A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING EFFICACY AND SAFETY OF ROZANOLIXIZUMAB IN ADULT PATIENTS WITH GENERALIZED MYASTHENIA GRAVIS

PROTOCOL MG0003 AMENDMENT 4

PHASE 3

Short title:

A Phase 3 study evaluating the safety and efficacy of rozanolixizumab in patients with myasthenia gravis.

Sponsor:

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Regulatory agency identifying number(s):

Eudra CT Number:	2019-000968-18
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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History		
Document	**Date**	**Type of amendment**
Protocol Amendment 4	23 Feb 2021	Substantial
Protocol Amendment 3	29 Jul 2020	Substantial
Protocol Amendment 2[a]	04 Mar 2020	Substantial
Protocol Amendment 1	30 Oct 2019	Substantial
Original Protocol	22 Feb 2019	Not applicable

[a] Protocol amendment 2 was an internally approved document, which was not implemented at the study sites or submitted to the regulatory authorities. Protocol amendment 3 included changes related to coronavirus disease 2019 (COVID-19) and incorporates protocol amendment 2 (Section 10.11).

Amendment 4 (23 Feb 2021)

Overall Rationale for the Amendment

The primary reasons for this protocol amendment are to 1) update the requirement for study participants receiving rescue therapy to be follow up through to the end of the Observation Period; 2) update the criteria for discontinuation due to other adverse events or medical conditions; and 3) remove the participant exit interview. Additional updates have been incorporated to provide further clarity on the protocol and/or to correct errors.

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Section # and Name	Description of Change	Brief Rationale
Global	Minor administrative, formatting, and typographical changes have been made.	Updated to provide clarity and remain consistent with remainder of protocol.
1.1 Synopsis, Objectives and Endpoints 3 Objectives and Endpoints	An additional other efficacy endpoint specific to change from baseline in MD-ADL (excluding ocular items) has been included. Additional wording "any time up to and including" has been included for the other efficacy endpoint specific to minimal symptom expression. For other efficacy endpoints specific to MG Impairment Index, “Observation Period” has been removed.	Updated as it was an omission from the previous protocol amendment. Updated as it was an omission from the previous protocol amendment. This PRO will not be assessed during the Observation Period.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, Objectives and Endpoints 3 Objectives and Endpoints	Footnote a has been updated to remove "serious" as a level of severity for the triggered AEs.	Updated to be consistent across the Phase 3 rozanolixizumab clinical program.
1.1 Synopsis 4.1 Overall Design	The following wording in reference to participants opting to receive rescue medication has been updated to include: "complete any remaining visits in the Observation Period and" Additionally, wording in reference to follow-up instructions after completion of rescue treatment has been removed.	Updated to provide clarity and remain consistent with the study design.
1.2 Schema	Study schematic updated to remove the following wording: "+ additional bi-weekly visits up to 8 weeks after last IVIg/PEX session."	Updated to remain consistent with the study design.
1.3 Schedule of activities	For the following activity, "Call or enter IRT to register the visit", Visits 2 (Baseline), 3, 7, 11, 12, and 13 have been removed. Footnote l has been updated to remove "serious" as a level of severity for the triggered AEs, and "at Visits 4, 5, 6, 8 and 9".	Updated to correct an error from the previous protocol amendment. Updated to be consistent across the Phase 3 rozanolixizumab clinical program.
2.3 Benefit/Risk Assessment	Wording on potential risks associated with administration of rozanolixizumab has been updated.	Updated to remove events that are no longer considered a potential risk across the Phase 3 rozanolixizumab clinical program.
5.1 Inclusion Criteria	#5a: The MG-ADL score was updated to replace > with ≥. #8b (now 8c): Wording on female study participants of childbearing potential and use of a highly effective method of birth control has been removed.	Updated to correct an error from the previous protocol amendment. Updated to for clarity and to remove repetitive information.
5.2 Exclusion Criteria	#13a (now 13b): Wording was slightly edited, and the following was removed: "history thereof in past 6 months prior to Visit 1." Table 5-1: A new biologic (inebulizumab) as well the treatment-free period were added.	Updated to be consistent across the Phase 3 rozanolixizumab clinical program.

Section # and Name	Description of Change	Brief Rationale
	#29 (now 29a): Update to replace family history with "current or medical."	
6.5.2 Prohibited concomitant treatments (medications and therapies)	The following concomitant medication was added: Vinca alkaloids (vincristine, vinblastine)	Updated for consistency and to correct an error from the previous protocol amendment.
6.7 Treatment after the End of the Study	The following wording in reference to participants opting to receive rescue medication has been updated to include: "complete any remaining visits in the Observation Period and" Additionally, wording in reference to participants considered for additional treatment with prophylactic antimicrobial therapy has been removed.	Updated to provide clarity and remain consistent with the study design.
7.1.3 Discontinuation due to other adverse events or medical conditions	Criterion #5 was updated to include recurrence severe AE of headache. New criterion (#7) relating to potential drug induced liver injury has been included.	Updated to be consistent across the Phase 3 rozanolixizumab clinical program.
8 Study Assessment and Procedures	The following wording has been removed: "follow study participants who experience symptom worsening during the 8-week observation period and opt to receive IVIg or PEX as rescue therapy."	A specific reason for an unscheduled visit is not required, as it can be conducted at the discretion of the Investigator.
8.1.4.1 MG-Activities of Daily Living	Additional wording specifically stating which items are considered ocular has been included.	Updated to provide clarity in relation to inclusion criteria #5 and Section 8.1.4.1.
8.2.6 Assessment and management of TB and TB risk factors	TB assessment by chest x-ray: Version year has been removed and replaced with "current."	Updated to ensure information related to TB assessment by chest x-ray is aligned with the up-to-date version of the WHO Global Tuberculosis Report.
8.2.6 Assessment and management of TB and TB risk factors	TB assessment by IGRA: New wording on indeterminate IGRA test results and an evaluation by a TB specialist relating to study participant eligibility have been included.	Updated to provide clarity on the requirements for a study participant's eligibility.

Section # and Name	Description of Change	Brief Rationale
8.3.3 Follow-up of AEs and SAEs	Adverse events of special monitoring have been added.	Updated to be consistent across the Phase 3 rozanolixizumab clinical program.
8.3.6 Adverse events of special interest	The definition for Hy's Law has been updated.	Updated to be consistent across the Phase 3 rozanolixizumab clinical program.
8.5 Treatment of Overdose	In relation to #3, autoantibodies have been replaced with "antibodies."	Updated to clarify all antibodies are measured.
8.9 Biomarkers	"Serious" has been removed as a level of severity for an AESM of headache. "Severe" has been added as a level of severity for an AESM of GI disorders.	Updated to be consistent across the Phase 3 rozanolixizumab clinical program.
8.11 Participant exit interview	This section has been removed.	The optional participant exit interview will no longer be conducted.
9.1 Definition of Analysis Sets	The Randomization Set replaces the Full Analysis Set as the primary analysis set for efficacy analyses.	Updated to be consistent with estimands table (Table 9-1).
9.3 Estimands	Wording for handling of intercurrent events due to treatment discontinuation has been updated.	Updated to provide further clarification.
9.3 Estimands, Table 9-1	The PLS (analysis) for the MG-ADL objective (secondary) was updated: difference in proportion has been replace by "odds ratio."	Updated to clarify the population summary being estimated.
10.2 Appendix 2: Clinical laboratory test	The following parameter, glucose, has been updated to include "fasting state, preferred." High-density lipoprotein, total cholesterol and triglycerides have been added.	Updated to clarify the specifics for fasting glucose. Updated to include lipid panel assessments.
10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information	Contraception guidance for male participants: Wording specific to the agreed use of a male condom plus partner use of a contraceptive method with a failure rate of <1% per year has been removed. Table 10-1: Contraception guidance for female participants and	Updated to provide further clarity on the use of contraception during the study.

Section # and Name	Description of Change	Brief Rationale
	vasectomized partner has been updated.	
10.11 Appendix 11: Protocol Amendment History	Details of the previous amendment (protocol amendment 3) have been added.	General update.
10.20 Appendix 20: MG Impairment Index	Current copy of MG Impairment Index has been updated to include a missing page (page containing questions 7 to 12).	Updated to correct an error from the previous protocol amendment.
10.23 Appendix 23: Management of Headache	The following wording has been included: "The questionnaire should be administered via an interview with the study participant."	Updated to provide further clarity on conducting the headache questionnaire.

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
Fax	**Europe and Rest of the World:** +32 2 386 24 21 **US and Canada:** +1 800 880 6949 or +1 866 890 3175
Email	**Global:** DS_ICT@ucb.com (for interventional clinical studies)

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

A Phase 3, randomized, double-blind, placebo-controlled study evaluating efficacy and safety of rozanolixizumab in adult patients with generalized myasthenia gravis.

Short Title:

A Phase 3 study evaluating the safety and efficacy of rozanolixizumab in patients with myasthenia gravis.

Rationale:

Myasthenia gravis (MG) is a serious, sometimes life threatening, debilitating condition associated with numerous symptoms including muscular weakness and fatigue. The major pathophysiology leading to MG is the abnormal production of immunoglobulin (Ig)G autoantibodies directed toward nicotinic acetylcholine receptor (AChR), or muscle-specific kinase (MuSK) protein. Several commonly prescribed treatments act, at least in part, by reducing the quantity of such circulating IgG autoantibodies. While the standard of care for MG involves the utilization of a variety of therapeutic agents including cholinesterase inhibitors, immunomodulators, corticosteroid, biologics, high dose intravenous immunoglobulin (IVIg), plasmapheresis or immunoadsorption, there remains a need for a safe and effective treatment devoid of significant side effects to conveniently treat patients with MG.

By blocking the activity of neonatal Fc receptor (FcRn), rozanolixizumab accelerates the catabolism of antibodies and reduces the serum IgG concentration, including pathogenic IgG in MG patients, thus offering a potentially safe, effective, and convenient alternative to existing treatments. This Phase 3 study will provide the required data to establish the safety and efficacy of rozanolixizumab in anti-AChR or anti-MuSK autoantibody-positive patients with generalized MG who experience moderate to severe symptoms and are being considered for additional treatment with IVIg or plasma exchange (PEX).

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To demonstrate the clinical efficacy of rozanolixizumab in patients with generalized MG	The primary efficacy endpoint is: • Change from Baseline to Day 43 (Visit 10) in MG-activities of daily living (ADL) score The secondary efficacy endpoints are: • MG-ADL responder (≥2.0 points improvement from Baseline) at Day 43 (Visit 10)

	• Change from Baseline to Day 43 (Visit 10) in the MG-Composite (MG-C) score • Change from Baseline to Day 43 (Visit 10) in quantitative myasthenia gravis (QMG) score • Change from Baseline to Day 43 (Visit 10) in the MG Symptoms patient-reported outcome (PRO) 'Muscle Weakness Fatigability' score • Change from Baseline to Day 43 (Visit 10) in the MG Symptoms PRO 'Physical Fatigue' score • Change from Baseline to Day 43 (Visit 10) in the MG Symptoms PRO 'Bulbar Symptoms' score The other efficacy endpoints are: • Use of rescue therapy due to worsening (IVIg, PEX) • Time to first rescue therapy • Time to MG-ADL response (≥2.0 points improvement from Baseline) • Change from Baseline in QMG at each scheduled assessment during Treatment and Observation Periods • QMG responder (≥3.0 points improvement from Baseline) at each scheduled assessment during Treatment and Observation Periods • Change from Baseline in MG-C score at each scheduled assessment during Treatment and Observation Periods • MG-C responder (≥5.0 points improvement from Baseline) at each scheduled assessment during Treatment and Observation Periods • Change from Baseline in MG-ADL at each scheduled assessment during Treatment and Observation Periods

	• MG-ADL responder (≥2.0 points improvement from Baseline) at each scheduled assessment during Treatment and Observation Periods • Change from Baseline in the MG Symptoms PRO 'Muscle Weakness Fatigability' score at each scheduled assessment during Treatment and Observation Periods • Change from Baseline in the MG Symptoms PRO 'Physical Fatigue' score at each scheduled assessment during Treatment and Observation Periods • Change from Baseline in the MG Symptoms PRO 'Bulbar Symptoms' score at each scheduled assessment during Treatment and Observation Periods • Change from Baseline in the MG Symptoms PRO 'Respiratory Symptoms' score at each scheduled assessment during Treatment and Observation Periods • Change from Baseline in the MG Symptoms PRO 'Ocular Symptoms' score at each scheduled assessment during Treatment and Observation Periods • Change from Baseline in Patient Global Impressions of Severity (PGI-S) at each scheduled assessment during the Treatment and Observation Periods • Patient Global Impressions of Change (PGI-C) at each scheduled assessment during Treatment and Observation Periods • Change from Baseline in MG-ADL (excluding ocular items) at each scheduled assessment during Treatment and Observation Periods • Change from Baseline in QMG (excluding ocular items) at each scheduled assessment during Treatment and Observation Periods

	• Change from Baseline in MG-C score (excluding ocular items) at each scheduled assessment during Treatment and Observation Periods • Change from Baseline to Day 43 (Visit 10) in Myasthenia Gravis Quality of Life (MG-QOL) 15r • Change from Baseline to Day 43 (Visit 10) in EuroQol(EQ)-5D-5L • Minimal symptom expression (MG-ADL score of 0 or 1) at any time up to and including Day 43 (Visit 10) • Change from Baseline in MG Impairment Index (MGII) scores at each scheduled assessment during Treatment Period • Change from Baseline in MGII ocular sub-scores at each scheduled assessment during Treatment Period • Change from Baseline in MGII generalized domain sub-scores at each scheduled assessment during Treatment Period
Secondary	
• To assess safety and tolerability of rozanolixizumab in MG patients	The secondary safety endpoints are: • Occurrence of treatment-emergent adverse events (TEAEs) • TEAEs leading to withdrawal of investigational medicinal product (IMP) The other safety endpoints are: • Occurrence of adverse event of special monitoring (AESM) • Vital sign changes from Baseline (systolic and diastolic blood pressure [BP] and pulse rate at each scheduled assessment during Treatment and Observation Periods) • 12-lead electrocardiogram (ECG) change from Baseline at each scheduled

	assessment during Treatment and Observation Periods • Laboratory changes from Baseline at each scheduled assessment during Treatment and Observation Periods (hematology, clinical chemistry, and urinalysis) • Suicidality as measured by the Columbia Suicide Severity Rating Scale (C-SSRS)
Other	
• To assess pharmacokinetic (PK) characteristics of rozanolixizumab	• Plasma concentration of rozanolixizumab at each scheduled assessment during the Treatment and Observation Periods
• To assess the pharmacodynamics (PD) effects of rozanolixizumab on IgG, disease-specific autoantibodies	• Change (absolute and percentage) from Baseline in MG-specific autoantibodies at each scheduled assessment during Treatment and Observation Periods • Change (absolute and percentage) from Baseline in serum total IgG and IgG subclasses concentrations at each scheduled assessment during Treatment and Observation Periods
• To evaluate the emergence and incidence of anti-drug antibody (ADA) and impact on PK and PD	• Anti-drug antibody at each scheduled assessment during the Treatment Period and Observation Periods
• To evaluate the effects of rozanolixizumab on the concentration of total protein, IgM, IgA, and IgE, serum and plasma complement levels and serum cytokines	• Change from Baseline in serum complement levels (C3 and C4) and plasma complement levels (C3a and C5a) at each scheduled assessment during Treatment Period[a] • Change from Baseline in serum cytokines at each scheduled assessment during Treatment Period[a] • Change from Baseline in serum immunoglobulin concentrations (total IgA, IgE, and IgM) at each scheduled assessment during Treatment and Observation Periods

• To assess the effect of rozanolixizumab on tetanus IgG antibodies	• Change from Baseline in anti-tetanus toxoid serum titers at each scheduled assessment during Treatment and Observation Period
• To assess the effect of rozanolixizumab on exploratory biomarkers and protein expression, and explore the relationship between protein, and metabolite biomarkers and cause, progression, and appropriate treatment of MG	• Exploratory biomarkers may be measured to evaluate the effect of rozanolixizumab. • Proteins, and metabolites changes that may be measured to understand the cause, progression, and appropriate treatment of MG

[a] To be performed for study participants with severe headache and/or infusion reaction or hypersensitivity reaction. Other exploratory safety biomarkers may be assessed.

Overall Design

This is a Phase 3 study of rozanolixizumab in anti-AChR or anti-MuSK autoantibody-positive patients with generalized MG who experience moderate to severe symptoms and are being considered for additional treatment such as IVIg or PEX. The primary objective of the study is to demonstrate the clinical efficacy of rozanolixizumab in patients with generalized MG.

Participants have the opportunity to rollover into an OLE study, as described below. The OLE study, MG0004 (52-week chronic treatment) will be replaced by MG0007, which consists of 6-week treatment cycles based on MG worsening. Upon study site approval of MG0007, as well as fulfilment of regulatory requirements, study participants will have the opportunity to rollover directly into MG0007. In the event a study participant has already started MG0004, a minimum treatment duration of 6 visits (if IMP treatment is held for low IgG, study participants missed dose(s) can be counted as part of the total 6 visits for completion of MG0004 and meet eligibility requirements for MG0007) must be completed prior to moving into MG0007. Once the site is active for MG0007, no further participants will enroll in MG0004 and the study will be closed at the site once all eligible study participants have discontinued MG0004 and had the opportunity to rollover into MG0007.

The study is composed of a Screening Period of up to 4 weeks, followed by a 6-week double-blind Treatment Period and a blinded Observation Period of 8 weeks:

1. All study participants who complete the 6-week Treatment Period will roll over into an 8-week Observation Period.
2. All eligible study participants who complete the Observation Period will be invited to be re-randomized into an open-label extension (OLE) study.
3. Study participants who experience disease worsening during the 6-week Treatment Period (eg, an increase of 2 points on the MG-ADL or 3 points on the QMG scale between two consecutive visits) may be considered for rescue therapy (IVIg or PEX) at the discretion of the Investigator.
4. Study participants who need rescue therapy during the 6-week Treatment Period will receive IVIg or PEX and complete any subsequent visit(s). No further infusions of IMP in MG0003

will be administered after initiation of rescue therapy. Once the participant completes the premature end of treatment (PEOT) Visit (Visit 10), he or she will move into the 8-week Observation Period.

5. Study participants who complete the Treatment Period and require initiation of rescue therapy after they start the 8-week Observation Period, may either opt to receive IVIg or PEX or complete the End of Study (EOS) visit and immediately roll over into an OLE study where the participant will receive rozanolixizumab. Study participants who opt to receive IVIg or PEX will complete any remaining visits in the Observation Period and will not be invited to join an OLE study.
6. Study participants who did not complete the 6-week Treatment Period because they needed rescue therapy and require initiation of a second course of rescue therapy while in the 8-week Observation Period can roll over to an OLE study if a minimum of 2 weeks have lapsed since completion of the last IVIg or PEX session. The EOS visit must be completed before enrolling into an OLE study. Alternatively, they can be treated with IVIg or PEX. Study participants who opt to receive IVIg or PEX will complete any remaining visits in the Observation Period and will not be invited to join an OLE study.
7. Study participants who discontinue study medication for any reason other than requiring rescue therapy will not be eligible for enrollment into an OLE study.

Number of Participants

A formal interim analysis will be conducted when approximately [redacted] eligible study participants have been treated and are evaluable for the primary endpoint, ie, approximately [redacted] study participants per dose group. If the study is not stopped for futility after the interim analysis, then depending upon the selection of one, or two, of the doses after the interim analysis and the calculation of conditional power, a further [redacted] eligible study participants will be randomized into the study. Thus, the total sample size of the study could range between [redacted] and [redacted] study participants if the study is not futile (for sample size determination, see Section 9.9).

Treatment Groups and Duration

The maximum duration of the study per study participant will be up to 18 weeks, consisting of a Screening Period (1 to 28 days to account for central laboratory turn-around time), a Treatment Period (6 weeks), and an Observation Period (8 weeks).

Fixed unit doses across body weight tiers and study arms will be employed.

The placebo arm will be 0.9% sodium chloride aqueous solution (physiological saline, preservative free) for subcutaneous (sc) administration.

Two sc treatment arms will assume fixed unit doses stratified on weight tiers as described below:

Treatment Arm 1 (rozanolixizumab) – equivalent to approximately [redacted]

- Bodyweight <50kg: dose to be administered [redacted]
- Bodyweight ≥50kg and <70kg: dose to be administered [redacted]
- Bodyweight ≥70kg and <100kg: dose to be administered [redacted]

- Bodyweight ≥100kg; dose to be administered [redacted]

Treatment Arm 2 (rozanolixizumab) – equivalent to approximately [redacted]

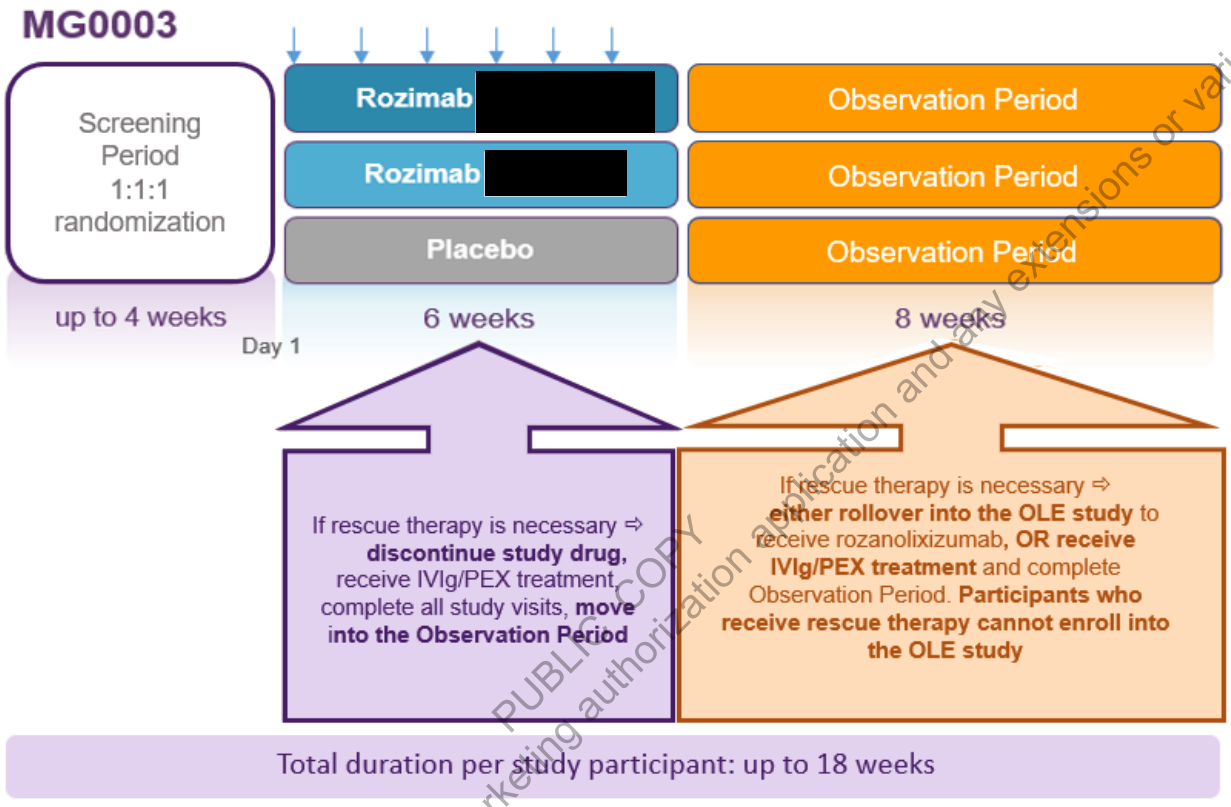
- Bodyweight <50kg: dose to be administered [redacted]
- Bodyweight ≥50kg and <70kg: dose to be administered [redacted]
- Bodyweight ≥70kg and <100kg: dose to be administered [redacted]
- Bodyweight ≥100kg: dose to be administered [redacted]

An independent Data Monitoring Committee (IDMC) will be formed to monitor the ongoing safety and efficacy of the study. Futility and samples size adjustment will also be reviewed and assessed by the IDMC during a formal interim analysis at the end of Stage 1, when [redacted] enrolled study participants are evaluable for the primary endpoint. Approximately 3 periodic data reviews (in addition to the futility analysis mentioned above) will be performed: the first periodic data review will be performed when approximately [redacted] study participants have completed the 6-week Treatment Period; the second periodic data review will be conducted after approximately [redacted] study participants have completed the 6-week Treatment Period (ad hoc as needed); and a third review will be conducted after approximately [redacted] study participants (dependent on the outcome of the interim analysis) have completed the 6-week Treatment Period. The timing of any further data reviews will be decided by the IDMC in conjunction with sponsor. Further details of the IDMC will be provided in a DMC charter.

1.2 Schema

A schematic diagram of the study is provided in Figure 1-1.

Figure 1-1: Study Schematic



IVIg=intravenous immunoglobulin G; OLE=open-label extension; PEX=plasma exchange; Rozimab=rozanolixizumab

The sample size for Stage 1 of the study is [redacted] (approximately [redacted] study participants per arm). Provided the study is not stopped for futility at the end of Stage 1, a further [redacted] study participants will be enrolled (See Section 9.8 for details) and the total sample size for this study will range between [redacted] study participants.

