PROTOCOL MG0002

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

PHASE 2A

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

[redacted]	[redacted]
[redacted]	[redacted]
ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
[redacted]	[redacted]
[redacted]	[redacted]
AST	aspartate aminotransferase
BAFF	B-cell activating factor
BP	blood pressure
CDMS	clinical data management system
CI	confidence interval
CPM	Clinical Project Manager
CRO	Contract Research Organization
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DCP	Data Cleaning Plan
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic Case Report Form
ES	Enrolled Set
FAS	Full Analysis Set
Fc	crystalizable fragment
FcRn	neonatal Fc receptor for IgG
FV	Final Visit
FVC	forced vital capacity
GCP	Good Clinical Practice
GI	gastrointestinal

GMP	Good Manufacturing Practice
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgA	immunoglobulin A
IgE	immunoglobulin E
IgG	immunoglobulin G
IGRA	interferon-gamma release assay
IgM	immunoglobulin M
IMP	investigational medicinal product
IPI	interpotential interval
IRB	Institutional Review Board
IRT	interactive response technology
ITP	immune thrombocytopenic purpura
iv	intravenous
IVIg	intravenous immunoglobulin
LLOQ	lower limit of quantification
LOCF	last observation carried forward
LS	least squares
LTBI	Latent tuberculosis infection
MCD	mean consecutive difference
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
miRNA	micro ribonucleic acid
mRNA	messenger ribonucleic acid
[redacted]	[redacted]
[redacted]	[redacted]
NMJ	neuromuscular junction

NTMBI	non-tuberculosis mycobacterium infection
PD	pharmacodynamic(s)
PDILI	potential drug-induced liver injury
PEOT	premature end of treatment
PK	pharmacokinetic(s)
PLEX	plasma exchange
PPS	Per-Protocol Set
PRO	patient-reported outcome
PS	Patient Safety
[redacted]	[redacted]
QMG	quantitative myasthenia gravis
QTc	corrected QT interval
RNA	ribonucleic acid
RS	Randomized Set
[redacted]	[redacted]
SAE	serious adverse event
SAP	Statistical Analysis Plan
sc	subcutaneous
SD	standard deviation
SFEMG	single fiber electromyography
SOP	Standard Operating Procedure
SS	Safety Set
TB	tuberculosis
TEAE	Treatment-emergent adverse event
TNIP1	TNFAIP3-interacting protein 1
TST	Tuberculin skin test
ULN	upper limit of normal
USA	United States of America

1 SUMMARY

The MG0002 study is a Phase 2a, multicenter, randomized, investigator- and subject-blind, placebo-controlled, 2-arm, repeat dose, treatment sequence study which will evaluate the efficacy, safety, and tolerability of chronic-intermittent treatment with UCB7665 in subjects with moderate to severe generalized myasthenia gravis (MG). UCB7665 will be administered as subcutaneous (sc) doses of 4mg/kg or 7mg/kg, in subjects ≥18 years of age.

The study is planned to be conducted at approximately 30 sites in United States of America (USA), Canada, and Europe, with possible extension to other regions and countries. A total of 42 subjects are planned to enter the Treatment Period in the study. The maximum study duration for an individual subject is approximately 18 weeks.

The study will consist of 3 Periods: Screening, Treatment, and Observation. After Screening, subjects will enter the Treatment Period, which will consist of Dosing Period 1 followed by Dosing Period 2. Subjects will receive 3 doses of investigational medicinal product (IMP) at weekly intervals during each dosing period as follows:

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

The Observation Period will span 8 weeks after the final dose of UCB7665, with a Final Visit (FV) being scheduled at Visit 20. The sc infusions will last approximately 30 minutes, and subjects will be required to remain in the hospital/clinic at least 4 hours for safety monitoring after each infusion.

A Data Monitoring Committee (DMC) will be implemented as described in Section 14.7.

The primary efficacy variable will be the change from Baseline in Quantitative MG (QMG) score to Visit 9 (Day 29). The secondary efficacy variables will be the change from Baseline in MG-Composite score to Visit 9 (Day 29) and the change from Baseline in MG-Activities of Daily Living (MGADL) score to Visit 9 (Day 29). Other efficacy variables will be the following: 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 severity, fatigue scales and Myasthenia Gravis Impairment Index (MGII) scores at each scheduled assessment during Treatment and Observation Periods; and change in mean consecutive difference (MCD) in jitter (single fiber electromyography [SFEMG]) studies from Baseline to Visit 9 for the subjects consenting to this measurement at participating sites.

Other and exploratory variables include: safety and tolerability variables, pharmacokinetic (PK), pharmacodynamic (PD), and immunologic variables.

Safety and tolerability variables include the following: occurrence of treatment-emergent adverse events (TEAEs); vital sign values and changes from Baseline (systolic and diastolic blood pressure [BP], temperature, pulse rate, respiratory rate, and body weight); 12-lead electrocardiogram (ECG) values and change from Baseline; laboratory values (hematology, clinical chemistry, and urinalysis) and changes from Baseline; change from Baseline in exploratory safety biomarkers (may include but not limited to [redacted] in subjects experiencing severe headache and/or moderate to severe gastrointestinal (GI) disturbance; and TEAEs leading to withdrawal of IMP.

Plasma concentration of UCB7665 over time will be assessed as the PK variable. The main PD variables will be the maximum decrease from Baseline in serum total immunoglobulin G (IgG) concentration; value and change from Baseline in total serum IgG concentrations at each scheduled assessment during Treatment and Observation Periods; value and change from Baseline in serum IgG subclass concentrations at each scheduled assessment during Treatment and Observation Periods; and change in MG-specific autoantibody [redacted] levels in serum from Baseline at each scheduled assessment during Treatment and Observation Periods. Additionally, change from Baseline in other immunological variables and other exploratory biomarkers during the Treatment and Observational Periods will be assessed.

During this study, subjects will also have the option of providing additional informed consent for exploratory deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) (ie, messenger RNA [mRNA] and micro RNA [miRNA]) analyses (see Section 5.1.1) to understand the cause, progression, and appropriate treatment of MG. Participation in this additional portion of the study is optional and does not preclude subject's eligibility for participation in the main study. The additional genomic samples must not be collected if the subject has not consented to participate in this exploratory genomic substudy.

2 INTRODUCTION

UCB7665 is a humanized anti-neonatal Fc receptor for IgG (FcRn) monoclonal antibody that has been specifically designed to inhibit IgG binding to FcRn without inhibiting albumin binding to FcRn. UCB7665 is being developed as an inhibitor of FcRn activity with the aim to reduce the concentration of pathogenic IgG in patients with IgG autoantibody mediated diseases.

The neonatal Major histocompatibility complex-class FcRn recycles IgG and albumin from most cells and transports it bi-directionally across epithelial barriers to affect systemic and mucosal immunity. It was shown that FcRn rescues both IgG and albumin from intracellular lysosomal degradation by recycling it from the sorting endosome to the cell surface (Anderson et al, 2006). With respect to IgG, this is achieved by interaction of IgG with the receptor, FcRn. Thus in effect FcRn salvages IgG, and blockade of FcRn accelerates removal of endogenous IgG.

As individual disease entities, IgG autoantibody mediated conditions are relatively rare. Treatment of these disorders remains a difficult clinical problem, requiring in many of these conditions the long-term use of high-dose corticosteroids alone or combined with cytotoxic agents. These therapeutic approaches are not effective in all patients and conditions and have broad immunosuppressive effects causing considerable toxicity and treatment-related morbidity.

Treatments aimed at reducing the quantity of circulating IgG autoantibody, including plasmapheresis, immunoadsorption, or high-dose intravenous immunoglobulin (IVIg), are being used for primary and secondary therapy of autoimmune disease, particularly where corticosteroid-based immune suppression is not or no longer effective (eg, immune thrombocytopenic purpura [ITP], MG, and chronic inflammatory demyelinating polyradiculoneuropathy). The therapeutic approach of these treatments is thought to be based on lowering levels of pathogenic autoantibodies, which represents rational and effective treatment modalities of autoimmune diseases.

Myasthenia gravis is a rare autoimmune disorder of the peripheral motor system in which autoimmune antibodies most commonly form [redacted] at the neuromuscular junction (NMJ). The [redacted] autoantibody impairs the ability of [redacted] to bind to receptors, and leads to the destruction of receptors, either by inducing the muscle cell to eliminate the receptors through endocytosis or by complement fixation. A second category of MG is due to autoantibodies against the [redacted] which is required for the formation of the NMJ. Antibodies against [redacted] inhibit signaling, resulting in a decrease in patency of the NMJ, and the consequent symptoms of MG. In both categories, this results in a characteristic pattern of progressively reduced muscle strength with repeated muscle use and muscle strength recovery following a period of rest. Additional antibodies have been found to be associated with MG but less is yet known about them and they appear less common than the main two. The essential role of the autoimmune antibodies in mediating this pathology is supported by the improvement seen after plasma exchange (PLEX). Plasma Exchange which reduces IgG levels including pathogenic IgG autoantibody is used both in patients non-responsive to [redacted] inhibitors or immunosuppressive treatments and in patients experiencing myasthenic crisis (Gilhus and Verschuuren, 2015).

Although the prognosis of MG has markedly improved over the last decades, with new therapies dramatically improving survival, significant mortality and even morbidity remains an issue. Treatment of MG remains a difficult clinical problem, requiring the long-term use of high-dose corticosteroids alone or combined with cytotoxic agents. Many of the therapies thought to be effective in MG have insufficient data to clearly support their use, are not effective in all patients and conditions, and have broad immunosuppressive effects causing considerable toxicity and treatment-related morbidity. Moreover, due to the natural fluctuations in the course of the disease, many patients need an effective treatment for acute situations requiring urgent treatment. Both PLEX and IVIg currently are used as the standard of care to improve symptoms in situations requiring chronic-intermittent treatment; however, neither treatment is approved in the US for MG, and the procedures often are burdensome for the patients. Thus a significant unmet medical need exists in this patient population for an effective chronic-intermittent treatment with increased convenience for patients with generalized MG.

UCB7665 is being developed as an inhibitor of FcRn activity with the aim to reduce the concentration of pathogenic IgG in patients with IgG autoantibody mediated diseases. UCB7665 was derived from a rat antibody with specificity for human FcRn.

Both preclinical studies in nonhuman primates and clinical studies suggest that treatment with UCB7665 may reduce the concentration of pathogenic IgG. The relationship between UCB7665 exposure and the primary PD effect on plasma IgG levels was studied in Cynomolgus monkeys

following single- and repeat dose administrations by both intravenous (iv) and sc routes. UCB7665 mediated a clear dose- and exposure-related decrease in plasma IgG concentrations, achieving 45% to ≥70% decreased IgG concentrations at dose levels ranging from 5 to 30mg/kg in the absence of adverse effects. No consistent or dose-related effects of UCB7665 on albumin levels were observed in these studies.

To date, UCB7665 has been administered to human subjects in 2 clinical studies, UP0018 and TP0001. UP0018 is a completed first-in-human study in 49 healthy subjects. The study evaluated the safety, tolerability, PK, and the PD effect on total IgG levels of single ascending doses of iv and sc administered UCB7665. Doses of UCB7665 1, 4, and 7mg/kg were administered by both iv and sc routes in 3 cohorts, respectively, as an 1 hour infusion. The information from the study is summarized below.

Dose-dependent statistically significant reductions in levels of serum total IgG and dose-dependent reductions in levels of IgG subclasses (IgG 1 to 4) were observed after UCB7665 was administered by iv or sc routes. There were no deaths or serious adverse events (SAEs) reported during the study, and no subjects discontinued the study due to TEAEs. UCB7665 was tolerated with an acceptable safety profile after the single administration of up to 4mg/kg iv and up to 7mg/kg sc doses. For iv administration of UCB7665, the most frequently reported TEAEs were headache (10 subjects [55.6%]) and nasopharyngitis, nausea, pyrexia, and vomiting (each reported by 7 subjects [38.9%]). Four TEAEs with a maximum intensity of severe were reported in this study: headache (3 subjects [50.0%]) and back pain (1 subject [16.7%]); all of which were reported in the UCB7665 7mg/kg iv group. For sc administration of UCB7665, the most frequently reported TEAEs were headache (5 subjects [27.8%]) and back pain and diarrhea (each reported by 3 subjects [16.7%]). Importantly, there were fewer incidences of headaches and GI disturbances following sc administration of UCB7665 compared with iv administration. The safety profile of the sc route of administration, up to 7mg/kg of UCB7665, was considered to be manageable, and all subject reported TEAEs had a maximum intensity of mild or moderate. The peak and total exposure of UCB7665 showed nonlinear increases consistent with target-mediated disposition. Based on the preliminary results, a minimal level of immunogenicity and minimal effects on [redacted] antibodies were observed.

An ongoing study, TP0001, is a multicenter, open-label, single- and multiple-dose, multiple-arm Phase 2a study to evaluate the safety, tolerability, and efficacy of UCB7665 administered as sc doses in adult subjects with primary ITP. This ongoing study is the first study to evaluate multiple doses of UCB7665 and will evaluate multiple Treatment Groups of UCB7665. The dose arms are as follows:

- Dose Arm 1 (15 subjects): UCB7665 4mg/kg sc (5 doses at an interval of 1 week)
- Dose Arm 2 (15 subjects): UCB7665 7mg/kg sc (3 doses at an interval of 1 week)
- Dose Arm 3 (6 to 12 subjects): UCB7665 10mg/kg sc (2 doses at an interval of 1 week)
- Dose Arm 4 (6 to 12 subjects): UCB7665 15mg/kg sc (1 dose)
- Dose Arm 5 (6 to 12 subjects): UCB7665 20mg/kg sc (1 dose)

To date, 15 subjects in Dose Arm 1 (5x4mg/kg) and 13 subjects in Dose Arm 2 (3x7mg/kg) have safely completed his/her treatment period.

MG0002 will be the first study of the use of UCB7665 in MG. The aim of the study is to evaluate the efficacy, safety, and immunological effect of UCB7665, and to gather data for future study planning to fully evaluate the use of UCB7665 in MG.

For more detailed information, refer to the current version of the UCB7665 Investigator's Brochure.

3 STUDY OBJECTIVES

3.1 Primary objective

The primary objective of the study is:

- To evaluate the clinical efficacy of UCB7665 as an chronic-intermittent treatment in subjects with generalized MG who are classified as moderate to severe

3.2 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 sc infusion in subjects with MG
- To assess the effect of UCB7665 as measured by total IgG concentrations in serum

3.3 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 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],

[redacted] only in subjects with severe headache and/or moderate to severe 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

4 STUDY VARIABLES

4.1 Efficacy variables

4.1.1 Primary efficacy variable

The primary efficacy variable is:

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

4.1.2 Secondary efficacy variable

The secondary efficacy variables are:

- Change from Baseline in MG-Composite score to Visit 9 (Day 29)
- Change from Baseline in MGADL score to Visit 9 (Day 29)

4.1.3 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
- 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 MGII scores at each scheduled assessment during Treatment and Observation Periods
- Change in the percentage of normal fiber pairs in jitter (SFEMG) studies from Baseline to Visit 9 for the subjects consenting to this measurement at the participating sites
- Change in 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 clinical improvement

4.2 Other and exploratory variables

4.2.1 Safety variables

The safety variables are the following:

- Occurrence of 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 IMP

The clinical safety laboratory tests are detailed in Table 12.2.

4.2.2 Pharmacokinetic variable

The PK variable is the following:

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

4.2.3 Pharmacodynamic variables

The PD variables are the following:

- Minimum value and maximum (absolute and percentage) decrease from Baseline in serum total 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

4.2.4 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] 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 predose 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

5 STUDY DESIGN

5.1 Study description

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 an chronic-intermittent treatment for subjects with moderate to severe generalized MG.

Approximately 42 randomized subjects will be enrolled at approximately 30 sites from USA, Canada, and Europe 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. During the Screening Visit (Visit 1), subjects will sign a written Informed Consent form prior to the conduct of any study-related procedures. The use of concomitant medication while in the study will be discussed and subjects' eligibility will be determined on the basis of the inclusion/exclusion criteria. 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. For all safety and efficacy measurements, the order specified in the Study Procedures Manual is recommended to be used as a guide.

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 (see Section 5.2, Schedule of Study 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 (see Section 5.2, Schedule of Assessments) in the order specified in Section 8. 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 (see Section 7.10 for further details regarding randomization). 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 postdose 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, 18, and 20 for efficacy and for safety assessments (see Section 5.2, Schedule of Assessments). Subjects will either return to the clinic/hospital, or, if possible and agreed by both investigator and subject, have home visits conducted by certified healthcare professionals, for Visits 17 and 19. 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.

5.1.1 Exploratory genomic analyses

During this study, subjects will also have the option of providing additional informed consent for exploratory genomic (DNA and RNA) analyses. Participation in this additional portion of the study is optional and does not preclude subject's eligibility for participation in the main study. The additional genomic samples must not be collected if the subject has not consented to participate in this exploratory genomic substudy.

If subject provides consent, through a separate informed consent form, blood samples will be drawn as follows:

For DNA: Blood samples will be collected at Baseline (Visit 2), at Visit 8, and prior to the last dose of IMP (Visit 13).

For RNA: Blood samples will be collected at Baseline (Visit 2), at Visit 4, at Visit 8, prior to the last dose of IMP (Visit 13), and at the FV (Visit 20).

For each DNA blood sample a volume of 6mL whole blood is needed and for each RNA sample a volume of 2.5mL whole blood is needed.

Any exploratory biomarker or genomic analysis will only ever be related to the exploration of the underlying causes of MG in patients, related biology, and drug response. Justification for additional genomic analyses is detailed in Section 5.4.3.

Details on the collection, storage, preparation, and shipping of samples will be presented in the Laboratory Manual provided separately.

Any results from this analysis will be reported separately and will not form a part of the main clinical study report.

5.1.2 Study duration per subject

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

Observation Period: 8 weeks

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

5.1.3 Planned number of subjects and sites

To ensure that at least 40 subjects are evaluable for the primary efficacy variables, a sample size of approximately 42 randomized subjects is planned at approximately 30 sites to achieve the targeted number of 40 evaluable subjects.

5.1.4 Anticipated regions and countries

It is planned to recruit subjects in USA, Canada, and Europe in this study, with possible extension to other regions and countries.

5.2 Schedule of study assessments

Table 5.1 presents a summary of study assessments.

Table 5.1: Schedule of assessments

Assessments	Screening		Treatment Period													Observation Period[a]						UV
			Dosing Period 1							Dosing Period 2												
	Visit	1	2 BL	3[b]	4	5[b]	6	7[b]	8	9	10[b]	11	12[b]	13	14[b]	15	16	17	18	19	20 FV/PEOT[c]	
	Day	-28 to -1	1	2	8[d] (± 2 days)	9	15[d] (± 2 days)	16	22[d] (± 2 days)	29[d] (± 2 days)	30	36[d] (± 2 days)	37	43[d] (± 2 days)	44	50	57	64	78	92	99 (± 2 days)	
																(± 2 days)						
Written informed consent[e]		X																				
Written informed consent for genomic substudy		X																				
Demographic data		X																				
Verification of inclusion /exclusion criteria		X	X																			
Call or enter IRT to register the visit		X			X		X					X		X							X	
Call or enter IRT/ Randomization			X							X												
Withdrawal criteria			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
General medical/ procedures history		X																				
Prior and concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medical procedures			X		X		X		X	X		X		X		X	X	X	X	X	X	X
Vital signs[f]		X	X		X		X		X	X		X		X		X	X	X	X	X	X	X
Body weight, height[g]		X								X											X	
Recording of AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 5.1: Schedule of assessments

Assessments	Screening		Treatment Period													Observation Period[a]						UV
			Dosing Period 1							Dosing Period 2												
	Visit	1	2 BL	3[b]	4	5[b]	6	7[b]	8	9	10[b]	11	12[b]	13	14[b]	15	16	17	18	19	20 FV/PEOT[c]	
	Day	-28 to -1	1	2	8[d] (± 2 days)	9	15[d] (± 2 days)	16	22[d] (± 2 days)	29[d] (± 2 days)	30	36[d] (± 2 days)	37	43[d] (± 2 days)	44	50	57	64	78	92	99 (± 2 days)	
																(± 2 days)						
Full physical examination		X																			X	
Brief physical examination			X							X												
Full neurological examination[h]		X																			X	
Brief neurological examination			X							X												
Query for suicidality[i]		X	X		X		X		X	X		X		X		X	X	X	X	X	X	X
12-lead ECG[j]		X	X		X		X		X	X		X		X		X			X		X	
Laboratory tests (hematology, chemistry, urinalysis)		X	X		X		X		X	X		X		X		X	X		X		X	
Serology testing for HIV, Hepatitis B, and Hepatitis C		X																				
IGRA tuberculosis test[k]		X																				
Tuberculosis Signs and Symptoms questionnaire		X																			X	
Blood sampling for PK of UCB7665[l]			X		X		X		X	X		X		X		X						

Table 5.1: Schedule of assessments

Assessments	Screening		Treatment Period												Observation Period[a]						UV
			Dosing Period 1							Dosing Period 2											
	Visit	1	2 BL	3[b]	4	5[b]	6	7[b]	8	9	10[b]	11	12[b]	13	14[b]	15	16	17	18	19	20 FV/PEOT[c]	
	Day	-28 to -1	1	2	8[d] (± 2 days)	9	15[d] (± 2 days)	16	22[d] (± 2 days)	29[d] (± 2 days)	30	36[d] (± 2 days)	37	43[d] (± 2 days)	44	50	57	64	78	92	99 (± 2 days)	
																(± 2 days)						
Blood sampling for DNA analysis sub-study[m]			X						X					X								
Blood sampling for RNA analysis sub-study[m]			X		X				X					X							X	
Serum pregnancy test		X																				
Urine pregnancy test[n]			X		X		X		X	X		X		X		X	X	X	X	X	X	
Administration of IMP			X		X		X			X		X		X								
[redacted]			X		X		X		X	X		X		X		X	X	X	X	X	X	
Serum complement (C3,C4) and plasma complement levels (C3a and C5a)[o]			X		X		X			X		X		X							X	
Immunoglobulins (total IgG and IgG subclasses)		X	X		X		X		X	X		X		X		X	X	X	X	X	X	
IgA, IgM, IgE			X						X	X		X		X		X	X				X	
MG-specific autoantibodies			X		X					X		X				X					X	

Table 5.1: Schedule of assessments

Assessments	Screening		Treatment Period												Observation Period[a]						UV
			Dosing Period 1							Dosing Period 2											
	Visit	1	2 BL	3[b]	4	5[b]	6	7[b]	8	9	10[b]	11	12[b]	13	14[b]	15	16	17	18	19	20 FV/PEOT[c]	
	Day	-28 to -1	1	2	8[d] (± 2 days)	9	15[d] (± 2 days)	16	22[d] (± 2 days)	29[d] (± 2 days)	30	36[d] (± 2 days)	37	43[d] (± 2 days)	44	50	57	64	78	92	99 (± 2 days)	
Blood sampling for exploratory biomarker analysis			X		X		X		X	X		X		X				X		X		
Blood sampling for safety biomarker analysis: may include but not limited to [redacted]			X		X		X		X	X		X		X		X	X	X	X	X	X	
BAFF analysis			X		X		X		X	X		X		X				X		X		
Cytokines[q]			X				X			X				X							X	X
Vaccination-specific antibody titers [redacted]		X																			X	
MG-composite scale[r]		X	X		X		X		X	X		X		X		X	X	X	X	X	X	
QMG scale[s]		X	X		X		X		X	X		X		X		X	X		X		X	
Muscle weakness severity and fatigability scale			X		X		X		X	X		X		X		X	X	X	X	X	X	
Fatigue scale			X		X		X		X	X		X		X		X	X	X	X	X	X	
MGADL scale			X							X						X		X			X	

Table 5.1: Schedule of assessments

Assessments	Screening		Treatment Period													Observation Period[a]						UV
			Dosing Period 1							Dosing Period 2												
	Visit	1	2 BL	3[b]	4	5[b]	6	7[b]	8	9	10[b]	11	12[b]	13	14[b]	15	16	17	18	19	20 FV/PEOT[c]	
	Day	-28 to -1	1	2	8[d] (± 2 days)	9	15[d] (± 2 days)	16	22[d] (± 2 days)	29[d] (± 2 days)	30	36[d] (± 2 days)	37	43[d] (± 2 days)	44	50	57	64	78	92	99 (± 2 days)	
																(± 2 days)						
MGII		X					X			X				X			X		X		X	
MGFA classification		X	X							X											X	
Jitter (SFEMG) measurement[t]			X							X												
Headache questionnaire[u]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Stool sample assessment[v]			X		X		X		X	X		X		X		X	X	X	X	X	X	X
Subject exit interview																					X	

AE=adverse event; BAFF=B-cell activating factor; BL=Baseline; BP=blood pressure; CSF=cerebrospinal fluid; CT=computed tomography; DNA=deoxyribonucleic acid; ECG=electrocardiogram; FV=Final Visit; GI=gastrointestinal; HIV=human immunodeficiency virus; IgA=immunoglobulin A; IgE=immunoglobulin E; IgG=immunoglobulin G; IGRA= interferon-gamma release assay; IgM=immunoglobulin M; IMP=investigational medicinal product; IRT=interactive response technology; LP=lumbar puncture; MG=myasthenia gravis; MGADL=myasthenia gravis-Activities of Daily Living; MGFA=Myasthenia Gravis Foundation of America; MRI=magnetic resonance imaging; PEOT=premature end of treatment; PK=pharmacokinetics; PR=pulse rate; RNA=ribonucleic acid; QMG=Quantitative Myasthenia Gravis; [redacted] B; SFEMG=single fiber electromyogram; TB=tuberculosis; UV=Unscheduled Visit

[a] Subjects will return to the clinic/hospital for Visits 15, 16, 18, and 20; for Visits 17 and 19 subjects will either return to the clinic/hospital, or, if possible and agreed by both the investigator and subject, have home visits conducted by certified healthcare professionals.

[b] This visit is a telephone contact 24 hours post-IMP dose start.

[c] Subjects who withdraw early will be encouraged to complete the PEOT Visit plus the FV (approximately 8 weeks after the final study drug administration).

[d] A visit window of ±2 days is allowed for the dosing visits. The visit window of ±2 days is relative to the first dosing visit date. However, there should be a minimum interval of 5 days and maximum interval of 9 days as compared to the previous dose.

[e] Includes consent for jitter (SFEMG) for the subjects consenting to this measurement at the participating sites. Additional informed consent is needed for participation in the exploratory genomic substudy.

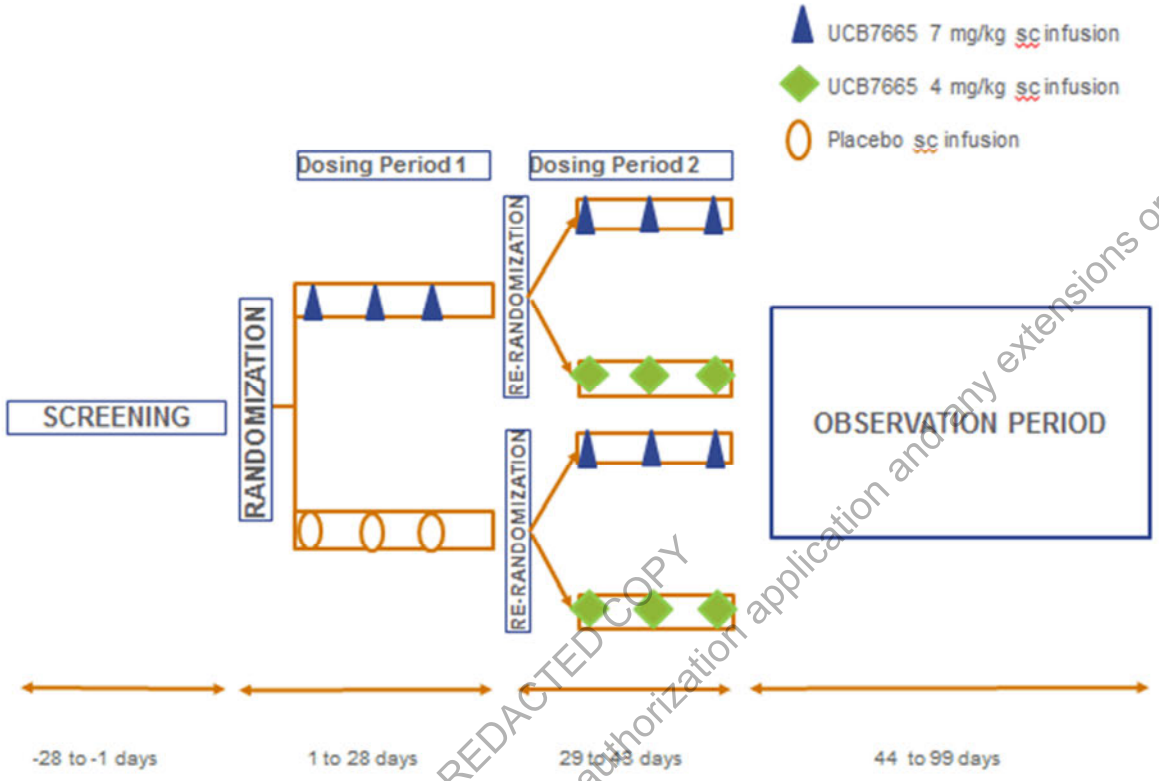
[f] Systolic and diastolic BP, pulse rate, temperature, and respiratory rate. On dosing days, vital signs will be measured prior to IMP administration, 15 minutes after the start of the infusion, at the end of the infusion, 2 hours after the end of infusion and 4 hours after the end of the infusion. At nondosing visits, vital signs need only be taken once during the visit.

[g] Body weight at Screening and at Visit 9 will be used for calculation of dose; height will be assessed only at Screening.
[h] In addition to Screening and the FV, a full neurological examination should be performed for any subject who experiences severe headache.
[i] A query for suicidal ideation will be asked by Investigator at each clinical visit (including Visit 17 or Visit 19 when it is conducted at the clinic). 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. If a subject has active suicidal ideation as confirmed by the answer 'Yes' to Question 4 or Question 5 of the C-SSRS assessments, the subject will be excluded or withdrawn from the study and immediately referred to a Mental Healthcare Professional.
[j] ECGs will be read by a central reader.
[k] The IGRA test will be performed in a central laboratory. Subject should not be dosed until IGRA result is available and negative.
[l] Pre- and postdose at Visits 2, 4, 6, 9, 11, and 13; postdose samples are to be taken 4 hours after the infusion has ended.
[m] Blood sample to be taken prior to dosing of IMP.
[n] Urine pregnancy test will be performed using a dipstick test; a positive urine pregnancy test must be confirmed using a serum pregnancy test.
[o] Sampling will be performed predose at Visit 2 and 4 hours postdose at Visits 2, 4, 6, 9, 11 and 13. A sample will be obtained at Visit 20.
[p] Sampling for exploratory safety biomarkers at Baseline (Visit 2) and 4 hours post dosing (Visit 2) for all subjects. During follow up only in subjects with severe headache and/or moderate to severe GI disturbances.
[q] Sampling will be performed pre- and 4 hours postdose at Visits 2, 6, 9 and 13. A sample will be obtained at Visit 20. Samples will be obtained at Visits 4 and 11 for subjects with an infusion reaction.
[r] This assessment will be performed at the clinic/hospital. If the subject has a home visit with certified health professionals at Visit 17 and Visit 19, this assessment will not be performed.
[s] Subjects should not take pyridostigmine (or any [redacted] inhibitor medication) from midnight before testing when medically safe to do so to standardize testing, but if not medically appropriate, then the treatment can be continued but the testing should be performed as best as possible at the same timeframe post last any [redacted] inhibitor dosing for each evaluation during the study.
[u] This assessment is applicable only to subjects experiencing severe headaches and will be performed 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). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator.
[v] Stool collection and analysis will be performed for subjects reporting moderate or severe diarrhea. The frequency of stool sampling will be as clinically indicated in the opinion of the investigator. Analysis of stool samples will be performed locally.

