AN OPEN-LABEL, CROSSOVER STUDY TO EVALUATE ROZANOLIXIZUMAB SELF-ADMINISTRATION BY STUDY PARTICIPANTS WITH GENERALIZED MYASTHENIA GRAVIS

PROTOCOL MG0020 AMENDMENT 5

PHASE 3

SHORT TITLE:

A Phase 3, open-label, crossover study to evaluate self-administration of rozanolixizumab by study participants with gMG

Sponsor:
UCB Biopharma SRL
Allée de la Recherche 60
1070 Brussels
BELGIUM

Regulatory agency identifying number(s):

EudraCT Number:	2022-003870-21
IND Number:	132407

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History		
Document	**Date**	**Type of amendment**
Protocol Amendment 5	30 Nov 2023	Substantial
Protocol Amendment 4	07 Sep 2023	Substantial
Protocol Amendment 3	09 Dec 2022	Non-substantial
Protocol Amendment 2	04 Nov 2022	Substantial [a]
Protocol Amendment 1	31 Aug 2022	Non-substantial [a]
Original Protocol	04 Aug 2022	Not applicable

[a] The Original Protocol and Protocol Amendment 1 were not submitted to any regulatory authorities prior to issuance of Protocol Amendment 2.

Amendment 5 (30 Nov 2023)

Overall rationale for the amendment

The primary reason for this protocol amendment is to update the text to reflect the total number of participants screened, and to update the End of Study definition.

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
1.1 Synopsis 4.1 Overall design 9.9 Determination of sample size	Text updated to reflect the total number of participants screened (from approximately 40 to a total of 75) and to note that a total of 30 randomized participants (15 per sequence) is the minimum evaluable number of participants.	To update the actual number of screened participants.
1.1 Synopsis 1.2 Schema 1.3 Schedule of activities 4.1 Overall design 4.4 End of study definition 6.8 Treatment after the end of the study	In addition to permitting participants access to post-trial rozanolixizumab (if available according to local guidance), the text has been updated to also permit participants access to commercially available rozanolixizumab, at the discretion of the investigator. Text also updated to note that participants moving to rozanolixizumab via either of these methods must have completed all Treatment Periods including the End of Treatment Visit prior to this move.	To offer study participants the option of re-starting treatment with rozanolixizumab at an earlier timepoint following the completion of all Treatment Periods (including the End of Treatment Visit), and at the investigator's discretion.

Section # and name	Description of change	Brief rationale
	A new footnote (footnote "s") has been added to the Schedule of Activities and a new footnote (footnote "a") has been added to the Schema to reflect this update.	
4.4 End of Study definition 1.1 Synopsis 3 Objectives and Endpoints	The definition of study completers has been updated to allow participants who completed the End of Treatment Visit and then subsequently moved on to a post-trial access program or commercially available product to be considered to have completed the study. The Week 26 timepoint for the End of Study Visit was removed from the respective endpoint definitions for consistency with the changes in the other sections.	To offer study participants the option of re-starting treatment with rozanolixizumab at an earlier timepoint following the completion of all Treatment Periods (including the End of Treatment Visit), and at the investigator's discretion.
9.3.3 Other safety analyses	Paragraph #3 has been updated to remove the description of the statistical methods for estimating success.	The confidence interval will be calculated for each self-administration method only for the primary endpoint.

SERIOUS ADVERSE EVENT REPORTING

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

For details, see Appendix 3 (Section 10.3).

REPORTING OF SELF-ADMINISTRATION MEDICATION ERRORS

Safety reporting of self-administration medication errors (within 7 days)	
Email	Complete paper Medication Error form and email to **Global**: DS_ICT@ucb.com

Fax	**Europe and Rest of the World:** +32 2 386 24 21 **US and Canada:** +1 800 880 6949 or +1 866 890 3175

Medication errors associated with adverse reaction(s) will be recorded and reported within 24 hours following the SAE recording and reporting procedures and using the Medication Error form. For details, see Section 8.3.7.

REPORTING OF ADVERSE DEVICE EFFECTS (SERIOUS AND NONSERIOUS) AND DEVICE DEFICIENCIES

Reporting of adverse device effects (serious and nonserious) and device deficiencies for non-UCB devices used in the study (24h)	
Email	Complete paper Adverse Event and Device Deficiency Form and email to MedicalDeviceSupport@parexel.com Note: Device deficiencies for non-UCB devices should not be captured in the electronic data collection tool.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol title: An open-label, crossover study to evaluate rozanolixizumab self-administration by study participants with generalized myasthenia gravis.

Short title: A Phase 3, open-label, crossover study to evaluate self-administration of rozanolixizumab by study participants with gMG.

Rationale: Generalized myasthenia gravis (gMG) is a chronic, autoimmune disease requiring long-term therapy. Successful self-administration of subcutaneous (SC) treatment has been demonstrated in gMG patients using immunoglobulin (Ig) (Alcantara et al, 2021). Currently, rozanolixizumab is administered SC by health care professionals (HCPs) using programmable syringe drivers at a [redacted]. There is considerable clinical interest in providing an alternative administration method to programmable syringe drivers as well as providing patients the option to self-administer rozanolixizumab. Given the relatively low volumes involved in rozanolixizumab therapy, the manual push technique is being explored as an alternative method, which offers the advantages of independence from constant use of a syringe driver, and reduced infusion times ([redacted] for abdominal sites). The manual push technique is also a well-established mode of self-administration of SC Ig (Bienvenu et al, 2018).

Rozanolixizumab has been administered using manual push in an ongoing single-dose healthy volunteer study (UP0106) and the manual push administration by HCP is planned to be included in gMG study MG0007; other indications may offer alternative administration options for rozanolixizumab in Phase 3 open-label extension studies.

Following a comprehensive training (consisting of [redacted] with the study participant practicing both methods at the study site), rozanolixizumab will be self-administered by both manual push and syringe driver in the clinic and unsupervised by an HCP at home. In addition to the evaluation of successful self-administration and safety, the participant's preference for HCP administration versus self-administration and preference for the manual push versus the syringe driver method of administration will be compared.

If required, only minimal assistance is allowed to support the study participant for a successful self-administration. However, if an informal caregiver is required, he/she must be fully trained (ie, attending all training sessions at the site) to perform the administration in this study on behalf of the study participant. In this case, the caregiver must perform all investigational medicinal product (IMP) administration activities described for the study participant throughout the Self-administration Periods.

Objectives and endpoints:

Objectives	Endpoints
Primary	
Primary objective: To evaluate the ability of study participants with gMG to successfully self-administer rozanolixizumab after training in the self-administration technique using the syringe driver and manual push methods	Primary endpoint: • Successful self-administration of rozanolixizumab (with correct use of syringe driver and manual push, respectively) during the Self-administration Period at Visit 13 ([redacted] last dose of Self-administration Period 1) and Visit 19 ([redacted]; last dose of Self-administration Period 2). Successful self-administration is defined by the participant (i) choosing the correct infusion site, (ii) administering SC, and (iii) delivering the intended dose.
Secondary	
Secondary objective: • To evaluate the safety of SC self-administration of rozanolixizumab	Secondary endpoints: • Occurrence of treatment-emergent adverse events (TEAEs) after syringe driver or manual push self-administration from Visit 2 ([redacted] up to the End of Study Visit (Visit 21). • Occurrence of local site reactions up to 24 hours after each administration during the Training Period and Self-administration Periods. • Occurrence of medication errors associated with adverse reactions during the 2 Self-administration Periods of the study.

Other	
Other objectives:	Other endpoints:
• To evaluate the study participant's preferred method of rozanolixizumab administration	• Participant's relative preference for: – Subcutaneous infusions performed by an HCP versus self-administration – The manual push method versus the use of a syringe driver for self-administration using the participant's preferred method of administration questions at Visit 19 ([redacted]).
• To evaluate symptom changes in study participants with gMG	• Myasthenia Gravis Activities of Daily Living (MG-ADL) score change from Baseline during the study.
• To assess the pharmacodynamics of rozanolixizumab	• Total IgG level over time during the Training Period and Self-administration Periods.
• To evaluate the immunogenicity of rozanolixizumab following SC self-administration	• Anti-rozanolixizumab antibodies (status and titer at trough during both Self-administration Periods).
• To assess the study participant's experience with self-administration of SC infusions at home	• [redacted]
• To assess the ability of study participants with gMG to successfully self-administer rozanolixizumab at home after training in the self-administration technique using the syringe driver and manual push methods	• Successful self-administration of rozanolixizumab via manual push method or using a syringe driver at each of the [redacted] visits during Self-administration Period 1 or 2, respectively. Successful self-administration via manual push or syringe driver is defined by the participant (i) choosing the correct infusion site, (ii) administering SC, and (iii) delivering the intended dose, as reported by the study participant to the site staff following each of the [redacted].
• To assess the safety and tolerability of rozanolixizumab in study participants with gMG	• Occurrence of TEAEs leading to permanent withdrawal of rozanolixizumab during the study.

Overall design:

MG0020 is a Phase 3, open-label, randomized, 2-period, 2-sequence crossover study planned to be conducted at multiple sites in Europe, Japan, and North America. In MG0020, the safe and effective self-administration of rozanolixizumab using the syringe driver and manual push administration methods by study participants with gMG will be evaluated using a crossover design (Table 1-1). Study participants are proposed to receive [redacted] weight tiered doses of rozanolixizumab for [redacted], as summarized in Table 1-2.

The weight tiered dosing will only be applicable to the study participants starting the Treatment Period after the approval of Protocol Amendment 4 in their respective countries. The study participants who are already in the Treatment Period when Protocol Amendment 4 is approved in their respective countries will continue with the [redacted] fixed doses as per Protocol Amendment 3 until study completion.

Rozanolixizumab-naïve study participants and study participants previously exposed to rozanolixizumab will be included in the study.

Table 1-1: MG0020 crossover design

	Administration method	
Sequence 1	Syringe driver	Manual push
Sequence 2	Manual push	Syringe driver

Table 1-2: Rozanolixizumab weight tiers

Body weight of study participant	[redacted] Dose	Volume to be infused
Study participants in Europe and Canada		
≥35kg to <50kg		
≥50kg to <70kg		
≥70kg to <100kg		
≥100kg		
Study participants in the US		
<50kg		
≥50kg to <100kg		
≥100kg		

Number of participants:

A total of 75 participants have been screened to achieve a minimum of 30 randomly assigned and evaluable participants for an estimated minimum total of 15 evaluable participants per sequence. See Section 9.9 for the determination of sample size.

Treatment groups and duration:

The total duration for each study participant is up to 29 weeks, including a Screening Period of up to 4 weeks, an [redacted] Treatment Period, and an up to 7-week Safety Follow-up Period (ie, End of Study Visit is 8 weeks after the last dose of rozanolixizumab in the Treatment Period, or earlier, if the study participant moves on to a post-trial access program or to commercially available rozanolixizumab during the Safety Follow-up Period).

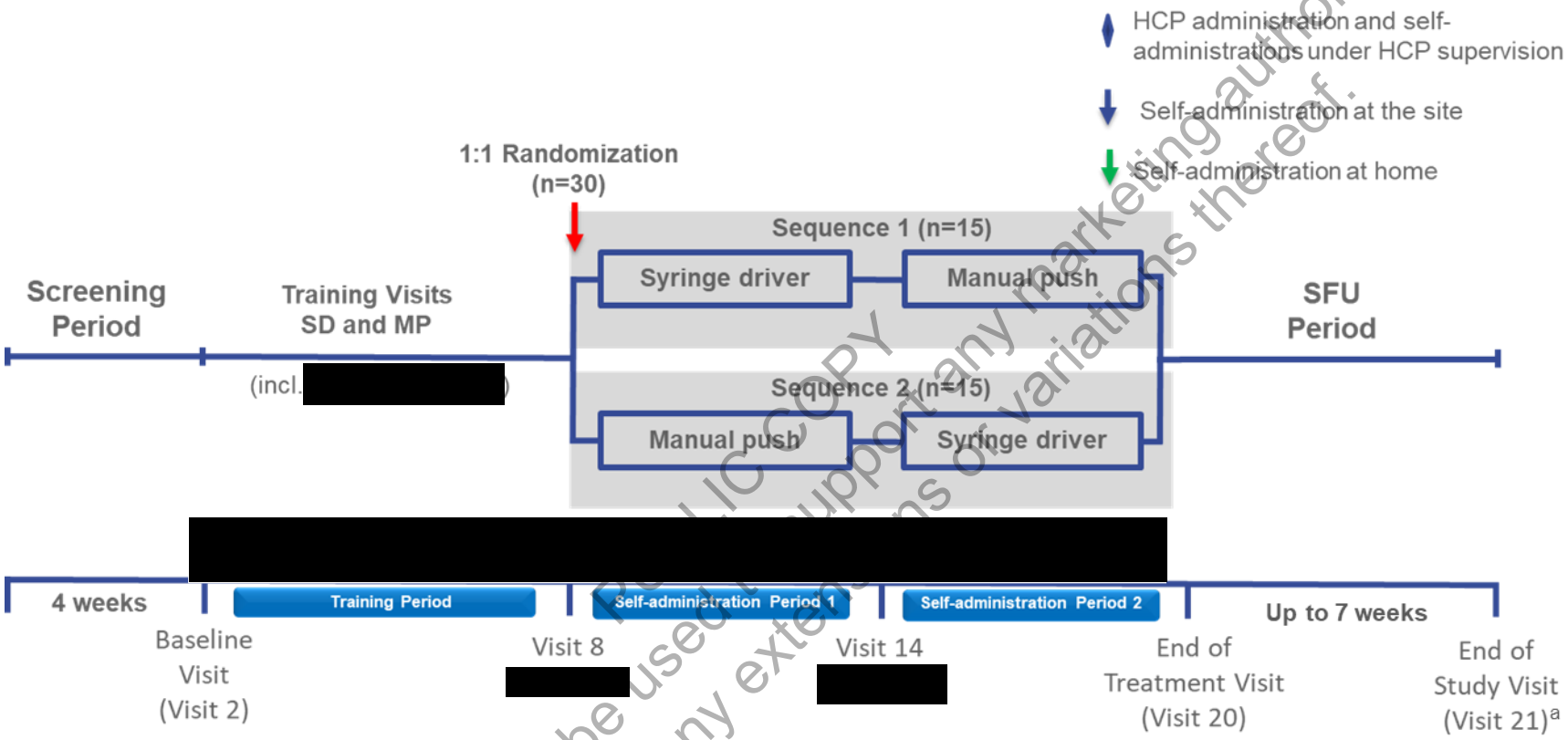
The [redacted] Treatment Period of MG0020 starts with standardized [redacted] trainings over the course of a [redacted] Training Period when the study participant is trained on both the manual push and the syringe driver administration methods. During the Training Period, the study participant will receive [redacted] doses of rozanolixizumab SC and should practice both methods of administration at the study site. To act as a reference for the preference question (HCP vs self-administration) and to demonstrate subcutaneous infusions of rozanolixizumab, the first administration will be imperatively performed by the HCP. For all remaining training visits, the study participant should perform as many self-administrations as possible (under HCP supervision) depending on their training status. Self-administration under HCP supervision or administration by HCP will be documented in the case report form (CRF). At Visit 8 ([redacted]), after the completion of the Training Period and following the investigator's confirmation of the eligibility to perform self-administration, the study participant will be randomized 1:1 to either the syringe driver or to the manual push administration method. After completing Self-administration Period 1 (at Visit 13 [redacted]), the study participant will crossover to the alternative administration method, entering Self-administration Period 2 (Visit 14 [redacted]). A final release of the study participant for home self-administration will be based on a successful demonstration of self-administration using the assigned mode of administration (manual push or syringe driver use) at Visit 9 ([redacted] and Visit 15 ([redacted]), respectively. Study participants who cannot be confirmed eligible for self-administration will not perform self-administration and can continue to be treated on-site per protocol based on investigator decision. Additionally, if a study participant becomes no longer eligible for self-administration during the Self-administration Periods, he/she can continue to be treated by HCP on-site per protocol based on investigator decision. The study medication administration can be performed either via syringe driver or manual push. Adverse events (AEs), concomitant medication, vital signs, ECG, suicidality, blood and urine samples for safety laboratory tests, pregnancy tests, and IgG will continue to be collected from these study participants until the End of Study Visit/Early Withdrawal Visit.