1.3 Schedule of Activities

Procedure	Screening	Treatment Period									Observation Period			
Visit	**V1**	**V2 (BL)**	**V3[a]**	**V4**	**V5**	**V6**	**V7[a]**	**V8**	**V9**	**V10 (EOT or PEOT)**	**V11[b]**	**V12**	**V13[b]**	**V14 (EOS)**
Day (days)[c]	**-28 to -1**	**1**	**3(±1)**	**8(±2)**	**15(±2)**	**22(±2)**	**24(±1)**	**29(±2)**	**36(±2)**	**43(±2)**	**57(±3)**	**71(±4)**	**85(±3)**	**99(±4)**
Written informed consent	X													
Optional PK sub-study consent[d]	X													
Demographic and Baseline[e]	X	X												
Verification of inclusion/exclusion criteria	X	X												
Prior and concomitant medications and medical procedures	X	X		X	X	X		X	X	X	X	X	X	X
General medical history	X													
Psychiatric history/C-SSRS	X													
Query for suicidality[f]		X		X	X	X		X	X	X		X		X
Chest X-ray[g]	X													
IGRA TB test[h]	X													
TB Signs and Symptoms questionnaire	X	X								X				X
12-lead ECG	X	X		X						X				X
Full physical examination	X	X								X		X		X
Brief physical examination				X	X	X		X	X					
Pregnancy test (serum)	X													
Pregnancy test (urine)[i]		X						X						X
Hematology, serum chemistry, urinalysis	X	X		X		X			X	X		X		X

Procedure	Screening	Treatment Period									Observation Period			
Visit	**V1**	**V2 (BL)**	**V3[a]**	**V4**	**V5**	**V6**	**V7[a]**	**V8**	**V9**	**V10 (EOT or PEOT)**	**V11[b]**	**V12**	**V13[b]**	**V14 (EOS)**
Day (days)[c]	**-28 to -1**	**1**	**3(±1)**	**8(±2)**	**15(±2)**	**22(±2)**	**24(±1)**	**29(±2)**	**36(±2)**	**43(±2)**	**57(±3)**	**71(±4)**	**85(±3)**	**99(±4)**
PTT and INR measurements	X	X												X
Serology testing for HIV, Hepatitis B, and Hepatitis C	X													
Anti-tetanus toxoid titer		X								X				X
Vital signs	X	X	X	X	X	X	X	X	X	X		X		X
Call or enter IRT to register the visit	X			X	X	X		X	X	X				X
Call or enter IRT/ Randomization		X												
Study participants identification card assigned		X												
Recording of AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug administration[j]		X		X	X	X		X	X					
Blood sampling for PK[k]		X	X		X		X			X				
Blood sampling for ADA	X	X			X		X			X		X		X
Blood sampling for exploratory safety biomarker analysis[l]		X												
Blood sampling for future exploratory biomarker analysis		X		X										X
Blood sampling for total IgG and IgG subclasses	X	X		X	X	X		X	X	X		X		X
Blood sampling for IgA, IgM, IgE		X								X				X
MG-specific autoantibodies[m]		X			X			X		X		X		X
Serum complement levels (C3,C4) and cytokines[n]		X							X					

Procedure	Screening	Treatment Period									Observation Period			
Visit	**V1**	**V2 (BL)**	**V3[a]**	**V4**	**V5**	**V6**	**V7[a]**	**V8**	**V9**	**V10 (EOT or PEOT)**	**V11[b]**	**V12**	**V13[b]**	**V14 (EOS)**
Day (days)[c]	**-28 to -1**	**1**	**3(±1)**	**8(±2)**	**15(±2)**	**22(±2)**	**24(±1)**	**29(±2)**	**36(±2)**	**43(±2)**	**57(±3)**	**71(±4)**	**85(±3)**	**99(±4)**
Plasma complement levels (C3a and C5a)[n]		X							X					
MGFA classification	X	X								X				X
QMG scale	X	X		X	X	X		X	X	X		X		X
MG-C scale	X	X		X	X	X		X	X	X		X		X
MG-ADL	X	X		X	X	X		X	X	X	X	X	X	X
MG Symptoms PRO	X	X		X	X			X		X		X		X
PGI-S	X	X			X			X				X		X
PGI-C					X			X				X		X
EQ-5D-5L		X								X				
MGII[o]		X								X				
MG-QOL15r		X								X				
Study drug discontinuation criteria				X	X	X		X	X					
Study withdrawal criteria	X	X	X	X	X	X	X	X	X	X	X	X	X	X

AChR=acetylcholine receptor; ADA=anti-drug antibody; AE=adverse event; AESM=adverse events of special monitoring; BL=Baseline; C-SSRS=Columbia Suicide Severity Rating Scale; ECG=electrocardiogram; EQ-5D-5L=EuroQol-5D-5L; EOS=End of Study; EOT=End of Treatment; GI=gastrointestinal; HIV=human immunodeficiency virus; IgA=immunoglobulin A; IgE=immunoglobulin E; IgG=immunoglobulin G; IgM= immunoglobulin M; IGRA=interferon-gamma release assay; IMP=investigational medicinal product; INR=international normalized ratio; IRT=interactive response technology; MG=myasthenia gravis; MG-ADL=myasthenia gravis-Activities of Daily Living; MG-C=Myasthenia Gravis Composite; MGFA=Myasthenia Gravis Foundation of America; MGII=Myasthenia Gravis Impairment Index; MG-QOL15r=Myasthenia Gravis Quality of Life; MuSK=muscle-specific kinase; PEOT=premature end of treatment; PGI-C=Patient Global Impression of Change; PGI-S=Patient Global Impression of Severity; PK=pharmacokinetics; PTT=partial thromboplastin time; PRO=patient-reported outcome; QMG=Quantitative Myasthenia Gravis; TB=tuberculosis; V=Visit

[a] This visit can be scheduled as a home visit, unless the study participant prefers to attend the site.

[b] This visit will be a virtual visit, unless the study participant prefers to attend the site.

[c] A visit window of ±1 day is allowed for V3 and V7. A visit window of ±2 day is allowed for all 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. A visit window of ±3 days is allowed for V11 and V13. A visit window of ±4 days is allowed for V12 and V14.

[d] Refer to Section 1.4.

[e] Only weight will be repeated at Baseline (V2).

[f] A full C-SSRS assessment will be performed only when study participant has a positive response to Question 1 of the suicidal ideation query. If a study participant has active suicidal ideation as confirmed by the answer 'Yes' to Question 4 or Question 5 of the C-SSRS assessments, the study participant will be excluded or withdrawn from the study and immediately referred to a Mental Healthcare Professional.

[g] Chest X-ray should only be performed at sites in countries at high risk for TB (see Section 8.2.6). If chest X-ray is performed, the study participant cannot be dosed until the result is available, and negative.

[h] The IGRA test will be performed in a central laboratory. Study participant should not be dosed in case of any positive IGRA or two indeterminate IGRAs until the study participants has been evaluated by a TB specialist.

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

[j] Study participants must be observed at site postdose for at least 4 hours following the first 2 infusions, and then 2 hours thereafter for subsequent infusions.

[k] At dosing visits, PK samples should be taken predose for all study participants.

[l] Additional exploratory safety samples must be collected 4 hours postdose or as soon as possible before the next IMP in case of AESM of severe headache and/or AESM of severe GI disorders as described in Section 8.3.7.

[m] MuSK and AChR antibodies will be tested at Baseline. All subsequent testing will be limited to the positive antibody.

[n] To be collected predose at V2, and 4 hours postdose at V9. Additional samples should be collected 2 hours and 4 hours postevent or as soon as possible before the next IMP for study participants with severe headache and/or infusion reaction or hypersensitivity reaction.

[o] MGII is optional for all study participants.

1.4 Schedule of Activities (sub-study)

Procedure	Treatment Period		
Visit	**V3a**	**V9a**	**V9b**
Day (days)	**6(±1)**	**38(±1)**	**41(±1)**
Blood sampling for PK[a]	X	X	**X**

PK=pharmacokinetics; V=Visit
The PK samples will be collected at selected sites for study participants who have consented to participate in the sub-study as described in Section 8.6.
[a] Samples can be obtained at home, if appropriate.

2 INTRODUCTION

Rozanolixizumab is a humanized IgG4 monoclonal antibody that is being developed as an inhibitor of the activity of the FcRn for IgG.

By blocking the activity of FcRn, rozanolixizumab accelerates the catabolism of IgG antibodies, including IgG pathogenic autoantibodies. The aim is to reduce the concentration of pathogenic IgG in patients with autoimmune diseases mediated by the action of IgG autoantibodies.

The FcRn recycles IgG and albumin and transports it bidirectionally across epithelial barriers. Recent studies have shown that FcRn rescues both IgG and albumin from intracellular lysosomal degradation by recycling it from the sorting endosome to the cell surface (Roopenian and Akilesh, 2007). FcRn may also mediate transcytosis of IgG to facilitate its distribution within tissues. Rozanolixizumab has been specifically designed to block IgG binding to FcRn without blocking the binding and recycling of albumin.

Rozanolixizumab binds with high affinity to FcRn at both neutral and acidic pH. Immunoglobulin G that is constitutively taken up by pinocytosis into cells fails to bind to FcRn, even at the acidic pH found in the endosome. It is therefore not recycled and is trafficked to the lysosomes for degradation.

Production of pathogenic IgG autoantibodies is the major pathophysiology leading to a number of autoimmune diseases, which include MG, pemphigus vulgaris, immune thrombocytopenia (ITP), Goodpasture's syndrome, neuromyelitis optica, Guillain-Barré Syndrome, and chronic inflammatory demyelinating polyradiculoneuropathy.

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 corticosteroids alone or combined with other immunomodulatory therapy. 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 autoantibodies, including plasmapheresis, immunoadsorption, or high dose IVIg, are being used for primary and secondary therapy of autoimmune diseases. The therapeutic approach of these treatments is thought in part to be based on lowering levels of pathogenic autoantibodies, which represents rational and effective treatment modalities of autoimmune diseases.

Therefore, specific removal of the IgG autoantibodies by FcRn blockade may provide an effective therapeutic option for IgG autoantibody-mediated autoimmune disorders.

More detailed information regarding the nonclinical and clinical development programs for rozanolixizumab, including all completed and ongoing studies, can be found in the latest version of the Investigator's Brochure (IB).

2.1 Study Rationale

Myasthenia gravis is a serious, sometimes life-threatening, debilitating condition associated with numerous symptoms including muscular weakness and fatigue. The major pathophysiology leading to MG is the abnormal production of IgG autoantibodies directed toward nicotinic AChR or MuSK protein. Most available treatments act, at least in part, by reducing the quantity of such circulating IgG autoantibodies. While the standard of care for MG involves a variety of

therapeutic agents including cholinesterase inhibitors, immunomodulators, corticosteroid, biologics interfering with IgG turnover, high dose IVIg, plasmapheresis or immunoadsorption, there remains a need for a safe and effective treatment devoid of significant side effects to conveniently treat patients with MG.

By blocking the activity of FcRn, rozanolixizumab accelerates the catabolism of antibodies and reduces the concentration of pathogenic IgG in MG patients, thus offering a safe, effective, and convenient alternative to existing treatments. This Phase 3 study will provide the required data to establish the safety and efficacy of rozanolixizumab in anti-AChR or anti-MuSK autoantibody-positive patients with generalized MG who experience moderate to severe symptoms and are being considered for additional treatment such as IVIg or PEX.

2.2 Background

To date, rozanolixizumab has been administered to human study participants in the following clinical studies: UP0018, MG0002, TP0001, TP0003, TP0006, CIDP01, CIDP04 and UP0060. UP0018 is a completed first-in-human study (FIH), and MG0002 is a completed Phase 2 study in study participants with generalized MG; and TP0001 is a completed Phase 2 study in study participants with primary ITP. CIPD01 is a Phase 2a study in study participants with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and UP0060 is a Phase 1 study in healthy volunteers.

UP0018 is a completed, FIH study conducted in 49 healthy volunteers. The study evaluated the safety, tolerability, PK, and the PD effect on total IgG levels of single ascending doses of intravenous (iv) and sc rozanolixizumab. Doses of rozanolixizumab [redacted] were administered by both iv and sc routes in 3 cohorts, respectively, as a [redacted] The information from the study is summarized below.

There were no deaths or serious adverse events (SAEs) reported during UP0018. Rozanolixizumab was tolerated with an acceptable safety profile after the single administration of [redacted] iv and [redacted] sc doses. Four TEAEs with a maximum intensity of severe were reported in this study: headache (3 study participants [50.0%]) and back pain (1 study participant [16.7%]); all of which were reported in the rozanolixizumab [redacted] iv group. For sc administration of rozanolixizumab, the most frequently reported TEAEs were headache (5 study participants [27.8%]), back pain and diarrhea (each reported by 3 study participants [16.7%]). No severe adverse events (AEs) were reported following sc administration. The peak and total exposure of rozanolixizumab showed nonlinear increases consistent with target-mediated drug disposition. Dose-dependent statistically significant reductions in levels of total IgG and dose-dependent reductions in levels of IgG subclasses (IgG 1 to 4) were observed after rozanolixizumab was administered by iv or sc routes.

MG0002 is a completed Phase 2a, multicenter, randomized, double-blind, placebo-controlled, treatment-sequence study evaluating the safety, tolerability, and efficacy of rozanolixizumab in study participants with moderate to severe MG. The study included 2 Dosing Periods:

- [redacted]
- [redacted]

[redacted]

The primary efficacy variable was the change from Baseline in QMG score to Visit 9 (Day 29).

Clinically relevant improvements in day-to-day functioning, as measured by change from Baseline to Day 29 in MG-ADL (secondary endpoint), were observed following treatment with rozanolixizumab [redacted] compared with placebo (p=0.036). Numerical differences in favor of rozanolixizumab [redacted] vs placebo were observed in reductions from Baseline in QMG (p=0.221) and MG-C score (p=0.089).

Overall, repeated administrations of rozanolixizumab at dose levels of [redacted] and [redacted] sc have been generally [redacted] and well tolerated, with an acceptable safety profile. No new safety concerns were identified. The TEAE profile was similar between rozanolixizumab and placebo, except for headaches where increased frequency and severity was observed in the rozanolixizumab treated study participants.

TP0001 is a completed Phase 2, multicenter, open-label, multiple-arm study designed to evaluate the safety, tolerability, and efficacy of rozanolixizumab in study participants with primary persistent or chronic ITP. The following dose arms were used in the study:

- Dose Arm 1 ([redacted] study participants): rozanolixizumab [redacted]
- Dose Arm 2 ([redacted] study participants): rozanolixizumab [redacted]
- Dose Arm 3 ([redacted] study participants): rozanolixizumab [redacted]
- Dose Arm 4 ([redacted] study participants): rozanolixizumab [redacted]
- Dose Arm 5 ([redacted] study participants): rozanolixizumab [redacted]

CIDP01 is a Phase 2a, multicenter, randomized, subject-blind, investigator-blind, placebo-controlled, parallel-group study with the primary objective of evaluating the clinical efficacy of rozanolixizumab as a treatment for subjects with CIDP. There are 2 treatment arms in this study:

- Treatment Arm 1: [redacted]
- Treatment Arm 2: [redacted]

UP0060 is a randomized, participant-blind, investigator-blind, placebo-controlled, single dose-ascending, cohort design to compare the safety, tolerability, and PK of rozanolixizumab, and to explore the PD of rozanolixizumab administered by sc infusion in Japanese, Chinese, and Caucasian healthy study participants.

Further details on UP0018, MG0002, TP0001, TP0003, TP0006, CIDP01, CIDP04 and UP0060 may be found in Section 5.1 of the current version of the IB.

2.3 Benefit/Risk Assessment

Generalized myasthenia gravis (gMG) is a rare, debilitating, chronic autoimmune disease driven by, in large part, IgG autoantibodies that target neuromuscular junctions (NMJs). Most current treatment approaches are not targeted treatments to the specific underlying pathology of IgG

autoantibody formation. Rather, they produce a broad cascade of immune suppression, which results in undesirable side effects such as those seen with high-dose chronic steroid use. Many treatments of choice often require invasive, expensive and time-consuming inpatient procedures such as PEX, or intravenous administration of immunoglobulins at a healthcare facility.

Rozanolixizumab represents an innovative, subcutaneous anti-FcRn monoclonal antibody that may provide a novel and specific therapeutic approach for the treatment of patients with gMG. Data shows that rozanolixizumab markedly lowers serum IgG and IgG autoantibody levels in patients with gMG. The completed Phase 2 study MG0002 established supportive evidence of efficacy for the treatment of MG, achieving significant and clinically meaningful improvements to Day 29 in MG-ADL with rozanolixizumab [redacted] compared with placebo (p=0.036). Repeated administrations of rozanolixizumab were generally [redacted] and well tolerated, with an acceptable safety profile and in-line with subcutaneous dosing in the Phase 1 program, and the safety profile observed in the proof of concept ITP study.

The most common adverse drug reactions observed after use of rozanolixizumab across indications are headaches and gastrointestinal (GI) disturbances (diarrhea, nausea, vomiting). Potential risks are serious infusion/hypersensitivity reactions, serious infections, and effects on vaccination response. The risks of serious infusion/hypersensitivity and serious infections can be mitigated by careful monitoring, exclusion of at-risk study participants, and appropriate protocol withdrawal and stopping criteria. Additionally, protocol guidance for management of GI disturbances, severe and/or serious headaches, and infusions is also provided as well as expedited reporting requirements of AESM.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of rozanolixizumab may be found in the current version of the IB.

3 OBJECTIVES AND ENDPOINTS

The objectives and corresponding endpoints for this study are presented in Table 3-1.

Table 3-1: Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To demonstrate the clinical efficacy of rozanolixizumab in patients with generalized MG	The primary efficacy endpoint is: • Change from Baseline to Day 43 (Visit 10) in MG-ADL score The secondary efficacy endpoints are: • MG-ADL responder (≥2.0 points improvement from Baseline) at Day 43 (Visit 10) • Change from Baseline to Day 43 (Visit 10) in the MG-C score • Change from Baseline to Day 43 (Visit 10) in QMG score

	• Change from Baseline to Day 43 (Visit 10) in the MG Symptoms PRO 'Muscle Weakness Fatigability' score • Change from Baseline to Day 43 (Visit 10) in the MG Symptoms PRO 'Physical Fatigue' score • Change from Baseline to Day 43 (Visit 10) in the MG Symptoms PRO 'Bulbar Symptoms' score The other efficacy endpoints are: • Use of rescue therapy due to worsening (IVIg, PEX) • Time to first rescue therapy • Time to MG-ADL response (≥2.0 points improvement from Baseline) • Change from Baseline in QMG at each scheduled assessment during Treatment and Observation Periods • QMG responder (≥3.0 points improvement from Baseline) at each scheduled assessment during Treatment and Observation Periods • Change from Baseline in MG-C score at each scheduled assessment during Treatment and Observation Periods • MG-C responder (≥5.0 points improvement from Baseline) at each scheduled assessment during Treatment and Observation Periods • Change from Baseline in MG-ADL at each scheduled assessment during Treatment and Observation Periods • MG-ADL responder (≥2.0 points improvement from Baseline) at each scheduled assessment during Treatment and Observation Periods • Change from Baseline in the MG Symptoms PRO 'Muscle Weakness Fatigability' score at each scheduled

	assessment during Treatment and Observation Periods • Change from Baseline in the MG Symptoms PRO 'Physical Fatigue' score at each scheduled assessment during Treatment and Observation Periods • Change from Baseline in the MG Symptoms PRO 'Bulbar Symptoms' score at each scheduled assessment during Treatment and Observation Periods • Change from Baseline in the MG Symptoms PRO 'Respiratory Symptoms' score at each scheduled assessment during Treatment and Observation Periods • Change from Baseline in the MG Symptoms PRO 'Ocular Symptoms' score at each scheduled assessment during Treatment and Observation Periods • Change from Baseline in Patient Global Impressions of Severity (PGI-S) at each scheduled assessment during the Treatment and Observation Periods • Patient Global Impressions of Change (PGI-C) at each scheduled assessment during Treatment and Observation Periods • Change from Baseline in MG-ADL (excluding ocular items) at each scheduled assessment during Treatment and Observation Periods • Change from Baseline in QMG (excluding ocular items) at each scheduled assessment during Treatment and Observation Periods • Change from Baseline in MG-C score (excluding ocular items) at each scheduled assessment during Treatment and Observation Periods • Change from Baseline to Day 43 (Visit 10) in MG-QOL 15r

	• Change from Baseline to Day 43 (Visit 10) in EuroQol(EQ)-5D-5L • Minimal symptom expression (MG-ADL score of 0 or 1) at any time up to and including Day 43 (Visit 10) • Change from Baseline in MG Impairment Index (MGII) scores at each scheduled assessment during Treatment Period • Change from Baseline in MGII ocular sub-scores at each scheduled assessment during Treatment Period • Change from Baseline in MGII generalized domain sub-scores at each scheduled assessment during Treatment Period
Secondary	
• To assess safety and tolerability of rozanolixizumab in MG patients	The secondary safety endpoints are: • Occurrence of TEAEs • TEAEs leading to withdrawal of IMP The other safety endpoints are: • Occurrence of AESM • Vital sign changes from Baseline (systolic and diastolic BP and pulse rate at each scheduled assessment during Treatment and Observation Periods) • 12-lead ECG change from Baseline at each scheduled assessment during Treatment and Observation Periods • Laboratory changes from Baseline at each scheduled assessment during Treatment and Observation Periods (hematology, clinical chemistry, and urinalysis) • Suicidality as measured by the Columbia Suicide Severity Rating Scale (C-SSRS)

Other	
• To assess pharmacokinetic (PK) characteristics of rozanolixizumab	• Plasma concentration of rozanolixizumab at each scheduled assessment during the Treatment and Observation Periods
• To assess the pharmacodynamics (PD) effects of rozanolixizumab on IgG, disease-specific autoantibodies	• Change (absolute and percentage) from Baseline in MG-specific autoantibodies at each scheduled assessment during Treatment and Observation Periods • Change (absolute and percentage) from Baseline in serum total IgG and IgG subclasses concentrations at each scheduled assessment during Treatment and Observation Periods
• To evaluate the emergence and incidence of anti-drug antibody (ADA) and impact on PK and PD	• Anti-drug antibody at each scheduled assessment during the Treatment Period and Observation Periods
• To evaluate the effects of rozanolixizumab on the concentration of total protein, IgM, IgA, and IgE, serum and plasma complement levels and serum cytokines	• Change from Baseline in serum complement levels (C3 and C4) and plasma complement levels (C3a and C5a) at each scheduled assessment during Treatment Period[a] • Change from Baseline in serum cytokines at each scheduled assessment during Treatment Period[a] • Change from Baseline in serum immunoglobulin concentrations (total IgA, IgE, and IgM) at each scheduled assessment during Treatment and Observation Periods
• To assess the effect of rozanolixizumab on tetanus IgG antibodies	• Change from Baseline in anti-tetanus toxoid serum titers at each scheduled assessment during Treatment and Observation Period
• To assess the effect of rozanolixizumab on exploratory biomarkers and protein expression, and explore the relationship between protein, and metabolite	• Exploratory biomarkers may be measured to evaluate the effect of rozanolixizumab. • Proteins, and metabolites changes that may be measured to understand the cause,

biomarkers and cause, progression, and appropriate treatment of MG	progression, and appropriate treatment of MG

[a] To be performed for study participants with severe headache and/or infusion reaction or hypersensitivity reaction. Other exploratory safety biomarkers may be assessed.

The primary efficacy analysis is the change from Baseline in MG-ADL score to Day 43 (Visit 10), as further detailed in Section 9.3.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, 3-arm, repeat dose study evaluating the efficacy and safety of two doses of rozanolixizumab and matching placebo in patients with generalized MG who experience moderate to severe symptoms (Myasthenia Gravis Foundation of America [MGFA II-IVa]) and are being considered for additional treatment such as IVIg or PEX (study schematic is provided in Figure 1-1).

Fixed unit doses across body weight tiers and study arms will be employed:

Treatment Arm 1 (rozanolixizumab) – equivalent to approximately [redacted]

- Bodyweight <50kg: dose to be administered [redacted]
- Bodyweight ≥50kg and <70kg: dose to be administered [redacted]
- Bodyweight ≥70kg and <100kg: dose to be administered [redacted]
- Bodyweight ≥100kg; dose to be administered [redacted]

Treatment Arm 2 (rozanolixizumab) – equivalent to approximately [redacted]

- Bodyweight <50kg: dose to be administered [redacted]
- Bodyweight ≥50kg and <70kg: dose to be administered [redacted]
- Bodyweight ≥70kg and <100kg: dose to be administered [redacted]
- Bodyweight ≥100kg; dose to be administered [redacted]

The placebo arm will be 0.9% sodium chloride aqueous solution (physiological saline, preservative free) for sc administration.

Approximately up to [redacted] study participants will be screened at about 135 sites from North America, Europe and Asia to achieve the minimum targeted number of [redacted] to a maximum of [redacted] evaluable study participants.

Participants have the opportunity to rollover into an OLE study, as described below. The OLE study, MG0004 (52-week chronic treatment) will be replaced by MG0007, which consists of 6-week treatment cycles based on MG worsening. Upon study site approval of MG0007, as well as fulfilment of regulatory requirements, study participants will have the opportunity to rollover directly into MG0007. In the event a study participant has already started MG0004, a minimum treatment duration of 6 visits (if IMP treatment is held for low IgG, study participants missed dose(s) can be counted as part of the total 6 visits for completion of MG0004 and meet eligibility requirements for MG0007) must be completed prior to moving into MG0007. Once the site is

active for MG0007, no further participants will enroll in MG0004 and the study will be closed at the site once all eligible study participants have discontinued MG0004 and had the opportunity to rollover into MG0007.

The maximum duration of the study per study participant will be up to 18 weeks, consisting of a Screening Period (1 to 28 days to account for central laboratory turn-around time), a Treatment Period (6 weeks), and a blinded Observation Period (8 weeks).

1. All study participants who complete the 6-week Treatment Period will roll over into an 8-week Observation Period.
2. All eligible study participants who complete the Observation Period will be invited to be re-randomized into an OLE study to either active dose arm 1 or 2.
3. Study participants who experience disease worsening during the 6-week Treatment Period (eg, an increase of 2 points on the MG-ADL or 3 points on the QMG scale between two consecutive visits) may be considered for rescue therapy (IVIg or PEX) at the discretion of the Investigator.
4. Study participants who need rescue therapy during the 6-week Treatment Period will receive IVIg or PEX and complete any subsequent visit(s). No further infusions of rozanolixizumab will be administered after initiation of rescue therapy. Once the participant completes Visit 10, he or she will move into the 8-week Observation Period.
5. Study participants who complete the Treatment Period and require initiation of rescue therapy after they start the 8-week Observation Period, may either opt to receive IVIg or PEX or complete the EOS visit and immediately roll over into an OLE study where the participant will receive rozanolixizumab. Study participants who opt to receive IVIg or PEX will complete any remaining visits in the Observation Period and will not be invited to join an OLE study.
6. Study participants who did not complete the 6-week Treatment Period because they needed rescue therapy and require initiation of a second course of rescue therapy while in the 8-week Observation Period can roll over to an OLE study if a minimum of 2 weeks have lapsed since completion of the last IVIg or PEX session. The EOS visit must be completed before enrolling into an OLE study. Alternatively, they can be treated with IVIg or PEX. Study participants who opt to receive IVIg or PEX will complete any remaining visits in the Observation Period and will not be invited to join an OLE study .
7. Study participants who discontinue study medication for any reason other than requiring rescue therapy will not be eligible for enrollment into an OLE study.

In exceptional circumstances (eg, pandemic, hurricanes, etc) where study-specific investigations may not be conducted according to study protocol, contingency measures will be in place (see Section 8).

An IDMC will be formed to monitor the ongoing safety and efficacy of the study. Futility and samples size adjustment will also be reviewed and assessed by the IDMC during a formal interim analysis at the end of Stage 1, when [redacted] enrolled study participants are evaluable for the primary endpoint. Approximately 3 periodic data reviews (in addition to the futility analysis mentioned above) will be performed: the first periodic data review will be performed when approximately [redacted] study participants have completed the 6-week Treatment Period; the second periodic data

review will be conducted after approximately [redacted] study participants have completed the 6-week Treatment Period (ad hoc as needed); and a third review will be conducted after approximately [redacted] study participants (dependent on the outcome of the interim analysis) have completed the 6-week Treatment Period. The timing of any further data reviews will be decided by the IDMC in conjunction with sponsor. Further details of the IDMC will be provided in a DMC charter.

4.2 Scientific Rationale for Study Design

MG0003 is designed to evaluate the efficacy, safety, and tolerability of rozanolixizumab given in dose exposures at [redacted] or [redacted] in study participants with MG. The previously conducted FIH study, UP0018, provided the safety, tolerability, and PK information for multiple dose exposures of [redacted] administered as iv or sc infusion over [redacted] in healthy volunteers.

The duration of the Treatment and Observation Periods were defined based on data from UP0018 and MG0002. In UP0018, results showed that upon administration of rozanolixizumab, the mean percentage change in total IgG over time demonstrated dose-dependent reductions across both the iv and sc routes of administration. Similar maximal reductions were observed for both the rozanolixizumab iv and sc doses (approximately 48% and 43%, respectively). The lowest level of IgG at maximum dose (both iv and sc) was reached by Day 10 on average. The total IgG levels generally returned to Baseline values by Day 57 on average.

Results from MG0002 showed that sc administration of rozanolixizumab resulted in a rapid reduction of serum IgG concentrations (Section 4.2.4.4), which also showed the greatest reductions from Baseline in QMG, MG-C, and MG-ADL after 6 infusions (Day 50). Therefore, a treatment duration of 6 weeks has been selected for MG0003 to ensure the maximum treatment effect of rozanolixizumab is captured. An 8-week Observation Period was defined in order to follow the recovery of IgG and AChR and MuSK antibodies, as well as monitoring the sustainability of the clinical effects after discontinuation.

The population in this study has been defined to exclude participants with severe weakness affecting oropharyngeal or respiratory muscles, or who have myasthenic crisis at Screening, as these participants would require urgent care incompatible with participation in the clinical study. This keeps consistent with the intended indication.

4.3 Justification for Dose

The selection of fixed unit dosing is introduced as part of future development plans to support patient self-injection with a medical device in a home setting. Dose stratified on weight tiers have been defined to replicate PD effects throughout the weight range that is similar to weight-based (mg/kg) dosing. The proposed doses and regimen of rozanolixizumab were selected based on the results from FIH study UP0018, alongside the efficacy and safety data from the MG Phase 2 study (MG0002).