5.3 Schematic diagram

Figure 5.1 presents a schematic diagram of the study design.

Figure 5.1: Schematic diagram



sc=subcutaneous

5.4 Rationale for study design and selection of dose

5.4.1 Choice of study design and endpoints

The primary objective of the study is to evaluate the clinical efficacy of UCB7665 as a chronic-intermittent treatment for subjects with moderate to severe generalized MG. Additionally, this study will provide 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.

During the first Treatment Period, a 2-arm parallel design study will allow comparison of the change from Baseline in QMG score to Visit 9 (Day 29) between UCB7665 7mg/kg and placebo.

The choice of the primary efficacy outcome measures and the timing of approximately 4 weeks after the first dose of study drug are predicted to be the optimal approach to measure improvements based on effect seen in other therapies and recommendations of the Scientific Advisory Board of the MGFA (Barth 2013; Benatar 2012; Howard 2013). Then the second Dosing Period with a rerandomization allows for additional supportive data to be evaluated as well as offering the placebo subjects a chance to receive UCB7665.

Each subject will be asked to participate up to a maximum of approximately 18 weeks, consisting of a Screening Period (14 to 28 days), Treatment Period (6 weeks) and an Observation Period (8 weeks). The Treatment Period will consist of Dosing Period 1 followed by Dosing Period 2. Dosing Period 1 will have 2 parallel Treatment Groups (UCB7665 7mg/kg or placebo) and last 4 weeks. Dosing Period 2 will have 2 parallel Treatment Groups (UCB7665 7mg/kg or UCB7665 4mg/kg) and last 3 weeks. Overall, this will result in 4 Treatment Groups:

Group 1: Subjects will receive 3 weekly doses of 7mg/kg in Dosing Period 1 followed by 3 weekly doses of 7mg/kg in Dosing Period 2.

Group 2: Subjects will receive 3 weekly doses of 7mg/kg in Dosing Period 1 followed by 3 weekly doses of 4mg/kg in Dosing Period 2.

Group 3: Subjects will receive 3 weekly doses of placebo in Dosing Period 1 followed by 3 weekly doses of 7mg/kg in Dosing Period 2.

Group 4: Subjects will receive 3 weekly doses of placebo in Dosing Period 1 followed by 3 weekly doses of 4mg/kg in Dosing Period 2.

All subjects participating in Dosing Period 2 will therefore receive UCB7665 treatment, and no subject will be treated with placebo for more than 4 weeks. The primary outcome measure, change from Baseline in QMG score compared to placebo at Visit 9, will be assessed for subjects treated with 7mg/kg UCB7665 vs subjects treated with placebo in Dosing Period 1. The comparison of the change from Baseline in QMG score at Visit 16 in Group 3 will strengthen analyses of the results of the primary outcome measure in Group 1. Because subjects in both Group 1 and 2 will be dosed for 6 times over 6 weeks, the data from these subjects will inform safety and the development of ADAs with extended dosing durations. Data regarding dose response and the time to clinical and PD response from Group 3 (7mg/kg) vs. Group 4 (4mg/kg) in the second Dosing Period will be able to be compared. Furthermore, safety and efficacy data from Group 2 in particular will provide information addressing the concept of treating subjects with a higher "loading" dose and then maintaining them on a lower dose regimen.

5.4.2 Rationale for dose selection

The dose and regimen of IMP to be used in the current study (UCB7665 7mg/kg sc) was selected based on the results from the first-in-human study UP0018. UP00018, a single ascending dose study in healthy subjects, explored the dose range of UCB7665 (between 1 and 7mg/kg) and characterized the PK and PD effect on total IgG. Data indicate that mean absolute decreases in IgG and mean percent change from Baseline IgG were greater in the active dose groups (n=6 each) compared to the pooled iv and sc placebo group (n=12) with maximum decreases of 49.3% (range: 44.6% to 55.9%) observed on Day 6 for a UCB7665 7mg/kg iv dose and 42.8% (range: 39.6% to 48.6%) on Day 9 for a UCB7665 7mg/kg sc dose. UCB7665 was tolerated with an acceptable safety profile after the single administration of a 7mg/kg sc dose, and all subject-reported TEAEs had a maximum intensity of mild or moderate.

The dose-exposure-response relationship, with serum total IgG as primary endpoint, was determined using nonlinear mixed effects modeling. The derived population PK-PD (structural PK-PD model based on that of Lowe [Lowe et al, 2010]) was then used to guide, through simulation, the selection of appropriate repeat-dose regimens that would mimic decreases achieved by plasmapheresis paradigms and result in an IgG reduction of 70% or greater. The

model based simulations demonstrate that weekly doses of UCB7665 7mg/kg for 3 consecutive weeks are expected to produce maximum mean IgG reductions of >70%. Thus, exploratory comparisons of the 4mg/kg and 7mg/kg dosing regimens for treating adult subjects with moderate to severe generalized MG will be evaluated in the current study, MG0002.

5.4.3 Justification for additional genomic analyses

DNA analysis

Monozygotic MG twin concordance is estimated to be about 35% supporting the central role of environmental factors in MG etiology. MicroRNAs provide a mechanistic link between environmental and genetic risk factors in disease development, and are providing support for specific epigenetic mechanisms associated with MG. Genetic studies have mainly pointed at specific human leukocyte antigen alleles implicated in MG susceptibility, however recently both [redacted] and [redacted] were indicated to be associated with MG in a genome wide association study.

Direct genetic and environmental/epigenetic influences are complex and require further elucidation to understand the cause, progression and potential treatment of MG. Through the collection of whole blood DNA from consenting subjects, this substudy will help enable further investigation of this complex disease, facilitate identification and characterization of genetic and/or epigenetic components of MG and will lead to important clues into the pathogenesis of MG and possibly advance understanding of drug response phenotypes.

RNA analysis

Gene expression (mRNA) analyses have identified distinct gene transcription signatures from whole blood associated with many autoimmune diseases including rheumatoid arthritis, systemic lupus erythematosus, ITP, and MG. Such signatures have provided molecular insight into disease biology and activity and can facilitate patient stratification via gene expression panels predictive of therapeutic response and clinical outcomes.

MicroRNAs are short (19-25 nucleotides) evolutionarily conserved single-stranded RNA molecules that regulate the expression of genes involved in diverse biological processes. The effect of miRNA on mRNA is mediated through the binding of the miRNA to the target mRNA ribonucleoprotein complex resulting in altered expression and decreased protein translation.

Collection of blood for RNA analysis will facilitate insight into the molecular etiology of MG at the genomic level and may enable identification of candidate markers for treatment effect and safety, and assessment of the feasibility of patient stratification.

In summary, the genetic, epigenetic, and genomic elements of MG require further elucidation to understand the cause, progression, and appropriate treatment of MG. Through the voluntary collection of blood DNA and RNA samples from consenting subjects, this substudy will help enable further investigation of this complex disease.

6 SELECTION AND WITHDRAWAL OF SUBJECTS

6.1 Inclusion criteria

To be eligible to participate in this study, all of the following criteria must be met:

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent form is signed and dated by the subject.
2. Subject is ≥18 years of age at Visit 1 (Screening).
3. Subject has a well-documented diagnosis of MG at Visit 1 (Screening), based on subject history and supported by previous evaluations.
4. Subject would currently be considered for treatment with immunological therapy (eg IVIG/PLEX) by the investigator.
5. Subject has a well-documented record of autoantibodies against [redacted] or [redacted] prior to Visit 1 (Screening).
6. Female subjects of child bearing potential must have a negative serum pregnancy test at the Screening Visit, which is confirmed to be negative by urine testing prior to the first dose of study drug at Week 1 (Visit 2) and prior to further dosing at each study visit thereafter.

   Female subjects of childbearing potential must agree to use a highly effective method of birth control, during the study and for a period 2 months after their final dose of study drug. According to the International Council for Harmonisation (ICH) M3 (R2), highly effective forms of birth control are methods which achieve a failure rate of less than 1% per year when used consistently and correctly. Highly effective methods of birth control include:

   - Combined (estrogen- and progesterone-containing) hormonal contraception (oral, implant, injectable) associated with inhibition of ovulation, (which must be stable for at least 1 full month prior to Screening [Visit 1], and should remain stable during the study).
   - Progesterone-only hormonal contraceptives (oral, implant, injectable) associated with inhibition of ovulation (which must be stable for at least 1 full month prior to Screening [Visit 1], and should remain stable during the study).
   - Progesterone-releasing intrauterine systems or the TCu 380A intrauterine device.
   - Vasectomized partner (provided sole partner and partner has medical proof of surgical success).
   - True heterosexual sexual abstinence is an acceptable form of contraception when this is in line with the preferred and usual lifestyle of the person. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence for the duration of the study, and withdrawal are not acceptable methods of contraception.

Women not agreeing to use birth control must be of nonchildbearing potential, defined as being:

- Postmenopausal (for at least 2 years before the Screening Visit), verified by serum follicle stimulating hormone level >40mIU/mL at the Screening Visit, or
- Permanently sterilized (eg, bilateral tubal occlusion, hysterectomy, bilateral salpingectomy), or

- Congenitally sterile

7. Contraception methods for male subjects and their female partners:
   - Male subject with a partner of childbearing potential must be willing to use a condom when sexually active during the study and for 3 months after the final administration of IMP.
   - In addition the female partner of childbearing potential of a male subject must be willing to use a highly effective method of contraception (as above), during the study period and for 3 months after the final administration of IMP.

6.2 Exclusion criteria

Subjects are not permitted to enroll in the study if any of the following criteria are met:

1. Subject has previously received treatment in this study or subject has previously been exposed to UCB7665.
2. Subject has participated in another study of an IMP (or a medical device) within the previous 30 days of Screening or is currently participating in another study of an IMP (or a medical device).
3. Subject has a known hypersensitivity to any components of the IMP.
4. Subject has a history of hyperprolinemia, since L-proline is a constituent of the UCB7665 IMP.

6.2.1 Exclusion criteria related to health status

5. Subjects with MG only affecting the ocular muscles.
6. Subjects with severe weakness affecting oropharyngeal or respiratory muscles, or who have myasthenic crisis at Screening or impending crisis.
7. Subject has QMG score of <11 at Baseline.
8. Subject has a serum total IgG level ≤6g/L at Screening.
9. Absolute neutrophil count <1500 cells/mm^3.
10. Subject has any medical condition (acute or chronic illness) or psychiatric condition that, in the opinion of the investigator, could jeopardize or would compromise the subject's ability to participate in this study.
11. Subject has any laboratory abnormality that, in the opinion of the investigator, is clinically significant, has not resolved at randomization, and could jeopardize or would compromise the subject's ability to participate in this study.
12. Subject has 12-lead ECG with changes considered to be clinically significant upon medical review. The ECG contains findings that may represent a significant abnormality. The clinical significance of the findings needs to be assessed by the investigator to determine eligibility, and any queries regarding continuation of the subject must be addressed with the medical monitor.

13. A screening glycosylated hemoglobin HbA1c value >8%, for subjects with known history of diabetes mellitus.
14. Subject has renal impairment, defined as:
    - Serum creatinine level of ≥1.4mg/dL for females and ≥1.5mg/dL for males at Screening Visit
15. Subject has >2x upper limit of normal (ULN) of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or >ULN total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome). If subject has elevations only in total bilirubin that are >ULN and <1.5xULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%).

    For randomized subjects with a Baseline result >ULN for ALT, AST, ALP, or total bilirubin but <1.5xULN, a Baseline diagnosis and/or the cause of any clinically meaningful elevation must be understood and recorded in the electronic Case Report Form (eCRF).

    If subject has >ULN, ALT, AST, or ALP that does not meet the exclusion limit at Screening, repeat the tests, if possible, prior to dosing to ensure there is no further ongoing clinically relevant increase. In case of a clinically relevant increase, inclusion of the subject must be discussed with the medical monitor.

    Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit (>2xULN) may be repeated once for confirmation. This includes rescreening.
16. Female subject who is pregnant or lactating.
17. Subject has planned an elective surgical procedure in the coming 6 months.
18. The subject is not considered reliable and capable of adhering to the protocol visit schedule, or medication intake according to the judgment of the investigator.
19. Subject has a history of chronic alcohol or drug abuse within the previous 12 months.
20. Subject has a clinically relevant active infection (eg, sepsis, pneumonia, or abscess) or has had a serious infection (resulting in hospitalization or requiring parenteral antibiotic treatment) within 6 weeks prior to the first dose of IMP.
21. Subject has a history of clinically relevant ongoing chronic infections including but not limited to human immunodeficiency virus (HIV), Hepatitis B, Hepatitis C, or who tests positive for HIV, Hepatitis B, or Hepatitis C at the Screening Visit.
22. Subject has a family history (immediate family member) of primary immunodeficiency.
23. Subject has active neoplastic disease or history of neoplastic disease within 5 years of study entry (except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the uterine cervix which has been definitively treated with standard of care approaches).
24. Subject has a history of a major organ transplant or hematopoietic stem cell/marrow transplant.

6.2.2 Exclusion criteria related to concomitant medications/procedures

25. Subject has received a live vaccination within 8 weeks prior to the Baseline Visit; or intends to have a live vaccination during the course of the study or within 7 weeks following the final dose of IMP.
26. Subject has received any experimental biological agent within or outside of a clinical study in the past 3 months or within 5 half-lives prior to Baseline (whichever is longer).
27. Subject has had prior treatment with rituximab in the 6 months prior to the Baseline Visit or subject has had prior treatment with rituximab in the 12 months prior to Baseline and B cells monitoring has shown they did not return to normal range.
28. Subject has been treated with immunosuppressants, biologics, and other therapies as detailed in the recent timeframe as detailed in Table 6.1 OR has not been on stable dosing regimens of the medications as detailed in Table 7.1.
29. Exclusion Criterion 29 was deleted per Protocol Amendment 1.
30. Subject had a thymectomy in the past 6 month or a thymoma at any time that required chemotherapy and/or radiotherapy.

Table 6.1: No-treatment periods for exclusionary immunosuppressants, biologics, and other therapies

Generic name (commercial/trade names)	Period relative to Baseline Visit (regardless of route)
Immunosuppressants	
Cyclophosphamide (Cytoxan®)	[redacted]
Pimecrolimus (Elidel®)	
Vinca alkaloids (vincristine, vinblastine)	
Biologics (mabs and fusion proteins)	
Abatacept (CTLA 4-Ig) (Orencia®)	
Belimumab (Benlysta™)	
Golimumab (Simponi™)	
Natalizumab (Tysabri®)	
Ofatumumab (Arzerra)	
Rituximab (Rituxan®) and ocrelizumab	
TACI-Ig (Atacicept)	
Veltuzumab	
Other biologics	
Others	
Intravenous or subcutaneous immunoglobulin	

Generic name (commercial/trade names)	Period relative to Baseline Visit (regardless of route)
IPP-201101 (Lupuzor™)	[redacted]
PLEX (plasma exchange)	
Immunoabsorption	

6.2.3 Exclusion criteria related to other risks

31. Subject has a lifetime history of suicide attempt (including an [redacted] or has suicidal ideation in the past 6 months as indicated by a positive response (Yes) to either Question 4 or Question 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) at Screening.
32. Subjects with known tuberculosis (TB) infection, at high risk of acquiring TB infection, or latent tuberculosis infection (LTBI), or current/history of nontuberculous mycobacterial infection (NTMBI) are excluded.

    a. Known TB infection whether present or past is defined as:

    – Active TB infection or clinical signs and symptoms suggestive of TB (pulmonary or extrapulmonary).
    – History of active TB infection involving any organ system or findings in other organ systems consistent with TB infection.
    – Any historical evidence by radiography or other imaging modalities consistent with previously active TB infection.

    b. High risk of acquiring TB infection is defined as:

    – Known exposure to another person with active TB infection within the 3 months prior to Screening.
    – Time spent in a healthcare delivery setting or institution where individuals infected with TB are housed and where the risk of transmission of infection is high.

    c. LTBI (see Section 12.3.1 for further details and instructions).

    d. NTMBI is defined as a group of lung infections caused by mycobacteria different from mycobacterium tuberculosis infections.

6.3 Rescreening and Rechecking

Subjects with isolated results that are outside the specified ranges and that are deemed potentially clinically significant will be allowed to rescreen at the discretion of the investigator, following discussion with the sponsor's medical monitor/study physician, if appropriate.

If a subject has 1 isolated test result outside the specific range which is deemed clinically nonsignificant, the abnormal value may be rechecked at the discretion of the investigator, following discussion with the sponsor's medical monitor/study physician. If the normalization of the test result occurs within the Screening Period, then no other Screening procedures need to be repeated.

6.4 Withdrawal criteria

Subjects are free to withdraw from the study at any time, without prejudice to their continued care.

Subjects MUST be withdrawn from the study if any of the following events occur:

1. Subject withdraws his/her consent.
2. Subject becomes pregnant during the study, as confirmed by a positive pregnancy test.

Subjects MUST discontinue IMP if any of the following events occur:

1. Subject develops an illness or has a change in health status that would interfere with his/her continued participation, including but not limited to:
    - Subject has a serious infective episode requiring hospitalization or iv antibiotic therapy (including but not limited to bacteremia or sepsis, bacterial meningitis, osteomyelitis or septic arthritis, bacterial pneumonia, or visceral abscess).
    - Subject experiences a severe adverse event (AE) of GI disturbance or severe headache which is considered related to the IMP in the opinion of the investigator (Section 12.1.10).
    - Subject has an AE of infusion reaction of severe intensity requiring corticosteroid and/or epinephrine therapy.
    - Subject has an AE of anaphylactic reaction requiring corticosteroid and/or epinephrine therapy.
    - Subject has a TB test that is confirmed positive or any further evidence suggestive of potential TB infection (eg, exposure) and further examinations result in a diagnosis of active TB or LTBI (refer to Section 12.3.1) for further details and instructions.
    - If an NTMBI is identified during a study, the same withdrawal procedures as those used for an active TB infection identified during the study should be followed.
2. The sponsor or a regulatory agency requests withdrawal of the subject.
3. Subject is treated with rescue therapy (refer to Section 7.8.3).
4. Subject received rituximab during the Treatment Period.
5. Subject received prohibited concomitant medications (as defined in Section 7.8.2 of this protocol) during the Treatment Period.
6. According to the investigator's judgment this is in the best interest of the patient.
7. Meets criteria for liver injury (Section 6.4.1).
8. Subject has active suicidal ideation as indicated by a positive response (Yes) to either Question 4 or Question 5 of the "Since Last Visit" version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional.

Subjects MAY be withdrawn from the study at the discretion of investigator, medical monitor, and study physician if any of the following events occur:

Subject is noncompliant with the study procedures or medications in the opinion of the investigator.

Subjects who withdraw from the study or discontinue IMP should complete the assessments outlined for the Premature End Of Treatment (PEOT) Visit (see Table 5.1 and Section 8.5). Subjects will be encouraged to return to the clinic/hospital to complete the Observation Period Visits and the FV (approximately 8 weeks after the final study drug administration).

Investigators should attempt to obtain information on subjects in the case of withdrawal.

For subjects considered as lost to follow up, the investigator should make an effort (at least 1 phone call and 1 written message to the subject), and document his/her effort (date and summary of the phone call and copy of the written message in the source documents), to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for IMP discontinuation and subject withdrawal, must be recorded in the source documents. The eCRF must document the primary reason for withdrawal or discontinuation, plus whether or not the blind was broken, with the reason and date for this.

Investigators should contact the medical monitor, whenever possible, to discuss the withdrawal of a subject in advance. Subjects who are withdrawn will not be replaced.

6.4.1 Potential drug-induced liver injury IMP discontinuation criteria

Subjects with potential drug-induced liver injury (PDILI) must be assessed to determine if IMP must be discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued.

The PDILI criteria below require ***immediate and permanent*** discontinuation of study drug:

- Subjects with either of the following:
  - ALT or AST ≥5xULN
  - ALT or AST ≥3xULN and coexisting total bilirubin ≥2xULN

The PDILI criterion below requires immediate discontinuation of study drug:

- Subjects with ALT or AST ≥3xULN who exhibit temporally associated symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, right upper quadrant pain or tenderness. Hypersensitivity symptoms include fever (without clear alternative cause), rash, or eosinophilia (ie, >5%).

If a nondrug-related cause for the symptoms can be confirmed, these subjects may resume study drug administration after discussion with the responsible UCB physician, but only when the requirements for rechallenge with study drug as provided in Section 12.2.1.2.1 are followed.

The PDILI criterion below allows for subjects to continue on study drug at the discretion of the investigator.

- Subjects with ALT or AST ≥3xULN (and ≥2x Baseline) and <5xULN, total bilirubin <2xULN, and no eosinophilia (ie, ≤5%), with no fever, rash, or symptoms of hepatitis (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness).

Evaluation of PDILI must be initiated as described in Section 12.2.1. If subjects are unable to comply with the applicable monitoring schedule, IMP must be discontinued immediately.

Investigators should attempt to obtain information on subjects in the case of IMP discontinuation to complete the final evaluation. Subjects with PDILI should not be withdrawn from the study until investigation and monitoring are complete. All results of these evaluations and observations, as well as the reason(s) for IMP discontinuation and subject withdrawal (if applicable), must be recorded in the source documents. The eCRF must document the primary reason for IMP discontinuation.

7 STUDY TREATMENT

7.1 Description of investigational medicinal product

UCB7665 product will be supplied as a [redacted] iv or sc administration, is supplied with a commercial source.

7.2 Treatments to be administered

Dosing Period 1: Subjects will be randomized in a 1:1 manner to receive either:

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

OR

- 3 sc doses of placebo [redacted] at 1 week intervals

After completing Dosing Period 1, subjects will enter Dosing Period 2.

Dosing Period 2: Subjects will be rerandomized in a 1:1 manner to receive either:

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

OR

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

The IMP will be administered as a sc infusion using an infusion pump.

The perfusor will be programmed at a constant flow rate of [redacted] for all subjects. In the case of any blockage of the infusion, a suitable flush (eg, [redacted]) is allowed. The infusion time will be set to [redacted] for all subjects.

The subject's body weight at the Screening Visit and Visit 9 will be used for the dose calculation. Screening Visit is for dosing in Period 1 and Visit 9 is for dosing in Period 2.

The exact procedure for dose preparation according to Treatment Group and body weight will be provided in an IMP Handling Manual.

The infusion rate may be reduced at any time at the discretion of the investigator. If an infusion is interrupted, it can be restarted if the investigator considers it appropriate to do so. The

chronology of these events (infusion start and stop time) should be recorded accurately in the source data and eCRF, along with the volume infused, and the location of the infusion.

7.3 Packaging

The IMP will be manufactured, packaged, and labeled according to Good Manufacturing Practice (GMP) guidelines and applicable laws or regulations. The IMP will be suitably packaged in such a way as to protect it from deterioration during transport and storage.

7.4 Labeling

Clinical drug supplies will be labeled in accordance with the current ICH guidelines on Good Clinical Practice (GCP) and GMP and will include any locally required statements. If necessary, labels will be translated into the local language.

7.5 Handling and storage requirements

The investigator (or designee) is responsible for the safe and proper storage of IMP at the site. Investigational medicinal product stored by the investigator is to be kept in a secured area with limited access according to the storage conditions mentioned on the label.

Appropriate storage conditions must be ensured either by controlling the temperature (eg, room, refrigeration unit) or by completion of a temperature log in accordance with local requirements on a regular basis (ie, every workday), showing actual and minimum/maximum temperatures reached over the time interval.

In case an out-of-range temperature is noted, it must be immediately reported as per instructions contained in the IMP Handling Manual.

7.6 Drug accountability

A Drug Accountability form will be used to record IMP dispensing and return information on a by-subject basis and will serve as source documentation during the course of the study. Details of any IMP lost, damaged (due to breakage or wastage), not used, partially used, disposed of at the study site, or returned to the sponsor or designee must also be recorded on the appropriate forms. All supplies and pharmacy documentation must be made available throughout the study for UCB (or designee) to review.

The investigator (or designee) is responsible for retaining all used, unused, and partially used containers of IMP until returned or destroyed.

The investigator may assign some of the investigator's duties for drug accountability at the study site to an appropriate pharmacist/designee.

The investigator must ensure that the IMP is used only in accordance with the protocol.

Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers), partially used, unused, damaged, and/or expired IMP must be reconciled and either destroyed at the site according to local laws, regulations, and UCB Standard Operating Procedure (SOPs), or returned to UCB (or designee). Investigational medicinal product intended for the study cannot be used for any other purpose than that described in this protocol.

7.7 Procedures for monitoring subject compliance

Drug accountability is ensured by administering the IMP as sc infusion by designated personnel. Drug accountability must be recorded on the Drug Accountability form.

7.8 Concomitant medication/treatment

7.8.1 Permitted concomitant medication

Table 7.1 lists the concomitant medications that are permitted during the course of the study at a stable dose.

Table 7.1: Permitted concomitant treatments

Permitted Medications	Dose	Comment
Oral Corticosteroids (eg, prednisolone)	-	[redacted]
Methotrexate	≤30mg/week	
Mycophenolate mofetil	≤3g/day	
Cyclosporin[a]	≤5mg/kg/day for unmodified ≤4mg/kg/day for modified (microemulsion)	
Azathioprine	≤3mg/kg/day	
Cholinesterase inhibitors	≤600mg Pyridostigmine/day	
Tacrolimus[b]	≤5mg/day	

[a] Doses higher than listed are permissible if trough level is ≤300ng/L.
[b] If the total daily weight-based dose is >5mg, then a plasma trough level should be checked to ensure subject is not above the recommended therapeutic range.

Subjects should not take pyridostigmine (or any [redacted]) from midnight before testing when medically safe to do so to standardize testing, but if not medically appropriate, then the treatment can be continued but the testing should be performed as best as possible at the same timeframe post any last [redacted] medication inhibitor dosing for each evaluation during the study.

In the event of a subject developing an infection during the course of the study, samples for culture will be taken prior to commencing antimicrobial treatment. Antimicrobial treatment may be modified accordingly when the identity of the infective organism is known.

7.8.2 Prohibited concomitant treatments (medications and therapies)

The following concomitant medications and therapies are prohibited during the study:

- IVIg
- All biologics including rituximab
- Cyclophosphamide
- Pimecrolimus
- IPP-201101 (Lupuzor™)
- PLEX
- Immunoadsorption
- Medications which could interfere with the function of the NMJ (and which therefore could impair subjects with MG), such as, but not limited to, the following medications. For a more detailed list please refer to the MGFA medication list (http://www.myasthenia.org/LivingwithMG/DrugstoAvoid.aspx).
  - botulinum toxin
  - aminoglycoside antibiotics
  - tetracycline antibiotics
  - penicillamine

If a subject needs or takes any prohibited medication or therapy (except IVIg, PLEX, or rituximab), the investigator will (where possible) discuss with the sponsor study physician and a decision will be made whether the subject can continue in the study or must be withdrawn. If the subject is treated with IVIg, rituximab, or PLEX, the subject must be withdrawn from the IMP, but should be encouraged to continue with Observation Period Visits.

For subjects who require a medical or surgical procedure that requires the use of general anesthesia, discussion must occur prior to the procedure with the medical monitor or study physician. In an emergency situation, discussion should occur as soon as possible after the procedure, such that a decision on the subject's continued participation in the study can be made.

7.8.3 Rescue medication

In the case of prolonged hypogammaglobulinemia the subject will be considered for treatment with prophylactic antimicrobial therapy. Subjects will be followed up until Ig levels return to within the normal range.

If, during the Treatment and Observation Period, in the opinion of the investigator, a subject has a significant deterioration in clinical condition, then rescue therapy such as IVIg or PLEX should be considered.

7.9 Blinding

7.9.1 Procedures for maintaining and breaking the treatment blind

7.9.1.1 Maintenance of study treatment blind

[redacted]

All subject treatment details, ie, UCB7665 4mg/kg, 7mg/kg sc, or placebo, will be allocated and maintained by the IRT system.

The following individuals will receive the randomization code at the start of the study:

- Sponsor and designated bioanalytical staff analyzing PK samples
- Sponsor clinical trial supply staff
- IRT provider

Study site pharmacists or other suitably qualified site personnel who are responsible for preparation of IMP treatments and any necessary assistants will have access to treatment allocations for individual subjects via the IRT. The unblinded pharmacy monitors from the Contract Research Organization (CRO), the Clinical Supply Manager, and the unblinded Clinical Project Manager (CPM) (or designee) will also have access to the treatment allocations and to the drug accountability records, if applicable.

The following individuals may, as necessary, have access to the randomization code as indicated:

- Sponsor Patient Safety (PS) staff as needed for reporting SAEs to regulatory authorities.
- On request, members of the DMC who participate in unblinded sessions will be given information about the IMP allocation for those subjects for whom data are provided at these sessions.
- Sponsor and/or CRO staff supporting preparation of the data outputs for the DMC review and/or any interim analyses.
- A Quantitative Clinical Pharmacologist/Modeling and Simulation Scientist may have access to the randomization code if PK data are requested for review by the DMC.

All subject treatment details will be allocated and maintained by the IRT system.

7.9.1.2 Breaking the treatment blind in an emergency situation

In the event of an emergency, it will be possible to determine to which Treatment Group and dose the subject has been allocated by contacting the IRT. All sites will be provided with details of how to contact the system for code breaking at the start of the study. The medical monitor or equivalent should be consulted prior to unblinding, whenever possible. **The study blind should not be broken except** in a medical emergency, **where knowledge of the study drug received would affect the treatment of the emergency**.

The CPM and medical monitor will be informed immediately via the IRT when a code is broken, but will remain blinded to specific treatment information. Any unblinding of the IMP performed

by the investigator must be recorded in the source documents and on the Study Termination eCRF page.

Inadvertent unblinding has to be listed as a major protocol deviation.

7.10 Randomization and numbering of subjects

An IRT will be used for assigning eligible subjects to the different treatment regimens (as applicable) based on a predetermined production randomization and/or packaging schedule. The 1:1 randomization schedules will be produced by the IRT vendor. The IRT vendor will also generate lists of IMP, as appropriate, according to the visit schedule, the Treatment Group and the subject's weight.

To enroll a subject (Visit 1), the investigator or designee will contact the IRT and provide brief details about the subject to be screened. Each subject will receive a 5-digit number assigned at Screening that serves as the subject identifier throughout the study. The subject number will be required in all communication between the investigator or designee and the IRT regarding a particular subject. Subject numbers and kit numbers will be tracked via the IRT.

To enroll a subject in Dosing Period 1, the investigator or designee will contact the IRT and provide brief details about the subject to be randomized. The IRT will allocate kit numbers to the subject based on the randomization number.

To enroll a subject in Dosing Period 2, the investigator or designee will again contact the IRT and provide the subject's screening number and weight at Visit 9. The subject will be rerandomized in a 1:1 ratio to receive one of the two doses of UCB7665. The IRT will stratify the rerandomization based on the treatment received in Dosing Period 1. At this rerandomization, the subject will receive a second randomization number which, as in Dosing Period 1, will be used by the IRT to allocate appropriate kit numbers.

8 STUDY PROCEDURES BY VISIT

A detailed schedule of study procedures is provided in Table 5.1.

For details of the standard safety hematology, clinical chemistry, and urinalysis, see Table 12.2.

8.1 Screening Period

8.1.1 Visit 1 (Day -28 to -1) Screening Visit

At Visit 1, subjects will be evaluated for their suitability for enrollment. Prior to the conduct of any study-related procedures, a complete explanation (both verbal and written) of the nature and purpose of the study will be given to the subject by the investigator (or designee). The subject is required to sign and date the IRB/IEC-approved Informed Consent form if he/she decides to participate in the study.

Subjects will also have the option of providing additional voluntary informed consent for collection of whole blood samples for exploratory genomic (DNA and RNA) analyses.

The subject's eligibility for the study will be determined on the basis of the inclusion/exclusion criteria and signature of an informed consent prior to any study-related procedures or evaluations.

