table 14-7: TEMA/PCS Values for Rozanolixizumab Clinical Development Program Based on CTCAE Grades

Domain	Term	Test	Criteria	Unit
Haematology	Platelet count decreased	Platelets	<50,000 (<50)	/mm^3 (10^9/L)
Haematology	Leukocytosis	WBC	>20,000	/mm^3
Haematology	White blood cell decreased	WBC	<2000 (<2)	/mm^3 (10^9/L)
Haematology	Monocytes increased	Monocytes	>2000 (>2)	/mm^3 (10^9/L)
Vital Signs	Hypertension	Blood pressure systolic	≥180 and an increase from Baseline of ≥15	mmHg
Vital Signs	Hypertension	Blood pressure diastolic	>105 and an increase from Baseline of ≥15	mmHg
Vital Signs	Hypotension	Blood pressure systolic	≤90 and a decrease from Baseline of ≥20	mmHg
Vital Signs	Hypotension	Blood pressure diastolic	<50 and a decrease from Baseline of ≥15	mmHg

15 AMENDMENT(S) TO THE STATISTICAL ANALYSIS PLAN (SAP) (IF APPLICABLE)

15.1 Amendment 1

15.1.1 Rationale for the amendment

Amendment 1 is added to include TEMA/PCS for laboratory measurements as well as ECGs and to substitute the already incorporated vital sign thresholds.

In addition small textual changes have been made.

15.1.2 Specific changes:

Change #1

In section 3.1 treatment groups for observation period were updated to include observation periods for subjects withdrawn after period 1.

Old text

For Dosing Period 2 and the Observation Period the following Treatment Groups will be considered for analysis:

- Placebo - UCB7665 7mg/kg
- Placebo - UCB7665 4mg/kg
- UCB7665 7mg/kg - UCB7665 7mg/kg
- UCB7665 7mg/kg - UCB7665 4mg/kg

New text

For Dosing Period 2 and the Observation Period the following treatment groups will be considered for analysis and will be displayed as such in the TFLs (the first two groups will only be utilized, for observation period, in case patients do not receive any dosing in period 2):

- Placebo
- UCB7665 7mg/kg
- Placebo - UCB7665 7mg/kg
- Placebo - UCB7665 4mg/kg
- UCB7665 7mg/kg - UCB7665 7mg/kg
- UCB7665 7mg/kg - UCB7665 4mg/kg

Change #2

In section 3.6 treatment groups for observation period were updated to include observation periods for subjects withdrawn after period 1.

Old text

For Dosing Period 2 and the Observation Period the following Treatment Groups will be considered for analysis:

- Placebo - UCB7665 7mg/kg
- Placebo - UCB7665 4mg/kg
- UCB7665 7mg/kg - UCB7665 7mg/kg
- UCB7665 7mg/kg - UCB7665 4mg/kg

New text

For Dosing Period 2 and the Observation Period the following treatment groups will be considered for analysis and will be displayed as such in the TFLs (the first two groups will only be utilized, for observation period, in case patients do not receive any dosing in period 2):

- Placebo
- UCB7665 7mg/kg
- Placebo - UCB7665 7mg/kg
- Placebo - UCB7665 4mg/kg
- UCB7665 7mg/kg - UCB7665 7mg/kg
- UCB7665 7mg/kg - UCB7665 4mg/kg

Change #3

In section 6.1 the population for summarizing demographic characteristics was updated;

Old text

All demographic characteristics obtained at the Screening visit will be summarized for the ES (apart from the date of birth).

New text

All demographic characteristics obtained at the Screening visit will be summarized for the RS (apart from the date of birth).

Change #4

In section 6.1 the following sentence was added;

The demographic characteristics listing will include a flag for BMI values identified as TEMA/PCS as defined by the criteria outlined in Table 14-7.

Change #5

Section 6.2 “Other Baseline characteristics” was added.

Change #6

In section 8.3.7, clinically meaningful improvement was defined.

Change #7

In section 11, treatment groups were updated as observation periods will be displayed for subjects withdrawn after period 1.

Change #8

In section 11.1 the following sentence were added;

In Dosing Period 1 subjects will be randomized (1:1) to receive one of the following treatments:

- 3 sc doses of UCB7665 7mg/kg at 1 week intervals
- 3 sc doses of placebo at 1 week intervals

In Dosing Period 2 subjects will be rerandomized (1:1) to receive one of the following treatments:

- 3 sc doses of UCB7665 7mg/kg at 1 week intervals
- 3 sc doses of UCB7665 4mg/kg at 1 week intervals

The randomization in Dosing Period 2 will be stratified by the treatment received in Dosing Period 1.

Change #9 In section 11.3 the following sentence was added;

In addition, the listings will include a flag for values identified as TEMA/PCS as defined by the criteria outlined in Table 14-7.

Change #10

In section 11.3.1 the potential drug-induced liver injury (PDILI) criteria were updated as follows;

Old text

- Alanine aminotransferase (ALT) ≥3x ULN or ≥2x baseline value
- Aspartate aminotransferase (AST) ≥3x ULN or ≥2x baseline value
- Total bilirubin ≥2x ULN

New text

- Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) ≥5x Upper limit of normal (ULN)
- ALT or AST increase ≥3x ULN and Total bilirubin ≥2x ULN
- ALT or AST ≥3x ULN who exhibit temporally associated symptoms of hepatitis or hypersensitivity
- ALT or AST ≥3xULN (and ≥2x Baseline) and <5xULN, total bilirubin <2xULN, and no eosinophilia (i.e., ≤5%), with no fever, rash, or symptoms of hepatitis.

Change #11

In section 11.4 a paragraph was updated as below and table 11-2 was deleted.

Old text

The listing will include a flag for measurements identified as treatment-emergent markedly abnormal (TEMA)/potentially clinically significant (PCS) as per criteria outlined in Table 11–2.

New text

The listing will include a flag for values identified as TEMA/PCS as defined by the criteria outlined in Table 14-7.

Change #12

In section 11.4.2 text was updated as below.

Next text

The following variables will be reported:

- Heart rate
- RR interval
- PQ/PR interval
- QRS duration
- QT interval
- QT corrected for heart rate using Bazett's formula ($QTcB = QT/RR^{1/2}$)
- QT corrected for heart rate using Fridericia's formula ($QTcF = QT/RR^{1/3}$)

The listing will also include a flag for values identified as TEMA/PCS as defined by the criteria outlined in Table 14-7.

Deleted text

The frequency of ECG outliers, defined as QTc>480 or QTc change from baseline >30, will be summarized by treatment group and time point.

Change #13

Section 14.6 was added.

Change #14

Section 6.2 was updated; including past medications and providing clarity about summaries to be produced.

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

This document has been reviewed and approved per the Review and Approval of Clinical Documents Standard Operating Procedures. Signatures indicate that the final version of the Statistical Analysis Plan (SAP) or amended SAP is released for execution.

Approval Signatures

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