A RANDOMIZED, OPEN-LABEL EXTENSION STUDY TO INVESTIGATE THE LONG-TERM SAFETY, TOLERABILITY, AND EFFICACY OF ROZANOLIXIZUMAB IN ADULT PATIENTS WITH GENERALIZED MYASTHENIA GRAVIS

PROTOCOL MG0004 AMENDMENT 2

PHASE 3

Short title:

A Phase 3 extension study to evaluate the safety, tolerability, and efficacy of rozanolixizumab in adult patients with generalized myasthenia gravis

Sponsor:
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Regulatory agency identifying numbers:

Eudra CT Number:	2019-000969-21
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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History		
Document	**Date**	**Type of amendment**
Protocol Amendment 2	30 Jul 2020	Substantial
Protocol Amendment 1	01 Nov 2019	Substantial
Original Protocol	21 Mar 2019	Not applicable

Amendment 2 (30 Jul 2020)

Overall Rationale for the Amendment

The primary reasons for this protocol amendment are to introduce the transition of study participants to MG0007 and closure of MG0004, once MG0007 is available as the open-label study to MG0003 and MGC003. In addition, changes have been made to decrease the complexity of assessments to be performed; clarify some operational aspects of the study; incorporate the harmonization of inclusion criteria with studies performed across the rozanolixizumab clinical development program; 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. Where applicable, the term "patient" has been replaced by "study participant."	Updated to provide clarity and to 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.*"
1.1 Objectives and Endpoints 1.3 Schedule of Activities 3 Objectives and Endpoints	Other efficacy endpoints PGI-S and PGI-C have been removed.	The endpoint was removed to decrease study complexity, as scientific value is limited.

Section # and Name	Description of Change	Brief Rationale
1.1 Objectives and Endpoints 1.3 Schedule of Activities 3 Objectives and Endpoints 8.7 Pharmacodynamics	The pharmacodynamic endpoint for neurofilament-light levels has been removed.	The endpoint was removed to decrease study complexity, as scientific value is limited.
1.1 Objectives and Endpoints 3 Objectives and Endpoints	Evaluation of the effects of rozanolixizumab on albumin, α- and β-globulins, and IgG subclasses was removed from the study objectives.	The objective was amended to decrease study complexity, as scientific value is limited.
1.1 Objectives and Endpoints 3 Objectives and Endpoints	The endpoints for exploratory biomarkers such as B-cell activating factor and Circulating Immune Complexes and proteins and metabolite changes have been removed.	The endpoint was removed to decrease study complexity, as scientific value is limited.
1.1 Objectives and Endpoints 3 Objectives and Endpoints	The following new sentence "Other exploratory safety biomarkers may be assessed" was added to footnote a under the Objectives and Endpoints table.	This addition was included to maintain consistency within the protocol and schedule of activities.
1.1 Overall design 4.1 Overall design	A new paragraph was inserted describing the rollover of participants from MG0004 to OLE study MG0007.	The current ongoing OLE study, MG0004 (52-week chronic treatment) will be replaced by MG0007, which is a less complex with [redacted] based on myasthenia gravis (MG) worsening.
1.3 Schedule of Activities	A new sentence describing visit and screening information for entry into MG0007 has been added.	The PEOT of MG0004 serves as the introductory baseline and will have to be completed for entry into MG0007.
1.3 Schedule of Activities	Week 52/Visit 52 PEOT and Week 60/Visit 53 EOS assessments have been harmonized to match MG0003.	Updated to ensure all screening criteria assessments match with MG0007. The PEOT of MG0004 serves as the introductory baseline and will have to be completed for entry into MG0007.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	A new assessment, MGFA classification, was added at Visit 52 or PEOT and Visit 53 EOS.	Updated as screening criteria for entering into MG0007.
1.3 Schedule of Activities	MG Symptoms PRO assessment has been removed at Visit 7.	Updated to simplify and decrease the complexity of the study.
1.3 Schedule of Activities	MGQoL15r assessment has been added at 52 or PEOT.	Updated to simplify and decrease the complexity of the study.
1.3 Schedule of Activities	Full physical examination assessment has been added at Visit 52 or PEOT.	This update was included to maintain consistency with the study design and protocol
1.3 Schedule of Activities	Brief physical examination assessment has been removed at Visit 52 or PEOT.	This update was included to maintain consistency with the study design and protocol
1.3 Schedule of Activities	Pregnancy test (urine) assessment has been removed at Visit 5.	Updated to simplify and decrease the complexity of the study.
1.3 Schedule of Activities	Hematology, serum chemistry, urinalysis assessment has been removed at Visit 5.	Updated to simplify and decrease the complexity of the study.
1.3 Schedule of Activities	Additional assessment for PTT and INR has been added at Visit 52 or PEOT.	Updated as screening criteria for entering into MG0007.
1.3 Schedule of Activities	An additional footnote was added for the Anti-tetanus toxoid titer at 1st visit for Weeks 9-48 (footnote j): The following new text “Every 6 months” was added.	Updated to be provide clarity for timings of this assessment.
1.3 Schedule of Activities	IGRA tuberculosis test assessment was added at Visit 52 or PEOT.	Updated as screening criteria for entering into MG0007.
1.3 Schedule of Activities	Blood sampling for PK assessment has been added at Visit 5.	Updated for consistency within the protocol.
1.3 Schedule of Activities	Blood sampling for ADA assessment has been removed at Visit 7 and Visit 49.	Updated to simplify and decrease the complexity of the study.
1.3 Schedule of Activities	Blood sampling for ADA was added to footnote o for 1st Visit for Weeks 9-48.	Updated for consistency within the protocol.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	Blood sampling IgA, IgM, IgE assessment has been added at 1st visit for Weeks 9-48 and Week 52 or PEOT.	Updated for consistency and to correct an error in protocol amendment 1.
1.3 Schedule of Activities	Blood sampling for exploratory biomarker analysis was removed.	Updated to simplify and decrease the complexity of the study.
1.3 Schedule of Activities	Blood sampling for exploratory safety biomarker analysis assessment was removed at Visits 1, 5, 7, 1st visit, and 49, and added at Visit 2-4.	Updated to clarify that it is event driven only and not applicable to all study participants.
1.3 Schedule of Activities	MG-specific autoantibodies assessments were added at Visits 5 and 52 or PEOT.	This was included as part of the entry requirements for MG0007.
1.3 Schedule of Activities	Footnote o was added to MG-specific autoantibodies assessment at 1st visit for Weeks 9-48.	Updated to provide clarity and be consistent with remainder of protocol.
1.3 Schedule of Activities	Assessment of serum complement levels (C3, C4) and cytokines has been combined into one procedure.	Updated to simplify and decrease the complexity of the study.
1.3 Schedule of Activities	Serum complement levels (C3,C4) and cytokines assessments was removed at Visits 1 and 49, and added at Visit 2-4 and at 1st visit for Weeks 9-48.	Updated to correct an error in the original protocol.
1.3 Schedule of Activities	Plasma complement levels (C3a and C5a) assessments were removed at Visits 1 and 49, and added at Visit 2-4 and at 1st visit for Weeks 9-48.	Updated to correct an error in the original protocol.
1.3 Schedule of Activities	Reference to the lead-in study, MGC003, has been added where applicable.	Updated for clarity and consistency within the protocol.
1.3 Schedule of Activities	Footnote d: The following new text "not older than 32 days" was added.	Updated for consistency and to provide clarity.
1.3 Schedule of Activities	An additional footnote was added for body weight (footnote e): "To be collected four times during the study: Screening/Baseline, Week 25 (site visit), Week 52 (or PEOT), and EOS Visit."	To provide clarity for exact timings for collection of body weight during the study.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	Footnote f: New wording was added regarding the first question of the C-SSRS to the suicidal ideation assessment query.	Updated for consistency and to provide clarity.
1.3 Schedule of Activities	Footnote f: New wording was added: "Complete C-SSRS will observe the "since last visit" version recorded at Visit 14 in MG0003 or MGC003."	Updated to provide clarity for the rollover visit from MG0003 to MG0004.
1.3 Schedule of Activities	An additional footnote was added for MGII (footnote g:) "MGII is optional for all study participants."	MGII has switched from mandatory to optional for each study visit.
1.3 Schedule of Activities	Footnotes s and t (previously p, q, r): "Severe headache" was added to the list of events.	Updated to correct an error in protocol amendment 1.
1.3 Schedule of Activities	Footnote s and t: "postdose" was replaced with "postevent."	Updated to correct terminology error.
1.3 Schedule of Activities	An additional footnote was added (footnote r).	Updated for consistency and to provide clarity.
1.3 Schedule of Activities	Footnote s: New wording "Baseline from MG0003 and MGC003 will serve as Baseline in MG0004. Additional exploratory safety samples must be collected 4 hours postevent or as soon as possible before the next IMP in case of AESM of serious or severe headache or AESM of GI disorders as described in Section 8.9" was added.	New text was added to provide clarity and consistency with the study design and procedures.
1.3 Schedule of Activities	Footnote t (previously footnote p): The first sentence "Serum complement levels" has been removed, and a new sentence "Baseline from MG0003 and MGC003 will serve as Baseline in MG0004" has been added.	New text was added to provide clarity and consistency with the study design and procedures.
4.1 Overall design 5.2 Exclusion criteria	New text "(not older than 32 days)" has been added to the laboratory measurement paragraphs.	Updated for consistency and to provide clarity.
4.1 Overall design	A new sentence relating to the updated language in Section 8 regarding contingency measures during a pandemic and other	Contingency measures have been implemented to ensure study participant safety in response to the

Section # and Name	Description of Change	Brief Rationale
	exceptional circumstances has been included.	COVID-19 pandemic causing the inability for sites to adhere to protocol visits and assessments.
5.1 Inclusion Criteria 8.3.5 Pregnancy 10.4.2 Contraception guidance	All reference to 3 months have been replaced with "at least 90 days."	Updated to be consistent across the Phase 3 rozanolixizumab clinical program.
5.2 Exclusion Criteria	Criterion #11: Amended definition (glomerular filtration rate less than 45ml/min/1.73m^2) was included for renal impairment.	To expand the population for a more generalized safety database.
5.2 Exclusion Criteria	Criterion #17: 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.
6.5.1 Permitted concomitant treatments (medications and therapies)	Footnote a under Table 6-2 has been modified to read "≤300ng/mL" from "≤300ng/L."	Updated to correct an error and ensure clarity.
7.1.1 Liver Chemistry Stopping Criteria 7.1.2 QTc Stopping Criteria	A new sentence was added to emphasize study participants should follow the visit schedule as described in the protocol and to complete the eCRF.	New wording was added to provide clarity.
7.1.3 Discontinuation of study medication due to other AEs or medical conditions	Language related to the temporary discontinuation of study medication was removed as it pertained to IgG levels and rescue medication.	Updated to simplify and decrease the complexity of the study.
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	Updated to be consistent across the Phase 3 rozanolixizumab clinical program.

Section # and Name	Description of Change	Brief Rationale
	discontinuation is required to low IgG levels.	
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.
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.
8.1.3 Patient-reported outcomes 8.1.3.3 Patient Global Impression of Severity 8.1.3.4 Patient Global Impression of Change	References to PGI-S and PGI-C, including both sections, have been deleted.	Updated to simplify and decrease the complexity of the study.
8.2 Safety assessments	The following wording was added: "until Week 7, where the participant can be observed for 1 hour at the Investigator's discretion."	Updated to be consistent with the Schedule of Activities.
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.
8.9 Biomarkers	For collection of additional samples, "postdose" was replaced with "postevent."	Updated to correct terminology error.
8.9 Biomarkers	The last sentence of the first paragraph was modified to read "Additional exploratory safety samples must be collected 4 hours postevent or as soon as possible before the next IMP in case of AESM of serious or severe headache or AESM of GI disorders."	Updated to provide clarity and be consistent with remainder of protocol.
8.9 Biomarkers	Language related to albumin, α- and β-globulins, B-cell activating	The endpoints were removed to decrease

Section # and Name	Description of Change	Brief Rationale
	factor, and Circulating Immune Complexes was removed.	study complexity, as scientific value is limited.
8.9.1 Immunology	For collection of additional samples, "postdose" was replaced with "postevent."	Updated to correct terminology error.
8.9.1 Immunology	The following was added: "Tetanus toxoid IgG" Information for the collection of samples has been amended: "Additional samples may be collected 2 hours and 4 hours postevent in case of severe headache, infusion reaction, or hypersensitivity reaction at Visits 5, 7, 1st visit (of the 4-week cycle from Weeks 9-48) and Visit 49."	To ensure consistency with the wording for Schedule of Activities footnotes specific to serum complement, serum cytokines, and plasma complement.
9.3.3.2 Pharmacodynamic analyses and biomarkers	Language related to albumin and α- and β-globulins was removed.	The endpoints were removed to decrease study complexity, as scientific value is limited.
10.2 Appendix 2: Clinical Laboratory Tests	The following parameters were added: "C-reactive protein" and "Albumin."	Updated to correct an error in protocol amendment 1.
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.
10.16 Appendix 16: Patient Global Impression of Severity 10.17 Appendix 17: Patient Global Impression of Change	These appendices were removed.	Updated to be consistent with the protocol.
10.20.1 Management of headache	This section was previously 10.22.1. 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.	The language updated to be consistent across the Phase 3 rozanolixizumab clinical program.

Section # and Name	Description of Change	Brief Rationale
10.20.2 Management of Diarrhea	This section was previously 10.22.2. The phrase "over baseline" has been removed.	Updated to be consistent across the Phase 3 rozanolixizumab clinical program.
10.20.2 Management of Diarrhea	This section was previously 10.22.2. 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.
10.20.3 Management of infections and hypgammaglobulinemia	This section was previously 10.22.3. Language related to mock infusions has been removed.	Updated to be consistent across the Phase 3 rozanolixizumab clinical program.
10.20.3 Management of infections and hypgammaglobulinemia	This section was previously 10.22.3. 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.
10.20.3 Management of infections and hypgammaglobulinemia	This section was previously 10.22.3. 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.
10.20.4 Management of infusion reactions or hypersensitivity reactions	This section was previously 10.22.4. Additional guidance for nurses administering IMP at home has been added.	Updated to be consistent across the Phase 3 rozanolixizumab clinical program.
10.23 Appendix 23: Columbia-Suicide Severity Rating Scale	This section was previously 10.25. 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 removed: James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson	Updated to maintain consistency within the protocol.

Section # and Name	Description of Change	Brief Rationale
	JA, et al. Pharmacokinetics of acetaminophen-protein adducts in adults with acetaminophen overdose and acute liver failure. Drug Metab Dispos. 2009; 37:1779-84	

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24-hour)	
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 randomized, open-label extension study to investigate the long-term safety, tolerability, and efficacy of rozanolixizumab in adult patients with generalized myasthenia gravis

Short title:

A Phase 3 extension study to evaluate the safety, tolerability, and efficacy of rozanolixizumab in adult patients with generalized myasthenia gravis

Rationale:

Myasthenia gravis (MG) is a serious, debilitating, sometimes life-threatening condition that is 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 a variety of therapeutic agents including cholinesterase inhibitors, immunomodulators, corticosteroid, biologics interfering with IgG turnover, high dose intravenous infusion of immunoglobulin (IVIg), plasmapheresis, or immunoadsorption, there remains a need for a safe and effective treatment devoid of significant side effects to conveniently treat study participants with MG.

Rozanolixizumab is a humanized IgG4 monoclonal antibody that is being developed as an inhibitor of the activity of the neonatal Fc receptor (FcRn) for IgG. By blocking the activity of FcRn, rozanolixizumab accelerates the catabolism of antibodies and reduces the serum IgG concentration, including pathogenic IgG in MG study participants, thus offering a potentially safe, effective, and convenient alternative to existing treatments. A Phase 3 study (MG0003) is underway to provide the required data to establish the efficacy and safety of rozanolixizumab in anti-AChR or anti-MuSK autoantibody-positive study participants with generalized MG who experience moderate to severe symptoms and are being considered for additional treatment with IVIg or plasma exchange (PEX).

MG0004 is a Phase 3 open-label extension study to evaluate the long-term safety, tolerability, and efficacy of rozanolixizumab with a [redacted] dosing regimen for 52 weeks in study participants with generalized MG. The MG0004 open-label extension study will provide the opportunity to assess the long-term safety of rozanolixizumab in study participants with MG who participated in MG0003 and will provide them with a chance to benefit from long-term treatment.

Objectives and endpoints:

Objectives	Endpoints
Primary	
To evaluate the long-term safety and tolerability of rozanolixizumab in study participants with generalized MG	The primary safety endpoints are: • Occurrence of TEAEs • Occurrence of TEAEs leading to permanent withdrawal of study medication The other safety endpoints are: • Occurrence of AESMs • Vital sign values and changes from Baseline (systolic and diastolic blood pressure and pulse rate) • 12-lead ECG values and change from Baseline at each scheduled assessment • Clinical laboratory findings (hematology, biochemistry, and urinalysis)
Secondary	
To evaluate the long-term efficacy of rozanolixizumab in study participants with generalized MG	The secondary efficacy endpoints are: • Change from Baseline in MG-ADL at each scheduled assessment during Treatment and Observation Periods • Change from Baseline in MG-Composite (MG-C) score at each scheduled assessment during Treatment and Observation Periods • Change from Baseline in QMG at each scheduled assessment during Treatment and Observation Periods • Use of rescue medication (IVIg or PEX) The other efficacy endpoints are: • Change from Baseline in MGII scores at each scheduled assessment during Treatment and Observation Periods • Change from Baseline in MGII ocular subscores at each scheduled assessment during Treatment and Observation Periods • Change from Baseline in MGII generalized domain subscores 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 the MG Symptoms PRO multicomponent total score, at each scheduled assessment during Treatment and Observation Periods • Change from Baseline in the enhanced MG Symptoms PRO total score, at each scheduled assessment during Treatment and Observation Periods • Change from Baseline in MGQoL15r at each scheduled assessment during Treatment and Observation Periods • Change from Baseline in EQ-5D-5L scores at each scheduled assessment during Treatment and Observation Periods For study participants who require rescue treatment during the Observation Period of MG0003 and subsequently enter MG0004, the following endpoints will be assessed: • QMG responder rate (≥3.0 point improvement from Baseline) at each scheduled assessment during the first 6 weeks of the Treatment Period • MG-C responder rate (≥5.0 point improvement from Baseline) at each

	scheduled assessment during the first 6 weeks of the Treatment Period • MG-ADL responder rate (≥2.0 point improvement from Baseline) at each scheduled assessment during the first 6 weeks of the Treatment Period
Other	
To assess the reduction in use of steroids in study participants receiving rozanolixizumab	• AUC of the oral steroid dose over time
To assess the plasma concentrations of rozanolixizumab administered by SC infusion	• Plasma concentration of rozanolixizumab at each scheduled assessment during the Treatment and Observation Periods
To assess the pharmacodynamic effects of rozanolixizumab as measured by IgG levels, IgG subclasses, and MG-specific autoantibodies levels	• Change from baseline in total IgG and IgG subclasses autoantibodies at each scheduled visit • Change from baseline in MG-specific autoantibodies at each scheduled visit
To evaluate the incidence and emergence of ADAs with respect to immunogenicity, PK, and pharmacodynamics	• ADAs at each scheduled assessment during the Treatment Period and Observation Periods
To assess the effect of rozanolixizumab on biomarkers including 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 and Observation Periods[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

ADA=anti-drug antibody; ADL=activities of daily living; AESM=adverse event of special monitoring; ECG=electrocardiogram; Ig=immunoglobulin; IVIg=intravenous infusion of immunoglobulin G; MG=myasthenia gravis; MG-ADL=myasthenia gravis-activities of daily living; MGII=myasthenia gravis impairment index; MGQoL15r=revised 15-item myasthenia gravis quality of life questionnaire; PEX=plasma exchange; PK=pharmacokinetic; PRO=patient-reported outcome; QMG=quantitative myasthenia gravis test; SC=subcutaneous(ly); TEAE=treatment-emergent adverse event

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

Overall design:

This is a randomized, open-label Phase 3 extension study to evaluate the long-term safety, tolerability, and efficacy of rozanolixizumab in study participants with generalized MG. Study participants will enter MG0004 from MG0003 or MGC003. Study participants in MG0003 or MGC003 who complete the Observation Period or who require rescue medication during the Observation Period will be invited to be rerandomized in MG0004 (except for study participants who opt to receive IVIg or PEX as rescue medication). Study participants who receive IVIg or PEX as rescue therapy during the Observation Period of MG0003 or MGC003 will not be eligible to enroll in MG0004. Study participants who discontinue study medication in MG0003 or MGC003 for any reason other than requiring rescue medication will not be eligible for MG0004.

In MG0004, study participants with generalized MG will be randomized in a 1:1 ratio to receive 1 of 2 doses of rozanolixizumab (equivalent to approximately [redacted], respectively). Rozanolixizumab will be administered subcutaneously (SC) on a [redacted] basis over a 52-week period. Study participants will be allowed to switch dose arms for tolerability and efficacy reasons at the discretion of the Investigator (see Section 6.6). At the end of the 52-week Treatment Period in MG0004, study participants will participate in an 8-week Observation Period.

This open-label extension (OLE) study will be replaced by MG0007, an OLE study with [redacted] based on MG worsening. Upon study site approval of MG0007, as well as fulfilment of regulatory requirements, MG0003 study participants will have the opportunity to rollover directly into MG0007 and will no longer have the opportunity to rollover to MG0004. In the event a study participant has already started MG0004, a minimum treatment duration of 6 visits must be completed (if IMP treatment is withheld 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), then the participant will discontinue MG0004 and have the opportunity to enter into MG0007. For study participants entering MG0007 from the treatment period of MG0004, he/she must complete the PEOT Visit in MG0004 which will serve both as the Screening Visit for MG0007 and as the End of Study (EOS) for MG0004. If a study participant completes the Treatment Period and is in the Observation Period of MG0004, he/she will then complete the EOS visit to serve as the Screening Visit for 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 rolled over into MG0007.

Number of participants:

No formal sample size calculation can be performed. Up to approximately 276 study participants will be enrolled into the lead-in study MG0003 and MGC003. All eligible study participants from lead-in study MG0003 will be invited to participate in MG0004.

At selected sites, study participants may also be able to participate in a substudy.

Treatment groups and duration:

Study participants will be randomized in a 1:1 ratio to receive 1 of 2 doses of rozanolixizumab (equivalent to approximately [redacted], respectively). Specifically, the following dose arms will be used in the study:

Dose arm 1: equivalent to approximately [redacted] rozanolixizumab

- 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]

Dose arm 2: equivalent to approximately [redacted] rozanolixizumab

- 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]

Further dose adjustment may be made if the study participant's bodyweight changes during the study.

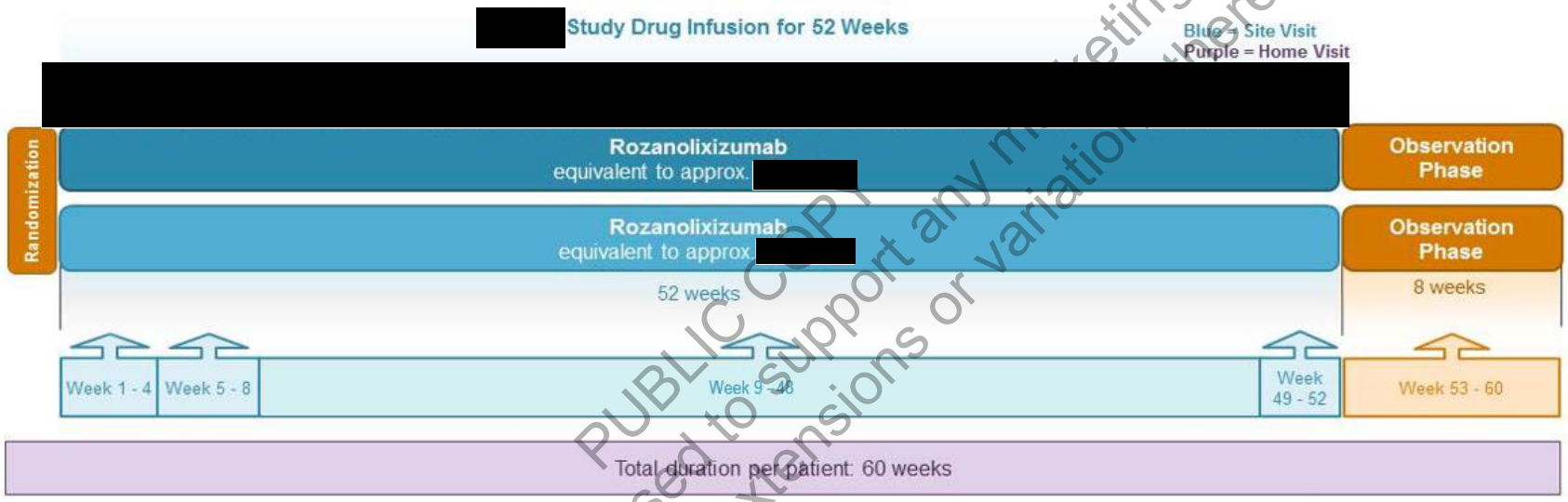
If a dose arm is determined to be futile and is discontinued after the interim analysis in MG0003 or MGC003, then that dose arm will be dropped from MG0004 as well, and study participants in the affected dose arm will be transferred to the continuing dose arm. An independent Data Monitoring Committee (IDMC) will be formed to monitor the ongoing safety and efficacy of the study. Further details of the IDMC will be provided in an IDMC charter.