The following assessments and procedures will be performed during Visit 1 of MG0002:

- Obtain written informed consent
- Obtain optional informed consent for genomic substudy
- Demographic data (includes date of birth, gender, and race/ethnicity)
- Verification of inclusion/exclusion criteria
- General medical history and medical procedures history (including history of tetanus immunization)
- Prior and concomitant medications
- Vital signs (systolic and diastolic BP, pulse rate, temperature, and respiratory rate)
- Body weight and height
- Recording of AEs
- Physical examination (Full)
- Neurological examination (Full)
- Assessment of MG status:
  - MG-composite scale
  - QMG scale
  - MGFA classification
- Query for suicidality (Screening)

  If positive response (Yes), a full C-SSRS will be performed.
- 12-lead ECG
- Blood samples:
  - Standard safety laboratory tests: hematology and clinical chemistry, plus serology testing for HIV, Hepatitis B, and Hepatitis C
  - Immunoglobulins (Total IgG and subclasses)
  - Vaccination-specific antibody titers ([redacted])
  - Serum pregnancy test for women of childbearing potential
- Tuberculosis assessments:
  - IGRA
  - Tuberculosis Sign and Symptoms questionnaire
- Standard safety urinalysis
- Call or enter IRT to register the visit

8.2 Dosing Period 1

In Dosing Period 1, visits will be performed at weekly intervals.

8.2.1 Visit 2 (Day 1, Baseline)

Visit 2 can occur at any time after Visit 1, but no later than 28 days after Visit 1. Eligible subjects will be randomized at Visit 2 and the first dose of IMP (UCB7665 7mg/kg sc infusion) or placebo will be administered as per the subject's randomization.

The following assessments and procedures will be performed at this visit:

Predose:

- Verification of inclusion/exclusion criteria
- Withdrawal criteria
- Prior and concomitant medications
- Concomitant medical procedures
- Vital signs (systolic and diastolic BP, pulse rate, temperature, and respiratory rate)
- Recording of AEs
- Physical examination (brief)
- Neurological examination (brief)
- Assessment of MG status:
  - MG-composite scale
  - QMG scale
  - Muscle weakness severity and fatigability scale
  - Fatigue scale
  - MGADL scale
  - MGII
  - MGFA classification
- Query for suicidality (since last visit):

  If positive response (Yes), a full C-SSRS will be performed.
- 12-lead ECG
- Blood samples:
  - Standard safety laboratories: hematology and clinical chemistry
  - PK of UCB7665
  - [redacted]
  - Serum complement (C3,C4) and plasma complement levels (C3a and C5a)
  - Ig (total IgG and subclasses)
  - IgA, IgM, and IgE

  - MG-specific autoantibodies
  - Exploratory biomarker analysis
  - Exploratory safety biomarkers: may include but not limited to [redacted]
  - BAFF
  - Cytokines
  - Collection of whole blood for exploratory genomic (DNA and RNA) analyses
- Standard safety urinalysis
- Urine pregnancy test for women of childbearing potential
- Call or enter to IRT/Randomization
- Jitter (SFEMG) measurement

During dosing of IMP:

- IMP administration
- Vital signs (systolic and diastolic BP, pulse rate, temperature, and respiratory rate)
- Recording of AEs

Postdose:

- Vital signs (systolic and diastolic BP, pulse rate, temperature, and respiratory rate)
- Recording of AEs
- Headache questionnaire (if required)
- Stool sample assessment (if required)
- Blood samples:
  - PK of UCB7665
  - Cytokines

8.2.2 Visit 3 (Day 2)

The subject will be contacted by telephone for collection of prior and concomitant medications, AEs, and withdrawal criteria data. Headache questionnaire will be completed if required. This visit should occur 24 hours after the IMP dose started.

8.2.3 Visit 4 (Day 8)

The following assessments and procedures will be performed at this visit:

Predose:

- Withdrawal criteria
- Prior and concomitant medications

- Concomitant medical procedures
- Vital signs (systolic and diastolic BP, pulse rate, temperature, and respiratory rate)
- Recording of AEs
- Assessment of MG status:
  - MG-composite scale
  - QMG scale
  - Muscle weakness severity and fatigability scale
  - Fatigue scale
- Query for suicidality (since last visit):

  If positive response (Yes), a full C-SSRS will be performed.
- 12-lead ECG
- Blood samples
  - Standard safety laboratories: hematology and clinical chemistry
  - PK of UCB7665
  - [redacted]
  - Ig (total IgG and subclasses)
  - MG-specific autoantibodies
  - Exploratory biomarker analysis
  - Exploratory safety biomarkers: may include but not limited to [redacted] only in subjects with severe headache and/or moderate to severe GI disturbance
  - BAFF
  - Collection of whole blood for exploratory RNA analysis
- Standard safety urinalysis
- Urine pregnancy test for women of childbearing potential
- Call or enter IRT to register the visit

During dosing of IMP:

- IMP administration
- Vital signs (systolic and diastolic BP, pulse rate, temperature, and respiratory rate)
- Recording of AEs

Postdose:

- Vital signs (systolic and diastolic BP, pulse rate, temperature, and respiratory rate)

- Recording of AEs
- Headache questionnaire if required
- Stool sample assessment if required
- Blood samples
  - Serum complement (C3,C4) and plasma complement levels (C3a and C5a)
  - PK of UCB7665
  - Cytokines should be collected if infusion reaction occurs

8.2.4 Visit 5 (Day 9)

The subject will be contacted by telephone for collection of prior and concomitant medications, AEs, and withdrawal criteria data. Headache questionnaire will be completed if required. This visit should occur 24 hours after the IMP dose started.

8.2.5 Visit 6 (Day 15)

The following assessments and procedures will be performed at this visit:

Predose:

- Withdrawal criteria
- Prior and concomitant medications
- Concomitant medical procedures
- Vital signs (systolic and diastolic BP, pulse rate, temperature, and respiratory rate)
- Recording of AEs
- Assessment of MG status:
  - MG-composite scale
  - QMG scale
  - Muscle weakness severity and fatigability scale
  - Fatigue scale
  - MGII
- Query for suicidality (since last visit):

  If positive response (Yes), a full C-SSRS will be performed.
- 12-lead ECG
- Blood samples:
  - Standard safety laboratories: hematology and clinical chemistry
  - PK of UCB7665
  - [redacted]

  - Ig (total IgG and subclasses)
  - Exploratory biomarker analysis
  - Exploratory safety biomarkers: may include but not limited to [redacted] only in subjects with severe headache and/or moderate to severe GI disturbance
  - BAFF
  - Cytokines
- Standard safety urinalysis
- Urine pregnancy test for women of childbearing potential
- Call or enter IRT to register the visit

During dosing of IMP:

- IMP administration
- Vital signs (systolic and diastolic BP, pulse rate, temperature, and respiratory rate)
- Recording of AEs

Postdose:

- Recording of AEs
- Headache questionnaire if required
- Stool sample assessment if required
- Blood samples
  - Serum complement (C3,C4) and plasma complement levels (C3a and C5a)
  - PK of UCB7665
  - Cytokines

8.2.6 Visit 7 (Day 16)

The subject will be contacted by telephone for collection of prior and concomitant medications, AEs, and withdrawal criteria data. Headache questionnaire will be completed if required. This visit should occur 24 hours after the IMP dose started.

8.2.7 Visit 8 (Day 22)

This is a nondosing visit. The following assessments and procedures will be performed at this visit:

- Assessment of withdrawal criteria
- Prior and concomitant medications
- Concomitant medical procedures

- Vital signs (systolic and diastolic BP, pulse rate, temperature, and respiratory rate)
- Recording of AEs
- Headache questionnaire if required
- Stool sample assessment if required
- Assessment of MG status:
  - MG-composite scale
  - QMG scale
  - Muscle weakness severity and fatigability scale
  - Fatigue scale
- Query for suicidality (since last visit):

  If positive response (Yes), a full C-SSRS will be performed.
- 12-lead ECG
- Blood samples:
  - Standard safety laboratories: hematology and clinical chemistry
  - PK of UCB7665

    [redacted]
  - Ig (total IgG and subclasses)
  - IgA, IgM, and IgE
  - Exploratory biomarker analysis
  - Exploratory safety biomarkers: may include but not limited to [redacted] only in subjects with severe headache and/or moderate to severe GI disturbance

    BAFF
  - Collection of whole blood for exploratory genomic (DNA and RNA) analyses
- Standard safety urinalysis
- Urine pregnancy test for women of childbearing potential

8.3 Dosing Period 2

In Dosing Period 2, visits will be performed at weekly intervals.

8.3.1 Visit 9 (Day 29)

Subjects will be rerandomized at Visit 9 and the IMP (UCB7665 7mg/kg or 4mg/kg sc infusion) will be administered as per the subject's randomization. The QMG and safety and efficacy assessments will be performed before rerandomization.

The following assessments and procedures will be performed at this visit:

Predose:

- Withdrawal criteria
- Prior and concomitant medications
- Concomitant medical procedures
- Vital signs (systolic and diastolic BP, pulse rate, temperature, and respiratory rate)
- Body weight
- Recording of AEs
- Physical examination (brief)
- Neurological examination (brief)
- Assessment of MG status:
  - MG-composite scale
  - QMG scale
  - Muscle weakness severity and fatigability scale
  - Fatigue scale
  - MGADL scale
  - MGII
  - MGFA classification
- Query for suicidality (since last visit):

  If positive response (Yes), a full C-SSRS will be performed.
- 12-lead ECG
- Blood samples:
  - Standard safety laboratories: hematology and clinical chemistry
  - PK of UCB7665
    [redacted]
  - Ig (total IgG and subclasses)
  - IgA, IgM, and IgE
  - MG-specific autoantibodies
  - Exploratory biomarker analysis
  - Exploratory safety biomarkers: may include but not limited to [redacted] only in subjects with severe headache and/or moderate to severe GI disturbance
  - BAFF

  - Cytokines
- Standard safety urinalysis
- Urine pregnancy test for women of childbearing potential
- Call or enter to IRT/Rerandomization
- Jitter (SFEMG) measurement

During dosing of IMP:

- IMP administration
- Vital signs (systolic and diastolic BP, pulse rate, temperature, and respiratory rate)
- Recording of AEs

Postdose:

- Recording of AEs
- Headache questionnaire if required
- Stool sample assessment if required
- Blood samples
  - Serum complement (C3,C4) and plasma complement levels (C3a and C5a)
  - PK of UCB7665
  - Cytokines

8.3.2 Visit 10 (Day 30)

The subject will be contacted by telephone for collection of prior and concomitant medications, AEs, and withdrawal criteria data. Headache questionnaire will be completed if required. This visit should occur 24 hours after the IMP dose started.

8.3.3 Visit 11 (Day 36)

The following assessments and procedures will be performed at this visit:

Predose:

- Withdrawal criteria
- Prior and concomitant medications
- Concomitant medical procedures
- Vital signs (systolic and diastolic BP, pulse rate, temperature, and respiratory rate)
- Recording of AEs
- Assessment of MG status:
  - MG-composite scale
  - QMG scale

  - Muscle weakness severity and fatigability scale
  - Fatigue scale
- Query for suicidality (since last visit):

  If positive response (Yes), a full C-SSRS will be performed.
- 12-lead ECG
- Blood samples:
  - Standard safety laboratories: hematology and clinical chemistry
  - PK of UCB766
  - [redacted]
  - Ig (total IgG and subclasses)
  - IgA, IgM, and IgE
  - MG-specific autoantibodies
  - Exploratory biomarker analysis
  - Exploratory safety biomarkers: may include but not limited to [redacted] only in subjects with severe headache and/or moderate to severe GI disturbance
  - BAFF
- Standard safety urinalysis
- Urine pregnancy test for women of childbearing potential
- Call or enter IRT to register the visit

During dosing of IMP:

- IMP administration
- Vital signs (systolic and diastolic BP, pulse rate, temperature, and respiratory rate)
- Recording of AEs

Postdose:

- Recording of AEs
- Headache questionnaire if required
- Stool sample assessment if required
- Blood samples
  - Serum complement (C3,C4) and plasma complement levels (C3a and C5a)
  - PK of UCB7665
  - Cytokines should be collected if infusion reaction occurs

8.3.4 Visit 12 (Day 37)

The subject will be contacted by telephone for collection of prior and concomitant medications, AEs, and withdrawal criteria data. Headache questionnaire will be completed if required. This visit should occur 24 hours after the IMP dose started.

8.3.5 Visit 13 (Day 43)

The following assessments and procedures will be performed at this visit:

Predose:

- Withdrawal criteria
- Prior and concomitant medications
- Concomitant medical procedures
- Vital signs (systolic and diastolic BP, pulse rate, temperature, and respiratory rate)
- Recording of AEs
- Assessment of MG status:
  - MG-composite scale
  - QMG scale
  - Muscle weakness severity and fatigability scale
  - Fatigue scale
  - MGII
- Query for suicidality (since last visit):

  If positive response (Yes), a full C-SSRS will be performed.
- 12-lead ECG
- Blood samples:
  - Standard safety laboratories: hematology and clinical chemistry
  - PK of UCB7665
  - [redacted]
  - Ig (total IgG and subclasses)
  - IgA, IgM, and IgE
  - Exploratory biomarker analysis
  - Exploratory safety biomarkers: may include but not limited to [redacted] only in subjects with severe headache and/or moderate to severe GI disturbance
  - BAFF
  - Cytokines

  - Collection of whole blood for exploratory genomic (DNA and RNA) analyses
- Standard safety urinalysis
- Urine pregnancy test for women of childbearing potential
- Call or enter IRT to register the visit
- Administration of IMP

During dosing of IMP:

- IMP administration
- Vital signs (systolic and diastolic BP, pulse rate, temperature, and respiratory rate)
- Recording of AEs

Postdose:

- Recording of AEs
- Headache questionnaire if required
- Stool sample assessment if required
- Blood samples
  - Serum complement (C3,C4) and plasma complement levels (C3a and C5a)
  - PK of UCB7665
  - Cytokines

8.3.6 Visit 14 (Day 44)

The subject will be contacted by telephone for collection of prior and concomitant medications, AEs, and withdrawal criteria data. Headache questionnaire will be completed if required. This visit should occur 24 hours after the IMP dose started.

8.4 Observation Period

During the Observation Period, visits will be performed at weekly intervals, apart from between Visits 17, 18, and 19, when visits will be performed at 2 weekly intervals. Subjects will return to the clinic for Visits 15, 16, 18, and 20 for efficacy and for safety assessments. Subjects will either return to the clinic, or, if possible and agreed by both the investigator and the subject, have home visits conducted by certified healthcare professionals, for Visits 17 and 19. No IMP will be administered in the Observation Period.

8.4.1 Visit 15 (Day 50)

The following assessments and procedures will be performed at this visit:

- Assessment of withdrawal criteria
- Prior and concomitant medications
- Concomitant medical procedures
- Vital signs (systolic and diastolic BP, pulse rate, temperature, and respiratory rate)

- Recording of AEs
- Headache questionnaire if required
- Stool sample assessment if required
- Assessment of MG status:
  - MG-composite scale
  - QMG scale
  - Muscle weakness severity and fatigability scale
  - Fatigue scale
  - MGADL scale
- Query for suicidality (since last visit):
  If positive response (Yes), a full C-SSRS will be performed.
- 12-lead ECG
- Blood samples:
  - Standard safety laboratories: hematology and clinical chemistry
  - PK of UCB7665
  - [redacted]
  - Ig (total IgG and subclasses)
  - IgA, IgM, and IgE
  - MG-specific autoantibodies
  - Exploratory safety biomarkers: may include but not limited to [redacted] only in subjects with severe headache and/or moderate to severe GI disturbance
- Standard safety urinalysis
- Urine pregnancy test for women of childbearing potential

8.4.2 Visit 16 (Day 57)

The following assessments and procedures will be performed at this visit:

- Withdrawal criteria
- Prior and concomitant medications
- Concomitant medical procedures
- Vital signs (systolic and diastolic BP, pulse rate, temperature, and respiratory rate)
- Recording of AEs
- Headache questionnaire if required

- Stool sample assessment if required
- Assessment of MG status:
  - MG-composite scale
  - QMG scale
  - Muscle weakness severity and fatigability scale
  - Fatigue scale
  - MGII
- Query for suicidality (since last visit):

  If positive response (Yes), a full C-SSRS will be performed.
- Blood samples:
  - Standard safety laboratories: hematology and clinical chemistry
  - [redacted]
  - Ig (total IgG and subclasses)
  - IgA, IgM, and IgE
  - Exploratory safety biomarkers: may include but not limited to [redacted] only in subjects with severe headache and/or moderate to severe GI disturbance
- Standard safety urinalysis
- Urine pregnancy test for women of childbearing potential

8.4.3 Visit 17 (Day 64)

The following assessments and procedures will be performed at this visit:

- Withdrawal criteria
- Prior and concomitant medications
- Concomitant medical procedures
- Vital signs (systolic and diastolic BP, pulse rate, temperature, and respiratory rate)
- Recording of AEs
- Headache questionnaire if required
- Stool sample assessment if required
- Assessment of MG status:
  - MG-composite scale (this assessment will be performed at the clinic/hospital. If the subject has a home visit with certified health professionals, this assessment will not be performed)
  - Muscle weakness severity and fatigability scale

  - Fatigue scale
  - MGADL scale
- Query for suicidality (since last visit):

  If positive response (Yes), a full C-SSRS will be performed.
- Blood samples:
  - [redacted]
  - Ig (total IgG and subclasses)
  - Exploratory biomarker analysis
  - Exploratory safety biomarkers: may include but not limited to [redacted] only in subjects with severe headache and/or moderate to severe GI disturbance

    BAFF
- Urine pregnancy test for women of childbearing potential

8.4.4 Visit 18 (Day 78)

The following assessments and procedures will be performed at this visit:

- Withdrawal criteria
- Prior and concomitant medications
- Concomitant medical procedures
- Vital signs (systolic and diastolic BP, pulse rate, temperature, and respiratory rate)
- Recording of AEs
- Headache questionnaire if required
- Stool sample assessment if required
- Assessment of MG status:
  - MG-composite scale
  - QMG scale
  - Muscle weakness severity and fatigability scale
  - Fatigue scale
  - MGII
- Query for suicidality (since last visit):

  If positive response (Yes), a full C-SSRS will be performed.
- 12-lead ECG

- Blood samples:
  - Standard safety laboratories: hematology and clinical chemistry
  - [redacted]
  - Ig (total IgG and subclasses)
  - Exploratory safety biomarkers: may include but not limited to [redacted] only in subjects with severe headache and/or moderate to severe GI disturbance
- Standard safety urinalysis
- Urine pregnancy test for women of childbearing potential

8.4.5 Visit 19 (Day 92)

The following assessments and procedures will be performed at this visit:

- Withdrawal criteria
- Prior and concomitant medications
- Concomitant medical procedures
- Vital signs (systolic and diastolic BP, pulse rate, temperature, and respiratory rate)
- Recording of AEs
- Headache questionnaire if required
- Stool sample assessment if required
- Assessment of MG status:
  - MG-composite scale (this assessment will be performed at the clinic/hospital. If the subject has a home visit with certified health professionals, this assessment will not be performed)
  - Muscle weakness severity and fatigability scale
  - Fatigue scale
- Query for suicidality (since last visit):

  If positive response (Yes), a full C-SSRS will be performed.
- Blood samples:
  - [redacted]
  - Ig (total IgG and subclasses)
  - Exploratory biomarker analysis
  - Exploratory safety biomarkers: may include but not limited to [redacted] only in subjects with severe headache and/or moderate to severe GI disturbance

- BAFF

- Urine pregnancy test for women of childbearing potential

8.4.6 Visit 20 (Day 99, Final Visit) and Premature End of Treatment Visit

Subjects who withdraw from the study drug will be encouraged to return to the clinic to complete a PEOT Visit and an FV approximately 8 weeks after the final dose of study drug. The following assessments and procedures will be performed at the FV (and PEOT Visit if applicable):

- Prior and concomitant medications
- Concomitant medical procedures
- Vital signs (systolic and diastolic BP, pulse rate, temperature, and respiratory rate)
- Body weight
- Recording of AEs
- Headache questionnaire if required
- Tuberculosis Sign and Symptoms questionnaire
- Stool sample assessment if required
- Physical examination (full)
- Neurological examination (full)
- Assessment of MG status:
  - MG-composite scale
  - QMG scale
  - Muscle weakness severity and fatigability scale
  - Fatigue scale
  - MGADL scale
  - MGII
  - MGFA classification
- Query for suicidality (since last visit):

  If positive response (Yes), a full C-SSRS will be performed.
- 12-lead ECG
- Blood samples:
  - Standard safety laboratories: hematology and clinical chemistry
  - [redacted]
  - Serum complement (C3,C4) and plasma complement levels (C3a and C5a)
  - Ig (total IgG and subclasses)

  - IgA, IgM, and IgE
  - MG-specific autoantibodies
  - Exploratory safety biomarkers: may include but not limited to [redacted] only in subjects with severe headache and/or moderate to severe GI disturbance
  - Vaccination-specific antibody titers ([redacted])
  - Cytokines
  - Collection of whole blood for exploratory RNA analyses
- Standard safety urinalysis
- Urine pregnancy test for women of childbearing potential
- Call or enter IRT to register the visit
- Subject Exit Interview

8.5 Premature End of Treatment Visit

All subjects who withdraw early from the study treatment should attend a PEOT Visit which will be scheduled as close as possible to the date of the decision for the study or treatment withdrawal. Subjects are encouraged to return to the clinic for all visits of the Observation Period following the PEOT Visit. An FV will be scheduled 8 weeks after the subject's final dose. In case a subject is not willing to attend the visits in the Observation Period, the subjects should still be strongly encouraged to attend at least the PEOT Visit and FV.

The assessments to be done at the PEOT Visit are the same as those at the FV (Visit 20).

8.6 Unscheduled Visit

Unscheduled visits may include the following assessments or other assessments deemed necessary by the investigator:

- Prior and concomitant medication
- Concomitant medical procedures
- Recording of AEs
- Headache questionnaire if required
- Stool sample assessment if required
- Vital signs (systolic and diastolic BP, pulse rate, temperature, and respiratory rate)
- Cytokines
- Query for suicidality (since last visit):

  If positive response (Yes), a full C-SSRS will be performed.

Other safety assessments (eg, physical examination, 12-lead ECG, laboratory assessments) may be performed at the discretion of the investigator.

In the event of a subject developing an infection during the course of the study, samples for culture will be taken prior to commencing antimicrobial treatment.

9 ASSESSMENT OF EFFICACY

9.1 Quantitative Myasthenia Gravis scale

For assessment of the QMG scale, investigators will follow the MGFA's QMG Manual instructions (see Section 18.1). Clinical personnel must complete mandatory training and be certified to assess subjects' QMG score (details are provided in the Study Procedures Manual). Subjects should not take pyridostigmine (or any [redacted] inhibitor medication) from midnight before testing when medically safe to do so to standardize testing, but if not medically appropriate, then the treatment can be continued but the testing should be performed as best as possible at the same timeframe post last [redacted] inhibitor dosing for each evaluation during the study. The scale tests 13 items, including ocular and facial involvement, swallowing, speech, limb strength, and forced vital capacity (FVC). For the assessment of FVC, the same spirometer should be used each time a subject is tested, and if possible, the same person should carry out the assessment. Parameters and normal values for FVC will be decided between the study sites, such that all sites are using the same information. The QMG is a validated assessment (Barnett et al, 2012), with a higher score indicating more severe disease. Scoring for each item ranges from no weakness (0) to severe weakness (3), with an overall score range from 0 to 39. A 3 point change in the total score is considered clinically relevant. The test takes approximately 30 minutes to perform.

9.2 MG-Composite scale

For assessment of the MG-Composite scale, the investigator will examine the subject to score all items, except for talking, chewing, and swallowing for which the subject will self-assess. The MG-Composite scale is a validated assessment (Burns et al, 2010), with a higher score indicating more severe disease (see Section 18.2) and a 3-point change being of clinical relevance. The scale tests 10 items, with individual items being weighted differently. The overall score ranges from 0 to 50. Clinical personnel must complete mandatory training and be certified to assess subjects' MG-Composite score (details are provided in the Study Procedures Manual).

9.3 Patient-reported outcomes

Subjects will complete 4 patient-reported outcomes (PROs) and participate in 1 subject exit interview as per time points mentioned in the schedule of study assessments in Section 5.2. Study personnel other than the treating physician should administer the PROs. The PROs should be completed by the subject themselves in a quiet place.

The PROs and the subject exit interview should be completed in the following order: MG muscle weakness and fatigability, Fatigue, MGADL and MGII, followed by the subject exit interview (which will be performed only at the FV). The PROs should only be checked for completeness. On dosing days, the PROs will be completed prior to dosing.

9.3.1 MG muscle weakness and fatigability

The MG muscle weakness and fatigability instrument (Appendix 18.3) consists of 27 items across 2 domains: 18 muscle weakness severity items and 9 symptom fatigability items. The subject will be asked to choose the response option that best describes the severity of muscle

weakness symptoms over the past 7 days using a 6-point Likert scale ("none" to "very severe") and how frequently they experienced symptom fatigability over the past 7 days using a 5-point Likert scale ("none of the time" to "all of the time"), respectively. The muscle weakness score ranges from 0 to 90; the fatigability score ranges from 0 to 36. The overall score ranges from 0 to 126, with a higher result indicating more severe muscle weakness and fatigability.

9.3.2 Fatigue

The fatigue instrument (Appendix 18.4) 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 overall score ranges from 55 to 275, with a higher result indicating more severe fatigue.

9.3.3 MG-Activities of Daily Living

The MGADL is an 8-item PRO instrument developed on the basis of the QMG (Wolfe et al, 1999) (Appendix 18.5). The MGADL targets symptoms and disability across ocular, bulbar, respiratory, and axial symptoms. In a recent study, reliability, validity, and responsiveness of the MGADL were further assessed. The questionnaire showed strong construct validity when evaluated against the MG-Composite as well as against the MG-QOL15, high test retest reliability in a 1 week interval, and it was demonstrated that a 2-point improvement indicates clinical improvement (Muppidi, 2012; Muppidi et al, 2011). The total MGADL score ranges from 0 to 24, with a higher score indicating more disability. Subjects will complete the MGADL by themselves as described in the standardized administration of PROs.

9.3.4 Myasthenia Gravis Impairment Index

The MGII is a measure of disease severity based on the signs and symptoms of Myasthenia Gravis patients (Appendix 18.6). It was developed using a patient-centered approach and following current guidelines for outcome measure development, incorporating patient input throughout the different development phases (Barnett et al, 2014, Barnett et al, 2016). The MGII has 22 patient-reported and 6 examination items, and scores are presented as a sum of all items for a total score but also as an ocular and generalized sub-score.

The MGII has shown construct validity and reliability in an outpatient setting. It has less floor effect compared to other commonly used outcome measures, and it can effectively discriminate among patients with different degrees of severity (Barnett et al, 2016). Finally, the MGII is sensitive to detect clinical change after interventions, and most importantly it can detect patient-meaningful change. Additionally, the MGII showed more relative efficiency than the QMGS, MGC and MG-ADL to detect change in short-term interventions for Myasthenia. Estimates for the minimal important difference were developed.

9.4 MGFA classification

The investigator will classify the subject's MG using the MGFA Clinical Classification (Section 18.6) (Jaretzki et al, 2000). This is a 5 stage classification (I to V), with a higher class indicating more severe disease.

9.5 Jitter (Single Fiber Electromyography)

At participating sites, subjects consenting to jitter (SFEMG) measurement should not take pyridostigmine from midnight before testing when medically safe to do so to standardize testing, but if not medically appropriate, then the treatment can be continued but the testing should be performed as best as possible at the same timeframe post last [redacted] inhibitor dosing for each evaluation during the study. If pyridostigmine is taken, the time must be documented. This measurement will be performed by adequately trained and equipped investigators. Jitter measurements may be performed with a single-fiber EMG (SFEMG) electrode having a side-ported recording surface with a 25µm diameter, or a disposable concentric needle electrode. This enables the measurement of fiber density and neuromuscular jitter (SFEMG) (which is a sensitive measurement of transmission across the NMJ) (Sanders, 2014). Jitter (SFEMG) can assist in demonstrating MG-associated abnormalities. In well treated MG, the jitter (SFEMG) displays a more normal profile.

Details of the jitter (SFEMG) performance will be described in the jitter (SFEMG) measurement manual.

9.6 Subject exit interview

At the FV, qualitative interviews will be conducted by a study nurse/study personnel using a semi-structured interview guide. The aim of the interview is to collect the subject's experience with MG in terms of symptoms and impact on daily activities, and the perceived changes during the course of the study. The extent to which the exploratory PRO items and scales used fully captured their experience will also be assessed. The interviews will be audio-recorded. If a subject leaves the study prematurely, he/she will also be invited to participate in an exit interview at the PEOT Visit.

10 ASSESSMENT OF PHARMACOKINETIC/ PHARMACODYNAMIC/PHARMACOGENOMIC VARIABLES

10.1 Pharmacokinetic variable

The plasma concentration of UCB7665 will be characterized. Blood samples will be drawn according to the schedule of study assessments (Section 5.2).

Blood samples will be collected pre- and post- UCB7665 dosing. Additional blood will be drawn at the predose sampling for standard clinical laboratory tests. Postdose samples will be taken 4 hours after the infusion has ended. At Visits 8 and 15, when no IMP is administered, blood for PK analysis will also be taken. The time and date of collection will be recorded in the eCRF.

Instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the Laboratory Manual for this study.

10.2 Pharmacodynamic variables

For all PD assessments, blood samples will be collected by qualified site personnel at the same time that samples are collected for standard clinical laboratory assessments. At dosing visits, these samples will be collected predose. Blood samples for PD analysis will be drawn according to the schedule of study assessments (Section 5.2). The time and date of collection will be recorded in the eCRF.

Instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the Laboratory Manual for this study.

The following will be measured:

- Serum total IgG concentrations
- Serum IgG subclass concentrations
- Serum MG-specific autoantibody ([redacted]) levels

11 ASSESSMENT OF OTHER VARIABLES

11.1 Assessment of other immunological variables

For all immunological assessments, blood samples will be collected by qualified site personnel at the same time that samples are collected for standard clinical laboratory assessments. At dosing visits, these samples will be collected predose. The time and date of the blood draws will be recorded in the eCRF. The following immunological assessments will be performed according to the schedule of study assessments (Section 5.2):

- Serum Ig concentrations
  - IgA
  - IgE
  - IgM
- Serum complement levels
  - C3
  - C4
- Plasma complement levels
  - C3a
  - C5a
- Serum BAFF levels
- Plasma [redacted] ([redacted]) status (negative or confirmed positive) and changes in relative mass units for all scheduled assessments or titre for those confirmed positive
- Cytokines
- [redacted]

12 ASSESSMENT OF SAFETY

12.1 Adverse events

12.1.1 Definitions

12.1.1.1 Adverse event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

In order to ensure complete safety data collection, all AEs occurring during the study (ie, after the signing of the Informed Consent form), including any pretreatment and posttreatment periods required by the protocol, must be reported in the eCRF even if no IMP was taken but specific study procedures were conducted. This includes all AEs not present prior to the initial visit and all AEs that recurred or worsened after the initial visit.

Signs or symptoms of the condition/disease for which the IMP is being studied should be recorded as AEs only if their nature changes considerably or their frequency or intensity increases in a clinically significant manner as compared to the clinical profile known to the investigator from the subject's history or the Baseline Period.

Treatment-emergent AEs are defined as AEs starting after the time of first IMP administration up to and including 8 weeks after the final dose.