During both Self-administration Period 1 and Self-administration Period 2, [redacted] (ie, unsupervised/not in the presence of an HCP) for [redacted]

After the Self-administration Periods, study participants will enter the 7-week Safety Follow-up Period.

Study participants who have completed all Treatment Periods (including the End of Treatment Visit) will have the option to subsequently move, at the discretion of the investigator, into either a post-trial access program for rozanolixizumab (if available according to local guidance) or on to commercially available rozanolixizumab.

1.2 Schema



HCP=health care professional; MP=manual push; SD=syringe driver; SFU=safety follow-up
[a] Participants completing all Treatment Periods, including the End of Treatment Visit, and moving on to either a post-trial access program or commercially available rozanolixizumab during the SFU Period must undergo an earlier End of Study Visit prior to this move (see Section 4.4 and Section 6.8).

1.3 Schedule of activities

The Schedule of Activities is provided in Table 1-3.

Table 1-3: Schedule of Activities

Procedure	Scr Period	Training Period						Self-administration Period 1						Self-administration Period 2							SFU Period
Visit	V1 Scr	V2 BL	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	EOT V20 /EW	EOS V21[s]
Visit type																					
Day (visit window)[a]																					
Week																					
Written informed consent	X																				
Demographic and Baseline characteristics	X																				
Verification of inclusion/ exclusion criteria	X	X																			
General medical history	X																				
Prior and concomitant medications and medical procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height and body weight	X																				

Table 1-3: Schedule of Activities

Procedure	Scr Period	Training Period						Self-administration Period 1						Self-administration Period 2							SFU Period
Visit	**V1 Scr**	**V2 BL**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**EOT V20 /EW**	**EOS V21[s]**
Visit type	[redacted]																				
Day (visit window)[a]																					
Week																					
Psychiatric history/ C-SSRS[b]	X	X																			
Query for suicidality[b]		X	X	X	X	X	X	X	X				X	X	X				X	X	
Tuberculosis Signs and Symptoms questionnaire	X																				
Complete physical examination	X																				
Brief physical examination[m]		X																		X	
Vital signs[c]	X	X	X	X	X	X	X	X	X				X	X	X				X	X	X
12-lead ECG[n]	X					X							X							X	
Recording of AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[d]	X	X						X						X							

Table 1-3: Schedule of Activities

Procedure	Scr Period	Training Period						Self-administration Period 1						Self-administration Period 2							SFU Period
Visit	**V1 Scr**	**V2 BL**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**EOT V20 /EW**	**EOS V21[s]**
Visit type	[redacted]																				
Day (visit window)[a]																					
Week																					
Hematology, clinical chemistry	X	X	X					X						X						X	X
Serology (HIV, Hepatitis B, and Hepatitis C)	X																				
Urinalysis	X	X	X					X						X						X	X
Blood sampling for ADA[e]		X						X[q]	X[q]				X[q]	X[q]	X[q]				X[q]	X[q]	X[q]
Blood sampling for total IgG	X	X	X	X	X	X	X	X	X				X	X	X				X	X	X
Blood sampling for exploratory safety biomarker analysis		X										X[r]									
MGFA classification	X																				

Table 1-3: Schedule of Activities

Procedure	Scr Period	Training Period						Self-administration Period 1						Self-administration Period 2							SFU Period
Visit	**V1 Scr**	**V2 BL**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**EOT V20 /EW**	**EOS V21[s]**
Visit type																					
Day (visit window)[a]																					
Week																					
Randomization								X[l]													
Call or enter IRT to register the visit	X	X	X	X	X	X	X	X[l]	X				X	X	X				X	X	X
Study drug admin[h]																					
Return of vials from home self-admin[o]													X						X		
MG-ADL	X	X[f]						X[f,q]		X[f,q]	X[f,q]	X[f,q]	X[f,q]	X[f,q]		X[f,q]	X[f,q]	X[f,q]	X[f,q]		
SIAQ (Infusion version)[g]																					
Site staff to evaluate study participant's safe and successful self-admin							X[i]		X[i,q]	X[j,q]	X[j,q]	X[j,q]	X[k,q]		X[i,q]	X[j,q]	X[j,q]	X[j,q]	X[k,q]		

Table 1-3: Schedule of Activities

Procedure	Scr Period	Training Period						Self-administration Period 1						Self-administration Period 2							SFU Period
Visit	**V1 Scr**	**V2 BL**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**EOT V20 /EW**	**EOS V21[s]**
Visit type																					
Day (visit window)[a]																					
Week																					
Participant self-assessment of home self-admin										$X^{j,q}$	$X^{j,q}$	$X^{j,q}$				$X^{j,q}$	$X^{j,q}$	$X^{j,q}$			
Questions on study participant's preferred method of admin																			X^{q}		

ADA=antidrug antibody; admin=administration; AE=adverse event; BL=Baseline; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; EOS=end of study; EOT=end of treatment; EW=early withdrawal; HC/SP=health care professional administration or self-administration under healthcare professional supervision; HIV=human immunodeficiency virus; HSA=home self-administration; IgG=immunoglobulin G; IRT=interactive response technology; MG-ADL=Myasthenia Gravis Activities of Daily Living; MGFA=Myasthenia Gravis Foundation of America; S=site visit; SC=subcutaneous; Scr=screening; SFU=safety follow-up; SIAQ=Self-Injection Assessment Questionnaire; SP=self-administration by the study participant; V=visit

Note: HSA=home self-administration, ie, unsupervised self-administration/not in the presence of an HCP.

[a] The visit windows are relative to the first dosing visit date. A visit window of ±2 days is allowed. However, there should be a minimum interval of 5 days and a maximum interval of 9 days between 2 doses of IMP.

[b] A full C-SSRS assessment will be performed for Screening and Baseline. For subsequent visits, a full C-SSRS assessment will only be performed if a study participant has a positive response to the query for suicidality. If a study participant has [redacted] 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.

[c] Vital signs comprise systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate. Vital signs will be taken at scheduled visits at the following timepoints. On Day 1 and Day 8, vital signs will be measured before rozanolixizumab administration (-5 mins), at the end of the infusion (+5 mins), and 2 hours (±15 mins) after the end of infusion. On Day 15, Day 22, Day 29, and Day 36, vital signs will be measured before rozanolixizumab administration (-5 mins) and 1 hour (±5 mins) after the end of infusion. For site visits from Day 43 onwards, vital signs will be measured before rozanolixizumab administration (-5 mins), at the end of the infusion (+5 mins), and 15 minutes (±5 mins) after the end of infusion. Additional vital sign measurements can be performed at the investigator's discretion.

[d] Serum pregnancy test at Screening and urine pregnancy test at all other indicated visits.

[e] Antidrug antibody sample collection predose.

[f] The MG-ADL will be completed predose.

[redacted]

[h] Study participants must be observed at site postdose for at least 2 hours following the first [redacted]. Vital signs will be assessed as described above.

[i] An HCP will conduct a mandatory evaluation of self-administration at site at the last visit of the Training Period and following the study participant's demonstration of self-administration using the assigned mode of administration (syringe driver or manual push) at Visit 9 [redacted] and Visit 15 [redacted]

[j] An HCP is required to have a direct contact with the study participant via telephone or video call as soon as possible after each home self-administration to confirm their health status. The direct telephone or video contact with the study participant will also be used to assess successful self-administration criteria.

[k] An HCP will conduct a mandatory evaluation of self-administration at site Visit 13 ([redacted]) and Visit 19 ([redacted]) to confirm (i) correct infusion site, (ii) administered SC, and (iii) delivered the intended dose. Refer to Appendix 15 (Section 10.15) for documents to be used.

[l] Participants will be randomized to a treatment sequence at Visit 8 ([redacted])

[m] In addition to a brief physical examination, a full neurological examination should be performed for any study participant who experiences severe and/or serious headache and for any study participant who experiences features suggestive of aseptic meningitis (see Appendix 14 [Section 10.14]). For details of the assessments included in these examinations, see Section 8.2.5. For additional assessments that may be required in case of these AESM, see Section 1.3.1 (Table 1-4).

[n] Single 12-lead ECGs, which will be read locally.

[o] Return of used and unused vials as well as all equipment and ancillary materials used for IMP administration.

[p] The timing between Screening and the Baseline Visit needs to be a minimum of 14 days to confirm eligibility and to ensure all prerequisites are met.

[q] Not applicable for study participants not considered eligible for self-administration, who will continue receiving IMP administered by the HCP at the study site (for additional details, see Section 4.1).

[r] Exploratory biomarker samples will be taken predose at Baseline (Day 1) for all study participants. In study participants who experience severe and/or serious headaches or features suggestive of aseptic meningitis, samples should also be collected 4 hours after the onset of the event, or otherwise as soon as possible within 72 hours after the onset of the event. For additional assessments that may be required in case of these AESM, see Section 1.3.1 (Table 1-4).

[s] Participants completing all Treatment Periods, including the EOT Visit, and moving on to either a post-trial access program or commercially available rozanolixizumab during the SFU Period must undergo an earlier EOS Visit prior to this move (see Section 4.4 and Section 6.8).

1.3.1 Additional study assessments

In addition to those detailed in Table 1-3, the assessments in Table 1-4 may be required in case of adverse events of special monitoring (AESM) of severe and/or serious headache, or suspected aseptic meningitis (see Section 8.3.8). Note that additional vital sign measurements and/or additional investigations may be performed at the discretion of the investigator.

Table 1-4: Additional study assessments

Assessment	When applicable
For study participants who experience severe and/or serious headache and for study participants with suspected aseptic meningitis	
Headache or suspected aseptic meningitis follow-up questionnaire	Headache follow-up questionnaire which sites will receive after reporting AESM of severe and/or serious headache should be completed promptly and returned to the sponsor via the SAE reporting process. Suspected aseptic meningitis follow-up questionnaire which sites will receive after reporting AESM of suspected aseptic meningitis should be completed promptly and returned to the sponsor via the SAE reporting process.
Full neurological examination	Assessments required for all study participants are detailed in the Schedule of Activities (Table 1-3). In study participants who report/are diagnosed with severe and/or serious headache or with a suspected aseptic meningitis at the clinic visit, a full neurological examination (including fundoscopy) should be performed (see Appendix 14 [Section 10.14]). In study participants who report a severe and/or serious headache while at home or features suggestive of aseptic meningitis, a visit to the site for the full neurological examination should be arranged for as soon as is practically possible.
Blood analysis	Blood sample collection for exploratory analysis.
Other	In study participants who report severe and/or serious headache, other diagnostic procedures including but not limited to CT scan, MRI (Gadolinium-enhanced preferred) and/or lumbar puncture for CSF collection are to be performed if indicated at the discretion of the investigator.
For study participants who experience suspected aseptic meningitis	
Lumbar puncture	In study participants who reported signs and/or symptoms of meningitis which required a lumbar puncture, results of the CSF analysis should be recorded in the eCRF, and preliminary data should be included on the SAE form used for reporting the event as an AESM within 24 hours (ie, preliminary data reported on the first reporting may not have CSF results yet, but the reporting should occur as soon as there is a suspected diagnosis. Full results should be communicated in subsequent exchanges with UCB).
Additional analysis	Results of all investigations should be recorded in the eCRF, and preliminary data should be included on the SAE form used for reporting the event as an AESM. Please include details on all investigations results including but not limited to blood or CSF cultures and analysis/ PCR test (including list of microorganisms tested) / MRI scans +/- gadolinium.

Table 1-4: Additional study assessments

Assessment	When applicable

AESM=adverse event of special monitoring; CSF=cerebrospinal fluid; CT=computed tomography; eCRF=electronic case report form; MRI=magnetic resonance imaging; PCR=polymerase chain reaction; SAE=serious adverse event

The frequency of the collection of samples for exploratory biomarkers after severe and/or serious headache or suspected aseptic meningitis are described in Table 1-3 (footnote r).

2 INTRODUCTION

Rozanolixizumab is a humanized monoclonal antibody being developed as an inhibitor of neonatal Fc receptor (FcRn; the major histocompatibility complex-class-I-like FcRn) activity with the aim to reduce the concentration of (pathogenic) IgG in patients with IgG autoantibody-mediated diseases, including gMG.

The FcRn recycles IgG and albumin and transports it bidirectionally across epithelial barriers. 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). Neonatal Fc receptor for IgG 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.

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 patients and conditions and have broad immunosuppressive effects causing considerable toxicity and treatment-related morbidity.

Treatments aimed at reducing the quantity of circulating IgG autoantibodies, including plasmapheresis, immunoadsorption, or high-dose intravenous immunoglobulin (IVIg), are being used as primary and secondary therapy of autoimmune diseases, particularly where corticosteroid based immune suppression is not or no longer effective. 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, removal of the IgG autoantibodies by FcRn blockade may provide an effective therapeutic option for IgG autoantibody-mediated autoimmune disorders.

To date, rozanolixizumab has been administered to human study participants in several clinical studies. 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.