Rozanolixizumab will be administered SC on a [redacted] basis over a 52-week Treatment Period, and study participants will then participate in an 8-week Observation Period. The maximum study duration per study participant is 60 weeks.

1.2 Schema

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

Figure 1-1: Study schematic



1.3 Schedule of activities

The schedule of activities is provided in Table 1-1. For study participants entering MG0007, he/she must complete at least 6 visits and then complete the PEOT visit in MG0004, which serves as the Screening Visit for MG0007 and as the EOS for MG0004. If a study participant has completed the Treatment Period and is in the Observation Period of MG0004, he/she will then complete the EOS visit to serve as the Screening Visit for MG0007.

Table 1-1: Schedule of activities

	Week	Weeks 1-4		Weeks 5-8				Weeks 9-48[a]		Weeks 49-51		Week 52	Week 60
	Visit[b]	1 (Screening /Baseline)[c]	2-4	5	6	7	8	1st visit	2nd, 3rd, and 4th visits	49	50 51	52 or PEOT	53 EOS
Assessments	Visit type	S	S	S	H	S	H	S	H	S	H	S	S
Written informed consent		X											
Verification of inclusion/exclusion criteria		X[d]											
Withdrawal criteria			X	X	X	X	X	X	X	X	X	X	
Medical history update		X		X				X		X		X	X
Concomitant medications and medical procedures		X	X	X	X	X	X	X	X	X	X	X	X
Body weight[e]		X						X				X	X
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS[f]		X											
Query for suicidality[f]			X	X		X		X		X		X	X
MGFA classification												X	X
QMG		X		X		X		X		X		X	X
MG-C Scale		X		X		X		X		X		X	X

Table 1-1: Schedule of activities

	Week	Weeks 1-4		Weeks 5-8				Weeks 9-48[a]		Weeks 49-51		Week 52	Week 60
	Visit[b]	1 (Screening /Baseline)[c]	2-4	5	6	7	8	1st visit	2nd, 3rd, and 4th visits	49	50 51	52 or PEOT	53 EOS
Assessments	Visit type	S	S	S	H	S	H	S	H	S	H	S	S
MG-ADL		X		X		X		X		X		X	X
MG Symptoms PRO		X		X				X		X		X	X
EQ-5D-5L		X						X				X	
MGII[g]		X						X				X	
MGQoL15r		X						X		X		X	X
Full physical examination		X										X	X
Brief physical examination			X	X		X		X		X			
12-lead ECG		X		X				X[h]				X	X
Pregnancy test (urine)[i]		X						X		X		X	X
Hematology, serum chemistry, urinalysis		X	X			X		X		X		X	X
PTT and INR measurements		X										X	X
Serology testing for HIV, hepatitis B, and hepatitis C		X											
Anti-tetanus toxoid titer								X[j]					X
IGRA tuberculosis test												X	X
Tuberculosis signs and symptoms questionnaire		X		X				X[k]				X	X

Table 1-1: Schedule of activities

	Week	Weeks 1-4		Weeks 5-8				Weeks 9-48[a]		Weeks 49-51		Week 52	Week 60
	Visit[b]	1 (Screening /Baseline)[c]	2-4	5	6	7	8	1st visit	2nd, 3rd, and 4th visits	49	50 51	52 or PEOT	53 EOS
Assessments	**Visit type**	**S**	**S**	**S**	**H**	**S**	**H**	**S**	**H**	**S**	**H**	**S**	**S**
Contact IRT		X	X	X	X	X	X	X	X	X	X	X	X
Study participants identification card assigned		X											
Recording of AEs		X	X	X	X	X	X	X	X	X	X	X	X
[redacted]													
Blood sampling for PK[n]		X		X								X	
Blood sampling for ADA		X		X				X[o]				X	X
Blood sampling for IgG and IgG subclasses[p]		X		X		X		X		X		X	X
Blood sampling for IgA, IgM, IgE		X						X[q]				X[r]	X
Blood sampling for exploratory safety biomarker analysis[s]		X											
MG-specific autoantibodies		X		X				X[o]				X	X
Serum complement levels (C3,C4) and cytokines[t]			X					X					
Plasma complement levels (C3a and C5a)[t]			X					X					

Table 1-1: Schedule of activities

	Week	Weeks 1-4		Weeks 5-8				Weeks 9-48[a]		Weeks 49-51		Week 52	Week 60
	Visit[b]	1 (Screening /Baseline)[c]	2-4	5	6	7	8	1st visit	2nd, 3rd, and 4th visits	49	50 51	52 or PEOT	53 EOS
Assessments	Visit type	S	S	S	H	S	H	S	H	S	H	S	S

ADA=anti-drug antibody; ADL=activities of daily living; AE=adverse event; AESM=adverse events of special monitoring; C-SSRS= Columbia Suicide Severity Rating Scale; ECG=electrocardiogram; EOS=End of Study; EQ-5D-5L=5-level European quality of life 5 dimension; GI=gastrointestinal; H=home visit; HIV=human immunodeficiency virus; Ig=immunoglobulin; IGRA=interferon gamma release assay; IMP=investigational medicinal product; INR=international normalized ratio; IRT=interactive response technology; MG=myasthenia gravis; MGII=myasthenia gravis impairment index; MG-ADL=myasthenia gravis-activities of daily living; MGFA=Myasthenia Gravis Foundation of America; MGQoL15r=revised 15-item myasthenia gravis quality of life questionnaire; PEOT=premature end of treatment; PK=pharmacokinetic(s); PRO=patient-reported outcome; PTT=partial thromboplastin time; QMG=quantitative myasthenia gravis test; S=site visit

[a] From Weeks 9 to 48, the schedule will operate on recurring 4-week cycles wherein the first visit of each 4 weeks will be site visits and the subsequent 3 visits (2nd, 3rd, and 4th visits) will be home visits. Accordingly, Visits 9, 13, 17, 21, 25, 29, 33, 37, 41, and 45 will be site visits and the remaining visits will be home visits. At the discretion of the Investigator, home visits may be changed to site visits. Study participants may also choose to complete the visits at the site on the scheduled home visits.

[b] Visit windows of ±2 days are allowed for all visits.

[c] For any study participant who enrolls in MG0004, the final visit in MG0003 (Visit 14) or MGC003 (Visit 14) will serve as Visit 1 in MG0004. All activities should be completed at Visit 1 (±1 week).

[d] For criteria pertaining to laboratory measures, the last available value from MG0003 or MGC003 will be used for evaluation of study participant eligibility, as long as the measurement was taken within the last 4 weeks (not older than 32 days) prior to MG0004 screening.

[e] To be collected four times during the study: Screening/Baseline,1 Week 25 (site visit), Week 52 (or PEOT), and EOS Visit.

[f] A full Columbia-Suicide Severity Rating Scale (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. Complete C-SSRS will observe the "since last visit" version recorded at Visit 14 in MG0003 or MGC003.

[g] MGII is optional for all study participants.

[h] From Weeks 9 to 48, an ECG will be performed every 3 months (ie, Weeks 9, 21, 33, and 45).

[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] Every 6 months.

[k] From Weeks 9 to 48, the tuberculosis questionnaire will be performed every 3 months (ie, Weeks 9, 21, 33, and 45).

[l] 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 until Week 7, where the participant can be observed for 1 hour at the Investigator's discretion.

[m] No IMP administration will occur during the PEOT visit for study participants who withdraw from the study or discontinue IMP.

[n] PK samples should be taken predose for all study participants.

[o] From Weeks 9 to 48, ADA- and MG-specific autoantibodies will be measured every 3 months (ie, Weeks 9, 21, 33, and 45).

[p] Total IgG will be assessed at all scheduled onsite visits; IgG subclasses will be assessed at Visit 1 and every 3 months thereafter.

[q] From Weeks 9 to 48, blood sampling for IgA, IgE and IgM will be measured every 3 months (ie, Weeks 9, 21, 33, and 45).

[r] To be performed only in the event of a PEOT Visit.

[s] Baseline from MG0003 and MGC003 will serve as Baseline in MG0004. Additional exploratory safety samples must be collected 4 hours postevent or as soon as possible before the next IMP in case of AESM of serious or severe headache or AESM of GI disorders as described in Section 8.9.

[t] Baseline from MG0003 and MGC003 will serve as Baseline in MG0004. Additional samples may be collected 2 hours and 4 hours postevent in case of severe headache, infusion reaction, or hypersensitivity reaction at Visits 5, 7, 1st visit (of the 4-week cycle from Weeks 9-48) and Visit 49.

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 autoantibodies. The aim is to reduce the concentration of pathogenic IgG in study participants 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 (PV), immune thrombocytopenia (ITP), Goodpasture's syndrome, neuromyelitis optica, Guillain-Barré Syndrome (GBS), 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 cytotoxic agents. These therapeutic approaches are not effective in all study participants 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 disease, particularly where corticosteroid based immune suppression is not or no longer effective (eg, ITP, MG, GBS, PV). 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, debilitating, sometimes life-threatening condition that is 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. 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, corticosteroids, 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 study participants with MG.

By blocking the activity of FcRn, rozanolixizumab accelerates the catabolism of antibodies and reduces the concentration of pathogenic IgG in MG study participants, thus offering a safe, effective, and convenient alternative to existing treatments. A Phase 3 study (MG0003) is underway to establish the safety and efficacy of rozanolixizumab in study participants with generalized MG who experience moderate-to-severe symptoms.

This open-label extension study (MG0004) will evaluate the long-term safety, tolerability, and efficacy of rozanolixizumab.

2.2 Background

Rozanolixizumab is a humanized anti-FcRn monoclonal antibody that has been specifically designed to inhibit IgG binding to FcRn without inhibiting albumin binding to FcRn. Rozanolixizumab is being developed as an inhibitor of FcRn activity with the aim to reduce the concentration of pathogenic IgG in study participants with IgG autoantibody-mediated diseases.

To date, rozanolixizumab has been administered to human study participants in 6 completed or ongoing clinical studies: UP0018, MG0002, MG0003, TP0001, CIDP01, and UP0060. UP0018 is a completed first-in-human study, 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, and UP0060 is an ongoing Phase 1 study comparing the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of rozanolixizumab in Chinese, Japanese and Caucasian healthy volunteers.

In MG0002, clinically relevant improvements in day-to-day functioning, as measured by change from Baseline to Day 29 in myasthenia gravis-activities of daily living (MG-ADL) (secondary endpoint), were observed following treatment with rozanolixizumab [redacted] compared with placebo (p=0.036). Numerical differences numerical in favor of rozanolixizumab [redacted] compared with placebo were observed in reductions from Baseline in quantitative myasthenia gravis (QMG) (p=0.221) and MG-C score (p=0.089). Overall, repeated administrations of rozanolixizumab at dose levels of [redacted] SC have been generally well tolerated, with an acceptable safety profile. No new safety concerns were identified. The treatment-emergent adverse event (TEAE) profile was similar between rozanolixizumab and placebo except for headaches where increased frequency and severity was observed in the rozanolixizumab study participants.

Final data from the proof-of-concept ITP study TP0001 demonstrated that rozanolixizumab was tolerated with an acceptable safety profile after multiple [redacted] and single [redacted] doses.

MG0003 is a Phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of 2 doses of rozanolixizumab (equivalent to approximately [redacted]

[redacted]) in study participants with generalized MG who experience moderate to severe symptoms and are being considered for treatment with IVIg or PEX.

This study (MG0004) is an open-label extension study for the global lead-in study MG0003 and China specific lead-in study, MGC003 (this study will mirror the study design of MG0003). MG0004 will evaluate the long-term safety, tolerability, and efficacy of rozanolixizumab in study participants with generalized MG. Study participants in MG0004 will be randomized to receive 1 of 2 doses of rozanolixizumab (equivalent to approximately [redacted], respectively) over a 52-week Treatment Period.

2.3 Benefit/Risk assessment

Generalized MG 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, but 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 (IV) administration of immunoglobulins at a healthcare facility.

Rozanolixizumab represents an innovative, SC anti-FcRn monoclonal antibody that may provide a novel and specific therapeutic approach for the treatment of study participants with MG. Data show that rozanolixizumab markedly lowers serum IgG and IgG autoantibody levels in study participants with generalized MG. 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 well tolerated, with an acceptable safety profile and in line with SC dosing in the Phase 1 program and the safety profile observed in TP0001.

The potential risks associated with SC administration of rozanolixizumab are gastrointestinal (GI) disturbances, headaches, infusion/hypersensitivity reactions, infections, potential effects on immunizations, effects on the kidney, and metabolic effect of FcRn on albumin. These risks 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 headaches, and infusions/hypersensitivity reactions is also provided as well as expedited reporting requirements of adverse events of special monitoring (AESMs).

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

3 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To evaluate the long-term safety and tolerability of rozanolixizumab in study participants with generalized MG	The primary safety endpoints are: • Occurrence of TEAEs • Occurrence of TEAEs leading to permanent withdrawal of study medication The other safety endpoints are: • Occurrence of AESMs • Vital sign values and changes from Baseline (systolic and diastolic blood pressure and pulse rate) • 12-lead ECG values and change from Baseline at each scheduled assessment • Clinical laboratory findings (hematology, biochemistry, and urinalysis)
Secondary	
To evaluate the long-term efficacy of rozanolixizumab in study participants with generalized MG	The secondary efficacy endpoints are: • Change from Baseline in MG-ADL 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 • Change from Baseline in QMG at each scheduled assessment during Treatment and Observation Periods • Use of rescue medication (IVIg or PEX) The other efficacy endpoints are: • Change from Baseline in MGII scores at each scheduled assessment during Treatment and Observation Periods • Change from Baseline in MGII ocular subscores at each scheduled assessment during Treatment and Observation Periods • Change from Baseline in MGII generalized domain subscores 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 the MG Symptoms PRO multicomponent total score, at each scheduled assessment during Treatment and Observation Periods • Change from Baseline in the enhanced MG Symptoms PRO total score, at each scheduled assessment during Treatment and Observation Periods • Change from Baseline in MGQoL15r at each scheduled assessment during Treatment and Observation Periods • Change from Baseline in EQ-5D-5L scores at each scheduled assessment during Treatment and Observation Periods For study participants who require rescue treatment during the Observation Period of MG0003 and subsequently enter MG0004, the following endpoints will be assessed: • QMG responder rate (≥3.0 point improvement from Baseline) at each scheduled assessment during the first 6 weeks of the Treatment Period • MG-C responder rate (≥5.0 point improvement from Baseline) at each

	scheduled assessment during the first 6 weeks of the Treatment Period • MG-ADL responder rate (≥2.0 point improvement from Baseline) at each scheduled assessment during the first 6 weeks of the Treatment Period
Other	
To assess the reduction in use of steroids in study participants receiving rozanolixizumab	• AUC of the oral steroid dose over time
To assess the plasma concentrations of rozanolixizumab administered by SC infusion	• Plasma concentration of rozanolixizumab at each scheduled assessment during the Treatment and Observation Periods
To assess the pharmacodynamic effects of rozanolixizumab as measured by IgG levels, IgG subclasses, and MG-specific autoantibodies levels	• Change from baseline in total IgG and IgG subclasses autoantibodies at each scheduled visit • Change from baseline in MG-specific autoantibodies at each scheduled visit
To evaluate the incidence and emergence of ADAs with respect to immunogenicity, PK, and pharmacodynamics	• ADAs at each scheduled assessment during the Treatment Period and Observation Periods
To assess the effect of rozanolixizumab on biomarkers including 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 and Observation Periods[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

ADA=anti-drug antibody; ADL=activities of daily living; AESM=adverse event of special monitoring; ECG=electrocardiogram; Ig=immunoglobulin; IVIg=intravenous infusion of immunoglobulin G; MG=myasthenia gravis; MG-ADL=myasthenia gravis-activities of daily living; MGII=myasthenia gravis impairment index; MGQoL15r=revised 15-item myasthenia gravis quality of life questionnaire; PEX=plasma exchange; PK=pharmacokinetic; PRO=patient-reported outcome; QMG=quantitative myasthenia gravis test; SC=subcutaneous(ly); TEAE=treatment-emergent adverse event

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

Estimands

The aim of MG0004 is to compare safety (primarily) of long-term treatment of 2 dose levels of rozanolixizumab. Rescue medication is allowed and is expected to be temporary; dose switching (up or down) is also allowed. Using a treatment policy estimand is considered the only viable option to deal with this complexity. Indeed, a hypothetical estimand that appropriately accounted for treatment switching in this study, differing lengths of treatment in MG0004, and differing exposure to rescue medications in both studies would be very assumption-rich. This estimand will be based on the Safety Set (SS).

For all variables, the population is the study participants meeting the protocol-specified inclusion/exclusion criteria. The main intercurrent events are the use of rescue medication during the course of the study, withdrawal due to TEAEs and treatment switching.

All safety variables, biomarkers, and anti-drug antibody (ADA) results will be summarized for the SS classified by first treatment dose received [redacted] in this study (ie, before any switching occurs), both with and without subdivision by treatment dose received in MG0003 (placebo or [redacted]).

Efficacy variables will be summarized using a 'treatment policy' approach as follows:

- Participant-level outcome: The given variable and time point being summarized (eg, value of MG-ADL at Week 5).
- Population-level summary measure: For categorical variables, unadjusted proportions by first treatment received and, for continuous variables, unadjusted means by first treatment received.

Missing values will not be imputed.

Further details will be provided in the Statistical Analysis Plan (SAP).

4 STUDY DESIGN

4.1 Overall design

This is a randomized, open-label Phase 3 extension study to evaluate the long-term safety, tolerability, and efficacy of rozanolixizumab in study participants with generalized MG. A study schema is provided in Figure 1-1 and a Schedule of Activities is provided in Table 1-1.

Study participants will enter MG0004 from lead-in studies MG0003 or MGC003. Study participants in MG0003 or MGC003 who complete the Observation Period or who require rescue medication during the Observation Period will be invited to be rerandomized in MG0004 (except for study participants who opt to receive IVIg or PEX as rescue medication). Study participants who receive IVIg or PEX as rescue therapy during the Observation Period of MG0003 or MGC003 will not be eligible to enroll in MG0004. Study participants who discontinue study medication in MG0003 or MGC003 for any reason other than requiring rescue medication will not be eligible for MG0004.

For any study participant who enrolls in MG0004, the final visit in MG0003 (Visit 14) or MGC003 will serve as the first visit in MG0004 (Visit 1). All activities should be completed at Visit 1 (±1 week). For criteria pertaining to laboratory measures, the last available value from MG0003 or MGC003 will be used for evaluation of study participant eligibility, as long as the

measurement was taken within the last 4 weeks (not older than 32 days) prior to MG0004 Screening. Up to approximately 276 study participants will be enrolled into the lead-in study MG0003 and MGC003. All eligible study participants from MG0003 or MGC003 will be invited to participate in MG0004.

In MG0004, study participants will be randomized in a 1:1 ratio to receive 1 of 2 doses of rozanolixizumab (equivalent to approximately [redacted], respectively). Specifically, the following dose arms will be used in the study:

Dose arm 1: equivalent to approximately [redacted] rozanolixizumab

- 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]

Dose arm 2: equivalent to approximately [redacted] rozanolixizumab

- 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]

If one of the doses described above is determined to be futile and is discontinued after the interim analysis in MG0003 or MGC003, then that dose arm will be dropped from MG0004 as well, and study participants in the affected dose arm will be transferred to the continuing dose arm. If both dose arms are used in MG0004, study participants will be allowed to switch dose arms for tolerability and efficacy reasons at the discretion of the Investigator (see Section 6.6).

In MG0004, rozanolixizumab will be administered SC on a [redacted] basis over a 52-week Treatment Period. Weekly visits will be either on-site or at home, as described in the Schedule of Activities (Section 1.3). During the first 4 weeks, the weekly visits will be on-site. From Weeks 5 to 8, on-site visits and at home visits will occur on an alternating basis. From Weeks 9 to 48, study participants will have 1 site visit every 4 weeks, such that 1 site visit will be followed by 3 home visits, unless the study participant chooses to complete the scheduled at-home assessments at the site. Weeks 49 to 51 will then involve 1 site visit followed by 2 home visits. At the end of the 52-week Treatment Period in MG0004, study participants will participate in an 8-week Observation Period.

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).

This OLE study will be replaced by MG0007, an OLE study with [redacted] 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 and will no longer have the opportunity to rollover to MG0004. In the event a study participant has

already started MG0004, a minimum treatment duration of 6 visits must be completed (if IMP treatment is withheld 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) and then the participant will discontinue MG0004 and have the opportunity to enter into MG0007. For study participants entering MG0007 from the treatment period of MG0004, he/she must complete the PEOT Visit in MG0004 which will serve both as the Screening Visit for MG0007 and as the EOS for MG0004. If a study participant completes the Treatment Period and is in the Observation Period of MG0004, he/she will then complete the EOS visit to serve as the Screening Visit for 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 rolled over into MG0007.

An IDMC will be formed to monitor the ongoing safety of the study. The IDMC will review implications of individual and cumulative cases to continuance of the study in an ongoing fashion.

4.2 Scientific rationale for study design

The lead-in studies, MG0003 and MGC003, will evaluate the efficacy, safety, and tolerability of rozanolixizumab compared with placebo in study participants with generalized MG who are treated with study medication over a [redacted] at [redacted]. Study participants in the lead-in studies will have generalized MG, as evidenced by the presence of anti-AChR or anti-MuSK antibodies. Additionally, study participants in the lead-in studies will have moderate to severe symptoms of MG and should be under consideration for IVIg or PEX therapy, indicating that they are in need of additional therapeutic intervention.

Study participants in MG0003 or MGC003 will be randomized to receive either placebo or 1 of 2 doses of rozanolixizumab. Study participants in MG0003 or MGC003 who require rescue medication (other than IVIg or PEX) during the Observation Period will be invited to be rerandomized in MG0004: this will offer all study participants, even those previously treated with placebo, a chance to be treated with rozanolixizumab. Rerandomization in MG0004 is applied to account for the limited efficacy information on the [redacted] dose. Due to the open-label design of MG0004, study participants are allowed to switch dose at the Investigator's discretion during the course of the study (dose modification recommendations for safety are provided in Section 6.6). Study participants developing TEAEs could be switched to a dose equivalent to [redacted] and study participants experiencing symptom worsening can be switched to a dose equivalent to [redacted].

MG0004 will then evaluate the long-term safety, tolerability, and efficacy of rozanolixizumab over a 52-week Treatment Period. An open-label study with a treatment duration of 52 weeks is considered sufficient to adequately assess long-term safety with rozanolixizumab for the proposed indication. The dose regimen for rozanolixizumab in MG0004 will be the same one that is used in MG0003 and MGC003 (equivalent to approximately [redacted]), although the dose may be modified based on interim analysis in MG0003 (Section 4.3). In MG0004, study participants will be rerandomized to 1 of 2 doses of rozanolixizumab, and will be allowed to switch between dose arms at the discretion of the Investigator. MG0004 will therefore allow study participants to switch their dose of study medication on an individual basis. MG0004 also offers study participants the chance to benefit from long-term treatment. MG0004

will conclude with an 8-week Observation Period, which is the anticipated duration of time required for antibodies to return to Baseline levels after rozanolixizumab treatment.

4.3 Justification for dose

The dose regimen for rozanolixizumab in MG0004 will be the same one that is used in MG0003 and MGC003 (see Section 4.1 for details of dosing according to weight). The fixed dosing units were introduced to support the potential for study participant self-injection in a home setting and doses have been defined to reach PD effect on IgG levels throughout a weight range that is similar to weight-based dosing.

The proposed doses and regimen of rozanolixizumab in MG0003 were based on the results from first-in-human study UP0018, alongside the efficacy and safety data from the MG Phase 2 study (MG0002), and safety and tolerability data from TP0001. UP0018 evaluated the effect of a single dose of rozanolixizumab (administered at doses of [redacted] as IV or SC infusions) in healthy study participants. The mean absolute decreases in IgG and mean percent change from Baseline IgG were greater in the active dose groups compared with placebo-treated study participants, and rozanolixizumab treatment was tolerated with an acceptable safety profile.

MG0002 evaluated the effect of repeated doses of rozanolixizumab (administered at doses of [redacted] as SC infusions) in study participants with generalized MG. Significant improvements in day-to-day functioning (measured by change from Baseline to Day 29) were observed. In general, responder rates for quantitative myasthenia gravis (QMG) score, MG-C score, and MG-activities of daily living (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, with a mean nadir of 3.3g/L for total IgG (~70% reduction from Baseline). Overall, repeated administrations of rozanolixizumab were generally well tolerated, with an acceptable safety profile.

TP0001 indicated that rozanolixizumab dose higher than [redacted] was tolerated with an acceptable safety profile after multiple [redacted] and [redacted] doses.

Based on these results, 2 SC rozanolixizumab treatment arms, equivalent to [redacted], were selected for MG0003. A population PK-PD 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 90% prediction interval) to the weight-based (mg/kg) dosing regimens studied previously. The proposed rozanolixizumab dosing regiments were selected to provide maximal reduction in autoantibody concentration and result in clinically significant improvements in MG-ADL score.