UP0018 was a randomized, Investigator- and study participant-blind, placebo-controlled, single dose-escalating study to evaluate the safety and PK and to explore the PD of rozanolixizumab doses of [redacted] administered as iv or sc infusion over [redacted] in [redacted] healthy male and female volunteers. Data indicate that mean absolute decreases in IgG and mean percent change from Baseline IgG were greater in the active dose groups ([redacted]) compared to

the pooled iv and sc placebo group ([redacted]) with median maximum decreases of [redacted] (range: [redacted]) observed on Day 9 postdose for a rozanolixizumab [redacted] sc dose. Rozanolixizumab was tolerated with an acceptable safety profile after the single administration of a [redacted] sc dose, and all participant-reported TEAEs were mild or moderate in severity.

MG0002 was a Phase 2, multicenter, randomized, Investigator- and study participant-blind, placebo-controlled, 2-arm repeat dose, treatment sequence study evaluating the safety and efficacy of rozanolixizumab sc ([redacted]) in [redacted] study participants with generalized MG. Marked improvements in patient-reported MG symptoms and disability, as measured by change from Baseline to Day 29 in MG-ADL, were observed following treatment with rozanolixizumab [redacted] compared with placebo. The least squares (LS) mean (Standard Error [SE]) change from Baseline was [redacted] for the Rozanolixizumab [redacted] Group and [redacted] for the Placebo Group. The difference between treatment groups was [redacted] (p=[redacted] [[redacted] upper confidence interval (CI): [redacted]]). Smaller but numerical differences in favor of rozanolixizumab [redacted] vs placebo were observed in reductions from Baseline in QMG on Day 29 with the LS mean (SE) change from Baseline of [redacted] for the Rozanolixizumab [redacted] Group and [redacted] for the Placebo Group. The LS mean (SE) change from Baseline in MG-C score to Day 29 was [redacted] for the Rozanolixizumab [redacted] Group and [redacted] for the Placebo Group. In general, responder rates for QMG score, MG-C score, and MG-ADL score were higher for the rozanolixizumab [redacted] group than the placebo group. Serum total IgG concentrations and AChR autoantibodies rapidly decreased from Baseline in the rozanolixizumab [redacted] group in Dosing Period 1 and continued to decline on further dosing with [redacted] to a mean nadir of [redacted] for total IgG ([redacted] reduction from Baseline). Overall, repeated administrations of rozanolixizumab at dose levels of [redacted] and [redacted] sc have been generally [redacted] and well tolerated, with an acceptable safety profile. No new safety concerns have been identified to date. The TEAE profile was similar between rozanolixizumab and placebo, except for headaches where increased frequency and severity was observed in the rozanolixizumab-treated study participants.

Consistent with the mechanism of action of rozanolixizumab, an increased catabolism of IgG will reduce disease-specific autoantibodies with corresponding improvements in clinical signs and symptoms. Two sc treatment arms, equivalent to individual [redacted] and [redacted] dosing, have been selected to provide maximal reduction in autoantibody concentration and result in clinically significant improvements in the primary endpoint. A dose of [redacted] has demonstrated clinical improvements in MG-ADL in study MG0002 (as described above). Additional data from the Phase 2 study in study participants with ITP (TP0001) demonstrated that rozanolixizumab was well tolerated at doses at [redacted] with further IgG reduction achieved. An individual equivalent dose of [redacted] has been included to assess if further improvements in MG-ADL (magnitude of response and time to onset of symptom relief) can be achieved at a higher dose level with greater and more rapid IgG reduction.

A population PKPD model that characterizes the dose-exposure-IgG relationship was used to guide, through simulation, the choice of fixed unit doses at each weight bracket that achieved equivalent IgG reductions (mean and [redacted] prediction interval) to the weight-based (mg/kg) dosing regimens studied previously. These models-based simulations demonstrate that the proposed [redacted] doses of rozanolixizumab for 6 consecutive weeks are expected to produce mean maximum IgG reductions of [redacted]. These reductions will be achieved rapidly and maintained consistently over the Treatment Period.

4.4 End of Study definition

A study participant is considered to have completed the study if he/she has completed all phases of the study including the Observation Period. Study participants will have an EOS Visit performed 8 weeks after the last dose of study medication, or upon discontinuation of the study.

The EOS is defined as the date of the last visit of the last study participant in the study.

5 STUDY POPULATION

5.1 Inclusion Criteria

Study participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Study participant must be ≥18 years of age, at the time of signing the informed consent.

Type of participant and disease characteristics

2. Study participant has documented diagnosis of gMG at Visit 1, based on study participant's history and supported by previous evaluations.

3a. Study participant has a confirmed positive record of autoantibodies against AChR or MuSK at Screening (Visit 1). The presence of autoantibodies may be confirmed with repeat testing at Visit 1.

4. Study participant has MGFA Class II to IVa at Visit 1.

5a. Study participant with a MG-ADL score of at least 3 (with ≥3 points from non-ocular symptom) AND a QMG score of at least 11 at Visit 1 and at Baseline (Visit 2).

6a. Study participant is considered for additional treatment such as IVIg or PEX by the Investigator.

Weight

7a. Body weight ≥35kg at Visit 1.

Sex

8c. Study participants may be male or female

- A male study participant must agree to use contraception as detailed in Appendix 4 (Section 10.4) of this protocol during the Treatment Period and for at least 90 days after the last dose of study treatment and refrain from donating sperm during this period.
- A female participant is eligible to participate if she is not pregnant (see Section 10.4), not breastfeeding, and at least one of the following conditions applies:
  - Not a woman of childbearing potential (WOCBP) as defined in Section 10.4
    OR
  - A WOCBP who agrees to follow the contraceptive guidance in Section 10.4 during the Treatment Period and for at least 90 days after the last dose of study treatment. The study participant must have a negative serum pregnancy test at Visit 1, which is

confirmed to be negative by urine testing prior to the first dose of study medication at Visit 2.

Informed consent

9. Capable of giving signed informed consent as described in Appendix 1, Section 10.1.3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2 Exclusion Criteria

Unless otherwise stated, each criterion is applicable to at Visit 1. Study participants are excluded from the study if any of the following criteria apply:

Medical conditions

1. Study participant has any medical or psychiatric condition that, in the opinion of the Investigator, could jeopardize or would compromise the study participant's ability to participate in this study.

2a. Study participant has a history of alcohol use disorder or other substance use disorder (as per Diagnostic and Statistical Manual of Mental Disorders-5) within 12 months prior to Visit 1.

3. Study participant has a known hypersensitivity to any components of the study medication or comparative drugs as stated in this protocol.

4a. Study participant has a known history of hyperprolinemia, since L-proline is a constituent of the rozanolixizumab formulation.

5. Study participant has a clinically relevant active infection (eg, sepsis, pneumonia, or abscess) in the opinion of the Investigator, or had a serious infection (resulting in hospitalization or requiring parenteral antibiotic treatment) within 6 weeks prior to the first dose of IMP.

6. Study participant with a known tuberculosis (TB) infection, at high risk of acquiring TB infection, or latent tuberculosis infection (LTBI), or current/history of nontuberculous mycobacterial infection (NTMBI) will be excluded.

Prior/Concomitant therapy

7. Study participant has previously received rozanolixizumab drug product.

8. Study participant has received a live vaccination within 8 weeks prior to Visit 2; or intends to have a live vaccination during the course of the study or within 8 weeks following the final dose of IMP.

9a. Study participant has been treated with prohibited immunosuppressants, biologics, and other therapies within timeframe shorter than no-treatment period detailed in Table 5-1.

10a. Study participant has been treated with any biological agent other than those listed in Table 5-1 in the past 3 months or within 5 half-lives prior to Visit 2, whichever was longer.

11. Study participant has prior treatment with rituximab in the 6 months prior to Visit 2 or study participant has prior treatment with rituximab in the 12 months prior to Visit 2 and B cells monitoring have shown they did not return to normal range.

12a.Study participant had a thymectomy in the past 6 months or a thymoma at any time that required chemotherapy and/or radiotherapy prior to Visit 1.

13b.Study participant has any of the following active GI disorders: inflammatory bowel disease (IBD), or GI ulceration or diverticulitis .

Table 5-1: Treatment-free Period for Exclusionary Immunosuppressants, Biologics, and Other Therapies Prior to Baseline (Visit 2)

Generic name (commercial/trade names)	Period relative to Baseline Visit (regardless of route)
Immunosuppressants	
Cyclophosphamide (Cytoxan®)	[redacted]
Pimecrolimus (Elidel®)	[redacted]
Vinca alkaloids (vincristine, vinblastine)	[redacted]
Biologics (Mabs and fusion proteins)	
Abatacept (CTLA 4-Ig) (Orencia®)	[redacted]
Eculizumab (Soliris®)	[redacted]
Belimumab (Benlysta®)	[redacted]
Golimumab (Simponi®)	[redacted]
Natalizumab (Tysabri®)	[redacted]
Ofatumumab (Arzerra)	[redacted]
Rituximab (Rituxan®)	[redacted] if B-cells did not return to normal range
Ocrelizumab (Ocrevus®)	[redacted] if B-cells did not return to normal range
TACI-Ig (Atacicept)	[redacted]
Veltuzumab	[redacted]
Other biologics	[redacted], or within [redacted] (whichever was longer) prior to the Baseline Visit
Inebulizumab	[redacted] (prior to Baseline Visit) and B-cells are within normal range
Others	
Intravenous or subcutaneous immunoglobulin	[redacted]
IPP-201101 (Lupuzor™)	[redacted]
PEX	[redacted]
Immunoadsorption	[redacted]

Table 5-1: Treatment-free Period for Exclusionary Immunosuppressants, Biologics, and Other Therapies Prior to Baseline (Visit 2)

Generic name (commercial/trade names)	Period relative to Baseline Visit (regardless of route)

Mabs=monoclonal antibodies; PEX=plasma exchange

Prior/Concurrent clinical study experience

14. Study participant has participated in another study of an IMP (and/or an investigational device) within the previous 3 months or is currently participating in another study of an IMP and/or an investigational device.

15a. Study participant has been previously randomized in this study (re-screening for screen-failed participants is allowed with prior consultation and permission of the medical monitor).

16. Study participant has experienced hypersensitivity reaction after exposure to other anti-FcRn drugs.

Diagnostic assessments

17a. Study participant with severe (defined as Grade 3 on the MG-ADL scale) weakness affecting oropharyngeal or respiratory muscles, or who has myasthenic crisis or impending crisis at Visit 1 or Visit 2.

18. Study participant has a serum total IgG level ≤5.5g/L.

19. Study participant has absolute neutrophil count <1500 cells/mm^3.

20. Study participant has any laboratory abnormality that, in the opinion of the Investigator, is clinically significant, has not resolved at randomization, and could jeopardize or compromise the study participant's ability to participate in this study.

21. Study participant has 12-lead ECG with findings considered to be clinically significant upon medical review. The clinical significance of the findings needs to be assessed by the Investigator to determine eligibility, and any queries regarding continuation of the study participants will have to be addressed with the Medical Monitor.

22b. Study participant has renal impairment, defined as glomerular filtration rate (GFR) less than 45ml/min/1.73m^2 at Visit 1.

23a. Alanine transaminase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) are >3x upper limit of normal (ULN), or bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).

Study participant has elevations only in total bilirubin that were >ULN and <1.5xULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%).

For randomized study participants 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 will have to be understood and recorded in the electronic Case Report form (eCRF).

If study participant has >ULN, ALT, AST, or ALP that does not meet the exclusion limit at Visit 1, the tests should be repeated, if possible, prior to dosing to ensure there was no further ongoing clinically relevant increase. In case of a clinically relevant increase, inclusion of the study participants will have to be discussed with the Medical Monitor.

Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit (>3xULN) will have to be repeated once for confirmation. This includes rescreening.

24. Presence of Hepatitis B surface antigen (HBsAg) at Visit 1.
25. Positive Hepatitis C antibody test result at Visit 1 or within 3 months prior to starting study treatment. NOTE: Study participant with a positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained.
26. Positive Hepatitis C RNA test result at Visit 1 or within 3 months prior to first dose of study treatment. NOTE: Test is optional and a study participant with negative Hepatitis C antibody test is not required to also undergo Hepatitis C RNA testing.

27b. Current unstable liver or biliary disease per Investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice, or cirrhosis. NOTE: with exception of stable hepatobiliary conditions (including Gilbert's syndrome, asymptomatic gallstones).

28. Study participant tests positive for human immunodeficiency virus (HIV).

29a. Study participant has a current or medical history of primary immunodeficiency.

30a. Study participant has active neoplastic disease or history of neoplastic disease within 5 years of study entry prior to Visit 1 (except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the uterine cervix that have been definitively treated with standard of care approaches).

31a. Study participant has a planned elective surgical procedure within 4 months after Visit 1.

32. Study participant has a history of a solid organ transplant or hematopoietic stem cell/marrow transplant.

33. Study participant has corrected QT interval (QTcF) >450 msec (for male participants) or QTc >470 msec (for female participants) or QTc >480 msec in participants with bundle branch block.

Other exclusions

34. The study participant is not considered capable of adhering to the protocol visit schedule, or medication intake according to the judgment of the Investigator.
35. A female study participant, who tests positive for pregnancy, plans to get pregnant during the participation in the study, or who is breastfeeding.
36. Study participant has a lifetime history of suicide attempt (including an active attempt, interrupted attempt, or aborted attempt), or had 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).

37. Criterion removed.

38. Participant with current or medical history of IgA deficiency.

39a. Participant with a medical history of splenectomy.

5.3 Lifestyle Restrictions

There are no lifestyle restrictions during the study unless deemed to interfere with compliance with the protocol as deemed by the investigator.

The use of medicinal cannabidiols and medicinal marijuana (prescribed by a physician) is permitted.

5.4 Screen Failures

Screen failures are defined as study participants who consent to participate in the clinical study but are not subsequently randomly assigned to study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure study participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened, following discussion with the sponsor's medical monitor/study physician. Rescreened study participants should be assigned a new participant number for rescreening and repeat all Visit 1 assessments.

If a study participant has isolated test results outside the specific range which is deemed clinically nonsignificant, the abnormal value may be rechecked at the discretion of the Investigator, following information of 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.

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

6 STUDY TREATMENTS

6.1 Treatments Administered

Study Treatment Name:	Rozanolixizumab (Treatment Arm 1)	Rozanolixizumab (Treatment Arm 2)	Placebo (Treatment Arm 3)
Dosage formulation:	Solution for infusion	Solution for infusion	Aqueous solution
Unit dose strength(s)/Dosage level(s):	[redacted]		0.9% sodium chloride aqueous solution (physiological saline, preservative free)
Route of Administration	Subcutaneous (sc)		
Dosing instructions:	[redacted] Bodyweight <50kg: dose to be administered [redacted] Bodyweight ≥50kg and <70kg: dose to be administered [redacted] Bodyweight ≥70kg and <100kg: dose to be administered [redacted] Bodyweight ≥100kg: dose to be administered [redacted]	[redacted] Bodyweight <50kg: dose to be administered [redacted] Bodyweight ≥50kg and <70kg: dose to be administered [redacted] Bodyweight ≥70kg and <100kg: dose to be administered [redacted] Bodyweight ≥100kg: dose to be administered [redacted]	6 sc doses of placebo at 1-week intervals
Packaging and Labeling	Rozanolixizumab and matching placebo are manufactured, packaged, and labeled according to Good Manufacturing Practice guidelines and applicable laws or regulations.		

Details on the preparation of study treatment for infusion, rate of infusion, administration, appropriate records handling, and blinded and unblinded site personnel roles are provided in the IMP Handling Manual. All site personnel delegated to handle study treatment storage, preparation and administration must be trained to IMP Handling Manual.

6.2 Preparation, Handling, Storage, and Accountability requirements

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator, or delegate is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

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

Further guidance and information for the final disposition of unused study treatment are provided in the IMP Handling Manual.

6.2.1 Drug accountability

A Drug Accountability form will be used to record study medication dispensing and return information on a by-participant basis and will serve as source documentation during the course of the study. Details of any study medication 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 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 study medication 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 study medication must be reconciled and either destroyed at the site according to local laws, regulations, and UCB Standard Operating Procedures (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.

6.3 Measures to Minimize Bias: Randomization and Blinding

An interactive response technology (IRT) will be used for assigning eligible study participants to a treatment regimen (as applicable) based on a predetermined production randomization and/or packaging schedule provided by UCB (or designee). The randomization schedule will be produced by the IRT vendor. The IRT will generate individual assignments for kits of study medication, as appropriate, according to the visit schedule.

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

To randomize a study participant, the Investigator or designee will contact the IRT and provide brief details about the study participant to be randomized. The IRT will automatically inform the Investigator or designee of the study participant's randomization number. The IRT will allocate

kit numbers to the study participant based on the participant number during the course of the study. The randomization number must be incorporated into the eCRF.

The randomization will be stratified by the following:

- MG-specific autoantibody (MuSK+ or AChR+)

6.3.1 Procedures for maintaining and breaking the treatment blind

6.3.1.1 Maintenance of study treatment blind

All study participant treatment details, rozanolixizumab treatment arm, planned dose, 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:

- Designated bioanalytical staff analyzing PK samples
- IRT provider

Study site pharmacists or other suitably qualified site personnel who are responsible for preparation of IMP treatments will have access to treatment allocations for individual study participants via the IRT. The unblinded pharmacy monitors from the Contract Research Organization (CRO), and the Clinical Supply Manager 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 staff as needed for reporting SAEs to regulatory authorities.
- Members of the IDMC who participate in unblinded sessions will be given information about the IMP allocation for those study participants for whom data are provided at these sessions.
- CRO staff supporting preparation of the data outputs for the IDMC review and/or any interim analyses.
- Independent Medical Monitor external to the sponsor for monitoring unblinded clinical laboratory data, such as total IgG levels.

If IgG levels drop below 1g/L, the IMP must be temporarily discontinued. If IgG levels is ≥1 and <2g/L, and study participant is experiencing a nonserious infection which is persisting or recurrent, rozanolixizumab treatment may be temporarily discontinued (Section 7.1.4). Temporary treatment discontinuation due to low IgG levels may informally unblind the treatment assignment to the participant and site personnel. Therefore, infusions will be continued but given as mock infusions with only placebo irrespective of IMP designation. Allocation of mock kit numbers will be handled via the IRT. An unblinded Medical Monitor will inform the Investigator of the initiation of mock infusions and bring attention to any potential infection risk. The Medical Monitor will continue to review available safety information for these study participants (eg, AEs for infection and white cell count) while the IgG levels are at the protocol-defined low threshold values, and directly contact the Investigator should this review identify additional information that may be important in the care of the study participants. When the IgG levels have returned to the protocol-defined levels to re-initiate IMP (Section 7.1.4), the unblinded Medical Monitor will inform the Investigator of this decision. Based on the clinical situation, the Investigator has the option of holding the dose until deemed appropriate.

Further details are provided in the study manual and site blinding plan.

6.3.1.2 Breaking the treatment blind in an emergency situation

In the event of an emergency, it will be possible to determine to which treatment arm and dose the study participant 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 Clinical Project Manager 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 study medication 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.

6.4 Treatment Compliance

Drug accountability must be recorded on the Drug Accountability form (see Section 6.2.1).

6.5 Concomitant Medication(s)/Treatment(s)

6.5.1 Permitted concomitant treatments (medications and therapies)

All concomitant treatments permitted during the study are presented in Table 6-1.

Any violation of the permitted treatment criteria would lead to prohibited treatment and should be discussed with the Investigator, sponsor and Medical Monitor.

Table 6-1: Permitted Concomitant Treatments

Permitted Medications	Dose	Comment
Oral Corticosteroids (eg, prednisolone)	No specific requirements	Stable for [redacted] prior to Baseline[a]
Methotrexate	≤30mg/week	Treated for previous [redacted] and on stable dose for [redacted] prior to Baseline[a]
Mycophenolate mofetil	≤3g/day	Treated for previous [redacted] and on stable dose for [redacted] prior to Baseline[a]
Cyclosporine[b]	≤5mg/kg/day for unmodified ≤4mg/kg/day for modified (microemulsion)	Treated for previous [redacted] and on stable dose for [redacted] prior to Baseline[a]
Azathioprine	≤3mg/kg/day	Treated for previous [redacted] and on stable dose for [redacted] prior to Baseline[a]
Cholinesterase inhibitors	≤600mg Pyridostigmine/day	Stable dose not required – dose [redacted] of efficacy outcomes

Permitted Medications	Dose	Comment
Tacrolimus[c]	≤5mg/day	Treated for previous [redacted] and on stable dose for [redacted] prior to Baseline[a]

[a] Must also be stable for duration of study.
[b] Doses higher than listed are permissible if trough level is ≤300ng/mL.
[c] If the total daily weight-based dose is >5mg, then a plasma trough level should be checked to ensure study participant is not above the recommended therapeutic range.

The use of medicinal cannabidiols and medicinal marijuana (prescribed by a physician) is also permitted. When applicable, the study participant must be on a stable dose of cannabidiols and/or medicinal marijuana for [redacted] prior to Screening, and remain stable for the duration of the study.

6.5.2 Prohibited concomitant treatments (medications and therapies)

The following concomitant medications are prohibited during the study:

- All biologics including rituximab
- Cyclophosphamide
- Pimecrolimus
- IPP-201101 (Lupuzor™)
- Immunoadsorption
- Vinca alkaloids (vincristine, vinblastine)

If a study participant needs or takes any prohibited medication or therapy, the Investigator will (where possible) discuss with the Medical Monitor and/or sponsor's Study Physician and a decision will be made whether the study participant can continue in the study or must be withdrawn. If the study participant is treated with rituximab, the study participant must be withdrawn from the IMP, but should be encouraged to continue with Observation Period visits.

For study participants 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 study participant's continued participation in the study can be made.

6.5.3 Treatments specific to NMJ interference

Treatments could interfere with the function of the NMJ (and which therefore could impair study participants with MG), such as, but not limited to, include the following medications:

- botulinum toxin
- aminoglycoside antibiotics
- tetracycline antibiotics
- penicillamine

– magnesium

For a more detailed list please refer to the MGFA medication list (https://myasthenia.org/What-is-MG/MG-Management/Cautionary-Drugs). The benefit-risk of starting these medications should be carefully considered by the Investigator, and where possible, the Investigator will discuss with the Medical Monitor and/or sponsor's Study Physician prior to initiating therapy that can affect the NMJ.

6.5.4 Rescue therapy

Rescue therapy for the study will consist of IVIg or PEX. The study site will supply rescue therapy that will be obtained locally.

Study participants who experience disease worsening (eg, an increase of 2 points on the MG-ADL or 3 points on the QMG scale between two consecutive visits) may be considered for rescue therapy at the discretion of the Investigator.

Study participants who need rescue therapy during the Treatment Period may receive IVIg or PEX at the discretion of the Investigator, will complete any subsequent visit(s) and will move into the Observation Period.

For study participants receiving IVIg or PEX as rescue therapy, the date and time of administration as well as the name and dosage regimen of the rescue therapy must be recorded.

6.6 Dose Modification

There is no dose modification allowed in this study.

6.7 Treatment after the End of the Study

Study participants who need rescue therapy during the 8-week Observation Period, or complete the Observation Period without rescue therapy, will be invited to enroll into the OLE study. They will be randomized to one of two rozanolixizumab dose arms, equivalent to approximately [redacted] or [redacted]. Alternatively, if a study participant opts to receive IVIg or PEX during the Observation Period, he or she will complete the Observation Period and will not be eligible to enter the OLE study.

In the case of prolonged hypogammaglobulinemia after treatment discontinuation, study participants must be followed up until IgG levels return to values within the normal range or to individual Baseline values.

For study participants not enrolling into the OLE study, there are no plans for continued provision with rozanolixizumab after the end of the study. The participant should discuss any needed care after the study with their healthcare provider.

7 DISCONTINUATION OF STUDY MEDICATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

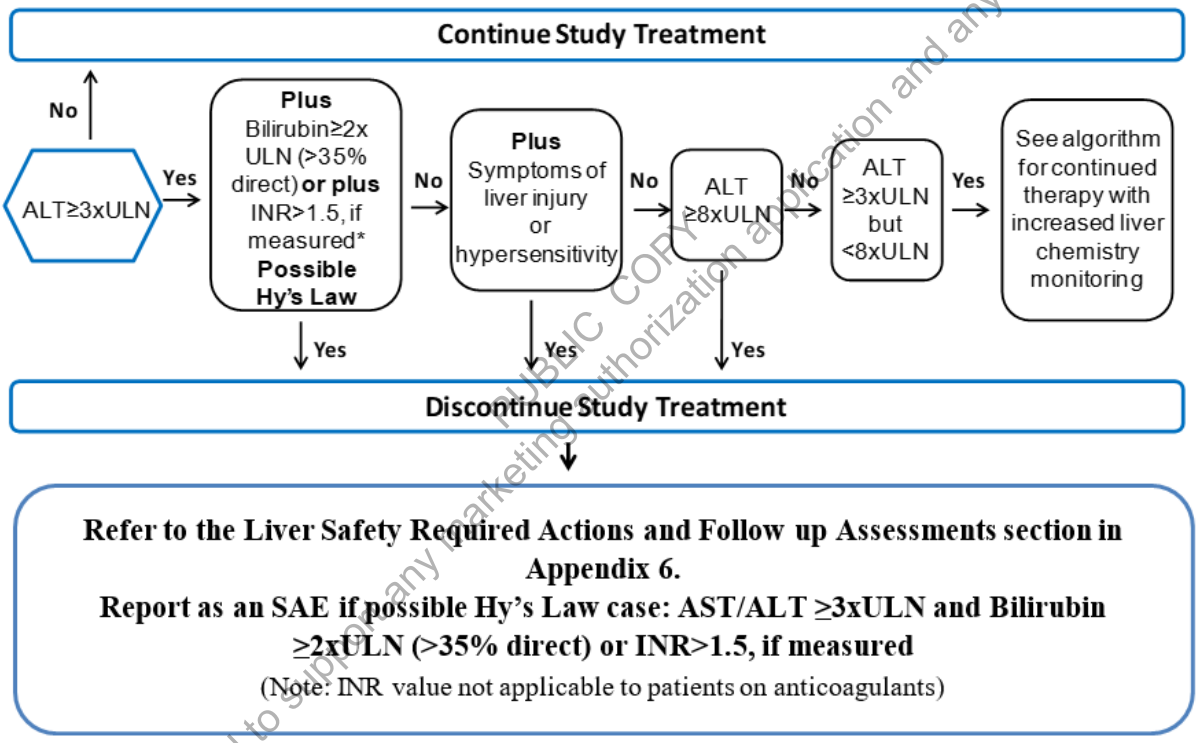
7.1 Discontinuation of Study Medication

7.1.1 Liver Chemistry Stopping Criteria

Discontinuation of study treatment for abnormal liver function should be considered by the Investigator when a study participant meets one of the conditions outlined in Figure 7-1 and Figure 7-2, or if the Investigator believes that it is in the best interest of the study participant.