2.1 Study rationale

Studies in patients with gMG have demonstrated improvements across a range of efficacy endpoints with rozanolixizumab treatment. These studies also indicated that rozanolixizumab has an acceptable safety profile and is generally well tolerated.

Generalized myasthenia gravis is a chronic, autoimmune disease requiring long-term therapy. Successful self-administration of SC treatment has been demonstrated in gMG patients using Ig (Alcantara et al, 2021). Currently, rozanolixizumab is administered SC by HCPs using programmable syringe drivers at a [redacted]. There is considerable clinical interest in providing an alternative administration method to programmable syringe drivers as well as providing patients the option to self-administer rozanolixizumab. Given the relatively low volumes involved in rozanolixizumab therapy, the manual push technique is being explored as an alternative method, which offers the advantages of independence from constant use of a syringe driver, and reduced infusion times ([redacted] for abdominal sites). The manual push technique is also a well-established mode of self-administration of SC Ig (Bienvenu et al, 2018).

Rozanolixizumab has been administered using manual push in an ongoing [redacted] healthy volunteer study (UP0106) and the manual push administration by HCP is planned to be included in gMG study MG0007; other indications may offer alternative administration options for rozanolixizumab in Phase 3 open-label extension studies.

Following a comprehensive training (consisting of [redacted] with the study participant practicing both methods at the study site), rozanolixizumab will be self-administered by both manual push and syringe driver in the clinic and unsupervised by an HCP at home. In addition to the evaluation of successful self-administration and safety, the participant's preference for HCP administration versus self-administration and preference for the manual push versus the syringe driver method of administration will be compared.

2.2 Background

Myasthenia gravis (MG) is a serious, sometimes life-threatening, debilitating condition associated with numerous symptoms including muscular weakness and fatigue. The major pathophysiology leading to MG is the production of IgG autoantibodies directed toward nicotinic acetylcholine receptor, or muscle-specific kinase 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, high-dose IVIg, plasmapheresis or immunoadsorption, there remains a need for a safe and effective treatment devoid of significant side effects to conveniently treat patients with MG.

In a randomized, participant- and investigator-blind, placebo-controlled, Phase 2 study (MG0002), clinically relevant improvements in day-to-day functioning, as measured by change from Baseline to Day 29 in MG-ADL (secondary endpoint), were observed following treatment with rozanolixizumab [redacted] compared with placebo (p=0.036). Numerical differences in favor of rozanolixizumab [redacted] compared with placebo were observed in reductions from Baseline in Myasthenia Gravis Composite (MG-C) score (p=0.089) and Quantitative Myasthenia Gravis (QMG) score (p=0.221). Overall, repeated administrations of rozanolixizumab at dose levels of [redacted] SC have been generally well tolerated, with an acceptable safety profile.

In the Phase 3 gMG program, clinically relevant improvements in day-to-day functioning were observed following treatment with rozanolixizumab compared with placebo.

Data suggest that repeated administrations of rozanolixizumab at a dose approximating [redacted] and [redacted] SC is generally well tolerated, with an acceptable safety profile. Treatment-emergent AEs were most frequently reported in the system organ class of nervous system disorders. Rapid, substantial, and sustained reductions in levels of total IgG and IgG subclasses (IgG 1 to 4) were observed after rozanolixizumab was administered.

In the randomized, double-blind, placebo-controlled, Phase 3 study (MG0003), the [redacted] clinical efficacy of rozanolixizumab was demonstrated by statistically significant results for the primary endpoint. At Day 43 (Visit 10), the differences in least square mean change from Baseline in MG-ADL score between groups (rozanolixizumab minus placebo) were: [redacted] (95% confidence interval [CI]: [redacted]; p<0.001) in the rozanolixizumab [redacted] group (in favor of rozanolixizumab) and [redacted] (95% CI: [redacted]; p<0.001) in the rozanolixizumab [redacted] group (in favor of rozanolixizumab). Clinically relevant and statistically significant reductions (improvements) from Baseline in MG-C score and QMG scores were observed for each rozanolixizumab treatment group versus placebo. Statistically significant improvements in MG Symptoms patient reported outcomes (PROs) "Muscle Weakness Fatigability", "Physical Fatigue", and "Bulbar Muscle Weakness" scores were observed for both rozanolixizumab treatment groups. In addition, results for all other efficacy endpoints were consistent and supported the primary endpoint. The most frequently reported TEAEs in rozanolixizumab-treated study participants were headache, diarrhoea, pyrexia, nausea, and arthralgia.

In a randomized, open-label extension study of MG0003 (MG0004), clinically relevant improvements from Baseline in the secondary efficacy endpoints MG-ADL, MG-C, and QMG mean total scores over time were observed for both the rozanolixizumab [redacted] treatment groups. The most frequently reported TEAEs were headache, diarrhea, blood immunoglobulin G decreased, nausea, pyrexia, and urinary tract infection.

MG0007 is a randomized, open-label extension study of MG0003 and MG0004 having as primary objective to assess the safety and tolerability of additional [redacted] treatment cycles with rozanolixizumab in study participants with gMG. Other study objectives are to assess the efficacy, pharmacokinetics, pharmacodynamics, and immunogenicity of rozanolixizumab. Study participants are randomized to receive an initial fixed [redacted] treatment cycle of a SC dose of rozanolixizumab equivalent to [redacted]. At the end of the Treatment Period, study participants will enter an Observation Period. In case of symptom worsening, resulting in a need for additional treatment, study participants will undergo another [redacted] treatment cycle followed by an Observation Period, based on the investigator's discretion.

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 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 plasma exchange (PEX), or intravenous (IV) administration of Ig at a healthcare facility.

Rozanolixizumab represents an innovative, SC anti-FcRn monoclonal antibody that may provide a novel and specific targeted therapeutic approach for the treatment of patients with gMG. Data show that rozanolixizumab markedly lowers serum IgG and IgG autoantibody levels in patients with gMG. The completed Phase 3 studies have established evidence of efficacy for the treatment of gMG. Repeated administrations of rozanolixizumab were well tolerated with an acceptable safety profile.

In MG0003, a Phase 3 study evaluating efficacy and safety of SC rozanolixizumab in adult study participants with gMG, the [redacted] clinical efficacy of rozanolixizumab was demonstrated by improvements versus placebo in all efficacy endpoints tested in the study. There were clinically meaningful and statistically significant reductions from Baseline in the primary endpoint, MG-ADL score, at Day 43 for both rozanolixizumab dose groups versus placebo.

The identified adverse drug reactions (ADRs) associated with SC administration of rozanolixizumab are headaches, diarrhoea, pyrexia, nausea, upper respiratory tract infections, arthralgia, rash, injections site reactions, vomiting, myalgia, and herpes simplex infections. Headache is the most commonly reported ADR. Headaches were mostly mild to moderate and easily managed with over-the-counter medications. Serious infections and hypersensitivity reactions are safety concerns with rozanolixizumab. Other safety topics of interest include effects on vaccination response, effects on the kidney, reductions in albumin and plasma proteins, drug-induced aseptic meningitis (DIAM), and [redacted] 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 severe and/or serious headaches (AESM), suspected aseptic meningitis (AESM), medication error associated with adverse reaction(s) (AESM), hypersensitivity reactions, and infections is also provided as well as expedited reporting requirements of AESM to UCB.

Restrictions on the use of live vaccines have been defined in exclusion criterion 7a. If vaccination with non-live vaccines (including coronavirus disease 2019 [COVID-19] vaccines) is considered necessary once a study participant has started treatment with rozanolixizumab, the degree of protection afforded with a vaccine may be compromised while the participant receives treatment. Based on its mechanism of action, rozanolixizumab will reduce total IgG levels including vaccine-specific IgG. Immunization with vaccines during rozanolixizumab treatment has not been studied and the response to immunization with any vaccine is unknown. Given the study population characteristics (eg, status of the underlying disease, concomitant immunosuppressive therapies), it is recommended to perform individualized benefit-risk assessment for vaccination and specifically vaccination against COVID-19 infection. If COVID-19 vaccination is planned, information regarding the vaccine should be recorded (Section 6.5.1). A COVID-19 vaccination should be scheduled, if at all possible, to allow differentiation of safety profiles of rozanolixizumab and vaccine (eg, a minimum of 72 hours between COVID-19 vaccination and rozanolixizumab administration). If any AEs occur, they should be handled as described in Section 8.4 with causality assessment provided for both rozanolixizumab and vaccine. Additionally, to further characterize the effect of rozanolixizumab on COVID-19 vaccination response, measurements of vaccine titers are being tested in rozanolixizumab development programs.

Considering the potential benefits, risks, and mitigation measures in place, UCB considers the overall benefit/risk to be favorable for participants in this study.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of rozanolixizumab may be found in the Investigator's Brochure.

3 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
Primary objective: To evaluate the ability of study participants with gMG to successfully self-administer rozanolixizumab after training in the self-administration technique using the syringe driver and manual push methods	Primary endpoint: • Successful self-administration of rozanolixizumab (with correct use of syringe driver and manual push, respectively) during the Self-administration Period at Visit 13 ([redacted]; last dose of Self-administration Period 1) and Visit 19 ([redacted]; last dose of Self-administration Period 2). Successful self-administration is defined by the participant (i) choosing the correct infusion site, (ii) administering SC, and (iii) delivering the intended dose.
Secondary	
Secondary objective: • To evaluate the safety of SC self-administration of rozanolixizumab	Secondary endpoints: • Occurrence of TEAEs after syringe driver or manual push self-administration from Visit 2 ([redacted] up to the End of Study Visit (Visit 21). • Occurrence of local site reactions up to 24 hours after each administration during the Training Period and Self-administration Periods. • Occurrence of medication errors associated with adverse reactions during the 2 Self-administration Periods of the study.

Other	
Other objectives:	Other endpoints:
• To evaluate the study participant's preferred method of rozanolixizumab administration	• Participant's relative preference for: – Subcutaneous infusions performed by an HCP versus self-administration – The manual push method versus the use of a syringe driver for self-administration using the participant's preferred method of administration questions at Visit 19 ([redacted]
• To evaluate symptom changes in study participants with gMG	• Myasthenia Gravis Activities of Daily Living score change from Baseline during the study.
• To assess the pharmacodynamics of rozanolixizumab	• Total IgG level over time during the Training Period and Self-administration Periods.
• To evaluate the immunogenicity of rozanolixizumab following SC self-administration	• Anti-rozanolixizumab antibodies (status and titer at trough during both Self-administration Periods).
• To assess the study participant's experience with self-administration of SC infusions at home	• [redacted]
• To assess the ability of study participants with gMG to successfully self-administer rozanolixizumab at home after training in the self-administration technique using the syringe driver and manual push methods	• Successful self-administration of rozanolixizumab via manual push method or using a syringe driver at each of the 3 home self-administration visits during Self-administration Period 1 or 2, respectively. Successful self-administration via manual push or syringe driver is defined by the participant (i) choosing the correct infusion site, (ii) administering SC, and (iii) delivering the intended dose, as reported by the study participant to the site staff following each of the 3 home self-administrations.
• To assess the safety and tolerability of rozanolixizumab in study participants with gMG	• Occurrence of TEAEs leading to permanent withdrawal of rozanolixizumab during the study.

4 STUDY DESIGN

4.1 Overall design

MG0020 is a Phase 3, open-label, randomized, 2-period, 2-sequence crossover study planned to be conducted at multiple sites in Europe, Japan, and North America. In MG0020, the safe and effective self-administration of rozanolixizumab using the syringe driver and manual push administration methods by study participants with gMG will be evaluated using a crossover design (Table 1-1). Study participants are proposed to receive [redacted] weight tiered doses of rozanolixizumab for [redacted], as summarized in Table 1-2.

The weight tiered dosing will only be applicable to the study participants starting the Treatment Period after the approval of Protocol Amendment 4 in their respective countries. The study participants who are already in the Treatment Period when Protocol Amendment 4 is approved in their respective countries will continue with the [redacted] fixed doses as per Protocol Amendment 3 until study completion.

Rozanolixizumab-naïve study participants and study participants previously exposed to rozanolixizumab will be included in the study.

A total of 75 participants have been screened to achieve a minimum of 30 randomly assigned and evaluable participants for an estimated minimum total of 15 evaluable participants per sequence. See Section 9.9 for the determination of sample size.

The total duration for each study participant is up to 29 weeks, including a Screening Period of up to 4 weeks, an [redacted] Treatment Period, and an up to 7-week Safety Follow-up Period (ie, End of Study Visit is 8 weeks after the last dose of rozanolixizumab in the Treatment Period, or earlier, if the study participant moves on to a post-trial access program or to commercially available rozanolixizumab during the Safety Follow-up Period).

The [redacted] Treatment Period of MG0020 starts with standardized [redacted] trainings over the course of a [redacted] Training Period when the study participant is trained on both the manual push and the syringe driver administration methods. During the Training Period, the study participant will receive [redacted] doses of rozanolixizumab SC and should practice both methods of administration at the study site. To act as a reference for the preference question (HCP vs self-administration) and to demonstrate subcutaneous infusions of rozanolixizumab, the first administration will be imperatively performed by the HCP. For all remaining training visits, the study participant should perform as many self-administrations as possible (under HCP supervision) depending on their training status. Self-administration under HCP supervision or administration by HCP will be documented in the CRF. At Visit 8 ([redacted]), after the completion of the Training Period and following the investigator's confirmation of the eligibility to perform self-administration, the study participant will be randomized 1:1 to either the syringe driver or to the manual push administration method. After completing Self-administration Period 1 (at Visit 13 [[redacted]]), the study participant will crossover to the alternative administration method, entering Self-administration Period 2 (Visit 14 [[redacted]]; see the study schema in Section 1.2). A final release of the study participant for home self-administration will be based on a successful demonstration of self-administration using the assigned mode of administration (manual push or syringe driver use) at Visit 9 ([redacted] and Visit 15 ([redacted]), respectively. Study participants who cannot be confirmed eligible for self-administration will not perform self-administration and can continue to be treated on-site per protocol based on investigator

decision. Additionally, if a study participant becomes no longer eligible for self-administration during the Self-administration Periods, he/she can continue to be treated by HCP on-site per protocol based on investigator decision. The study medication administration can be performed either via syringe driver or manual push. Adverse events, concomitant medication, vital signs, ECG, suicidality, blood and urine samples for safety laboratory tests, pregnancy tests, and IgG will continue to be collected from these study participants until End of Study Visit/Early Withdrawal Visit. Handling of replacement participants is described in Section 7.2.

During both Self-administration Period 1 and Self-administration Period 2, [redacted] (ie, unsupervised/not in the presence of an HCP) for [redacted]

After the Self-administration Periods, study participants will enter the 7-week Safety Follow-up Period.