Since MG0004 is the open-label extension study for MG0003 and MGC003, the same rozanolixizumab dose regimens will also be used in all 3 studies. MG0004. However, if any safety concerns are identified in the lead-in studies, or if one of the dose arms is determined to be futile and is discontinued in MG0003, corresponding changes will be made in the MG0004 dosing scheme. If both dose arms are used in MG0004, study participants will be allowed to switch dose arms for tolerability and efficacy reasons at the discretion of the Investigator (see Section 6.6 for dose modification recommendations for safety).

4.4 End of study definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the End of Study (EOS) Visit (Week 60; see Section 1.3). The end of the study is defined as the date of the last visit of the last participant in the study. The maximum study duration per study participant is 60 weeks.

5 STUDY POPULATION

5.1 Inclusion criteria

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

Age

1. Participant must be ≥18 years of age at the time of signing the informed consent.

Type of participant and disease characteristics

2a. Participant was eligible for MG0003 or MGC003 at the time of enrollment into either study and the participant either completed the Observation Period of MG0003 or MGC003 or required rescue therapy during the Observation Period of the lead-in studies.

Weight

3a. Body weight ≥35kg at Visit 1.

Sex

4. Participants may be male or female.
   - A male 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.
   - Female study participants of childbearing potential must agree to use a highly effective method of birth control during the study and for a period of at least 90 days after their final dose of study medication. According to the International Council for Harmonisation (ICH) M3 (R2), highly effective forms of birth control are methods that achieve a failure rate of less than 1% per year when used consistently and correctly.
   - A female participant is eligible to participate if she is not pregnant (see Appendix 4, Section 10.4), not breastfeeding, and at least one of the following conditions applies:
     - Not a woman of childbearing potential (WOCBP) as defined in Appendix 4 (Section 10.4)
       OR
     - A WOCBP who agrees to follow the contraceptive guidance in Appendix 4 (Section 10.4) during the Treatment Period and for at least 90 days after the last dose of study treatment.

Informed consent

5. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1) which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2 Exclusion criteria

For criteria pertaining to laboratory measures, the last value from MG0003 or MGC003 will be used for evaluation of study participant eligibility, as long as the measurement was taken within the last 4 weeks (not older than 32 days) prior to MG0004 screening.

Unless otherwise stated, each criterion is applicable to the Screening visit (Visit 1). Participants are excluded from the study if any of the following criteria apply:

Medical conditions

1. 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. Participant has a history of use disorder or other substance use disorder (as per Diagnostic and Statistical Manual of Mental Disorders-5) within the previous 12 months.

3. Participant has a known hypersensitivity to any components of the study medication.

4a. Evidence of active or latent tuberculosis (TB) as documented by medical history and examination, if applicable, chest X-rays (posterior anterior and lateral), and TB testing by a positive (not indeterminate) QuantiFERON®-TB Gold Plus.

Prior/Concomitant therapy

5. Participant has received a live vaccination within 8 weeks prior to the Baseline visit; or intends to have a live vaccination during the course of the study or within 8 weeks following the final dose of study medication.

Prior/Concurrent clinical study experience

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

Diagnostic assessments

7. 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.

8. Participant has absolute neutrophil count <1500 cells/mm^3.

9. 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.

10. Participant has 12-lead electrocardiogram (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 participant must be addressed with the Medical Monitor.

11b. Study participant has renal impairment, defined as glomerular filtration rate less than 45ml/min/1.73m^2.

12a. Study participant has >3x upper limit of normal (ULN) of any of the following at Visit 1: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).

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

For randomized 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 must be understood and recorded in the electronic Case Report form (eCRF).

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

13. Study participant has positive human immunodeficiency virus antibody test.

Other exclusions

14a. Study participant met any mandatory withdrawal or mandatory study drug discontinuation criteria MG0003 or MGC003, or discontinued study medication in either study, with the exception of discontinuation due to a need for rescue treatment

15. Study participant is not considered capable of adhering to the protocol visit schedule, or medication intake according to the judgment of the Investigator.

16. Study participant has a lifetime history of suicide attempt (including an active attempt, interrupted attempt, or aborted attempt), or had suicidal ideation since the last visit in MG0003 as indicated by a positive response (Yes) to either Question 4 or Question 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS).

17. Criterion removed.

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

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 cannabidiols and medicinal marijuana (prescribed by a physician) is permitted (see Section 6.5.1).

5.4 Screen failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered into the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure 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 serious adverse events (SAEs).

If a study participant has 1 isolated test result outside the specific range which is deemed clinically nonsignificant, the abnormal value may be rechecked at the discretion of the Investigator, following discussion with the Sponsor's medical monitor/study physician.

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

6 STUDY TREATMENTS

Study treatment is defined as any investigational treatment(s), intended to be administered to a study participant according to the study protocol.

6.1 Treatments administered

A summary of study treatments is provided in Table 6-1.

Table 6-1: Study treatments administered

Study Treatment Name:	**Rozanolixizumab** [redacted]	**Rozanolixizumab** [redacted]
Dosage formulation:	Solution for infusion	Solution for infusion
Unit dose strength(s)/Dosage level(s):	[redacted]	[redacted]
Route of administration	SC	SC
Dosing instructions:	[redacted] SC doses of rozanolixizumab for 52 weeks: 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] SC doses of rozanolixizumab for 52 weeks: 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]

Table 6-1: Study treatments administered

Study Treatment Name:	Rozanolixizumab [redacted]	Rozanolixizumab [redacted]
Packaging and labeling	Rozanolixizumab is manufactured, packaged, and labeled according to Good Manufacturing Practice guidelines and applicable laws or regulations.	

SC=subcutaneous(ly); w/v=weight/volume

Note: [redacted] administration of rozanolixizumab will be either on-site or at home, as described in the Schedule of Activities (Section 1.3). During the first 4 weeks, the weekly visits will be on-site. From Weeks 5 to 8, on-site visits and at-home visits will occur on an alternating basis. From Weeks 9 to 48, study participants will have 1 site visit every 4 weeks, such that 1 site visit will be followed by 3 home visits, unless the study participant chooses to complete the scheduled at-home visit at the site. Weeks 49 to 51 will then involve 1 site visit followed by 2 home visits.

Details on the preparation of study treatment for infusion, rate of infusion, administration, appropriate records handling, and site personnel roles are provided in the investigational medicinal product (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, institution, or the head of the medical institution (where applicable) 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.

The Investigator (or designee) will instruct the participant to store the study medication following the instructions on the label.

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

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

The Investigator must ensure that the 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 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

An interactive response technology (IRT) will be used for assigning eligible 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. Study participants will retain the same 5-digit number assigned in MG0003 or MGC003 that serves as the participant identifier throughout the study. The participant number will be required in all communication between the Investigator or designee and the IRT regarding a particular participant. Participant numbers and kit numbers will be tracked via the IRT.

To randomize a participant, the Investigator or designee will contact the IRT and provide brief details about the participant to be randomized. The IRT will automatically inform the Investigator or designee of the participant's randomization number. The IRT will allocate kit numbers to the participant based on the participant number during the course of the study. The randomization number must be incorporated into the eCRF.

6.3.1 Procedures for maintaining and breaking the treatment blind

6.3.1.1 Maintenance of study treatment blind

This is an open-label study and treatment details (ie, dose arm) will not be blinded.

6.3.1.2 Breaking the treatment blind in an emergency situation

Not applicable.

6.4 Treatment compliance

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

6.5 Concomitant medications/treatments

6.5.1 Permitted concomitant treatments (medications and therapies)

The concomitant medications in Table 6-2 are permitted during the study for the treatment of MG, and dose adjustments are allowed during the study.

Any violation of the permitted treatment criteria should be discussed with the Investigator, Sponsor, and Medical Monitor.

Table 6-2: Permitted concomitant medications for the treatment of myasthenia gravis

Permitted medications	Dose
Oral corticosteroids (ie, prednisolone)	No specific requirements
Methotrexate	≤30mg/week
Mycophenolate mofetil	≤3g/day
Cyclosporin [a]	≤5mg/kg/day for unmodified ≤4mg/kg/day for modified (microemulsion)
Azathioprine	≤3mg/kg/day
Cholinesterase inhibitors	≤600mg pyridostigmine/day
Tacrolimus [b]	≤5mg/day

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

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

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

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 study medication, 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.

6.5.2.1 Treatments specific to NMJ interference

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

- botulinum toxin
- aminoglycoside antibiotics
- tetracycline antibiotics
- penicillamine
- magnesium

For a more detailed list please refer to the Myasthenia Gravis Foundation of America 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.

6.5.3 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 2 consecutive visits) may be considered for rescue therapy at the discretion of the Investigator.

If the study participant receives IVIg or PEX as rescue therapy during the study, treatment with rozanolixizumab should be discontinued or paused for a minimum of 2 weeks, but continue with visits as per Schedule of Activities, after which the participant may continue to receive rozanolixizumab at the discretion of the Investigator. This 2-week period may be extended at the discretion of the Investigator, but for no longer than 6 weeks. Following the temporary discontinuation of study medication, study participants should be restarted at the same dose of rozanolixizumab as previously. Study participants at a dose level of [redacted] rozanolixizumab can be restarted at [redacted] rozanolixizumab at the discretion of the Investigator.

6.6 Dose modification

Study participants will be allowed to switch dose arms for tolerability and efficacy reasons, as well as bodyweight changes at the discretion of the Investigator after the first dose of rozanolixizumab. However, when possible, the dose assigned at randomization should be maintained for at least 6 weeks, unless a dose modification is required earlier for tolerability or efficacy reasons. If a dose adjustment is made, the Investigator should encourage study

participants to stay on the modified dose for at least 6 weeks, unless further dose adjustments or discontinuation of study medication is required for the safety of the study participant.

Study participants who experience any AEs that meet the study medication discontinuation criteria (Section 7.1 and Section 0) should have rozanolixizumab discontinued. Study participants in the [redacted] cohort who experience a possibly related toxicity other than those that met the study drug discontinuation criteria as defined in Section 7.1 and Section 0 are allowed to switch to [redacted] at the Investigator's discretion. Recommended dose modifications due to toxicities may include (but not exclusive):

- Moderate to severe headaches that are considered to be related to rozanolixizumab (Section 10.20.1)
- Moderate to severe GI disturbances that are considered to be related to rozanolixizumab
- Moderate to severe toxicities (≥Grade 2 as defined by CTCAE, version 5) for which rozanolixizumab cannot be excluded as a cause
- Recurrent hypogammaglobulinemia with a serum total IgG <2g/L

The date and reason for dose change of rozanolixizumab is to be recorded on each study participant's eCRF.

If any safety concerns are identified in MG0003 (ie, as recommended by the IDMC), or if one of the dose arms is determined to be futile and is discontinued in MG0003, corresponding changes may be made in the MG0004 dosing scheme. A study participant on a dose that was discontinued will switch doses immediately.

6.7 Home visits

During the 52-week Treatment Period, the at-home visits will be conducted by fully trained healthcare professional visiting the study participant at his or her home. Alternatively, these visits can be conducted at the site as deemed necessary by site personnel and/or the study participant. For home/self-dosing, the same safety monitoring schedule will be followed as per onsite dosing. The home nurse will be present during the full duration of the visit. Home visits can be conducted if the following conditions are met:

- The study participant is willing to be dosed and monitored at home by a home nurse.
- The study participant has shown good acute tolerability to previous administrations of IMP (namely, he or she must have had no moderate or severe infusion reactions or other AEs that the Investigator considers could increase the risk of home administration).

The Investigator should complete a checklist to confirm that criteria for home self-administration have been fully evaluated.

6.8 Treatment after the end of the study

Study participants who complete participation in MG0004 may have the possibility to continue receiving rozanolixizumab through a managed access program as per applicable local regulations.

In the case of prolonged hypogammaglobulinemia after treatment discontinuation, study participants can be considered for treatment with prophylactic antimicrobial therapy per local

guidelines. Study participants must be followed up until IgG levels return to values within the normal range or to individual Baseline values.

7 DISCONTINUATION OF STUDY MEDICATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

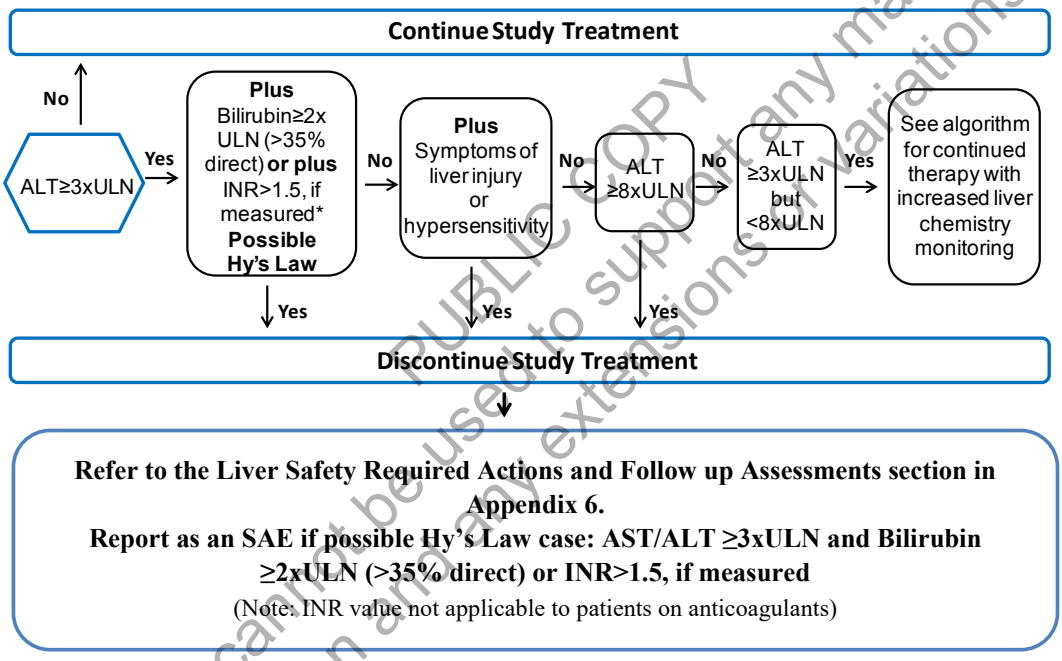
7.1 Discontinuation of study medication

7.1.1 Liver chemistry stopping criteria

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

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

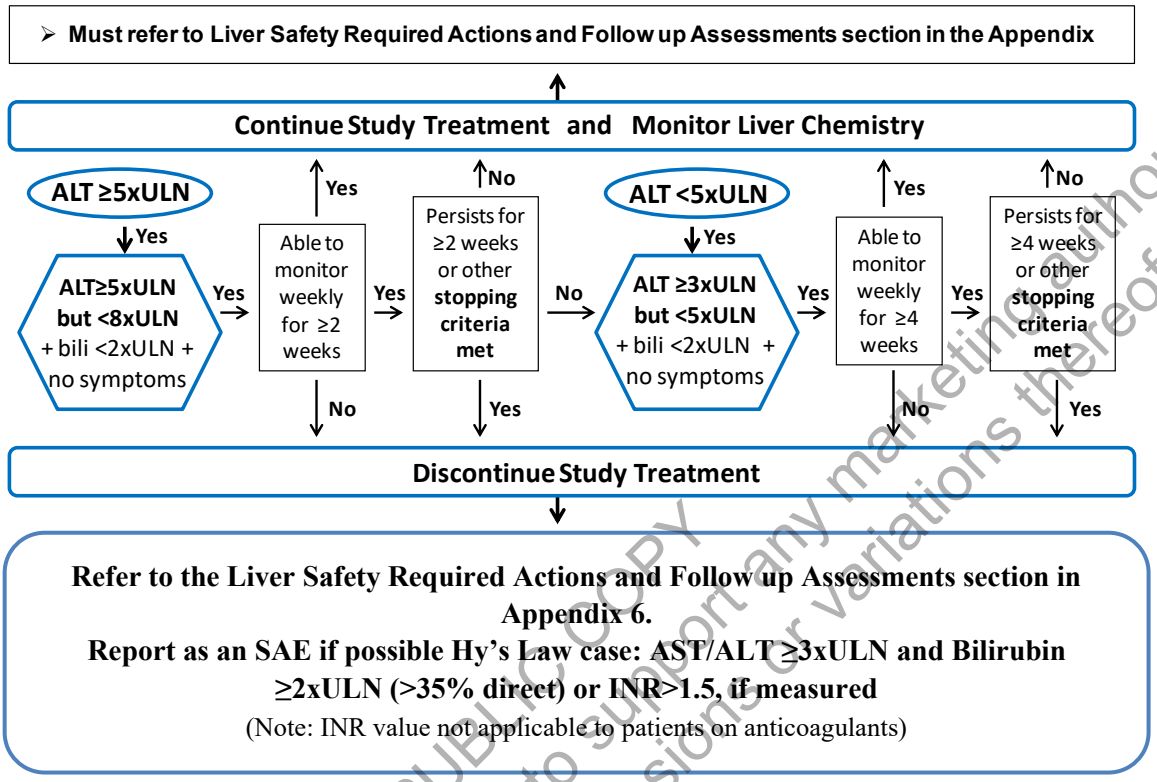
Figure 7-1: Liver chemistry stopping criteria and increased monitoring algorithm



ALT=alanine aminotransferase; AST=aspartate aminotransferase; INR=international normalized ratio; SAE=serious adverse event; ULN=upper limit of normal
* The INR value is not applicable to study participants on anticoagulants.

Treatment with study medication may be continued with increased monitoring if a study participant meets one of the criteria outlined in Figure 7-2.

Figure 7-2: Liver chemistry increased monitoring algorithm with continued study intervention for participants with ALT at least 3xULN but less than 8xULN



ALT=alanine aminotransferase; 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 (PDILI) are provided in Appendix 6 (Section 10.6).

7.1.2 QTc stopping criteria

If a clinically significant finding is identified after enrollment (including, but not limited to changes from Baseline in QT interval corrected using QT interval corrected for heart rate using Fridericia's formula [QTcF]), the Investigator or qualified designee will determine if the 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 either bulleted criterion based on the average of triplicate ECG readings will be withdrawn from study medication 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 >600msec
- Change from baseline of QTc >60msec

For 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
<450msec	>500msec
450 to 480msec	≥530msec

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 complete the eCRF accordingly.

7.1.3 Discontinuation of study medication due to other AEs or medical conditions

A study participant **must** permanently discontinue study medication if any of the following events occur:

1. Study participant develops an illness that would interfere with his or her continued participation.
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 (including but not limited to bacteremia or sepsis, meningitis, osteomyelitis or septic arthritis, pneumonia, or visceral abscess).
4. Study participant meets potential drug-induced liver injury (PDILI) permanent discontinuation criteria.
5. Study participant has a TB test that is confirmed positive or any further evidence suggestive of potential TB infection (ie, exposure) and further examinations result in a diagnosis of active TB or latent TB infection (LTBI).
6. If a nontuberculosis mycobacterium infection (NTMB) 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. Study participant experiences a serious AE of headache which is considered related to the study medication in the opinion of the Investigator.
8. Study participant has an AE of severe or serious infusion or anaphylactic reaction requiring corticosteroid and/or epinephrine therapy (see Section 10.22) (Sampson et al, 2006).

Study participants **may** permanently discontinue study medication at the discretion of the Investigator, Medical Monitor, and Study Physician if any of the following events occur:

9. Study participant is noncompliant with the study procedures or medications in the opinion of the Investigator.
10. Study participant takes prohibited concomitant medications as defined in this protocol.

Investigators should contact the Medical Monitor, whenever possible, to discuss the withdrawal of a participant in advance. Investigators should attempt to obtain information on study participants in the event of withdrawal (eg, reason for withdrawal, any safety information).

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 22; Section 10.22.3).
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 22; Section 10.22.3).
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 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 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. Study participant becomes pregnant during the study, as confirmed 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 participant should be referred immediately to a mental healthcare professional.

Study participants who withdraw from the study or discontinue study medication during the Treatment Period should complete the assessments outlined for premature end of treatment (PEOT) visit and enter the Observation Period.

Study participants who withdraw for any reason will not be eligible to participate in the managed access program.

7.3 Lost to follow-up

A 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 participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the 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 participant, must be recorded in the source documents. The eCRF must document the primary reason for withdrawal.

Should the 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).

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.

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 will be performed:

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

Blood samples for PK, IgG, hematology, biochemistry, other laboratory testing and assessments may be performed as clinically indicated 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

Planned timepoints for all efficacy assessments are provided in the Schedule of Activities (Section 1.3).

8.1.1 Quantitative Myasthenia Gravis scale

For assessment of the QMG scale, Investigators or qualified designee will follow the Myasthenia Gravis Foundation of America's QMG Manual instructions (Section 10.12, Appendix 12). Clinical personnel must complete mandatory training and be certified to assess study participants' QMG scores (details are provided in the Study Procedures Manual). Study participants should not take pyridostigmine (or any acetylcholinesterase [AChE] inhibitor medication) at any point after midnight before testing when medically safe to do so to standardize testing. If it is not medically appropriate to halt AChE inhibitor medications, then the treatment can be continued but the testing should be performed as best as possible at the same time relative to the most recent dose of AChE inhibitor during the study.

The scale tests 13 items, including ocular and facial involvement, swallowing, speech, limb strength, and forced vital capacity (FVC). For the assessment of FVC, the same spirometer should be used each time a study participant is tested, and if possible, the same person should carry out the assessment. Parameters and normal values for FVC will be decided between the study sites, such that all sites are using the same information. The QMG is a validated assessment (Barnett et al, 2012), with a higher score indicating more severe disease. Scoring for each item ranges from no weakness (0) to severe weakness (3), with an overall score range from 0 to 39. A 3-point change in the total score is considered clinically relevant.

8.1.2 Myasthenia Gravis-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 any other acetylcholinesterase [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 (Section 10.13, Appendix 13), and a 3-point change is considered clinically relevant (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 and be certified 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.

8.1.3 Patient-reported outcomes

Patient-reported outcomes (PROs) must be completed as per timepoints 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, EQ-5D-5L, MGII, 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.

8.1.3.1 MG-Activities of Daily Living scale

The MG-ADL is an 8-item PRO instrument developed on the basis of the QMG (Wolfe et al, 1999) (Section 10.14, Appendix 14). The MG-ADL targets symptoms and disability across ocular, 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. It was also 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.

8.1.3.2 MG Symptoms PRO

The MG Symptoms PRO instrument (Appendix 15, Section 10.15) consists of 42 items across 5 scales: ocular symptoms (items 1 to 5); bulbar symptoms (items 6 to 15); respiratory symptoms (items 16 to 18); physical fatigability (items 19 to 33) and muscle weakness fatigability (items 34 to 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 he or she experiences 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.

8.1.3.3 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 16, Section 10.16).

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

The descriptive system comprises 5 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 study participant is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the 5 dimensions can be combined into a 5-digit number that describes the study participant's health state.

The EQ VAS records the study participant'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 reflects the study participant's own judgement.

8.1.3.4 Myasthenia Gravis Impairment Index

The MGII is a measure of disease severity based on the signs and symptoms of study participants with MG (Appendix 17, Section 10.17). It was developed using a study participant-centered approach and following current guidelines for outcome measure development, incorporating study participant input throughout the different development phases (Barnett et al, 2014; Barnett et al, 2016). The MGII has 22 study participant-reported and 6 examination items, and scores are presented as a sum of all items for a total score but also as ocular and generalized sub-scores. 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 study participants 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).

8.1.3.5 Revised 15-item myasthenia gravis quality of life questionnaire

The MG-QOL15r is a brief survey, completed by the study participant, which 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 18, Section 10.18).

When completing the 15-item MG-QOL15r, MG study participants 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 until Week 7, where the participant can be observed for 1 hour at the Investigator’s discretion.

8.2.1 Physical examinations

Complete physical examination

A complete 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, musculoskeletal, and hepatic systems. Height and weight will also be measured and recorded. Body weight will be measured 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 complete 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 (BP) 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 ECGs will be obtained as outlined in the Schedule of Activities (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures pulse rate (PR), QRS, QT, and QTc intervals. Refer to Section 7.1.2 for QTc withdrawal criteria and any additional 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 ECGs 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 (Section 10.2) for the list of clinical laboratory tests to be performed and 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 until they 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, must be conducted in accordance with the laboratory manual and the Schedule of Activities.

8.2.5 Suicidal risk monitoring

Participants being treated with rozanolixizumab should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior.

Consideration should be given to discontinuing rozanolixizumab in participants who experience signs of suicidal ideation or behavior.

Families and caregivers of 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 23, Section 10.23]). This scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study.

8.2.6 Assessment and management of tuberculosis and tuberculosis 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, genitourinary 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, and abdominal pain (mimicking inflammatory bowel disease). Unusual presentations should always be considered.

If available, respiratory or other specimens must also be smear- and culture-negative for TB (CDC 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]

[redacted] should not be allowed into the study pending further assessments (including TB specialist consult) as outlined previously.

A detailed description of the TB questionnaire is provided in Appendix 19 (Section 10.19).

TB assessment by interferon gamma release assay

The TB screening test interferon gamma release assay (IGRA) performed at MG0003 entry will be used as the Baseline result. Additional IGRA tests may be performed if indicated (eg, presence of signs and symptoms suggestive of TB, recent exposure).