12.1.1.2 Serious adverse event

Once it is determined that a subject experienced an AE, the seriousness of the AE must be determined. An SAE must meet 1 or more of the following criteria:

- Death
- Life-threatening

  (Life-threatening does not include a reaction that might have caused death had it occurred in a more severe form)
- Significant or persistent disability/incapacity
- Congenital anomaly/birth defect (including that occurring in a fetus)
- Important medical event that, based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent 1 of the other outcomes listed in the definition of serious

  (Important medical events may include, but are not limited to, potential Hy's Law [see Section 12.1.1.3], allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)
- Initial inpatient hospitalization or prolongation of hospitalization

(A patient admitted to a clinic/hospital, even if he/she is released on the same day, meets the criteria for the initial inpatient hospitalization. An emergency room visit that results in admission to the clinic/hospital would also qualify for the initial inpatient hospitalization criteria. However, emergency room visits that do not result in admission to the clinic/hospital would not qualify for this criteria and, instead, should be evaluated for 1 of the other criteria in the definition of serious [eg, life-threatening adverse experience, important medical event]).

Hospitalizations for reasons not associated with the occurrence of an AE [eg, preplanned surgery or elective surgery for a pre-existing condition that has not worsened or manifested in an unusual or uncharacteristic manner] do not qualify for reporting. For example, if a subject has a condition recorded on his/her medical history and later has a preplanned surgery for this condition, it is not appropriate to record the surgery or hospitalization as an SAE, since there is no AE upon which to assess the serious criteria. Please note that, if the pre-existing condition has worsened or manifested in an unusual or uncharacteristic manner, this would then qualify as an AE and, if necessary, the seriousness of the event would need to be determined.)

12.1.1.2.1 Anticipated serious adverse events

Myasthenic crisis is anticipated to occur in the population studied in this protocol at some frequency that is independent of drug exposure.

This information does not change the investigator's obligation to report all SAEs (including Anticipated SAEs) as detailed in Section 12.1.2.3.

12.1.1.3 Adverse events of special interest

An AE of special interest is any AE that a regulatory authority has mandated be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a UCB product/compound.

Potential Hy's Law, defined as ≥3xULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality, must ALWAYS be reported to UCB as an AE of special interest (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should then be reported if an alternative etiology is identified during investigation and monitoring of the subject.

12.1.1.4 Adverse events of interest

For UCB7665, AEs of interest that require immediate reporting to UCB are:

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

12.1.1.5 Immediate reporting of adverse events

The following AEs must be reported immediately using the SAE Report Form according to the procedure in Section 12.1.2.3:

- SAE: AE that the investigator classifies as serious by the above definitions regardless of causality
- Suspected transmission of an infectious agent via a medicinal product
- AE of special interest (see Section 12.1.1.3)
- AE of interest (see Section 12.1.1.4)
- Confirmed LTBI, active TB, and NTMBI (see Section 12.3.1)

12.1.2 Procedures for reporting and recording adverse events

The subject will be given the opportunity to report AEs spontaneously. A general prompt will also be given at each study visit to detect AEs. For example:

"Did you notice anything unusual about your health (since your last visit)?"

12.1.2.1 Description of adverse events

When recording an AE, the investigator should use the overall diagnosis or syndrome using standard medical terminology, rather than recording individual symptoms or signs. The eCRF and source documents should be consistent. Any discrepancies between the subject's own words and the corresponding medical terminology should be clarified in the source documentation.

For recording an AE, Common Terminology Criteria for Adverse Events (CTCAE) will be used, and only if it is impossible to assess severity using CTCAE, then AE intensity will be used, using a scale of mild, moderate, or severe.

Details for completion of the AE eCRF (including judgment of relationship to IMP) are described in the eCRF Completion Guidelines.

12.1.2.2 Rule for repetition of an adverse event

An increase in the intensity of an AE should lead to the repetition of the AE being reported with:

- The outcome date of the first AE that is not related to the natural course of the disease being the same as the start date of the repeated AE, and the outcome of "worsening"
- The AE verbatim term being the same for the first and repeated AE, so that the repeated AE can be easily identified as the worsening of the first one

12.1.2.3 Additional procedures for reporting serious adverse events

If an SAE is reported, UCB must be informed within 24 hours of receipt of this information by the site (see contact information for SAE reporting listed in the Serious Adverse Event Reporting section at the front of the protocol). The investigator must forward to UCB (or its representative) a duly completed "Investigator SAE Report Form for Development Drug" (SAE Report Form) provided by UCB, even if the data are incomplete, or if it is obvious that more data will be needed in order to draw any conclusions. Information recorded on this form will be entered into the global safety database.

An Investigator SAE Report Form will be provided to the investigator. The Investigator SAE Report Form must be completed in English.

It is important for the investigator, when completing the SAE Report Form, to include the assessment as to a causal relationship between the SAE and the IMP administration. This insight from the investigator is very important for UCB to consider in assessing the safety of the IMP and in determining whether the SAE requires reporting to the regulatory authorities in an expedited manner.

Additional information (eg, autopsy or laboratory reports) received by the investigator must be provided within 24 hours. All documents in the local language must be accompanied by a translation in English, or the relevant information included in the same document must be summarized in the Investigator SAE Report Form.

The investigator is specifically requested to collect and report to UCB (or its representative) any SAEs (even if the investigator is certain that they are in no way associated with the IMP), up to 30 days from the end of the study for each subject, and to also inform participating subjects of the need to inform the investigator of any SAE within this period. Serious AEs that the investigator thinks may be associated with the IMP must be reported to UCB regardless of the time between the event and the end of the study.

Upon receipt of the SAE Report Form, UCB will perform an assessment of expectedness of the reported SAE. The assessment of the expectedness of the SAE is based on the Investigator's Brochure.

12.1.3 Follow up of adverse events

An AE should be followed until it has resolved, has a stable sequelae, the investigator determines that it is no longer clinically significant, or the subject is lost to follow up. This follow-up requirement applies to AEs, SAEs, and AEs of special interest; further details regarding follow up of PDILI events is provided in Section 12.2.1.4.

If an AE is ongoing at the end of the study for a subject, follow up should be provided until resolution/stable level of sequelae is achieved, or until the investigator no longer deems that it is clinically significant, or until the subject is lost to follow up. If no follow up is provided, the investigator must provide a justification. The follow up will usually be continued for 8 weeks after the subject has discontinued his/her IMP.

Information on SAEs obtained after clinical database lock will be captured through the PS database without limitation of time.

12.1.4 Pregnancy

If an investigator is notified that a subject has become pregnant after the first intake of any IMP, the investigator must immediately notify UCB's PS department by providing the completed Pregnancy Report and Outcome form (for contact details see SAE reporting information at the beginning of this protocol). The subject should be withdrawn from the study as soon as pregnancy is known (by positive pregnancy test), and the following should be completed:

- The subject should return for a PEOT Visit.
- The subject should immediately stop the intake of the IMP or be down-titrated as instructed at the PEOT Visit.

The investigator must inform the subject of information currently known about potential risks and about available treatment alternatives.

The pregnancy will be documented on the Pregnancy Report and Outcome form provided to the investigator. The progression of the pregnancy and the eventual birth (if applicable) must be followed up using the Pregnancy Report and Outcome form in which the investigator has to report on the health of the mother and of the child. Every reasonable attempt should be made to follow the health of the child for 30 days after birth for any significant medical issues. In certain circumstances, UCB may request that follow up is continued for a period longer than 30 days. If the subject is lost to follow up and/or refuses to give information, written documentation of attempts to contact the subject needs to be provided by the investigator and filed at the site. UCB's PS department is the primary contact for any questions related to the data collection for the pregnancy, eventual birth, and follow up.

In cases where the partner of a male subject enrolled in a clinical study becomes pregnant, the investigator or designee is asked to contact the subject to request consent of the partner via the Partner Pregnancy Consent form that has been approved by the responsible IRB/IEC and should be available in the investigator site file. In case of questions about the consent process, the investigator may contact the UCB/CRO contract monitor for the study. The investigator will complete the Pregnancy Report and Outcome form and send it to UCB's PS department (for contact details see SAE reporting information at the beginning of this protocol) only after the partner has agreed that additional information can be captured and has provided the signed Partner Pregnancy Consent form. UCB's PS department is also the primary contact for any questions related to the data collection for the partner pregnancy, eventual birth, and follow up.

A pregnancy becomes an SAE in the following circumstances: miscarriage, abortion (elective or spontaneous), unintended pregnancy after hormonal contraceptive failure (if the hormonal contraceptive was correctly used), ectopic pregnancy, fetal demise, or any congenital anomaly/birth defect of the baby. Those SAEs must be additionally reported using the Investigator SAE Report Form.

12.1.5 Suspected transmission of an infectious agent via a medicinal product

For the purposes of reporting, any suspected transmission of an infectious agent via a medicinal product should be considered as an SAE; such cases must be reported immediately, recorded in the AE module of the eCRF, and followed as any other SAE. Any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

12.1.6 Suicidality

At screening, the Investigator will query each subject if he/she has a lifetime history of suicide attempt (including an [redacted] or suicidal ideation in the past 6 months. A full C-SSRS "Lifetime recent" assessment will be performed only when the subject has a positive response to this query. This scale will be assessed by trained study personnel. When suicide attempt or suicidal ideation is confirmed by a positive response (Yes) to either Question 4 or Question 5 of the C-SSRS, the subject must be excluded and immediately referred to a Mental Healthcare Professional.

At each clinical visit, the investigator must query the suicidal ideation since the last visit. A full C-SSRS "Since last visit" assessment will be performed only when the subject has a positive response to this query. When suicide attempt or suicidal ideation is confirmed by a positive

response (Yes) to either Question 4 or Question 5 of the C-SSRS, the subject must be withdrawn and immediately referred to a Mental Healthcare Professional. The details of C-SSRS will be provided in the Study Procedures Manual.

12.1.7 Overdose of investigational medicinal product

Excessive dosing (beyond that prescribed in the protocol and including overdose) should be recorded in the eCRF. Any SAE or nonserious AE associated with excessive dosing must be followed as any other SAE or nonserious AE. These events are only considered AEs or SAEs if there are associated clinical signs and symptoms or if the act of taking the excess medicine itself is an AE or SAE (eg, suicide attempt).

12.1.8 Safety signal detection

An unblinded DMC will oversee at least 1 interim analysis during the course of the study during which the safety of UCB7665 will be assessed. The safety variables to be used and the decision rules will be specified in the DMC charter. Further details of these interim analyses are given in Section 14.7.

Thus, selected data from this study will be reviewed periodically to detect as early as possible any safety concern(s) related to the IMP so that investigators, clinical study subjects, regulatory authorities, and IRBs/IECs will be informed appropriately and as early as possible.

The sponsor study physician or medically qualified designee/equivalent will conduct an ongoing review of SAEs and perform ongoing SAE reconciliations in collaboration with the PS representative.

As appropriate for the stage of development and accumulated experience with the IMP, medically qualified personnel at UCB may identify additional safety measures (eg, AEs, vital signs, laboratory or ECG results) for which data will be periodically reviewed during the course of the study.

12.1.9 Hypersensitivity and adverse reactions

In the event of a severe infusion or anaphylactic reaction requiring corticosteroid and/or epinephrine therapy, the subject must permanently discontinue IMP and be managed as described in Section 18.8.

In case of occurrence of a hypersensitivity reaction (not determined by the investigator to be a minor local reaction at the infusion site, such as minimal itching) and depending upon its severity, appropriate countermeasures will immediately be taken by the investigator. The cytokine samples must be taken for infusion reactions.

If the investigator does not initially choose to discontinue the infusion of IMP and symptoms persist or escalate during continued infusion, the infusion should be stopped. In case of any severe infusion reaction(s), the infusion of IMP must be stopped immediately and appropriate treatment initiated, as necessary, at the discretion of the investigator and in accordance with the standard of care.

Moderate or severe anaphylactic reactions should be diagnosed using Sampson's Criteria (Sampson et al, 2006) as described in Section 18.9. In the event of an anaphylactic reaction the infusion must be discontinued immediately and appropriate emergency resuscitation measures implemented.

12.1.10 Management of severe headache

Severe headache is defined as severe pain limiting self-care activities of daily living (ADL) or new/prolonged hospitalization for management of headache or life-threatening consequences requiring urgent medical intervention. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, and taking medications. Treatment of headache will be provided as clinically indicated according to the local guidelines.

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 scan, magnetic resonance imaging and/or a lumbar puncture for cerebral spinal fluid 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.

Details of neurological examination to be performed are provided in Section 12.3.6. The Headache Questionnaire is available in Section 18.10.

12.1.11 Management of moderate or severe diarrhea

Moderate or severe diarrhea is defined as an increase of ≥4 stools per day over Baseline or incontinence due to urgency of diarrhea or new/prolonged hospitalization for management of diarrhea or limiting self-care ADL or life-threatening consequences requiring urgent medical intervention.

Stool collection and analysis will be performed for subjects reporting moderate or severe diarrhea. The frequency of stool sampling will be as clinically indicated in the opinion of the investigator. Analysis of stool samples will be performed locally. In addition, collection of blood samples for assessment of exploratory safety biomarkers is required for subjects with moderate to severe GI disturbances including diarrhea.

Treatment of diarrhea will be provided as clinically indicated according to the local guidelines.

12.2 Laboratory measurements

Blood and urine specimens for routine assay of hematology, clinical chemistry, and urinalysis testing, and as well as serum and urine pregnancy testing, will be performed according to the schedule of assessments (Section 5.2) to monitor the safety of subjects. All clinical chemistry, hematology, and urinalysis parameters will be assessed by the designated central laboratory with the exception the urine pregnancy test prior to each dose. Specific details regarding the handling and processing of the serum chemistry, hematology, and urinalysis samples are provided in the study laboratory manuals.

Table 12.2 lists the laboratory parameters that will be measured.

Table 12.2: Safety laboratory measurements

Hematology	Chemistry	Urinalysis	Pregnancy test
Hematocrit	Electrolytes (calcium, phosphate, sodium, potassium, chloride, and magnesium)	Albumin	Urine HCG
Hemoglobin		Protein	Serum HCG[a]
Platelet count		Nitrite	
RBC count	ALP	Glucose	
WBC count (including differential)	AST	pH	
	ALT	Leukocytes	
HbA1c[b]	GGT	Blood	
	Total and direct bilirubin	Bilirubin	
Serology[c]		Urobilinogen	
HBsAg	LDH	Ketone	
HCV Ab	Total cholesterol	Creatinine	
HIV (anti-HIV1 or anti-HIV2 antibodies)	LDL - cholesterol		
	HDL – cholesterol, triglycerides		
Tuberculosis[d]			
	Amylase		
Exploratory Safety Biomarkers[e]	Creatine kinase		
[redacted]	Creatinine		
	Total protein		
	Albumin		
	alpha- and beta–globulins		
	Urea-N		
	Procalcitonin		
	hsCRP		

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma glutamyltransferase; HbA1c=hemoglobin A1c; HBsAG=hepatitis B surface antigen; HCG=human chorionic gonadotropin; HCV Ab=hepatitis C virus antibody; HDL=high density lipoprotein; HIV=human immunodeficiency virus; hsCRP=high-sensitivity C-reactive protein; LDH=lactate dehydrogenase; LDL=low density lipoprotein; RBC=red blood cell; [redacted] B; WBC=white blood cell

[a] Serum pregnancy testing is only performed at Visit 1 and, in the event of a positive pregnancy test, to confirm the results of a urine test
[b] HbA1c is performed at Screening only
[c] This serology performed at Screening only
[d] Interferon-gamma release assay by central laboratory.
[e] May include but not limited to the following biomarkers listed below. Samples collected for exploratory safety biomarkers at Baseline (Visit 2) and 4 hours post dosing (Visit 2) for all subjects and during follow up only in subjects with severe headache and/or moderate to severe GI disturbances. The Baseline samples will only be analysed in case the subject experienced a severe headache and/or moderate to severe GI disturbance.

12.2.1 Evaluation of PDILI

The PDILI IMP discontinuation criteria for this study are provided in Section 6.4.1, with the accompanying required follow-up investigation and monitoring detailed below. All PDILI events must be reported as an AE and reported to the study site and sponsor within 24 hours of learning of their occurrence. Any PDILI event that meets the criterion for potential Hy's Law must be reported as an AE of special interest (see Section 12.1.1.3), and, if applicable, also reported as an SAE (see Section 12.1.1.2).

Evaluation of PDILI consists of the diagnostic testing and continued monitoring included in Table 12.3 (specific tests dependent on laboratory results and corresponding symptoms) and consultation with a local hepatologist (if applicable; discussed in Section 12.2.1.1). The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. Additional investigation and monitoring may be required and adapted based on the diagnosis after the cause of the liver injury/abnormality is confirmed (details in Section 12.2.1.4).

The results of all monitoring, including laboratory testing and other testing, should be made available to the study site and sponsor.

All initial tests resulting in abnormal hepatic laboratory values need to be repeated, but appropriate medical action must not be delayed waiting for the repeat result.

If tests are done locally for more rapid results, a concurrent sample should also be sent to the central laboratory whenever possible. Medical care decisions are to be made initially using the most rapidly available results and a conservative approach must be taken if the results from the 2 laboratory tests are significantly different. Data from the local and central laboratory are to be recorded on the applicable eCRF pages.

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. In these cases, the investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

When IMP is stopped due to PDILI (as described in Section 6.4.1), IMP must be permanently discontinued unless a subsequent alternative diagnosis fully explains the hepatic findings. If a subsequent alternative diagnosis fully explains the hepatic findings, and the requirements provided in Section 12.2.1.2.1 are met, rechallenge with IMP may be appropriate.

Rechallenge with a substance potentially causing drug-induced liver injury is dangerous, may be fatal, and must not occur.

Table 12.3 below summarizes the approach to investigate PDILI.

Table 12.3: Required investigations and follow up for PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥3xULN	≥2xULN[b]	NA	Hepatology consult.[c] Medical monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with medical monitor ASAP.	Immediate, permanent IMP discontinuation.	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 12.2.1.3); recommended to occur at the site with HCP.	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within Baseline values.[d]
≥3xULN	NA	Yes		Immediate, temporary or permanent, IMP discontinuation.		
≥3xULN (and ≥2x Baseline) and <5xULN	<2xULN	No	Discussion with medical monitor required if the criterion that allows for IMP continuation is met.	Further investigation – immediate IMP discontinuation not required (see Section 12.2.1.2).	Not required unless otherwise medically indicated (at discretion of investigator).	
≥5xULN (and ≥2x Baseline)	<2xULN	No	Discussion with medical monitor required. Hepatology consult required if ALT or AST ≥8xULN	Immediate, permanent IMP discontinuation.	Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48 hours at the site with HCP (see Section 12.2.1.3).	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within Baseline values.[d]

Table 12.3: Required investigations and follow up for PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**

ALP=alkaline phosphatase; ALT=alanine aminotransferase; ASAP=as soon as possible; AST=aspartate aminotransferase; HCP=healthcare practitioner; IMP=investigational medicinal product; NA=not applicable; PDILI=potential drug-induced liver injury; ULN=upper limit of normal

[a] Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

[b] If the subject also has ≥2xULN ALP, the possibility of an indication of biliary obstruction should be discussed with the medical monitor.

[c] Details provided in Section 12.2.1.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist.

[d] Unless an alternative monitoring schedule is agreed by the investigator and UCB responsible physician. Determination of stabilization is at the discretion of the investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

12.2.1.1 Consultation with medical monitor and local hepatologist

Potential drug-induced liver injury events require notification of the medical monitor within 24 hours (eg, by laboratory alert), and the subject must be discussed with the medical monitor as soon as possible. If required, the subject must also be discussed with the local hepatologist or gastroenterologist. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. If determined necessary, this discussion should be followed by a full hepatology assessment (see Section 12.2.1.3) and SAE report (if applicable).

12.2.1.2 Immediate action: determination of IMP discontinuation

All PDILI events require immediate action, testing, and monitoring.

The immediate action is dependent on the laboratory values and symptoms of hepatitis or hypersensitivity and ranges from continuation of IMP (followed by immediate investigation) to immediate and permanent discontinuation (see Section 6.4.1 and Table 12.3 for details).

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. The investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

12.2.1.2.1 IMP restart/rechallenge (if applicable)

Rechallenge with a substance potentially causing drug-induced liver injury is dangerous, may be fatal, and must not occur.

Subjects who are immediately discontinued from IMP due to having met certain criteria for PDILI (as described in Section 6.4.1 and Table 12.3), but for whom an alternative diagnosis is confirmed, can rarely restart IMP. Rechallenge with IMP can occur only if ALL of the following requirements are met:

- The results of additional testing and monitoring described in Section 12.2.1.3 and Section 12.2.1.4 confirm a nondrug-related cause for the abnormal hepatic laboratory parameters and any associated symptoms (ie, a subsequent alternative diagnosis fully explains the hepatic findings).
- No alternative treatment options are available to the subject.
- The subject has shown clear therapeutic benefit from the IMP.
- Subject's ALT or AST elevations do not exceed ≥3xULN.
- Subject's total bilirubin is <1.5xULN.
- Subject has no signs or symptoms of hypersensitivity.
- The rechallenge is approved by the UCB responsible physician, DMC, and a hepatologist. The hepatologist must be external to UCB but may be a member of the DMC. It is recommended that the hepatologist be a local hepatology expert or the hepatologist treating the subject.
- Subject agrees to the investigator-recommended monitoring plan.

12.2.1.3 Testing: identification/exclusion of alternative etiology

The measurements and additional information required for the assessment of PDILI events when there is a reasonable possibility that they may have been caused by the IMP are detailed in Table 12.4 (laboratory measurements) and Table 12.5 (additional information). Results of the laboratory measurements and information collected are to be submitted to the sponsor on the corresponding eCRF. If the medical history of the subject indicates a requirement for other assessments not included below, these additional assessments should be completed and submitted, as applicable.

All blood samples should be stored, if possible. If tests are done locally for more rapid results, a concurrent sample must also be sent to the central laboratory.

The measurements detailed in Table 12.4 are to be assessed.

Table 12.4: PDILI laboratory measurements

Virology-related	Hepatitis A IgM antibody
	HBsAg
	Hepatitis E IgM antibody
	HBcAb-IgM
	Hepatitis C RNA
	Cytomegalovirus IgM antibody
	Epstein-Barr viral capsid antigen IgM antibody (if unavailable, obtain heterophile antibody or monospot testing)
Immunology	Anti-nuclear antibody (qualitative and quantitative)
	Anti-smooth muscle antibody (qualitative and quantitative)
	Type 1 anti-liver kidney microsomal antibodies (qualitative and quantitative)
Hematology	Eosinophil count
Urinalysis	Toxicology screen
Chemistry	Amylase
	If total bilirubin ≥1.5xULN, obtain fractionated bilirubin to obtain % direct bilirubin
	Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation
Additional	Prothrombin time/INR[a]
	Serum pregnancy test
	PK sample

ALT=alanine aminotransferase; CPK=creatine phosphokinase; HBcAb-IgM=hepatitis B core antibody-IgM; HBsAg=hepatitis B surface antigen; IgM=immunoglobulin M; INR=international normalized ratio; LDH=lactate dehydrogenase; PDILI=potential drug-induced liver injury; PK=pharmacokinetic; RNA=ribonucleic acid; ULN=upper limit of normal

[a] Measured only for subjects with ALT >8xULN, elevations in total bilirubin, and symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

The following addition information listed in Table 12.5 is to be collected:

Table 12.5: PDILI information to be collected

New or updated information
Concomitant prescription and over-the-counter medications (eg, acetaminophen, herbal remedies, vitamins); dosages and dates should be included
Pertinent medical history, including the following: • History of liver disease (eg, autoimmune hepatitis, nonalcoholic steatohepatitis or other "fatty liver disease") • Adverse reactions to drugs • Allergies • Relevant family history or inheritable disorders (eg, Gilbert's syndrome, alpha-1 antitrypsin deficiency) • Recent travel • Progression of malignancy involving the liver (Note: Metastatic disease to the liver, by itself, should not be used as an explanation for significant AST and/or ALT elevations)
The appearance or worsening of clinical symptoms of hepatitis or hypersensitivity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, decreased appetite, abdominal pain, jaundice, fever, or rash)
Recent clinically significant hypotension or hypoxemia with compromised cardiopulmonary function
Alcohol and illicit drug use
Results of liver imaging or liver biopsy, if done
Results of any specialist or hepatology consult, if done
Any postmortem/pathology reports

ALT=alanine aminotransferase; AST=aspartate aminotransferase; PDILI=potential drug-induced liver injury

12.2.1.4 Follow-up evaluation

Potential drug-induced liver injury events require follow-up monitoring as described in Table 12.3. Monitoring should continue until liver chemistry values normalize, stabilize, or return to Baseline. Determination of stabilization is at the discretion of the investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

12.3 Other safety measurements

12.3.1 Assessment and management of TB and TB risk factors

With the currently available data, TB is not considered as an important potential or identified risk for treatment with UCB7665. As immunomodulation may carry risk of new or activation of LTBI, UCB has conservatively developed TB detection and management procedures taking into account the most current recommendations of international guidelines (2010 WHO) and most recent literature, covering any infection by the mycobacteria tuberculosis complex.

Appropriate rigorous precautions are being taken within this protocol to monitor the risk of TB infection in this study (see Section 6.2.3 [Exclusion Criterion 32] and Section 6.4 [Withdrawal Criteria 1]). Following are the key considerations of these procedures:

TB Tests at Screening

IGRA and TB questionnaire are required as indicated in Schedule of Assessments (Table 5.1).

- TB screening is mandatory both before study entry and during the conduct of the study. The preferred screening test is **IGRA performed at a Central Laboratory.**
  - The IGRA result must be negative for subjects to enroll in this study
  - Subjects who test positive for IGRA test should be excluded from the study and referred for appropriate medical evaluation according to the local medical practice guidelines.
  - If the result of the IGRA test is indeterminate, the particular IGRA test previously performed may be repeated once; if positive or indeterminate on retest, the subject must not be randomized to study drug and, if already randomized, must undergo appropriate study specified withdrawal procedures. The retest must be done during the protocol-defined Screening Period.
- In addition to IGRA test, subjects will be evaluated for signs and symptoms of latent or active TB infection and for risk factors of exposure to TB, using the TB questionnaire, at Screening. See the 'TB signs and symptoms questionnaire' section for further instructions on using the questionnaire. Subjects with known TB, at a high risk of acquiring TB or with LTBI should be excluded from this study as described in Exclusion Criteria.

Monitoring for TB during the study

Subjects will be monitored for signs/symptoms of TB using routine pharmacovigilance measures for Adverse Events. Subjects reporting AEs related to signs/symptoms of TB will be evaluated for LTBI and active TB according to the local medical practice guidelines.

Subjects with confirmed LTBI or active TB or NTMBI will be immediately withdrawn from the study as described in Withdrawal Criteria. Confirmed LTBI, active TB, and NTMBI must be reported to the Sponsor immediately regardless of seriousness using the SAE Report Form. Additional information received by the Investigator should be provided to the Sponsor within 24 hours of awareness.

Once withdrawn from study treatment, subjects should return for the PEOT, complete all early withdrawal assessments, and complete the follow-up visits.

TB tests at Final/PEOT Visit

Subjects will be evaluated for signs and symptoms of latent or active TB infection and for risk factors of exposure to TB, using the TB questionnaire, at the Final/PEOT Visit. See the 'TB signs and symptoms questionnaire' section for further instructions on using the questionnaire.

Signs and symptoms of TB

The Investigator should consider all potential sites of infection when assessing for TB during the physical examination, and other evaluations, and based on the subject's history.

Common symptoms with which the subject may present with include cough, blood in sputum, night sweats, lymphadenitis, joint pain/swelling, spinal deformity, headache/confusion, abdominal pain mimicking inflammatory bowel disease, frequent or painful urination, scrotal mass in men and pelvic inflammatory disease in women as well as other symptoms, or nonspecific symptoms. This is not an exhaustive list and unusual presentations should always be considered.

TB signs and symptoms questionnaire

The questionnaire "Evaluation of signs and symptoms of tuberculosis" should be used as a source document. The questionnaire will assist with the identification of subjects who may require therapy for TB. A subject who answers "Yes" to the question [redacted] at Screening is excluded. A "Yes" response to any of the other questions within the questionnaire at Screening should trigger further careful assessment to determine if subject has latent or active TB (see Section 6.2.3 [Exclusion Criterion 32]). A "Yes" response to any of the questions at the end of the study should trigger further assessments as per local medical guidelines to determine if the subject has either LTBI or active TB infection.

LTBI, active TB or other NMTB identified during study

During the study, subjects who develop evidence of LTBI or active TB or NMTBI must immediately stop further administration of study drug and will be referred to an appropriate medical specialist for further evaluation.

Confirmed LTBI or active TB or NTMBI must be reported to the Sponsor immediately as described above.

12.3.2 Pregnancy testing

Pregnancy testing will consist of a serum test at Screening Visit (Visit 1) and urine tests at all other visits, as indicated in the schedule of study assessments (Table 5.1). The Screening Visit serum pregnancy test results must be negative and should be confirmed by a negative urine pregnancy test prior to first dose of IMP. The urine pregnancy test will be performed locally. A negative urine pregnancy test result should be obtained prior to each dose of IMP. A positive urine pregnancy test must be confirmed using a serum pregnancy test. Pregnancy tests should be administered to all female subjects of childbearing potential, regardless of their use of birth control.

12.3.3 Vital signs

Vital signs will be measured at all visits as indicated in the schedule of study assessments (Table 5.1).

Vital signs to be assessed are as follows:

- Pulse rate
- Systolic/diastolic BP
- Temperature (oral preferred, ear or axillary allowed)
- Respiratory rate

Subjects will be sitting for at least 5 minutes prior and during the measurement of BP, PR, and respiration rate. On dosing days, vital signs will be measured prior to IMP administration, once during the infusion (at the halfway time point), at the end of infusion, 2 hours after end of infusion, and 4 hours after end of infusion. At nondosing visits, vital signs need only be taken once during the visit.

12.3.4 Body weight and height

The subject's body weight (without shoes) will be determined at Screening (Visit 1), Visit 9, and at the FV (Visit 20). Height will be measured at Screening (Visit 1) only.

12.3.5 Physical examination

Physical examination (full or brief) will be performed at visits as specified in the schedule of study assessments (Table 5.1) and findings will be recorded in the eCRF.

Clinically important abnormal changes in subsequent physical examinations will be recorded as AEs. Physical examinations must be documented in source documentation.

12.3.5.1 Full physical examination

The following body systems will be examined as a part of the full physical examination:

- General appearance
- Ear, nose, and throat
- Eyes
- Hair and skin
- Respiratory
- Cardiovascular
- GI
- Musculoskeletal
- Hepatic
- Neurological (including limb reflexes)
- Mental status

12.3.5.2 Brief physical examination

The following body systems will be examined as a part of the brief physical examination at the visits outlined in the schedule of assessments (Table 5.1):

- General appearance
- Ear, nose, and throat
- Eyes
- Skin
- Respiratory
- GI
- Neurological (focused assessment of sensitivity and power)

12.3.6 Neurological examination

In addition to the Screening and FV, a full neurological examination should be performed for any subject who experiences severe headache (see Section 12.1.10). Neurological examination (full or brief) will be performed at visits as specified in the schedule of study assessments (Table 5.1) and findings will be recorded in the eCRF.

A full neurological assessment will include: 1) General appearance, including posture, motor activity and meningeal signs and, if indicated, following assessments to be done; 2) Cranial nerves examination; 3) Motor system examination, including muscle tone and power and sensory system examination – light touch; 4) Reflexes, including deep tendon reflexes; 5) Coordination, gait (if possible) and; 6) Fundoscopy.

A brief neurological assessment will include a selected assessment of the following: cognition, general reflexes, muscle strength, and coordination/cerebellar function.

12.3.7 12-lead ECG

A standard 12-lead ECG will be performed at visits as specified in the schedule of study assessments (Table 5.1).

Care should be taken to assure proper lead placement and quality ECG recordings. Subjects should rest in a supine position in a controlled, calm environment for at least 15 minutes prior to the recording and should be motionless during the recording. The ECG will be performed in triplicate prior to blood collection for assessment of laboratory parameters.

The ECGs will be read by a central reader. The PR, RR, QRS, QT, and corrected QT (QTc) intervals and heart rate will be assessed.