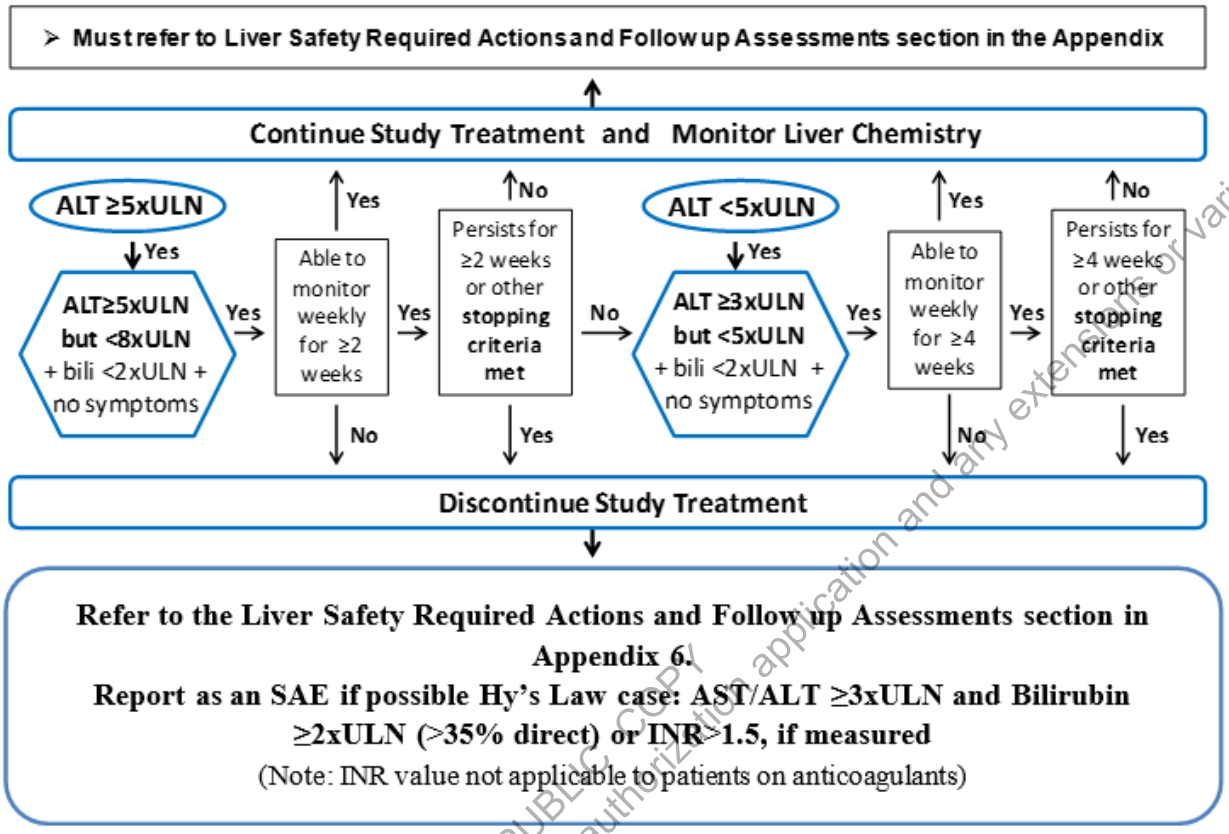
The study participant should follow the visit schedule as described in the protocol and the eCRF be completed accordingly.

Figure 7-1: Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm



ALT=alanine transaminase; AST=aspartate aminotransferase; INR=international normalized ratio; SAE=serious adverse event; ULN=upper limit of normal

Figure 7-2: Liver Chemistry Increased Monitoring Algorithm with Continued Study Intervention for Participants with ALT ≥3xULN but ≤8ULN



ALT=alanine transaminase; AST=aspartate aminotransferase; bili=bilirubin; INR=international normalized ratio; SAE=serious adverse event; ULN=upper limit of normal

Specific assessments and follow-up actions for potential drug-induced liver injury are provided in Appendix 6 (Section 10.6).

7.1.2 QTc Stopping Criteria

If a clinically significant finding is identified (including, but not limited to changes from Baseline in QT interval corrected using Fridericia's formula [QTcF]) after enrollment, the Investigator or qualified designee will determine if the study participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

A study participant who meets the bulleted criteria based on the average of triplicate ECG readings will discontinue rozanolixizumab and move into the Observation Period. The study participant should be referred to a specialist (ie, cardiologist) and managed as per local guidance.

- QTc >500 msec OR Uncorrected QT >600 msec
- Change from Baseline of QTc >60 msec

For study participants with underlying bundle branch block, follow the discontinuation criteria listed below:

Baseline QTc with Bundle Branch Block	Discontinuation QTc Threshold with Bundle Branch Block
< 450 msec	> 500 msec
450 to 480 msec	≥ 530 msec

See the Schedule of Activities (Section 1.3) for data to be collected at the time of treatment discontinuation and follow-up, and for any further evaluations that need to be completed.

The study participant should follow the visit schedule as described in the protocol and the eCRF be completed accordingly.

7.1.3 Discontinuation due to other adverse events or medical conditions

Study participants **must** permanently discontinue rozanolixizumab **and** move into the Observation Period if any of the following events occur:

1. Study participant develops an illness that would interfere with his/her continued exposure to rozanolixizumab.
2. Study participant has new onset or recurrent neoplastic disease (except for superficial basal or squamous cell carcinoma of the skin not requiring targeted biological therapy, chemotherapy or radiation).
3. Study participant has a serious infective episode requiring hospitalization or iv antibiotic therapy (ie, bacteremia or sepsis, meningitis, osteomyelitis or septic arthritis, pneumonia, or visceral abscess) (see Section 10.25).
4. Study participant has an AE of severe or serious infusion or anaphylactic reaction requiring corticosteroid and/or epinephrine therapy (see Section 10.28) (Sampson et al, 2006).
5. Study participant experiences a serious or recurrent (ie, second occurrence) severe AE of headache, which is considered related to the study medication in the opinion of the investigator.
6. Study participant 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 (Section 8.2.6).
7. Study participant meets potential drug-induced liver injury permanent discontinuation criteria.

If a 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.

7.1.4 Temporary IMP discontinuation

Study participant ***must be*** TEMPORARILY discontinued from the IMP if any of the following events occur:

1. The study participant develops an event of hypogammaglobulinemia with a serum total IgG of <1g/L irrespective of infection. When the IgG level reaches ≥2g/L, the study participant may be allowed to continue treatment with IMP (see Appendix 25; Section 10.25).

2. In the event of confirmed COVID-19 infection. IMP may be restarted if clinically appropriate when signs and symptoms have resolved.

Study participants ***may be TEMPORARILY discontinued from the IMP*** if the following events occur:

1. The study participant develops a non-serious persisting or recurrent infection with serum total IgG level between ≥1 and <2g/L. Upon resolution of infection and the IgG returning to level of ≥2g/L, the study participant may be allowed to resume treatment with the IMP (see Appendix 25; Section 10.25).
2. In the event of suspected (eg, signs/symptoms such as fever, cough, shortness of breath) COVID-19 infection, or known exposure sufficient to necessitate testing or self-imposed quarantine, IMP may be restarted when clinically appropriate if:
   a. COVID-19 test is negative, and signs and symptoms have resolved.
   b. If test is not available, resolution of signs and symptoms and 14 days have passed since initial presentation of the clinical signs/symptoms.
   c. If asymptomatic, 14 days have passed since known exposure.

The investigator should discuss with sponsor's study physician prior to re-initiating the IMP. As appropriate, virtual assessments could continue (eg, AE collection, PRO assessments).

If IMP treatment is resumed, continue the next dose as previously scheduled. No "make up" dose is permitted. The participant should subsequently follow the visit schedule as described in the protocol and the eCRF should be completed accordingly.

The study participant should follow the visit schedule as described in the protocol and the eCRF completed accordingly.

7.2 Participant Discontinuation/Withdrawal from the study

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

A study participant may also be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

If the study participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a study participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

See the Schedule of Activities (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

Study participants **must** be withdrawn from the study if any of the following events occur:

1. Study participant withdraws his or her consent.
2. The sponsor or a regulatory agency requests withdrawal of the study participant.
3. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.

4. Study participant 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 study participants should be referred immediately to a Mental Healthcare Professional.

Investigators should contact the Medical Monitor, whenever possible, to discuss the withdrawal of a participant in advance.

Study participants **may** permanently discontinue rozanolixizumab **and** move into the Observation Period at the discretion of the Investigator, Medical Monitor, and Study Physician if any of the following events occur:

5. Study participant is noncompliant with the study procedures or medications in the opinion of the Investigator.
6. Study participant takes prohibited concomitant medications during the Treatment Period as defined in this protocol (Section 6.5.2).

Study participants who permanently discontinue IMP for reasons other than requiring rescue therapy will not be eligible for enrollment into the OLE study.

Study participants who withdraw from the study during the Treatment Period should complete the assessments outlined PEOT Visit and enter the Observation Period.

7.3 Lost to Follow up

A study participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the study participant wishes to and/or should continue in the study.
- Before a study participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the study participant (at least 1 phone call and 1 written message to the participant), 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 removing the study participant, must be recorded in the source documents. The eCRF must document the primary reason for withdrawal.

Should the study participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up documented in the eCRF.

Investigators should contact the Medical Monitor, whenever possible, to discuss the withdrawal of a study participant in advance. Study participants who are withdrawn will not be replaced.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedule of Activities (Section 1.3).

If needed, the study participant will be allowed to rest before starting any study procedures. Quantitative Myasthenia Gravis scale, MG-C scale, MG-ADL and all other PROs should be administered by the investigator or qualified designee before any other invasive procedures are performed.

Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor or Medical Monitor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities (Section 1.3), is essential and required for study conduct.

All Screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. Screening assessments can be performed on different days throughout the 28-day Screening Period, if required. The Investigator will maintain a Screening log to record details of all participants screened and to confirm eligibility or record reasons for Screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for Screening or Baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities (Section 1.3).

An Unscheduled Visit can be conducted at the discretion of the Investigator (eg, due to an AE).

During the Unscheduled Visit, the following assessments must be performed:

- AE reporting
- Concomitant medications
- Review of withdrawal criteria
- Brief physical examination
- Vital signs

Blood samples for PK, IgG, hematology, biochemistry, other laboratory testing and assessments may be performed as clinically indicated, at the discretion of the Investigator.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Some study-specific investigations may not be conducted according to the study protocol during a pandemic or other exceptional circumstances (eg, hurricanes) due to the need to implement safety measures and guidance from regulatory authorities. In such a situation, which may be accompanied by local or global containment or other measures, sites may need to prohibit access to study participants and study-related personnel. Study participants visits to the study site may be replaced by contingency measures. These measures are primarily established to ensure the safety of study participants during the course of the study and to maintain the study participants treatment schedule, if the Investigator considers it appropriate. These measures include but are not limited to virtual visits or home-nursing visits replacing site visits, eg, telemedicine contacts

or home-nursing visits when treatment and/or blood sampling is scheduled. The contingency measures are described in a contingency plan and will be implemented as required.

8.1 Efficacy Assessments

8.1.1 MGFA Classification

The Investigator will classify the study participant's MG using the MGFA Clinical Classification (Appendix 12, Section 10.12) (Jaretzki et al, 2000). This is a 5-stage classification (I to V), with a higher class indicating more severe disease. To be eligible for this study, a participant must be graded MGFA CLASS II to IVa at Visit 1, as per inclusion criteria (Section 5.1).

8.1.2 Quantitative Myasthenia Gravis scale

For assessment of the QMG scale, investigators or qualified designee will follow the MGFA's QMG Manual instructions (Appendix 13, Section 10.13). Clinical personnel must complete mandatory training to assess study participants' QMG score (details are provided in the Study Procedures Manual). 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 acetylcholinesterase AChE inhibitor dosing for each evaluation during the study. Study participants should not take pyridostigmine (or other AChE inhibitor medication) from midnight before testing when medically safe to do so to standardize testing (ie, if AChE inhibitors cannot be stopped). 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 study participant is tested, and if possible, the same person should carry out the assessment. 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. Where possible, the same person should carry out the assessment at each visit.

8.1.3 MG-Composite scale

For assessment of the MG-C scale, the Investigator or qualified designee will examine the study participant to score all items, except for talking, chewing, and swallowing for which the study participant will self-assess. Study participants should not take pyridostigmine (or other AChE inhibitor medication) from midnight before testing when medically safe to do so to standardize testing. The MG-C scale is a validated assessment (Burns et al, 2010), with a higher score indicating more severe disease (Appendix 14, Section 10.14) and a 3-point change being of clinical relevance (Muppidi et al, 2011). 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 to assess study participants' MG-C score (details are provided in the Study Procedures Manual). Where possible, the same person should carry out the assessment at each visit.

8.1.4 Patient-reported outcomes

Patient-reported outcomes must be completed as per time points mentioned in the Schedule of Activities (Section 1.3). The PROs should be completed prior to any intrusive procedures in a quiet place.

The PROs should be completed in the following order: MG-ADL, MG Symptoms PRO, PGI-S, PGI-C, EQ-5D-5L, MGII (optional assessment), and MG-QOL15r. The PROs should only be checked for completeness. On dosing days, the PROs will be completed prior to dosing. Study participants should not take pyridostigmine (or other AChE inhibitor medication) from midnight before the days when efficacy assessments are performed, when medically safe to do so to standardize testing.

8.1.4.1 MG-Activities of Daily Living

Independently of study visit type (site, home, or virtual), the MG-ADL must be completed by study participants in a quiet place by themselves without the help of a partner or caregiver, before any clinical examination takes place. Study participants should be informed of the importance of this questionnaire and instructed to read the items and instructions carefully. They should be informed that there are no correct or incorrect answers.

Study personnel are not allowed to interpret the items for the participant. If a participant asks for guidance, study personnel should instruct him/her to respond according to their best understanding of the item. The MG-ADL should only be checked for completeness by study personnel. In the event a few questionnaire items have not been completed, study personnel should only query this with the study participant, if this results from an omission. Study personnel shall neither complete missing data nor suggest changes to participant responses. As with other study data, responses to the questionnaire should be treated as confidential information. Data privacy considerations apply.

In the specific context of virtual and home visits, paper copies of the MG-ADL should be made available to study participants ahead of the visit. Site coordinators or study personnel (or an automatic alert mechanism) should remind study participants to complete the MG-ADL before visit start and to record the date upon completion of the questionnaire. Once they have completed the MG-ADL, study participants should transfer it electronically to site personnel. In the event study personnel finds out that the MG-ADL has not been completed before the visit, study participants should be allowed some additional time to complete the questionnaire before any study related assessment is initiated.

The MG-ADL is an 8-item PRO instrument developed on the basis of the QMG (Wolfe et al, 1999) (Appendix 15, Section 10.15). The MG-ADL targets symptoms and disability across ocular (items #7 [double vision] and #8 [eyelid droop]), bulbar, respiratory, and axial symptoms. In a recent study, reliability, validity, and responsiveness of the MG-ADL were further assessed. The questionnaire showed strong construct validity when evaluated against the MG-C as well as against the MG-QOL15r; 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 MG-ADL score ranges from 0 to 24, with a higher score indicating more disability.

8.1.4.2 MG Symptoms PRO

The MG Symptoms PRO instrument (Appendix 16, Section 10.16) consists of 42 items across 5 scales: ocular symptoms (items 1-5); bulbar symptoms (items 6-15); respiratory symptoms (items 16-18); physical fatigue (items 19-33) and muscle weakness fatigability (items 34-42).

The study participant will be asked to choose the response option that best describes the severity of ocular, bulbar, and respiratory symptoms over the past 7 days using a 4-point Likert scale ("none" to "severe") and how frequently they experience physical fatigue and muscle weakness fatigability over the past 7 days using a 5-point Likert scale ("none of the time" to "all of the time"), respectively. A score can be obtained for each scale. All scores range from 0 to 100, with higher scores indicating more severe symptoms.

8.1.4.3 Patient Global Impression of Severity

Patient Global Impression of Severity is a single-state, self-report measure that rates a participant's severity of specific condition (Appendix 17, Section 10.17). The PGI-S is a 5 point scale depicting a participant's rating of overall symptoms ("none," "mild," "moderate," "severe," "very severe,").

8.1.4.4 Patient Global Impression of Change

Patient Global Impression of Change is a single-state, self-report measure that reflects a participant's belief about the efficacy of treatment for a specific condition (Appendix 18, Section 10.18). The PGI-C is a 7-point scale depicting a participant's rating of overall improvement ("very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," or "very much worse").

8.1.4.5 EQ-5D-5L

The 5-level EQ-5D (EQ-5D-5L) is designed to improve the instrument's sensitivity and to reduce ceiling effects (Appendix 19, Section 10.19).

The EQ-5D-5L essentially consists of 2 pages: the EQ-5D descriptive system and the EuroQol visual analogue scale (EQ VAS).

The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state.

The EQ VAS records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The VAS can be used as a quantitative measure of health outcome that reflect the patient's own judgement.

8.1.4.6 MG Impairment Index

The MGII is a measure of disease severity based on the signs and symptoms of MG patients (Appendix 20, Section 10.20). 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 is an optional assessment (see Section 1.3). The Investigator or qualified designee will examine the study participant prior

to scoring all items. Where possible, the same person should carry out the assessment at each visit.

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, Barnett et al, 2017). The MGII is sensitive to detect clinical change after interventions. Additionally, the MGII showed more relative efficiency than the QMG scale, MG-C, and MG-ADL to detect change in short-term interventions for MG. Estimates for the minimal important difference were developed (5.5 for individuals).

8.1.4.7 MG-QOL15r

The MG-QOL15r is a brief survey, completed by the study participant, that is designed to assess some aspects of "quality of life" related to MG. The MG-QOL15r was designed to assess the "patient perspective" in the everyday clinic setting or in a clinical study (Appendix 21, Section 10.21).

When completing the 15-item MG-QOL15r, MG study participant should consider only how their MG affects these items. For example, if a study participant has no leg weakness but has a painful hip (unrelated to the MG) that causes walking trouble, the study participant should report "not at all" to the item of, "I have trouble walking." This is because any hip-related walking trouble is unrelated to the MG. One other note of clarification: if the study participant is retired (unrelated to MG), he or she should report "not at all" to the item about whether the MG negatively impacts job/occupational status.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the Schedule of Activities (Section 1.3).

Study participants must be observed at site postdose for at least 4 hours following the first 2 infusions, and then 2 hours thereafter for subsequent infusions.

8.2.1 Physical examination

Full physical examination

A full physical examination will include, at a minimum, general appearance; ear, nose, and throat; eyes, hair, and skin; and assessments of the cardiovascular, respiratory, GI, neurological, and musculoskeletal systems. Height and weight will be measured and recorded at the Visit 1 (Screening). Body weight will be measured at Visit 1 and Baseline (Visit 2) only (as defined in Section 1.3) with the study participant wearing light clothing and without wearing shoes.

Brief physical examination

A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

For full and brief physical examinations, Investigators should pay special attention to clinical signs related to previous serious illnesses, as well as signs and symptoms of infections.

Clinically relevant findings or worsening of previous findings will be recorded as AEs.

8.2.2 Vital signs

Oral, tympanic, or axillary temperature, pulse rate, and blood pressure will be assessed.

Blood pressure (systolic and diastolic), and pulse rate measurements should be preceded by at least 5 minutes of rest for the study participant in a quiet setting without distractions (eg, television, cell phones). All measurements will be assessed in a sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.

All vital signs should be taken before any blood sampling.

8.2.3 Electrocardiograms

Triplicate 12-lead ECG will be obtained as outlined in the Schedule of Activities (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7.1.2 for QTc withdrawal criteria and any additional QTc readings that may be necessary.

All ECG recordings should be taken with the study participant resting in the supine position for at least 5 minutes before the recording.

At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession

8.2.4 Clinical safety laboratory assessments

See Appendix 2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Section 1.3) for the timing and frequency.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

All laboratory tests with values considered clinically significantly abnormal during participation in the study, should be repeated until the values return to normal or Baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

For clinically significant abnormal values, the etiology should be identified and the sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the Schedule of Activities (Section 1.3).

8.2.5 Suicidal risk monitoring

Study participants being treated with rozanolixizumab should be monitored appropriately for suicidal ideation and behavior or any other unusual changes in behavior. Consideration should be given to discontinuing rozanolixizumab in study participants who experience signs of suicidal ideation or behavior.

Families and caregivers of study participants being treated with rozanolixizumab should be instructed to monitor participants for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior, and to report such symptoms immediately to the study Investigator.

Suicidality will be assessed by trained study personnel using the C-SSRS (Columbia University Medical Center, 2008 [Appendix 28, Section 10.28]). This scale will be used for Screening, Baseline and all subsequent visits to assess suicidal ideation and behavior that may occur during the study. The C-SSRS will be performed at the scheduled timepoints as described in the Schedule of Activities (Section 1.3).

8.2.6 Assessment and management of TB and TB risk factors

Appropriate rigorous precautions are being taken within this protocol to monitor the risk of TB infection in this study (see Section 5.2). Any presumptive diagnosis or diagnosis of a TB infection is a reportable event.

Physical Examination

The Investigator should consider all potential sites of infection when assessing for TB during the physical examination, and other evaluations, and based on the study participant's medical or social history. Sites commonly infected by TB include: the lungs, larynx, lymph glands, pleura, GI system, genito urinary tract (including renal), bones and joints, meninges, peritoneum, pericardium, and skin. This is not an exhaustive list and unusual presentations and areas of involvement should always be considered.

Some common symptoms that the study participant may present are dependent on the primary focus of infection and may include cough, blood in sputum, night sweats, lymphadenitis, joint pain/swelling, spinal deformity, headache/confusion, abdominal pain (mimicking inflammatory bowel disease), etc. Unusual presentations should always be considered.

Note: If available, respiratory or other specimens must also be smear and culture negative for TB (Center for Disease Control and Prevention diagnosis of LTB infection [http://www.cdc.gov/TB/topic/testing/default.htm]).

TB signs and symptoms questionnaire

In addition to a physical examination done intermittently throughout the study, study participants will be evaluated both for signs and symptoms of latent or active TB infection and for risk factors for exposure to TB using the TB questionnaire as indicated in the Schedule of Activities (Section 1.3).

The TB questionnaire should be completed accurately and filed as a critical source document. The questionnaire will assist with the identification of study participants who may require therapy for TB.

A "Yes" response to any of the questions in the TB questionnaire during the study may trigger further assessment to determine if the study participant has either LTBI and must receive prophylactic LTBI therapy or active TB infection and must be withdrawn from the study. As an example, a study participant who answers "Yes" at Screening to the question "[redacted] should not be allowed into the study pending further assessments (including TB specialist consult) as outlined previously.

TB assessment by IGRA

The TB screening is mandatory both before study entry and during the conduct of the study. The preferred screening test is interferon-gamma release assay (IGRA) performed at a Central

Laboratory by QuantiFERON tube test. Additional IGRA test may be performed if indicated (eg, presence of signs and symptoms suggestive of TB, recent exposure).

In high TB incidence countries, it is recommended that the IGRA be the first test performed at screening to reduce the number of unnecessary screening procedures on any IGRA positive study participants that may need to be treated for TB prophylaxis or potentially withdrawn from the study.

The test results will be reported as positive, negative, or indeterminate.

If an IGRA is positive or indeterminate the study participant must be evaluated by a TB specialist.

- Positive IGRA

The positive IGRA may represent new LTBI or active TB infection. The positive IGRA result may also reflect positivity from a recently diagnosed and adequately treated (in progress or completed within the past 12 months) LTBI or from adequately treated past TB infection. In such cases, the study participants must be evaluated by a TB specialist.

- Indeterminate IGRA

If the IGRA test result is indeterminate, the IGRA previously performed may be repeated once. The retest must be done during the protocol-defined screening window. If the test is positive or indeterminate on retest, the study participant must be evaluated by a TB specialist.

Study participants who have two indeterminate or any positive IGRA test and are cleared by a TB specialist will be potentially eligible to be randomized into the study after discussion with and approval from study physician (medical monitor).

In such circumstances, the study participant must be subsequently evaluated by a TB specialist at protocol defined TB monitoring visits (in lieu of IGRA testing as it is likely to be positive).

TB assessment by chest X-ray

Chest X-ray is not required at Screening in countries where TB incidence is low (≤20 per 100,000, 2018 TB incidence estimate by the current version of the World Health Organization (WHO) Global Tuberculosis Report ANNEX 4). It can, however, be performed at the Investigator's discretion in study participants with risk factors (ie, patient aged 60 or older, prolonged steroid use).

In countries (eg, Russian Federation) where TB incidence is >20 per 100,000 by the current version of the WHO Global Tuberculosis Report ANNEX 4, a plain posterioanterior chest X-ray should be performed during the Screening and results must be available during Baseline before first drug administration unless a chest X-ray (or a computed tomography of the chest) has been done from 3 months prior to the Screening Visit. The official report of the imaging must specifically indicate the absence of findings suggestive of current active TB or prior inactive TB.

A chest X-ray or other imaging test after Screening should be performed only if indicated (eg, presence of signs and symptoms suggestive of TB, close exposure to persons with TB), and interpreted by a qualified specialist (ie, radiologist or pulmonologist).

Test Conversion

Tuberculosis test conversion is defined as a positive or indeterminate (and confirmed indeterminate on repeat) IGRA result for the current test when previous IGRA test results were negative. The IGRA result must be negative for study participants to enroll in this study. During the study, all study participants with positive or indeterminate IGRA test results must immediately stop study drug administration.

In case of an IGRA test conversion, the study participant must be considered as having either a suspected new latent or an active TB infection and be promptly referred to an appropriate specialist (eg, pulmonologist, infectious disease specialist) for further evaluation. If test conversion indicates LTBI, active TB, or NTMB then, TB test conversion (confirmed) should be classified adequately, either as due to LTBI, active TB infection, or NTMB, respectively. Additional assessments (eg, blood tests or IGRA, chest X-rays, or other imaging) should be performed where medically relevant and documented. Such conversions should be reported as AEs as described in the protocol. The AE term would need to be updated with final diagnosis once available.

Latent TB

Latent TB infection is defined as the absence of signs, symptoms (eg, evidence of organ specific involvement), or physical findings suggestive of TB infection with a positive IGRA test (or 2 indeterminate IGRA test results) and a chest X-ray (or other imaging) without evidence of TB infection.

LTBI must be reported as an AE and graded appropriately as described in the protocol. Follow-up reports should be completed as per protocol requirement until such time as the LTBI resolves.

Active TB or non-tuberculosis mycobacterium infection

Study participants who develop active TB or NTMB infection during the study (conversion demonstrated by IGRA) must be withdrawn from the study. The study participant must be immediately permanently discontinued from study medication and a PEOT Visit must be scheduled as soon as possible, but no later than the next scheduled visit. Treatment for active TB or NTMB should be started immediately based on local guidelines.

Confirmed active TB is always considered Serious Adverse Event. UCB's process requires that these must be captured on an SAE report form and provided to the Sponsor in accordance with SAE reporting requirements. Follow-up reports should be completed as per protocol requirement until such time as the TB infection resolves.

LTBI, active TB or other NTMB identified during study

During the study, study participants who develop evidence of LTBI, active TB or NTMB infection must immediately stop further administration of study medication and will be referred to an appropriate TB specialist (pulmonologist or infectious disease specialist) for further evaluation. Study participants diagnosed with active TB or LTBI should receive appropriate TB or prophylaxis therapy. The study participant should be transferred to the care of their physician and managed according to the standard of care.

If infection with NTMB is identified during the study, the same procedure as for active TB acquired during the study and compliant TB treatment shall be followed.

Follow-up information of suspected and confirmed TB cases should be provided to UCB at least after 3, 9, and 12 months of the start date of anti TB treatment, including hematological and biochemical safety parameters, X-ray evolution data, and TB diagnostic procedures used to follow-up and confirm recovery of TB.

8.3 Adverse Events

The definitions of an AE or SAE can be found in Appendix 3 (Section 10.3).

Adverse events can be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the participant to discontinue the study treatment or MG0003 (see Section 7).

8.3.1 Time period and frequency for collecting AE and SAE information

All SAEs will be collected from the signing of the ICF until the EOS visit at the time points specified in the Schedule of Activities (Section 1.3).

All AEs will be collected from the signing of the ICF until the EOS visit at the time points specified in the Schedule of Activities (Section 1.3).

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

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 study medication), up to 30 days from the end of the study for each participant, and to also inform study participants of the need to inform the Investigator of any SAE within this period. Serious AEs that the Investigator thinks may be associated with the study medication must be reported to UCB regardless of the time between the event and the end of the study.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

8.3.2 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs and SAEs, (and non-serious AEs of special interest and adverse events of special monitoring [AESM], as defined in Section 8.3.6 and Section 8.3.7, respectively), will be followed until resolution, stabilization, the Investigator determines that it is no longer clinically significant, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

Prompt notification (24 hrs) by the Investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate, according to local requirements.