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. If the test is positive or indeterminate on retest, the study participant must not be randomized to study medication.

TB assessment by chest x-ray

A Screening chest x-ray is not required for this study.

However, a chest x-ray or other imaging test can be performed if indicated (eg, presence of signs and symptoms suggestive of TB, close exposure to persons with TB).

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 the event of an IGRA test conversion, the study participant must be considered as having either a suspected new LTBI or an active TB infection and be promptly referred to an appropriate specialist (eg, pulmonologist, infectious disease specialist) for further evaluation. If the 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 should be updated with a final diagnosis once it is 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.

Any 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-TB 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 an PEOT Visit must be scheduled as soon as possible, but no later than the next scheduled visit. The study participant should be encouraged to keep the EOS Visit as specified by the protocol. Treatment for active TB or NTMB should be started immediately based on local guidelines.

Confirmed active TB is always considered an SAE. UCB's process requires that these events 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.

Latent tuberculosis infection, 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 3, 9, and 12 months after 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 from 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 rozanolixizumab treatment or from MG0004 (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 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 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 until the End of Study Visit for each participant, and to also inform 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 nonleading 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 nonserious AESMs, as defined in Section 8.3.6), 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 serious adverse events

Prompt notification (24 hours) by the Investigator to the Sponsor of a 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 IB 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, in female partners of male participants will be collected after the start of study treatment and until at least 90 days 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 participant should be withdrawn from the study as soon as pregnancy is known (by positive pregnancy test), and the following should be completed:

- The 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 reported within 24 hours.

Potential Hy's Law, defined as ≥3xULN ALT and ≥2xULN bilirubin (>35% direct bilirubin) or ALT ≥3xULN and international normalized ratio (INR) >1.5, if INR measured, with no alternative explanation for the biochemical abnormality, must ALWAYS be reported to UCB as an AESI (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 AE recording and reporting procedures as indicated in Appendix 3 (Section 10.3).

8.3.7 Adverse events of special monitoring

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

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

In case of severe headache or serious headache (regardless of severity), the headache questionnaire (Appendix 21 [Section 10.21]) must be completed. Additional procedures for management of headaches are provided in Appendix 20 (Section 10.20.1).

Procedures for the management of diarrhea, and infections and hypogammaglobulinemia are provided in Appendix 20 (Section 10.20.2 and Section 10.20.3, respectively).

Although hypersensitivity reactions including infused-related reactions and anaphylaxis are not classified as AESM, these AEs will be monitored by the Investigators. If such an event is suspected, it should be managed according the guidance provided in Appendix 20 (Section 10.20.4). In case of suspected anaphylaxis, the Sampson's Criteria Questionnaire (Sampson et al, 2006) in Appendix 22 (Section 10.22) should be completed.

All AESMs 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 IDMC will periodically review and monitor safety data from this study and advise UCB. Details are provided in the IDMC 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, 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 [redacted] 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 and laboratory abnormalities for at least 5 days.
3. Obtain a plasma sample for PK analysis and IgG (total and subclasses) autoantibodies 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). Blood samples may be collected at additional timepoints 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 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.

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.

Blood samples for the measurement of plasma concentrations of rozanolixizumab will be collected at additional timepoints in a local substudy.

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

For all PD 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

Not applicable.

8.9 Biomarkers

Collection of samples for other biomarker research is also part of this study. Blood samples for biomarker research are required and will be collected from all 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 postevent or as soon as possible before the next IMP in case of AESM of serious or severe headache or AESM of GI disorders.

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)
- Serum cytokines
- Plasma complement (C3a, C5a)
- Tetanus toxoid IgG

Samples for IgA, IgE, IgM are collected predose.

Additional samples may be collected 2 hours and 4 hours postevent in case of severe headache, infusion reaction, or hypersensitivity reaction at Visits 5, 7, 1st visit (of the 4-week cycle from Weeks 9-48) and Visit 49.

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 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 SAP.

9.1 Definition of analysis sets

The following analysis sets will be created in the study:

- Enrolled Set: All study participants who sign the informed consent.
- Randomized Set: All enrolled study participants who are randomized.
- Safety Set: All randomized study participants who received at least 1 dose of study medication in this study. Analysis of this set will be according to the treatment the study participants first received, and will be used for the efficacy, demographic, and safety analyses.

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 by dose levels of rozanolixizumab first received in this study.

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

9.3 Planned safety and other analyses

9.3.1 Analysis of the primary safety endpoints

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 participants experiencing the TEAE, percentage of participants, and number of TEAEs. A TEAE is defined as any event that was not present prior to the first administration of study medication or any unresolved event already present before the first administration of study medication that worsens in intensity following exposure to treatment, up to and including 8 weeks after the end of the Treatment Period or 8 weeks after the last of study medication in study participants who discontinue the study or study medication.

All safety analyses will be based on the SS (Section 9.1).

9.3.2 Analysis of the other safety endpoints

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.

9.3.3 Other analyses

9.3.3.1 Pharmacokinetic analyses

Pharmacokinetic variables such as AUC or C_{max} cannot be derived, since blood sampling will be performed at 1 time point per visit only. Thus, PK analysis is restricted to rozanolixizumab concentration data. In addition to the general descriptive display, of 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). Individual concentrations of rozanolixizumab will also be displayed graphically.

All PK analyses will be based on the SS (Section 9.1).

9.3.3.2 Pharmacodynamic analyses and biomarkers

The levels of anti-MuSK, anti-AChR, and biomarkers (potentially including but not limited to total IgG, IgG subclasses, IgA, IgE, IgM, serum complement, and plasma complement) will be presented as continuous variables (Section 9.2).

All pharmacodynamic and biomarker analyses will be based on the SS (Section 9.1).

9.3.3.3 Anti-drug antibody analyses

A tiered ADA approach will be used for the study. Anti-drug antibody assessments 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.

All immunogenicity analyses will be based on the SS (Section 9.1).

9.4 Planned efficacy analyses

Data 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. For categorical variables, frequency counts and percentages will be produced.

All efficacy analyses will be based on the SS (Section 9.1).

9.5 Handling of protocol deviations

Important protocol deviations will be identified as part of the data cleaning process in the Data Cleaning Plan. 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 Data Cleaning Plan and discuss exclusion of study participants from analysis populations. Furthermore, overall trends in protocol deviations will be discussed at the Data Evaluation Meeting. Through this ongoing data cleaning and evaluation process, all decisions

regarding important protocol deviations and exclusions from analysis populations are made on an ongoing basis.

9.6 Handling of dropouts or missing data

All imputation of missing or partial dates for safety assessments will be detailed in the SAP. Efficacy data will be summarized only and no imputation will be performed..

9.7 Planned interim analysis and data monitoring

9.7.1 Interim analysis

There are no plans for hypothesis testing in this study and therefore no formal interim analysis will be conducted. Interim cuts of open label data may be conducted to provide information on the ongoing study.

9.7.2 Data monitoring

The IDMC will oversee the safety of the study by reviewing safety data at periodic data reviews.

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.

9.8 Determination of sample size

No formal sample size calculation can be performed. Up to approximately 276 study participants will be enrolled into the lead-in studies, MG0003 and MGC003. All eligible study participants from MG0003 and MGC003 will be invited to participate in MG0004.

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, ICH-Good Clinical Practice (GCP), and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator/UCB will ensure that an appropriately constituted IRB/IEC that complies with the requirements of the current ICH-GCP version or applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to initiation of the study, the Investigator/UCB will forward copies of the protocol, ICF, IB, and 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 contract research organization agreements, as applicable.

10.1.3 Informed consent process

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

Prior to obtaining informed consent, information should be given in a language and at a level of complexity understandable to the 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 ICF 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 ICF. 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 ICF 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 ICF 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 to be enrolled in the study when he/she has signed the ICF. An eCRF 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 participant's confidentiality. Throughout this study, all data forwarded to UCB (or designee) will be identified only by the 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.

An IDMC will be set up in line with the FDA regulatory requirements and EMA 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 contract research organization, and have no conflict of interest related to the conduct or the outcomes of the study.

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. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

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, respectively.
- 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

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC Count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry [a]	BUN	Potassium	AST/SGOT	Total and direct bilirubin
	Creatinine	Sodium	ALT/SGPT	Total Protein
	Glucose (fasting)	Calcium	Alkaline phosphatase	Albumin
	Lactate dehydrogenase	CRP		
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, albumin, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Urine human chorionic gonadotropin pregnancy test (as needed for women of childbearing potential) [b] • Serology testing for HIV, hepatitis B, and hepatitis C • All study-required laboratory assessments will be performed by a central laboratory.			

Laboratory Assessments	Parameters
	• The results of each test must be entered into the eCRF.

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CRP=C-reactive protein; eCRF=electronic Case Report form; HIV=human immunodeficiency virus; IEC=Independent Ethics Committee; IRB=Internal Review Board; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; RBC=red blood cell count; SAE=serious adverse event; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase; ULN=upper limit of normal; WBC=white blood cell count

[a] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1.1 and Appendix 6 (Section 10.6). All events of ALT ≥3 × ULN and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and 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.

10.3 Appendix 3: Adverse events – definitions and procedures for recording, evaluating, follow-up, and reporting

10.3.1 Definition of adverse event

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 serious adverse event

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 adverse events and/or serious adverse events

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 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 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 a 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 AESIs.
- 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 eCRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of serious adverse events

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 they become 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

10.4.1 Definitions

10.4.1.1 Woman of childbearing potential

A woman is considered fertile following menarche and until becoming postmenopausal 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 nonestrogen 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.

10.4.2 Contraception guidance

Male participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following 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 plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 10-1 when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.
- 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 last 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 for at least 90 days after the last dose of study medication.

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 vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the woman of childbearing potential 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.

[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 instruction 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

- A WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine pregnancy test.
- Additional pregnancy testing should be performed during the Treatment Period (Section 1.3), 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. Urine pregnancy tests will be performed at all other visits.

10.4.2.1 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.
- 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 24 hours 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.

10.4.2.2 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 24 hours 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 study medication 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 PDILI 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 PDILI should not be withdrawn from the study until investigation and monitoring are complete. All results of these evaluations and observations, as well as the reason(s) for study medication discontinuation and/or participant withdrawal (if applicable), must be recorded in the source documents. The eCRF 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 >5xULN. The monitoring plan should include any necessary follow-up assessments (until resolution of the abnormal lab values).

Phase 3 liver chemistry stopping criteria are designed to assure participant safety and to evaluate liver event etiology. Stopping criteria are presented in Table 10-2 and increased monitoring criteria are presented in Table 10-3.

Table 10-2: Phase 3 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 [b]	ALT ≥3xULN **and** INR >1.5, if INR measured
Cannot mMonitor	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 the Sponsor within **24 hours.**
- Complete the liver event eCRF, and complete as SAE data collection tool if the event also met the criteria for an SAE. [b]
- 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:

For bilirubin or INR criteria

- Repeat liver chemistry tests (include ALT, 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.

For all other criteria

- 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.
- 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 HBsAg), quantitative hepatitis B DNA and hepatitis delta antibody. [e]
- Obtain blood sample for PK analysis as soon as feasible after the most recent dose. [f]
- Serum CPK and 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 AE report form.
- Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications eCRF.
- Record alcohol use on the liver event alcohol intake eCRF.
- Exclude pregnancy.
- Urine drug screen.

For bilirubin or INR criteria:

- 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 eCRFs.

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CPK=creatine phosphokinase; DNA=deoxyribonucleic acid; eCRF=electronic case report form; HBsAg=hepatitis B virus surface antigen; HCsAg=hepatitis C virus surface antigen; HPLC=high performance liquid chromatography; IgM=immunoglobulin M; INR=international normalized ratio; LDH=lactate dehydrogenase; PK=pharmacokinetic; RNA=ribonucleic acid; SAE=serious adverse event; ULN=upper limit of normal

[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 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 of hepatitis D RNA virus (where needed) (Le Gal et al, 2005).

[f] 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 eCRF. 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: Phase 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 but <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
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
AESM	adverse event of special monitoring
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BP	blood pressure
CPMP	Committee for Proprietary Medicinal Products
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
IDMC	Independent Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
EOS	End of Study
EQ-5D-5L	5-level European quality of life 5 dimension
EQ VAS	EQ visual analogue scale
FcRn	neonatal Fc receptor
FSH	follicle stimulating hormone
FVC	forced vital capacity
GBS	Guillain-Barré Syndrome
GCP	Good Clinical Practice
GI	gastrointestinal
HRT	hormonal replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee

Ig	immunoglobulin
IGRA	interferon gamma release assay
IMP	investigational medicinal product
INR	international normalized ratio
IRB	Institutional Review Board
IRT	interactive response technology
ITP	immune thrombocytopenia
IV	intravenous
IVIg	intravenous infusion of immunoglobulin G
LLOQ	lower limit of quantification
LTBI	latent tuberculosis infection
MedDRA	Medical Dictionary for Regulatory Activities
MG	myasthenia gravis
MG-ADL	myasthenia gravis-activates of daily living
MGII	myasthenia gravis impairment index
MGQoL15r	revised 15-item myasthenia gravis quality of life questionnaire
MuSK	muscle-specific kinase
NMJ	neuromuscular junctions
NTMB	nontuberculosis mycobacterium infection
OLE	open-label extension
PD	pharmacodynamic(s)
PDILI	potential drug-induced liver injury
PEF	peak expiratory flow
PEOT	premature end of treatment
PEX	plasma exchange
PK	pharmacokinetic(s)
PRO	patient-reported outcome
PV	pemphigus vulgaris
QMG	quantitative myasthenia gravis test
QTc	QT interval corrected for heart rate
SAE	serious adverse event
SAP	Statistical Analysis Plan

SC	subcutaneous(ly)
SD	standard deviation
SS	Safety Set
TB	tuberculosis
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WOCBP	woman of childbearing potential

10.11 Appendix 11: Protocol amendment history

Amendment 1 (01 Nov 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 have 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 2.2 Background 4.1 Overall Design 4.2 Scientific Rationale for Study Design 4.3 Justification for Dose 5.1 Inclusion Criteria 5.2 Exclusion Criteria 9.8 Determination of Sample Size	Reference to another lead-in study, MGC003, has been made throughout.	General update.
1.1 Synopsis 4.1 Overall Design 9.8 Determination of Sample Size	The number of study participants was changed.	The new number of study participants includes an approximate total from the China-specific study, MCG003.
1.1 Synopsis	Number of participants: Additional wording has been included to allow study participants (at selected sites) to enroll into a substudy.	This is to allow for study participants to be included in Bioequivalence or Human Factor substudies.
1.1 Synopsis 3 Objectives and Endpoints	The term "Value" has been removed from all endpoints, where applicable.	Updated for consistency, as there were redundancies.
1.1 Synopsis 3 Objectives and Endpoints	An additional exploratory objective and endpoint was added	This was added to assess the effect of rozanolixizumab on tetanus IgG antibodies.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 3 Objectives and Endpoints	An additional exploratory objective and endpoint was added.	This was added to capture the reduction steroid use in study participants receiving rozanolixizumab.
1.1 Synopsis	Additional text has been included to highlight dose adjustments can be made if the study participant's bodyweight changes during the study.	Updated to provide further clarification.
1.3 Schedule of Activities 4.4 End of Study definition 8.2.6 Assessment and management of TB and TB risk factors 8.3.1 Time period and frequency for collecting AE and SAE information 10.4.3 Pregnancy testing	Change last study visit from Final Visit to End of Study.	The update was made to harmonize across the rozanolixizumab Phase 3 clinical program.
1.3 Schedule of Activities	The frequency of bodyweight measurements has been reduced to every 6 months.	Updated to provide further clarification, as bodyweight does not frequently change.
1.3 Schedule of Activities	Urine drug screen procedure was removed from the study.	The exclusionary criterion pertaining to use of marijuana was removed.
1.3 Schedule of Activities	Study participants identification card assigned has been added.	Missing activity from original protocol.
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 for the effect of rozanolixizumab on tetanus IgG antibodies.
1.3 Schedule of Activities	Blood sampling for pharmacokinetics at Visits 5 and the first visit during Weeks 9 to 48 have been removed.	Pharmacokinetic concentrations are expected to be Below the Limit of Quantitation at these visits.
1.3 Schedule of Activities	Blood sampling for IgA, IgE and IgM was added.	Missing activity from original protocol.
1.3 Schedule of Activities	Footnote f (any recreational or medicinal use of cannabis [ie, marijuana] or cannabidiols is not authorized in the study) was removed.	The use of cannabidiols and medicinal marijuana (prescribed by a physician) is now part of the permitted concomitant treatments list.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	Footnote j changed to k: The following wording "At dosing visits" was removed.	The text no longer applied to these assessments
1.3 Schedule of Activities 4.1 Overall design	A visit window for the Screening Visit has been added.	The addition of ±1 week has been added to provide flexibility for Screening activities and randomization.
2.2 Background	The number of rozanolixizumab clinical studies has been amended from 4 to 6 due to the additional studies; CIDP01 and MG0003.	General update.
2.2 Background	An additional country has been added in reference to the study population in UP0060.	General update.
4.4 End of Study definition	The word "lacking in" has been changed to "**limited**"	This change was made to clarify some efficacy information on the [redacted] dose is available.
5.1 Inclusion criteria	Criterion #3: the bodyweight 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.
5.2 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 testing for documented active or latent tuberculosis has been updated to QuantiFERON®-TB Gold Plus	QuantiFERON®-TB Gold test is no longer commercially available.
5.2 Exclusion Criteria	Criterion #11: Amended definition (GFR less than 60ml/min/1.73m^2) has been included for renal impairment.	The update was made to harmonize the exclusion criterion across the rozanolixizumab Phase 3 clinical program.
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.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion criteria	Criterion #17: The description for the use of prescribed cannabidiols and/or medicinal marijuana has been amended and is no longer part of the exclusion criteria list. The new text has been placed under Section 6.5.1 Permitted concomitant treatments (medications and therapies).	Original criterion was restrictive and could significantly limit the number of study participants in US and potentially other countries.
5.2 Exclusion criteria	Criterion #12: 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	New criterion has been added, #18: Study participant has corrected QT interval (QTc) >450 msec (for male participants) or QTc >470 msec (for female participants) or QTc >480 msec in participants with bundle branch block.	The addition was made to harmonize the exclusion criterion across the MG studies.
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 cannabidiols, as prescribed by a physician.	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.
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.
6.5.1 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 subject must be on a stable dose of cannabidiols and/or medicinal	Due to the lack of pharmacodynamic and pharmacokinetic interactions between marijuana/ cannabidiols and rozanolixizumab, this criterion was revised.

Section # and Name	Description of Change	Brief Rationale
	marijuana for 4 weeks prior to Screening Visit and remain stable for the duration of the study. Table 6-2 Permitted concomitant medications for the treatment of myasthenia gravis: The dose for oral corticosteroids has been amended to state "no specific requirements".	
6.5.3 Treatments specific to NMJ interference	Correct reference has been added for the MGFA classification list. Additional wording to provide clarity that participants on rescue therapy continue to attend study visits.	General update for clarification.
6.6 Dose modification 8.3.7 Adverse events of special monitoring	Change in terminology: GI disorders was changed to GI disturbances	The update was made to harmonize across the rozanolixizumab Phase 3 clinical program.
6.7 Home visits	New section added on home visits.	Included to provide clear information for home visits.
6.7 Treatment after the end of the study	Now Section 6.8, the word "will" was replaced with "**may**" in the following sentence: Study participants who complete participation in MG0004 **will** have the possibility to continue receiving rozanolixizumab through a managed access program as per applicable local regulations.	There is no guarantee as suggested with the previous wording, as a managed access program will not be available in some countries.
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.

Section # and Name	Description of Change	Brief Rationale
8.1 Efficacy assessments	Order of efficacy assessments were amended.	Order of efficacy assessments were amended to align with study procedure manual.
8.1.1 Patient-reported outcomes 8.1.2 QMG scale 8.1.3 MG-Composite scale	New wording has been added: "Study participants should not take pyridostigmine (or any AChE inhibitor medication) from midnight before testing when medically safe to do so to standardize testing"	Updated to provide clear guidance for each assessment.
8.1.3 Patient-reported outcomes	Order of PROs (PGI-S, PGI-C, EQ-5D-5L, MGII, MG-QOL15r) were amended.	Order of PRO assessments were amended to align with study procedure manual.
8.1.3.1 Myasthenia gravis-activities of daily living scale	Section number has been changed to 8.1.1.1	To align with study procedure manual.
8.1.3.2 MG Impairment Index	Section number has been changed to 8.1.1.6. There is an additional step to the assessment, where the Investigator will examine the study participant prior to scoring all items.	To align with study procedure manual.
8.1.3.3 MG PRO Symptoms	Section number has been changed to 8.1.1.2. In addition, a total score range was included to this PRO description, as per scale presented in Appendix 15.	Order of efficacy assessments were amended to align with study procedure manual.
8.1.3.4 Revised 15-item myasthenia gravis quality of life questionnaire	Section number has been changed to 8.1.1.7	To align with study procedure manual.
8.1.3.5 Patient Global Impression of Severity	Section number has been changed to 8.1.1.3	To align with study procedure manual.
8.1.3.6 Patient Global Impression of Change	Section number has been changed to 8.1.1.4	To align with study procedure manual.
8.2 Safety Assessment	Additional information on onsite observation timings postdose was included.	Added to provide clarification for postdose observations.
8.2.2 Vital signs	The measurement of respiratory is no longer required as part of vital signs assessment.	To be consistent with other Rozanolixizumab protocols.

Section # and Name	Description of Change	Brief Rationale
8.2.6 Assessment and management of TB and TB risk factors	Layout and structure of assessment and management of TB and TB risk factors has been modified.	To be consistent with other Rozanolixizumab protocols.
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 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 hypersensitivity 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-emergent adverse event.
8.5 Treatment of Overdose	Definition of overdose was amended: Any increase of 10% or greater from the assigned dose 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 have been added.	To be consistent with the ICF and other Rozanolixizumab protocols. Further, to remove detail redundancies covered in the laboratory manual.
8.6 Pharmacokinetics and antidrug antibodies	New text pertaining to PK blood sample collection at additional timepoints in a local substudy has been added.	New wording introduced to align with the Phase 3 clinical program.
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.
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	The information was repetitive.

Section # and Name	Description of Change	Brief Rationale
	document as defined above" was removed.	
10.2 Appendix 2: Clinical laboratory tests	Serology testing (for hepatitis B, hepatitis C, and HIV) has been added. C-reactive protein was removed.	Consistency with study design
10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information	The guidance and procedures for contraception and collection of pregnancy information has been amended.	The information was amended to provide additional information and to keep consistency across the 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 10.20 Appendix 12 to 20	Order of appendices were changed to match the order shown in the body of the protocol.	General consistency.
10.22.1 Appendix 22: 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.
10.22.2 Appendix 22: 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.**	The language updated to clarify the actions necessary by the PI in case of severe diarrhea.
10.22.4 Appendix 22: 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 harmonize.