For the QTc, the following correction formula will be applied:

Fridericia's correction: $QTc = QT/RR^{0.33}$

The investigator may consult with the cardiologist at the central ECG laboratory to confirm the presence of a clinically significant ECG abnormality. It remains the responsibility of the investigator to decide whether an ECG finding is of clinical significance on the basis of the

complete clinical picture and whether this finding influences the subject's participation in the study.

13 STUDY MANAGEMENT AND ADMINISTRATION

13.1 Adherence to protocol

The investigator should not deviate from the protocol. However, the investigator should take any measure necessary in deviation from or not defined by the protocol in order to protect clinical study subjects from any immediate hazard to their health and safety. In this case, this action should be taken immediately, without prior notification of the regulatory authority, IRB/IEC, or sponsor.

After implementation of such measure, the investigator must notify the CPM of the sponsor within 24 hours and follow any local regulatory requirements.

13.2 Monitoring

UCB (or designee) will monitor the study to meet the sponsor's monitoring SOPs, ICH-GCP guideline, and applicable regulatory requirements, and to ensure that study initiation, conduct, and closure are adequate. Monitoring of the study may be delegated by UCB to a CRO or a contract monitor.

The investigator and his/her staff are expected to cooperate with UCB (or designee) and to be available during the monitoring visits to answer questions sufficiently and to provide any missing information. The investigator(s)/institution(s) will permit direct access to source data/documents for study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s).

The investigator will allow UCB (or designee) to periodically review all eCRFs and corresponding source documents (eg, clinic/hospital and laboratory records for each study participant). Monitoring visits will provide UCB (or designee) with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of eCRFs, ensure that all protocol requirements, applicable authorities' regulations, and investigator's obligations are being fulfilled, and resolve any inconsistencies in the study records.

13.2.1 Definition of source data

All source documents must be accurate, clear, unambiguous, permanent, and capable of being audited. They should be made using some permanent form of recording (ink, typing, printing, optical disc). They should not be obscured by correction fluid or have temporary attachments (such as removable self-stick notes). Photocopies and /or printouts of eCRFs are not considered acceptable source documents.

Source documents are original records in which raw data are first recorded. These may include clinic/hospital/general practitioner records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records, ECG or other printouts, completed scales, or quality of life questionnaires, for example. Source documents should be kept in a secure, limited access area.

The following data will be recorded directly in the eCRF and will not appear in a separate source document as defined above.

Source documents that are computer generated and stored electronically must be printed for review by the monitor (eg, ECG reports). Once printed, these copies should be signed and dated by the investigator and become a permanent part of the subject's source documents. The investigator will facilitate the process for enabling the monitor to compare the content of the printout and the data stored in the computer to ensure all data are consistent.

Electronic data records, such as Holter monitor records or electroencephalogram records, must be saved and stored as instructed by UCB (or designee).

13.2.2 Source data verification

Source data verification ensures accuracy and credibility of the data obtained. During monitoring visits, reported data are reviewed with regard to being accurate, complete, and verifiable from source documents (eg, subject files, recordings from automated instruments, tracings [ECG], x-ray films, laboratory notes). All data reported on the eCRF should be supported by source documents, unless otherwise specified in Section 13.2.1.

13.3 Data handling

13.3.1 Case Report Form completion

The investigator is responsible for prompt reporting of accurate, complete, and legible data in the eCRFs and in all required reports.

Any change or correction to the eCRF after saving must be accompanied by a reason for the change.

Corrections made after the investigator's review and approval (by means of a password/electronic signature) will be reapproved by the investigator.

The investigator should maintain a list of personnel authorized to enter data into the eCRF.

Detailed instructions will be provided in the eCRF Completion Guidelines.

13.3.2 Database entry and reconciliation

Case Report forms/external electronic data will be entered/loaded into a validated electronic database using a clinical data management system (CDMS). Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. The data are entered into the eCRFs once by the designated site personnel and are subsequently verified.

An electronic audit trail system will be maintained within the CDMS to track all data changes in the database once the data have been saved initially into the system or electronically loaded. Regular backups of the electronic data will be performed.

13.3.3 Subject Screening and Enrollment log/Subject Identification Code list

The subject's screening and enrollment will be recorded in the Subject Screening and Enrollment Log.

The investigator will keep a Subject Identification Code list. This list remains with the investigator and is used for unambiguous identification of each subject.

The subject's consent and enrollment in the study must be recorded in the subject's medical record. These data should identify the study and document the dates of the subject's participation.

13.4 Termination of the study

UCB reserves the right to temporarily suspend or prematurely discontinue this study either at a single site, multiple sites, or at all sites at any time for reasons including, but not limited to, safety or ethical issues, inaccurate or incomplete data recording, noncompliance, or unsatisfactory enrollment with respect to quality or quantity.

If the study is prematurely terminated or suspended, UCB (or its representative) will inform the investigators/institutions and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension, in accordance with applicable regulatory requirement(s). The IRB/IEC should also be informed and provided with reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s). In addition, arrangements will be made for the return of all unused IMP and other material in accordance with UCB procedures for the study.

13.5 Archiving and data retention

The investigator will maintain adequate records for the study, including eCRFs, medical records, laboratory results, informed consent documents, drug dispensing and disposition records, safety reports, information regarding participants who discontinued, and other pertinent data.

All essential documents are to be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or by an agreement with UCB (CPMP/ICH/135/95, 2002 [Section 4.9.5]). The investigator will contact UCB for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The investigator will also notify UCB should he/she relocate or move the study-related files to a location other than that specified in the sponsor's trial master file.

13.6 Audit and inspection

The investigator will permit study-related audits mandated by UCB, after reasonable notice, and inspections by domestic or foreign regulatory authorities.

The main purposes of an audit or inspection are to confirm that the rights and well-being of the subjects enrolled have been protected, that enrolled subjects (ie, signing consent and undergoing study procedures) are appropriate for the study, and that all data relevant for the evaluation of the IMP have been processed and reported in compliance with the planned arrangements, the protocol, investigational site, and IRB/IEC SOPs, ICH-GCP, and applicable regulatory requirements.

The investigator will provide direct access to all study documents, source records, and source data. If an inspection by a regulatory authority is announced, the investigator will immediately inform UCB (or designee).

13.7 Good Clinical Practice

Noncompliance with the protocol, ICH-GCP, or local regulatory requirements by the investigator, institution, institution staff, or designees of the sponsor will lead to prompt action by UCB to secure compliance. Continued noncompliance may result in the termination of the site's involvement in the study.

14 STATISTICS

A description of statistical methods follows and will be described in more detail in the SAP.

14.1 Definition of analysis sets

Enrolled Set:

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

Randomized Set:

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

Safety Set:

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

Safety 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.

Full Analysis Set:

The Full Analysis Set (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.

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.

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

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.

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 IgG or IgG subclasses.

14.2 General statistical considerations

All analyses will be performed using SAS® version 9.3 or later (SAS Institute, Cary, NC, USA). Continuous variables will be summarized by visit (where applicable) with the statistics including the number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized by visit (where applicable) with frequency counts and percentages.

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:

- 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 (due to the character of the study, no alpha adjustment for multiplicity will be done). For Dosing Period 2, only descriptive analyses will be performed.

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

Baseline will be the last non-missing data collected prior to the first dose of IMP in Dosing Period 1, and measurement-specific Baseline values will be defined in the SAP.

14.3 Planned efficacy analyses

For all efficacy analyses the Treatment Groups used for analysis during Dosing Period 1 and during Dosing Period 2/Observation Period will be as defined in Section 14.2. Efficacy endpoints will be analyzed using descriptive statistics for data obtained during Treatment Period 2 and Observation Period. Further details will be provided in SAP.

14.3.1 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.

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 there is no difference in the change from Baseline between Treatment Groups. 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 based on a mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) that includes terms for treatment group, week, the Baseline QMG score, and the interaction between treatment group and week. The model will define patient as a random effect and utilize an unstructured covariance pattern.

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) and 1-sided 95% confidence interval (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.

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 for the PPS. A further analysis will utilize the Last Observation Carried Forward (LOCF) approach; 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.

14.3.2 Other efficacy analyses

The secondary variables and change from Baseline in QMG score, MG-Composite score, MGADL score, MGII score, muscle weakness severity and fatigability scale score and fatigue scale score, at each assessed post-Randomization Visit (during Dosing Period 1 including Visit 9) will also be analyzed utilizing the MMRM approach similarly to the change from Baseline in QMG for the FAS as described in Section 14.3.1.

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

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

Psychometric analyses of the newly developed measures MG muscle weakness severity and fatigability and fatigue scales will be performed blinded from treatment arms. The association between PROs and clinical variables will also be explored, as well as the association between the various PROs. A psychometric analysis of the MG muscle weakness severity and fatigability scale and fatigue scale using Rasch analysis will be performed, but reported separately from the CSR.

Changes in MCD of the IPI, and normal fiber pairs in jitter (SFEMG) will be summarized using descriptive statistics, by treatment group and time point, including changes from Baseline. A reduction in MCD of ≥9µs in jitter (SFEMG) studies will also be summarized using descriptive statistics, by treatment group and time point, including changes from Baseline.

14.4 Planned other and exploratory analyses

14.4.1 Safety analyses

For all safety analyses the Treatment Groups used for analysis during Dosing Period 1 and during Dosing Period 2/Observation Period will be as defined in Section 14.2 and as described in the SAP.

The absolute and relative frequencies for subjects with a given TEAE with respect to the preferred term according to the latest available version of the Medical Dictionary for Regulatory Activities, as well as the absolute frequencies of the individual TEAEs that have occurred, will be determined within each system organ class. Additional tables will summarize TEAEs by maximum intensity and causal relationship with IMP, as judged by the investigator. Adverse events will be categorized by severity according to the CTCAE Version 4.03 grading. In case the CTCAE grading is not available, the intensity (mild/moderate/severe) will be utilized. For the purpose of the tabulations CTCAE grades will be aligned with the intensity classifications (mild/moderate/severe) to enable pooling of the AEs in the summaries. The TEAEs leading to discontinuation of IMP and treatment-emergent SAEs will also be summarized. The action taken, time of onset relative to dosing, and duration of each AE will be listed only.

Adverse events will be assigned to a Dosing Period based on the start date of the event relative to the first dose of IMP received in the respective period.

For the continuous laboratory variables, the values and changes from Baseline will be summarized at each time point. For categorized values according to the reference range, shift tables from Baseline to each post-Baseline time point will be presented for selected variables to be defined in the SAP. Values outside the reference range will be flagged in the data listings.

Exploratory safety biomarkers will be summarized by treatment group and visit using descriptive statistics.

Normal vs abnormal findings with regard to the various ECG parameters and the overall ECG will be analyzed as required. The focus of the 12-lead ECG analysis will be the identification of outliers and of any trends for changes following administration of UCB7665 with respect to QT/QTc. Descriptive statistics will be presented for ECG value and changes from Baseline over time based on the mean of the triplicate assessments at each time point.

Descriptive statistics will be reported for all vital sign measurements (including pulse rate, systolic/diastolic BP, temperature, and respiratory rate). Measured values and changes from Baseline will be summarized by treatment group.

Physical and neurological examination findings and the results of any pregnancy testing will be presented in listings only.

14.4.2 Pharmacokinetic analysis

The PK variable is the plasma concentration of UCB7665. Pharmacokinetic parameters such as C_{max} 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 and summarized at each scheduled time point. Descriptive statistics of concentrations will be calculated only if at least two thirds of the individual data points are quantifiable (≥lower limit of quantification [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.

14.4.3 Pharmacodynamic analysis

For all PD variables, descriptive statistics for the change from Baseline, and percentage change from Baseline will be tabulated by treatment group and time point.

The PD variables will include MG-specific autoantibodies [redacted], serum total IgG, and IgG subclasses. In addition, for serum total IgG, the minimum value and maximum decrease from Baseline (including percentage decrease) will be evaluated and summarized.

Population PK analyses and PK/PD analyses may be conducted for the PD variables of interest. All such PK and PK/PD analyses will be described in a separate Data Analysis Plan; however, results will not be reported in the clinical study report.

14.4.4 Immunological variables

All immunological variables including concentrations of Igs (IgA, IgE, and IgM), serum complement levels (C3 and C4) and plasma complement levels (C3a and C5a), and serum BAFF will be listed and summarized, using descriptive statistics, by Treatment Group and visit including changes from Baseline. Concentrations of cytokines will be listed and summarized if there are sufficient data. Figures of mean values and changes from Baseline of immunological variables may be presented, and will be described in the SAP.

The [redacted] status (negative or confirmed positive) and either changes in relative mass units from Baseline for all scheduled assessments or titres for those confirmed positive will be listed and summarized by treatment group.

The [redacted] antibodies will be listed and summarized by treatment group.

14.4.5 Subject exit interview

The anonymous audio-recordings will be analyzed by a third party and reported outside the clinical study report.

14.5 Handling of protocol deviations

Important protocol deviations are identified as part of the data cleaning process in the Data Cleaning Plan (DCP). Ongoing data cleaning meetings will be held throughout the duration of the study. Objectives of these meetings include to review and update (if necessary) the important protocol deviations in the DCP and discuss exclusion of subjects from analysis populations. Furthermore, overall trends in protocol deviations will be discussed at the Data Evaluation Meeting. Through this ongoing data cleaning and evaluation process, all decisions regarding important protocol deviations and exclusions from analysis populations are made on an ongoing basis.

14.6 Handling of dropouts or missing data

All imputation of missing or partial dates for safety assessments, as well as handling missing efficacy data (where applicable), will be detailed in the SAP.

14.7 Planned interim analysis 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 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.

If needed, subsequent DMC meetings will take place. The timing of further interim analyses and reviews of data by DMC will be decided by the DMC. Ad hoc DMC meetings can be held for reasons determined appropriate by the sponsor.

The deliberations and decisions of the DMC will be formally minuted/documented.

A detailed description of the DMC composition, processes, and responsibilities will be provided in a separate DMC charter.

14.8 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] CI) of the 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 approximately [redacted] of the randomized subjects cannot be utilized for the FAS and, hence [redacted] subjects will be randomized.

15 ETHICS AND REGULATORY REQUIREMENTS

15.1 Informed consent

Subject's informed consent must be obtained and documented in accordance with local regulations, ICH-GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

Prior to obtaining informed consent, information should be given in a language and at a level of complexity understandable to the subject in both oral and written form by the investigator (or designee). Each subject will have the opportunity to discuss the study and its alternatives with the investigator.

Prior to participation in the study, the Informed Consent form should be signed and personally dated by the subject, or his/her legal representative, and by the person who conducted the informed consent discussion (investigator or designee). The subject or his/her legal representative must receive a copy of the signed and dated Informed Consent form. As part of the consent process, each subject must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection.

If the Informed Consent form is amended during the study, the investigator (or the sponsor, if applicable) must follow all applicable regulatory requirements pertaining to the approval of the amended Informed Consent form by the IRB/IEC and use of the amended form.

All studies conducted at centers in the USA must include the use of a Health Insurance Portability and Accountability Act Authorization form.

The subject may withdraw his/her consent to participate in the study at any time. A subject is considered as enrolled in the study when he/she has signed the Informed Consent form. An eCRF must not be started, nor may any study specific procedure be performed for a given subject, without having obtained his/her written consent to participate in the study.

Subjects have the right to withdraw their consent for the exploratory genomic substudy at any point without any impact on their care or participation in the main study. In this case, any data already generated on the samples will be retained and used, but no further analysis will occur.

15.2 Subject identification cards

Upon signing the Informed Consent and Assent form (as applicable), the subject or legal representative will be provided with a subject identification card in the language of the subject. The investigator will fill in the subject identifying information and medical emergency contact information. The investigator will instruct the subject to keep the card with him/her at all times.

15.3 Institutional Review Boards and Independent Ethics Committees

The study will be conducted under the auspices of an IRB/IEC, as defined in local regulations, ICH-GCP, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

The investigator/UCB will ensure that an appropriately constituted IRB/IEC that complies with the requirements of the current ICH-GCP version or applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to

initiation of the study, the investigator/UCB will forward copies of the protocol, Informed Consent form, Investigator's Brochure, investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other subject-related documents to be used for the study to the IRB/IEC for its review and approval.

Before initiating a study, the investigator will have written and dated full approval from the responsible IRB/IEC for the protocol.

The investigator will also promptly report to the IRB/IEC all changes in the study, all unanticipated problems involving risks to human subjects or others, and any protocol deviations, to eliminate immediate hazards to subjects.

The investigator will not make any changes in the study or study conduct without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to the subjects. For minor changes to a previously approved protocol during the period covered by the original approval, it may be possible for the investigator to obtain an expedited review by the IRB/IEC as allowed.

As part of the IRB/IEC requirements for continuing review of approved studies, the investigator will be responsible for submitting periodic progress reports to the IRB/IEC (based on IRB/IEC requirements), at intervals appropriate to the degree of subject risk involved, but no less than once per year. The investigator should provide a final report to the IRB/IEC following study completion.

UCB (or its representative) will communicate safety information to the appropriate regulatory authorities and all active investigators in accordance with applicable regulatory requirements. The appropriate IRB/IEC will also be informed by the investigator or the sponsor, as specified by the applicable regulatory requirements in each concerned country. Where applicable, investigators are to provide the sponsor (or its representative) with evidence of such IRB/IEC notification.

15.4 Subject privacy

UCB staff (or designee) will affirm and uphold the subject's confidentiality. Throughout this study, all data forwarded to UCB (or designee) will be identified only by the subject number assigned at Screening.

The investigator agrees that representatives of UCB, its designee, representatives of the relevant IRB/IEC, or representatives of regulatory authorities will be allowed to review that portion of the subject's primary medical records that directly concerns this study (including, but not limited to, laboratory test result reports, ECG reports, admission/discharge summaries for clinic/hospital admissions occurring during a subject's study participation, and autopsy reports for deaths occurring during the study).

15.5 Protocol amendments

Protocol changes may affect the legal and ethical status of the study and may also affect the statistical evaluations of sample size and the likelihood of the study fulfilling its primary objective.

Significant changes to the protocol will only be made as an amendment to the protocol and must be approved by UCB, the IRB/IEC, and the regulatory authorities (if required), prior to being implemented.

16 FINANCE, INSURANCE, AND PUBLICATION

Insurance coverage will be handled according to local requirements.

Finance, insurance, and publication rights are addressed in the investigator and/or CRO agreements, as applicable.

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18.2 MG-Composite score

Figure 18.2: MG-Composite score

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, e.g. 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
Neck flexion or extension (weakest) (physician examination)	Normal = 0	Mild weakness = 1	Moderate weakness (i.e., ~50% weak, ±15%) = 3*	Severe weakness = 4
Shoulder abduction (physician examination)	Normal = 0	Mild weakness = 2	Moderate weakness (i.e., ~50% weak, ±15%) = 4*	Severe weakness = 5
Hip flexion (physician examination)	Normal = 0	Mild weakness = 2	Moderate weakness (i.e., ~50% weak, ±15%) = 4*	Severe weakness = 5

*Moderate weakness for neck and limb 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.

(Burns, 2010)

18.8 Suggested management guidelines for infusion reactions

Table 18.1: Suggested management guidelines for infusion reactions

Type of reaction	Sponsor recommendations for management
Acute – Mild eg, flushing, dizziness, headache, sweating, palpitations, nausea	Slow infusion rate to [redacted] Infuse [redacted] 500-1000mL/h iv. Administer antihistamine iv/im. Administer paracetamol 1g orally. Monitor vital signs every 10 minutes until back to Baseline. [redacted] as tolerated until intended dose has been given.
Acute – Moderate eg, flushing, chest tightness, dyspnea, hypo/hypertension (change >20mmHg in systolic blood pressure), raised temperature, palpitations, urticaria	Stop infusion. Infuse [redacted] 500-1000mL/h iv. Administer antihistamine iv/im. Administer paracetamol 1g orally. Monitor vital signs every 5 minutes until back to Baseline. Wait 20 minutes. If there is no indication of anaphylaxis (eg, generalized urticaria and/or bronchospasm) and if clinically appropriate, consider restarting the infusion at a lower rate following this suggested regimen: Restart infusion at [redacted]. Increase infusion rate to [redacted] as tolerated until intended dose has been given.
Acute – Severe eg, hypo/hypertension (change >40mmHg in systolic blood pressure), raised temperature with rigors, chest tightness, dyspnea with wheezing, stridor	Stop infusion definitively. Alert crash team. Maintain airway, ensure oxygen is available. If wheezing, give epinephrine 0.5mg im (0.5mL 1:1000 epinephrine). Administer antihistamine iv/im. Administer corticosteroids iv. Monitor vital signs every 2 minutes until back to Baseline.

im=intramuscular; iv=intravenous

18.9 Diagnosis of anaphylactic reactions

Anaphylaxis is highly likely when any of the following 3 criteria is fulfilled (Sampson et al, 2006):

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

AND AT LEAST ONE OF THE FOLLOWING

a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)

b. Reduced blood pressure [BP] or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips tongue-uvula)

b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)

d. Persistent GI symptoms (eg, crampy abdominal pain, vomiting)

3. Reduced blood pressure after exposure to known allergen for that subject (minutes to several hours): Systolic BP of less than 90mmHg or greater than 30% decrease from the subject's Baseline systolic BP value.

18.10 Headache Questionnaire

Table 18.2: Headache Questionnaire

Symptoms & Frequency of Severe Headaches				
1. Date of collection:			Time of collection:	
DD	MMM	YY	HH	MM
2. Is the subject suffering from a severe headache?				
Yes				
No				
a. Which of the following best describes how the subject is affected?				
Able to function normally				
Activity impaired to some degree				
Activity severely impaired				
Bed rest required				
b. Rate your pain on a scale of 0 - 10:				

Table 18.2: Headache Questionnaire

Symptoms & Frequency of Severe Headaches
3. During the course of this headache, has the subject experienced any of the following?
a. Nausea:
0 = Never
1 = Rarely
2 = Less than half the time
3 = Half the time or more
b. Vomiting:
0 = Never
1 = Rarely
2 = Less than half the time
3 = Half the time or more
c. Dizziness:
0 = Never
1 = Rarely
2 = Less than half the time
3 = Half the time or more
i. Vertigo:
0 = Never
1 = Rarely
2 = Less than half the time
3 = Half the time or more
ii. Nonvertigo:
0 = Never
1 = Rarely
2 = Less than half the time
3 = Half the time or more
d. Increased neck pain or stiffness:
0 = Never
1 = Rarely
2 = Less than half the time
3 = Half the time or more

Table 18.2: Headache Questionnaire

Symptoms & Frequency of Severe Headaches
e. Increased sensitivity to light:
0 = Never
1 = Rarely
2 = Less than half the time
3 = Half the time or more
f. Increased sensitivity to noise:
0 = Never
1 = Rarely
2 = Less than half the time
3 = Half the time or more
g. Increased sensitivity to smell:
0 = Never
1 = Rarely
2 = Less than half the time
3 = Half the time or more
h. Pain made worse by routine physical activity:
0 = Never
1 = Rarely
2 = Less than half the time
3 = Half the time or more
i. Pain on one side of head only:
0 = Never
1 = Rarely
2 = Less than half the time
3 = Half the time or more
j. Pulsating/throbbing headaches:
0 = Never
1 = Rarely
2 = Less than half the time
3 = Half the time or more
k. Weakness on one side:

Table 18.2: Headache Questionnaire

Symptoms & Frequency of Severe Headaches	
0 = Never	
1 = Rarely	
2 = Less than half the time	
3 = Half the time or more	
l. Seeing shimmering lights, lines, dark spots, other shapes or colors before the eyes, before or during the headache and lasts more than a few minutes but less than an hour:	
0 = Never	
1 = Rarely	
2 = Less than half the time	
3 = Half the time or more	
m. One-sided numbness of lips, tongue, fingers, or legs that migrates or moves and starts before the headache becomes severe and lasts less than an hour:	
0 = Never	
1 = Rarely	
2 = Less than half the time	
3 = Half the time or more	
General	The questionnaire should be administered via an interview with the subject. The recall period for the first time the questionnaire is administered is since the severe headache began. The recall period for subsequent questionnaires should be since the prior administration of the questionnaire, not since the start of the severe headache. Mark an X in only 1 box for each question. Do not write in any other choices. Transcribe the subject's responses to the eCRF screen.

DD MMM YYYY *(v.2009-09-09)*

18.12 Protocol Amendment 1

Rationale for the amendment

The protocol has been amended to incorporate the feedback from the U.S. Food and Drug administration (FDA) received on 09 December 2016 and the new company standard in TB management.

In addition, minor administrative changes have been made.

The following shows the changes made in Amendment 1 compared to the original protocol, dated 21 Oct 2016.

Modifications and changes

Global changes

The following changes were made throughout the protocol:

- Secondary efficacy variables and other efficacy variables were updated. Statistical analyses sections were updated accordingly.
- Sections covering collection of exploratory biomarker samples and exploratory safety biomarker sample were simplified.
- Exploratory biomarker sampling was separated from exploratory safety biomarker sampling.
- Timing of the IRT to be called was updated (at Screening and on dosing visits only, not every single visit).
- Wording for home visit at Visit 20 to be conducted at home was revised throughout the protocol. Now the home visits are allowed at Visits 17 and 19.
- The C-SSRS was added to address the request of the FDA that prospective assessments for suicidality should be included in clinical trials involving all drugs for neurological indications.
- The detailed tuberculosis assessment was added to ensure the subject safety.
- The term on-demand treatment was revised into chronic-intermittent treatment.
- Editorials and revisions on abbreviations were implemented.

Specific changes

Change #1

1 SUMMARY, 3rd paragraph

The study will consist of 3 Periods: Screening, Treatment, and Observation. After Screening, subjects will enter the Treatment Period, which will consist of 2 successive Dosing Periods.

Subjects will receive 3 doses of investigational medicinal product (IMP) at weekly intervals during both Dosing Period 1 and Dosing Period 2. Dosing Period 1 will be 4 weeks, with 2 parallel arms (UCB7665 7mg/kg or placebo). Dosing Period 2 will be 2 weeks, with 2 parallel treatment arms (UCB7665 7mg/kg or UCB7665 4mg/kg).

Has been changed to:

The study will consist of 3 Periods: Screening, Treatment, and Observation. After Screening, subjects will enter the Treatment Period, which will consist of Dosing Period 1 followed by Dosing Period 2. Subjects will receive 3 doses of investigational medicinal product (IMP) at weekly intervals during each dosing period as follows:

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

Change #2

1 SUMMARY, 4rd and 5th paragraph

A Data Monitoring Committee (DMC) will oversee at least 1 interim analysis for safety and for futility during the course of the study (see Section 14.7). Details of the interim analysis will be provided in the DMC charter and interim Statistical Analysis Plan (SAP).

The primary efficacy variable will be the change from Baseline in Quantitative MG (QMG) score to Visit 9 (Day 29). Other efficacy variables will be the following: change from Baseline in MG-Composite score to Visit 9 (Day 29); value and change from Baseline in QMG at each scheduled assessment during Treatment and Observation Periods; proportion of 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; proportion of MG-Composite responder (≥3.0 point improvement from Baseline) at each scheduled assessment during Treatment and Observation Periods; value and change from Baseline in MG muscle weakness severity and fatigue scales at each scheduled assessment during Treatment and Observation Periods; value and change from Baseline in MG-Activities of Daily Living (MGADL) at each scheduled assessment during Treatment and Observation Periods; and change in mean jitter in single fiber electromyography (SFEMG) from Baseline to Visit 9 for the subjects consenting to this measurement at participating sites.

Has been changed to:

1 SUMMARY, 5th and 6th paragraph

A Data Monitoring Committee (DMC) will be implemented as described in Section 14.7.

The primary efficacy variable will be the change from Baseline in Quantitative MG (QMG) score to Visit 9 (Day 29). The secondary efficacy variables will be the change from Baseline in MG-Composite score to Visit 9 (Day 29) and the change from Baseline in MG-Activities of Daily Living (MGADL) score to Visit 9 (Day 29). Other efficacy variables will be the following: 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 severity and fatigue scales at each scheduled assessment during Treatment and Observation Periods; and change in mean jitter in single fiber electromyography (SFEMG) from Baseline to Visit 9 for the subjects consenting to this measurement at participating sites.

Change #3

1 SUMMARY, 6th to 8th paragraph

Plasma concentration of UCB7665 over time will be assessed as the pharmacokinetic (PK) variable. The main pharmacodynamic (PD) variables will be the maximum decrease from Baseline in serum total immunoglobulin G (IgG) concentration; value and change from Baseline in serum IgG subclass concentrations at each scheduled assessment during Treatment and Observation Periods; and value and change from Baseline in total serum IgG concentrations at each scheduled assessment during Treatment and Observation Periods.

Safety and tolerability variables will include occurrence of treatment-emergent adverse events (TEAEs); vital sign values and changes from Baseline (systolic and diastolic blood pressure [BP], temperature, pulse rate, respiratory rate, and body weight); 12-lead electrocardiogram (ECG) values parameters and change from Baseline; laboratory values (hematology, clinical chemistry, and urinalysis) and changes from Baseline; change from Baseline in exploratory safety biomarkers [redacted]) only in subjects experiencing severe headache and/or moderate to severe gastrointestinal (GI) disturbance; and TEAEs leading to withdrawal of IMP.

During this study, subjects will also have the option of providing additional informed consent for exploratory deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) (ie, messenger RNA [mRNA] and micro RNA [miRNA]) analyses (see Section 5.1.1). Participation in this additional portion of the study is optional and does not preclude subject's eligibility for participation in the main study. The additional genomic samples must not be collected if the subject has not consented to participate in this exploratory genomic substudy.

Has been changed to:

1 SUMMARY, 7th to 10th paragraph

Other and exploratory variables include: safety and tolerability variables, pharmacokinetic (PK), pharmacodynamic (PD), and immunologic variables.

Safety and tolerability variables include the following: occurrence of treatment-emergent adverse events (TEAEs); vital sign values and changes from Baseline (systolic and diastolic blood pressure [BP], temperature, pulse rate, respiratory rate, and body weight); 12-lead

electrocardiogram (ECG) values and change from Baseline; laboratory values (hematology, clinical chemistry, and urinalysis) and changes from Baseline; change from Baseline in exploratory safety biomarkers (may include but not limited to [redacted] in subjects experiencing severe headache and/or moderate to severe gastrointestinal (GI) disturbance; and TEAEs leading to withdrawal of IMP.

Plasma concentration of UCB7665 over time will be assessed as the PK variable. The main PD variables will be the maximum decrease from Baseline in serum total immunoglobulin G (IgG) concentration; value and change from Baseline in total serum IgG concentrations at each scheduled assessment during Treatment and Observation Periods; value and change from Baseline in serum IgG subclass concentrations at each scheduled assessment during Treatment and Observation Periods; and change in MG-specific autoantibody [redacted] levels in serum from Baseline at each scheduled assessment during Treatment and Observation Periods. Additionally, change from Baseline in other immunological variables and other exploratory biomarkers during the Treatment and Observational Periods will be assessed.

During this study, subjects will also have the option of providing additional informed consent for exploratory deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) (ie, messenger RNA [mRNA] and micro RNA [miRNA]) analyses (see Section 5.1.1) to understand the cause, progression, and appropriate treatment of MG. Participation in this additional portion of the study is optional and does not preclude subject's eligibility for participation in the main study. The additional genomic samples must not be collected if the subject has not consented to participate in this exploratory genomic substudy.

Change #4

2 INTRODUCTION, 11th paragraph

MG0002 will be the first study of the use of UCB7665 in MG.

Has been changed to:

2 INTRODUCTION, 11th paragraph

MG0002 will be the first study of the use of UCB7665 in MG. The aim of the study is to evaluate the efficacy, safety, and immunological effect of UCB7665, and to gather data for future study planning to fully evaluate the use of UCB7665 in MG.