8.3.5 Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study treatment and until 3 months after the last dose.

If a pregnancy is reported, the Investigator must immediately inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).

The study participant must be withdrawn from the study as soon as pregnancy is known (by positive pregnancy test), and the following should be completed:

- The study participant should return for an early discontinuation (PEOT) visit.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6 Adverse events of special interest

An AE of special interest (AESI) 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. An AESI should be immediately reported within 24 hrs to UCB. Potential Hy's Law, defined as ALT or AST ≥3xULN with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality (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 participant.

All AESIs will follow the SAE recording and reporting procedures as indicated in Appendix 3 (Section 10.3).

8.3.7 Adverse events of special monitoring

For rozanolixizumab, AESM that require immediate reporting (within 24 hrs regardless of seriousness) to UCB are:

- Severe headache
- Severe GI disorders (ie, abdominal pain, diarrhea, vomiting)
- Opportunistic infection

In case of severe headache or serious headache (regardless of severity), the headache questionnaire (Appendix 27 [Section 10.27]) must be completed. Additional procedures for management of headaches are provided in Appendix 23 (Section 10.23).

Procedures for the management of diarrhea, and infections and hypogammaglobulinemia are provided in Appendix 24 (Section 10.24), and Appendix 25 (Section 10.25), respectively.

Although infusion-related reactions as well as hypersensitivity reactions or anaphylaxis are not classified as AESM, these AEs will be monitored by the investigator. If such an event is suspected it should be managed according the guidance provided in Appendix 26, Section 10.26. In case of suspected anaphylaxis, the Sampson's Criteria (Sampson et al, 2006) in Appendix 28 (Section 10.28) should be completed.

All AESM will follow the SAE recording and reporting procedures as indicated in Appendix 3 (Section 10.3).

8.3.8 Treatment-emergent adverse events

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.

8.4 Safety Signal Detection

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

In addition, an unblinded IDMC will periodically review and monitor safety data from this study and advise UCB. Details are provided in the DMC Charter.

The Study Physician or medically qualified designee/equivalent will conduct an ongoing review of SAEs and perform ongoing SAE reconciliations in collaboration with the Patient Safety representative.

As appropriate for the stage of development and accumulated experience with the study medication, 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.

8.5 Treatment of Overdose

Any dose increase of 10% or greater from the assigned dose for each administered dose of IMP per week should be considered an overdose, irrespective of the weight tier band. Overdose events

are only considered AEs or SAEs if there are associated clinical signs and symptoms or if the act of taking the excess study medication itself is an AE or SAE (eg, suicide attempt).

UCB does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator or treating physician should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE or laboratory abnormality for at least 5 days.
3. Obtain a plasma sample for PK analysis and IgG (total and subclasses) antibodies and within 3 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.6 Pharmacokinetics and Anti-drug Antibodies

Whole blood samples will be collected for measurement of plasma concentrations of rozanolixizumab and ADA as specified in the Schedule of Activities (Section 1.3). Additional PK samples will be collected (Section 1.4) at selected sites for study participants who have consented to participate in the sub-study. Blood samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the sponsor. Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be used to evaluate the PK of rozanolixizumab and ADA and may be used for establishing assay parameters (eg, ADA cut point setting and PK selectivity assessment). Samples collected for analyses of rozanolixizumab concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Participant confidentiality will be maintained. At visits during which plasma/serum samples for the determination of multiple aspects of rozanolixizumab will be taken, one sample of sufficient volume can be used.

Drug concentration information that may unblind the study will not be reported to study sites or blinded personnel until the study has been unblinded.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

8.7 Pharmacodynamics

Venous blood samples will be collected at timepoints specified in the Schedule of Activities (Section 1.3) for measurement of:

- Serum IgG and IgG sub-classes concentrations

- Serum MG-specific autoantibodies (anti-MuSK/anti-AChR) levels (all subsequent testing will be limited to the positive antibody)

For all immunological assessments, blood samples will be collected predose. Instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the laboratory manual.

8.8 Genetics

Genetics are not evaluated in this study.

8.9 Biomarkers

Collection of samples for exploratory biomarker research is also part of this study. Blood samples for biomarker research are required and will be collected from all study participants in this study as specified in the Schedule of Activities (Section 1.3). Exploratory samples are collected predose. Additional exploratory safety samples must be collected 4 hours postdose or as soon as possible before the next IMP in case of AESM of severe headache and/or AESM of severe GI disorders, regardless of severity at Visits 4, 5, 6, 8, 9.

Protein and metabolites biomarkers may be measured to assess the effect of rozanolixizumab on exploratory biomarkers, and explore the relationship between protein, and metabolite biomarkers and cause, progression, and appropriate treatment of MG.

If not used immediately, these samples will be stored at -80°C for up to 20 years for later exploratory analyses. Any exploratory biomarker will only ever be related to the exploration of cause, progression, and appropriate treatment of MG. They may also be used to develop tests/assays including diagnostic tests related to rozanolixizumab and/or FcRn inhibitor and MG.

The nature and format of these tentative additional analyses will be determined at a later time. Details on the collection, storage, preparation, and shipping of samples will be presented in the laboratory manual provided separately. Instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the laboratory manual for this study. Detailed information on sample analyses will be provided in a bioanalytical report.

8.9.1 Immunology

Blood samples for immunological testing are required and will be collected from all study participants in this study as specified in the Schedule of Activities (Section 1.3) for measurement of:

- IgA, IgE, IgM
- Serum complement (C3, C4) and serum cytokines
- Plasma complement (C3a, C5a)
- Tetanus toxoid IgG

Samples for IgA, IgE, IgM are collected predose.

Samples for serum complement (C3, C4), plasma complement (C3a, C5a) and serum cytokines are collected predose at Visit 2 and 4 hours postdose at Visit 9. Additional samples should be collected 2 hours and 4 hours postevent for study participants with severe headache and/or

infusion reaction or hypersensitivity reaction as specified in the Schedule of Activities (Section 1.3).

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

8.10 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters will not be measured for this study.

9 STATISTICAL CONSIDERATIONS

A description of statistical methods follows and will be described in more detail in the Statistical Analysis Plan (SAP).

The statistical design of this study involves two stages, with an interim analysis at the end of Stage 1.

9.1 Definition of Analysis Sets

- Enrolled Set: All study participants who have signed the informed consent.
- Randomized Set (RS): All enrolled study participants who were randomized.
- Safety Set (SS): All randomized study participants who received at least one dose of IMP. Analysis of this set will be according to the treatment the study participants actually received, and will be used for the demographic and safety analyses.
- Pharmacokinetic Per-Protocol Set (PK-PPS): A subset of the Safety Set, consisting of those study participants who received 1 dose, had at least 1 valid PK measurement post first dose of study treatment, and no important protocol deviations affecting the PK variable, as confirmed during a pre-analysis review of the data prior to database lock.
- Full Analysis Set (FAS): Consists of all study participants in the SS, who have a Baseline and least 1 post-Baseline MG-ADL measurement.
- The RS is the primary analysis set for efficacy analyses. Analysis of the RS will be according to the treatment to which the study participants were randomized.

9.2 General Statistical Considerations

Statistical evaluation will be performed by the sponsor or designee and supervised by the Exploratory Statistics Department of UCB. Data will be summarized as follows:

- Summarized by dose levels of rozanolixizumab or placebo

All analyses will be performed using Statistical Analysis System (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 study participants (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized by visit (where applicable) with frequency counts and percentages.

If not otherwise stated, Baseline values will be the last available predose value and will be clearly defined in the SAP. All relevant data will be listed by treatment group and study participant. Placebo-treated study participants will be summarized globally.

9.3 Estimands

The primary efficacy analysis will evaluate the 'hypothetical' estimand in anti-AChR or anti-MuSK autoantibody-positive participants with generalized MG who experience moderate to severe symptoms and are being considered for additional treatment such as IVIg or PEX, where the main intercurrent events are the use of rescue medication prior to Day 43 and treatment discontinuation (or withdrawal from study) due to TEAEs. The primary efficacy analysis is the change from Baseline in MG-ADL score to Day 43 (Visit 10).

A hypothetical strategy will be used for rescue medication, ie, the intervention effect will be estimated under the hypothetical condition where rescue medication is not given. In the case of TEAEs leading to treatment discontinuation, observed data after treatment discontinuation will be utilized where possible.

The reason why a hypothetical estimand approach has been selected as the primary approach is because the use of rescue medication is likely to have a significant effect on subsequent efficacy data and for those study participants who discontinue treatment due to AEs, they are likely to also commence rescue medication in which case the hypothetical strategy will be applied once rescue medication has been initiated.

Missing data will be imputed under a missing at random assumption.

Data handling conventions for data affected by COVID-19 will be detailed fully in the SAP.

To check the assumptions of the primary analysis and definition of the Estimand, sensitivity and supplemental analyses of the change from Baseline in MG-ADL score to Day 43 (Visit 10) will be provided and are detailed in Table 9-1.

Table 9-1: Estimand Details and Attributes

		Estimand			
Objective Clinical Category	**Statistical Category**	**Variable/ Endpoint**	**Population**	**IES**	**PLS (Analysis)**
Primary Objective: To demonstrate the clinical efficacy of rozanolixizumab in patients with gMG					
MG-ADL	Primary	Change from Baseline to Day 43 (Visit 10) in MG-ADL score	RS	The main intercurrent events are the use of rescue therapy prior to Day 43 (Visit 10) and treatment discontinuation (or withdrawal from study) due to TEAEs. A **hypothetical strategy** will be used for rescue therapy, ie, the intervention effect will be estimated under the hypothetical condition where rescue therapy is not given. The same strategy will be used for TEAEs leading to treatment discontinuation.	Difference in mean change from Baseline (LSMD from CfB MMRM) to Day 43 (Visit 10) in the MG-ADL score for participants receiving rozanolixizumab versus placebo. Under MMRM, missing values are assumed to be Missing at Random (MAR).
MG-ADL	Sensitivity	Change from Baseline to Day 43 (Visit 10) in MG-ADL score	FAS	**Hypothetical strategy,** as for the primary analysis.	Difference in mean change from Baseline (LSMD from CfB MMRM) to Day 43 (Visit 10) in the MG-ADL score for participants receiving rozanolixizumab versus placebo. Under MMRM, missing values are assumed to be MAR.
MG-ADL	Sensitivity	Change from Baseline to Day 43 (Visit 10) in MG-ADL score	RS	**Hypothetical strategy**, as for the primary analysis.	Difference in mean change from Baseline (LSMD from CfB MMRM) to Day 43 (Visit 10) in the MG-ADL score for participants receiving rozanolixizumab versus placebo. A Jump-to-reference multiple imputation

		Estimand			
Objective Clinical Category	**Statistical Category**	**Variable/ Endpoint**	**Population**	**IES**	**PLS (Analysis)**
					approach will be utilised to assess the validity of the MAR assumption. Missing data across all treatment groups will be imputed using the placebo distribution.
MG-ADL	Supplemental	Change from Baseline to Day 43 (Visit 10) in MG-ADL score	RS	The main intercurrent events are the use of rescue therapy prior to Day 43 (Visit 10) and treatment discontinuation (or withdrawal from study) due to due to TEAEs. The intercurrent events will be handled using a **composite strategy**, ie, the occurrence of an intercurrent event will be handled by evaluating the corresponding participants as treatment failures and imputed with a worst score.	A trimmed mean approach will be used where all missing data (including the main intercurrent events) will be imputed with the worst score. A permutation-based test will be carried out, with the % trimming applied adaptively. The mean treatment difference of the trimmed population will be calculated on covariate-adjusted scores which are derived from an ANCOVA analysis of completers data.
MG-ADL	Sensitivity	Change from Baseline to Day 43 (Visit 10) in MG-ADL score	Subgroup of the RS who received all 6 (sc) doses. Only those participants who complete a full treatment course will be included in the analysis.	**Hypothetical strategy**, as for the primary analysis.	Difference in mean change from Baseline (LSMD from CfB MMRM) to Day 43 (Visit 10) in the MG-ADL score for participants receiving rozanolixizumab versus placebo. Under MMRM, missing values are assumed to be MAR.
MG-ADL	Supplemental	Change from Baseline to Day 43 (Visit 10) in	RS	The main intercurrent events are the use of rescue therapy prior to Day 43 (Visit 10)	Difference in mean change from Baseline (LSMD from CfB MMRM) to Day 43

		Estimand			
Objective Clinical Category	**Statistical Category**	**Variable/ Endpoint**	**Population**	**IES**	**PLS (Analysis)**
		MG-ADL score		and treatment discontinuation (or withdrawal from study) due to TEAEs. The intercurrent events will be handled using a **treatment policy strategy**, whereby the data from the treatment period to Day 43 is used regardless of whether the intercurrent event occurred.	(Visit 10) in the MG-ADL score for participants receiving rozanolixizumab versus placebo. Under MMRM, missing values are assumed to be MAR.
MG-ADL	Secondary	MG-ADL responder (≥2.0 points improvement from Baseline) at Day 43 (Visit 10)	RS	The main intercurrent events are the use of rescue therapy prior to Day 43 (Visit 10) and treatment discontinuation (or withdrawal from study) due to TEAEs. The intercurrent events will be handled using a **composite strategy**, ie, the occurrence of an intercurrent event will be handled by evaluating the corresponding participants as nonresponders.	Odds ratio at Day 43 (Visit 10) analyzed using logistic regression model adjusting for covariates for participants receiving rozanolixizumab versus placebo.
MG-C	Secondary	Change from Baseline to Day 43 (Visit 10) in MG-C score	RS	**Hypothetical strategy**, as described for the primary analysis of MG-ADL endpoint.	Difference in mean change from Baseline (LSMD from CfB MMRM) to Day 43 (Visit 10) in the MG-C score for participants receiving rozanolixizumab versus placebo. Under MMRM, missing values are assumed to be MAR.
MG-C	Sensitivity	Change from Baseline to	RS	**Hypothetical strategy**, as	Difference in mean change from Baseline

		Estimand			
Objective Clinical Category	**Statistical Category**	**Variable/ Endpoint**	**Population**	**IES**	**PLS (Analysis)**
		Day 43 (Visit 10) in MG-C score		described for the primary analysis of the MG-ADL endpoint.	(LSMD from CfB MMRM) to Day 43 (Visit 10) in the MG-ADL score for participants receiving rozanolixizumab versus placebo. A Jump-to-reference multiple imputation approach will be utilised to assess the validity of the MAR assumption. Missing data across all treatment groups will be imputed using the placebo distribution.
MG-C	Supplemental	Change from Baseline to Day 43 (Visit 10) in MG-C score	RS	The main intercurrent events are the use of rescue therapy prior to Day 43 (Visit 10) and treatment discontinuation (or withdrawal from study) due to TEAEs. The intercurrent events will be handled using a **composite strategy**, ie, the occurrence of an intercurrent event will be handled by evaluating the corresponding participants as treatment failures and imputed with a worst score. For simplicity, other intercurrent events leading to missing data which are not necessarily related to treatment will be handled in the same way, since this will include all randomized participants and is	A trimmed mean approach will be used where all missing data (including the main intercurrent events) will be imputed with the worst score. A permutation-based test will be carried out, with the % trimming applied adaptively. The mean treatment difference of the trimmed population will be calculated on covariate-adjusted scores which are derived from an ANCOVA analysis of completers data.

		Estimand			
Objective Clinical Category	**Statistical Category**	**Variable/ Endpoint**	**Population**	**IES**	**PLS (Analysis)**
				unlikely to introduce bias.	
QMG	Secondary	Change from Baseline to Day 43 (Visit 10) in QMG score	RS	**Hypothetical strategy**, as described for the primary analysis of the MG-ADL endpoint.	Difference in mean change from Baseline (LSMD from CfB MMRM) to Day 43 (Visit 10) in the QMG score for participants receiving rozanolixizumab versus placebo. Under MMRM, missing values are assumed to be MAR.
QMG	Sensitivity	Change from Baseline to Day 43 (Visit 10) in QMG score	RS	**Hypothetical strategy**, as described for the primary analysis of the MG-ADL endpoint.	Difference in mean change from Baseline (LSMD from CfB MMRM) to Day 43 (Visit 10) in the MG-ADL score for participants receiving rozanolixizumab versus placebo. A Jump-to-reference multiple imputation approach will be utilised to assess the validity of the MAR assumption. Missing data across all treatment groups will be imputed using the placebo distribution.
QMG	Supplemental	Change from Baseline to Day 43 (Visit 10) in QMG score	RS	**Composite strategy**, as for the MG-C sensitivity analysis	A trimmed mean approach will be used where all missing data (including the main intercurrent events) will be imputed with the worst score. A permutation-based test will be carried out, with the % trimming applied adaptively. The mean treatment difference of the trimmed population will be calculated on

		Estimand			
Objective Clinical Category	**Statistical Category**	**Variable/ Endpoint**	**Population**	**IES**	**PLS (Analysis)**
					covariate-adjusted scores which are derived from an ANCOVA analysis of completers data.
MG Symptoms PRO	Secondary	Change from Baseline to Day 43 (Visit 10) in the MG Symptoms PRO 'Muscle Weakness Fatigability' score	RS	**Hypothetical strategy**, as described for the primary analysis of the MG-ADL endpoint.	Difference in mean change from Baseline (LSMD from CfB MMRM) to Day 43 (Visit 10) in the MG Symptoms PRO 'Muscle Weakness Fatigability' score for participants receiving rozanolixizumab versus placebo. Under MMRM, missing values are assumed to be MAR.
MG Symptoms PRO	Sensitivity	Change from Baseline to Day 43 (Visit 10) in the MG Symptoms PRO 'Muscle Weakness Fatigability' score	RS	**Hypothetical strategy**, as described for the primary analysis of the MG-ADL endpoint.	Difference in mean change from Baseline (LSMD from CfB MMRM) to Day 43 (Visit 10) in the MG-ADL score for participants receiving rozanolixizumab versus placebo. A Jump-to-reference multiple imputation approach will be utilised to assess the validity of the MAR assumption. Missing data across all treatment groups will be imputed using the placebo distribution.
MG Symptoms PRO	Supplemental	Change from Baseline to Day 43 (Visit 10) in the MG Symptoms PRO 'Muscle Weakness	RS	**Composite strategy**, as for the MG-C sensitivity analysis	A trimmed mean approach will be used where all missing data (including the main intercurrent events) will be imputed with the worst score. A permutation-based test will be carried out,

		Estimand			
Objective Clinical Category	**Statistical Category**	**Variable/ Endpoint**	**Population**	**IES**	**PLS (Analysis)**
		Fatigability' score			with the % trimming applied adaptively. The mean treatment difference of the trimmed population will be calculated on covariate-adjusted scores which are derived from an ANCOVA analysis of completers data.
MG Symptoms PRO	Secondary	Change from Baseline to Day 43 (Visit 10) in the MG Symptoms PRO 'Physical Fatigue' score	RS	**Hypothetical strategy**, as described for the primary analysis of the MG-ADL endpoint.	Difference in mean change from Baseline (LSMD from CfB MMRM) to Day 43 (Visit 10) in the MG Symptoms PRO 'Physical Fatigue' score for participants receiving rozanolixizumab versus placebo. Under MMRM, missing values are assumed to be MAR.
MG Symptoms PRO	Sensitivity	Change from Baseline to Day 43 (Visit 10) in the MG Symptoms PRO 'Physical Fatigue score	RS	**Hypothetical strategy**, as described for the primary analysis of the MG-ADL endpoint.	Difference in mean change from Baseline (LSMD from CfB MMRM) to Day 43 (Visit 10) in the MG-ADL score for participants receiving rozanolixizumab versus placebo. A Jump-to-reference multiple imputation approach will be utilised to assess the validity of the MAR assumption. Missing data across all treatment groups will be imputed using the placebo distribution.
MG Symptoms PRO	Supplemental	Change from Baseline to Day 43	RS	**Composite strategy**, as for the MG-C sensitivity analysis	A trimmed mean approach will be used where all missing data

		Estimand			
Objective Clinical Category	**Statistical Category**	**Variable/ Endpoint**	**Population**	**IES**	**PLS (Analysis)**
		(Visit 10) in the MG Symptoms PRO 'Physical Fatigue' score			(including the main intercurrent events) will be imputed with the worst score. A permutation-based test will be carried out, with the % trimming applied adaptively. The mean treatment difference of the trimmed population will be calculated on covariate-adjusted scores which are derived from an ANCOVA analysis of completers data.
MG Symptoms PRO	Secondary	Change from Baseline to Day 43 (Visit 10) in the MG Symptoms PRO 'Bulbar Symptoms' score	RS	**Hypothetical strategy**, as described for the primary analysis of the MG-ADL endpoint.	Difference in mean change from Baseline (LSMD from CfB MMRM) to Day 43 (Visit 10) in the MG Symptoms PRO 'Bulbar Symptoms' score for participants receiving rozanolixizumab versus placebo. Under MMRM, missing values are assumed to be MAR.
MG Symptoms PRO	Sensitivity	Change from Baseline to Day 43 (Visit 10) in the MG Symptoms PRO 'Bulbar Symptoms' score	RS	**Hypothetical strategy**, as described for the primary analysis of the MG-ADL endpoint.	Difference in mean change from Baseline (LSMD from CfB MMRM) to Day 43 (Visit 10) in the MG-ADL score for participants receiving rozanolixizumab versus placebo. A Jump-to-reference multiple imputation approach will be utilised to assess the validity of the MAR assumption. Missing data across all

		Estimand			
Objective Clinical Category	**Statistical Category**	**Variable/ Endpoint**	**Population**	**IES**	**PLS (Analysis)**
					treatment groups will be imputed using the placebo distribution.
MG Symptoms PRO	Supplemental	Change from Baseline to Day 43 (Visit 10) in the MG Symptoms PRO 'Bulbar Symptoms' score	RS	**Composite strategy**, as for the MG-C sensitivity analysis	A trimmed mean approach will be used where all missing data (including the main intercurrent events) will be imputed with the worst score. A permutation-based test will be carried out, with the % trimming applied adaptively. The mean treatment difference of the trimmed population will be calculated on covariate-adjusted scores which are derived from an ANCOVA analysis of completers data.

ANCOVA=analysis of covariance; CfB=Change from Baseline; FAS=Full Analysis Set; IES=intercurrent event(s) strategy; gMG=generalized myasthenia gravis; LSMD=Least Squares Mean Difference; MAR=Missing at Random; MG=Myasthenia Gravis; MG-ADL=Myasthenia Gravis-Activities of Daily Living; MG-C=Myasthenia Gravis Composite; MMRM=mixed model for repeated measures; PLS=Population-level summary; PRO=patient-reported outcome; QMG=quantitative myasthenia gravis; RS=Randomized Set; sc=subcutaneous; TEAE=treatment-emergent adverse event.

9.4 Planned Efficacy/Outcome Analyses

9.4.1 Analysis of the primary efficacy endpoint

Analysis of the primary efficacy variable will be listed and descriptive statistics will be generated for the observed values and changes from Baseline. Summary outputs will be presented by treatment group and visit.

The formal testing strategy proposed is a flexible combination test based on the inverse normal method (Lehmacher and Wassmer, 1999) with equal weighting of Stage 1 (up to the formal interim analysis) and Stage 2 (post-interim analysis) data. Confirmatory testing of single hypotheses is based on a closed-testing procedure. For the closed testing procedure the Bonferroni approach is used as the intersection test for testing the global and intersection hypotheses. If a dose other than that defined by the "Select the best dose (and any dose with a mean response not worse than 1 point than the selected "best dose")" option (see Section 9.8 for details) is chosen for Stage 2 the adjusted p-value for the chosen dose(s) will be used in the combination test.

The primary efficacy analysis of the study will include the cohort of study participants from Stage 1 (n=[redacted]) and those who received the selected doses in Stage 2. The primary endpoint, Change from Baseline in MG-ADL, will be analyzed by stage-wise mixed model for repeated measures (MMRM) ANCOVA including a term for Baseline MG-ADL score, region, treatment group, the treatment group by week interaction term, and a term for the stratification factor (categorized as AChR or MuSK). The model will define patient as a random effect and utilize an unstructured covariance pattern. If the model does not converge using the unstructured pattern then an autoregressive covariance structure will be used.

The t-test statistics for each dose group (at each stage) will be used to calculate unadjusted p-values and these will be used to form the p-value combination test(s) as described above. The multiplicity introduced by having potentially 2 doses at the end of the study will be addressed by using a Bonferroni approach. The critical value for this test will be the upper 1.25% percentile of the standard normal distribution (because no alpha will be spent in Stage 1, the futility criterion is not binding and in Stage 2 the alpha is divided between the 2 doses). Similar presentations within each stratification factor may be provided.

9.4.2 Analysis of secondary and other efficacy endpoints

All continuous secondary efficacy variables will be analyzed using the combination testing strategy and model defined for the primary analysis. The binary secondary efficacy variable of MG-ADL responder (≥2.0 points improvement from Baseline) at Day 43 (Visit 10) will be analyzed using logistic regression, including a term for Baseline MG-ADL score, treatment group, and a term for the stratification factor (categorized as AChR or MuSK).

In addition, all continuous secondary efficacy variables will be listed and summarized descriptively by treatment group and week. Descriptive statistics will be generated for the observed values and the change from Baseline. For the binary variable, frequency counts and percentages will be produced.

A sequential hierarchical test procedure will be applied to protect the overall significance level for the multiplicity of endpoints. The predefined order of formal hypotheses testing for the secondary endpoints will be performed in the following sequence:

- Change from Baseline to Day 43 (Visit 10) in MG-C score.
- Change from Baseline to Day 43 (Visit 10) in QMG score.
- Change from Baseline to Day 43 (Visit 10) in the MG Symptoms PRO ‘Muscle Weakness Fatigability’ score.
- Change from Baseline to Day 43 (Visit 10) in the MG Symptoms PRO ‘Physical Fatigue’ score.
- Change from Baseline to Day 43 (Visit 10) in the MG Symptoms PRO ‘Bulbar Symptoms’ score.

All other variables will be listed and summarized descriptively. Time to first MG-ADL response (defined as ≥2.0 point improvement from Baseline) will be analyzed using a Cox Proportional Hazards model including a fixed term for treatment, and a term for the stratification factor (categorized as AChR or MuSK). The statistical model will be applied to each stage and the results combined using in a similar fashion to the primary analysis. An overall study used to

calculate the Hazard Ratio (test/reference), 95% CI and p-values for each treatment comparison of interest will be presented. The time to first MG-ADL response will be presented graphically using a Kaplan-Meier curve. Study participants will be censored at time of initiation of rescue therapy or end of treatment.

Further exploratory analysis may be performed using adequate statistical methods; details will be provided in the SAP.

9.5 Planned Safety and other Analyses

9.5.1 Safety analyses

The frequency and severity of all TEAEs will be presented for each treatment group separately by System Organ Class, high level term, and preferred term (Medical Dictionary for Regulatory Activities [MedDRA]®). The data will be displayed as number of study participants experiencing the TEAE, percentage of study participants, and number of TEAEs. A TEAE is defined as any event that was not present prior to the first administration of IMP or any unresolved event already present before the first administration of IMP that worsens in intensity following exposure to treatment.

Laboratory evaluations and vital signs as well as ECG data will be analyzed over time. All safety analyses will be listed and summarized for the SS.

9.5.2 Other analyses

9.5.2.1 Pharmacokinetic analyses

The PK-PPS dataset will be used. Pharmacokinetic variables of rozanolixizumab like AUC (area under the curve), C_{max} (maximum concentration) cannot be derived, since blood sampling will be performed at 1 time point post-dosing per visit only. Thus, PK is restricted to concentration data. In addition to the general descriptive display, concentration data will be summarized by treatment group and time point using the number of available observations, mean, median, SD, minimum, maximum, geometric mean (and associated 95% CI), and geometric coefficient of variation (assuming log-normally distributed data). Values below the lower limit of quantification (LLOQ) will be reported with a clear sign indicating that they were below the LLOQ. Descriptive statistics of concentrations will be calculated if at least two-thirds of the individual data points are quantifiable (≥LLOQ). The concentration data will be also summarized by treatment group and ADA. Individual concentrations of rozanolixizumab will also be displayed graphically.