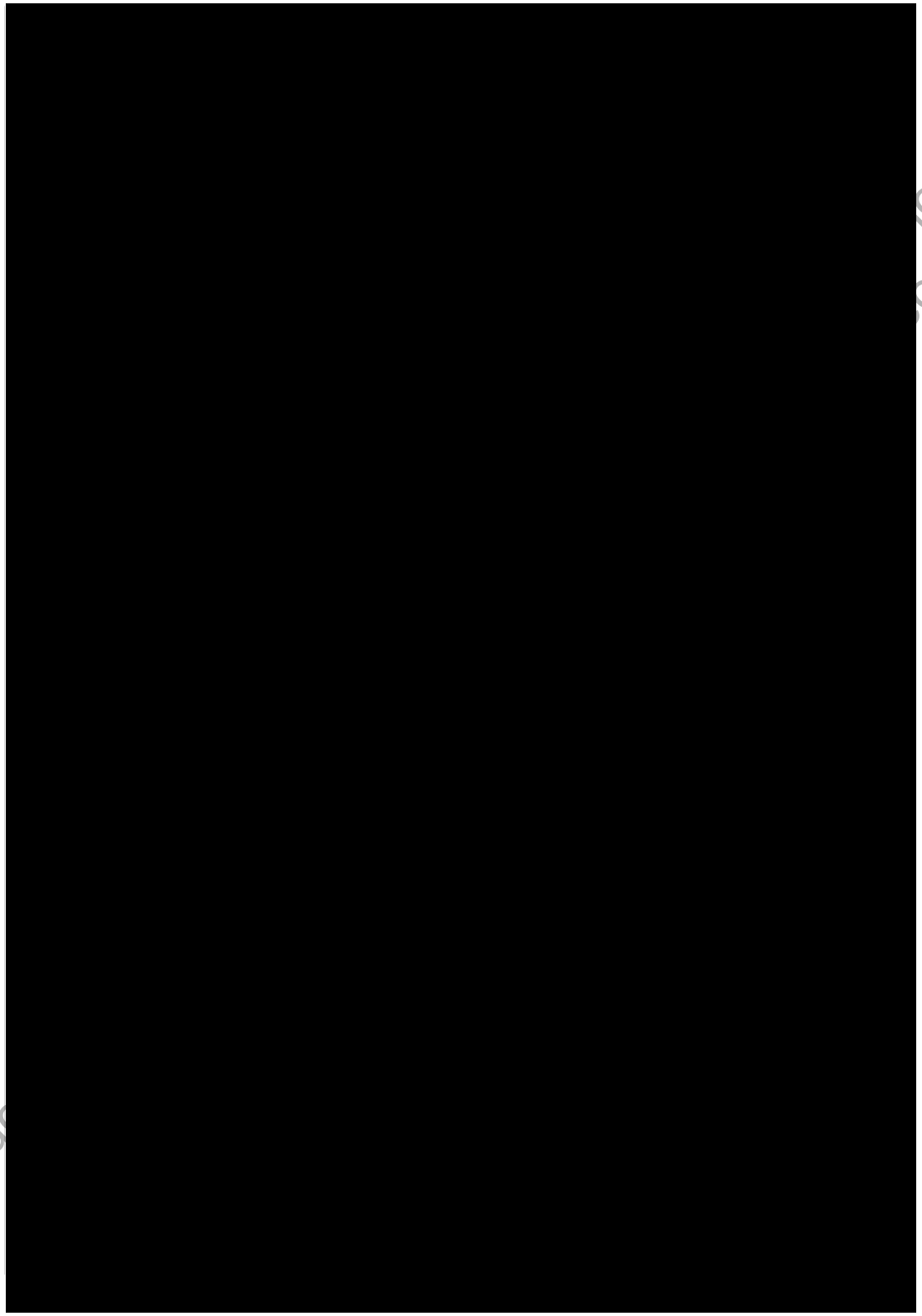
Section # and Name	Description of Change	Brief Rationale
10.25 Appendix 25: Columbia-Suicide Severity Rating Scale	New appendix for C-SSRS (screening and last visit versions) has been included.	Missing appendix

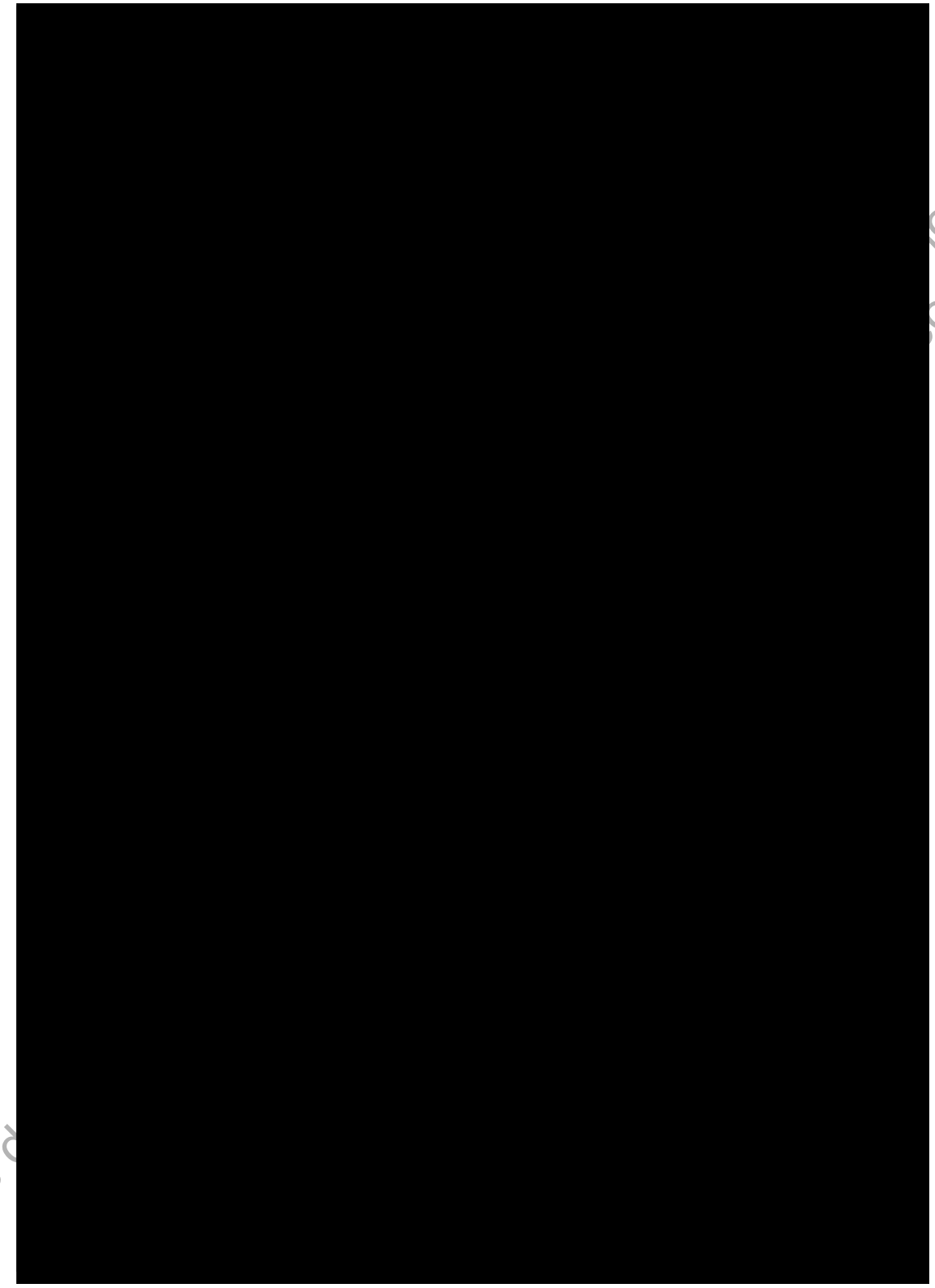
10.12 Appendix 12: Quantitative Myasthenia Gravis Scale

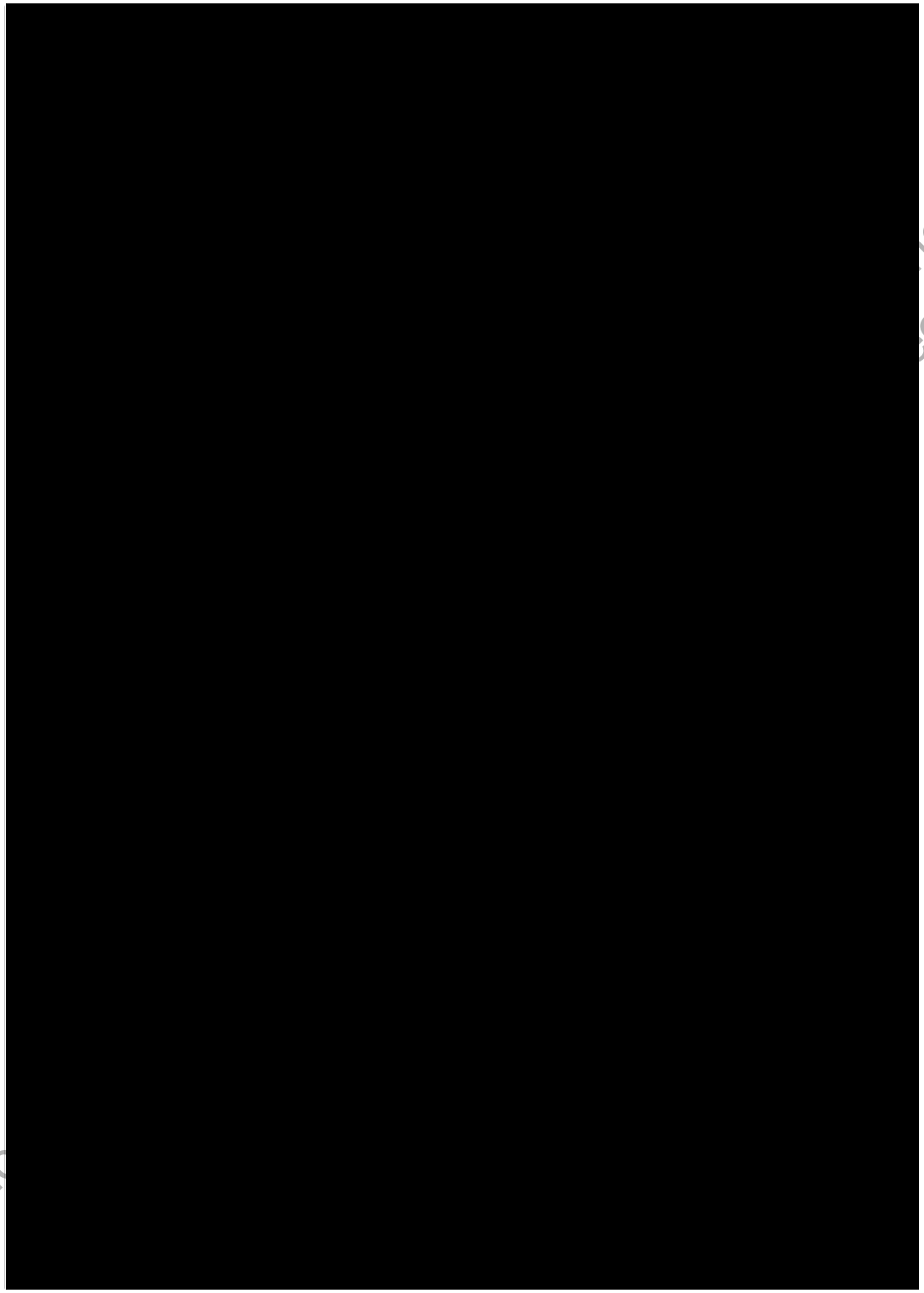
Quantitative MG Testing

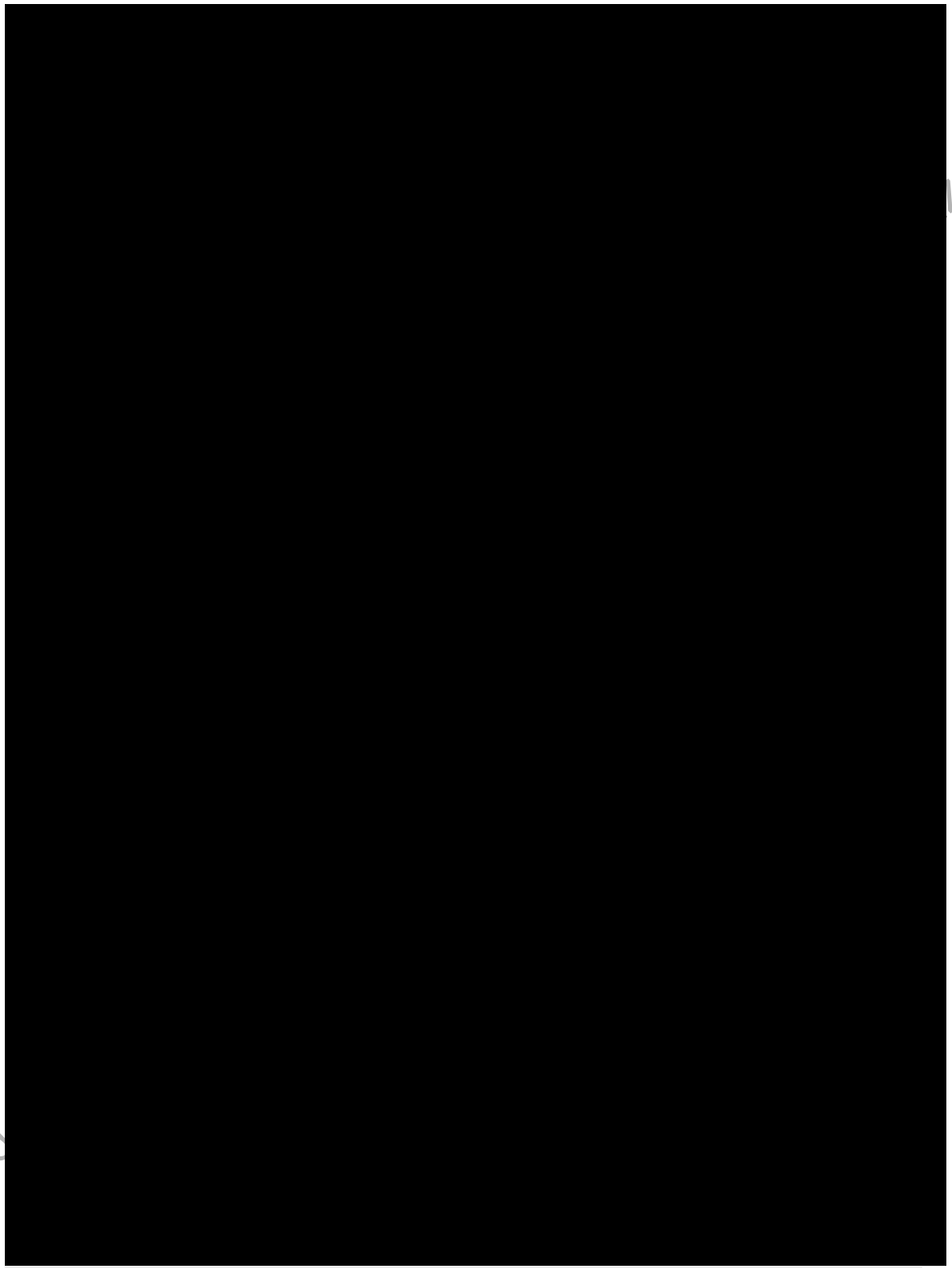
[redacted]

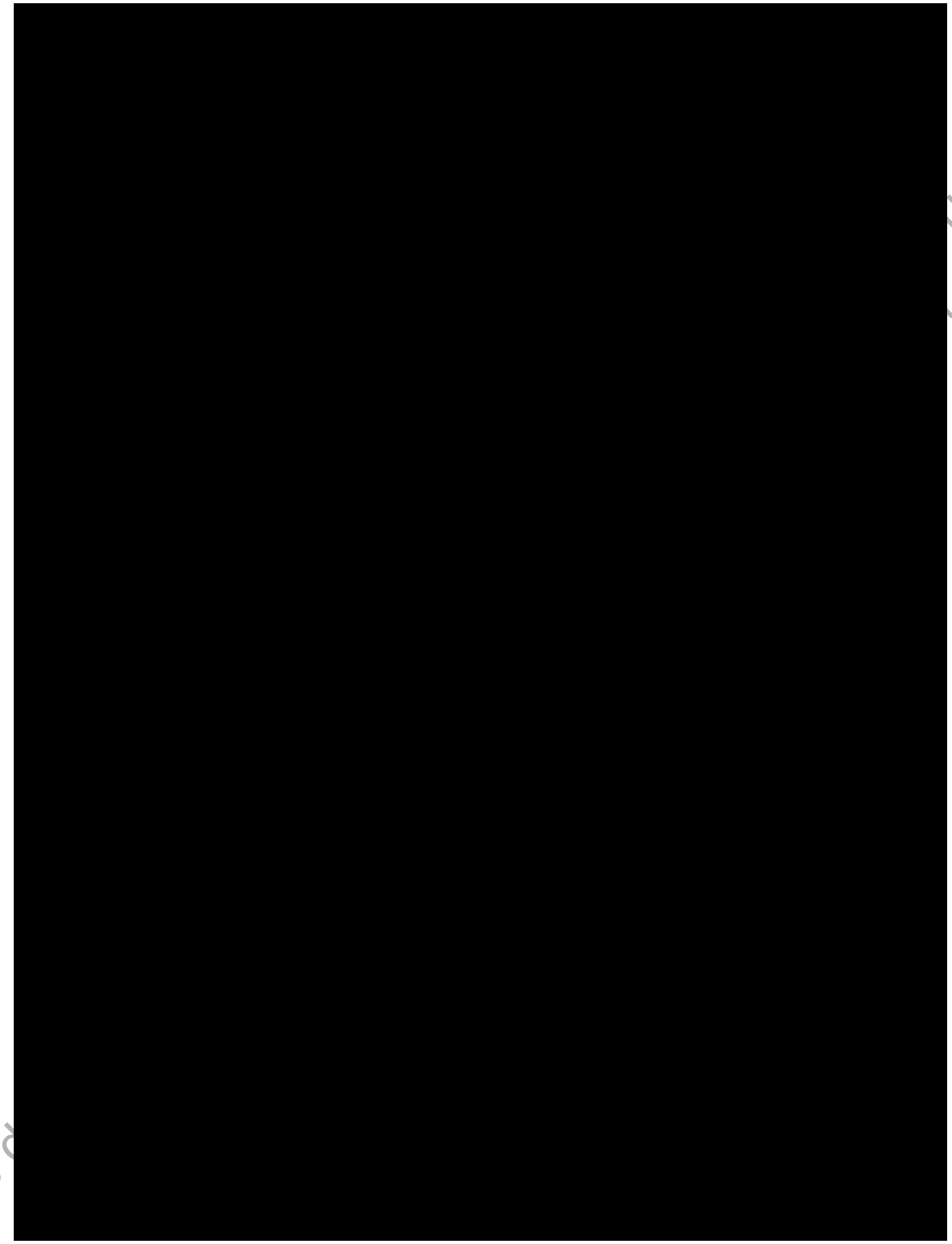
[redacted]

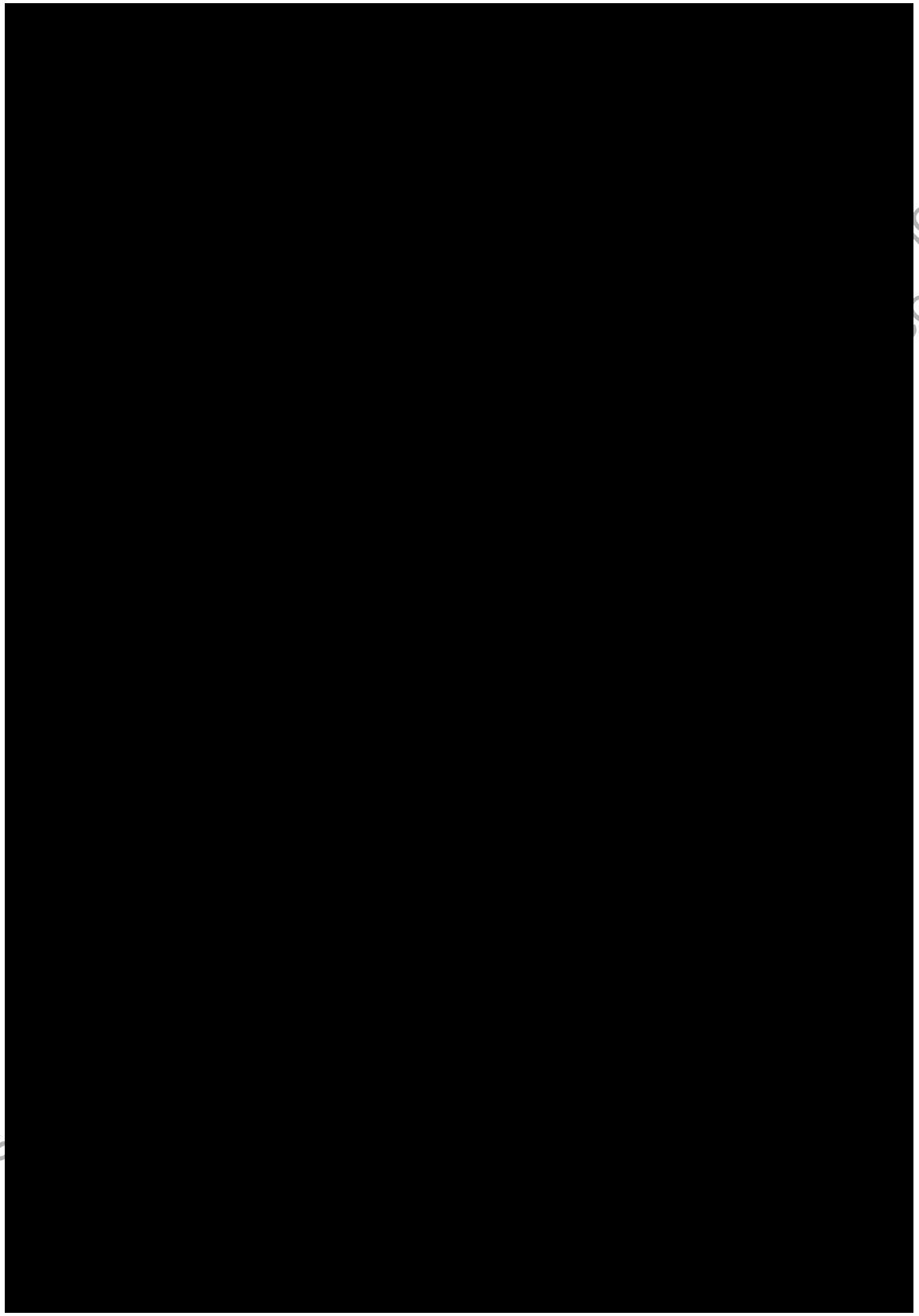










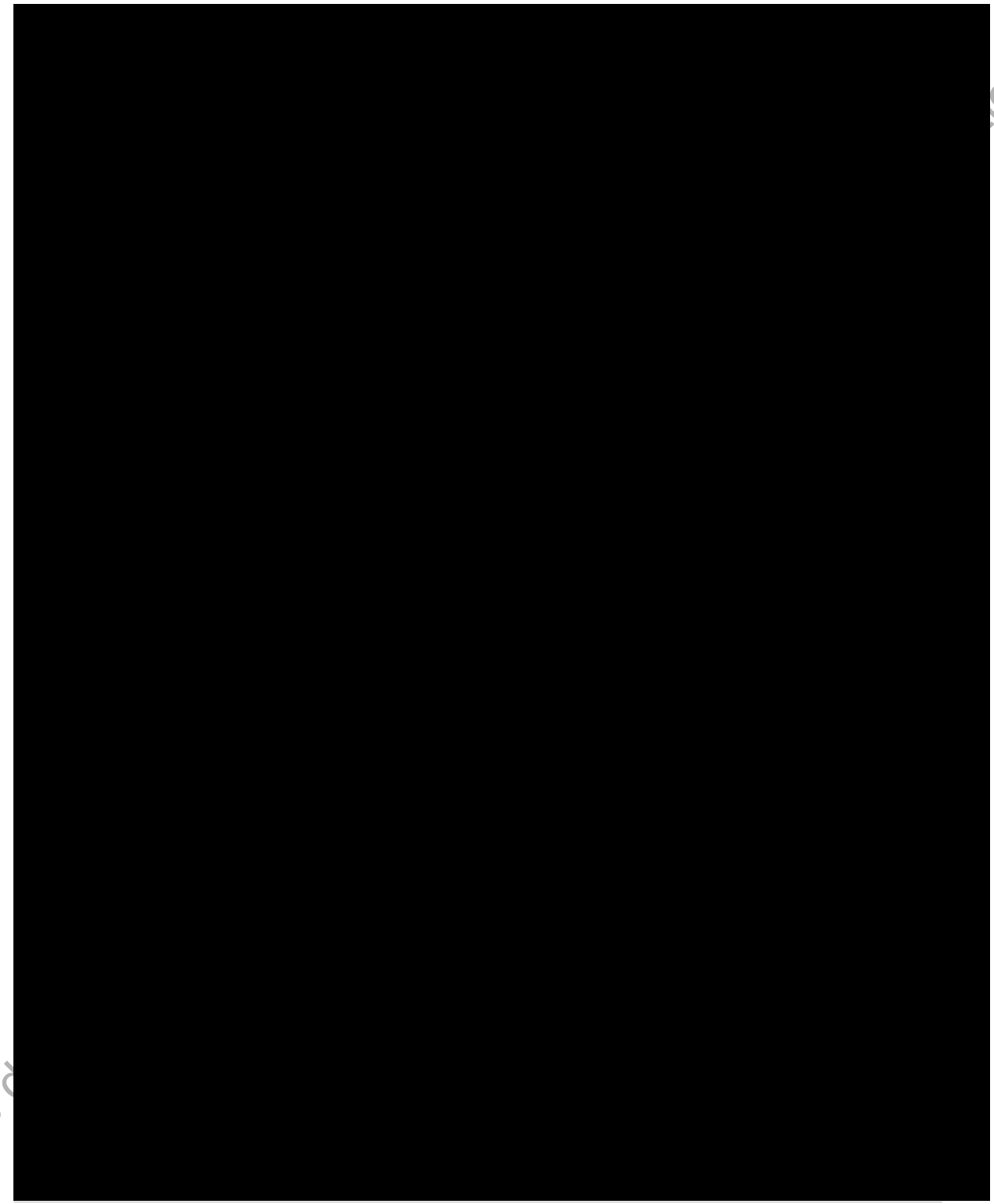


10.13 Appendix 13: Myasthenia Gravis-Composite scale

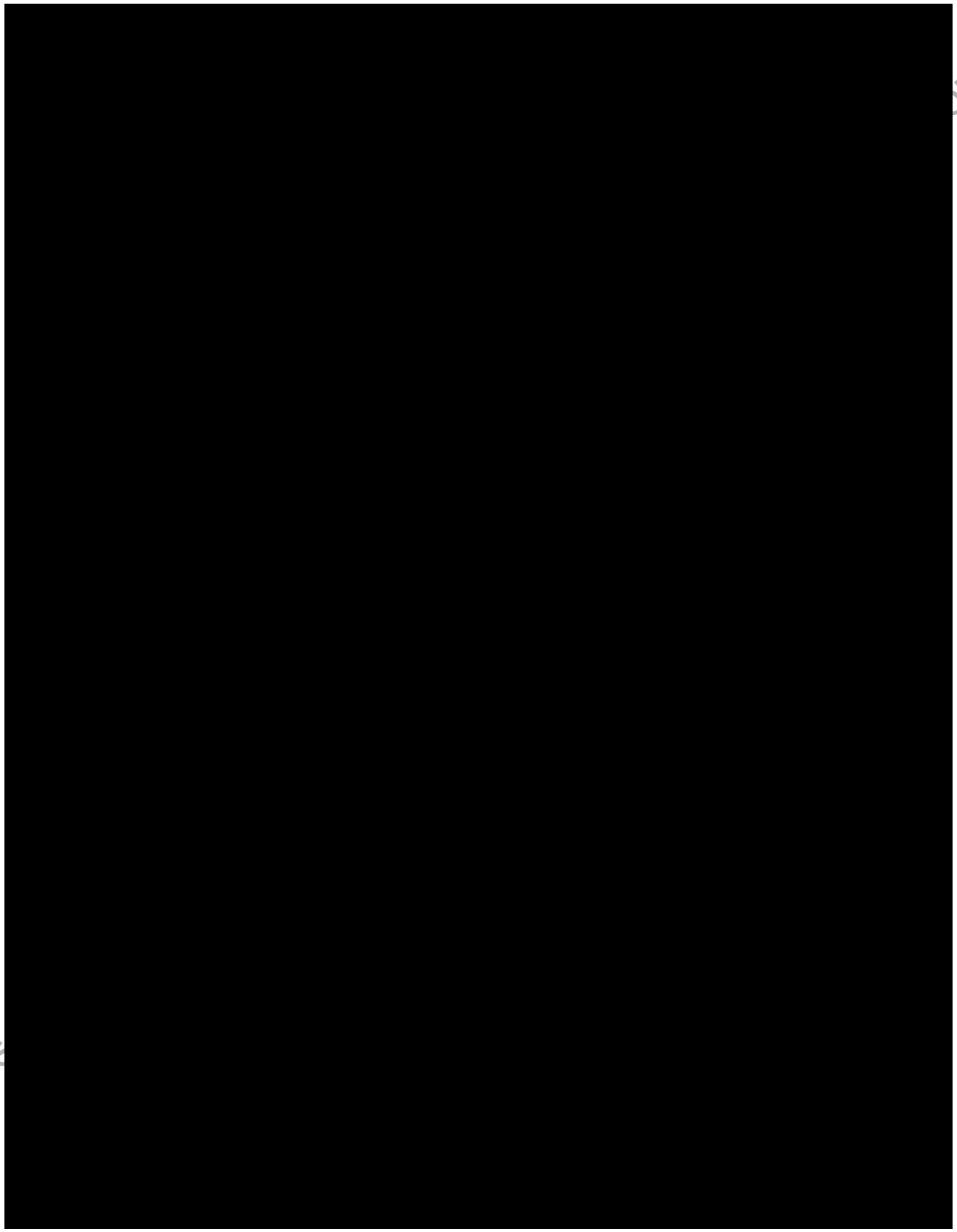
Study: MG0003	Visit: _____	Visit Date: DD MMM YY	Subject No.:	Page 1 of 1