Study participants who have completed all Treatment Periods (including the End of Treatment Visit) will have the option to subsequently move, at the discretion of the investigator, into either a post-trial access program for rozanolixizumab (if available according to local guidance) or on to commercially available rozanolixizumab.

If required, only minimal assistance is allowed to support the study participant for a successful self-administration. However, if an informal caregiver is required, he/she must be fully trained (ie, attending all training sessions at the site) to perform the administration in this study on behalf of the study participant. In this case, the caregiver must perform all investigational medicinal product (IMP) administration activities described for the study participant throughout the Self-administration Periods.

4.1.1 Unscheduled visit

An Unscheduled Visit can be conducted at the discretion of the investigator (eg, due to an AE; see Section 8).

4.2 Scientific rationale for study design

Manual push administration of SC Ig treatments has been demonstrated to be a safe and viable technique in primary immunodeficiency patients that allows individualization of treatment (Cowan et al, 2021, Bienvenu et al, 2018, Shapiro 2013).

Manual push administration of a [redacted] rozanolixizumab SC dose has been performed ([redacted]) in an ongoing [redacted] healthy volunteer study (UP0106). Preliminary pharmacokinetic and local tolerability data suggest that administration via manual push is comparable to administration using a syringe driver.

MG0020 will be conducted in study participants with gMG to evaluate the relative preference for HCP versus self-administration and the manual push method versus the syringe driver mode of administration in this patient population.

An open-label design is required as the study will evaluate self-administration of rozanolixizumab using the syringe driver and manual push methods.

A crossover design is used to allow each study participant to evaluate both methods of self-administration.

4.3 Justification for dose

The proposed weight-tiered doses of rozanolixizumab in Europe and Canada, [redacted] (see Table 1-2), are equivalent to the weight-tiered dose approximating [redacted] evaluated in the Phase 3 studies in gMG. Based on the positive benefit-risk profile of the studied weight-tiered doses of [redacted] rozanolixizumab in the MG0003 Phase 3 pivotal study in gMG, a dose of [redacted] is proposed for this study as no consistent incremental benefit of the [redacted] dose compared with the [redacted] dose was observed. Pharmacodynamic data showed a desired reduction in IgG levels of [redacted] from Baseline for both weight-tiered doses.

The proposed weight-tiered doses of rozanolixizumab in the US, [redacted] (see Table 1-2), are consistent with the recommended doses in the FDA-approved US Prescribing Information.

4.4 End of Study definition

A participant is considered to have completed the study if he/she has:

- Completed all periods of the study including the End of Study Visit (Visit 21)

or

- Completed all the Treatment Periods, including the End of Treatment Visit, and has subsequently moved on to a post-trial access program

or

- Completed all the Treatment Periods, including the End of Treatment Visit, and has subsequently moved on to commercially available rozanolixizumab

Participants moving to either a post-trial access program or commercially available rozanolixizumab during the Safety Follow-up Period must undergo an earlier End of Study Visit prior to this move.

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

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

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 inclusive at the time of signing the informed consent form (ICF).

Type of participant and disease characteristics

2. Study participant must have a documented diagnosis of gMG, based on study participant's history and supported by previous evaluations.

3. Study participant is willing to perform and capable of performing (according to the investigator's judgment) home self-administration by using both the syringe driver method and the manual push method (or caregiver is willing to perform and capable of performing the administration).

4. Study participant is considered by the investigator for additional rozanolixizumab treatment with the posology proposed in this study.

5a. Study participant has a serum total IgG level ≤16g/L and ≥5.5g/L at Screening (Visit 1) (except for study participants receiving an anti-FcRn treatment within 8 weeks prior to the Screening Visit, who must have a serum total IgG level at the Screening Visit ≥2g/L).

Weight

6. Body weight ≥35kg at Screening (Visit 1).

Sex

7. Study participants may be male or female:

   a) 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:

      i) Not a woman of childbearing potential (WOCBP) as defined in Appendix 4 (Section 10.4)

      OR

      ii) 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 medication. The study participant must have a negative serum pregnancy test at Screening (Visit 1) and a negative urine pregnancy test before the first dose of study medication during the Training Period and each of the Self-administration Periods.

Informed consent

8. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICF.

9. Study participant is considered reliable and capable of adhering to the protocol visit schedule, or medication intake according to the judgment of the investigator.

5.2 Exclusion criteria

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

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

2. Study participant has a history of alcohol use disorder or other substance use disorder (as per Diagnostic and Statistical Manual of Mental Disorders-5 [American Psychiatric Association, 2013]) within the previous 12 months before Screening (Visit 1).

3a. Study participant has a known hypersensitivity to other anti-FcRn medications, to any components of the study medication, to any of the excipients (including [redacted]), or has a known history of [redacted], since both [redacted] and [redacted] are constituents of the rozanolixizumab formulation.

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

5. Study participant has a clinically relevant active infection or a history of serious infection (resulting in hospitalization or requiring IV antibiotic treatment) within 6 weeks before the Baseline Visit (Visit 2 [redacted]

6a. The study participant previously participated in any rozanolixizumab MG study and met any mandatory withdrawal criteria (unless the reason is directly related to MG0020 participation) or mandatory study drug discontinuation criteria.

Prior or concomitant therapy

7a. Study participant has received a live vaccination within 4 weeks before starting treatment, or a BCG vaccine within 1 year before starting treatment; or intends to have a live vaccination during the course of the study or within 8 weeks following the last dose of rozanolixizumab.

8. Study participant received treatment with rituximab or other anti-CD20 or anti-CD19 medication within [redacted] before the Baseline Visit (Visit 2 [redacted]

9a. Study participant has received treatment with IVIg, SC Ig, or PEX within [redacted] before the Baseline Visit (Visit 2 [redacted] treatment with efgartigimod within [redacted] before the Baseline Visit; treatment with eculizumab [redacted] before the Baseline Visit; treatment with ravulizumab within [redacted] before the Baseline Visit or prior treatment with cyclophosphamide.

Diagnostic assessments

10. Study participant has absolute neutrophil count <1500 cells/mm^3 at Screening (Visit 1).

11. 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.

12. Study participant has renal impairment, defined as glomerular filtration rate less than 30mL/min/1.73m^2 at Screening (Visit 1).

13. Study participant has 12-lead electrocardiogram (ECG) at Screening (Visit 1) 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.

14. Study participant has >3.0xULN of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) at Screening (Visit 1).

   – If participant has >upper limit of normal (ULN) for ALT, AST, or ALP that does not meet the exclusion limit at Screening (Visit 1), repeat the tests, if possible, before dosing to ensure there is no further ongoing clinically relevant increase.

- For participants with a Baseline result >ULN for ALT, AST, ALP, or total bilirubin, a Baseline diagnosis and/or the cause of any clinically meaningful elevation must be recorded in the CRF.

15. Study participant has bilirubin >1.5xULN at Screening (Visit 1) (unless confirmed Gilbert's syndrome). If participant has elevations only in total bilirubin, the fractionate bilirubin needs to be checked, to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%).
16. Current unstable liver or biliary disease, at Screening (Visit 1), per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice, or cirrhosis. NOTE: with exception of stable hepatobiliary conditions (including Gilbert's syndrome, asymptomatic gallstones).
17. Presence of Hepatitis B surface antigen (HBsAg) or positive Hepatitis C antibody test result at Screening (Visit 1). Note: a study participant with a positive hepatitis C antibody test due to prior resolved disease can be enrolled only if a confirmatory negative Hepatitis C RNA test is obtained.
18. Study participant tests positive for human immunodeficiency virus at Screening (Visit 1).

19a. Study participant has active malignant neoplastic disease or history of malignant neoplastic disease within 5 years of study entry before Screening (Visit 1) (except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the uterine cervix that have been definitively treated with standard of care approaches or thymoma that did not require chemotherapy and/or radiotherapy after removal).

Other

20. Study participant has a lifetime history of [redacted] as indicated by a positive response (Yes) to either Question 4 or Question 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) at Screening (Visit 1).

5.3 Lifestyle restrictions

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

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

5.4 Screen failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently allocated to treatment during the Training Period. 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 publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Additional rescreening of these individuals following upfront discussion with

the medical monitor or study physician might be allowed. Rescreened study participants should be assigned a new participant number for rescreening.

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 consultation with the sponsor's medical monitor or study physician. If the normalization of the test result occurs within the Screening Period, then no other Screening procedures need to be repeated.

6 STUDY TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol. Treatments in this study vary based on either an approved label in a region (US) or a proposed dosing under review in a region (Europe and Canada).

6.1 Treatments administered

Study treatment name	Treatment	Treatment
Intervention name	Rozanolixizumab	Rozanolixizumab
Type	Biologic	Biologic
Dose formulation	[redacted]	[redacted]
Unit dose strength(s)	[redacted]	
Dosage level(s) US	[redacted] fixed doses of [redacted] for study participants <50kg, [redacted] for study participants ≥50kg to <100kg or [redacted] for study participants ≥100kg.	[redacted] fixed doses of [redacted] for study participants <50kg, [redacted] for study participants ≥50kg to <100kg or [redacted] for study participants ≥100kg.
Dosage level(s) Europe and Canada	[redacted] fixed doses of [redacted] for participants ≥35kg to <50kg, [redacted] for study participants ≥50kg to <70kg, [redacted] for study participants ≥70kg to <100kg or [redacted] for study participants ≥100kg.	[redacted] fixed doses of [redacted] for participants ≥35kg to <50kg, [redacted] for study participants ≥50kg to <70kg, [redacted] for study participants ≥70kg to <100kg or [redacted] for study participants ≥100kg.
Route of administration	Subcutaneous infusion via syringe driver	Subcutaneous infusion via manual push
Use	Experimental	Experimental
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor

Packaging and labeling	Packaging will be described in the IMP Handling Manual. Packaging will be labeled as required per country requirement.	Packaging will be described in the IMP Handling Manual. Packaging will be labeled as required per country requirement.
Current/Former name(s) or alias(es)	UCB7665	UCB7665

Abbreviations: IMP=investigational medicinal product; NIMP=noninvestigational medicinal product

6.1.1 Medical devices

Other medical devices (not manufactured by or for UCB) are provided for SC infusion. Medical devices used as part of this clinical study will be used within their approved intended use. Proof of registration will be kept on file and available for inspection.

Instructions for use are provided in the IMP Handling Manual.

All adverse device effects (ADEs), serious adverse device effects (SADEs), and device deficiencies (including malfunctions, use errors, and inadequate labeling) shall be documented and reported by the investigator throughout the study (see Section 8.3.9) and appropriately managed by the sponsor.

6.2 Preparation, handling, storage, and accountability requirements

Details on the preparation of study medication for infusion, methods of administration, rate of infusion, as well as supply of kits for self-administration are provided in the IMP Handling Manual.

The investigator or designee and the study participant (at home self-administration visits) must confirm that appropriate temperature conditions have been maintained during transit for all study medication received, and any discrepancies are reported and resolved before use of the study medication.

Only participants enrolled in the study may receive study medication. All study medication 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 or authorized site staff and to the study participant or caregiver during home self-administration visits.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study medication 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 and in the IMP Handling Manual.

Further guidance and information for the final disposal of unused study medication are provided in the Study Reference Manual.

6.2.1 Drug/Device accountability

A Drug/Device 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 or 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 or partially used containers), 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 and blinding

This is an open-label study without blinding; however, the order that a specific intervention is to be taken by a participant will be assigned using an interactive response technology (IRT). Potential bias will be reduced using central randomization. The IRT will be used for assigning eligible participants to a treatment sequence (see Table 1-1) based on a predetermined production randomization and/or packaging schedule provided by UCB (or designee). The randomization schedule will be produced by the IRT vendor. The IRT will generate individual assignments for kits of study medication, as appropriate, according to the visit schedule.

To enroll a study participant (Visit 1), the investigator or designee will contact the IRT and provide brief details about the participant to be enrolled. Each participant will receive a 5-digit number assigned at Screening 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.

At Visit 2 (Baseline), the investigator or designee will contact the IRT to confirm participant's eligibility (including the participant's body weight as recorded at Screening). The IRT will allocate kit numbers to the participant.

At Visit 8, in order to randomize a participant to a treatment sequence (see Table 1-1), 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 CRF. The site will record the intervention assignment on the applicable CRF, if required.

6.4 Treatment compliance

Participants must return all used and unused vials as well as all equipment and ancillary materials used for IMP administration at Visit 13 ([redacted]) and Visit 19 ([redacted]). Drug accountability must be done in the participant's presence in order to obtain explanations regarding discrepancies in compliance with the dosing regimen. Drug accountability must be recorded on the Drug Accountability form.

The intended dose is based on Table 1-2 (the acceptable administered range is ≥80% of the total volume used based on visual inspection of the residual IMP at site).

For home self-administrations, the study participant should provide a respective photographic documentation to allow the HCP to assess the volume of IMP administered, using the mobile phone provided by UCB. Further details are provided in the IMP Handling Manual.

If a participant is found to be persistently noncompliant (eg, does not comply with visit schedule or protocol procedures), the sponsor, in conjunction with the investigator, will make a decision as to whether the participant should be withdrawn from the study.

6.5 Concomitant medication(s)/treatment(s)

6.5.1 Permitted concomitant treatments (medications and therapies)

Concomitant medications listed in Table 6-1 are permitted during the study for the treatment of gMG. With the exception of corticosteroids and acetylcholinesterase inhibitors, the dose of permitted concomitant medications should be maintained, if possible.

If a study participant receives a COVID-19 vaccine, the product name and date of administration(s) should be captured in the CRF as a concomitant medication.

Table 6-1: Permitted concomitant treatments

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

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

6.5.2 Prohibited concomitant treatments (medications and therapies)

The following concomitant medications are prohibited during the study:

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

6.5.3 Treatments specific to NMJ interference

Treatments that could interfere with the function of the NMJ (and which therefore could impair study participants with gMG) 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 (MGFA) medication list (https://myasthenia.org/What-is-MG/MG-Management/Cautionary-Drugs). The benefit-risk of starting these medications should be carefully considered by the investigator, and where possible, the investigator will discuss with the medical monitor and/or sponsor's study physician before initiating therapy that can affect the NMJ.

6.5.4 Rescue medication

The study site will supply rescue therapy that will be obtained locally. Rescue therapy will be given as per standard of care and at the discretion of the investigator. Study participants who continue to experience moderate to severe symptoms despite treatment with rozanolixizumab may receive treatment with the following as rescue therapy:

- Intravenous Ig (ATC code: [redacted] [Immunoglobulins, normal human])
- Subcutaneous Ig (ATC code: [redacted] [Immunoglobulins, normal human])
- Plasma exchange or plasmapheresis
- Intravenous corticosteroids at a higher dose than previous oral dose (ATC code: [redacted] [Corticosteroids for systemic use, plain])

Study participants who received treatment with rescue therapy will be withdrawn from the study.