A population PK and population PKPD analysis will be performed to evaluate PK and PKPD of rozanolixizumab. Details of such analysis will be further described in a separate Data Analysis Plan. The results of the analysis would be reported in a separate report outside the CSR. If required, an unblinded and relevant data transfer may be planned in order to initiate the PKPD analysis.

9.5.2.2 Anti-drug antibodies analyses

A tiered ADA approach will be used for the study. Anti-drug antibody assessment will involve Screening (above or below the cutpoint) of all samples for ADA, followed by a confirmatory assessment (confirmed or not confirmed positive) leading to an anti-rozanolixizumab antibody positive or negative assessment for each sample and a subsequent titration of those anti-

rozanolixizumab antibody positive samples during treatment and observation periods. For anti-rozanolixizumab antibody positive samples (or subset of) further characterization for neutralizing ADA potential in vitro will be performed.

The impact of ADA will be evaluated on PK, PD, efficacy and safety endpoints when relevant.

9.6 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. 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 are made on an ongoing basis.

9.7 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.

9.8 Planned interim analysis and data monitoring

9.8.1 Interim analysis

A formal interim analysis is planned for this study at the end of Stage 1, once approximately [redacted] (see Section 9.9 for sample size details) enrolled study participants [redacted]) are evaluable for the primary endpoint (having completed up to Day 43). Study enrollment will not be halted during planned IDMC review of the safety and efficacy data. The interim analysis is based on an adaptive design and is based on the primary efficacy analysis of Change from Baseline in MG-ADL. Data will be presented to and reviewed by the IDMC and the following decisions will be made:

1. Early stopping for futility will be allowed in the event that there is no evidence of either dose of rozanolixizumab being effective.
2. If futility is not established, then the "best dose" of rozanolixizumab (and any dose with a mean response not worse than 1 point than the selected "best dose") is selected for Stage 2 of the study. See dose selection section below for further details.
3. Sample size re-estimation will be conducted to ensure that the sample size in Stage 2 is appropriate to ensure an overall conditional power of [redacted] or until a predefined maximum increase in sample size has been reached. See Section 9.9 for further details.

Early stopping for Efficacy

Early stopping for efficacy will not take place, ie, there is no alpha spending function implemented.

Early Stopping for Futility

The futility stopping rule (non-binding) utilized for the study requires that the nominal Stage 1 p-value of each dose to be greater than [redacted] This corresponds to both estimated treatment effects being in the wrong direction, ie, inferiority.

Dose Selection

The statistical selection procedure proposed is equivalent to the "Select arm compared to the best and not worse than epsilon" option of ADDPLAN MC, where epsilon is equal to 1. This approach selects the dose with largest effect defined in terms of the observed mean responses and any doses with a mean response no worse than the best dose by 1 point providing that they are not dropped due to futility, ie, to be retained nominal p-value must be less than [redacted] However, this may not be the sole criterion for selecting the dose, since, additionally, the IDMC will take account of factors, including safety, which will be detailed in the IDMC charter.

Sample Size Re-estimation

The sample size re-estimation will be performed with the only option to increase the sample size. The default sample size of [redacted] for the study [redacted] study participants per arm in each of Stage 1 and Stage 2) is based on a set of assumptions concerning the effect sizes and variability (see Section 9.9 for details). However, it is considered prudent to conduct a mid-study sample size re-estimation to assess these important assumptions. The approach to be used is to determine the Stage 2 sample size required to give a conditional power of [redacted] for the overall study, based on the observed effect sizes at the interim analysis.

9.8.2 Periodic Data Reviews

Approximately 3 periodic data reviews (in addition to the futility analysis) will be performed for the IDMC to oversee the safety of the study: the first periodic data review will be performed when approximately [redacted] study participants have completed the 6-week Treatment Period; the second periodic data review will be conducted after approximately [redacted] study participants have completed the 6-week Treatment Period (ad hoc as needed); and a third periodic data review will be conducted after approximately [redacted] study participants (dependent on the outcome of the interim analysis) have completed the 6-week Treatment Period. The timing of any further data reviews will be decided by the IDMC in conjunction with sponsor.

9.8.3 Data monitoring

Data from the interim analysis will be presented to and reviewed by the IDMC by an unblinded statistician who will receive data from an independent statistical center. All information including electronic data capture, randomization and drug kit numbers are contained in a single database. The randomization and drug kit numbers are stored in encrypted form on the database and access to the database is strictly controlled by function so that project team members do not have access to the encryption key. The unblinded, independent statistician will provide the IDMC with information and will update the randomization lists following the choice of dose by the IDMC. The IDMC will evaluate efficacy by reviewing pre-specified efficacy data during the interim evaluation and make recommendations on implementation of the adaptive design options as detailed in Section 9.8.

The IDMC will also oversee the safety of the study by reviewing safety and efficacy data at periodic data reviews to assess the benefit risk of rozanolixizumab.

The IDMC will consist of members independent from UCB. Study enrollment will not be halted during planned IDMC review of the safety and efficacy data. The objectives and procedures for the IDMC will be detailed in the IDMC Charter.

9.9 Determination of sample size

As detailed in in Section 9.8, this study may consist of 2 stages, with a formal interim analysis at the end of Stage 1.

Based on historical data, the difference in adjusted changes from Baseline of MG-ADL at Day 43, between rozanolixizumab and placebo, is assumed to be [redacted] to [redacted] and the standard deviation is assumed to be [redacted] to [redacted] A difference of [redacted] could be judged to be clinically meaningful.

It is proposed that the interim analysis will be conducted when approximately [redacted] eligible study participants have been treated and are evaluable for the primary endpoint, ie, approximately [redacted] study participants per dose group in Stage 1. If the study is not stopped for futility after Stage 1, then depending upon the selection of one, or two, of the doses after Stage 1 and the calculation of conditional power, a further [redacted] to [redacted] eligible study participants will be randomized in Stage 2 of the study. Thus, the total sample size of the study could range between [redacted] and [redacted] study participants if the study is not futile.

The power of the study using the above adaptive design and expected sample sizes with a sample size cap of [redacted] and various scenarios of true treatment effect and standard deviation were determined from a stimulation study using the statistical software ADDPLAN MC, the results of which are summarized in Table 9-2.

The simulation results also indicate that across the various scenarios the average sample size for the study ranges between [redacted] and [redacted] study participants. The power for scenarios [redacted] to [redacted] that is, when the high dose has an effect compared to placebo of 2 points, are at least [redacted] indicating that the sample size re-assessment process helps maintain reasonable power when only one dose has a clinically meaningful effect of 2 and the data variability is greater than anticipated [redacted]

The chances of stopping for futility, when at least one dose has a clinically meaningful effect of [redacted] or more versus placebo, is [redacted]

These results support the strategy of entering [redacted] eligible study participants per dose group in Stage 1 and between [redacted] to [redacted] study participants per dose group in Stage 2. Note that ADDPLAN MC implements the sample size increase rule 'per arm' rather than 'per stage', so that if only one dose is selected for Stage 2, then the maximum sample size for this stage is [redacted] whereas if two doses are selected than the maximum Stage 2 sample size is [redacted] Therefore, if an overall study sample size cap of [redacted] (ie, [redacted] in Stage 2) were implemented, irrespective of whether one or two doses are selected, then we would expect power for each scenario to be slightly increased compared to those contained in Table 9-2.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1 Regulatory and ethical considerations

The study will be conducted under the auspices of an IRB/IEC, as defined in local regulations, International Council on Harmonisation-Good Clinical Practice (ICH-GCP), and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

UCB or designee 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, UCB or designee will forward copies of the protocol, Informed Consent form, Investigator's Brochure, Investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other participant-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 participants or others, and any protocol deviations, to eliminate immediate hazards to participants.

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 participants. 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 participant 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.

10.1.2 Financial disclosure

Insurance coverage will be handled according to local requirements.

Finance and insurance are addressed in the Investigator and/or CRO agreements, as applicable.

10.1.3 Informed consent process

Participant's informed consent, as well as a separate informed consent for the sub-study, 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. A separate informed consent may be obtained requesting the participation in a market research interview.

Prior to obtaining informed consent, information should be given in a language and at a level of complexity understandable to the participant in both oral and written form by the Investigator (or designee). Each participant 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 participant, or his/her legal representative, and by the person who conducted the informed consent discussion (Investigator or designee). The participant or his/her legal representative must receive a copy of the signed and dated Informed Consent form. As part of the consent process, each participant 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 United States must include the use of a Health Insurance Portability and Accountability Act Authorization form.

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

10.1.4 Data protection

UCB staff (or designee) will affirm and uphold the study participant's confidentiality. Throughout this study, all data forwarded to UCB (or designee) will be identified only by the study participant 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 participant's primary medical records that directly concerns this study (including, but not limited to, laboratory test result reports, ECG reports, admission/discharge summaries for hospital admissions occurring during a participant's study participation, and autopsy reports for deaths occurring during the study).

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5 Committees structure

An IDMC will review the safety and tolerability data in this study in order to make recommendations for the Sponsor to decide on whether to proceed with the study.

The data review by the IDMC will be unblinded data.

An IDMC will be set up in line with the Food and Drug Administration regulatory requirements and European Medicines Agency Guideline on iDMCs (EMEA/CHMP/EWP/5872/03 Corr, adopted 27/05/2005). The IDMC will consist of external experts who are independent from UCB and the clinical operations CRO, and have no conflict of interest related to the conduct or the outcomes of the study. The voting members of the IDMC will include, at minimum, an expert in clinical pharmacology, and two neurologists.

10.1.6 Data quality assurance

All participant data relating to the study will be recorded on printed or eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH-GCP, and all applicable regulatory requirements.

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 study medication/investigational device. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or by an agreement with UCB (Committee for Proprietary Medicinal Products [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.

10.1.6.1 Electronic 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.

10.1.6.2 Apps

Not applicable.

10.1.7 Source documents

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 hospital/clinic/general practitioner records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records, ECG or other printouts, completed scales, quality of life questionnaires, or video, for example. Source documents should be kept in a secure, limited access area.

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 participant'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).

10.1.8 Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator

- Discontinuation of further study medication development

10.1.9 Publication Policy

The results of this study may be published or presented at scientific meetings.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in the table below will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be entered into the eCRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Protocol-Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th colspan="4">Parameters</th></tr>
<tr><td>Hematology</td><td>Platelet Count
Red blood cell (RBC) count
Hemoglobin
Hematocrit</td><td colspan="2">RBC Indices:
Mean corpuscular volume
Mean corpuscular hemoglobin
%Reticulocytes</td><td>White blood cell count with Differential:
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td rowspan="4">Clinical Chemistry[a]</td><td>Blood Urea Nitrogen (BUN)</td><td>Potassium</td><td>Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)</td><td>Total and direct bilirubin</td></tr>
<tr><td>Creatinine</td><td>Sodium</td><td>Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)</td><td>Total Protein
Albumin</td></tr>
<tr><td>Glucose (fasting state, preferred)</td><td>Calcium</td><td>Alkaline phosphatase</td><td>C-reactive protein (CRP)</td></tr>
<tr><td>Lactate dehydrogenase (LDH)</td><td>High-density lipoprotein (HDL)</td><td>Total Cholesterol</td><td>Triglycerides</td></tr>
<tr><td>Routine Urinalysis</td><td colspan="4">• Specific gravity</td></tr>
</table>

Laboratory Assessments	Parameters
	• pH, glucose, protein, blood, ketones, albumin, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)
Other Screening Tests	• Serum or urine human chorionic gonadotropin pregnancy test (as needed for women of childbearing potential)[b] • PTT and INR tests • Serology testing (for Hepatitis B, Hepatitis C, and HIV) • All study-required laboratory assessments will be performed by a central laboratory. • The results of each test must be entered into the CRF.
NOTES : [a] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 10.6 and Appendix 6. All events of ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN and international normalized ratio (INR) >1.5, if INR measured, may indicate severe liver injury (possible Hy's Law) and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis). [b] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.	

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

10.3 Appendix 3: Adverse Events – Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study medication, whether or not considered related to the study medication.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study medication.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study medication administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study medication or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the study participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Important medical events:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include, but are not limited to, potential Hy's law, invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to UCB in lieu of completion of the UCB AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by UCB. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to UCB.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe (eg, a severe AE may be either serious or not serious, depending on whether these criteria are also met).

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) should be used as a supportive standardization instrument to evaluate AEs and SAEs but the final intensity grading by the Investigator must be mild, moderate, or severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study medication and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study medication administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to UCB. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to UCB.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by UCB to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- 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 participant is lost to follow-up. This follow-up requirement applies to AEs, SAEs, and AEs of special interest.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide UCB with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to UCB within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting to UCB via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to UCB will be the electronic data collection tool.
- If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section).
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section).
- Contacts for SAE reporting can be found in SERIOUS ADVERSE EVENT REPORTING.

SAE Reporting to UCB via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to UCB, see SERIOUS ADVERSE EVENT REPORTING.

- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in SERIOUS ADVERSE EVENT REPORTING.

10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories **are not considered WOCBP**:

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following during the Treatment Period and for at least 90 days after the final dose of study treatment:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.
- Agree to use a male condom when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

In addition, male participants must refrain from donating sperm for the duration of the study and for at least 90 days after the final dose of study medication.

Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration throughout the duration of the study and for at least **90 days** after the final dose of study treatment.

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 10-1.

Table 10-1: Highly Effective Contraceptive Methods[a]

Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[c] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent[b]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation • Intrauterine device • Intrauterine hormone-releasing system • Bilateral tubal occlusion
Vasectomized partner A vasectomy is a highly effective contraception method provided that the vasectomized partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study medication. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

NOTES:
[a] In case of newly started contraception pills/IUDs, PI should consider the correct timing of starting/applying such methods in relation to the menstrual cycle and the manufacturing instructions as when these newly started methods would become effective.
[b] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.
[c] Hormonal contraception may be susceptible to interaction with the study medication, which may reduce the efficacy of the contraceptive method. In this case, two highly effective methods of contraception should be utilized during the treatment period and for at least 90 days after the last dose of study medication.

Pregnancy testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine or serum pregnancy test.
- Additional pregnancy testing should be performed once during the treatment period and at the EOS Visit, corresponding to protocol-defined time frame in Section 10.4 after the last dose of study medication and as required locally.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- Pregnancy testing, with a sensitivity of ≥25mIU/mL will be performed. A serum and urine pregnancy test will be completed at Screening and Baseline, respectively.

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study medication. If the study participant is later found to be on placebo, then pregnancy data collection can stop.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the sponsor within once working day of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be at least 12 months after the delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants who become pregnant

- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.
- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within one working day of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, the follow-up will be at least

12 months after the delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy-related SAE considered reasonably related to the IMP by the investigator will be reported to the sponsor as described in Section 8.3.5. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

10.5 Appendix 5: Genetics

Not applicable.

10.6 Appendix 6: Liver Safety – Suggested Actions and Follow-up Assessments

Participants with potential drug-induced liver injury must be assessed to determine if study medication must be discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued.

Investigators should attempt to obtain information on study participants in the case of study medication discontinuation to complete the final evaluation.

Study participants with potential drug-induced liver injury 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 study medication discontinuation and/or participant withdrawal (if applicable), must be recorded in the source documents. The CRF must document the primary reason for discontinuation of study medication.

A specific monitoring plan must be agreed between the UCB study physician and the Investigator for study participants who have ALT >5 ULN. The monitoring plan should include any necessary follow-up assessments (until resolution of the abnormal lab values).

Table 10–2: Liver Chemistry Stopping Criteria and Follow-Up assessments

Liver Chemistry Stopping Criteria	
ALT-absolute	ALT ≥8xULN
ALT Increase	ALT ≥5xULN but <8xULN persists for ≥2 weeks ALT ≥3xULN but <5xULN persists for ≥4 weeks
Bilirubin[a, b]	ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin)
INR[2]	ALT ≥3xULN **and** international normalized ratio (INR) >1.5, if INR measured
Cannot Monitor	ALT ≥5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks ALT ≥3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks
Symptomatic[c]	ALT ≥3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Suggested Actions and Follow up Assessments	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study medication. • Report the event to UCB within **24 hours.** • Complete the liver event case report form (CRF), and complete a serious adverse event (SAE) data collection tool if the event also met the criteria for an SAE.[b]	• Viral hepatitis serology[d] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen,

• Perform liver chemistry follow-up assessments. • Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to Baseline (see **MONITORING**). • **Do not restart/rechallenge** participant with study medication. • If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study medication and continue participant in the study for any protocol specified follow-up assessments.Consider the need for a toxicology Screening. **MONITORING:** **<u>For bilirubin or INR criteria</u>** • Repeat liver chemistry tests (include ALT, aspartate transaminase [AST], alkaline phosphatase, bilirubin) and perform liver event follow-up assessments within **24 hours.** • Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to Baseline. • A specialist or hepatology consultation is recommended. **<u>For all other criteria</u>** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver chemistry follow-up assessments within **24 to 72 hours.** • Monitor participants weekly until liver chemistry abnormalities resolve, stabilize, or return to Baseline.	quantitative hepatitis B deoxyribonucleic acid (DNA) and hepatitis delta antibody[e]) • Obtain blood sample for pharmacokinetic (PK) analysis as soon as feasible after the most recent dose[f] • Serum creatine phosphokinase and lactate dehydrogenase (LDH) • Fractionate bilirubin, if total bilirubin ≥ 2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the adverse event (AE) report form • Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications CRF. • Record alcohol use on the liver event alcohol intake CRF • Exclude pregnancy • Urine drug screen **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG or gamma globulins. • A serum acetaminophen adduct assay for assessing the potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week. • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRFs.

a. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study medication if ALT ≥3xULN **and** bilirubin ≥2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.

b. All events of ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN **and** INR >1.5 may indicate severe liver injury **(possible 'Hy's Law') and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**. The INR measurement is not required and the stated threshold value will not apply to participants receiving anticoagulants.

c. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).

d. Includes:Hepatitis A immunoglobulin M (IgM) antibody; HBsAg and HBcAb; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.

e. If hepatitis delta antibody assay cannot be performed, it can be replaced with a polymerase chain reaction (PCR) of hepatitis D RNA virus (where needed) [Le Gal et al, 2005].Record the date/time of the PK blood sample draw and the date/time of the last dose of study medication prior to the PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the IMP Handling Manual.

Table 10–3: Liver chemistry increased monitoring criteria with continued study medication

Liver Chemistry Increased Monitoring Criteria	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3xULN and <5xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	• Notify the Sponsor Medical Monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study medication. • Participant must return weekly for repeat liver chemistry tests (ALT, AST, alkaline phosphatase, bilirubin) until the abnormalities resolve, stabilize, or return to baseline. • If at any time, the participant meets liver chemistry stopping criteria, proceed as described in Section 7.1.1. • If ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN and <5xULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor participants twice monthly until liver chemistry tests resolve, stabilize, or return to baseline.

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal

10.7 Appendix 7: Medical Device Incidents – Definition and Procedures for Recording, Evaluating, Follow-up, and reporting

Not applicable.

10.8 Appendix 8: Rapid Alert Procedures

Not applicable.

10.9 Appendix 9: Country-specific Requirements

Not applicable.

10.10 Appendix 10: Abbreviations and Trademarks

AChE	acetylcholinesterase
AChR	acetylcholine receptor
ADA	anti-drug antibody
AE	adverse event
AESM	adverse event of special monitoring
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BP	blood pressure
BUN	blood urea nitrogen
CI	confidence interval
CIDP	chronic inflammatory demyelinating polyradiculoneuropathy
COVID-19	coronavirus disease 2019
CPMP	Committee for Proprietary Medicinal Products
CRF	Case Report form
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
EOS	End of Study
eCRF	electronic Case Report form
EQ VAS	EuroQol visual analogue scale
FAS	Full Analysis Set
FcRn	neonatal Fc receptor
FIH	first in human
FSH	follicle stimulating hormone

FVC	forced vital capacity
GCP	Good Clinical Practice
GI	gastrointestinal
gMG	generalized myasthenia gravis
HBsAg	Hepatitis B surface antigen
HIV	human immunodeficiency virus
HPLC	high performance liquid chromatography
HRT	hormonal replacement therapy
IB	Investigator's Brochure
IBD	inflammatory bowel disease
ICF	Informed Consent form
ICH	International Council for Harmonisation
ICH-GCP	International Council for Harmonisation-Good Clinical Practice
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
Ig	immunoglobulin
IGRA	interferon-gamma release assay
INR	international normalized ratio
IMP	investigational medicinal product
IRB	Institutional Review Board
IRT	interactive response technology
ITP	immune thrombocytopenia purpura
iv	intravenous
IVIg	intravenous immunoglobulin
LDH	lactate dehydrogenase
LLOQ	lower limit of quantification
LS	least squares
LTBI	latent tuberculosis infection
MedDRA	Medical Dictionary for Regulatory Activities
MG	myasthenia gravis
MG-ADL	Myasthenia Gravis-Activities of Daily Living

MG-C	Myasthenia Gravis Composite
MGFA	Myasthenia Gravis Foundation of America
MG-QOL15r	Myasthenia Gravis Quality of Life
MGII	Myasthenia Gravis Impairment Index
MMRM	mixed model for repeated measures
MuSK	muscle-specific kinase
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NMJ	neuromuscular junction
NTMBI	nontuberculous mycobacterial infection
OLE	open-label extension
PD	pharmacodynamics(s)
PEF	peak expiratory flow
PEOT	premature end of treatment
PEX	plasma exchange
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	pharmacokinetic(s)
PK-PPS	Pharmacokinetic Per-Protocol Set
PRO	patient-reported outcome
PTT	partial thromboplastin time
QMG	quantitative myasthenia gravis
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System
sc	subcutaneous
SD	standard deviation
SE	standard error
SOP	Standard Operating Procedure
SS	Safety Set

TB	tuberculosis
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WHO	World Health Organization
WOCBP	women of childbearing potential

10.11 Appendix 11: Protocol Amendment History

Amendment 3 (29 Jul 2020)

Overall Rationale for the Amendment

The primary reason for this protocol amendment is to introduce the MG0007 study as the open-label extension (OLE) study to MG0003 and closure of MG0004 once MG0007 study is available, decrease the complexity of assessments to be performed, clarify some operational aspects of the study, and to include the management of study participant treatment during the coronavirus disease 2019 (COVID-19) pandemic including contingency measures.

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Section # and Name	Description of Change	Brief Rationale
Global	Minor administrative, formatting, and typographical changes have been made.	Updated to provide clarity and be consistent with remainder of protocol.
Global	Where applicable, all reference to the rollover OLE study, MG0004, has been replaced to introduce the new OLE study, MG0007.	The current ongoing OLE study, MG0004 (52-week chronic treatment) will be replaced by MG0007, which is a less complex study with 6-week treatment cycles based on myasthenia gravis (MG) worsening.
1.1 Objectives and Endpoints 3 Objectives and Endpoints	An additional other efficacy endpoint has been added: "Minimal symptom expression Myasthenia Gravis-Activities of Daily Living (MG-ADL [score of 0 or 1]) at Day 43 (Visit 10)"	This endpoint reflects the current scientific and medical interests.
1.1 Objectives and Endpoints 3 Objectives and Endpoints	Other efficacy endpoints related to MG Impairment Index (MGII) scores have been moved to the end of the list.	MGII has switched from mandatory to optional and will be performed at fewer study visits.
1.1 Objectives and Endpoints 3 Objectives and Endpoints	An additional other safety endpoint has been added: "Suicidality as measured by the Columbia Suicide Severity Rating Scale (C-SSRS)"	Updated to be consistent with the statistical analysis plan (SAP).
1.1 Objectives and Endpoints 3 Objectives and Endpoints	The pharmacodynamic endpoint for neurofilament-light (NF-L) levels has been removed.	The endpoint was removed to decrease study complexity, as scientific value is limited.
1.1 Objectives and Endpoints	The objective relating to anti-drug antibody (ADA) was updated to include the impact it has on	Updated for consistency with the clarifying text in Section 9.5.2.2.