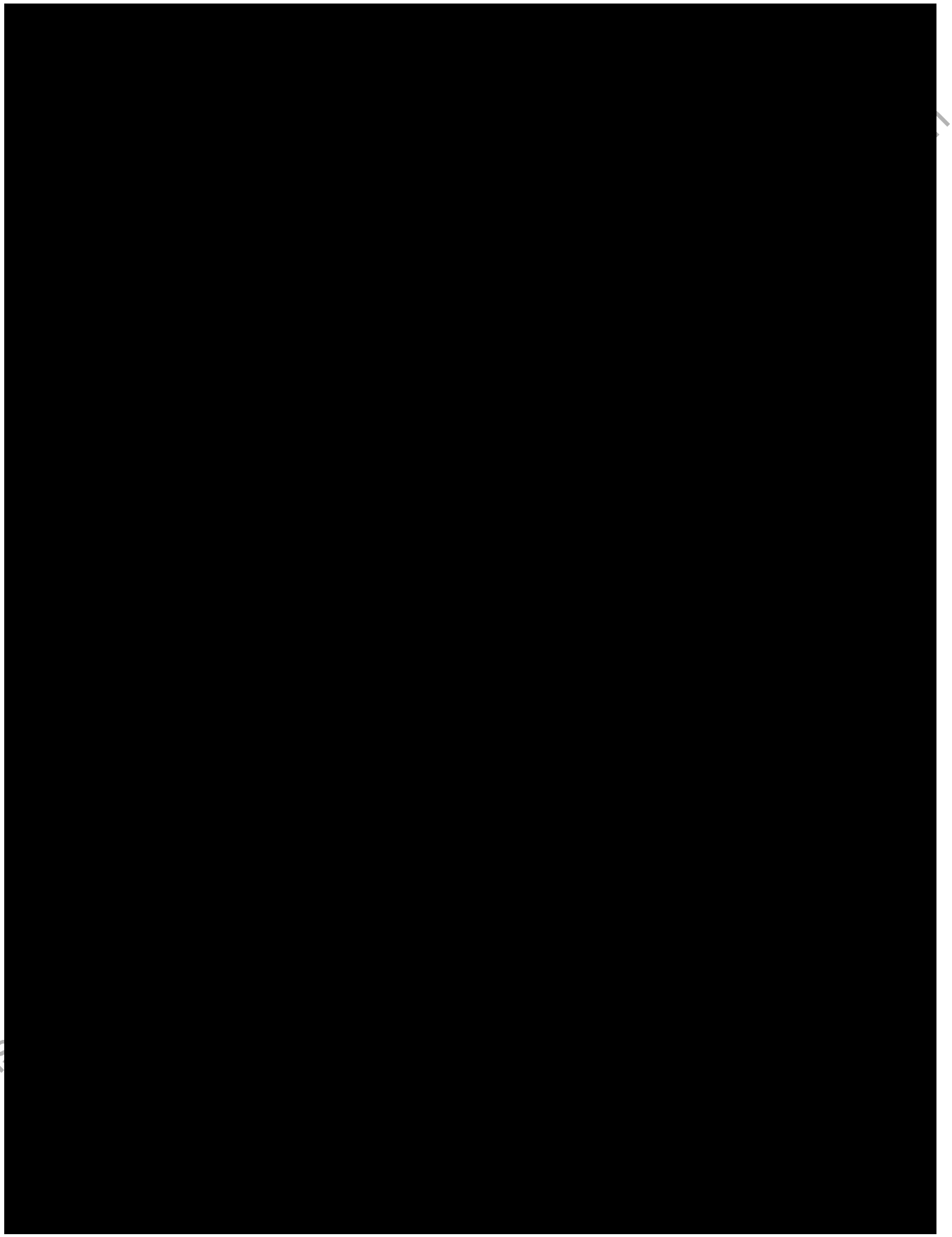
[redacted]

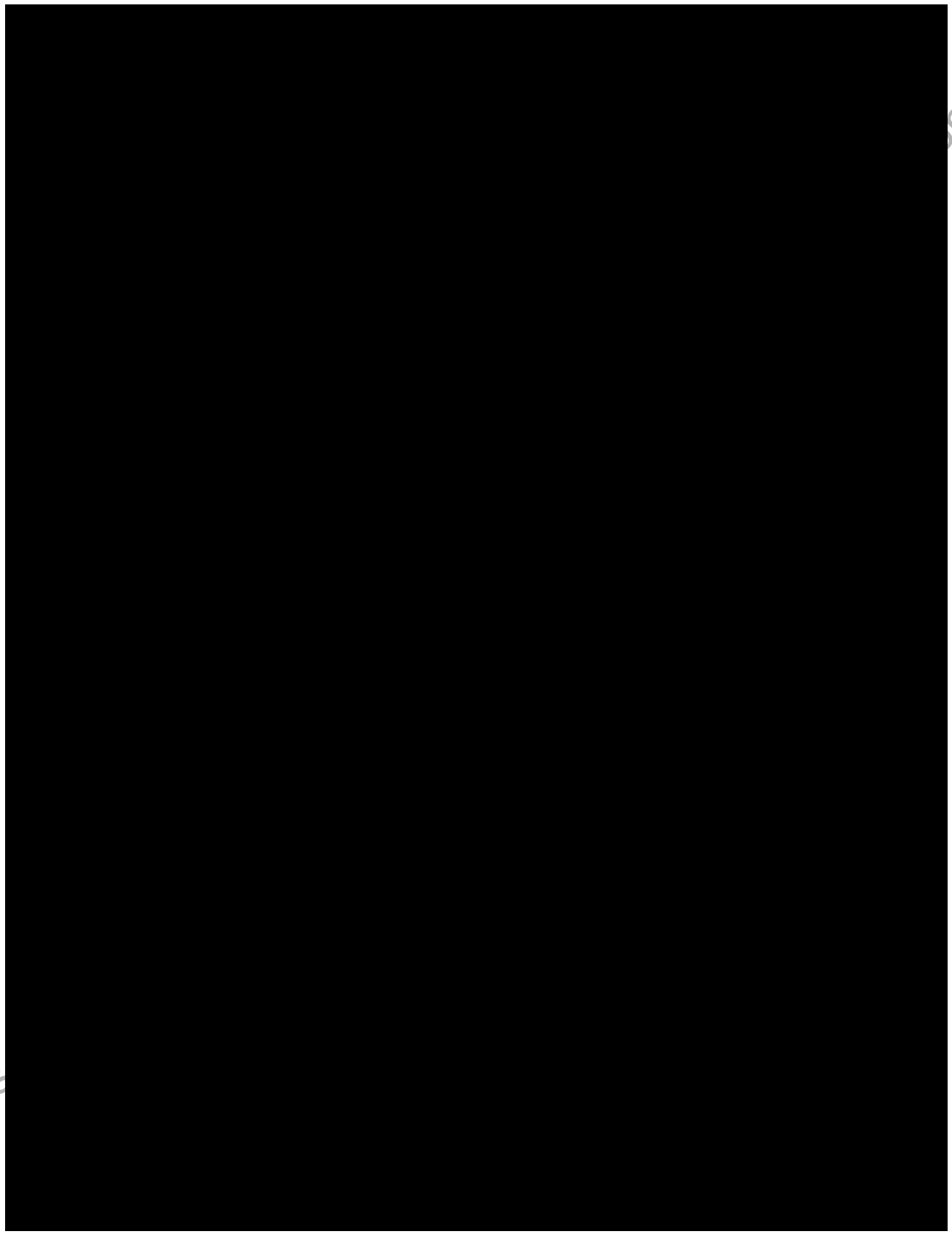
10.14 Appendix 14: Myasthenia Gravis-Activities of Daily Living



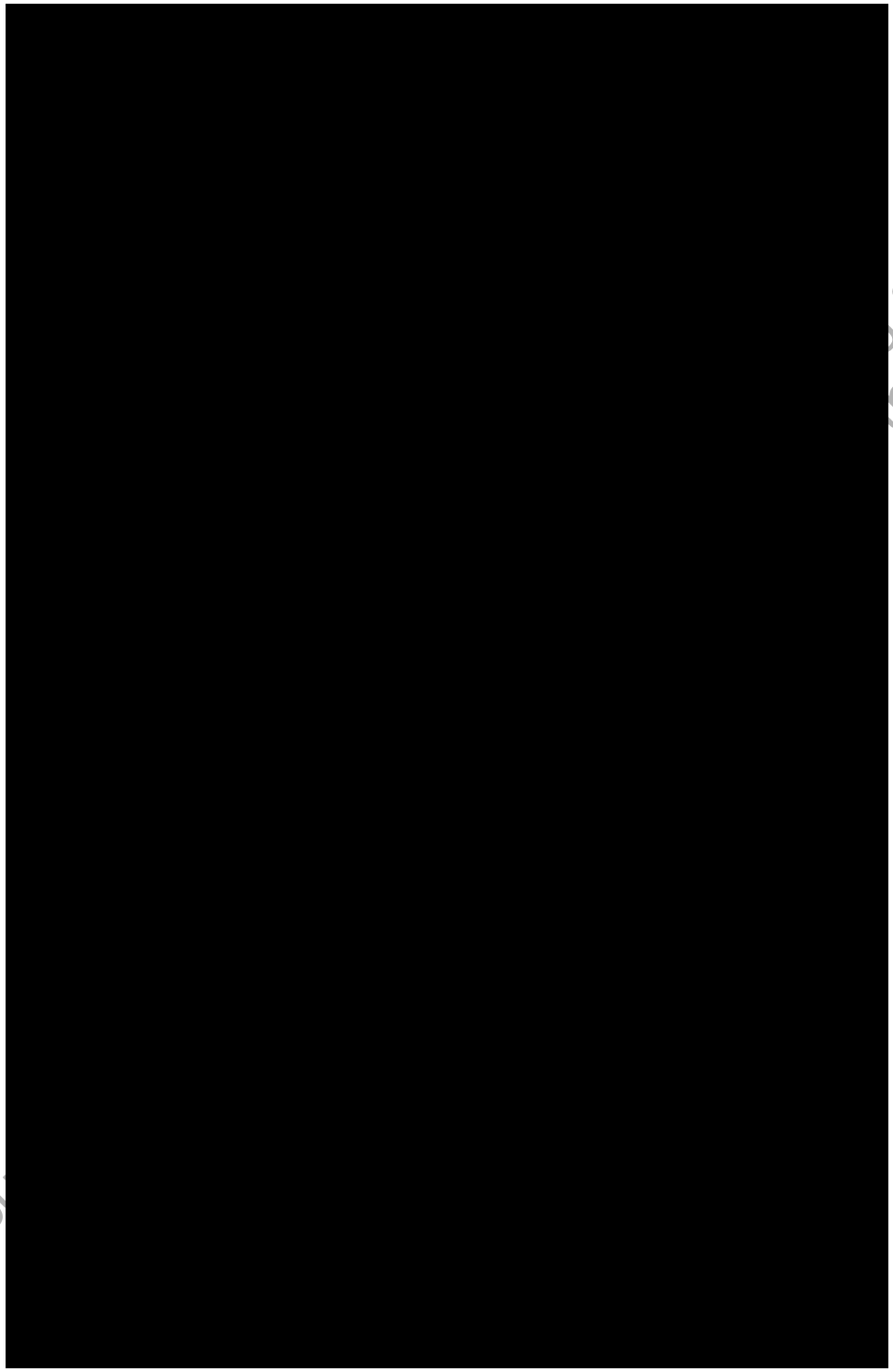
10.15 Appendix 15 Myasthenia Gravis Symptoms PRO

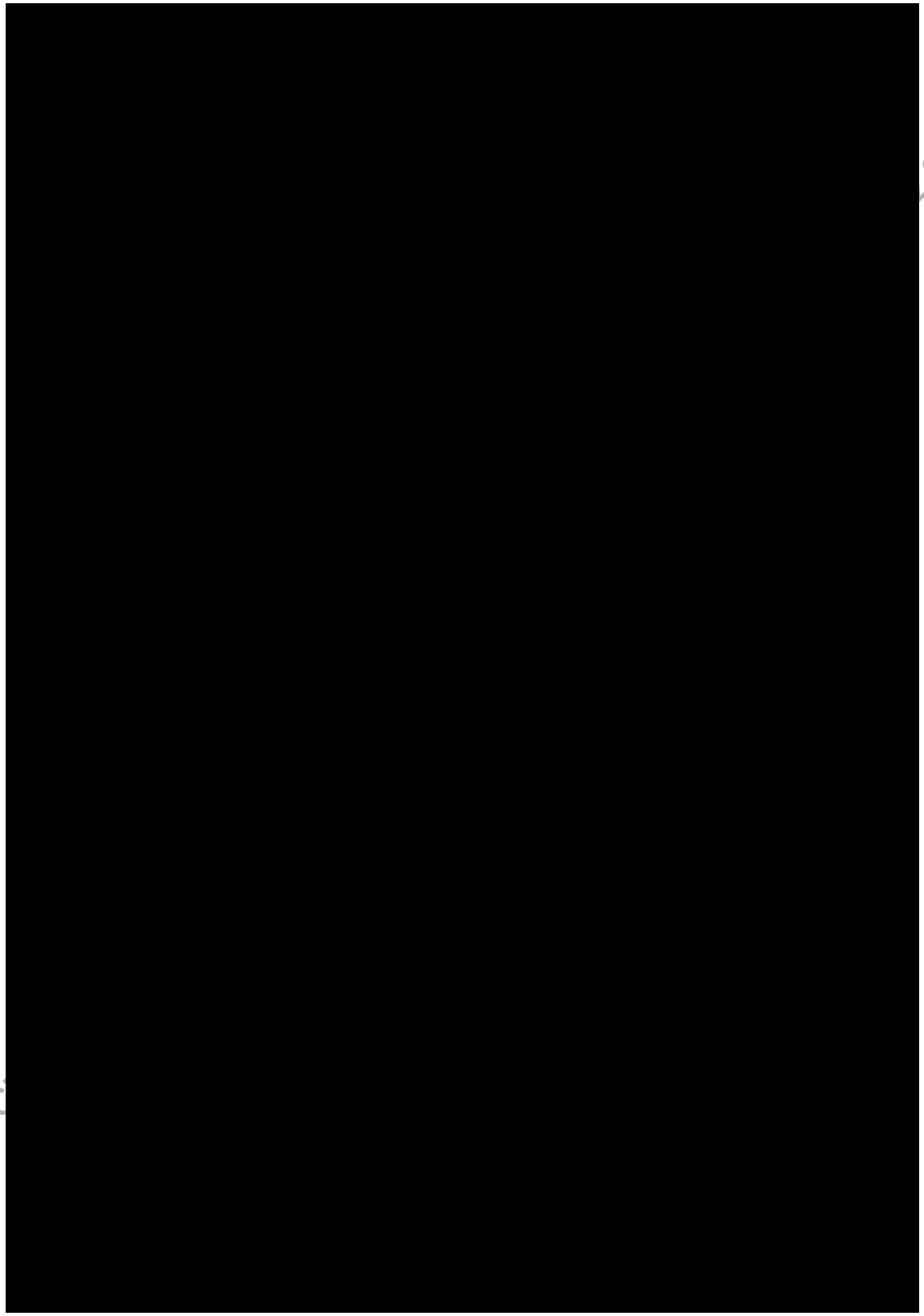




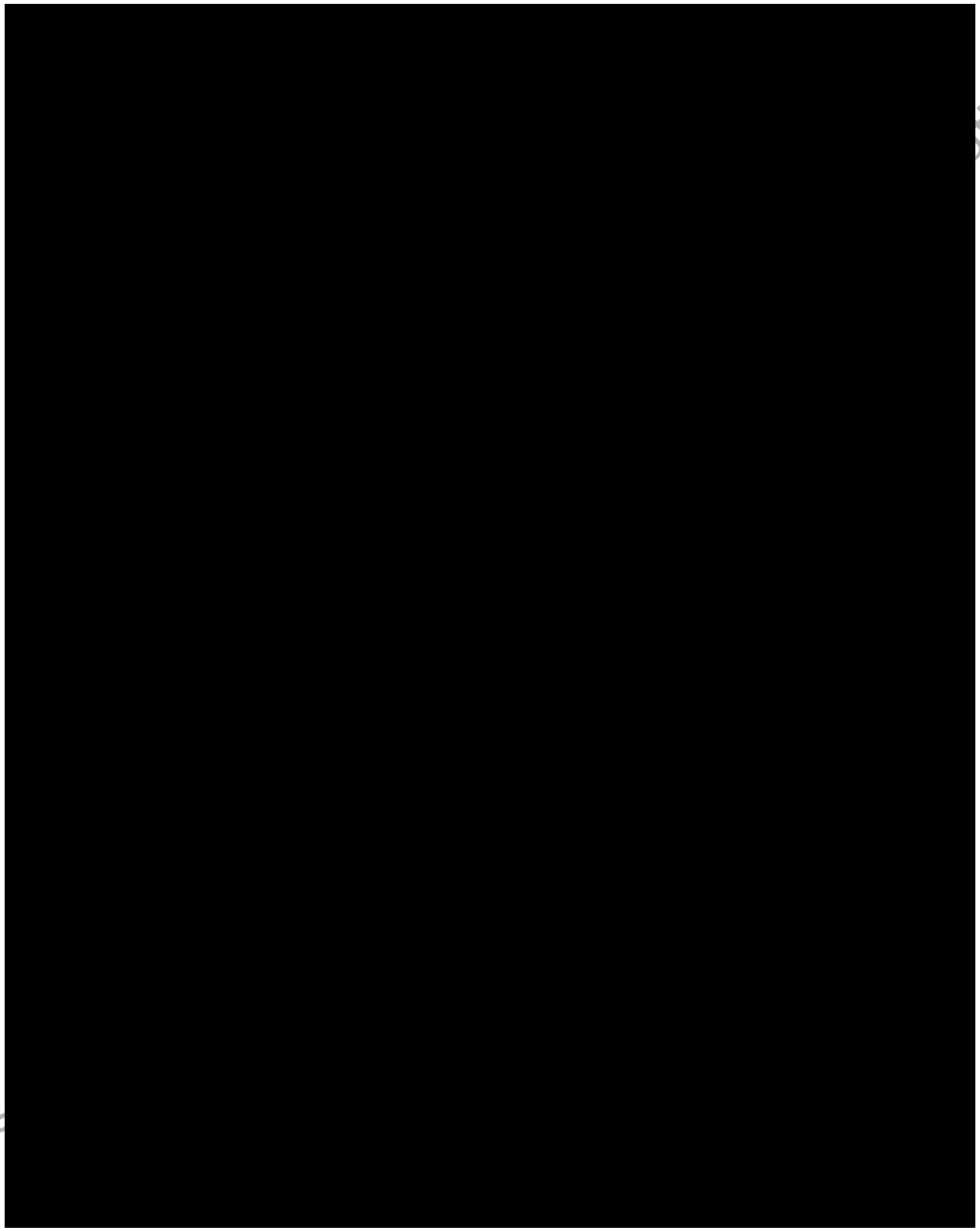


10.16 Appendix 16: 5-Level European quality of life 5 dimensions





10.17 Appendix 17: Myasthenia Gravis Impairment Index



MG Impairment Index (MGII)™ - Patient Questionnaire

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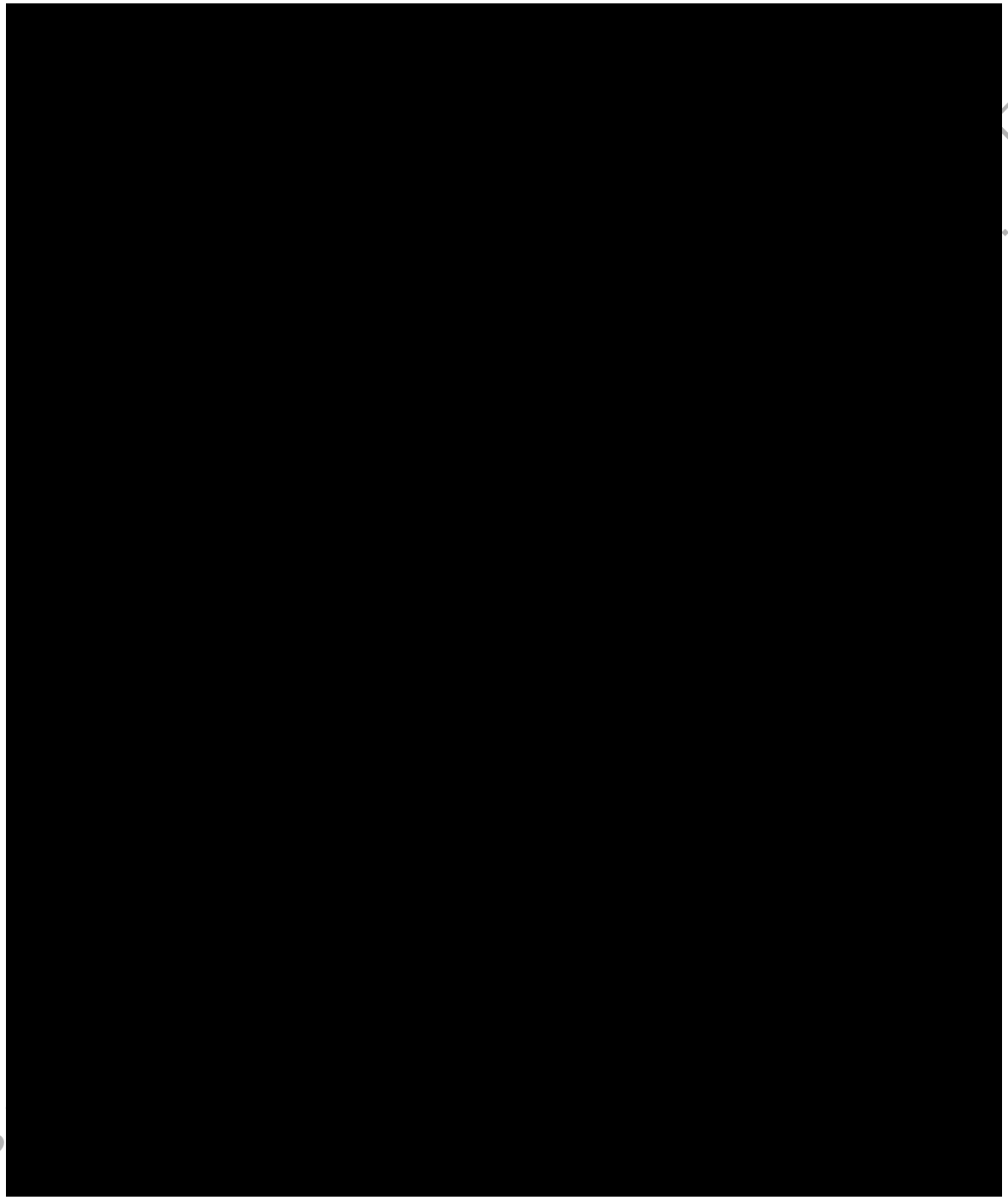