The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

6.6 Dose modification

There is no dose modification allowed in this study, ie, study participants must maintain their dose (based on body weight as recorded at Screening) throughout.

6.7 Criteria for study hold or dosing stoppage

Not applicable.

6.8 Treatment after the end of the study

Study participants who have completed all Treatment Periods (including the End of Treatment Visit) will have the option to subsequently move, at the discretion of the investigator, into either a post-trial access program for rozanolixizumab (if available according to local guidance) or on to commercially available rozanolixizumab.

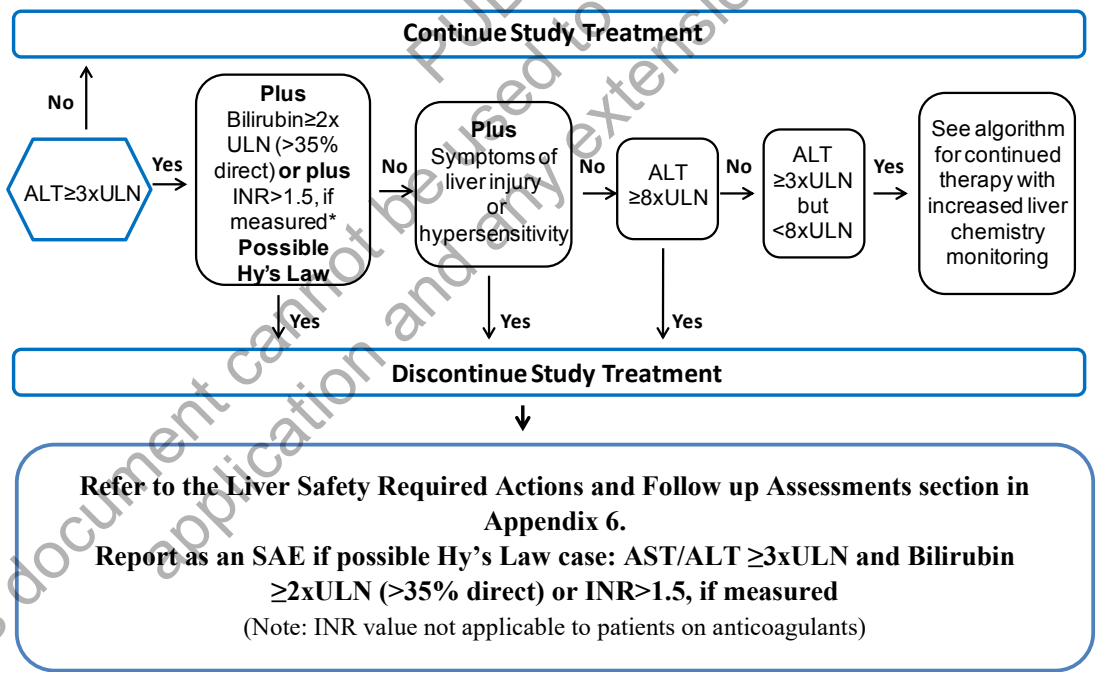
7 DISCONTINUATION OF STUDY MEDICATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

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 and Figure 7-2 or if the investigator believes that it is in best interest of the participant.

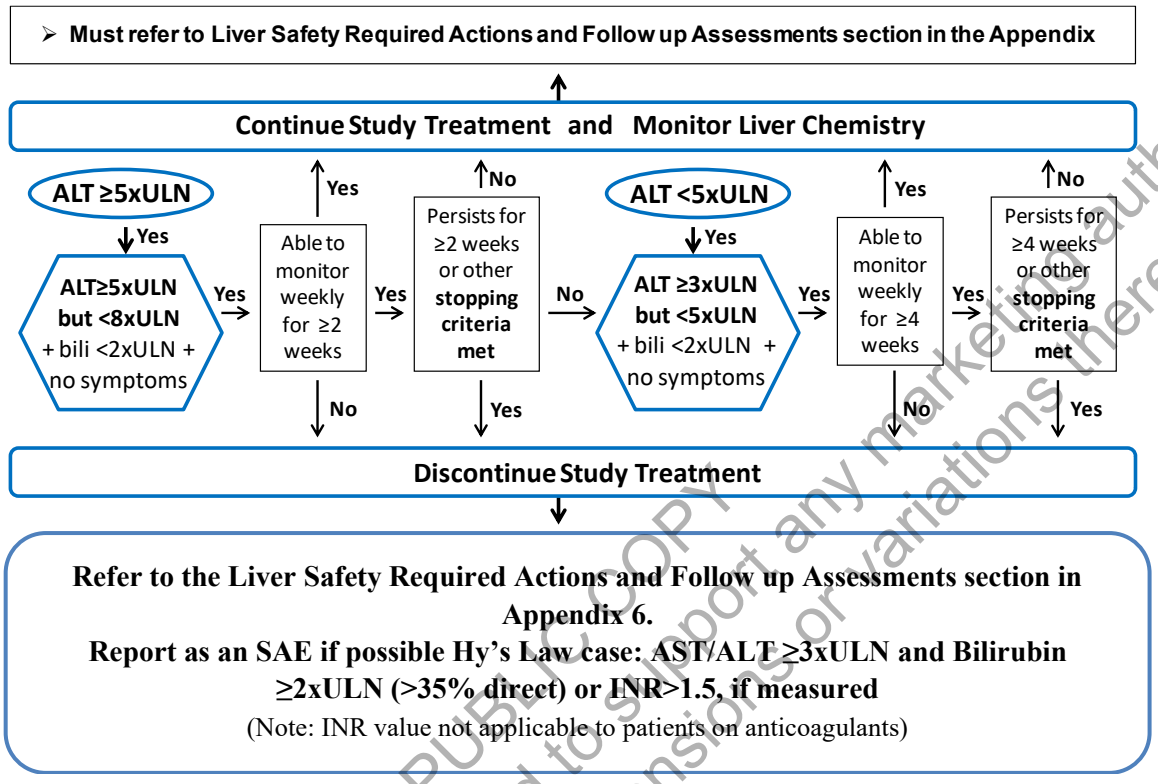
Figure 7-1: Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm



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

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 ≥3xULN but <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 Temporary IMP discontinuation

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

1. Symptomatic cases of confirmed COVID-19 infection. The IMP may be restarted if clinically appropriate when signs and symptoms have resolved and in agreement with local guidelines.
2. Study participant has a first diagnosis of suspected aseptic meningitis. The IMP may be restarted if clinically appropriate when signs and symptoms have resolved. Refer to Section 7.1.3 for permanent discontinuation criteria (criterion #9).

Study participants ***may be*** TEMPORARILY discontinued from the IMP if 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 13 [Section 10.13.2]).

2. The study participant develops a nonserious 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 13 [Section 10.13.2]).
3. Asymptomatic or suspected cases of COVID-19 infection. The IMP may be restarted when clinically appropriate as deemed by the investigator and in agreement with local guidelines.
4. Study participant may be temporarily discontinued from study medication at the discretion of the investigator in cases deemed strictly necessary for the participant's medical care. Efforts should be made to keep the length of temporary discontinuation to a minimum.

The investigator should discuss with the medical monitor and/or sponsor's study physician before reinitiating the IMP. As appropriate, virtual assessments could continue (eg, AE collection, patient-reported outcome [PRO] assessments as per contingency measures described in Section 8).

If IMP treatment is resumed, the study participant should continue with the next dose as previously scheduled and subsequently follow the visit schedule as described in the protocol. The CRF should be completed accordingly, including the information if the visit was impacted by COVID-19 infection.

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

7.1.3 Study medication permanent discontinuation criteria

Study participants **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.

2a. Study participant has new onset or reoccurrence of malignant neoplastic disease (except for superficial basal or squamous cell carcinoma of the skin not requiring targeted biological therapy, chemotherapy or radiation).3. Study participant experiences an infective episode including but not limited to bacteremia or sepsis, infectious meningitis, septic arthritis, osteomyelitis, complicated pneumonia, or visceral abscess, which may or may not result in hospitalization during a Treatment Period (Appendix 13 [Section 10.13.2]). This list is not intended to be all inclusive, and the investigator is expected to apply their judgment on continuing IMP based on the clinical situation.

4. Study participant meets 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 LTBI.
6. If a NTMBI is identified during a study, the same withdrawal procedures as those used for an active TB infection identified during the study should be followed.

7. Study participant has an AE of severe or serious infusion-related reaction, hypersensitivity, or anaphylactic reaction requiring corticosteroid and/or epinephrine therapy (Sampson et al, 2006; Appendix 13 [Section 10.13.1]).
8. Study participant takes prohibited concomitant medications as defined in this protocol.
9. Study participant has a recurrence of aseptic meningitis (see also Appendix 14 [Section 10.14]).
10. Study participant has [redacted] as indicated by a positive response (Yes) to either Question 4 or Question 5 of the "Since Last Visit" version of the C-SSRS. The study participants should be referred immediately to a mental healthcare professional.

Study participants **may** permanently discontinue rozanolixizumab at the discretion of the investigator (following consultation with the sponsor's medical monitor or study physician if necessary) if the study participant is noncompliant or becomes unable to comply with the study procedures or medications in the opinion of the investigator.

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).

Study participants who permanently discontinue study medication should undergo an Early Withdrawal Visit and move into the Safety Follow-up Period. Handling of replacement participants is described in Section 7.2.

7.2 Participant discontinuation/withdrawal from the study

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

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

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

A participant **may** withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

If study participants discontinue before the end of the Self-administration Period 2, replacement participants may be considered at the discretion of the sponsor, depending on how the discontinuation affects the study's ability to collect sufficient data to support the study objectives. For each case of participant discontinuation, the decision on whether to recruit a replacement and the reason behind the decision will be documented.

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

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

See the Schedule of Activities in Section 1.3 for data to be collected at the Early Withdrawal Visit and for any further evaluations that need to be completed. In all cases except for withdrawal of consent, the study participant should also return to the site for an End of Study Visit.

Investigators should contact the medical monitor, whenever possible, to discuss the withdrawal of a study participant in advance.

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 CRF must document the primary reason for withdrawal.

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

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 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, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within 4 weeks of the assessment timepoint in the Schedule of Activities.

An Unscheduled Visit can be conducted at the discretion of the investigator (eg, due to an AE) (see Section 4.1.1).

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, and other laboratory testing and assessments may be performed as clinically indicated at the discretion of the investigator.

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

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500mL.

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

Not applicable.

8.2 Safety assessments

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

8.2.1 Safe and successful self-administration

Safe and successful self-administration as defined in the endpoints (Section 3) will be evaluated at the site by the HCP supervising the self-administration process and via a mandatory direct contact with the study participant via telephone or video call as soon as possible after each home self-administration. The direct telephone or video contact with the study participant will also be used to document the study participant's self-assessment on the process of home self-administration, eg, on potential challenges and deficiencies.

The HCP evaluation materials supporting the collection of data for Visit 13 ([redacted]) and Visit 19 ([redacted]) relating to primary endpoints are provided in Appendix 15 (Section 10.15).

8.2.2 Participant's preferred method of rozanolixizumab administration questions

The study participants will be asked to evaluate their relative preference for SC infusions performed by an HCP versus self-administration and the preference for the manual push method versus the use of a syringe driver for self-administration.

Materials supporting the collection of data relating to the participant's preferred method of rozanolixizumab administration are provided in Appendix 16 (Section 10.16).

8.2.3 Self-Injection Assessment Questionnaire (Infusion version)

[redacted]

8.2.4 Myasthenia Gravis Activities of Daily Living

The MG-ADL is an 8-item PRO instrument developed on the basis of the QMG (Wolfe et al, 1999). 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; and it was demonstrated that a 2-point improvement indicates clinical improvement (Muppidi, 2012; Muppidi et al, 2011). The total MG-ADL score ranges from 0 to 24, with a higher score indicating more disability (Appendix 17 [Section 10.17]).

The MG-ADL is being utilized in MG0020 as a parameter of symptom monitoring rather than an assessment of treatment benefit.

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

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

8.2.5 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, gastrointestinal, neurological, and musculoskeletal 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.

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

A full neurological examination should be performed for any study participant who experiences severe and/or serious headache and for any study participant who experiences features suggestive of aseptic meningitis (Appendix 14 [Section 10.14]). A full neurological assessment will include: (1) General appearance, including posture, motor activity and meningeal signs and, if indicated, the following assessments will be performed; (2) Cranial nerves examination; (3) Motor system examination, including muscle tone and power and sensory system examination – light touch; (4) Reflexes, including deep tendon reflexes; (5) Coordination, gait (if possible); and (6) Fundoscopy.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

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

8.2.6 Vital signs

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

Blood pressure and pulse 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.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 1 blood pressure measurement. The blood pressure reading will be recorded on the CRF.

8.2.7 Electrocardiograms

Twelve-lead ECGs will be obtained as outlined in the Schedule of Activities using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

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

The ECGs will be read locally. All ECG readings from an individual study participant should be read by the same reader, if possible. Findings will be recorded in the CRF.

8.2.8 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 CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 8 weeks after the last dose of study medication should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal or baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

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

If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE), then the results must be recorded in the CRF.

8.2.9 Suicidal risk monitoring

A full C-SSRS assessment (Columbia University Medical Center, 2008) will be performed by trained study personnel for Screening (Visit 1) and Baseline (Visit 2 [redacted]). For subsequent visits, a full C-SSRS assessment will only be performed if a study participant has a positive response to the query for suicidality. See Section 7.1.3 for related criteria for study medication permanent discontinuation.

8.2.10 Assessment and management of TB and TB risk factors

Precautions are being taken within this protocol to monitor the risk of TB infection in this study (see Exclusion Criterion 4). Any presumptive diagnosis or diagnosis of a TB infection is a

reportable event. Assessment and management of TB and TB risk factors should follow local or national guidelines.

8.2.10.1 Tuberculosis assessment

Monitoring for TB during the study

Study participants will be monitored for signs and symptoms of TB using routine pharmacovigilance measures for AEs. Study participants reporting AEs related to signs and symptoms of TB will be evaluated for LTB and active TB according to the local medical practice guidelines.

Confirmed LTBI, active TB, and NTMBI must be reported to UCB immediately regardless of seriousness using the SAE Report Form and the study participants must be immediately withdrawn from the study treatment. Additional information received by the investigator should be provided within 24 hours of awareness.

Once withdrawn from study treatment, study participants should return for the Early Withdrawal Visit.