Change #5

3.2 Secondary objectives

The following was added:

- 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

Change #6

3.3 Exploratory objectives

- To evaluate the effect of UCB7665 on B-cell activating factor (BAFF) and on cytokines (for subjects experiencing infusion reactions)
- To evaluate the effects of UCB7665 on blood biomarkers for safety ([redacted]) only in subjects with severe headache and/or moderate to severe GI disturbance)

Has been changed to:

3.3 Exploratory objectives

- To evaluate the effect of UCB7665 on B-cell activating factor (BAFF) and on cytokines (in all subjects)
- 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 GI disturbance

In addition, the following were added:

- To evaluate the effect of UCB7665 on cytokines in subjects experiencing infusion reactions
- To evaluate peripheral blood biomarkers in relation to disease etiology, progression and treatment outcome

Change #7

4.1.2 Secondary efficacy variable

The secondary efficacy variable is:

- Change from Baseline in MG-Composite score to Visit 9 (Day 29)

Has been changed to:

4.1.2 Secondary efficacy variable

The secondary efficacy variables are:

- Change from Baseline in MG-Composite score to Visit 9 (Day 29)
- Change from Baseline in MGADL score to Visit 9 (Day 29)

Change #8

4.1.3 Other efficacy variables

- Proportion of QMG responder (≥3.0 point improvement from Baseline) at each scheduled assessment during Treatment and Observation Periods
- Proportion of MG-Composite responder (≥3.0 point improvement from Baseline) at each scheduled assessment during Treatment and Observation Periods

Has been changed to:

4.1.3 Other efficacy variables

- QMG responder (≥3.0 point improvement from Baseline) 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

In addition, the following was added:

- MGADL responder (≥3.0 point improvement from Baseline) at each scheduled assessment during Treatment and Observation Periods

Change #9

Sections 4.2 to 4.4 have been restructured:

4.2 Pharmacokinetic and pharmacodynamic variables

4.2.1 Pharmacokinetic variable

4.2.2 Pharmacodynamic variables

4.3 Immunological variables

4.4 Safety variables

Has been changed to:

4.2 Other and exploratory variables

4.2.1 Safety variables

4.2.2 Pharmacokinetic variable

4.2.3 Pharmacodynamic variables

4.2.4 Immunological variables

Change #10

4.2 Pharmacodynamic variables (previous heading number)

The heading number was changed to the below:

4.2.3 Pharmacodynamic variables

The below was deleted:

- Change from Baseline total IgG concentration pre- and post-ADA depletion at each scheduled assessment during Treatment and Observation Periods

Change #11

4.3 Immunological variables (previous heading number)

Additional exploratory biomarkers may be investigated if needed using the samples already available.

Has been changed to:

4.2.4 Immunological variables (new heading number)

- Change from Baseline in exploratory biomarkers relating to mechanism of action, disease activity, treatment response, and clinical outcome

Change #12

4.4 Safety variables (previous heading number)

- Change from Baseline in exploratory safety biomarkers ([redacted] at each scheduled assessment during Treatment and Observation Periods (only in subjects with severe headache and/or moderate to severe GI disturbance)

Has been changed to:

4.2.1 Safety variables (new heading number)

- 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

Change #13

5.1 Study description

Treatment Period: The Treatment Period will consist of 2 successive Dosing Periods. Subjects will receive 3 doses of IMP at weekly intervals during both Dosing Period 1 and Dosing Period 2. 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).

Has been changed to:

5.1 Study description

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).

Change #14

5.1 Study description

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 (see Section 5.2, Schedule of 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.

A DMC will be established to monitor mainly safety data during the study. In addition efficacy data will be assessed once during the study for futility. The DMC will be unblinded and details of the DMC composition, processes, and responsibilities will be documented in the DMC charter.

Has been changed to:

5.1 Study description

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, 18, and 20 for efficacy and for safety assessments (see Section 5.2, Schedule of 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 and 19. 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.

Change #15

Changes on the tables and footnotes

Table 5.1: Schedule of assessments

Assessments	Screening		Treatment Period													Observation Period[a]						UV
			Dosing Period 1							Dosing Period 2												
	Visit	1	2 BL	3[b]	4	5b	6	7b	8	9	10b	11	12b	13	14b	15	16	17	18	19	20 FV/PEOT[c]	
	Day	-28 to -1	1	2	8 (± 2 days)	9	15 (± 2 days)	16	22 (± 2 days)	29 (± 2 days)	30	36 (± 2 days)	37	43 (± 2 days)	44	50	57	64	78	92	99 (± 2 days)	
																(± 2 days)						
Written informed consent[d]		X																				
Written informed consent for genomic substudy		X																				
Demographic data		X																				
Verification of inclusion /exclusion criteria		X	X																			
Call or enter IRT to register the visit		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Call to IRT / Randomization			X							X												
Withdrawal criteria			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
General medical/procedures history		X																				
Prior and concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medical procedures			X		X		X		X	X		X		X		X	X	X	X	X	X	X
Vital signs[e]		X	X		X		X		X	X		X		X		X	X	X	X	X	X	X

Table 5.1: Schedule of assessments

Assessments	Screening		Treatment Period													Observation Period[a]						UV
			Dosing Period 1							Dosing Period 2												
	Visit	1	2 BL	3[b]	4	5b	6	7b	8	9	10b	11	12b	13	14b	15	16	17	18	19	20 FV/PEOT[c]	
	Day	-28 to -1	1	2	8 (± 2 days)	9	15 (± 2 days)	16	22 (± 2 days)	29 (± 2 days)	30	36 (± 2 days)	37	43 (± 2 days)	44	50	57	64	78	92	99 (± 2 days)	
																(± 2 days)						
Body weight, height[f]		X								X											X	
Recording of AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Full physical examination		X																			X	
Brief physical examination			X							X												
Full neurological examination[g]		X																			X	
Brief neurological examination			X							X												
12-lead ECG[h]		X	X		X		X		X	X		X		X		X			X		X	
Laboratory tests (hematology, chemistry, urinalysis)		X	X		X		X		X	X		X		X		X	X		X		X	
Serology testing for HIV, Hepatitis B, Hepatitis C, and active or latent TB		X																				
Blood sampling for PK of UCB7665[i]			X		X		X		X	X		X		X		X						
Blood sampling for DNA analysis (optional)			X[j]						X[j]					X[j]								
Blood sampling for RNA analysis (optional)			X[j]		X[j]				X[j]					X[j]							X[j]	
Serum pregnancy test		X																				

Table 5.1: Schedule of assessments

Assessments	Screening		Treatment Period													Observation Period[a]						UV
			Dosing Period 1							Dosing Period 2												
	Visit	1	2 BL	3[b]	4	5b	6	7b	8	9	10b	11	12b	13	14b	15	16	17	18	19	20 FV/PEOT[c]	
	Day	-28 to -1	1	2	8 (± 2 days)	9	15 (± 2 days)	16	22 (± 2 days)	29 (± 2 days)	30	36 (± 2 days)	37	43 (± 2 days)	44	50	57	64	78	92	99 (± 2 days)	
																(± 2 days)						
Urine pregnancy test[k]			X		X		X		X	X		X		X		X	X	X	X	X	X	
Administration of IMP			X		X		X			X		X		X								
[redacted]			X		X		X		X	X		X		X		X	X	X	X	X	X	
Serum complement (C3,C4) and plasma complement levels ($C3_A$ and C5a)			X		X		X		X	X		X		X		X	X				X	
Immunoglobulins (total IgG and IgG subclasses)	X	X		X		X		X	X		X		X		X	X	X	X	X	X		
IgG depletion assay		X		X		X		X	X		X		X		X	X	X	X	X	X		
IgA, IgM, IgE		X						X	X		X		X		X	X				X		
MG-specific autoantibodies		X		X					X		X				X					X		
Exploratory biomarkers : including [redacted]		X		X		X		X	X		X		X		X	X	X	X	X	X		
BAFF analysis		X		X		X		X	X		X		X				X		X			
Cytokines[m]		X		X		X		X	X		X		X		X	X	X	X	X	X	X	
Vaccination-specific antibody titer [redacted]	X																				X	
MG-composite scale	X	X		X		X		X	X		X		X		X	X	X	X	X	X		

Table 5.1: Schedule of assessments

Assessments	Screening		Treatment Period													Observation Period[a]						UV
			Dosing Period 1							Dosing Period 2												
	Visit	1	2 BL	3[b]	4	5b	6	7b	8	9	10b	11	12b	13	14b	15	16	17	18	19	20 FV/PEOT[c]	
	Day	-28 to -1	1	2	8 (± 2 days)	9	15 (± 2 days)	16	22 (± 2 days)	29 (± 2 days)	30	36 (± 2 days)	37	43 (± 2 days)	44	50	57	64	78	92	99 (± 2 days)	
																(± 2 days)						
QMG scale[n]		X	X		X		X		X	X		X		X		X	X		X		X	
Muscle weakness severity and fatigability scale			X		X		X		X	X		X		X		X	X	X	X	X	X	
Fatigue scale			X		X		X		X	X		X		X		X	X	X	X	X	X	
MGADL scale			X							X						X		X			X	
MGFA classification		X	X							X											X	
SFEMG measurement[o]			X							X												
Headache questionnaire[p]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Stool sample assessment[q]			X		X		X		X	X		X		X		X	X	X	X	X	X	X
Subject exit interview																					X	

AE=adverse event; BAFF=B-cell activating factor; BL=Baseline; BP=blood pressure; CSF=cerebrospinal fluid; CT=computed tomography; DNA=deoxyribonucleic acid; ECG=electrocardiogram; FV=Final Visit; GI=gastrointestinal; HIV=human immunodeficiency virus; IgA=immunoglobulin A; IgE=immunoglobulin E; IgG=immunoglobulin G; IgM=immunoglobulin M; IMP=investigational medicinal product; IRT=interactive response technology; LP=lumbar puncture; MG=myasthenia gravis; MGADL=myasthenia gravis-Activities of Daily Living; MGFA=Myasthenia Gravis Foundation of America; MRI=magnetic resonance imaging; PEOT=premature end of treatment; [redacted] PK=pharmacokinetics; PR=pulse rate; RNA=ribonucleic acid; QMG=Quantitative Myasthenia Gravis; [redacted] SFEMG=single fiber electromyogram; TB=tuberculosis; UV=Unscheduled Visit

a Subjects will return to the clinic for Visits 15, 16, and 18; for Visits 17, 19, and 20, subjects with either return to the clinic/hospital, or, if possible and agreed by the investigator and subject, have home visits conducted by certified healthcare professionals.

b This visit is a telephone contact 24 hours post-IMP dose start.

c Subjects who withdraw early will be encouraged to complete the PEOT Visit plus the FV (approximately 8 weeks after the final study drug administration).

e Includes consent for SFEMG for the subjects consenting to this measurement at the participating sites. Additional informed consent is needed for participation in the exploratory genomic substudy.

f Systolic and diastolic BP, pulse rate, temperature, and respiratory rate. On dosing days, vital signs will be measured prior to IMP administration, 15 minutes after the start of the infusion, at the end of the infusion, 2 hours after the end of infusion and 4 hours after the end of the infusion. At nondosing visits, vital signs need only be taken once during the visit.

g Body weight at Screening will be used for calculation of dose; height will be assessed only at Screening.

h In addition to Screening and the FV, a full neurological examination should be performed for any subject who experiences severe headache.

j ECGs will be read by a central reader.
Pre- and postdose at Visits 2, 4, 6, 9, 11, and 13; postdose samples are to be taken 4 hours after the infusion has ended.

j Blood sample to be taken prior to dosing of IMP.

n Urine pregnancy test will be performed using a dipstick test; a positive urine pregnancy test must be confirmed using a serum pregnancy test.

l Serum safety biomarkers levels measured at Baseline for all subjects and during follow up only in subjects with severe headache or moderate to severe GI disturbances.

q At Baseline and subsequently only in subjects with infusion reaction.

n Subjects must be off pyridostigmine (or any [redacted] inhibitor medication) from midnight before testing when medically safe to do so to standardize testing, but if not medically appropriate, then the treatment can be continued but the testing should be performed as best as possible at the same timeframe post last [redacted] inhibitor dosing for each evaluation during the study.

t For subjects consenting to this measurement at the participating sites; subjects should not take pyridostigmine from midnight before testing when medically safe to do so to standardize testing, but if not medically appropriate, then the treatment can be continued but the testing should be performed as best as possible at the same timeframe post last [redacted] inhibitor dosing for each evaluation during the study.

u This assessment is applicable only to subjects experiencing severe headaches and will be performed 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). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator.

v Stool collection and analysis will be performed for subjects reporting moderate or severe diarrhea. The frequency of stool sampling will be as clinically indicated in the opinion of the investigator. Analysis of stool samples will be performed locally.

Has been changed to:

Table 5.1: Schedule of assessments

Assessments	Screening		Treatment Period													Observation Period[a]						UV
			Dosing Period 1							Dosing Period 2												
	Visit	1	2 BL	3[b]	4	5[b]	6	7[b]	8	9	10[b]	11	12[b]	13	14[b]	15	16	17	18	19	20 FV/PEOT[c]	
	Day	-28 to -1	1	2	8[d] (± 2 days)	9	15[d] (± 2 days)	16	22[d] (± 2 days)	29[d] (± 2 days)	30	36[d] (± 2 days)	37	43[d] (± 2 days)	44	50	57	64	78	92	99 (± 2 days)	
																(± 2 days)						
Written informed consent[e]		X																				
Written informed consent for genomic substudy		X																				
Demographic data		X																				
Verification of inclusion /exclusion criteria		X	X																			
Call or enter IRT to register the visit		X			X		X					X		X							X	
Call or enter IRT/ Randomization			X							X												
Withdrawal criteria			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
General medical/ procedures history		X																				
Prior and concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medical procedures			X		X		X		X	X		X		X		X	X	X	X	X	X	X
Vital signs[f]		X	X		X		X		X	X		X		X		X	X	X	X	X	X	X
Body weight, height[g]		X								X											X	

Table 5.1: Schedule of assessments

Assessments	Screening		Treatment Period													Observation Period[a]						UV
			Dosing Period 1							Dosing Period 2												
	Visit	1	2 BL	3[b]	4	5[b]	6	7[b]	8	9	10[b]	11	12[b]	13	14[b]	15	16	17	18	19	20 FV/PEOT[c]	
	Day	-28 to -1	1	2	8[d] (± 2 days)	9	15[d] (± 2 days)	16	22[d] (± 2 days)	29[d] (± 2 days)	30	36[d] (± 2 days)	37	43[d] (± 2 days)	44	50	57	64	78	92	99 (± 2 days)	
																(± 2 days)						
Recording of AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Full physical examination		X																			X	
Brief physical examination			X							X												
Full neurological examination[h]		X																			X	
Brief neurological examination			X							X												
Query for suicidality[i]		X	X		X		X		X	X		X		X		X	X	X	X	X	X	X
12-lead ECG[j]		X	X		X		X		X	X		X		X		X			X		X	
Laboratory tests (hematology, chemistry, urinalysis)		X	X		X		X		X	X		X		X		X	X		X		X	
Serology testing for HIV, Hepatitis B, and Hepatitis C		X																				
IGRA tuberculosis test[k]		X																				
Tuberculosis Signs and Symptoms questionnaire		X																			X	
Blood sampling for PK of UCB7665[l]			X		X		X		X	X		X		X		X						

Table 5.1: Schedule of assessments

Assessments	Screening		Treatment Period												Observation Period[a]						UV
			Dosing Period 1							Dosing Period 2											
	Visit	1	2 BL	3[b]	4	5[b]	6	7[b]	8	9	10[b]	11	12[b]	13	14[b]	15	16	17	18	19	20 FV/PEOT[c]	
	Day	-28 to -1	1	2	8[d] (± 2 days)	9	15[d] (± 2 days)	16	22[d] (± 2 days)	29[d] (± 2 days)	30	36[d] (± 2 days)	37	43[d] (± 2 days)	44	50	57	64	78	92	99 (± 2 days)	
																(± 2 days)						
Blood sampling for DNA analysis sub-study[m]			X						X					X								
Blood sampling for RNA analysis sub-study[m]			X		X				X					X							X	
Serum pregnancy test		X																				
Urine pregnancy test[n]			X		X		X		X	X		X		X		X	X	X	X	X	X	
Administration of IMP			X		X		X			X		X		X								
[redacted]			X		X		X		X	X		X		X		X	X	X	X	X	X	
Serum complement (C3,C4) and plasma complement levels (C3a and C5a)			X		X		X		X	X		X		X		X	X				X	
Immunoglobulins (total IgG and IgG subclasses)		X	X		X		X		X	X		X		X		X	X	X	X	X	X	
IgA, IgM, IgE			X						X	X		X		X		X	X				X	
MG-specific autoantibodies			X		X					X		X				X					X	

Table 5.1: Schedule of assessments

Assessments	Screening		Treatment Period												Observation Period[a]						UV
			Dosing Period 1							Dosing Period 2											
	Visit	1	2 BL	3[b]	4	5[b]	6	7[b]	8	9	10[b]	11	12[b]	13	14[b]	15	16	17	18	19	20 FV/PEOT[c]	
	Day	-28 to -1	1	2	8[d] (± 2 days)	9	15[d] (± 2 days)	16	22[d] (± 2 days)	29[d] (± 2 days)	30	36[d] (± 2 days)	37	43[d] (± 2 days)	44	50	57	64	78	92	99 (± 2 days)	
																(± 2 days)						
Blood sampling for exploratory biomarker analysis			X		X		X		X	X		X		X				X		X		
Blood sampling for safety biomarker analysis: may include but not limited to [redacted]			X		X		X		X	X		X		X		X	X	X	X	X	X	
BAFF analysis			X		X		X		X	X		X		X				X		X		
Cytokines[p]			X		X		X		X	X		X		X		X	X	X	X	X	X	X
Vaccination-specific antibody titers ([redacted])		X																			X	
MG-composite scale		X	X		X		X		X	X		X		X		X	X	X	X	X	X	
QMG scale[q]		X	X		X		X		X	X		X		X		X	X		X		X	
Muscle weakness severity and fatigability scale			X		X		X		X	X		X		X		X	X	X	X	X	X	
Fatigue scale			X		X		X		X	X		X		X		X	X	X	X	X	X	
MGADL scale			X							X						X		X			X	

Table 5.1: Schedule of assessments

Assessments	Screening		Treatment Period													Observation Period[a]						UV
			Dosing Period 1							Dosing Period 2												
	Visit	1	2 BL	3[b]	4	5[b]	6	7[b]	8	9	10[b]	11	12[b]	13	14[b]	15	16	17	18	19	20 FV/PEOT[c]	
	Day	-28 to -1	1	2	8[d] (± 2 days)	9	15[d] (± 2 days)	16	22[d] (± 2 days)	29[d] (± 2 days)	30	36[d] (± 2 days)	37	43[d] (± 2 days)	44	50	57	64	78	92	99 (± 2 days)	
																(± 2 days)						
MGFA classification		X	X							X											X	
SFEMG measurement[r]			X							X												
Headache questionnaire[s]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Stool sample assessment[t]			X		X		X		X	X		X		X		X	X	X	X	X	X	X
Subject exit interview																					X	

AE=adverse event; BAFF=B-cell activating factor; BL=Baseline; BP=blood pressure; CSF=cerebrospinal fluid; CT=computed tomography; DNA=deoxyribonucleic acid; ECG=electrocardiogram; FV=Final Visit; GI=gastrointestinal; HIV=human immunodeficiency virus; IgA=immunoglobulin A; IgE=immunoglobulin E; IgG=immunoglobulin G; IGRA= interferon-gamma release assay; IgM=immunoglobulin M; IMP=investigational medicinal product; IRT=interactive response technology; LP=lumbar puncture; MG=myasthenia gravis; MGADL=myasthenia gravis-Activities of Daily Living; MGFA=Myasthenia Gravis Foundation of America; MRI=magnetic resonance imaging; PEOT=premature end of treatment; PK=pharmacokinetics; PR=pulse rate; RNA=ribonucleic acid; QMG=Quantitative Myasthenia Gravis; [redacted] SFEMG=single fiber electromyogram; TB=tuberculosis; UV=Unscheduled Visit

[a] Subjects will return to the clinic/hospital for Visits 15, 16, 18, and 20; for Visits 17 and 19 subjects will either return to the clinic/hospital, or, if possible and agreed by both the investigator and subject, have home visits conducted by certified healthcare professionals.

[b] This visit is a telephone contact 24 hours post-IMP dose start.

[c] Subjects who withdraw early will be encouraged to complete the PEOT Visit plus the FV (approximately 8 weeks after the final study drug administration).

[d] A visit window of ±2 days is allowed for the dosing visits. The visit window of ±2 days is relative to the first dosing visit date. However, there should be a minimum interval of 5 days and maximum interval of 9 days as compared to the previous dose.

[e] Includes consent for SFEMG for the subjects consenting to this measurement at the participating sites. Additional informed consent is needed for participation in the exploratory genomic substudy.

[f] Systolic and diastolic BP, pulse rate, temperature, and respiratory rate. On dosing days, vital signs will be measured prior to IMP administration, 15 minutes after the start of the infusion, at the end of the infusion, 2 hours after the end of infusion and 4 hours after the end of the infusion. At nondosing visits, vital signs need only be taken once during the visit.

[g] Body weight at Screening and at Visit 9 will be used for calculation of dose; height will be assessed only at Screening.

[h] In addition to Screening and the FV, a full neurological examination should be performed for any subject who experiences severe headache.

[i] A query for suicidal ideation will be asked by Investigator at each clinical visit (including Visit 17 or Visit 19 when it is conducted at the clinic). A full C-SSRS assessment will be performed only when subject has a positive response to the suicidal ideation query. If a subject has active suicidal ideation as confirmed by the answer 'Yes' to Question 4 or Question 5 of the C-SSRS assessments, the subject will be excluded or withdrawn from the study and immediately referred to a Mental Healthcare Professional

[j] ECGs will be read by a central reader.

[k] The IGRA test will be performed in a central laboratory. Subject should not be dosed until IGRA result is available and negative.

[l] Pre- and postdose at Visits 2, 4, 6, 9, 11, and 13; postdose samples are to be taken 4 hours after the infusion has ended.

[m] Blood sample to be taken prior to dosing of IMP.

[n] Urine pregnancy test will be performed using a dipstick test; a positive urine pregnancy test must be confirmed using a serum pregnancy test.

[p] Sampling for exploratory safety biomarkers at Baseline (Visit 2) and 4 hours post dosing (Visit 2) for all subjects. During follow up only in subjects with severe headache and/or moderate to severe GI disturbances.

[q] Sampling at Baseline for all subjects and subsequently only in subjects with infusion reaction.

[s] Subjects must be off pyridostigmine (or any [redacted] inhibitor medication) from midnight before testing when medically safe to do so to standardize testing, but if not medically appropriate, then the treatment can be continued but the testing should be performed as best as possible at the same timeframe post last any [redacted] inhibitor dosing for each evaluation during the study.

[t] For subjects consenting to this measurement at the participating sites; subjects should not take pyridostigmine from midnight before testing when medically safe to do so to standardize testing, but if not medically appropriate, then the treatment can be continued but the testing should be performed as best as possible at the same timeframe post last [redacted] inhibitor dosing for each evaluation during the study. If pyridostigmine is taken, the time must be documented.

[u] This assessment is applicable only to subjects experiencing severe headaches and will be performed 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). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator.

[v] Stool collection and analysis will be performed for subjects reporting moderate or severe diarrhea. The frequency of stool sampling will be as clinically indicated in the opinion of the investigator. Analysis of stool samples will be performed locally.

Change #16

5.4.1 Choice of study design and endpoints

The primary objective of the study is to evaluate the clinical efficacy of UCB7665 as an on-demand treatment for subjects with moderate to severe generalized MG.

During the first Treatment Period a 2-arm parallel design study will allow comparison of the change from Baseline in QMG score to Visit 9 (Day 29) between IMP and placebo.

The choice of the primary outcome measures and the timing of approximately 4 weeks after the first dose of study drug are predicted to be the optimal approach to measure improvements based on effect seen in other therapies and recommendations of the Scientific Advisory Board of the MGFA (Barth 2013; Benatar 2012; Howard 2013). Then the second Dosing Period with a rerandomization allows for additional supportive data to be evaluated as well as minimizes the need for prolonged exposure of some subjects to placebo.

Has been changed to:

5.4.1 Choice of study design and endpoints

The primary objective of the study is to evaluate the clinical efficacy of UCB7665 as a chronic-intermittent treatment for subjects with moderate to severe generalized MG. Additionally, this study will provide 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.

During the first Treatment Period, a 2-arm parallel design study will allow comparison of the change from Baseline in QMG score to Visit 9 (Day 29) between UCB7665 7mg/kg and placebo.

The choice of the primary efficacy outcome measures and the timing of approximately 4 weeks after the first dose of study drug are predicted to be the optimal approach to measure improvements based on effect seen in other therapies and recommendations of the Scientific Advisory Board of the MGFA (Barth 2013; Benatar 2012; Howard 2013). Then the second Dosing Period with a rerandomization allows for additional supportive data to be evaluated as well as offering the placebo subjects a chance to receive UCB7665.

Change #17

6.1 Inclusion criteria

The following inclusion criterion was amended.

6. Female subjects of child bearing potential must have a negative serum pregnancy test at the Screening Visit, which is confirmed to be negative by urine testing prior to the first dose of study drug at Week 1 (Visit 2) and prior to further dosing at each study visit thereafter.

   Female subjects of childbearing potential must agree to use a highly effective method of birth control, during the study and for a period 2 months after their final dose of study drug. Highly effective forms of birth control are methods which achieve a failure rate of less than 1% per year when used consistently and correctly. Highly effective methods of birth control include:

Has been changed to:

6.1 Inclusion criteria

6. Female subjects of child bearing potential must have a negative serum pregnancy test at the Screening Visit, which is confirmed to be negative by urine testing prior to the first dose of study drug at Week 1 (Visit 2) and prior to further dosing at each study visit thereafter.

   Female subjects of childbearing potential must agree to use a highly effective method of birth control, during the study and for a period 2 months after their final dose of study drug. According to the International Council for Harmonisation (ICH) M3 (R2), highly effective forms of birth control are methods which achieve a failure rate of less than 1% per year when used consistently and correctly. Highly effective methods of birth control include:

Change #18

The following exclusion criteria were amended.

6.2.1 Exclusion criteria related to health status

7. Subject has QMG score of <10.5 at Baseline.

12. Subject has 12-lead ECG with changes considered to be clinically significant upon medical review.

15. Subject has >1.5x upper limit of normal (ULN) of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or >ULN total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome). If subject has elevations only in total bilirubin that are >ULN and <1.5xULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%).

    For randomized subjects with a Baseline result >ULN for ALT, AST, ALP, or total bilirubin but <1.5xULN, a Baseline diagnosis and/or the cause of any clinically meaningful elevation must be understood and recorded in the electronic Case Report form (eCRF).

    If subject has >ULN, ALT, AST, or ALP that does not meet the exclusion limit at Screening, repeat the tests, if possible, prior to dosing to ensure there is no further ongoing clinically relevant increase. In case of a clinically relevant increase, inclusion of the subject must be discussed with the medical monitor.

    Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit (>1.5xULN) may be repeated once for confirmation. This includes rescreening.

21. Subject has a history of clinically relevant ongoing chronic infections including but not limited to human immunodeficiency virus (HIV), Hepatitis B, Hepatitis C, active or latent tuberculosis (TB) or who tests positive for HIV, Hepatitis B, or Hepatitis C at the Screening Visit.

22. Subject has a family history of primary immunodeficiency.

Has been changed to:

6.2.1 Exclusion criteria related to health status

7. Subject has QMG score of <11 at Baseline.

12. Subject has 12-lead ECG with changes considered to be clinically significant upon medical review. The ECG contains findings that, according to the sponsor, may represent a significant abnormality. The clinical significance of the findings needs to be assessed by the investigator to determine eligibility as defined by the protocol, and any queries regarding continuation of the subject must be addressed with the medical monitor.

15. Subject has >2x upper limit of normal (ULN) of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or >ULN total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome). If subject has elevations only in total bilirubin that are >ULN and <1.5xULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%).

    For randomized subjects with a Baseline result >ULN for ALT, AST, ALP, or total bilirubin but <1.5xULN, a Baseline diagnosis and/or the cause of any clinically meaningful elevation must be understood and recorded in the electronic Case Report form (eCRF).

    If subject has >ULN, ALT, AST, or ALP that does not meet the exclusion limit at Screening, repeat the tests, if possible, prior to dosing to ensure there is no further ongoing clinically relevant increase. In case of a clinically relevant increase, inclusion of the subject must be discussed with the medical monitor.

    Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit (>2xULN) may be repeated once for confirmation. This includes rescreening.

21. Subject has a history of clinically relevant ongoing chronic infections including but not limited to human immunodeficiency virus (HIV), Hepatitis B, Hepatitis C, or who tests positive for HIV, Hepatitis B, or Hepatitis C at the Screening Visit.

22. Subject has a family history (immediate family member) of primary immunodeficiency.

Change #19

The following exclusion criteria were amended. Exclusion criterion #29 was deleted.

6.2.2 Exclusion criteria related to concomitant medications/procedures

27. Subject has had prior treatment with rituximab in the 6 months prior to the Baseline Visit or subject has had prior treatment with rituximab in the 12 months prior to Baseline and B cells are not within the normal range.

28. Subject has not completed the washout period for the immunosuppressants, biologics, and other therapies as detailed in Table 6.1.

29. Subjects receiving immunoadsorption treatment.

30. Subject had a thymectomy in the past 6 months, a history of thymoma World Health Organization grade B2 or B3, or Masaoka grade III or IV, or thymoma requiring chemotherapy and/or radiotherapy.

Has been changed to:

6.2.2 Exclusion criteria related to concomitant medications/procedures

27. Subject has had prior treatment with rituximab in the 6 months prior to the Baseline Visit or subject has had prior treatment with rituximab in the 12 months prior to Baseline and B cells monitoring has shown they did not return to normal range.
28. Subject has been treated with the immunosuppressants, biologics, and other therapies as detailed in the recent timeframe as detailed in Table 6.1 OR has not been on stable dosing regimens of the medications as detailed in Table 7.1.
29. Exclusion Criterion 29 was deleted per Protocol Amendment 1.
30. Subject had a thymectomy in the past 6 months, a history of thymoma World Health Organization grade B2 or B3, or Masaoka grade III or IV, or history of a thymoma requiring chemotherapy and/or radiotherapy.

Change #20

Table 6.1: Washout periods for immunosuppressants, biologics, and other therapies

Generic name (commercial/trade names)	**Washout Period relative to Baseline Visit (regardless of route)**
Others	
Intravenous immunoglobulin	[redacted]

Has been changed to:

Table 6.1: No treatment periods for exclusionary immunosuppressants, biologics, and other therapies

Generic name (commercial/trade names)	**Period relative to Baseline Visit (regardless of route)**
Others	
Intravenous or subcutaneous immunoglobulin	[redacted]

Change #21

The below section was added:

6.2.3 Exclusion criteria related to other risks

31 Subject has a lifetime history of suicide attempt (including an [redacted] or has suicidal ideation in the past 6 months as indicated by a positive response (Yes) to either Question 4 or Question 5 of the Columbia Suicide Severity Rating Scale (C-SSRS) at Screening.

32 Subjects with known tuberculosis (TB) infection, at high risk of acquiring TB infection, or latent tuberculosis infection (LTBI), or current/history of nontuberculous mycobacterial infection (NTMBI) are excluded.

a. Known TB infection whether present or past is defined as:

- Active TB infection or clinical signs and symptoms suggestive of TB (pulmonary or extrapulmonary).
- History of active TB infection involving any organ system or findings in other organ systems consistent with TB infection.
- Any historical evidence by radiography or other imaging modalities consistent with previously active TB infection.

b. High risk of acquiring TB infection is defined as:

- Known exposure to another person with active TB infection within the 3 months prior to Screening.
- Time spent in a healthcare delivery setting or institution where individuals infected with TB are housed and where the risk of transmission of infection is high.

c. LTBI (see Section 12.3.1 for further details and instructions).

d. NTMBI is defined as a group of lung infections caused by mycobacteria different from mycobacterium tuberculosis infections.