MG Impairment Index (MGII)™ - Patient Questionnaire

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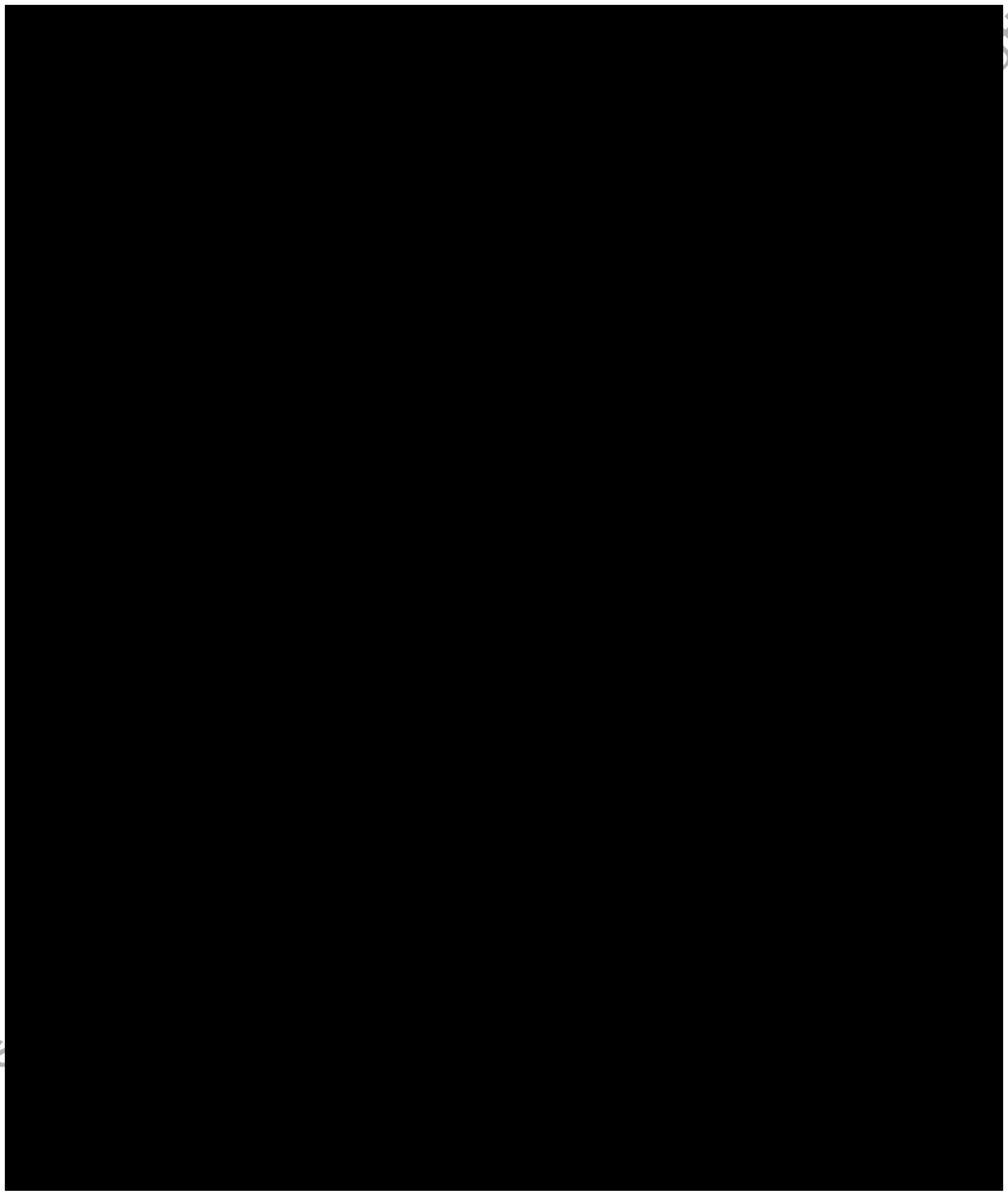
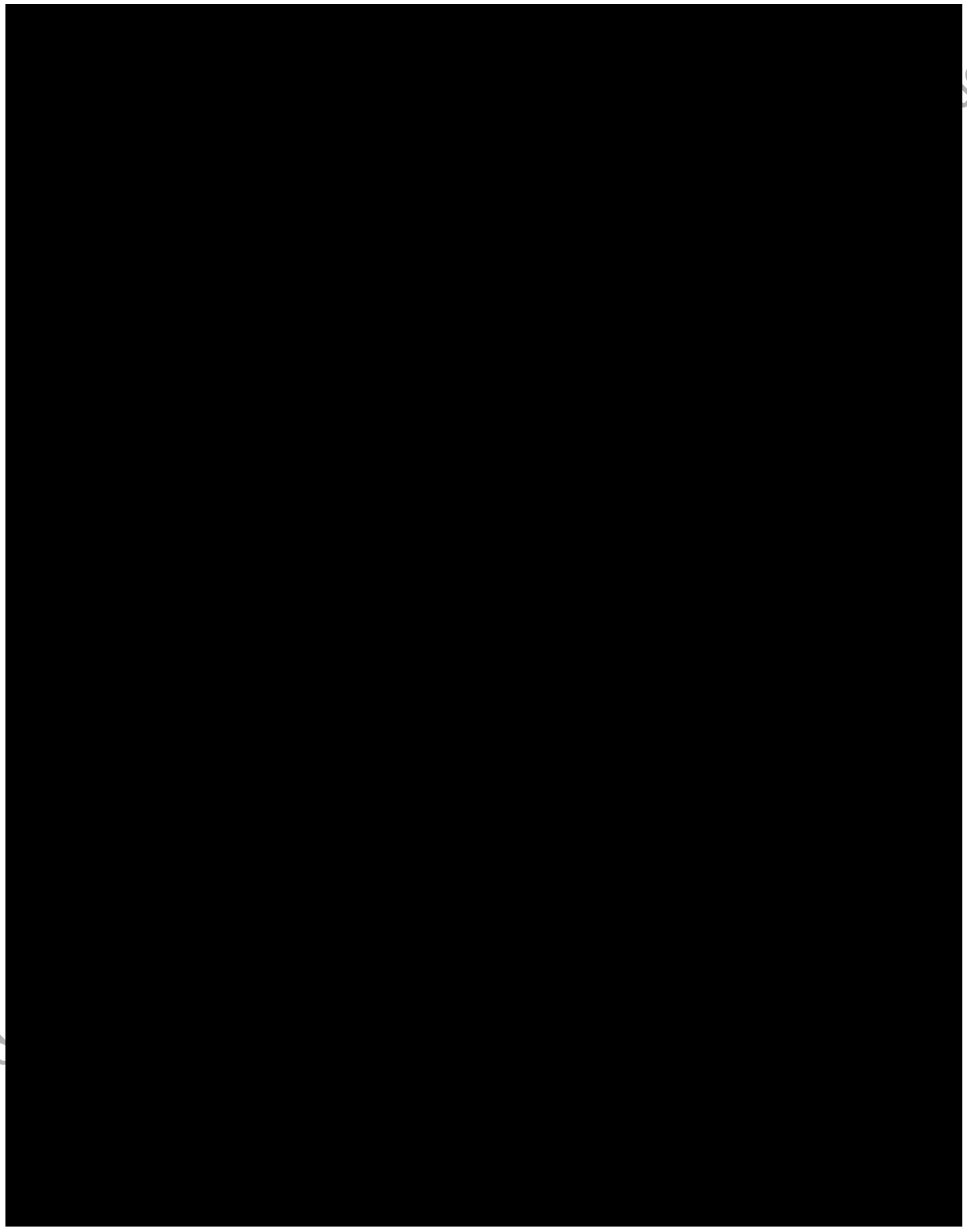
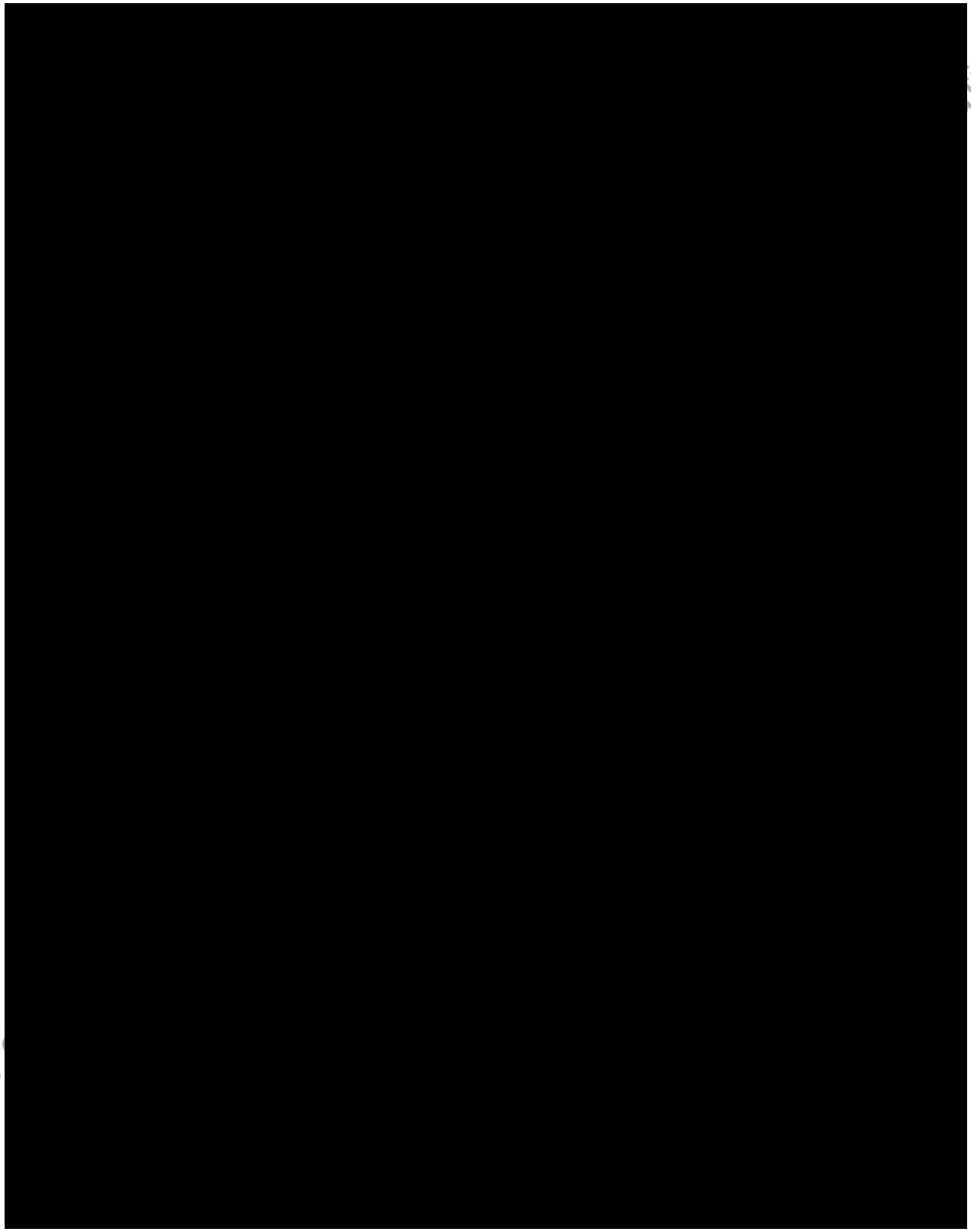


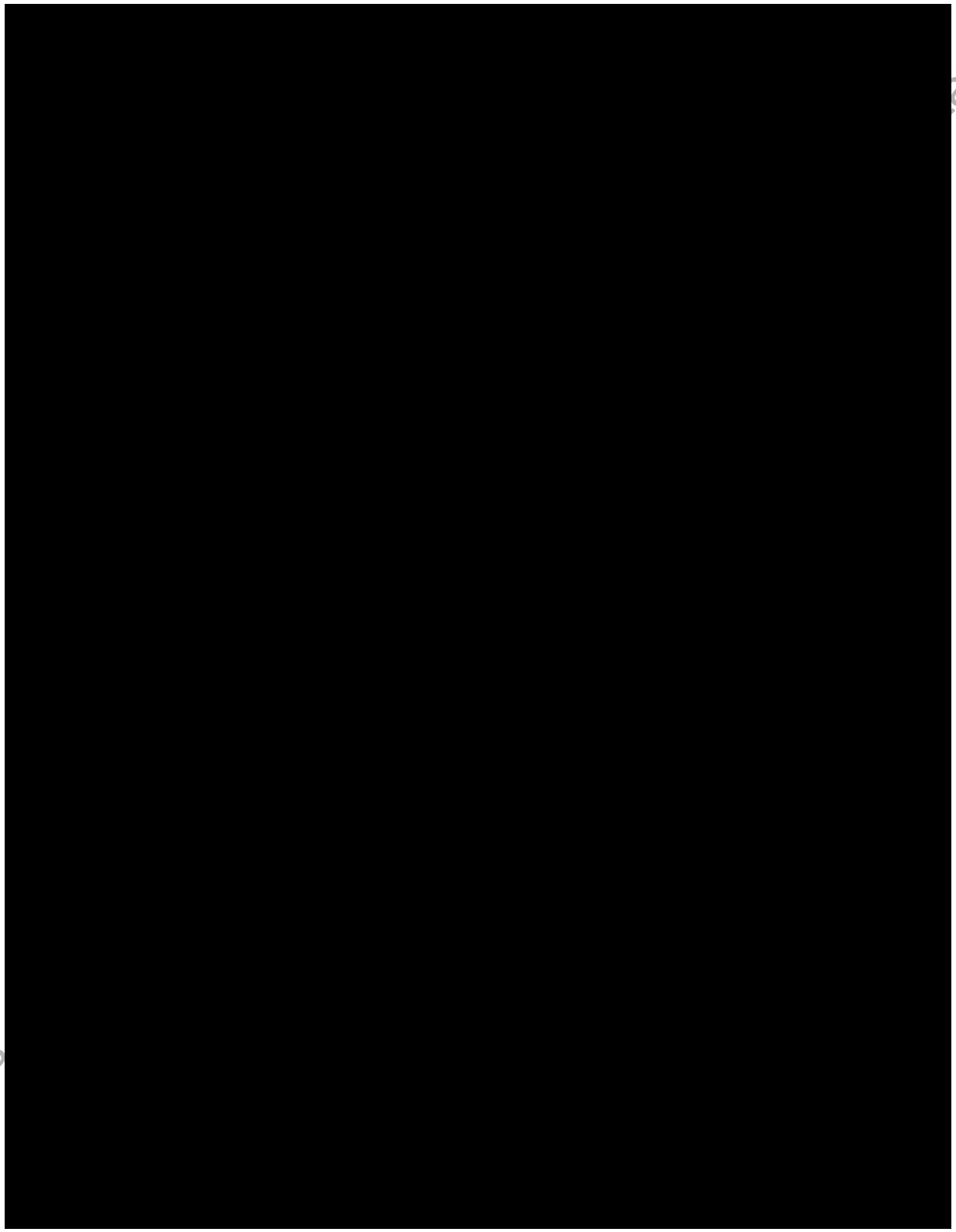
MG Impairment Index (MGII) - Examination



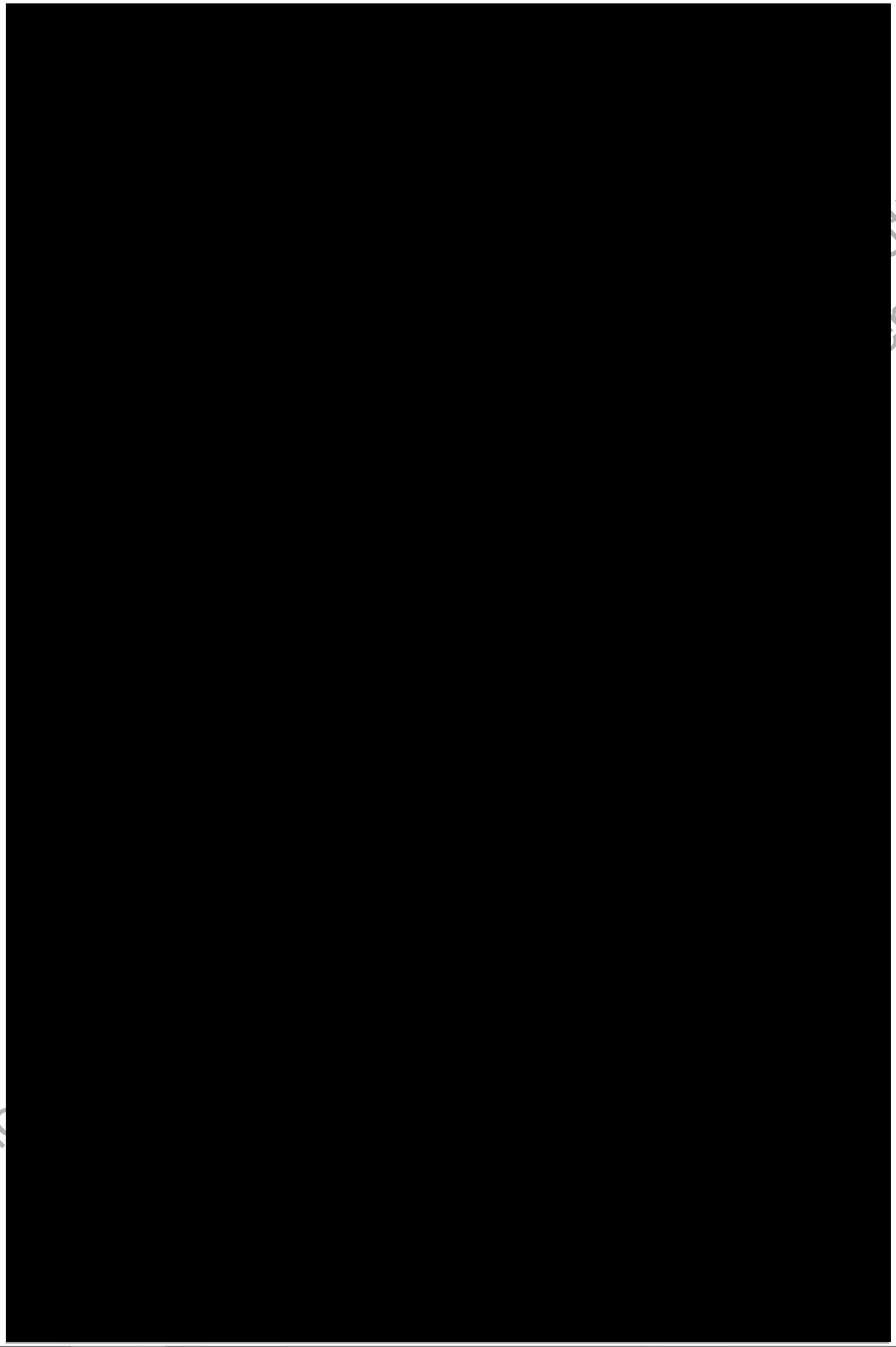
Myasthenia Gravis Impairment Index (MGII) - Examination Manual



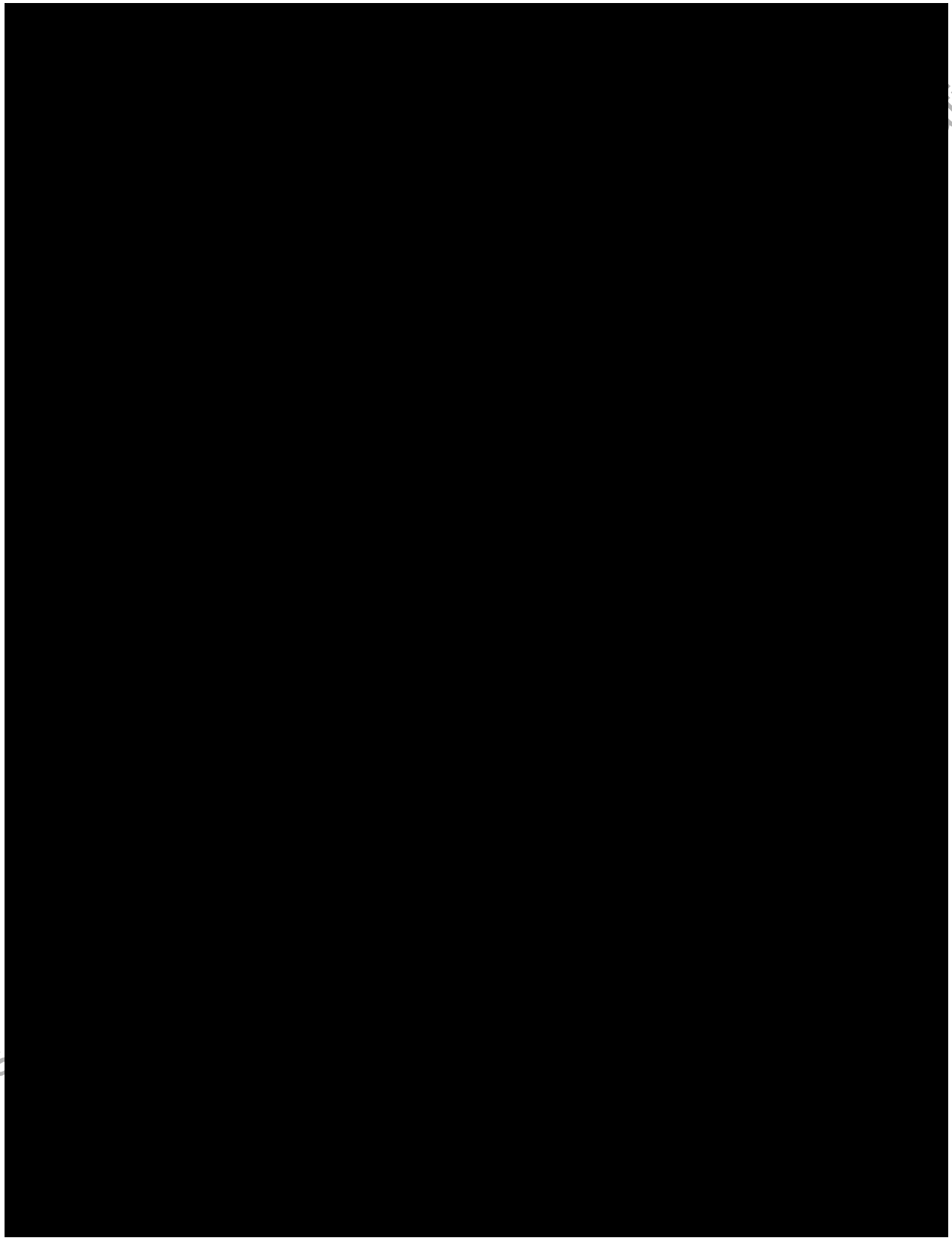
Myasthenia Gravis Impairment Index (MGII) - Scoring Sheet

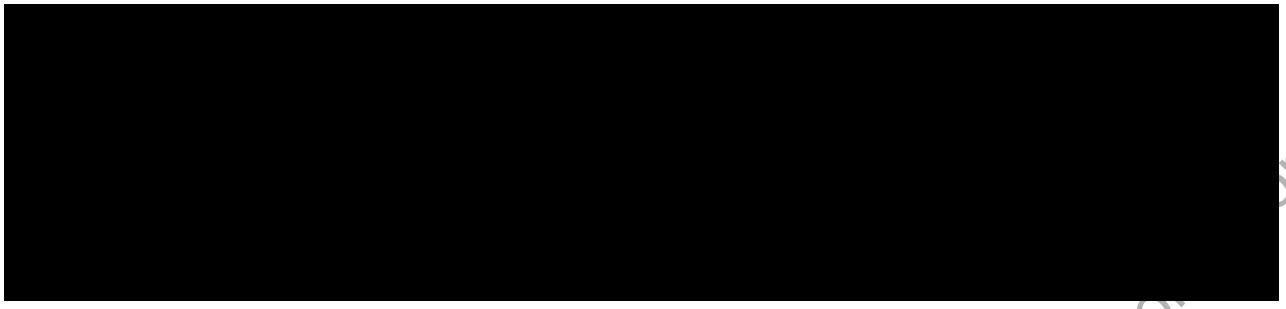


10.18 Appendix 18: Revised 15-item myasthenia gravis quality of life questionnaire



10.19 Appendix 19: Tuberculosis questionnaire





10.20 Appendix 20: Management of headaches, diarrhea, and infections and hypogammaglobulinemia

10.20.1 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 National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (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 10.21, Appendix 21) daily until resolving or resolution (ie, if headache becomes nonserious, moderate or mild or completely resolved, whichever comes first). 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 should be temporarily put on hold if a study participant experiences a severe AE of headache that is considered related to the study medication 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 local 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. The benefit risk of continuing treatment with IMP and chronic prophylactic with analgesics must be carefully evaluated by the Investigator.