Tuberculosis signs and symptoms questionnaire

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 (Appendix 19 [Section 10.19]), 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 may trigger further assessment to determine if the participant has either LTBI and must receive prophylactic LTBI therapy or treatment for active TB infection and screen failed/not randomized in the study. As an example, a participant who answers "Yes" at Screening to the question "Has the subject been in close (eg, sleeping in the same room) contact with an individual with active TB, or an individual who has recently been treated for TB?" should not be allowed into the study pending further assessments per local and national guidelines.

8.2.11 COVID-19 precautions

This clinical study is likely to run during the ongoing COVID-19 pandemic and will be done in accordance with the clinical study center COVID-19 risk mitigation policy, which documents the clinical study center's COVID-19 virus testing strategy for study participants and staff, social distancing measures, and management of COVID-19-like symptoms. The risk to study participants will be re-evaluated by the sponsor throughout the COVID-19 pandemic if deemed necessary by emerging events.

Study participants will be closely monitored for any signs and symptoms of COVID-19 (ie, fever, dysgeusia [taste loss or change], dysosmia [loss or distortion or change of smell], or persistent cough) throughout the study. If symptoms and/or clinical signs of infection are identified, the investigator will decide whether these findings will be handled as suspected or confirmed COVID-19 (see Section 7.1.2 for COVID-19-related temporary IMP discontinuation

criteria). The use of testing for severe acute respiratory syndrome coronavirus 2 will be determined by reference to the regulatory and healthcare guidance in place locally at the time.

8.2.12 MGFA classification

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

8.3 Adverse events and serious adverse events

The definitions of AE and SAE can be found in Appendix 3 (Section 10.3). Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

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

For results disclosure on public registries (eg, ClinicalTrials.gov), treatment-emergent AEs and treatment-emergent SAEs will be published.

The definitions of device-related safety events, ADEs and SADEs can be found in Appendix 7 (Section 10.7). Device deficiencies are addressed in Appendix 7.

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs and SAEs will be collected from the signing of the ICF until the End of Study Visit (Visit 21) at the time points specified in the Schedule of Activities (Section 1.3).

All TEAEs occurring from the first administration of rozanolixizumab during the Training Period up to the first administration of rozanolixizumab in Self-administration Period 1 will be considered treatment-emergent in the Training Period.

All TEAEs occurring during Self-administration Period 1 up to the first administration of rozanolixizumab in Self-administration Period 2 will be considered treatment-emergent in Self-administration Period 1.

All TEAEs occurring during Self-administration Period 2 up to 8 weeks after the last administration of rozanolixizumab will be considered treatment-emergent in Self-administration Period 2.

Local site reaction AEs will be considered treatment-emergent up to 24 hours after each administration during the Training Period and Self-administration Periods.

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

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

The investigator is specifically requested to collect and report to UCB (or its representative) any SAEs (even if the investigator is certain that they are in no way associated with the study medication), up to 30 days from the end of the study for each participant, and to also inform 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 or contacts. All SAEs, nonserious AEs of special interest (as defined in Section 8.3.6), and AESMs (as defined in Section 8.3.8) will be followed until resolution, stabilization, the investigator determines that it is no longer clinically significant, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

Prompt notification of an SAE by the investigator to the sponsor 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 (IRBs)/Independent Ethics Committees (IECs), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary. SUSAR reporting will be in adherence to requirements of EU pharmacovigilance legislation, clinical trial legislation and guidance, Clinical Trial Regulation EU 536/2014; CT-3, and all other applicable local regulations.

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

8.3.5 Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study treatment and until 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 immediately stop the intake of the study medication.
- The participant should return for an Early Withdrawal Visit.
- Safety follow-up should be scheduled after the participant has discontinued her study medication.

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 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 or compound.For rozanolixizumab, the following events require immediate reporting (within 24 hours regardless of seriousness) to UCB:

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

8.3.7 Medication errors associated with self-administration

The definitions of medication errors can be found in Appendix 12 (Section 10.12). The medication errors reported by the study participant (or, when appropriate, by a caregiver, or observed by the investigator) shall be recorded in the paper Medication Error form by the investigator and emailed to the Global mailbox: DS_ICT@ucb.com. The fax and mobile number are also provided in case of urgent necessity. All medication errors except those considered as AESM (see Section 8.3.8) will be recorded and reported to the sponsor or designee within 7 days of awareness. Medication errors that are considered AESM (see Section 8.3.8) will be recorded and reported within 24 hours following the SAE recording and reporting procedures as indicated in Appendix 3 (Section 10.3) and using the Medication Error form. If the medication error is observed from other periods of the study (apart from Self-administration Periods), the medical monitor should be informed for further advice.

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of a medication error and remain responsible for following up medication errors that are considered AESM (see Section 8.3.8).

8.3.8 Adverse events of special monitoring

An AESM is a product-specific AE, adverse reaction, or safety topic requiring special monitoring by UCB.

For rozanolixizumab, the following events require immediate reporting (within 24 hours regardless of seriousness) to UCB:

- Severe and/or serious headache
- Suspected aseptic meningitis
- Medication error associated with adverse reaction(s)

Procedures for the management of AESM are provided in Appendix 14 (Section 10.14).

Although infections and hypersensitivity reactions including infusion-related reactions and anaphylaxis are not classified as AESM, these AEs will be monitored by the investigator. If such an event is suspected, it should be managed according to the guidance provided in Appendix 13 (Section 10.13). Suspected anaphylaxis reactions should be diagnosed using Sampson's Criteria (Sampson et al, 2006).

All AESM will follow the SAE recording and reporting procedures as indicated in Appendix 3 (Section 10.3). Medication error associated with adverse reaction(s) should also be assessed, recorded, and reported using the Medication Error form as indicated in Section 8.3.7.

8.3.9 Medical device – adverse events (ADEs, unanticipated ADEs, SAEs, SADEs, and unanticipated SADEs) and device deficiencies

Medical devices are being provided for administration of IMP in this study. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of ADEs, SADEs, and device deficiencies that occur during the study with such devices.

Adverse events will be reported according to the ISO 14155:2020, while recognizing and following requirements including reporting timelines specified in other specific laws, regulations, directives, standards and/or guidelines as appropriate and as required by the countries in which the clinical investigation is conducted.

The definition of an ADE, SADE, and device deficiency can be found in Appendix 7 (Section 10.7).

NOTE: Events fulfilling the definition of an AE or SAE will also follow the processes outlined in Section 8.3.3 and Appendix 3 (Section 10.3) of the protocol.

8.3.9.1 Time period for detecting ADEs and device deficiencies

Any ADEs or device deficiencies of the device will be detected, documented, and reported during all periods of the study in which the medical device is used.

If the investigator learns of any deficiency at any time after a participant has been discharged from the study, and such event(s) is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting medical device deficiency is provided in Appendix 7 (Section 10.7).

8.3.9.2 Follow-up of ADEs and device deficiencies

Follow-up applies to all study participants, including those who discontinue study medication and/or the study.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

8.3.9.3 Prompt reporting of ADEs and device deficiencies to sponsor

Any ADEs or device deficiencies will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of an ADE or device deficiency.

The Adverse Event and Device Deficiency Report Form will be sent to the sponsor using the paper form.

The sponsor will then notify the ADE and device deficiency reports to the corresponding device manufacturer. The device manufacturer is responsible for the subsequent vigilance evaluation and reporting, if applicable.

8.3.9.4 Regulatory reporting requirements for ADEs and device deficiencies

The investigator will promptly report all ADEs and device deficiencies occurring with any medical device provided for use to the sponsor. The sponsor will then notify the device manufacturer in order for the device manufacturer to fulfill vigilance responsibilities.

The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB or IEC.

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.

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

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

8.5 Treatment of overdose

Unintentional overdose events are considered Medication Errors and should be reported as described in Section 8.3.7 and Section 8.3.8.

For the purpose of this study an overdose will be defined as a dose that is 10% over the acceptable variance of 20% of the intended dose. For study participants assigned a [redacted] dose, a rozanolixizumab dose of [redacted] at any time will be considered an overdose. For study participants assigned a [redacted] dose, a rozanolixizumab dose of [redacted] at any time will be considered an overdose. For study participants assigned a dose of [redacted], a rozanolixizumab dose of [redacted] at any time will be considered an overdose. For study participants assigned a [redacted] dose, a rozanolixizumab dose of [redacted] at any time will be considered an overdose.

Intentional overdose events (eg, suicide attempt) are not considered Medication Errors and must be reported as an SAE as described in Section 8.3.1.

UCB does not recommend specific treatment for an overdose. Single subcutaneous dose of up to [redacted] and [redacted] subcutaneous doses of around [redacted] for up to [redacted] weeks have been administered per protocol in clinical studies without dose limiting toxicity.

However, 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 pharmacokinetic analysis within 72 hours from the date of the last dose of study medication 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 CRF.

Decisions regarding dose interruptions will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.6 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study. Pharmacokinetic blood sample in the event of PDILI could be collected as described in Appendix 6 (Section 10.6).

8.7 Pharmacodynamics

Venous blood samples will be collected at time points specified in the Schedule of Activities (Section 1.3) for measurement of serum total IgG concentrations.

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

8.8 Biomarkers

Blood samples for exploratory safety biomarker analysis will be collected at Baseline for all study participants. In study participants who experience severe and/or serious headaches or features suggestive of aseptic meningitis, samples should also be collected 4 hours after the onset of the event, or otherwise as soon as possible within 72 hours after the onset of the event.

These samples will only ever be used to further explore if biomarkers can advance the understanding of the pathological drivers of the AESM of severe and/or serious headache or suspected aseptic meningitis.

If not used immediately, these samples will be stored at -80°C for up to 20 years for later exploratory analyses.

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

8.9 Immunogenicity assessments

Antibodies to rozanolixizumab will be evaluated in serum samples collected from all participants according to the Schedule of Activities (Section 1.3). Additionally, serum samples should also be collected at the final visit from participants who discontinued study medication or were withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee.

Serum samples will be screened for antibodies binding to rozanolixizumab and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to rozanolixizumab and/or further characterize the immunogenicity of rozanolixizumab.

The detection and characterization of antibodies to rozanolixizumab will be performed using a validated assay method by or under the supervision of the sponsor. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study medication(s). Samples may be stored for a maximum of 20 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the sponsor to enable further analysis of immune responses to rozanolixizumab. In addition, surplus immunogenicity assessment samples may be stored and used for potential future biomarker research (including assay development and optimization), but not for future genetic biomarker research.

8.10 Medical resource utilization and health economics

Medical resource utilization and health economics parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

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

9.1 Definition of analysis sets

- Enrolled Set: All study participants who have signed the informed consent form.
- Safety Set: All study participants who received at least 1 dose of IMP (partial or full). Analysis of this set will be according to the administration method the participants actually used and will be used for analyses of safety and demography outcomes as required.
- Randomized Safety Set: All randomized study participants who received at least 1 dose of IMP (partial or full). Analysis of this set will be according to the administration method the participants actually used and will be used for analyses of safety, demography, and efficacy/outcomes.

- Full Analysis Set: All randomized study participants who received at least 1 dose of IMP (partial or full) and completed both Self-administration Periods.

9.2 General statistical considerations

All analyses will be performed using Statistical Analysis System (SAS®) version 9.3 or later (SAS Institute, Cary, NC, USA).

This is an estimation study design with no formal statistical hypothesis testing. The study will estimate the true population proportion and/or mean of self-administration–related endpoints for each self-administration method separately. Summary statistics for continuous variables will include number of available observations, mean, standard deviation, minimum, median, and maximum. For categorical variables, the number and proportion of participants will be presented. If not otherwise specified, summary statistics will be displayed by sequence and overall for demographics and by period and by self-administration method for period-specific assessments.

The Baseline value is defined as the last nonmissing measurement before the first administration at Visit 2 (Baseline) if not otherwise specified. All data recorded in the CRF and questionnaires will be listed.

9.3 Planned safety analyses

9.3.1 Analysis of the primary safety endpoint

The primary outcome variable is the proportion of study participants able to successfully self-administer rozanolixizumab using both syringe driver and the manual push method, respectively, during the Self-administration Periods. Successful self-administration includes a correct SC infusion with the intended dose at the correct infusion site. Treatment success will be defined as a successful self-administration at the last dose of self-administration using the syringe driver (Visit 13 [redacted] for Sequence 1 and Visit 19 [redacted] for Sequence 2) or via manual push (Visit 19 [redacted] for Sequence 1 and Visit 13 [redacted] for Sequence 2).

The number and proportion of participants deemed a treatment success will be tabulated separately for each self-administration method considering the Full Analysis Set. The proportion of success together with its 90% CI will be estimated for each self-administration with syringe driver and manual push.

9.3.2 Analysis of the secondary safety endpoint

The secondary endpoints of the occurrence of TEAEs after syringe driver or manual push self-administration, the occurrence of local site reactions up to 24 hours after each administration, and the occurrence of medication errors associated with adverse reactions will be summarized during the Self-administration Periods by the number and proportion of participants separately by self-administration method. This analysis will be based on the Randomized Safety Set. Occurrence of TEAEs and occurrence of local site reactions during the Training Period will also be summarized based on the Safety Set.

9.3.3 Other safety analyses

All other safety analyses will be based on the Randomized Safety Set or Safety Set as appropriate.

To assess the participant's experience with self-administration of SC infusions, a within-participant assessment of treatment success or nonsuccess with self-administration with the syringe drive or manual push will be tabulated through the use of a 2x2 table presenting the number and proportion of participants in each category. The last dose in each of the Self-administration Periods will be considered. The tabulation will be presented by sequence and overall.

The number and proportion of participants who achieved a successful self-administration at each of the 3 home self-administration visits will be tabulated separately for each self-administration method.

The participant's relative preference for SC infusions performed by an HCP versus self-administration as well as the preference for self-administration using the manual push method versus the use of a syringe driver will be summarized by sequence and overall.

The PRE-SIAQ (Infusion version) domain scores will be summarized at Baseline by sequence and overall. The POST-SIAQ (Infusion version) will be summarized for each self-administration method.

The change from Baseline MG-ADL score will be summarized by visit and period. Worsening in MG-ADL score will be defined by a $\geq$2 points increase from Baseline. Baseline value will be defined for each period separately. The number and proportion of study participants experiencing a worsening of their MG-ADL symptoms during the Self-administration Period will be summarized for each self-administration method. The proportion of worsening together with its 90% CI for each self-administration with syringe driver and manual push will be estimated considering the period and sequence as fixed effects and participant as a random effect to encompass the within-participant correlation.