Change #22

6.3 Rescreening and Rechecking

Subjects with isolated results that are outside the specified ranges and that are deemed potentially clinically nonsignificant will be allowed to rescreen at the discretion of the investigator, following discussion with the sponsor's medical monitor/study physician, if appropriate.

If a subject has 1 isolated test result outside the specific range which is deemed clinically significant, the abnormal value may be rechecked at the discretion of the investigator, following discussion with the sponsor's medical monitor/study physician. If the normalization of the test result occurs within the Screening Period, then no other Screening procedures need to be repeated.

Has been changed to:

Subjects with isolated results that are outside the specified ranges and that are deemed potentially clinically significant will be allowed to rescreen at the discretion of the investigator, following discussion with the sponsor's medical monitor/study physician, if appropriate.

If a subject has 1 isolated test result outside the specific range which is deemed clinically nonsignificant, the abnormal value may be rechecked at the discretion of the investigator, following discussion with the sponsor's medical monitor/study physician. If the normalization of the test result occurs within the Screening Period, then no other Screening procedures need to be repeated.

Change #23

6.4 Withdrawal criteria

Subjects MUST be withdrawn from IMP if any of the following events occur:

1. Subject develops an illness or has a change in health status that would interfere with his/her continued participation, including but not limited to:

The below was added:

- Subject has a TB test that is confirmed positive or any further evidence suggestive of potential TB infection (eg, exposure) and further examinations result in a diagnosis of active TB or LTBI (refer to Section 12.3.1) for further details and instructions.
- If an NTMBI is identified during a study, the same withdrawal procedures as those used for an active TB infection identified during the study should be followed.

Additionally, the below was added:

8. Subject has active suicidal ideation as indicated by a positive response (Yes) to either Question 4 or Question 5 of the "Since Last Visit" version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional.

Change #24

7.8.1 Permitted concomitant medication

The following was added:

Subjects should not take pyridostigmine (or any [redacted] inhibitor medication) from midnight before testing when medically safe to do so to standardize testing, but if not medically appropriate, then the treatment can be continued but the testing should be performed as best as possible at the same timeframe post last or any [redacted] inhibitor medication inhibitor dosing for each evaluation during the study.

Change #25

7.8.2 Prohibited concomitant treatments (medications and therapies)

- Dexamethasone

3rd paragraph:

If a subject needs or takes any prohibited medication or therapy (except IVIg, PLEX, dexamethasone, or rituximab), the investigator will (where possible) discuss with the sponsor study physician and a decision will be made whether the subject can continue in the study or must be withdrawn. If the subject is treated with IVIg, rituximab, or PLEX, the subject must be withdrawn from the IMP, but should be encouraged to continue with Observation Period Visits.

Has been changed to:

7.8.2 Prohibited concomitant treatments (medications and therapies)

Dexamethasone was removed from the bullet list and the following text.

3rd paragraph:

If a subject needs or takes any prohibited medication or therapy (except IVIg, PLEX, or rituximab), the investigator will (where possible) discuss with the sponsor study physician and a decision will be made whether the subject can continue in the study or must be withdrawn. If the subject is treated with IVIg, rituximab, or PLEX, the subject must be withdrawn from the IMP, but should be encouraged to continue with Observation Period Visits.

Change #26

8.1.1 Visit 1 (Day -28 to -1) Screening Visit

- Blood sample for the following laboratory parameters:
  - Standard safety laboratory tests: hematology and clinical chemistry, plus serology testing for HIV, Hepatitis B, Hepatitis C, and active or latent TB

Has been changed to:

8.1.1 Visit 1 (Day -28 to -1) Screening Visit

- Blood samples:
  - Standard safety laboratory tests: hematology and clinical chemistry, plus serology testing for HIV, Hepatitis B, and Hepatitis C

Additionally, the following were added:

- Query for suicidality (Screening)

  If positive response (Yes), a full C-SSRS will be performed.
- Tuberculosis assessments:
  - IGRA
  - Tuberculosis Sign and Symptoms questionnaire

Change #27

The following laboratory parameters were updated.

8.2.1 Visit 2 (Day 1, Baseline)

- Blood sample for the following laboratory parameters:
  - IgG depletion assay
  - Exploratory safety biomarkers: [redacted] only in subjects with severe headache and/or moderate to severe GI disturbance
  - Cytokines (only in subjects with infusion reaction)

Has been changed to:

8.2.1 Visit 2 (Day 1, Baseline)

- Blood samples:
  - Exploratory biomarker analysis
  - Exploratory safety biomarkers: may include but not limited to [redacted]
  - Cytokines

In addition, the following were added:

- Tuberculosis Sign and Symptoms questionnaire
- Query for suicidality (Screening)

  If positive response (Yes), a full C-SSRS will be performed.

Change #28

The following changes were made in Section 8.2.3, 8.2.5, 8.2.7, 8.3.1, 8.3.3, 8.3.5, 8.4.3, and 8.4.5.

- Blood sample for the following laboratory parameters:
  - IgG depletion assay
  - Safety biomarkers: [redacted] in subjects with severe headache and/or moderate to severe GI disturbance

Has been changed to:

- Blood samples:
  - Exploratory biomarker analysis
  - Exploratory safety biomarkers: may include but not limited to [redacted] in subjects with severe headache and/or moderate to severe GI disturbance

In addition, the following was added:

- Query for suicidality (since last visit):

  If positive response (Yes), a full C-SSRS will be performed.

Change #29

The following changes were made in Section 8.4.1, 8.4.2, 8.4.4, and 8.4.6.

- Blood sample for the following laboratory parameters:
  - IgG depletion assay
  - Exploratory safety biomarkers: [redacted] only in subjects with severe headache and/or moderate to severe GI disturbance

Has been changed to:

- Blood samples:
  - Exploratory safety biomarkers: may include but not limited to [redacted] in subjects with severe headache and/or moderate to severe GI disturbance

In addition, the following was added:

- Query for suicidality (since last visit):

  If positive response (Yes), a full C-SSRS will be performed.

The following was added into Section 8.4.6 only:

- Tuberculosis Sign and Symptoms questionnaire

Change #30

The following sentence was deleted in Section 8.2.2, 8.2.4, 8.2.6, 8.3.2, 8.3.4, and 8.3.6.

"The IRT should be called to register the visit."

Change #31

The following item was deleted in Section 8.2.7 and 8.4.1 to 8.4.6.

- Call or enter IRT to register the visit

Change #32

8.4 Observation Period

During the Observation Period, visits will be performed at weekly intervals, apart from between Visits 17, 18, and 19, when visits will be performed at 2 weekly intervals. 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, or, if possible and agreed by both the investigator and the subject, have home visits conducted by certified healthcare professionals, for Visits 17, 19, and 20. No IMP will be administered in the Observation Period.

Has been changed to:

8.4 Observation Period

During the Observation Period, visits will be performed at weekly intervals, apart from between Visits 17, 18, and 19, when visits will be performed at 2 weekly intervals. Subjects will return to the clinic for Visits 15, 16, 18, and 20 for efficacy and for safety assessments. Subjects will either return to the clinic, or, if possible and agreed by both the investigator and the subject, have home visits conducted by certified healthcare professionals, for Visits 17 and 19. No IMP will be administered in the Observation Period.

Change #33

8.6 Unscheduled Visit

The following was added:

- Query for suicidality (since last visit):

  If positive response (Yes), a full C-SSRS will be performed.

Change #34

9.5 Single Fiber EMG, 1st paragraph:

At participating sites, subjects consenting to SFEMG measurement should not take pyridostigmine from midnight before testing when medically safe to do so to standardize testing, but if not medically appropriate, then the treatment can be continued but the testing should be performed as best as possible at the same timeframe post last [redacted] inhibitor dosing for each evaluation during the study. […]

Has been changed to:

9.5 Single Fiber EMG, 1st paragraph:

At participating sites, subjects consenting to SFEMG measurement should not take pyridostigmine from midnight before testing when medically safe to do so to standardize testing, but if not medically appropriate, then the treatment can be continued but the testing should be performed as best as possible at the same timeframe post last [redacted] inhibitor dosing for each evaluation during the study. If pyridostigmine is taken, the time must be documented.

Change #35

10.2 Pharmacodynamic variables

The following was deleted:

- IgG concentrations pre- and post-[redacted] depletion

Change #36

12.1.1.5 Immediate reporting of adverse events

The following AEs must be reported immediately using the Serious Adverse Event form:

- SAE: AE that the investigator classifies as serious by the above definitions regardless of causality
- Suspected transmission of an infectious agent via a medicinal product
- AE of special interest (see Section 12.1.1.3)
- AE of interest (see Section 12.1.1.4)

Has been changed to:

12.1.1.5 Immediate reporting of adverse events

The following AEs must be reported immediately using the SAE Report Form according to the procedure in Section 12.1.2.3:

- SAE: AE that the investigator classifies as serious by the above definitions regardless of causality
- Suspected transmission of an infectious agent via a medicinal product
- AE of special interest (see Section 12.1.1.3)
- AE of interest (see Section 12.1.1.4)
- Confirmed LTBI, active TB, and NTMBI (see Section 12.3.1)

Change #37

The following was added to clarify the suicidality assessment:

12.1.6 Suicidality

At screening, the Investigator will query each subject if he/she has a lifetime history of suicide attempt (including an [redacted] or suicidal ideation in the past 6 months. A full C-SSRS "Lifetime recent" assessment will be performed only when the subject has a positive response to this query. This scale will be assessed by trained study personnel. When suicide attempt or suicidal ideation is confirmed by a positive response (Yes) to either Question 4 or Question 5 of the C-SSRS, the subject must be excluded and immediately referred to a Mental Healthcare Professional.

At each clinical visit, the investigator must query the suicidal ideation since the last visit. A full C-SSRS "Since last visit" assessment will be performed only when the subject has a positive response to this query. When suicide attempt or suicidal ideation is confirmed by a positive response (Yes) to either Question 4 or Question 5 of the C-SSRS, the subject must be withdrawn and immediately referred to a Mental Healthcare Professional. The details of C-SSRS will be provided in the Study Procedures Manual.

Change #38

12.1.7 Safety signal detection, 1st paragraph

An unblinded DMC will oversee at least 1 interim analysis during the course of the study during which the safety and futility of UCB7665 will be assessed.

Has been changed to:

12.1.7 Safety signal detection, 1st paragraph

An unblinded DMC will oversee at least 1 interim analysis during the course of the study during which the safety of UCB7665 will be assessed.

Change #39

Assessment of safety biomarkers was clarified.

12.1.10 Management of moderate or severe diarrhea (previous heading number), 2nd paragraph

Stool collection and analysis will be performed for subjects reporting moderate or severe diarrhea. The frequency of stool sampling will be as clinically indicated in the opinion of the investigator. Analysis of stool samples will be performed locally. In addition, assessment of safety biomarkers is required for subjects with moderate to severe GI disturbances including diarrhea.

Has been changed to:

12.1.11 Management of moderate or severe diarrhea (new heading number), 2nd paragraph

Stool collection and analysis will be performed for subjects reporting moderate or severe diarrhea. The frequency of stool sampling will be as clinically indicated in the opinion of the investigator. Analysis of stool samples will be performed locally. In addition, collection of blood samples for assessment of exploratory safety biomarkers is required for subjects with moderate to severe GI disturbances including diarrhea.

Change #40

12.2 Laboratory measurements, Table 12.2

Duplicate laboratory tests were removed and footnotes are updated.

Table 12.2: Safety laboratory measurements

Hematology	Chemistry	Urinalysis	Pregnancy test
Hematocrit	Calcium	Albumin	Urine HCG
Hemoglobin	Chloride	Protein	Serum HCG[a]
Platelet count	Magnesium	Nitrite	
RBC count	Electrolytes (calcium, phosphate, sodium, potassium, chloride, and magnesium)	Glucose	
WBC count (including differential)		pH	
	Phosphate	Protein	
	ALP	Leukocytes	
HbA1c[b]	AST	Blood	
Hemoglobin (RBC and platelet count)	ALT	Bilirubin	
Hematocrit	GGT	Urobilinogen	
Serology[c]	Total and direct bilirubin	Ketone	
HBsAg	LDH	Creatinine	
HCV Ab	Total cholesterol	Glucose	
HIV (anti-HIV1 or anti-HIV2 antibodies)	LDL - cholesterol	Albumin	
Tuberculosis[d]	HDL – cholesterol, triglycerides		
	Amylase		
Serum biomarkers[e]	Creatine kinase		
[redacted]	Creatinine		
	Total protein		
	Albumin		
	alpha- and beta–globulins		

Table 12.2: Safety laboratory measurements

Hematology	Chemistry	Urinalysis	Pregnancy test
[redacted]	Urea-N		
	Procalcitonin		
	hsCRP		

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; FSH=follicle stimulating hormone; GGT=gamma glutamyltransferase; HbA1c=hemoglobin A1c; HBsAG=hepatitis B surface antigen; HCG=human chorionic gonadotropin; HCV Ab=hepatitis C virus antibody; HDL=high density lipoprotein; HIV=human immunodeficiency virus; hsCRP=high-sensitivity C-reactive protein; LDH=lactate dehydrogenase; LDL=low density lipoprotein; [redacted]; RBC=red blood cell; [redacted] WBC=white blood cell

Serum pregnancy testing is only performed at Visit 1 and, in the event of a positive pregnancy test, to confirm the results of a urine test

HbA1c is performed at Screening only

This serology performed at Screening only

By QuantiFERON-TB Gold® test

Serum biomarkers levels measured at Screening, Baseline, and at each scheduled assessment during Treatment and Observation Periods in subjects with severe headache and/or moderate to severe GI disturbance

Has been changed to:

Hematology	Chemistry	Urinalysis	Pregnancy test
Hematocrit	Electrolytes (calcium, phosphate, sodium, potassium, chloride, and magnesium)	Albumin	Urine HCG
Hemoglobin		Protein	Serum HCG[a]
Platelet count		Nitrite	
RBC count	ALP	Glucose	
WBC count (including differential)	AST	pH	
	ALT	Leukocytes	
HbA1c[b]	GGT	Blood	
	Total and direct bilirubin	Bilirubin	
Serology[c]		Urobilinogen	
HBsAg	LDH	Ketone	
HCV Ab	Total cholesterol	Creatinine	
HIV (anti-HIV1 or anti-HIV2 antibodies)	LDL - cholesterol		
	HDL – cholesterol, triglycerides		
Tuberculosis[d]			
	Amylase		
Exploratory Safety Biomarkers[e]	Creatine kinase		
[redacted]	Creatinine		
	Total protein		
	Albumin		
	alpha- and beta–globulins		
	Urea-N		
	Procalcitonin		
	hsCRP		

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma glutamyltransferase; HbA1c=hemoglobin A1c; HBsAG=hepatitis B surface antigen; HCG=human chorionic gonadotropin; HCV Ab=hepatitis C virus antibody; HDL=high density lipoprotein; HIV=human immunodeficiency virus; hsCRP=high-sensitivity C-reactive protein; LDH=lactate dehydrogenase; LDL=low density lipoprotein; RBC=red blood cell; [redacted] WBC=white blood cell

[a] Serum pregnancy testing is only performed at Visit 1 and, in the event of a positive pregnancy test, to confirm the results of a urine test
[b] HbA1c is performed at Screening only
[c] This serology performed at Screening only
[d] Interferon-gamma release assay by central laboratory.
[e] May include but not limited to the following biomarkers listed below. Samples collected for exploratory safety biomarkers at Baseline (Visit 2) and 4 hours post dosing (Visit 2) for all subjects and during follow up only in subjects with severe headache and/or moderate to severe GI disturbances. The Baseline samples will only be analysed in case the subject experienced a severe headache and/or moderate to severe GI disturbance.

Change #41

12.2.1.1 Consultation with medical monitor and local hepatologist

Potential drug-induced liver injury events require notification of the medical monitor within 24 hours (eg, by laboratory alert), and the subject must be discussed with the medical monitor as soon as possible. If required, the subject must also be discussed with the local hepatologist.

Has been changed to:

Potential drug-induced liver injury events require notification of the medical monitor within 24 hours (eg, by laboratory alert), and the subject must be discussed with the medical monitor as soon as possible. If required, the subject must also be discussed with the local hepatologist or gastroenterologist.

Change #42

The below was added:12.3.1 Assessment and management of TB and TB risk factors

With the currently available data, TB is not considered as an important potential or identified risk for treatment with UCB7665. As immunomodulation may carry risk of new or activation of LTBI, UCB has conservatively developed TB detection and management procedures taking into account the most current recommendations of international guidelines (2010 WHO) and most recent literature, covering any infection by the mycobacteria tuberculosis complex.

Appropriate rigorous precautions are being taken within this protocol to monitor the risk of TB infection in this study (see Section 6.3.2 [Exclusion Criterion 32] and Section 6.4 [Withdrawal Criteria 1]). Following are the key considerations of these procedures:

TB Tests at Screening

IGRA and TB questionnaire are required as indicated in Schedule of Assessments (Table 5.1).

- TB screening is mandatory both before study entry and during the conduct of the study. The preferred screening test is **IGRA performed at a Central Laboratory**.
  - The IGRA result must be negative for subjects to enroll in this study
  - Subjects who test positive for IGRA test should be excluded from the study and referred for appropriate medical evaluation according to the local medical practice guidelines.
  - If the result of the IGRA test is indeterminate, the particular IGRA test previously performed may be repeated once; if positive or indeterminate on retest, the subject must not be randomized to study drug and, if already randomized, must undergo appropriate

study specified withdrawal procedures. The retest must be done during the protocol-defined Screening Period.

- In addition to IGRA test, subjects will be evaluated for signs and symptoms of latent or active TB infection and for risk factors of exposure to TB, using the TB questionnaire, at Screening. See the 'TB signs and symptoms questionnaire' section for further instructions on using the questionnaire. Subjects with known TB, at a high risk of acquiring TB or with LTBI should be excluded from this study as described in Exclusion Criteria.

Monitoring for TB during the study

Subjects will be monitored for signs/symptoms of TB using routine pharmacovigilance measures for Adverse Events. Subjects reporting AEs related to signs/symptoms of TB will be evaluated for LTBI and active TB according to the local medical practice guidelines.

Subjects with confirmed LTBI or active TB or NTMBI will be immediately withdrawn from the study as described in Withdrawal Criteria. Confirmed LTBI, active TB, and NTMBI must be reported to the Sponsor immediately regardless of seriousness using the SAE Report Form. Additional information received by the Investigator should be provided to the Sponsor within 24 hours of awareness.

Once withdrawn from study treatment, subjects should return for the PEOT, complete all early withdrawal assessments, and complete the follow-up visits.

TB tests at Final/PEOT Visit

Subjects will be evaluated for signs and symptoms of latent or active TB infection and for risk factors of exposure to TB, using the TB questionnaire, at the Final/PEOT Visit. See the 'TB signs and symptoms questionnaire' section for further instructions on using the questionnaire

Signs and symptoms of TB

The Investigator should consider all potential sites of infection when assessing for TB during the physical examination, and other evaluations, and based on the subject's history.

Common symptoms with which the subject may present with include cough, blood in sputum, night sweats, lymphadenitis, joint pain/swelling, spinal deformity, headache/confusion, abdominal pain mimicking inflammatory bowel disease, frequent or painful urination, scrotal mass in men and pelvic inflammatory disease in women as well as other symptoms, or nonspecific symptoms. This is not an exhaustive list and unusual presentations should always be considered.

TB signs and symptoms questionnaire

The questionnaire "Evaluation of signs and symptoms of tuberculosis" should be used as a source document. The questionnaire will assist with the identification of subjects who may require therapy for TB. A subject who answers "Yes" to the question [redacted] at Screening is excluded. A "Yes" response to any of the other questions within the questionnaire at Screening should trigger further careful assessment to determine if subject has latent or active TB (see Section 6.2.3 [Exclusion Criterion 32]). A "Yes" response to any of the questions at the end of the study should trigger further assessments as per local medical guidelines to determine if the subject has either LTBI or active TB infection.

LTBI, active TB or other NMTBI identified during study

During the study, subjects who develop evidence of LTBI or active TB or NMTBI must immediately stop further administration of study drug and will be referred to an appropriate medical specialist for further evaluation.

Confirmed LTBI or active TB or NTMBI must be reported to the Sponsor immediately as described above.

Change #43

12.3.6 12-lead ECG

The heading numbering was changed as below:

12.3.7 12-lead ECG

In addition, the below was added:

The investigator may consult with the cardiologist at the central ECG laboratory to confirm the presence of a clinically significant ECG abnormality. It remains the responsibility of the investigator to decide whether an ECG finding is of clinical significance on the basis of the complete clinical picture and whether this finding influences the subject's participation in the study.

Change #44

14.2 General statistical considerations, 5th paragraph

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.

Has been changed to:

14.2 General statistical considerations, 5th paragraph

Unless stated otherwise, all statistical tests will be 1-sided and conducted at 0.05 alpha levels (due to the character of the study, no alpha adjustment for multiplicity will be done). For Dosing Period 2, only descriptive analyses will be performed.

Change #45

14.3.1 Analysis of the primary efficacy variable, 2nd paragraph to the last paragraph

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 there is no difference in the change from Baseline between Treatment Groups. The alternative hypothesis is that the mean change from Baseline in QMG score is greater in the UCB7665 7mg/kg group than the placebo group.

The primary efficacy variable will be analyzed for the FAS using an analysis of covariance model with treatment as a factor and Baseline QMG as a covariate. 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) and 1-sided 95% confidence interval (CI). Last Observation Carried Forward (LOCF) imputation will be utilized to account for missing data at Visit 9.

The analysis of the primary efficacy variable will repeated for the PPS using the same methodology as described above.

Has been changed to:

14.3.1 Analysis of the primary efficacy variable, 2nd paragraph to the last paragraph

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 there is no difference in the change from Baseline between Treatment Groups. 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 based on a mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) that includes terms for treatment group, the Baseline QMG score, and the interaction between treatment group and week. The model will define patient as a random effect and utilize an unstructured covariance pattern.

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) and 1-sided 95% confidence interval (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.

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 for the PPS. A further analysis will utilize the Last Observation Carried Forward (LOCF) approach; 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.

Change #46

14.3.2 Other efficacy analyses, 1st to 4th paragraph

The change from Baseline in QMG score, MG-Composite score, muscle weakness severity and fatigability scale score and fatigue scale score, and MGADL score, at each assessed post-Randomization Visit (during Dosing Period 1 including Visit 9) will be analyzed similarly to the change from Baseline in QMG for the FAS as described in Section 14.3.1. However instead of LOCF, observed cases will be utilized.

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

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

Psychometric analyses of the newly developed measures MG muscle weakness severity and fatigability and fatigue scales will be performed blinded from treatment arms. The association between PROs and clinical variables will also be explored, as well as the association between the various PROs. A psychometric analysis of the MG muscle weakness severity and Fatigue scale using Rasch analysis will be performed, but reported separately from the CSR.

Has been changed to:

14.3.2 Other efficacy analyses, 1st to 4th paragraph

The secondary variables and change from Baseline in QMG score, MG-Composite score, MGADL score, muscle weakness severity and fatigability scale score and fatigue scale score, at each assessed post-Randomization Visit (during Dosing Period 1 including Visit 9) will also be analyzed utilizing the MMRM approach similarly to the change from Baseline in QMG for the FAS as described in Section 14.3.1.

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

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

Psychometric analyses of the newly developed measures MG muscle weakness severity and fatigability and fatigue scales will be performed blinded from treatment arms. The association between PROs and clinical variables will also be explored, as well as the association between the various PROs. A psychometric analysis of the MG muscle weakness severity and fatigability scale and fatigue scale using Rasch analysis will be performed, but reported separately from the CSR.

Change #47

14.4 Planned safety and other analyses

14.4.1 Safety analyses, 5th paragraph

Exploratory safety serum biomarkers will be summarized by treatment group and visit using descriptive statistics [redacted] Figures of mean values over time and changes from Baseline may be presented.

Has been changed to:

14.4 Planned other and exploratory analyses

14.4.1 Safety analyses, 5th paragraph

Exploratory safety biomarkers will be summarized by treatment group and visit using descriptive statistics.

Change #48

14.4.2.2 Pharmacodynamic analysis 2nd paragraph

The following was deleted:

Figures of mean values over time and changes from Baseline will be presented. The IgG concentrations pre- and post-[redacted] depletion at each scheduled assessment will be listed and summarized by treatment group and visit.

Change #49

14.7 Planned interim analysis and data monitoring, 1st and 2nd paragraph

Two interim analyses will be performed. The first interim analysis will be conducted after 20 subjects (receiving 6 sc infusions) have attended the second visit of the observational period (ie, the visit 2 weeks after last dosing). Based on this unblinded analysis the safety of UCB7665 will be assessed by the DMC. The safety variables to be used and the decision rules to be applied will be specified in the DMC charter. The DMC can either recommend to continue the study as planned or to stop the study. In addition futility of UCB7665 will be assessed based on QMG score and MG-Composite score data. In case of futility, the study will be stopped. The decision rules for futility will be described in the DMC charter. During this review recruitment will not be stopped. The second interim analysis will be performed once all subjects have attended Visit 9, 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 variable 'change from Baseline to Visit 9 (Day 29) in MG-Composite score'. For the second 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 safety and efficacy data (as specified in the DMC charter), which will be available at the time the 20th subject attended Visit 16. For both 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.

Has been changed to:

14.7 Planned interim analysis and data monitoring, 1st and 2nd paragraph

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 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.

Change #50

14.8 Determination of sample size, 3rd paragraph

Assuming a treatment difference of 3.4 points in the mean change from Baseline in QMG at Visit 9 between the placebo and UCB7665 treatment arm with SD equal to 3.4, a sample size of 40 subjects (20 for each treatment group) provides >90% power to detect a treatment difference. Approximately 5% of the randomized subjects cannot be utilized for the FAS and, hence 42 subjects will be randomized.

Has been changed to:

14.8 Determination of sample size, 3rd paragraph

Assuming a treatment difference of 3.4 points in the mean change from Baseline in QMG at Visit 9 between the placebo and UCB7665 treatment arm with SD equal to 3.4, a sample size of 40 subjects (20 for each treatment group) provides >90% power to detect a treatment difference. Further it will be assumed that approximately 5% of the randomized subjects cannot be utilized for the FAS and, hence 42 subjects will be randomized.

18.13 Protocol Amendment 2

Rationale for the amendment

The protocol has been amended to include an additional patient-reported outcome assessment, intended as a measure of disease severity. This patient-centered index has been developed for an outpatient setting and is sensitive to detect clinical change after interventions, and most importantly detect patient-meaningful change. Two additional other efficacy variables have been added to capture changes for mean consecutive difference and normal fiber pairs in jitter (SFEMG) studies to show the clinical trend from pre- to postdose treatment.

Furthermore, permitted concomitant medications have been revised to include: modified and unmodified dose formulations for cyclosporin; and increased dose strength for tacrolimus. With no specific dosing for tacrolimus, dosing is variable in patients with MG, but for transplant related immunosuppression, higher doses are cited in literature; therefore a slightly higher fixed dose has been allowed.

Administrative and stylistic changes may not be included in the summary of changes since they are considered minor.

The following shows the changes made in Amendment 2 compared to Protocol Amendment 1, dated 07 Feb 2017.

Modifications and changes

Global changes

The following changes were made throughout the protocol:

- Other efficacy and immunological variables were updated. Statistical analyses sections were updated accordingly.
- Additional term ‘jitter’ for the SFEMG performance for relevant sections. The term has been modified to be presented as ‘jitter (SFEMG) measurement’.
- Instructions for subjects using pyridostigmine have been reworded to clarify the requisite for the QMG assessment. Subjects ‘should not take’ pyridostigmine.
- Study assessments and procedures for treatment visits only have been categorized as pre-during- and postdose throughout Section 8 in line with the Schedule of Study Assessments.