Section # and Name	Description of Change	Brief Rationale
3 Objectives and Endpoints	pharmacokinetics (PK) and pharmacodynamics (PD).	
1.1 Objectives and Endpoints 3 Objectives and Endpoints	Evaluation of the effects of rozanolixizumab on albumin and the α- and β-globulins was removed from the study objectives.	The objective was amended to decrease study complexity, as scientific value limited.
1.1 Objectives and Endpoints 3 Objectives and Endpoints	Evaluation of the effects of rozanolixizumab on serum cytokines was added to the study objectives.	Updated for consistency within the protocol.
1.1 Objectives and Endpoints 3 Objectives and Endpoints	'Observation Period' was removed from the endpoint relating to serum cytokines.	Updated for consistency within the protocol.
1.1 Objectives and Endpoints 3 Objectives and Endpoints	Assessment of the effect of rozanolixizumab on deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) was removed from the study objectives and associated endpoints.	The objective and endpoints were amended to decrease study complexity, as scientific value limited.
1.1 Objectives and Endpoints 3 Objectives and Endpoints	Genetics was removed from the study objective and endpoint.	The objective and endpoints were amended to decrease study complexity, as scientific value limited.
1.1 Objectives and Endpoints 3 Objectives and Endpoints	The objective and endpoints for exploratory biomarkers was made more general.	The objective and endpoints were amended to decrease study complexity, as scientific value limited.
1.1 Objectives and Endpoints 3 Objectives and Endpoints	The table footnote was updated to include serious headache and to clarify that other safety biomarkers may be assessed.	Updated for consistency within the protocol.
1.1 Treatment groups and Duration 4.1 Overall Design 9.8.2 Periodic Data Reviews	The timing of the second and third periodic data reviews has been amended.	To ensure appropriate timing of periodic data reviews relative to the interim analysis.
1.2 Schema	The study schematic and footnote were updated.	Updated to reflect changes and be consistent with the introduction of MG0007.
1.3 Schedule of Activities	Visits 11 and 13 have been changed to virtual visits.	This change was made to decrease the complexity of the study.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	Optional pharmacogenomic sub-study consent has been removed.	Decrease study complexity as scientific value.
1.3 Schedule of Activities	Optional PK and ADA sub-study consent updated to remove ADA.	The sub-study does not include ADA.
1.3 Schedule of Activities	The hemoglobin A1c (HbA1c) test at screening has been removed from the study.	Participants with diabetes are not excluded from the study and therefore this additional test is not required.
1.3 Schedule of Activities	Hematology, serum chemistry and urinalysis assessments have been removed at Visits 5 and 8.	This change was made to decrease the complexity of the study and reduce the burden for the study participants.
1.3 Schedule of Activities	Measurement of partial thromboplastin time (PTT) and international normalized ratio (INR) was added for the Screening Visit (Visit 1).	Updated to correct an error in the Schedule of Activities.
1.3 Schedule of Activities	Vital signs assessments have been removed at Visits 11 and 13.	Removed because these visits have become virtual visits.
1.3 Schedule of Activities	Call or enter interactive response technology (IRT) was added for Visits 2, 3, 7, 11, 12 and 13.	Updated to correct an error in protocol amendment 2.
1.3 Schedule of Activities	Blood sampling for PK has been removed at Visits 8 and 9.	Updated to decrease the complexity of the study.
1.3 Schedule of Activities	Blood sampling for exploratory safety biomarker analysis has been removed at Visits 4, 5, 6, 8 and 9.	Updated to clarify that it is event driven only and not applicable to all study participants.
1.3 Schedule of Activities	The α- and β-globulins have been removed from future exploratory biomarker analysis.	Updated to decrease the complexity of the study.
1.3 Schedule of Activities	Blood sampling for total immunoglobulin (Ig)G and IgG subclasses has been removed at Visit 3.	Updated to decrease the complexity of the study.
1.3 Schedule of Activities	Blood sampling for IgA, IgM and IgE has been removed at Visits 5 and 8.	Updated to decrease the complexity of the study.
1.3 Schedule of Activities	Blood sampling for DNA and RNA has been removed throughout the study.	Updated to decrease the complexity of the study.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	Assessment of serum complement levels (C3, C4) and cytokines has been combined into one procedure.	Updated to decrease the complexity of the study.
1.3 Schedule of Activities	Assessment of serum complement levels (C3, C4), cytokines and plasma complement levels (C3a and C5a) has been removed from Visits 4, 5, 6 and 8.	Updated to correct an error in the original protocol.
1.3 Schedule of Activities	Assessment of NF-L has been removed throughout the study.	Updated to decrease the complexity of the study.
1.3 Schedule of Activities	Assessment of MG Symptoms patient-reported outcome (PRO) has been removed at Visits 6 and 9.	Updated to decrease the complexity of the study.
1.3 Schedule of Activities	Assessment of EQ-5D-5L has been removed at Visit 14 (End of Study [EOS]).	Updated to decrease the complexity of the study.
1.3 Schedule of Activities	Assessment of MGII has been removed at Screening, Visit 4 and Visit 14 (EOS). In addition, it has become an optional assessment at the other visits.	Updated to decrease the complexity of the study.
1.3 Schedule of Activities	Assessment of Myasthenia Gravis Quality of Life (MG-QOL)15r has been removed at Visit 6 and Visit 14 (EOS).	Updated to decrease the complexity of the study.
1.3 Schedule of Activities	Abbreviations have been updated to reflect the changes made in the table.	Updated for consistency within the protocol.
1.3 Schedule of Activities	The order of the footnotes has been updated to reflect the changes made in the table.	Updated for consistency within the protocol.
1.3 Schedule of Activities	Footnote b: "This visit will be a virtual visit, unless the study participant prefers to attend the site." has been added.	Added to indicate that Visits 11 and 13 are virtual visits.
1.3 Schedule of Activities	Footnote d: "Refer to Section 1.4." has been added.	Added to indicate the details can be found in that Section 1.4.
1.3 Schedule of Activities	Footnote k: (Assessment is optional for all study participants) has been removed.	The instruction applied to blood sampling for DNA and RNA and no longer applies as the assessments were removed.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	Footnote l (previously footnote j): Updated to include severe headache and AESM of gastrointestinal (GI) disorders.	Updated for consistency within the protocol.
1.3 Schedule of Activities	Footnote n: "postdose" was replaced with "postevent".	Updated to correct terminology error.
1.3 Schedule of Activities	Footnote o: "MGII is optional for all study participants." has been added.	MGII has switched from mandatory to optional for each study visit.
1.4 Schedule of Activities (sub-study)	Visit 3 has been corrected to 3a.	Updated to correct an error in protocol amendment 2.
1.4 Schedule of Activities (sub-study)	Abbreviations have been updated to reflect the changes made in the table.	Updated for consistency within the protocol.
1.4 Schedule of Activities (sub-study)	Details have been added specify that PK samples will only be collected for study participants who have consented to participate in the sub-study.	Updated to clarify that the sub-study is optional.
1.4 Schedule of Activities (sub-study)	Footnote a: "Samples can be obtained at home, if appropriate." has been added.	To simplify and decrease complexity of the study.
2.2 Background	The number of rozanolixizumab clinical studies has been amended to include the 3 additional studies; TP0003, TP0006 and CIDP04.	Updated to be consistent across the Phase 3 rozanolixizumab clinical program.
4.1 Overall Design	The number of sites has been changed from 125 to 135. In addition, Asia has been added as a region for the study to be performed.	Number of sites and countries have been expanded for the study to account for increased recruitment challenges during/post the COVID 19 pandemic.
4.1 Overall Design	A new sentence has been added to explain that contingency measures during a pandemic and other exceptional circumstances has been put in place.	Contingency measures have been implemented to ensure study participant safety in response to the COVID-19 pandemic causing the inability for sites to adhere to protocol visits and assessments.
5.1 Inclusion Criteria	Inclusion criterion #5a: The MG-ADL score at screening was updated to clarify that participants had to have ≥3 points from non-ocular symptom.	To ensure target population (generalized myasthenia gravis [gMG]) is fully captured.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion criteria	Exclusion criterion #22b: glomerular filtration rate (GFR) entry criteria has been adjusted from less than 60ml/min/1.73m^2 to less than 45ml/min/1.73m^2 at Visit 1.	To expand the population for a more generalized safety database and minimizes the risk of a potential effect unique to neonatal Fc receptor (FcRn) renal dynamics.
5.2 Exclusion criteria	Exclusion criterion #39a: Criteria updated to exclude all participants with a medical history of splenectomy.	To minimize the potential risk of overwhelming post-splenectomy infection.
5.4 Screen Failures	Clarified when isolated test results outside the specific range at Screening need to be rechecked with the sponsor's medical monitor/study physician.	Clarification of procedure.
6.3.1.1 Maintenance of study treatment blind	New wording was included to clarify that treatment must be temporarily discontinued for any participant with IgG levels below 1g/L and may be temporarily discontinued for any participant with IgG levels ≥1g/L and <2g/L with nonserious infection which is persisting or recurrent.	Updated to clarify the procedure on when treatment discontinuation is required.
6.5.1 Permitted concomitant treatments (medications and therapies)	Footnote b updated to correct the units for cyclosporine from "ng/L" to "ng/mL".	Updated to correct an error in protocol amendment 2.
7.1.3 Discontinuation due to other adverse events or medical conditions	Criterion #3: Details regarding serious infective episodes was updated.	Updated for consistency within the protocol.
7.1.4 Temporary IMP discontinuation	New details have been included to replace text pertaining to procedures for temporary IMP discontinuation. Furthermore, additional clarity has been included for procedures undertaken when temporary treatment discontinuation is required to low IgG levels.	Updated to be consistent across the Phase 3 rozanolixizumab clinical program.
7.1.4 Temporary IMP discontinuation	In addition, details have been added for participants that have suspected or confirmed COVID-19.	Updated to clarify the procedures on when treatment discontinuation is required in response to the COVID-19 pandemic.

Section # and Name	Description of Change	Brief Rationale
8 Study Assessments and Procedures	A new paragraph describing contingency measures during a pandemic and other exceptional circumstances has been included.	Contingency measures have been implemented to ensure study participant safety in response to the COVID-19 pandemic causing the inability for sites to adhere to protocol visits and assessments.
8.1.4 Patient-reported outcomes	Text updated to clarify that MGII is an optional assessment.	MGII has switched from mandatory to optional for each study visit.
8.1.4.1 MG-Activities of Daily Living	Details have been added explaining how the MG-ADL should be completed.	This has been updated to ensure the avoidance of bias when completing the MG-ADL.
8.1.4.6 MG Impairment Index	Text updated to clarify that MGII is an optional assessment.	MGII has switched from mandatory to optional for each study visit.
8.2.6 Assessment and management of TB and TB risk factors	A cross reference to the Schedule of Activities has been added.	Updated for consistency within the protocol.
8.2.6 Assessment and management of TB and TB risk factors	The World Health Organization (WHO) Global Tuberculosis Report was updated to the 2019 version.	Updated in line with the current version.
8.5 Treatment of Overdose	Details related to monitoring of participants any adverse event (AE)/serious adverse event (SAE) or laboratory abnormality have been updated.	Updated to be consistent across the Phase 3 rozanolixizumab clinical program.
8.7 Pharmacodynamics	Assessment of serum NF-L levels have removed from the study.	Updated due to limited scientific value and to decrease the complexity of the study.
8.8.1 Pharmacogenomics	This section has been deleted.	Pharmacogenomics are not evaluated in this study.
8.8.2 Immunology	This section was moved from Section 8.8 and put into Section 8.9 and has been renumbered as 8.9.1.	Updated to be consistent across the Phase 3 rozanolixizumab clinical program.
8.9 Biomarkers	Evaluation of the effects of rozanolixizumab on albumin, the α- and β-globulins, B-cell activating factor and Circulating Immune Complexes has been removed.	Updated to decrease the complexity of the study.
8.9 Biomarkers	Updated to include serious or severe headache.	Updated for consistency within the protocol.

Section # and Name	Description of Change	Brief Rationale
8.9.1 Immunology	Serum complement levels (C3, C4) and serum cytokines combined into one procedure.	Updated to decrease the complexity of the study.
8.9.1 Immunology	For collection of additional samples, “postdose” was replaced with “postevent”.	Updated to correct terminology error.
8.11 Participant Exit Interview	A new section has been added explaining that study participants may be asked to sign a separate informed consent for possible participation in a market research interview.	Additional consent has been included with the aim to collect the study participant’s experience with MG and the perceived changes during the course of the study.
9.3 Estimands	A sentence was added to explain that data handling conventions for data affected by COVID-19 will be detailed fully in the SAP.	Added to confirm that the potential effects of COVID-19 on the data analysis will be addressed.
9.3 Estimands	Table 9-1: Estimand Details and Attributes has been updated to be consistent with the SAP.	Updated to be consistent with the SAP.
9.3 Estimands	Table 9-1: Estimand Details and Attributes: an additional sensitivity analysis has been added for MG-ADL.	Added to assess the validity of the MAR assumption in the primary endpoint.
9.3 Estimands	Table 9-1: Estimand Details and Attributes: Details for secondary estimands have been added to the table.	Updated to be consistent with the SAP.
9.3 Estimands	Abbreviations have been updated to reflect the changes made in the table.	Updated for consistency within the protocol.
9.5.2.2 Anti-drug antibodies analyses	Text added to clarify that the impact of ADA will be evaluated on PK, PD, efficacy and safety endpoints when relevant.	Updated to be consistent with the SAP.
10.1.3 Informed consent process	A sentence has been added explaining that study participants may be asked to sign a separate informed consent for possible participation in a market research interview.	Additional consent has been included with the aim to collect the study participant’s experience with MG and the perceived changes during the course of the study.
10.2 Appendix 2: Clinical Laboratory Tests	The following parameter was added: “albumin”.	Updated for consistency within the protocol.

Section # and Name	Description of Change	Brief Rationale
10.2 Appendix 2: Clinical Laboratory Tests	The HbA1c test at screening has been removed from the study.	Participants with diabetes are not excluded from the study and therefore this additional test is not required.
10.5 Appendix 5: Genetics	All text related to genetic testing and analyzing have been removed.	Genetics are not evaluated in this study.
10.10 Appendix 10: Abbreviations and Trademarks	Two additions (COVID-19 and PTT) and two deletions (NF-L and HbA1c) were made to the list of abbreviations.	Updated to reflect the parameters measured in the study.
10.11 Appendix 11: Protocol Amendment History	Details of the previous amendment (protocol amendment 2) have been added.	General update.
10.23 Appendix 23: Management of Headache	Clarified that treatment may be temporarily put on hold if a study participant experiences a severe AE of headache that is not resolved prior to the next scheduled study treatment.	Updated for consistency within the protocol.
10.24 Appendix 24: Management of Diarrhea	Definition of severe (grade 3) diarrhea has been updated.	Updated to be consistent across the Phase 3 rozanolixizumab clinical program.
10.25 Appendix 25: Management of Infections and Hypogammaglobulinemia	The following sentence “Ad hoc assessment can be performed to monitor the recovery of IgG levels.” has been added.	Updated to be consistent across the Phase 3 rozanolixizumab clinical program.
10.25 Appendix 25: Management of Infections and Hypogammaglobulinemia	The following sentence was modified to include “must”: Treatment must be temporarily discontinued for the study participant who develops an event of hypogammaglobulinemia with a serum total IgG of <1g/L irrespective of infection.	Updated to be consistent across the Phase 3 rozanolixizumab clinical program.
11 References	Order of references corrected.	Updated to be consistent with the style guide.

Amendment 2 (04 Mar 2020)

Overall Rationale for the Amendment

The primary reason for this protocol amendment is to incorporate the harmonization of inclusion criteria with studies performed across the rozanolixizumab development program, and include a new section to include temporary discontinuation of IMP in case of low IgG levels observed in

study participants. Furthermore, additional blood and pharmacokinetic samples, as well details pertaining to a sub-study have been incorporated to provide the opportunity to increase confidence in the PK exposure from the selected doses and help clinically validate the ADA assays drug tolerance through analysis of a drug onboard postdose sample as opposed to the pre-dose samples that are likely to be BLQ.

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Protocol amendment 2 was an internally approved document, which was not implemented at the study sites or submitted to the regulatory authorities. Protocol amendment 3 included changes related to COVID-19 and incorporates protocol amendment 2.

Section # and Name	Description of Change	Brief Rationale
Global	Minor administrative, formatting, and typographical changes have been made.	Updated to provide clarity and be consistent with remainder of protocol.
Title page	Sponsor name has been updated.	Belgium has recently adopted a new Code of Companies and Associations, resulting in a mandatory change of the name of the legal form of the entity "*société privée à responsabilité limitée*", abbreviated "*SPRL*", to "*société à responsabilité limitée*", abbreviated "*SRL*".
1.3 Schedule of Activities	End of Treatment "EOT" was added to Visit 10.	Updated to provide clarity that Visit 10 is not only a PEOT Visit.
1.3 Schedule of Activities	New activity was added: "Optional PK and ADA sub-study consent"	Updated to due to the optional sub-study.
1.3 Schedule of Activities	The scheduled timepoint for blood sampling for ADA was changed from Visit 8 to Visit 7.	Updated to correct an error in protocol amendment 1.
1.3 Schedule of Activities	Addition of "BL" and "EOT" to abbreviation list.	Updated for consistency.
1.3 Schedule of Activities	Footnote c: Visit 14 (EOS) was removed as a scheduled visit for the collection of body weight.	Updated to correct an error in protocol amendment 1.
1.4 Schedule of Activities	An additional SoA for the sub-study has been added to include additional PK samples.	Updated to due to the optional sub-study.
4.1 Overall Design	The number of sites has changed from 106 to 125.	The number of potential sites participating in the study has increased.

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria	Inclusion criterion #8a: All reference to 90 days should be preceded with "at least".	Updated to be consistent across the Phase 3 rozanolixizumab clinical program.
5.2 Exclusion Criteria	Criterion #22b: Definition for renal impairment has changed with GFR less than "41"ml/min/1.73m.	Updated to be consistent across the Phase 3 rozanolixizumab clinical program.
5.2 Exclusion Criteria	Criterion #27a: chronic liver disease has been replaced with "hepatobiliary conditions"	Updated to be consistent across the Phase 3 rozanolixizumab clinical program.
5.2 Exclusion Criteria	Exclusion criterion #37: The number was reinserted, but the criterion itself remains removed from the study.	Updated to be consistent with UCB standards, and to correct an error in protocol amendment 1.
5.3.1 Meals and dietary restrictions 5.3.2 Caffeine, alcohol, and tobacco	Both sections have been removed.	These sections were deemed unnecessary as the wording in Section 5.3 (Lifestyle Restrictions) cover the content.
5.4 Screen Failures	The number of isolated tests result outside the specific range deemed clinically nonsignificant has changed.	Updated to remove the limit and to be consistent across the Phase 3 rozanolixizumab clinical program.
6.3.1.1 Maintenance of study treatment blind	Clarification that treatment will be discontinued for any participant with IgG levels below 1g/L or 2g/L with no infection on consectitive visits.	Updated to clarify when treatment discontinuation is required.
7.1.1 Liver Chemistry Stopping Criteria 7.1.2 QTc Stopping Criteria	A new sentence was added to emphasise study participants should follow the visit schedule as described in the protocol.	New wording was added to provide clarity for each subsection under 7.1.
7.1.4 Temporary IMP discontinuation	New subsection has been added: Temporary IMP discontinuation, covering procedure for implementation of mock infusions.	This section was added to include the management of temporary IMP discontinuation for low IgG values in any study participant
8.2.1 Physical examination (full physical examination)	New wording "Visit 1 and Baseline (Visit 2) only" has been added to replace at other timepoints.	Updated to be consistent with the Schedule of Activities.
8.6 Pharmacokinetics and Anti-drug Antibodies	Additional wording has been provided to details on additional PK blood sampling: "Additional PK samples will be collected (Section1.4) at selected sites for study particpants who have consented to participate in the sub-study"	Updated to due to the optional sub-study.

Section # and Name	Description of Change	Brief Rationale
8.8.2 Immunology	"Tetanus toxoid IgG" was added to the list of measurements.	Updated to be consistent with the Schedule of Activities.
9.3 Estimands, Table 9-1	An additional sensitivity analysis of primary endpoint, MG-ADL was added.	Included for study participants who need to miss doses due to low IgG levels.
10.1.3 Informed consent process	Additiotnal wording pertaining to the sub-study and required informed consent has been added.	Updated to due to the optional sub-study.
10.2 Appendix 2: Clinical Laboratory Tests	The following tests have been removed at Screening: Serology testing ("for Hepatitis A"), and "serum or urine alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines". The following parameter was added: "C-reactive protein".	Updated to correct an error in protocol amendment 1.
10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information	All reference to 3 months had been replaced by "90 days". All reference to 90 days should be preceded with "at least".	Updated to be consistent across the Phase 3 rozanolixizumab clinical program.
10.6 Appendix 6: Liver Safety – Suggested Actions and Follow-up Assessments	The choice of specific assay for the bilirubin or INR criteria.	Updated to remove the description of a specific assay to give the investigator a broader range of tests to choose from.
10.24 Appendix 24: Management of Diarrhea	Stool sample collection has been amended: Stool samples may be collected for stool "analysis" to "rule out infection" for study participants reporting severe diarrhea. Stool sampling will be as clinically indicated in the opinion of the investigator and assessed per local guidance.	The language updated to be consistent across the Phase 3 rozanolixizumab clinical program.
10.29 Appendix 29: Columbia-Suicide Severity Rating Scale	New text, "Screening" and "Since Last Visit" have been included to define each version provided in the appendix.	Updated to provide clarity for each example.
11 References	The following reference was added: 5th ed. Arlington. Diagnostic and Statistical Manual of Mental	Updated to maintain consistency.

Section # and Name	Description of Change	Brief Rationale
	Disorders. American Psychiatric Association. 2013. The following reference was removed: James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, et al. Pharmacokinetics of acetaminophen-protein adducts in adults with acetaminophen overdose and acute liver failure. Drug Metab Dispos. 2009; 37:1779-84	

Amendment 1 (30 Oct 2019)

Overall Rationale for the Amendment

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Section # and Name	Description of Change	Brief Rationale
Serious Adverse Event Reporting	All reporting instructions for Japan has been removed.	This study will be conducted in Japan as a part of global study
Global	Where applicable, the term "subject" has been replaced by "study participant"	The change has been made as per UCB template and to remain consistent with the Phase 3 rozanolixizumab clinical program.
1.1 Synopsis 3 Objectives and Endpoints	An additional other efficacy endpoint was added: "Time to first rescue therapy". An additional exploratory objective and endpoint on tetanus IgG anibodies was added. The following secondary efficacy endpoint was amended to include specific text: Change from Baseline to Day 43 (Visit 10) in the MG Symptoms patient-reported outcome (PRO) '**Muscle Weakness** Fatigability' score The following secondary efficacy endpoint was amended to remove specific text: Change from Baseline to Day 43 (Visit 10) in the MG Symptoms	"Time to first rescue therapy" added to further characterize rozanolixizumab clinical benefits. Tetanus IgG antibodies was added to assess the effect of rozanolixizumab on tetanus IgG antibodies. Other updates were implemented for consistency, as there were redundancies.

Section # and Name	Description of Change	Brief Rationale
	PRO 'Physical Fatigue**, Limb and Axial Weakness**' score The following other efficacy endpoints have been removed: Value and change from Baseline in the MG Symptoms PRO multi-component total score, at each scheduled assessment during Treatment and Observation Periods Value and change from Baseline in the enhanced MG Symptoms PRO total score, at each scheduled assessment during Treatment and Observation Periods The term "Value" has been removed from all endpoints, where applicable.	
1.1 Synopsis 4.1 Overall Design	The description for the overall design has been amended. Additional text to provide follow-up instructions for study participants who receive IVIg and discontinue the study.	Updated wording has been included to provide further clarification of the overall study design.
1.2 Schema	The study schematic was updated.	Update was made to reflect changes to study design.
1.3 Schedule of Activities	Additional visits (Visits 4, 5, 6, 8, 9, 10, and 14) have been added for IRT registering.	Visits have been added to the Schedule of Activities to be consistent with the study design.
1.3 Schedule of Activities	Blood sampling for pharmacokinetics at additional visits (Visits 4, 6, and 11) have been removed.	Pharmacokinetic concentrations are expected to be Below the Limit of Quantitation at these visits.
1.3 Schedule of Activities	Additional visits (Visits 8 and 14 [EOS]) have been added for blood sampling for ADA.	For Visit 8, information on the onset of ADA will be obtained. For the EOS visit, information on the ADA persistency in the system once drug is not on board wil be obtained.
1.3 Schedule of Activities	Additional visits (Visits 4, 5, 6, 8, and 9) have been added for blood sampling for DNA and RNA.	Visits have been added to the Schedule of Activities to be consistent with the study design.
1.3 Schedule of Activities	An additional activity "anti-tetanus toxoid titer" was added.	Anti-tetanus toxoid titer will be collected as part of the assessment

Section # and Name	Description of Change	Brief Rationale
		for the effect of rozanolixizumab on tetanus IgG antibodies.
1.3 Schedule of Activities	Urine drug screen procedure has been removed from the study.	The exclusionary criterion pertaining to use of marijuana was removed.
1.3 Schedule of Activities	Myasthenia Gravis Impairment Index was added for the Baseline Visit (Visit 2).	Missing activity for that visit.
1.3 Schedule of Activities	An additional visit was added for PGI-S.	Visit 1 collection was added to capture Baseline data.
1.3 Schedule of Activities	Additional abbreviations previously missing have been added.	General consistency.
1.3 Schedule of Activities	Footnote b: A visit window of ±4 days has been added for Visits 12 and 14.	General consistency.
1.3 Schedule of Activities	Footnote c: Body weight will also be collected at Visit 14 (EOS).	Updated to provide Baseline value for the open-label extension study.
1.3 Schedule of Activities	Footnote d: The addition of "Question 1" has been added to the existing wording.	Updated for further clarity.
1.3 Schedule of Activities	Footnote g (any recreational or medicinal use of cannabis [ie, marijuana] or cannabidiols is not authorized in the study) has been removed.	The use of cannabidiols and medicinal marijuana (prescribed by a physician) is now part of the permitted concomitant treatments list.
1.3 Schedule of Activities	Footnote h: The following was added: "Study participants must be observed at site postdose for at least 4 hours following the first 2 infusions, and then 2 hours thereafter for subsequent infusions"	The footnote was included to provide clear instructions for postdose observation.
1.3 Schedule of Activities	Footnote j: Current wording has been modified to allow the collection of additional exploratory safety samples 4 hours postdose or as soon as possible before the next IMP in case of AESM and serious headaches regardless of severity at Visits 4, 5, 6, 8, and 9.	The footnotes were modified to provide clear instructions and to ensure consistency within Section 8.9 of the protocol.
1.3 Schedule of Activities	Footnote l (now footnote m): wording has been modified: "To be collected predose at Visit 2, and 4 hours postdose at Visit 9.	The footnote was modified to provide clear instructions and to ensure consistency with other blood sampling assessments.

Section # and Name	Description of Change	Brief Rationale
	Additional samples must be collected 2 hours and 4 hours postdose or as soon as possible before the next IMP for study participants with severe headache and/or infusion reaction or hypersensitivity reaction."	
1.3 Schedule of Activities	Footnote m has been replaced with footnote l (now listed as m since the updates).	Updated for consistency.
1.3 Schedule of Activities	Footnote n has been removed.	The instruction applied to the study withdrawal assessment no longer applies.
2.2 Background	The number of rozanolixizumab clinical studies has been amended from 3 to 5 due to the two additional studies; CIDP01 and UP0060.	General update.
3 Objectives and Endpoints	The primary efficacy analysis "the change from Baseline in MG-ADL score to Day 43 (Visit 10)" has been added to this section.	General update.
4.1 Overall Design	This section was modified to update the approximate number of study participants screened from [redacted] In addition, China has been removed as a possible participant for this study, and Hong Kong and Taiwan have been added.	An increase in the range of screened study participants has been made based on an anticipated percentage (up to [redacted]) screening failures. With [redacted] participants screened and a [redacted] screening failure, the study will randomize [redacted] study participants.
4.3 Justification for Dose	This section was amended to include additional text for UP0018 data.	To provide accurate information on maximum mean decreases for Baseline IgG.
5.1 Inclusion Criteria	Criterion #3: For Visit 1, replaced "prior to" with "at" for the requirement to have confirmed positive record of autoantibodies against AChR or MuSK. New wording has been added to allow repeated testing at Visit 1 for confirmed presence of autoantibodies.	This change is to allow confirmation from medical history information during the Screening Period, if needed.
5.1 Inclusion Criteria	Criterion #6: added "additional" and "such as" to broaden the	Updated for consistency.

Section # and Name	Description of Change	Brief Rationale
	criteria for treatments considered by the Investigator.	
5.1 Inclusion Criteria	Criterion #7: the body weight parameter was changed from greater than (“>”) to equal to or greater than (“≥”).	The update was made to harmonize the inclusion criterion across the rozanolixizumab Phase 3 clinical program.
5.1 Inclusion Criteria	Criterion #8: The following wording: “and prior to further dosing at each study visit thereafter” was removed.	Updated for consistency, as this conflicted with part of the study design.
5.2 Exclusion Criteria	New wording has been included to provide clarity on timing of each exclusion criteria, where applicable.	Updated to provide clarity for timing of each exclusion criterion.
5.2 Exclusion Criteria	Criterion #2: Replaced “drug abuse” with “other substance disorder use” and clarified study participants history is based on 12 months **prior to Screening Visit**.	The criterion was updated to reflect the new language adopted in DSM-5.
5.2 Exclusion Criteria	Criterion #4: The study participant must have “known” history of hyperprolinemia.	Updated to clarify previously obtained medical records can be used.
5.2 Exclusion Criteria	Criterion #9 and #10: Associated table was amended.	The change was implemented based on feedback of investigators, and to align the exclusionary period of biologics in the protocol.
5.2 Exclusion Criteria	Criterion #12, #13, #30: All three criterias have been amended to include “prior to Visit 1”	Updated to provide clarity for timing of each exclusion criterion.
5.2 Exclusion Criteria	Criterion #13: Diverticular disease has been added as historical condition or disease in the past 6 months.	Updated to be consistent with adverse reactions across the rozanolixizumab clinical program.
5.2 Exclusion Criteria	Table 5-1: The treatment period prior to Baseline for the following were changed: Eculizumab (Solaris®): 6 to **3** months Other biologics: 6 months to 3 months, **or within 5 half-lives (whichever was longer) prior to the Baseline Visit**.	The change was implemented based on feedback of investigators, and to align the exclusionary period of biologics in the protocol.