All AE data will be listed, and no statistical testing will be performed. The frequency and severity of all TEAEs during the Self-administration Period will be presented separately for self-administration by syringe driver and via manual push separately by system organ class, high level term, and preferred term (Medical Dictionary for Regulatory Activities). The data will be displayed as number of participants experiencing the TEAE, percentage of participants, and number of TEAEs. The frequency and severity of all TEAEs during the Training Period will also be summarized.

The occurrence of TEAEs leading to permanent withdrawal of rozanolixizumab will be summarized during the Self-administration Periods by the number and proportion of participants separately by self-administration method. The occurrence of these TEAEs together with its 90% CI for each self-administration with syringe driver and manual push will be estimated considering the period and sequence as fixed effects and participant as a random effect to encompass the within-participant correlation. Occurrence of TEAEs leading to permanent withdrawal of rozanolixizumab during the Training Period will also be summarized.

Laboratory evaluations and vital signs as well as ECG data will be analyzed over time. All safety analyses will be based on the Safety Set and Randomized Safety Set as required.

Further analyses will be described in the Statistical Analysis Plan.

9.4 Planned efficacy/outcome analyses

Not applicable.

9.5 Other planned analyses

The IgG levels at each visit will be summarized. Spaghetti plots of the IgG levels over time will be presented.

Anti-rozanolixizumab antibodies (status and titer at trough) will be summarized.

9.6 Handling of protocol deviations

Important protocol deviations are 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 the review of important protocol deviations and the update (if necessary) of the important protocol deviation specification. Furthermore, overall trends in protocol deviations will be discussed at the Data Evaluation Meetings. Through this ongoing data cleaning and evaluation process, all decisions regarding important protocol deviations are made on an ongoing basis.

9.7 Handling of dropouts or missing data

All imputation of missing or partial dates for safety assessments will be detailed in the Statistical Analysis Plan.

A sensitivity analysis will be performed to assess the primary endpoint by imputing a self-administration failure for any Visit 13 ([redacted]) or Visit 19 ([redacted]) missed by a randomized participant considering the Randomized Safety Set.

9.8 Planned interim analysis and data monitoring

No interim analysis is planned.

A program Independent Data Monitoring Committee (pIDMC) has been established to provide a periodic review of safety data from studies across the rozanolixizumab program. Data emerging from this study will be included in the pIDMC periodic data reviews to assess the benefit-risk of rozanolixizumab.

9.9 Determination of sample size

This study will not be powered with respect to any endpoint and sample size is based on practical considerations. Confidence intervals expected to be observed under assumptions of the true success rate are provided in Table 9-1. It is planned to have a minimum of 30 participants in total (minimum 15 per sequence) who will perform self-administration using both the syringe driver and the manual push administration methods.

Table 9-1: Expected 90% confidence intervals considering different success rates and 30 study participants completing both Treatment Periods

Success rate	Expected 90% confidence interval [a]
80%	64.3 to 90.9
90%	76.1 to 97.2
97%	85.1 to 99.8

[a] Exact Clopper Pearson confidence intervals

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Regulatory and ethical considerations

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

The investigator/UCB will ensure that an appropriately constituted IRB/IEC that complies with the requirements of the current ICH-GCP version or applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to initiation of the study, the investigator/UCB will forward copies of the protocol, ICF, Investigator's Brochure, investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other participant-related documents to be used for the study to the IRB/IEC for its review and approval.

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

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

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

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

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

10.1.2 Financial disclosure

Insurance coverage will be handled according to local requirements.

Finance and insurance are addressed in the investigator and/or contract research organization agreements, as applicable.

10.1.3 Informed consent process

Participant's informed consent and caregiver's informed consent (if applicable) 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, the caregiver (if applicable [latest at the Baseline visit]), and by the person who conducted the informed consent discussion (investigator or designee). The participant, or his/her legal representative, and the caregiver (if applicable) 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 US must include the use of a Health Insurance Portability and Accountability Act authorization form.

The participant or the caregiver (if applicable) 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. A CRF must not be started, nor may any study specific procedure be performed for a given participant, without having obtained his/her written consent to participate in the study.

If the caregiver withdraws consent, the study participant can be treated on-site per protocol based on investigator decision.

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 and 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.

The contract between UCB and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

10.1.5 Committees structure

Given this is an open-label study, oversight of individual study data will be maintained on an ongoing basis by regular reviews of the safety data performed by the medical monitors in collaboration with the UCB study physician, patient safety representative, and program safety review team. In addition, selected safety data across all studies, including MG0020, will be reviewed at a program level by a pIDMC. Details of the pIDMC composition, processes, and responsibilities will be documented in the pIDMC Charter.

10.1.6 Dissemination of clinical study data

All Phase 1 to 4 clinical studies in patients will be registered on ClinicalTrials.gov with results posted after completion of the study.

A plain language summary of the results of all Phase 1 to 4 clinical studies will be developed and shared on UCB's website.

UCB is committed to submitting all Phase 2 to 4 clinical study results, irrespective of outcome, for publication in a credible, peer-reviewed journal. While there are some exceptions owing to intellectual property considerations in early clinical development, our policy is also to submit Phase 1 study results for publication in a peer-reviewed journal wherever possible.

Data from this study may be requested by qualified researchers 6 months after product approval in the US and/or Europe, or global development is discontinued, and 18 months after study completion. Investigators may request access to anonymized individual patient-level data and redacted study documents which may include analysis-ready datasets, study protocol, annotated CRFs, statistical analysis plan, dataset specifications, and clinical study report. Prior to use of the data, proposals need to be approved by an independent review panel at www.Vivli.org and a signed data sharing agreement will need to be executed. All documents are available in English

only, for a prespecified time, typically 12 months, on a password protected portal. This plan may change if the risk of re-identifying study participants is determined to be too high after the study is completed; in this case and to protect participants, individual patient-level data would not be made available.

10.1.7 Data quality assurance

All participant data relating to the study will be recorded on printed or electronic CRF 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 CRF.

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

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 CRF by authorized site personnel are accurate, legible, contemporaneous, original, and attributable 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 must be retained by the investigator for the minimum retention period mandatory under the applicable local laws and regulations. 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.

Quality tolerance limits will be established for the study using parameters related to patient safety reporting and reliability of study results. The parameters will be monitored throughout the study to identify systematic issues. Parameters used, parameter values, important deviations from the quality tolerance limits, and actions taken will be summarized in the clinical study report.

10.1.7.1 Case report form completion

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

Any change or correction to the CRF 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 electronic CRF.

Detailed instructions will be provided in the CRF Completion Guidelines.

10.1.7.2 Apps

Study participants will be provided with a mobile phone with a preinstalled application (app) that will collect data from each participant throughout the study. The app will support the participant to complete study-specific activities, as follows:

- Receiving reminders and notifications such as for the Visits, Patient Preference, MG-ADL, and the SIAQ questionnaires
- Scheduling visits with the investigator and/or authorized site representative(s)

The investigator and authorized site representative(s) will have access to a secure website portal via unique access credentials to access the study data from the completed activities noted above. Data will be reviewed by the investigator via the website portal view of participant-entered data results.

Furthermore, this app is designed to only record data to support study participation, and therefore it is neither designed nor intended to be used to collect or report safety-related information about the participant. The primary functionality of the app consists of data storage and communication of unmodified data. This stored data will not be used to make clinical patient management decisions. Therefore, the aggregated app data will not provide benefit to any single study participant.

Based on the current functionality, the app falls outside medical device regulations in the EU, US, and Japan. The app's medical device status must be re-assessed upon future modification of the patient facing app functionality. Furthermore, risks to the patients related to cybersecurity and patients' privacy must be addressed prior to app utilization in the clinical trial.

10.1.8 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 CRFs 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).

10.1.9 Study and site start and closure

The start of recruitment

The start of recruitment is the first participant's first visit and is also the start date of the clinical study.

Study/site termination

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

10.1.10 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 medication 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 CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 10-1: Protocol-required safety laboratory assessments

Laboratory Assessments	Parameters			
Hematology	Platelet count	White blood cell (WBC) Count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils		
	Red blood cell (RBC) count			
	Hemoglobin			
	Hematocrit			
Clinical Chemistry[a]	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein Albumin
	Glucose (fasting state preferred) [c]	Calcium	Alkaline phosphatase	C-reactive protein (CRP)
	Lactate dehydrogenase (LDH)	Triglycerides	Low-density lipoprotein (LDL) High-density lipoprotein (HDL)	Total Cholesterol
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	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only)			

Table 10-1: Protocol-required safety laboratory assessments

Laboratory Assessments	Parameters
	• Serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[b] • Serology testing (for human immunodeficiency virus, Hepatitis B, and Hepatitis C) All study-required laboratory assessments will be performed by a central laboratory. The results of each test must be entered into the CRF.
NOTES : For additional assessments that may be required in case of AESM of severe and/or serious headache or suspected aseptic meningitis, see Table 1-4. [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 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, may indicate severe liver injury (possible Hy's Law) and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis). [b] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC. [c] To be done at Screening only	

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

Definition of AE

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

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

Definition of SAE

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

A 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.

Recording and follow-up of AE and/or SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- 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 CRF 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 a 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 a SAE, NOT when it is rated as severe (eg, a severe AE may be either serious or not serious, depending on whether these criteria are also met).

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

Assessment of causality

- The investigator is obligated to assess the relationship between study medication and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study medication administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, 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 a 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 AEs of special interest.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide UCB with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

Reporting of SAEs

SAE reporting to UCB via an electronic data collection tool

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

- Contacts for SAE reporting can be found in SERIOUS ADVERSE EVENT REPORTING.

SAE reporting to UCB via paper CRF

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

10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

Definitions

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming 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.

Contraception guidance

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 the table below.

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 • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly effective methods that are user independent
Implantable progestogen only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomized partner Vasectomy is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study medication. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
NOTES: [a] In case of newly started contraception pills/IUDs, PI should consider the correct timing of starting/applying such methods in relation to the menstrual cycle and the manufacturing instruction as to 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.

Pregnancy testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test.
- Additional pregnancy testing should be performed as specified in the Schedule of Activities (Section 1.3) corresponding to protocol-defined time frame in Appendix 4 after the last dose of study medication and as required locally.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

- Pregnancy testing, with a sensitivity of ≥25mIU/mL will be performed. A serum pregnancy test will be completed at Screening. Urine pregnancy tests will be performed at all other timepoints.

Male participants with partners who become pregnant

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

Female participants who become pregnant

- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.
- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within one working day of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, the follow-up will be at least 12 months after the delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be a 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 a 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 CRF must document the primary reason for discontinuation of study medication.

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

Phase 3-4 liver chemistry stopping criteria are designed to assure participant safety and to evaluate liver event etiology.

Table 10-2: Phase 3-4 liver chemistry stopping criteria and follow-up assessments

Liver chemistry stopping criteria	
ALT-absolute	ALT ≥8x ULN
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 monitor	ALT ≥5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks ALT ≥3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks
Symptomatic[c]	ALT ≥3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Table 10-2: Phase 3-4 liver chemistry stopping criteria and follow-up assessments

Liver chemistry stopping criteria	
Suggested actions and follow-up assessments	
Actions	**Follow-up assessments**
• **Immediately** discontinue study medication. • Report the event to UCB within **24 hours.** • Complete the liver event CRF, and complete a SAE data collection tool if the event also met the criteria for a 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 unless allowed per protocol and UCB approval is granted. • If restart/rechallenge is **not allowed per protocol or not granted**, permanently discontinue study medication, and continue participant in the study for any protocol-specified follow-up assessments.Consider the need for a toxicology screening. **MONITORING:** **<u>For bilirubin or INR criteria</u>** • Repeat liver chemistry tests (include ALT, AST, ALP, bilirubin) and perform liver event follow-up assessments within **24 hours.** • Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to Baseline. • A specialist or hepatology consultation is recommended. **<u>For all other criteria</u>** • Repeat liver chemistry tests (include ALT, AST, ALP, 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 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 (eg, fatigue, nausea, vomiting, right upper quadrant pain), or hypersensitivity, on the AE CRF • Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications CRF. • Record alcohol use on the liver event alcohol intake CRF • Exclude pregnancy **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG or gamma globulins. • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James et al, 2009]). **NOTE: Not required in China**. • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete liver imaging and/or liver biopsy CRFs.

Table 10-2: Phase 3-4 liver chemistry stopping criteria and follow-up assessments

Liver chemistry stopping criteria

AE=adverse event; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CPK=creatine phosphokinase; CRF=case report form; HBsAg=hepatitis B surface antigen; HBcAb=hepatitis B core antibody; HPLC=high performance liquid chromatography; IgG=immunoglobulin G; IgM=immunoglobulin M; INR=international normalized ratio; LDH=lactate dehydrogenase; PCR=polymerase chain reaction; PK=pharmacokinetic; 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 a 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 PCR of hepatitis delta RNA virus (where needed) (Le Gal et al, 2005).

[f] PK sample may not be required for participants known to be receiving placebo or noncomparator interventions. Record the date/time of the PK blood sample draw and the date/time of the dose of study medication prior to the PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the (Study Reference Manual).

Table 10-3: Phase 3-4 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 UCB 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, ALP, 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.

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

10.7 Appendix 7: Medical device adverse events (AEs), adverse device effects (ADEs), serious adverse events (SAEs), and device deficiencies: Definition and procedures for recording, evaluating, follow-up, and reporting

The definitions and procedures detailed in this appendix are in accordance with ISO 14155.

The detection and documentation procedures described in this protocol also apply to medical devices provided for use in the study.

The Adverse Event and Device Deficiency Report Form will be sent to the sponsor using the paper form. The sponsor will then forward the ADE and device deficiency reports to the corresponding device manufacturer. The device manufacturer is responsible for the subsequent vigilance evaluation and reporting, if applicable.

10.7.1 Definition of AE and ADE

AE and ADE Definition
• An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, users, or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices. • An adverse device effect (ADE) is defined as an adverse event related to the use of an investigational medical device. This definition includes any adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.7.2 Definition of SAE, SADE, and unanticipated SADE

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

A SAE is an AE that:
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: 1. A life-threatening illness or injury. 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 2. A permanent impairment of a body structure or a body function 3. Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a SAE 4. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
c. Led to fetal distress, fetal death, or a congenital abnormality or birth defect

SADE definition
• A serious adverse device effect (SADE) is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
USADE definition
• An unanticipated serious adverse device effect (USADE) is a serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report (see Section 8.3.9).

10.7.3 Definition of device deficiency

Device deficiency definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.