10.20.2 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 (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.

10.20.3 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, bacterial meningitis, osteomyelitis or septic arthritis, bacterial pneumonia, or visceral abscess)**.**

To maintain the study integrity, IgG level will remain blinded to the study sites and the UCB study team for the first 4 weeks of the study. 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.

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.

10.20.4 Management of infusion reactions or hypersensitivity reactions

Study participants must be closely monitored for reactions during and after the study treatment administration period. Standard precautions must be taken for the study participants with regard to SC infusion complications. Suggested management guidelines for infusion-related reactions and anaphylaxis at the study site are provided in Table 10-4. Definitions of mild, moderate, and severe events will be consistent with CTCAE version 5.0 (Section 10.3). Nurses administering the IMP at home should follow their own management guidelines, which should be reviewed and endorsed by the Investigator prior to first home administration.

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).

Conditions in which anaphylaxis is likely should be diagnosed using Sampson's Criteria (Sampson et al, 2006) as described in (Appendix 22, Section 10.22). The infusion must be discontinued immediately, and emergency resuscitation measures implemented.

If an infusion-related reaction or anaphylaxis occurs, a blood sample will be collected from the study participant 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), serum cytokines, and plasma complement (C3a, C5a) 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.

10.21 Appendix 21: Headache questionnaire

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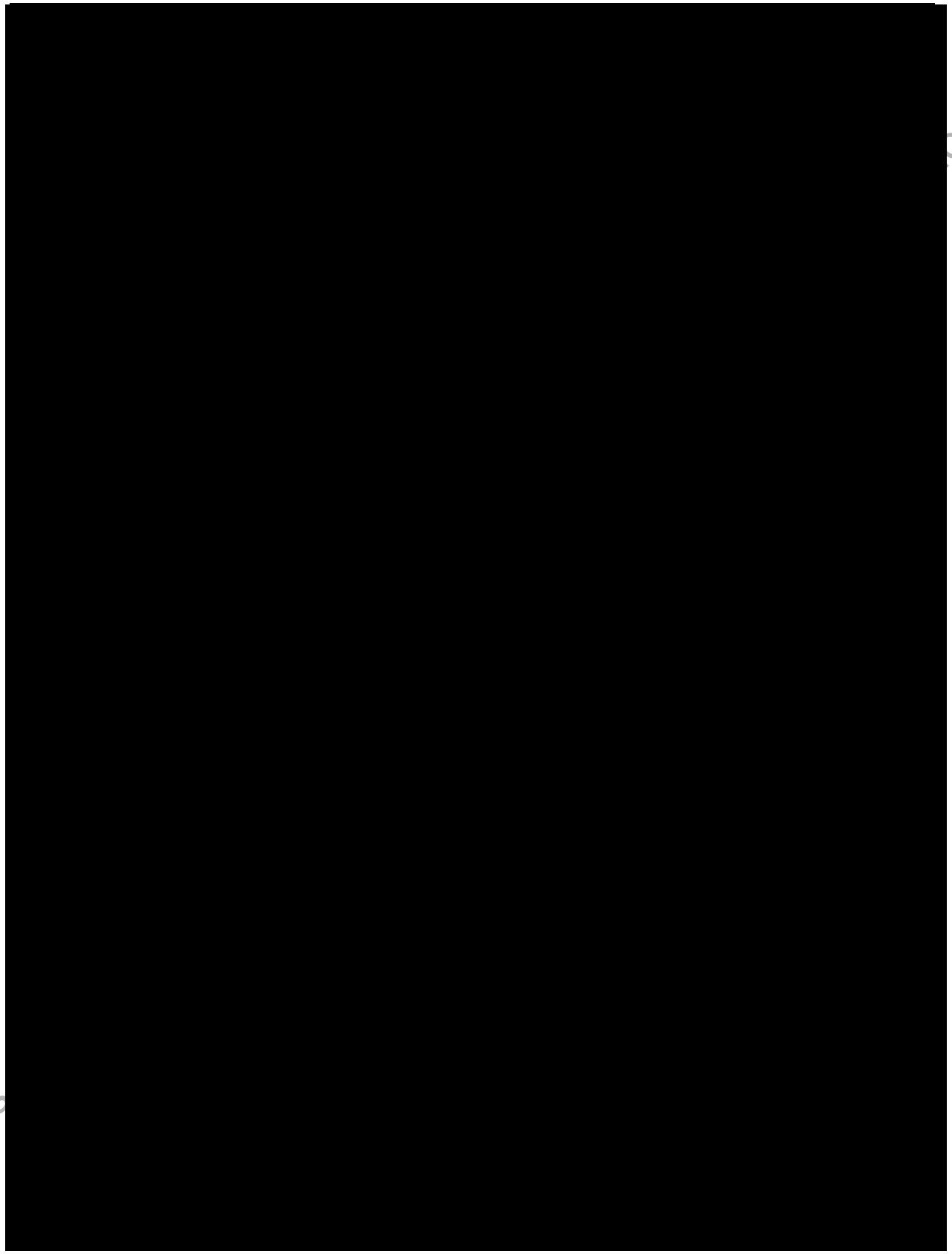
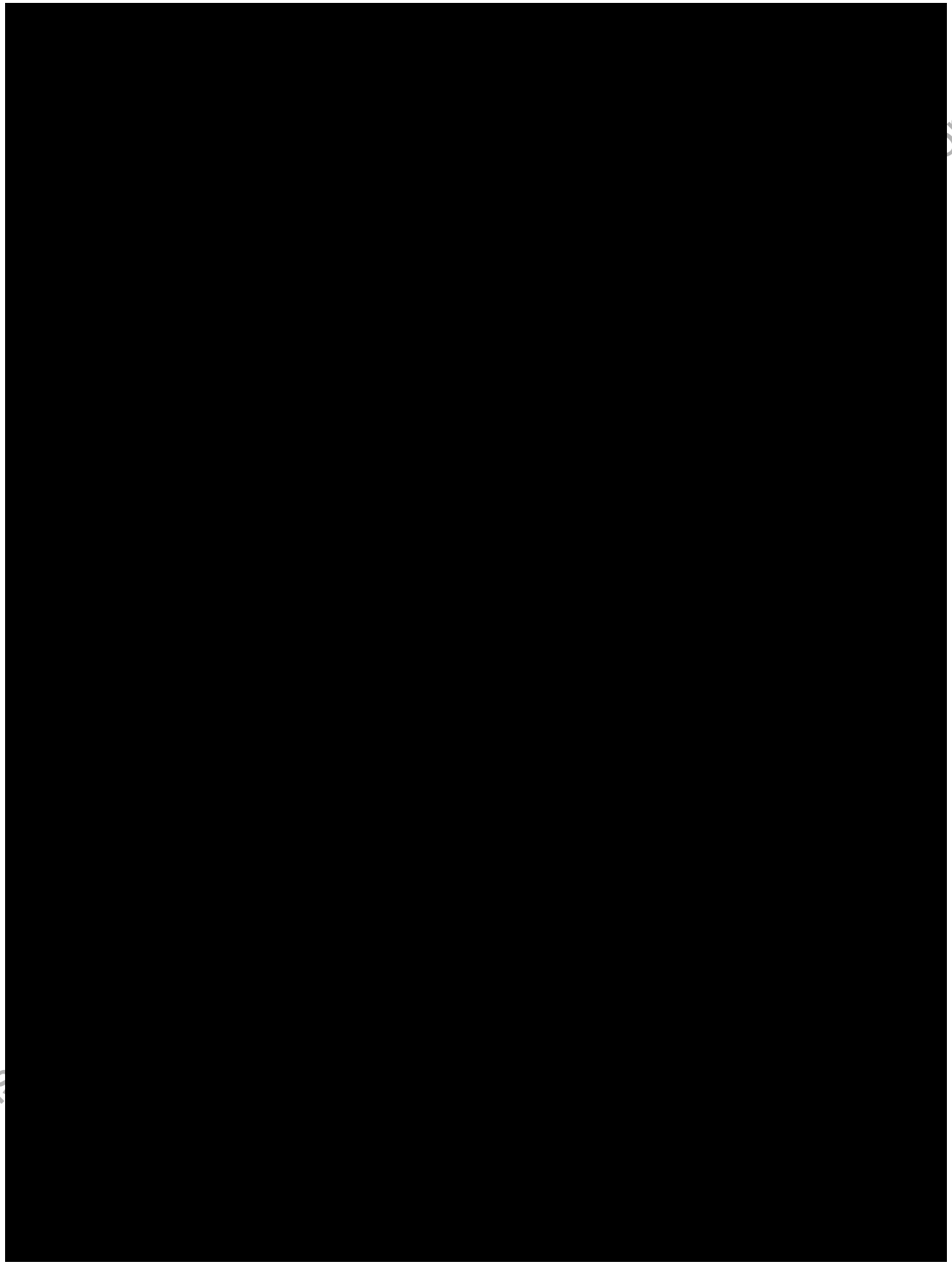




10.22 Appendix 22: Sampson Criteria Questionnaire

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

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

e. Reduced 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)

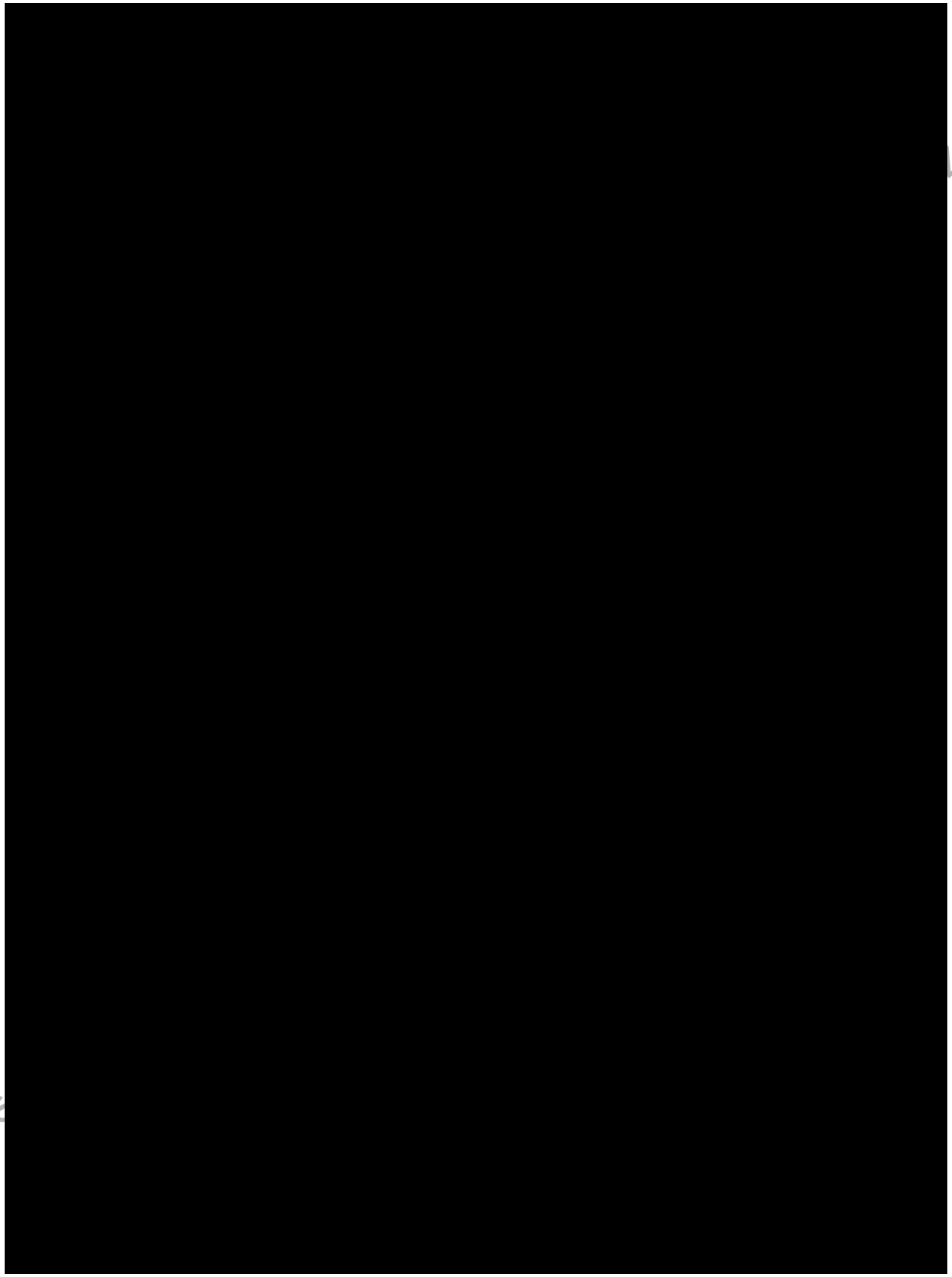
b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

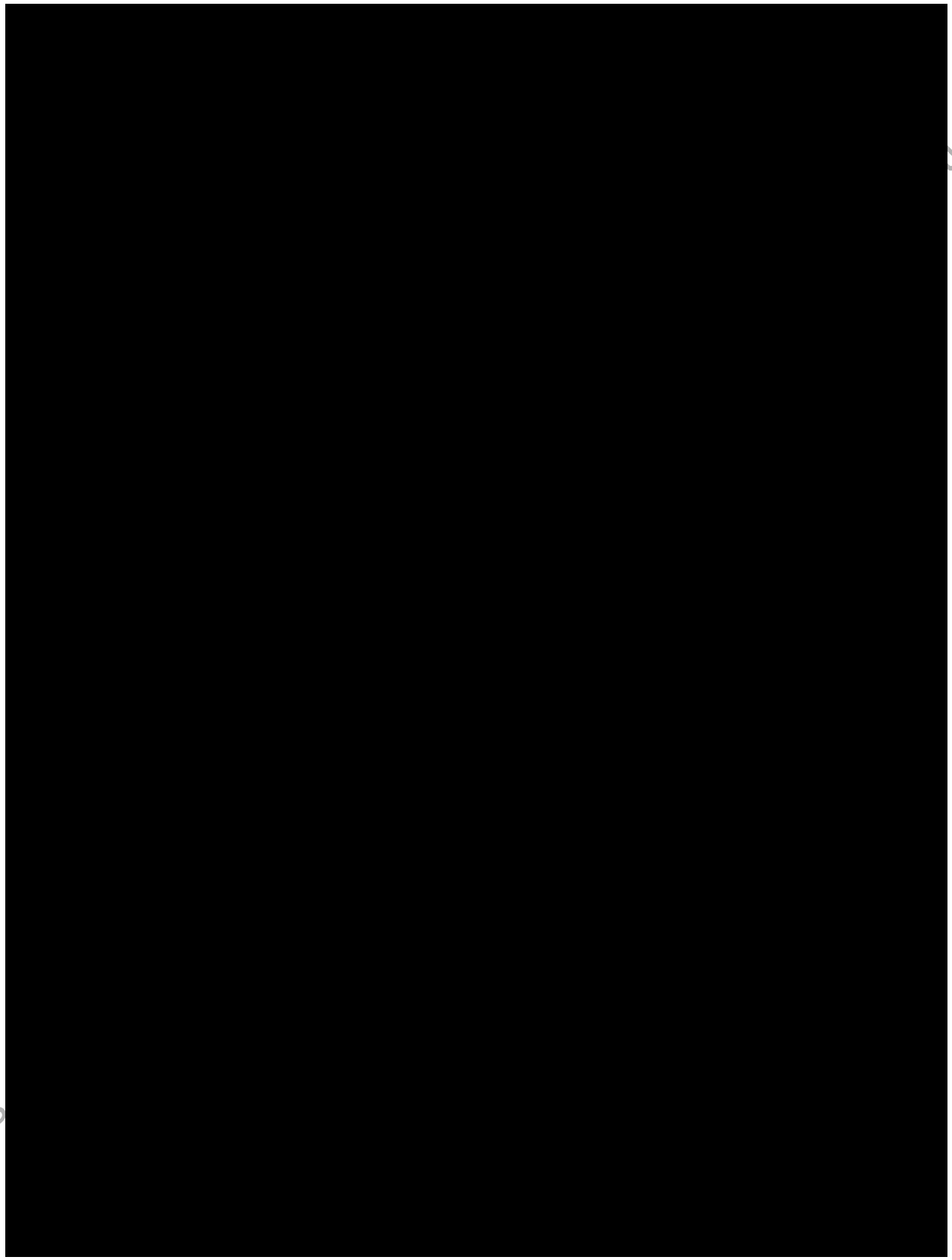
c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)

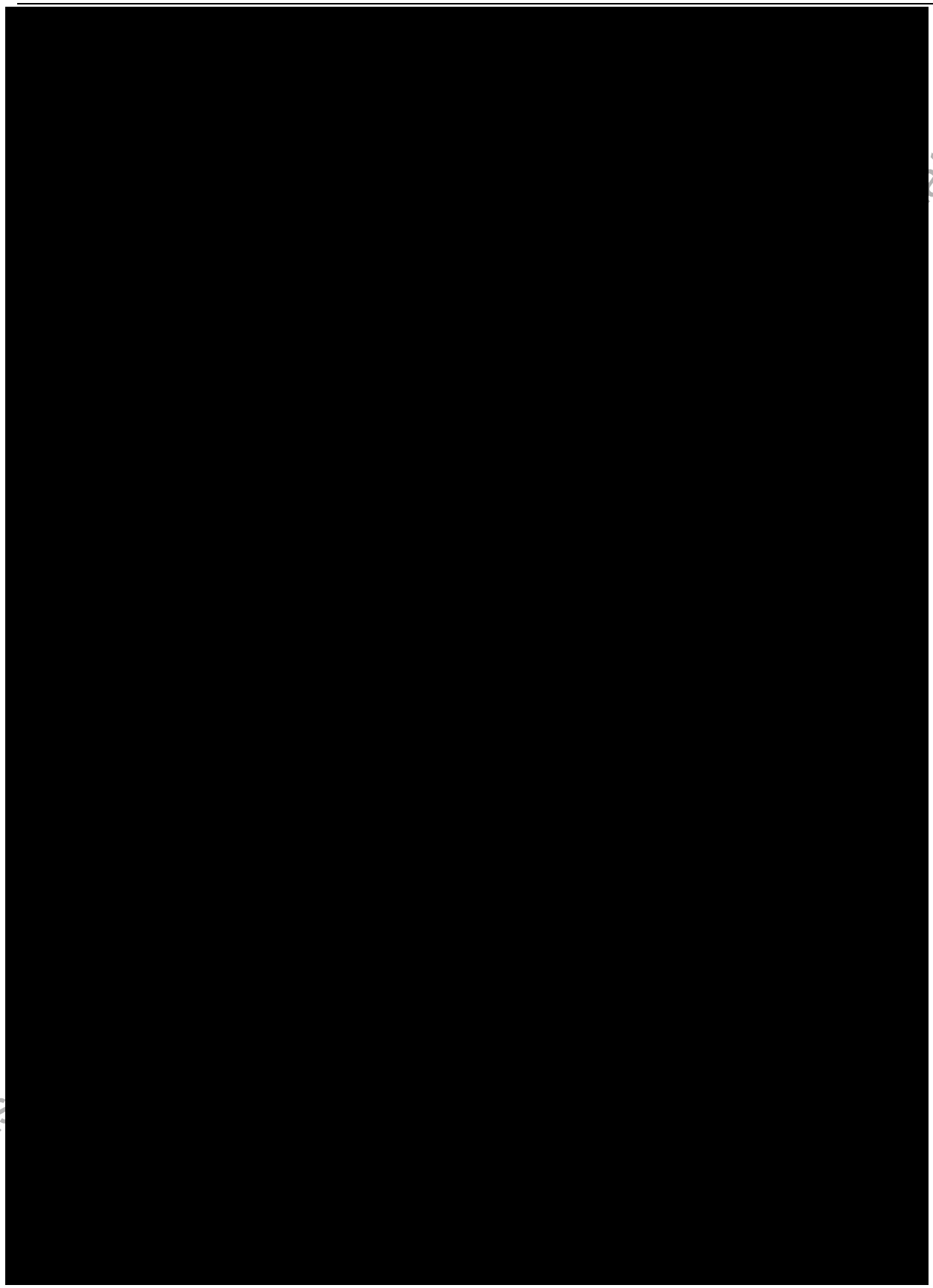
d. Persistent GI symptoms (eg, crampy abdominal pain, vomiting)

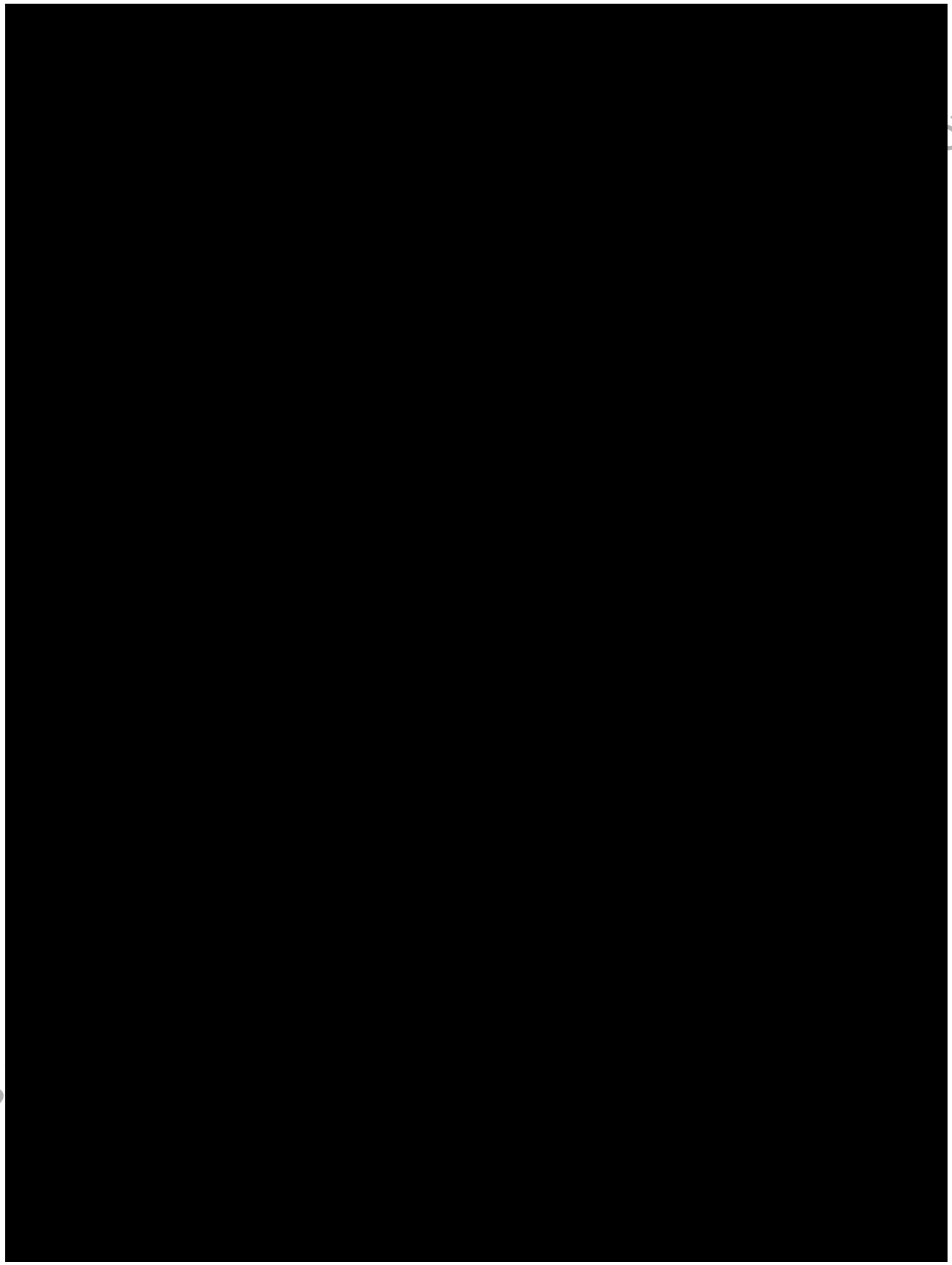
Reduced BP after exposure to known allergen for that subject (minutes to several hours): Systolic BP of less than 90mmHg or greater than 30% decrease from the subject's Baseline systolic BP value.

10.23 Appendix 23: Columbia-Suicide Severity Rating Scale









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SPONSOR DECLARATION

I confirm that I have carefully read and understand this protocol and agree to conduct this clinical study as outlined in this protocol and according to current Good Clinical Practice.

Approval Signatures

Name: mg0004-protocol-amendment-2

Version: 1.0

Document Number: CLIN-000156421

Title: mg0004-protocol-amendment-2

Approved Date: 31 Jul 2020

Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 31-Jul-2020 05:07:28 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 31-Jul-2020 08:01:40 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Subject Matter Expert Date of Signature: 31-Jul-2020 15:33:59 GMT+0000