Specific changes

Change #1

Sponsor Study Physician

Name:	[redacted]
Address:	UCB Biosciences, Inc. 8010 Arco Corporate Drive Raleigh, NC 27617 UNITED STATES

Phone:	[redacted]
Fax:	-

Has been changed to:

Name:	[redacted]
Address:	UCB Biosciences, Inc. 8010 Arco Corporate Drive Raleigh, NC 27617 UNITED STATES
Phone:	[redacted]
Fax:	-

Change #2

List of Abbreviations – additional abbreviations

IPI	interpotential interval
MCD	mean consecutive difference
MGII	Myasthenia Gravis Impairment Index

Change #3

4.1.3 Other efficacy variables

- Change in mean jitter in SFEMG from Baseline to Visit 9 for the subjects consenting to this measurement at the participating sites

Has been changed to:

- Change in the percentage of normal fiber pairs in jitter (SFEMG) studies from Baseline to Visit 9 for the subjects consenting to this measurement at the participating sites
- Change in 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 clinical improvement

Change #4

4.2.4 Immunological variables

- Change from Baseline in serum complement levels (C3 and C4) and plasma complement levels (C3a and C5a) at each scheduled assessment during Treatment and Observation Periods
- [redacted] status (negative/positive) and change from Baseline in relative mass units at each scheduled assessment during Treatment and Observation Periods
- Change from Baseline in serum BAFF levels

- Change from Baseline in cytokines (in subjects experiencing infusion reactions) at assessments during Treatment and Observation Periods

Has been changed to:

- 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] 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 #5

5.2 Schedule of study assessments

Table 5.1: Schedule of assessments

Assessments	Screening		Treatment Period													Observation Period[a]						UV
			Dosing Period 1							Dosing Period 2												
	Visit	1	2 BL	3[b]	4	5[b]	6	7[b]	8	9	10[b]	11	12[b]	13	14[b]	15	16	17	18	19	20 FV/PEOT[c]	
	Day	-28 to -1	1	2	8[d] (± 2 days)	9	15[d] (± 2 days)	16	22[d] (± 2 days)	29[d] (± 2 days)	30	36[d] (± 2 days)	37	43[d] (± 2 days)	44	50	57	64	78	92	99 (± 2 days)	
																(± 2 days)						
Written informed consent[e]		X																				
Written informed consent for genomic substudy		X																				
Demographic data		X																				
Verification of inclusion /exclusion criteria		X	X																			
Call or enter IRT to register the visit		X			X		X					X		X							X	
Call or enter IRT/ Randomization			X							X												
Withdrawal criteria			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
General medical/ procedures history		X																				
Prior and concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medical procedures			X		X		X		X	X		X		X		X	X	X	X	X	X	X
Vital signs[f]		X	X		X		X		X	X		X		X		X	X	X	X	X	X	X

Table 5.1: Schedule of assessments

Assessments	Screening	Treatment Period													Observation Period[a]						UV
		Dosing Period 1							Dosing Period 2												
Visit	1	2 BL	3[b]	4	5[b]	6	7[b]	8	9	10[b]	11	12[b]	13	14[b]	15	16	17	18	19	20 FV/PEOT[c]	
Day	-28 to -1	1	2	8[d] (± 2 days)	9	15[d] (± 2 days)	16	22[d] (± 2 days)	29[d] (± 2 days)	30	36[d] (± 2 days)	37	43[d] (± 2 days)	44	50	57	64	78	92	99 (± 2 days)	
															(± 2 days)						
Body weight, height[g]	X								X											X	
Recording of AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Full physical examination	X																			X	
Brief physical examination		X							X												
Full neurological examination[h]	X																			X	
Brief neurological examination		X							X												
Query for suicidality[i]	X	X		X		X		X	X		X		X		X	X	X	X	X	X	X
12-lead ECG[j]	X	X		X		X		X	X		X		X		X			X		X	
Laboratory tests (hematology, chemistry, urinalysis)	X	X		X		X		X	X		X		X		X	X		X		X	
Serology testing for HIV, Hepatitis B, and Hepatitis C	X																				
IGRA tuberculosis test[k]	X																				
Tuberculosis Signs and Symptoms questionnaire	X																			X	

Table 5.1: Schedule of assessments

Assessments	Screening		Treatment Period												Observation Period[a]						UV
			Dosing Period 1							Dosing Period 2											
	Visit	1	2 BL	3[b]	4	5[b]	6	7[b]	8	9	10[b]	11	12[b]	13	14[b]	15	16	17	18	19	20 FV/PEOT[c]	
	Day	-28 to -1	1	2	8[d] (± 2 days)	9	15[d] (± 2 days)	16	22[d] (± 2 days)	29[d] (± 2 days)	30	36[d] (± 2 days)	37	43[d] (± 2 days)	44	50	57	64	78	92	99 (± 2 days)	
																(± 2 days)						
Blood sampling for PK of UCB7665[l]			X		X		X		X	X		X		X		X						
Blood sampling for DNA analysis sub-study[m]			X						X					X								
Blood sampling for RNA analysis sub-study[m]			X		X				X					X							X	
Serum pregnancy test		X																				
Urine pregnancy test[n]			X		X		X		X	X		X		X		X	X	X	X	X	X	
Administration of IMP			X		X		X			X		X		X								
[redacted]			X		X		X		X	X		X		X		X	X	X	X	X	X	
Serum complement (C3,C4) and plasma complement levels (C3a and C5a)			X		X		X		X	X		X		X		X	X				X	
Immunoglobulins (total IgG and IgG subclasses)		X	X		X		X		X	X		X		X		X	X	X	X	X	X	
IgA, IgM, IgE			X						X	X		X		X		X	X				X	
MG-specific autoantibodies			X		X					X		X				X					X	

Table 5.1: Schedule of assessments

Assessments	Screening		Treatment Period												Observation Period[a]						UV
			Dosing Period 1							Dosing Period 2											
	Visit	1	2 BL	3[b]	4	5[b]	6	7[b]	8	9	10[b]	11	12[b]	13	14[b]	15	16	17	18	19	20 FV/PEOT[c]	
	Day	-28 to -1	1	2	8[d] (± 2 days)	9	15[d] (± 2 days)	16	22[d] (± 2 days)	29[d] (± 2 days)	30	36[d] (± 2 days)	37	43[d] (± 2 days)	44	50	57	64	78	92	99 (± 2 days)	
																(± 2 days)						
Blood sampling for exploratory biomarker analysis			X		X		X		X	X		X		X				X		X		
Blood sampling for safety biomarker analysis: may include but not limited to [redacted]			X		X		X		X	X		X		X		X	X	X	X	X	X	
BAFF analysis			X		X		X		X	X		X		X				X		X		
Cytokines[p]			X		X		X		X	X		X		X		X	X	X	X	X	X	X
Vaccination-specific antibody titers [redacted]		X																			X	
MG-composite scale		X	X		X		X		X	X		X		X		X	X	X	X	X	X	
QMG scale[q]		X	X		X		X		X	X		X		X		X	X		X		X	
Muscle weakness severity and fatigability scale			X		X		X		X	X		X		X		X	X	X	X	X	X	
Fatigue scale			X		X		X		X	X		X		X		X	X	X	X	X	X	
MGADL scale			X							X						X		X			X	

Table 5.1: Schedule of assessments

Assessments	Screening		Treatment Period													Observation Period[a]						UV
			Dosing Period 1							Dosing Period 2												
	Visit	1	2 BL	3[b]	4	5[b]	6	7[b]	8	9	10[b]	11	12[b]	13	14[b]	15	16	17	18	19	20 FV/PEOT[c]	
	Day	-28 to -1	1	2	8[d] (± 2 days)	9	15[d] (± 2 days)	16	22[d] (± 2 days)	29[d] (± 2 days)	30	36[d] (± 2 days)	37	43[d] (± 2 days)	44	50	57	64	78	92	99 (± 2 days)	
																(± 2 days)						
MGFA classification		X	X							X											X	
SFEMG measurement[r]			X							X												
Headache questionnaire[s]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Stool sample assessment[t]			X		X		X		X	X		X		X		X	X	X	X	X	X	X
Subject exit interview																					X	

AE=adverse event; BAFF=B-cell activating factor; BL=Baseline; BP=blood pressure; CSF=cerebrospinal fluid; CT=computed tomography; DNA=deoxyribonucleic acid; ECG=electrocardiogram; FV=Final Visit; GI=gastrointestinal; HIV=human immunodeficiency virus; IgA=immunoglobulin A; IgE=immunoglobulin E; IgG=immunoglobulin G; IGRA= interferon-gamma release assay; IgM=immunoglobulin M; IMP=investigational medicinal product; IRT=interactive response technology; LP=lumbar puncture; MG=myasthenia gravis; MGADL=myasthenia gravis-Activities of Daily Living; MGFA=Myasthenia Gravis Foundation of America; MRI=magnetic resonance imaging; PEOT=premature end of treatment; PK=pharmacokinetics; PR=pulse rate; RNA=ribonucleic acid; QMG=Quantitative Myasthenia Gravis; [redacted] SFEMG=single fiber electromyogram; TB=tuberculosis; UV=Unscheduled Visit

[a] Subjects will return to the clinic/hospital for Visits 15, 16, 18, and 20; for Visits 17 and 19 subjects will either return to the clinic/hospital, or, if possible and agreed by both the investigator and subject, have home visits conducted by certified healthcare professionals.

[b] This visit is a telephone contact 24 hours post-IMP dose start.

[c] Subjects who withdraw early will be encouraged to complete the PEOT Visit plus the FV (approximately 8 weeks after the final study drug administration).

[d] A visit window of ±2 days is allowed for the dosing visits. The visit window of ±2 days is relative to the first dosing visit date. However, there should be a minimum interval of 5 days and maximum interval of 9 days as compared to the previous dose.

[e] Includes consent for SFEMG for the subjects consenting to this measurement at the participating sites. Additional informed consent is needed for participation in the exploratory genomic substudy.

[f] Systolic and diastolic BP, pulse rate, temperature, and respiratory rate. On dosing days, vital signs will be measured prior to IMP administration, 15 minutes after the start of the infusion, at the end of the infusion, 2 hours after the end of infusion and 4 hours after the end of the infusion. At nondosing visits, vital signs need only be taken once during the visit.

[g] Body weight at Screening and at Visit 9 will be used for calculation of dose; height will be assessed only at Screening.

[h] In addition to Screening and the FV, a full neurological examination should be performed for any subject who experiences severe headache.

[i] A query for suicidal ideation will be asked by Investigator at each clinical visit (including Visit 17 or Visit 19 when it is conducted at the clinic). A full C SSRS assessment will be performed only when subject has a positive response to the suicidal ideation query. If a subject has active suicidal ideation as confirmed by the answer 'Yes' to Question 4 or Question 5 of the C SSRS assessments, the subject will be excluded or withdrawn from the study and immediately referred to a Mental Healthcare Professional

[j] ECGs will be read by a central reader.

[k] The IGRA test will be performed in a central laboratory. Subject should not be dosed until IGRA result is available and negative.

[l] Pre- and postdose at Visits 2, 4, 6, 9, 11, and 13; postdose samples are to be taken 4 hours after the infusion has ended.

[m] Blood sample to be taken prior to dosing of IMP.

[n] Urine pregnancy test will be performed using a dipstick test; a positive urine pregnancy test must be confirmed using a serum pregnancy test.

[p] Sampling for exploratory safety biomarkers at Baseline (Visit 2) and 4 hours post dosing (Visit 2) for all subjects. During follow up only in subjects with severe headache and/or moderate to severe GI disturbances.

[q] Sampling at Baseline for all subjects and subsequently only in subjects with infusion reaction.

[s] Subjects must be off pyridostigmine (or any [redacted] inhibitor medication) from midnight before testing when medically safe to do so to standardize testing, but if not medically appropriate, then the treatment can be continued but the testing should be performed as best as possible at the same timeframe post last any [redacted] inhibitor dosing for each evaluation during the study.

[t] For subjects consenting to this measurement at the participating sites; subjects should not take pyridostigmine from midnight before testing when medically safe to do so to standardize testing, but if not medically appropriate, then the treatment can be continued but the testing should be performed as best as possible at the same timeframe post last [redacted] inhibitor dosing for each evaluation during the study. If pyridostigmine is taken, the time must be documented.

[u] This assessment is applicable only to subjects experiencing severe headaches and will be performed 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). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator.

[v] Stool collection and analysis will be performed for subjects reporting moderate or severe diarrhea. The frequency of stool sampling will be as clinically indicated in the opinion of the investigator. Analysis of stool samples will be performed locally.

Has been changed to:

Table 18.1: Schedule of assessments

Assessments	Screening		Treatment Period													Observation Period[a]						UV
			Dosing Period 1							Dosing Period 2												
	Visit	1	2 BL	3[b]	4	5[b]	6	7[b]	8	9	10[b]	11	12[b]	13	14[b]	15	16	17	18	19	20 FV/PEOT[c]	
	Day	-28 to -1	1	2	8[d] (± 2 days)	9	15[d] (± 2 days)	16	22[d] (± 2 days)	29[d] (± 2 days)	30	36[d] (± 2 days)	37	43[d] (± 2 days)	44	50	57	64	78	92	99 (± 2 days)	
																(± 2 days)						
Written informed consent[e]		X																				
Written informed consent for genomic substudy		X																				
Demographic data		X																				
Verification of inclusion /exclusion criteria		X	X																			
Call or enter IRT to register the visit		X			X		X					X		X							X	
Call or enter IRT/ Randomization			X							X												
Withdrawal criteria			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
General medical/ procedures history		X																				
Prior and concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medical procedures			X		X		X		X	X		X		X		X	X	X	X	X	X	X
Vital signs[f]		X	X		X		X		X	X		X		X		X	X	X	X	X	X	X
Body weight, height[g]		X								X											X	

Table 18.1: Schedule of assessments

Assessments	Screening		Treatment Period													Observation Period[a]						UV
			Dosing Period 1							Dosing Period 2												
	Visit	1	2 BL	3[b]	4	5[b]	6	7[b]	8	9	10[b]	11	12[b]	13	14[b]	15	16	17	18	19	20 FV/PEOT[c]	
	Day	-28 to -1	1	2	8[d] (± 2 days)	9	15[d] (± 2 days)	16	22[d] (± 2 days)	29[d] (± 2 days)	30	36[d] (± 2 days)	37	43[d] (± 2 days)	44	50	57	64	78	92	99 (± 2 days)	
																(± 2 days)						
Recording of AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Full physical examination		X																			X	
Brief physical examination			X							X												
Full neurological examination[h]		X																			X	
Brief neurological examination			X							X												
Query for suicidality[i]		X	X		X		X		X	X		X		X		X	X	X	X	X	X	X
12-lead ECG[j]		X	X		X		X		X	X		X		X		X			X		X	
Laboratory tests (hematology, chemistry, urinalysis)		X	X		X		X		X	X		X		X		X	X		X		X	
Serology testing for HIV, Hepatitis B, and Hepatitis C		X																				
IGRA tuberculosis test[k]		X																				
Tuberculosis Signs and Symptoms questionnaire		X																			X	
Blood sampling for PK of UCB7665[l]			X		X		X		X	X		X		X		X						

Table 18.1: Schedule of assessments

Assessments	Screening		Treatment Period												Observation Period[a]						UV
			Dosing Period 1							Dosing Period 2											
	Visit	1	2 BL	3[b]	4	5[b]	6	7[b]	8	9	10[b]	11	12[b]	13	14[b]	15	16	17	18	19	20 FV/PEOT[c]	
	Day	-28 to -1	1	2	8[d] (± 2 days)	9	15[d] (± 2 days)	16	22[d] (± 2 days)	29[d] (± 2 days)	30	36[d] (± 2 days)	37	43[d] (± 2 days)	44	50	57	64	78	92	99 (± 2 days)	
																(± 2 days)						
Blood sampling for DNA analysis sub-study[m]			X						X					X								
Blood sampling for RNA analysis sub-study[m]			X		X				X					X							X	
Serum pregnancy test		X																				
Urine pregnancy test[n]			X		X		X		X	X		X		X		X	X	X	X	X	X	
Administration of IMP			X		X		X			X		X		X								
[redacted]			X		X		X		X	X		X		X		X	X	X	X	X	X	
Serum complement (C3,C4) and plasma complement levels (C3a and C5a)[o]			X		X		X			X		X		X							X	
Immunoglobulins (total IgG and IgG subclasses)		X	X		X		X		X	X		X		X		X	X	X	X	X	X	
IgA, IgM, IgE			X						X	X		X		X		X	X				X	
MG-specific autoantibodies			X		X					X		X				X					X	
Blood sampling for exploratory biomarker analysis			X		X		X		X	X		X		X				X		X		
Blood sampling for			X		X		X		X	X		X		X		X	X	X	X	X	X	

Table 18.1: Schedule of assessments

Assessments	Screening		Treatment Period												Observation Period[a]						UV
			Dosing Period 1							Dosing Period 2											
	Visit	1	2 BL	3[b]	4	5[b]	6	7[b]	8	9	10[b]	11	12[b]	13	14[b]	15	16	17	18	19	20 FV/PEOT[c]	
	Day	-28 to -1	1	2	8[d] (± 2 days)	9	15[d] (± 2 days)	16	22[d] (± 2 days)	29[d] (± 2 days)	30	36[d] (± 2 days)	37	43[d] (± 2 days)	44	50	57	64	78	92	99 (± 2 days)	
safety biomarker analysis: may [redacted]																	(± 2 days)					
BAFF analysis			X		X		X		X	X		X		X				X		X		
Cytokines[q]			X				X			X				X							X	X
Vaccination-specific antibody titers [redacted]		X																			X	
MG-composite scale[r]		X	X		X		X		X	X		X		X		X	X	X	X	X	X	
QMG scale[s]		X	X		X		X		X	X		X		X		X	X		X		X	
Muscle weakness severity and fatigability scale			X		X		X		X	X		X		X		X	X	X	X	X	X	
Fatigue scale			X		X		X		X	X		X		X		X	X	X	X	X	X	
MGADL scale			X							X						X		X			X	
MGII			X				X			X				X			X		X		X	
MGFA classification		X	X							X											X	
Jitter (SFEMG)			X							X												

Table 18.1: Schedule of assessments

Assessments	Screening		Treatment Period													Observation Period[a]						UV
			Dosing Period 1							Dosing Period 2												
	Visit	1	2 BL	3[b]	4	5[b]	6	7[b]	8	9	10[b]	11	12[b]	13	14[b]	15	16	17	18	19	20 FV/PEOT[c]	
	Day	-28 to -1	1	2	8[d] (± 2 days)	9	15[d] (± 2 days)	16	22[d] (± 2 days)	29[d] (± 2 days)	30	36[d] (± 2 days)	37	43[d] (± 2 days)	44	50	57	64	78	92	99 (± 2 days)	
																(± 2 days)						
measurement[t]																						
Headache questionnaire[u]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Stool sample assessment[v]			X		X		X		X	X		X		X		X	X	X	X	X	X	X
Subject exit interview																					X	

AE=adverse event; BAFF=B-cell activating factor; BL=Baseline; BP=blood pressure; CSF=cerebrospinal fluid; CT=computed tomography; DNA=deoxyribonucleic acid; ECG=electrocardiogram; FV=Final Visit; GI=gastrointestinal; HIV=human immunodeficiency virus; IgA=immunoglobulin A; IgE=immunoglobulin E; IgG=immunoglobulin G; IGRA= interferon-gamma release assay; IgM=immunoglobulin M; IMP=investigational medicinal product; IRT=interactive response technology; LP=lumbar puncture; MG=myasthenia gravis; MGADL=myasthenia gravis-Activities of Daily Living; MGFA=Myasthenia Gravis Foundation of America; MRI=magnetic resonance imaging; PEOT=premature end of treatment; PK=pharmacokinetics; PR=pulse rate; RNA=ribonucleic acid; QMG=Quantitative Myasthenia Gravis; [redacted] SFEMG=single fiber electromyogram; TB=tuberculosis; UV=Unscheduled Visit

[a] Subjects will return to the clinic/hospital for Visits 15, 16, 18, and 20; for Visits 17 and 19 subjects will either return to the clinic/hospital, or, if possible and agreed by both the investigator and subject, have home visits conducted by certified healthcare professionals.

[b] This visit is a telephone contact 24 hours post-IMP dose start.

[c] Subjects who withdraw early will be encouraged to complete the PEOT Visit plus the FV (approximately 8 weeks after the final study drug administration).

[d] A visit window of ±2 days is allowed for the dosing visits. The visit window of ±2 days is relative to the first dosing visit date. However, there should be a minimum interval of 5 days and maximum interval of 9 days as compared to the previous dose.

[e] Includes consent for jitter (SFEMG) for the subjects consenting to this measurement at the participating sites. Additional informed consent is needed for participation in the exploratory genomic substudy.

[f] Systolic and diastolic BP, pulse rate, temperature, and respiratory rate. On dosing days, vital signs will be measured prior to IMP administration, 15 minutes after the start of the infusion, at the end of the infusion, 2 hours after the end of infusion and 4 hours after the end of the infusion. At nondosing visits, vital signs need only be taken once during the visit.

[g] Body weight at Screening and at Visit 9 will be used for calculation of dose; height will be assessed only at Screening.

[h] In addition to Screening and the FV, a full neurological examination should be performed for any subject who experiences severe headache.

[i] A query for suicidal ideation will be asked by Investigator at each clinical visit (including Visit 17 or Visit 19 when it is conducted at the clinic). 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. If a subject has active suicidal ideation as confirmed by the answer 'Yes' to Question 4 or Question 5 of the C-SSRS assessments, the subject will be excluded or withdrawn from the study and immediately referred to a Mental Healthcare Professional.

[j] ECGs will be read by a central reader.

[k] The IGRA test will be performed in a central laboratory. Subject should not be dosed until IGRA result is available and negative.

[l] Pre- and postdose at Visits 2, 4, 6, 9, 11, and 13; postdose samples are to be taken 4 hours after the infusion has ended.

[m] Blood sample to be taken prior to dosing of IMP.

[n] Urine pregnancy test will be performed using a dipstick test; a positive urine pregnancy test must be confirmed using a serum pregnancy test.

[o] Sampling will be performed predose at Visit 2 and 4 hours postdose at Visits 2, 4, 6, 9, 11 and 13. A sample will be obtained at Visit 20.

[p] Sampling for exploratory safety biomarkers at Baseline (Visit 2) and 4 hours post dosing (Visit 2) for all subjects. During follow up only in subjects with severe headache and/or moderate to severe GI disturbances.

[q] Sampling will be performed pre- and 4 hours postdose at Visits 2, 6, 9 and 13. A sample will be obtained at Visit 20. Samples will be obtained at Visits 4 and 11 for subjects with an infusion reaction.

[r] This assessment will be performed at the clinic/hospital. If the subject has a home visit with certified health professionals at Visit 17 and Visit 19, this assessment will not be performed.

[s] Subjects should not take pyridostigmine (or any [redacted] medication) from midnight before testing when medically safe to do so to standardize testing, but if not medically appropriate, then the treatment can be continued but the testing should be performed as best as possible at the same timeframe post last any [redacted] inhibitor dosing for each evaluation during the study.

[u] This assessment is applicable only to subjects experiencing severe headaches and will be performed 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). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator.

[v] Stool collection and analysis will be performed for subjects reporting moderate or severe diarrhea. The frequency of stool sampling will be as clinically indicated in the opinion of the investigator. Analysis of stool samples will be performed locally.

Change #6

6.1 Inclusion Criteria

4. Subject would currently be considered for treatment with immunological therapy such as IVIG/PLEX by the investigator.
5. Subject has a well-documented presence (current or historical) evidence in his/her medical history or at Screening of detectable autoantibodies ([redacted]).

Has been changed to:

4. Subject would currently be considered for treatment with immunological therapy (eg IVIG/PLEX) by the investigator.
5. Subject has a well-documented record of autoantibodies against [redacted] prior to Visit 1 (Screening).

Change #7

6.2.2 Exclusion criteria related to concomitant medications/procedures

30. Subject had a thymectomy in the past 6 months, a history of thymoma World Health Organization grade B2 or B3, or Masaoka grade III or IV, or history of a thymoma requiring chemotherapy and/or radiotherapy.

Has been changed to:

30. Subject had a thymectomy in the past 6 month or a thymoma at any time that required chemotherapy and/or radiotherapy.

Change #8

6.4 Withdrawal Criteria

Changes to criterions #1 and #5.

Subjects MUST be withdrawn from IMP if any of the following events occur:

1. Subject develops an illness or has a change in health status that would interfere with his/her continued participation, including but not limited to:
   - Subject has a serious infective episode requiring hospitalization or iv antibiotic therapy (including but not limited to bacteremia or sepsis, bacterial meningitis, osteomyelitis or septic arthritis, bacterial pneumonia, or visceral abscess).
   - Subject experiences a severe adverse event (AE) of GI disturbance or headache which is considered related to the IMP in the opinion of the investigator.
5. Subject received IVIg or PLEX during the Treatment Period.

Has been changed to:

Subjects MUST discontinue IMP if any of the following events occur:

1. Subject develops an illness or has a change in health status that would interfere with his/her continued participation, including but not limited to:
   - Subject has a serious infective episode requiring hospitalization or iv antibiotic therapy (including but not limited to bacteremia or sepsis, bacterial meningitis, osteomyelitis or septic arthritis, bacterial pneumonia, or visceral abscess).
   - Subject experiences a severe adverse event (AE) of GI disturbance or severe headache which is considered related to the IMP in the opinion of the investigator.
5. Subject received prohibited concomitant medications (as defined in Section 7.8.2 of this protocol) during the Treatment Period.

Change #9

7.8.1 Permitted concomitant medications

Table 7.1 lists the concomitant medications that are permitted during the course of the study at a stable dose.

Table 7.1: Permitted concomitant treatments

Permitted Medications	Dose	Comment
Oral Corticosteroids (eg, prednisolone)	-	[redacted]
Methotrexate	≤30mg/week	
Mycophenolate mofetil	≤3g/day	
Cyclosporin	≤5mg/day	
Azathioprine	≤3mg/kg/day	
Cholinesterase inhibitors	≤600mg Pyridostigmine/day	
Tacrolimus	3mg/day	

Has been changed to:

Table 7.1 lists the concomitant medications that are permitted during the course of the study at a stable dose.

Table 7.1: Permitted concomitant treatments

Permitted Medications	Dose	Comment
Oral Corticosteroids (eg, prednisolone)	-	[redacted]
Methotrexate	≤30mg/week	
Mycophenolate mofetil	≤3g/day	
Cyclosporin[a]	≤5mg/kg/day for unmodified ≤4mg/kg/day for modified (microemulsion)	
Azathioprine	≤3mg/kg/day	
Cholinesterase inhibitors	≤600mg Pyridostigmine/day	
Tacrolimus[b]	≤5mg/day	

[a] Doses higher than listed are permissible if trough level is ≤300ng/L.
[b] If the total daily weight-based dose is >5mg, then a plasma trough level should be checked to ensure subject is not above the recommended therapeutic range.

Change #10

7.8.2 Prohibited concomitant treatments (medications and therapies)

- Medications which could interfere with the function of the NMJ (and which therefore could impair subjects with MG), such as, but not limited to, the following medications. For a more detailed list please refer to the Study Procedures Manual.

Has been changed to:

- Medications which could interfere with the function of the NMJ (and which therefore could impair subjects with MG), such as, but not limited to, the following medications. For a more detailed list please refer to the MGFA medication list (http://www.myasthenia.org/LivingwithMG/DrugstoAvoid.aspx).

Change #11

9.3 Patient-reported outcomes

Subjects will complete 3 patient-reported outcomes (PROs) and participate in 1 subject exit interview as per time points mentioned in the schedule of study assessments in Section 5.2. Study personnel other than the treating physician should administer the PROs. The PROs should be completed by the subject themselves in a quiet place.

The PROs and the subject exit interview should be completed in the following order: MG muscle weakness and fatigability, Fatigue, and MGADL, followed by the subject exit interview (which will be performed only at the FV). The PROs should only be checked for completeness. On dosing days, the PROs will be completed prior to dosing

Has been changed to:

Subjects will complete 4 patient-reported outcomes (PROs) and participate in 1 subject exit interview as per time points mentioned in the schedule of study assessments in Section 5.2. Study personnel other than the treating physician should administer the PROs. The PROs should be completed by the subject themselves in a quiet place.

The PROs and the subject exit interview should be completed in the following order: MG muscle weakness and fatigability, Fatigue, MGADL and MGII, followed by the subject exit interview (which will be performed only at the FV). The PROs should only be checked for completeness. On dosing days, the PROs will be completed prior to dosing.

Change #12

Additional subsection:

9.3.4 Myasthenia Gravis Index Impairment

The MGII is a measure of disease severity based on the signs and symptoms of Myasthenia Gravis patients (Appendix 18.6). It was developed using a patient-centered approach and following current guidelines for outcome measure development, incorporating patient input throughout the different development phases (Barnett et al, 2014, Barnett et al, 2016). The MGII has 22 patient-reported and 6 examination items, and scores are presented as a sum of all items for a total score but also as an ocular and generalized sub-score.

The MGII has shown construct validity and reliability in an outpatient setting. It has less floor effect compared to other commonly used outcome measures, and it can effectively discriminate among patients with different degrees of severity (Barnett et al, 2016). Finally, the MGII is sensitive to detect clinical change after interventions, and most importantly it can detect patient-meaningful change. Additionally, the MGII showed more relative efficiency than the QMGS, MGC and MG-ADL to detect change in short-term interventions for Myasthenia. Estimates for the minimal important difference were developed.

Change #13

9.5 Single Fiber Electromyography

At participating sites, subjects consenting to SFEMG measurement should not take pyridostigmine from midnight before testing when medically safe to do so to standardize testing, but if not medically appropriate, then the treatment can be continued but the testing should be

performed as best as possible at the same timeframe post last [redacted] inhibitor dosing for each evaluation during the study. If pyridostigmine is taken, the time must be documented. This measurement will be performed by adequately trained and equipped investigators. Via a single fiber needle inserted into a muscle, this investigation permits the recording of the action potentials in individual muscle fibers. This enables the measurement of fiber density and neuromuscular jitter which is a sensitive measurement of transmission across the NMJ) (Sanders, 2014). Jitter can assist in demonstrating MG-associated abnormalities. In well treated MG, the SFEMG displays a more normal profile.

Details of the SFEMG performance will be described in the SFEMG manual.

Has been changed to:

9.5 Jitter (Single Fiber Electromyography)

At participating sites, subjects consenting to jitter (SFEMG) measurement should not take pyridostigmine from midnight before testing when medically safe to do so to standardize testing, but if not medically appropriate, then the treatment can be continued but the testing should be performed as best as possible at the same timeframe post last [redacted] inhibitor dosing for each evaluation during the study. If pyridostigmine is taken, the time must be documented. This measurement will be performed by adequately trained and equipped investigators. Jitter measurements may be performed with a single-fiber EMG (SFEMG) electrode having a side-ported recording surface with a 25µm diameter, or a disposable concentric needle electrode. This enables the measurement of fiber density and neuromuscular jitter (SFEMG) (which is a sensitive measurement of transmission across the NMJ) (Sanders, 2014). Jitter (SFEMG) can assist in demonstrating MG-associated abnormalities. In well treated MG, the jitter (SFEMG) displays a more normal profile.

Details of the jitter (SFEMG) performance will be described in the SFEMG manual Subjects.

Change #14

11.1 Assessment of other immunological variables

- Plasma ADA ([redacted] status (negative/positive) and changes in relative mass units

Has been changed to:

- Plasma ADA ([redacted] status (negative or confirmed positive) and changes in relative mass units for all scheduled assessments or titre for those confirmed positive

Change #15

14.3.2 Other efficacy analyses

The secondary variables and change from Baseline in QMG score, MG-Composite score, MGADL score, muscle weakness severity and fatigability scale score and fatigue scale score, at each assessed post Randomization Visit (during Dosing Period 1 including Visit 9) will also be analyzed utilizing the MMRM approach similarly to the change from Baseline in QMG for the FAS as described in Section 14.3.1.

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

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

Psychometric analyses of the newly developed measures MG muscle weakness severity and fatigability and fatigue scales will be performed blinded from treatment arms. The association between PROs and clinical variables will also be explored, as well as the association between the various PROs. A psychometric analysis of the MG muscle weakness severity and fatigability scale and fatigue scale using Rasch analysis will be performed, but reported separately from the CSR.

Changes in SFEMG will be summarized using descriptive statistics, by treatment group and time point, including changes from Baseline

Has been changed to:

The secondary variables and change from Baseline in QMG score, MG-Composite score, MGADL score, MGII score, muscle weakness severity and fatigability scale score and fatigue scale score, at each assessed post Randomization Visit (during Dosing Period 1 including Visit 9) will also be analyzed utilizing the MMRM approach similarly to the change from Baseline in QMG for the FAS as described in Section 14.3.1.

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

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

Psychometric analyses of the newly developed measures MG muscle weakness severity and fatigability and fatigue scales will be performed blinded from treatment arms. The association between PROs and clinical variables will also be explored, as well as the association between the various PROs. A psychometric analysis of the MG muscle weakness severity and fatigability scale and fatigue scale using Rasch analysis will be performed, but reported separately from the CSR.

Changes in MCD of the IPI, and normal fiber pairs in jitter (SFEMG) will be summarized using descriptive statistics, by treatment group and time point, including changes from Baseline. A reduction in MCD of ≥9µs in jitter (SFEMG) studies will also be summarized using descriptive statistics, by treatment group and time point, including changes from Baseline.

Change #16

14.4.4 Immunological variables

All immunological variables including concentrations of Igs (IgA, IgE, and IgM), serum complement levels (C3 and C4) and plasma complement levels (C3a and C5a), and serum BAFF will be listed and summarized, using descriptive statistics, by Treatment Group and visit including changes from Baseline. Concentrations of cytokines will be listed and summarized if

there are sufficient data. Figures of mean values and changes from Baseline of immunological variables may be presented, and will be described in the SAP.

The [redacted] status (negative/positive) and changes in relative mass units from Baseline will be listed and summarized by treatment group.

The [redacted] antibodies will be listed and summarized by treatment group.

Has been changed to:

All immunological variables including concentrations of Igs (IgA, IgE, and IgM), serum complement levels (C3 and C4) and plasma complement levels (C3a and C5a), and serum BAFF will be listed and summarized, using descriptive statistics, by Treatment Group and visit including changes from Baseline. Concentrations of cytokines will be listed and summarized if there are sufficient data. Figures of mean values and changes from Baseline of immunological variables may be presented, and will be described in the SAP.

The [redacted] status (negative or confirmed positive) and either changes in relative mass units from Baseline for all scheduled assessments or titres for those confirmed positive will be listed and summarized by treatment group.

The [redacted] antibodies will be listed and summarized by treatment group.

Change #17

Additional in-text references:

17 References

Barnett C, Bril V, Kapral M, Kulkarni A, Davis AM. A conceptual framework for evaluating impairments in myasthenia gravis. PLos One. 2014;9(5).

Barnett C, Bril V, Kapral M, Kulkarni A, Davis AM Development and validation of the Myasthenia Gravis Impairment Index. Neurology. 2016; 87(9): 879–886.

19 DECLARATION AND SIGNATURE OF INVESTIGATOR

I confirm that I have carefully read and understood this protocol and agree to conduct this clinical study as outlined in this protocol, according to current Good Clinical Practice and local laws and requirements.

I will ensure that all subinvestigators and other staff members read and understand all aspects of this protocol.

I have received and read all study-related information provided to me.

The objectives and content of this protocol as well as the results deriving from it will be treated confidentially, and will not be made available to third parties without prior authorization by UCB.

All rights of publication of the results reside with UCB, unless other agreements were made in a separate contract.

Investigator:

Printed name	Date/Signature

20 SPONSOR DECLARATION

I confirm that I have carefully read and understand this protocol and agree to conduct this clinical study as outlined in this protocol and according to current Good Clinical Practice.

mg0002-protocol-amend-#2

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Approval Date (dd-mon-yyyy (HH:mm))
[redacted]	Clinical Approval	20-Sep-2017 10:00 GMT+02
[redacted]	Clinical Approval	20-Sep-2017 14:01 GMT+02
[redacted]	Clinical Approval	21-Sep-2017 05:27 GMT+02