Section # and Name	Description of Change	Brief Rationale
	Intravenous and subcutaneous IgG and PEX: from 6 to **4** weeks Immunoadsorption: from 6 to **4** weeks	
5.2 Exclusion Criteria	Criterion #15: This criterion has been amended to provide additional information for study participants who have previously been randomized in this study.	Clarification has been provided on the rules with regards to previous randomization in this study.
5.2 Exclusion Criteria	Criterion #17: Additional visit (Baseline [Visit 2]) has been added.	Visit 2 was added to provide additional clarity on the applicable timeframe for Exclusion Criterion #17
5.2 Exclusion Criteria	Criterion #22: Amended definition (GFR less than 60ml/min/1.73m^2) has been included for renal impairment.	The inclusion of mild renal impairment is applicable to the Phase 3 clinical program with prior Phase 2 experience and no observations on renal impact.
5.2 Exclusion Criteria	Criterion #23: Amended upper limit of normal for alanine transaminase, aspartate aminotransferase, or alkaline phosphatase was changed from >2x to **>3x**.	The inclusion of mild renal impairment is applicable to the Phase 3 clinical program with prior Phase 2 experience and no observations on hepatics impact.
5.2 Exclusion Criteria	Criterion #31: Amended to include "after Visit 1"	Updated to provide clarity for timing the exclusion criterion.
5.2 Exclusion Criteria	Criterion #37: The description for this criterion has been removed and reworded to fit into Section 6.5.1 (permitted concomitant treatments [medications and therapies]).	Original criterion was restrictive, and could significantly limit the number of study participants, therefore has been reworded to fit into the permitted concomitant treatments.
5.2 Exclusion Criteria	New criterion has been added, #38 Participant with current or medical history of IgA deficiency.	Per EMA request to minimise the risk of infection
5.2 Exclusion Criteria	New criterion has been added, #39: Participant has undergone a splenectomy in the 2 years prior to the Baseline Visit.	Per EMA request to reduce the potential overwhilming post-splenectomy infection
5.3 Lifestyle Restrictions	Study participants will abstain from recreational use of cannabis has now been removed. Study participants will be allowed to use medicinal marijuana or	Due to the change for cannabis (ie, medicinal marijuana) or cannabidiols use (as prescribed by a physician), the lifestyle restriction no longer applies to the study.

Section # and Name	Description of Change	Brief Rationale
	cannabidiols, as prescribed by a physician.	
5.4 Screen Failures	Additonal wording was included: "repeat all Visit 1 assessments".	Updated to provide clarity for details of rescreened study participants.
6.1 Treatments administered	Additional wording for the details (rate of infusion, administration, appropriate records handling, blinded and unblinded site personnel roles) available in the IMP Handling Manual have been included.	Previous wording did not accurately provide information for what contents are available in the IMP Handling Manual.
6.3 Measure to Minimize Bias	Additional wording was included: "The randomization will be stratified by the following: MG-specific autoantibody (MuSK+ or AChR+)".	Missing information.
6.5.1 Permitted concomitant treatments (medications and therapies	Additional wording has been added as part of permitted medication use: The use of cannabidiols and medicinal marijuana (prescribed by a physician) is also permitted. When applicable, the study participant must be on a stable dose of cannabidiols and/or medicinal marijuana for [redacted] prior to Screening Visit, and remain stable for the duration of the study. Table 6-1 Permitted concomitant medications for the treatment of myasthenia gravis: The dose for oral corticosteroids has been amended to state "no specific requirements" and "stable for [redacted] prior to Baseline instead of [redacted] Cholinesterase inhibitors: Dose hold was changed from [redacted] An additional footnote was added to include "Must also be stable for duration of study".	Due to the lack of pharmacodynamic and pharmacokinetic interactions between marijuana/ cannabidiols and rozanolixizumab, this criterion was revised. The table was updated to reflect changes made to the study design.
6.5.3 Treatments specific to NMJ interference	Correct reference has been added for the MGFA classification list.	General update.

Section # and Name	Description of Change	Brief Rationale
6.5.4 Rescue therapy	Additional wording on completion of remaining visits was added.	Updated to provide clarity.
6.7 Treatment after the End of the Study	Additional wording to include instructions that additional unscheduled visits every other week for 8 weeks from the completion of last IVIg or PEX session are required for study participants who opt for IVIg or PEX.	New language was added to allow study participants to complete the planned 6 weeks of treatment visits at the request of EMA.
7.1.3 Discontinuation due to other adverse events or medical conditions	An additional event "study participant has new onset or recurrent neoplastic disease (except for superficial basal or squamous cell carcinoma of the skin not requiring targeted biological therapy, chemotherapy or radiation" as added.	New language was added to align withdraw criteria with exclusion criteria, and not expose study participants with neoplastic disease to rozanolixizumab.
8 Study Assessments and Procedures	Additional information on Unscheduled Visits have been added.	There were no specific details and instructions for the assessments needed at an Unscheduled Visit.
8.1 Efficacy assessments	Efficacy assesments were reordered.	Order of efficacy assessments were amended to align with study procedure manual.
8.1.2 Patient-reported outcomes	Has become Section 8.1.4 and order of PROs (PGI-S, PGI-C, EQ-5D-5L, MGII, MG-QOL15r) were amended to align with Study Procedures manual. New wording has been added: "Study participants should not take pyridostigmine (or other AChE inhibitor medication) from midnight when efficacy assessments are performed when medically safe to do so to standardize testing"	Order of efficacy assessments were amended to align with study procedure manual.
8.1.2.3 Quantitative Myasthenia Gravis scale	Moved to standalone efficacy assessment (Section 8.1.2), as QMG scale is not a PRO. New wording has been added: In addition, "qualified designee" has been added to the text as another individual aside from the	The QMG scale is not a PRO. Added to provide clairification and harmonize how the assessment is performed at the site.

Section # and Name	Description of Change	Brief Rationale
	Investigator who can examine the study participant. "Study participants should not take pyridostigmine (or other AChE inhibitor medication) from midnight before testing when medically safe to do so to standardize testing" "Where possible, the same person should carry out the assessment at each visit."	
8.1.2.4 MG-Composite scale	Moved to standalone efficacy assessment (Section 8.1.3), as MG-C scale is not a PRO. In addition, "qualified designee" has been added to the text as another individual aside from the Investigator who can examine the study participant. New wording has been added: "Study participants should not take pyridostigmine (or other AChE inhibitor medication) from midnight before testing when medically safe to do so to standardize testing" "Where possible, the same person should carry out the assessment at each visit."	The MG-C scale is not a PRO. Added to provide clairification and harmonize how the assessment is performed at the site.
8.1.4.2 MG Symptoms PRO	The minimum total score was corrected to "from 0 to 100" as per scale presented in Appendix 16.	The original minimum total score was incorrect.
8.1.4.6 MG Impairment Index	There is an additional step to the assessment, where the Investigator or qualified designee will examine the study participant prior to scoring all items. New wording has been added: "Where possible, the same person should carry out the assessment at each visit."	Added to provide clairification and harmonize how the assessment is performed at the site.
8.2 Safety Assessment	Additional information on onsite observation timings postdose was included.	Added to provide clairification for postdose observations.

Section # and Name	Description of Change	Brief Rationale
8.2.2 Vital signs	The measurement of respiratory rate is no longer required as part of vital signs assessment.	To be consistent other Rozanolixizumab protocols.
8.2.5 Suicidal risk monitoring	Additional wording has been added to include C-SSRS at "Baseline and all subsequent visits".	To ensure consistency throughout the protocol.
8.2.6 Assessment and management of TB and TB risk factors	Latent TB: The following sentence has been deleted; "It is the Sponsor's requirement that all study participants who are on LTBI treatment at Baseline must comply with the full therapy course". Active TB or non-tuberculosis mycobacterium infection: The text was changed to replace WD with PEOT (premature end of treatment).	The deleted sentence states that participants may continue in the study provided they remain on the LTBI treatment, however, exclusion critierion (#6) states participants with LTBI should be excluded. To ensure consistency throughout the protocol.
8.2.6 Assessment and management of TB and TB risk factors	TB assessment by chest X-ray: China has been removed as an example from the list of countries.	The TB incidence rate of >20 per 100,000 does not apply to China.
8.2.6 Assessment and management of TB and TB risk factors	For chest X-rays, additional wording was added to ensure the assessment was performed by a qualified specialist (ie, radiologist or pulmonologist).	As a non-study specifc procedure, the designee responsile for assessing a chest x-ray or equivalent computer imaging needed to be defined.
8.2.6 Assessment and management of TB and TB risk factors	LTBI, active TB or other NTMB identified during study: The following sentence has been deleted; "If a TB specialist excludes an active TB infection, the subject can restart the study medication no earlier than 4 weeks after the start of an appropriate prophylactic therapy"	There is no restart procedure in place for particpants with an active TB infection.
8.3 Adverse Events	The following sentence was amendment to include "study treatment in place of rozanolixizumab: "AEs that are serious, considered related to the study treatment or study procedures, or that caused the participant to discontinue the study treatment or MG0003.	This change was made to include any AE cases that included study participants receivng placebo.

Section # and Name	Description of Change	Brief Rationale
8.3.6 Adverse events of special interest	Measurements for ALT, and bilirubin or ALT were amended to: 3xULN ALT and ≥2xULN bilirubin (>35% direct bilirubin) or ALT ≥3xULN and international normalized ratio (INR) >1.5, if INR measured.	Original wording was inconsistent with Section 10.2, Appendix 2 Clinical Laboratory Tests.
8.3.7 Adverse events of interest	This section has renamed to "Adverse events of special monitoring" New information to include that AEs of hypersenstitivy reactions and infused-related reactions will be monitored by the investigators	Terminology change for consistency. Harmonize the AEs of special monitoring across the rozanolixizumab Phase 3 clinical program.
8.3.8 Treatment-emergent adverse events	A new subsection has been added.	To provide a clear definition of a treatment-emrgent adverse event.
8.5 Treatment of Overdose	Definition of overdose was amended: Any dose increase of 10% or greater from the assigned dose for each administered dose of IMP per week should be considered, irrespective of the weight tier band.	The change was made to provide further clarification on the definition of overdose.
8.6 Pharmacokinetics and antidrug antibodies	Use of samples for establishing assay parameters added.	To be consistent with the ICF and other Rozanolixizumab protocols. Further, to remove detail redundancies covered in the laboratory manual.
8.7 Pharmacodynamics	Additional information has been added on limited testing to the positive antibody.	To be consistent with the ICF and other rozanolixizumab protocols. Further, to remove detail redundancies covered in the laboratory manual.
8.8.1 Pharmacogenomics	The following text has been deleted: Details on the collection, storage, preparation, and shipping of samples will be presented in the laboratory manual provided separately.	Repetitive text.
8.8.2 Immunology	The following text was added: "Tetatnus toxoid IgG"	Anti-tetanus toxoid titer will be collected as part of the assessment for the effect of rozanolixizumab on tetanus IgG antibodies

Section # and Name	Description of Change	Brief Rationale
8.9 Biomarkers	The following sentence has been amended to in include **AESM**, and to ensure safety samples **must** rather than may be collected.	New wording introduced to align on UCB safety procedures.
9.1 Definition of Analysis Sets	Amended to say that efficacy data should be analysed as randomized and safety data should be analysed as treated. In addition, Per-Protocol Set and Pharmacokinetic Per-Protocol Set have been included as analysis sets.	Original wording was not consistent with the routine analysis format for a Phase 3 study.
9.3 Estimands	Estimands section has been amended to include a new table (Table 9-1:), such that the primary estimand now uses a hypothetical strategy to deal with intercurrent events and missing data is imputed using a jump to reference approach.	This section has been amended such that the primary estimand assumes rescue therapy to be a serious treatment failure.
9.3.1 Hypothetical estimand 9.3.2 Treatment policy estimand	Both sections were removed.	These sections were removed due to changes in the primary estimand.
9.4.1 Analysis of primary efficacy endpoint	The text has been amended to: Remove "other covariance structures will be investigated and used" and to provide an alternative approach: **If the model does not converge using the unstructured pattern then an autoregressive covariance structure will be used.** Amended the closed testing procedure from Dunnett's test to Bonferroni approach.	Using data from MG0002, it has been deemed that an autoregressive covariance structure is the most appropriate backup should the model not converge using an unstructured covariance structure.
9.4.2 Analysis of secondary and other efficacy endpoints	The text has been amended to include: term for **the** stratification factor (**categorized** as AChR **or** MuSK) A **sequential** hierarchical test procedure will be applied to protect the overall significance level for the multiplicity of endpoints	The section was amended to provide further clarity.
9.5.2.1 Pharmacokinetic analyses	PK-PPS dataset has been included. The following new wording has been added: "A population PK and	To provide clarity on which data analysis set would be used in the study.

Section # and Name	Description of Change	Brief Rationale
	population PKPD analysis will be performed to evaluate PK and PKPD of rozanolixizumab. Details of such analysis will be further described in a separate Data Analysis Plan. The results of the analysis would be reported in a separate report outside the CSR. If required an unblinded and relevant data transfer may be planned in order to initiate the PKPD analysis"	
9.8.1 Interim analysis	Further clarity has been provided for the definition of "best dose". "Best dose" and any higher dose has been amended to "best dose" and any dose with a mean response not worse than 1 point than the selected "best dose").	The additional criteria relating to the maximum difference of 1 point between the two doses in order to carry both forward has been added such that both doses are not carried forward if the higher dose is much worse than the "best dose".
9.8.1 Interim analysis	Paragraph on Early Stopping for Futility was amended to give the second paragraph a separate sub heading "dose selection"	The section was amended to provide further clarity.
9.9 Determination of sample size	The text was modified to update the average sample size for the study ranges: [redacted] have been updated to [redacted] respectively.	As a result of the amended dose selection criteria at the interim analysis, the sample size range has changed slightly.
9.9 Determination of sample size	The text was modified to update chances of stopping for futility: when a clinically meaningful effect of [redacted] more versus placebo, is less than [redacted].	As a result of the amended dose selection criteria at the interim analysis, the chance of stopping for futility at the interim has changed slightly.
9.9 Determination of sample size	Table 9-2: The table was modified to include updated simulation results for all scenarios: Power, Proportion Futility, Proportion Selecting Low Dose, Proportion Selecting High Dose, and Average Sample Size.	As a result of the amended dose selection criteria at the interim analysis, the simulation results have changed slightly.
10.1.7 Source documents	The following sentence, "The following data will be recorded directly in the eCRF and will not appear in a separate source document as defined above" was removed.	The information was repetative.

Section # and Name	Description of Change	Brief Rationale
10.2 Appendix 2: Clinical Laboratory Tests	Additional tests have been included: Serology testing (for Hepatitis A, Hepatitis B, Hepatitis C, and HIV). The following parameter was removed: C-reactive protein.	Consistency with study design.
10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information	Additional text for contraception guidance for male study participants was updated. Table 10-1: additional footnote 'a', was added.	The update was made to be consistent across the Phase 3 rozanolixizumab clinical program.
10.6 Appendix 6: Liver Safety – Suggested Actions and Follow-up Assessments	Serum acetaminophen adduct assay changed from HPLC to spectrophotometry.	High performance liquid chromatography (HPLC) is more time-consuming and samples will have to be sent to a referred ICON laboratory, ARUP.
10.10 Appendix 10: Abbreviations and Trademarks	Several additions, deletions, and edits were made to the list of abbreviations.	General updates and typographical corrections for consistency.
10.12 to 10.21 Appendix 12 to 21	Order of appendices were changed to match the order shown in the body of the protocol.	General consistency
10.23 Appendix 23: Management of Headaches	The procedure for the management of headaches was amended to provide additional information.	The updates were made to enhance the management of headache and to harmonize the procedures across the rozanolixizumab clinical program.
10.24 Appendix 24: Management of Diarrhea	Stool sample collection has been amended to remove biomarker analysis to include: **At the discretion of the Investigator, stool samples may be collected for local safety analysis for study participants reporting severe diarrhea.**	The language updated to clarify the actions necessary by the PI in case of severe diarrhea.
10.26 Appendix 26: Management of Infusion Reactions or Hypersensitivity Reactions	New appendix was added for the management of infusion reactions or hypersensitivity reactions	The addition of management guidance for infusion reaction was requested by FDA for ITP phase 3 studies. This is also added to MG studies to harmoninize
10.29 Appendix 29: Columbia-Suicide Severity Rating Scale	New appendix for C-SSRS (screening and last visit versions) has been included.	Missing appendix

Section # and Name	Description of Change	Brief Rationale
11 References	Additonal references (2) have been included.	General update.

10.12 Appendix 12: MGFA Classification

MGFA Clinical Classification

Class I: Any ocular muscle weakness; may have weakness of eye closure. All other muscle strength is normal.

Class II: Mild weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.

A. IIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
B. IIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

Class III: Moderate weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.

A. IIIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
B. IIIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

Class IV: Severe weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.

A. IVa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
B. IVb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

Class V: Defined as intubation, with or without mechanical ventilation, except when employed during routine postoperative management. The use of a feeding tube without intubation places the patient in class IVb.

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10.14 Appendix 14: MG Composite Scale

Study: MG0003	Visit: _____	Visit Date: DD MMM YY	Subject No.:	Page 1 of 1

MG composite scale

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 eye 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, for example necessitating change 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
TOTAL				_____

Note: Please note that "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."

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10.17 Appendix 17: Patient Global Impression of Severity

Myasthenia Gravis (MG)
Patient Global Impression of Severity (PGI-S)

The following question asks you about your current overall symptoms.

Please check the box that best describes your current situation.

How would you describe your MG symptoms during the past week?

☐	None
☐	Mild
☐	Moderate
☐	Severe
☐	Very severe

10.18 Appendix 18: Patient Global Impression of Change

Myasthenia Gravis (MG)
Patient Global Impression of Change (PGI-C)

The following question asks you about your overall symptoms now compared to before starting treatment within this clinical trial.

Please check the box that best describes your current situation.

How would you describe your current MG symptoms compared to before you started treatment in this clinical trial?

☐	Very much worse
☐	Much worse
☐	A little bit worse
☐	No change
☐	A little bit improved
☐	Much improved
☐	Very much improved

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English - USA

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10.21 Appendix 21: MG-QOL15r

Please indicate how true each statement has been (over the past few weeks).

	Not at all	Somewhat	Very much
	0	1	2
1. I am frustrated by my MG			
2. I have trouble using my eyes because of my MG (e.g. double vision)			
3. I have trouble eating because of MG			
4. I have limited my social activity because of my MG			
5. My MG limits my ability to enjoy hobbies and fun activities			
6. I have trouble meeting the needs of my family because of my MG			
7. I have to make plans around my MG			
8. I am bothered by limitations in performing my work (include work at home) because of my MG			
9. I have difficulty speaking due to MG			
10. I have lost some personal independence because of my MG (e.g. driving, shopping, running errands)			
11. I am depressed about my MG			
12. I have trouble walking due to MG			
13. I have trouble getting around public places because of my MG			
14. I feel overwhelmed by my MG			
15. I have trouble performing my personal grooming needs due to MG			

MG-QOL15r
Muscle and Nerve 2016 Dec;54(6):1015-1022.

Total MG-QOL15r score

MG-QOL15r - United States/English.
MG-QOL15r_AU1.0_eng-USorl.doc

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10.23 Appendix 23: Management of Headache

Based on current available clinical data, headache is the most commonly reported adverse drug reaction in study participants treated with rozanolixizumab. Study participants should be well informed of this potential adverse drug reaction and should be instructed on how to manage it.

Determination of the severity of headache will be consistent with Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (Appendix 3, Section 10.3). Severe headache is defined as severe pain limiting self-care activities of daily living (ADL). Self-care activities of daily living (ADL) refers to bathing, dressing and undressing, feeding self, using the toilet, and taking medications.

In the event of headache investigators will take medical history of previous headaches, concomitant medication, and co-morbidities (eg, asthma) in consideration.

Study participants experiencing severe and/or serious headache will complete the Headache Questionnaire (Section 10.27, Appendix 27) daily until resolving or resolution (ie, if headache becomes non-serious, moderate or mild, or completely resolved, whichever comes first). The questionnaire should be administered via an interview with the study participant. If the severe or serious headache is initially reported at a home visit or during a telephone call, the study participant should be reviewed at the study site as soon as is practically possible for further investigations. Study participants should be monitored for signs and symptoms suggestive of central nervous system involvement and evaluated immediately if other causes (eg, meningitis, intracranial bleeding) are suspected. Further neurological workup may be performed (if indicated) at the discretion of the investigator or the treating physician and may include, a computed tomography scan, magnetic resonance imaging and/or a lumbar puncture for cerebral spinal fluid collection. In addition, samples for exploratory safety biomarkers should be collected for study participants experiencing severe headache or serious headaches when possible. These investigations will be performed to further understand the mechanism of headaches in the study participants.

Treatments must be permanently discontinued if a study participant has a serious headache that is considered related to the IMP in the opinion of the Investigator. Treatment may be temporarily put on hold if a study participant experiences a severe AE of headache that is considered related to the IMP in the opinion of the Investigator, and is not resolved prior to the next scheduled study treatment. If deemed appropriate by the Investigator and agreed upon by the study participant and the sponsor, the study treatment can resume upon the resolution of the severe headache event. The benefit and risk of the treatment should be carefully considered prior to reinitiating the IMP. However, if a treatment related severe headache reoccurs, the treatment must be permanently discontinued.

Headaches will be treated as clinically indicated according to national guidelines. It is recommended to start the analgesic at early onset of headache. At the discretion of the Investigator, study participants may carry a recommended analgesic with the instruction for frequency and dosage provided. Study participants experiencing any treatment related headache will be followed until resolution of the event.

Prophylactic treatment of headaches may be permitted for study participants who have experienced previous episodes of treatment related moderate or severe headache after discussion with the medical monitor.

10.24 Appendix 24: Management of Diarrhea

Severe (Grade 3) diarrhea is defined as an increase of ≥7 stools per day or hospitalization for management of diarrhea or limiting self-care ADL. Determination of the severity of diarrhea will be consistent with CTCAE version 5.0 (see Appendix 3, Section 10.3).

Diarrhea will be treated as clinically indicated according to the local guidelines.

Stool samples may be collected for stool analysis to rule out infection for study participants reporting severe diarrhea. Stool sampling will be as clinically indicated in the opinion of the investigator and assessed per local guidance. In addition, collection of blood samples for assessment of exploratory safety biomarkers is required for study participants with severe GI disturbances including diarrhea.

10.25 Appendix 25: Management of Infections and Hypogammaglobulinemia

Study participants who have signs or symptoms of any infection should be monitored closely and managed according to local guidelines. This may include tests for specific organisms if clinically indicated.

Study participants **MUST discontinue IMP AND move** into **the SFU Period** if any of the following events occur: Study participant has a serious infective episode requiring hospitalization or iv antibiotic therapy (ie, bacteremia or sepsis, meningitis, osteomyelitis or septic arthritis, pneumonia, or visceral abscess).

To maintain the study integrity, IgG level will remain blinded to the study sites and the UCB study team. To ensure patient safety, serum IgG level will be monitored by an independent medical monitor external to UCB including signs and symptoms of infection and associated laboratory parameters. The IMP may be temporarily discontinued as requested by the independent medical monitor when deemed appropriate. Mock infusions will be administered to maintain the blind in case of low IgG levels (see Section 7.1.4).

In the event of a non-serious infection, the Benefit-Risk of continuing treatment with IMP must be carefully evaluated by the investigator in collaboration with the medical monitor. Treatment may be temporarily discontinued for the study participant who develops a non-serious persisting or recurrent infection with a serum total IgG level between ≥1g/L and <2g/L. Upon resolution of infection and the IgGs returning to the level of ≥2g/L, the study participant may be allowed to resume treatment with the IMP. Ad hoc assessment can be performed to monitor the recovery of IgG levels.

Treatment must be temporarily discontinued for the study participant who develops an event of hypogammaglobulinemia with a serum total IgG of <1g/L irrespective of infection. When the IgG level reaches ≥2g/L, the study participant may be allowed to continue treatment with IMP.

10.26 Appendix 26: Management of Infusion Reactions or Hypersensitivity Reactions

Study participants must be closely monitored for reactions during and after the study drug administration period. Standard precautions must be taken for the study participants with regards to potential infusion related reactions. Suggested management guidelines for infusion-related reactions or anaphylaxis are provided in Table 10-4. Definitions of severity of the relevant events should be consistent with CTCAE version 5.0 (Section 10.3).

Table 10-4: Suggested management guidelines for infusion reactions or anaphylaxis

Type of reaction	Suggested action
Acute – Mild Grade 1	Monitor vital signs every 10 min. If the reaction worsens to Grade 2, follow the instruction below.
Acute – Moderate Grade 2	Interrupt/hold infusion temporarily to further assess and initiate treatment if necessary. Consider the use of iv fluid and antihistamine iv/im. Consider administering paracetamol or NSAIDs. Monitor vital signs initially every 5 min. If the reaction improves and upon further assessment it is clear that the event is not an anaphylaxis, restart the infusion cautiously. Continue monitor vital signs every 5 minutes. If reaction recurs or worsens to Grade 3, discontinue infusion.
Acute – Severe Grade 3 or anaphylaxis	Discontinue IMP infusion permanently. Alert crash team. Maintain airway; ensure oxygen is available. Administer: – Antihistamine iv/im, corticosteroids iv, epinephrine im, and iv fluids as appropriate. – Monitor vital signs every 2 min. – Hospitalize, if condition not improving or worsens – Monitor patient until symptoms resolve.

CTCAE=Common Terminology Criteria for Adverse Events; im=intramuscular; IMP=investigational medicinal product; iv=intravenous(ly); NSAID=nonsteroidal anti-inflammatory drug
Note: Management criteria were adapted from the CTCAE v5.0 (National Cancer Institute, 2017).

In case of suspected anaphylaxis, the Sampson's Criteria (Sampson et al, 2006) should be accessed and Appendix 28 (Section 10.28, Sampson Criteria Questionnaire) should be completed. The infusion must be discontinued immediately and emergency resuscitation measures implemented.

In study participants experiencing an infusion-related reaction or anaphylaxis, blood samples will be collected as soon as possible, while the event is ongoing, to investigate the nature of the reaction as per Schedule of Activities (Section 1.3).

Samples for serum complement (C3, C4), Plasma complement (C3a, C5a) and serum cytokines should be collected as specified in the Schedule of Activities (Section 1.3). Additional tests such as IgE levels, tryptase may be performed when there is a suspicion of Type I or III hypersensitivity reaction. The results of all monitoring, including laboratory testing, should be made available to the study site and Sponsor.

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10.28 Appendix 28: Sampson Criteria Questionnaire

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)

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.

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11 REFERENCES

American Psychiatric Association (US). Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Arlington: American Psychiatric Association; 2013

Barnett C, Katzberg H, Nabavi M, Bril V. The quantitative myasthenia gravis score: comparison with clinical, electrophysiological, and laboratory markers. J Clin Neuromuscul Dis. 2012;13(4):201-5.

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):879-86.

Barnett C, Bril V, Kapral M, Kulkarni A, Davis AM. Myasthenia Gravis Impairment Index Responsiveness, meaningful change, and relative efficacy. Neurology. 2017;89(23):2357-64.

Burns TM, Conaway M, Sanders DB; MG Composite and MG-QOL15 Study Group. The MG Composite: A valid and reliable outcome measure for myasthenia gravis. Neurology. 2010;74(18):1434-40.

CPMP/ICH/135/95 Note for guidance on Good Clinical Practice (EMEA) Jul 2002.

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, et al. Quantification of hepatitis delta virus RNA in serum by consensus real-time PCR indicates different patterns of virological response to interferon therapy in chronically infected patients. J Clin Microbiol. 2005;43(5):2363-9.

Lehmacher W and Wassmer G. Adaptive Sample Size Calculations in Group Sequential Trials. Biometrics. 1999;55:1286-90.

Muppidi S. The myasthenia gravis-specific activities of daily living profile. Ann N Y Acad Sci. 2012;1274:114-9

Muppidi S, Wolfe GI, Conaway M, Burns TM, MG composite and MG-QOL15 study group. MG-ADL: still a relevant outcome measure. Muscle Nerve. 2011;44(5):727-31

Jaretzki A, Barohn RJ, Ernstoff MD, Kaminski HJ, Keesey MD, Penn AS, et al. Myasthenia gravis: Recommendations for clinical research standards. Neurol. 2000;55:16-23.

Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117(2):391-7.

Roopenian DC, Akilesh S. FcRn: the neonatal Fc receptor comes of age. Nat Rev Immunol. 2007;7(9):715-25.

Wolfe GI, Herbelin L, Nations SP, Foster B, Bryan WW, Barohn RJ. Myasthenia gravis activities of daily living profile. Neurology. 1999 Apr 22;52(7):1487-9.

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