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

ADE	adverse device effect
ADL	activities of daily living
ADR	adverse drug reaction
AE	adverse event
AESM	adverse event(s) of special monitoring
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
C-SSRS	Columbia-Suicide Severity Rating Scale
CI	confidence interval
CNS	central nervous system
COVID-19	coronavirus disease 2019
CRF	case report form
CSF	cerebrospinal fluid
DIAM	drug-induced aseptic meningitis
ECG	electrocardiogram
FcRn	neonatal Fc receptor
FSH	follicle-stimulating hormone
gMG	generalized myasthenia gravis
GCP	Good Clinical Practice
HCP	health care professional
HRT	hormonal replacement therapy
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IMP	investigational medicinal product
IRB	Institutional Review Board
IRT	interactive response technology
IV	intravenous
IVIg	intravenous immunoglobulin

LTBI	latent tuberculosis infection
MG	Myasthenia Gravis
MG-ADL	Myasthenia Gravis Activities of Daily Living
MG-C	Myasthenia Gravis Composite
MGFA	Myasthenia Gravis Foundation of America
NMJ	neuromuscular junction
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NTMBI	nontuberculous mycobacterial infection
pIDMC	program Independent Data Monitoring Committee
PRO	patient reported outcome
PDILI	potential drug-induced liver injury
PEX	plasma exchange
QMG	Quantitative Myasthenia Gravis
QTc	corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
SADE	serious adverse device effect
SAE	serious adverse event
SAS	Statistical Analysis System
SC	subcutaneous
SIAQ	Self-Injection Assessment Questionnaire
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WOCBP	woman of childbearing potential

10.11 Appendix 11: Protocol amendment history

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 4 (07 Sep 2023)

Overall rationale for the amendment

The primary reason for this protocol amendment is to align with the approved label in the US and with the proposed dosing regimen under review in Europe.

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
1.1 Synopsis (Overall design)	Text amended to explain study participants will receive [redacted] fixed weight tiered doses of rozanolixizumab. A paragraph was added to explain dosing for existing and new study participants starting the Treatment Period	To align with the approved label in the US and with the proposed dosing regimen under review in Europe.
1.1 Synopsis (Overall design)	A table has been added to include the doses to be used in the US, Europe, and Canada.	To align with the approved label in the US and with the proposed dosing regimen under review in Europe.
1.1 Synopsis (Treatment groups and duration)	A sentence was added to paragraph #2 to clarify the method of administration for participants who are no longer eligible for self-administration.	Updated to provide clarity.
1.3 Schedule of activities	Footnote "c": Updated to clarify that vital signs on Day 15 will be measured before rozanolixizumab administration, at the end of the infusion, and 1 hour after the end of infusion. In addition, the requirement to measure vital signs 4 hours after the end of the infusion was removed for all days.	To be consistent with remainder of protocol.
1.3 Schedule of activities	Footnote "c": time windows added for vital signs measurements. An additional sentence was added that additional vital sign measurements can be performed at the investigator's discretion.	For logistical reasons.

Section # and name	Description of change	Brief rationale
1.3 Schedule of activities	Footnote "g": Updated to clarify that the [redacted]	Updated to provide clarity.
1.3 Schedule of activities	Footnote "h": postdose observation was updated from 4 to 2 hours.	To align with the last postdose vital sign measurement.
4.1 Overall design	Text amended to explain study participants will receive [redacted] weight-tiered doses of rozanolixizumab. A paragraph was added to explain dosing for existing and new study participants starting the Treatment Period.	To align with the approved label in the US and with the proposed dosing regimen under review in Europe.
4.1 Overall design	A sentence was added to paragraph #6 to clarify the method of administration for participants who are no longer eligible for self-administration.	Updated to provide clarity.
4.1.1 Unscheduled visit	New section added for unscheduled visits.	Updated to provide clarity.
4.3 Justification for dose	The doses used in the US, Europe, and Canada have been updated.	To align with the approved label in the US and with the proposed dosing regimen under review in Europe.
5.1 Inclusion criteria	Criterion #5 (now 5a) was updated to add an exception for study participants receiving an anti-FcRn treatment within 8 weeks prior to the Screening Visit, who must have a serum total IgG level at the Screening Visit ≥2g/L.	To facilitate the enrollment of potential study participants recently treated with an anti-FcRn (rozanolixizumab in another MG study, or efgartgimod), considering that low levels of IgG are to be expected and explained by the mode of action of anti-FcRn treatments.
5.2 Exclusion criteria	Criterion #3 (now 3a) has been updated to "Study participant has a known hypersensitivity to other anti-FcRn medications, to any components of the study medication, to any of the excipients (including [redacted]), or has a known history of [redacted], since both [redacted] and [redacted] are constituents of the rozanolixizumab formulation."	To align with the contraindications in the Investigator's Brochure.

Section # and name	Description of change	Brief rationale
5.2 Exclusion criteria	Criterion #6 (now 6a) has been updated to include "(unless the reason is directly related to MG0020 participation)."	Updated to provide clarity.
5.2 Exclusion criteria	Criterion #9 (now 9a) has been updated to include "treatment with ravulizumab within [redacted] before the Baseline Visit or prior treatment with cyclophosphamide."	Updated to include the second intravenous C5 inhibitor approved for the treatment of gMG (ravulizumab), and to be consistent across the rozanolixizumab clinical program.
5.2 Exclusion criteria	Criterion #19 (now 19a) has been updated to add "malignant" before neoplastic disease. An additional exception was added for thymoma that did not require chemotherapy and/or radiotherapy after removal.	To align with previous rozanolixizumab MG studies.
5.3 Lifestyle restrictions	Reference to Japan-specific regulations in Appendix 9 (Section 10.9) was removed.	Japan-specific changes are covered in a separate protocol amendment.
6 STUDY TREATMENTS	An additional sentence was added to state that treatments in this study vary based on either an approved label in a region (US) or a proposed dosing under review in a region (Europe and Canada).	Updated to provide further clarity.
6.1 Treatments administered	Dosage level(s) have been updated.	To align with the approved label in the US and with the proposed dosing regimen under review in Europe.
6.4 Treatment compliance	A cross reference was added to Table 1-2 in reference to the intended dose.	Updated to provide clarity.
6.6 Dose modification	The following text has been updated "ie, study participants must maintain **their** dose (based on body weight as recorded at Screening) throughout."	Updated to provide clarity.
7.1.2 Temporary IMP discontinuation	Change to the temporary IMP discontinuation criterion with IgG threshold of hypogammaglobulinemia from a "must be" to "may be" category.	To provide increased treatment flexibility considering that data from the rozanolixizumab completed clinical studies did not show an increased infection rate in study participants treated with similar dose regimens of

Section # and name	Description of change	Brief rationale
		rozanolixizumab as proposed for MG0020.
7.1.3 Study medication permanent discontinuation criteria	Criterion #2 (now 2a) has been updated to add "reoccurrence of malignant" before neoplastic disease.	To be consistent with the exclusion criteria.
8 STUDY ASSESSMENTS AND PROCEDURES	Details regarding unscheduled visits have been added.	Updated to provide clarity.
8.2.3 Self-Injection Assessment Questionnaire (Infusion version)	Updated to clarify that the [redacted]	Updated to provide clarity.
8.3 Adverse events and serious adverse events	A sentence was added: For results disclosure on public registries (eg, ClinicalTrials.gov), treatment-emergent AEs and treatment-emergent SAEs will be published.	Added for additional clarity in regard to results posting.
8.5 Treatment of overdose	Clarification of intentional and nonintentional overdose, and overdose thresholds for each dose provided.	Updated to provide clarity and to provide overdose values for all doses.
9.3.1 Analysis of the primary safety endpoint	The last sentence was updated to remove the explanation on fixed and random effects.	The confidence interval will be calculated for each self-administration method therefore the last part of the sentence is not applicable.
10.9 Appendix 9: Country-specific requirements	Country-specific requirements for Japan have been removed.	There is a local protocol for Japan.
10.11 Appendix 11: Protocol amendment history	Details of the previous amendment (Protocol Amendment 3) have been added.	General update.
10.1.3 Informed consent process	Updated to clarify that the caregiver must sign the informed consent form by the Baseline visit, if applicable.	Updated to provide clarity.
10.13.2: Management of infections and hypogammaglobulinemia	Change to the temporary IMP discontinuation criterion with IgG threshold of hypogammaglobulinemia from a "must be" to "may be" category.	Adapted as per the updated discontinuation criteria.
10.15 Appendix 15: Evaluation by HCP at site of	The intended doses were removed from the form	Updated for clarity.

Section # and name	Description of change	Brief rationale
safe and successful self-administration (to collect data for primary endpoints)		

Amendment 3 (09 Dec 2022)

Overall rationale for the amendment

The reason for this protocol amendment is to add the EudraCT number to the regulatory agency identifying numbers listed in the title page of the protocol. No other changes have been made.

Amendment 2 (04 Nov 2022)

Overall rationale for the amendment

The primary reason for this protocol amendment is to provide an update on the safety information in line with the updated Investigator's Brochure (IB) dated Sep 2022, updates on the adverse events of special monitoring (AESM), and an update on the planned fixed dose of rozanolixizumab based on study participants' body weight. The secondary endpoint related to the occurrence of medication errors, the Schedule of Activities, the criteria for study medication discontinuation and for participant discontinuation from the study have also been updated. Additional updates have been incorporated to provide further clarity on the protocol.

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 editorial and formatting changes have been made.	To provide clarity and remain consistent with remainder of protocol.
Safety reporting contact page	The contact details for the reporting of AEs (serious and nonserious) have been deleted and the contact details for the reporting of SAEs and self-administration medication errors have been added.	To update the reporting (24h) of AEs and add the reporting of self-administration medication errors.
1.1 Synopsis (rationale) 2.1 Study rationale	The text has been updated to replace "IgG" with "Ig" when applicable and to delete "(also referred to as "rapid push")" in reference to the manual push technique.	Updated to provide clarity.

Section # and name	Description of change	Brief rationale
1.1 Synopsis (objectives and endpoints) 3 Objectives and endpoints	The secondary objective has been updated to add "of rozanolixizumab." The secondary endpoint related to the occurrence of medication errors has been updated to "Occurrence of medication errors associated with adverse reactions during the 2 Self-administration Periods of the study."	Updated to provide clarity. To update the type of medication errors informing the secondary endpoint and the time frame for the collection of medication errors in the study.
1.1 Synopsis (overall design) 4.1 Overall design 4.3 Justification for dose 6.1 Treatments administered 6.4 Treatment compliance 8.5 Treatment of overdose 10.15 Appendix 15: Evaluation by HCP at site of safe and successful self-administration (to collect data for primary endpoints)	For study participants weighing ≥35kg to <50kg, [redacted] fixed doses of rozanolixizumab [redacted] will be administered.	To add a lower fixed dose of rozanolixizumab for study participants weighing ≥35kg to <50kg.
1.1 Synopsis (overall design) 4.1 Overall design	The overall design wording has been updated to add that rozanolixizumab-naïve study participants and study participants previously exposed to rozanolixizumab will be included in the study.	Updated to provide clarity.
1.1 Synopsis (treatment groups and duration) 4.1 Overall design	The text in reference to the randomization at Visit 8 has been updated to add "after the completion of the Training Period."	Updated to provide clarity and remain consistent with the study design.
1.1 Synopsis (treatment groups and duration) 4.1 Overall design	The text in reference to participants who cannot be confirmed eligible for self-administration has been updated to delete "at Visit 8, 9, or 15."	Updated to simplify the protocol text.

Section # and name	Description of change	Brief rationale
1.1 Synopsis (treatment groups and duration) 4.1 Overall design	The following wording has been added "Additionally, if a study participant becomes no longer eligible for self-administration during the Self-administration Periods, he/she can continue to be treated on-site per protocol based on investigator decision."	To provide further clarification.
1.1 Synopsis (treatment groups and duration) 4.1 Overall design 6.8 Treatment after the end of the study	The managed access program has been replaced with a post-trial access to rozanolixizumab.	To provide clarity on the access to rozanolixizumab at the time of completion of the study.
1.3 Schedule of activities	Added table caption and reference to the Schedule of Activities table.	To be consistent with remainder of protocol.
1.3 Schedule of activities	Footnote "m": Updated to clarify that a full neurological examination should be performed in the event of severe and/or serious headache or suspected aseptic meningitis. Added cross-reference to Section 8.2.5 and to Section 1.3.1 (Table 1-3). Added row for blood sampling for exploratory safety biomarker analysis and related footnote "r".	The accumulated safety data on rozanolixizumab led to an update of the adverse events requiring special monitoring. As of the cut-off date of the IB (13 Jul 2022), the following serious adverse events (SAEs) [redacted] (PT terms) suggest a possible causal relationship to rozanolixizumab; based on both their temporal association with investigational medicinal product (IMP) infusion (primarily initial infusion) and given the events have occurred more than once in the rozanolixizumab clinical development program.
1.3.1 Additional study assessments	New section added to detail additional study assessments that may be required in case of AESM of severe and/or serious headache or the new AESM of suspected aseptic meningitis.	
2.3 Benefit/risk assessment	Revised text on most common adverse drug reactions, safety concerns, and other safety topics of interest.	
8.3.8 Adverse events of special monitoring	Added suspected aseptic meningitis to the list of AESM. Wording on infections and hypersensitivity reactions including infusion-related reactions and anaphylaxis and their guidance has been added.	

Section # and name	Description of change	Brief rationale
8.8 Biomarkers 10.2 Appendix 2: Clinical Laboratory Tests, Table 10-1	Added the details of biomarkers evaluation. Added cross-reference to Table 1-3.	
1.3 Schedule of activities	Added row for brief physical examination. Footnote "m" and scheduled visits after V1 have been removed from the complete physical examination and added to the brief physical examination.	To further clarify the physical examination assessment after Screening (V1).
1.3 Schedule of activities	Added row for randomization.	To provide clarity and remain consistent with the study design.
1.3 Schedule of activities	The following note has been added "HSA=home self-administration, ie, unsupervised self-administration/not in the presence of an HCP."	To provide clarity on HSA.
1.3 Schedule of activities	Footnote "q"; Updated to delete "at the Visit 7 ([redacted] evaluation" and to add a cross-reference to Section 4.1	Updated to provide clarity and remain consistent with the study design.
2 Introduction 2.2 Background	The text has been updated to add that rozanolixizumab has been administered to human study participants in several clinical studies. A summary of the results of the Phase 3 gMG program has been added. The text in reference to the Phase 2 and Phase 3 gMG studies has been updated.	Updated in line with studies status at the time of this amendment and to provide clarity.
2.3 Benefit/risk assessment	Results of the Phase 3 study, MG0003, have been added.	To provide data from the Phase 3 study, MG0003.
6.1 Treatments administered	References to vial and carton have been removed from the packaging and labeling row.	Packaging will be described in the IMP Handling Manual.
6.2 Preparation, handling, storage, and accountability requirements	The text in reference to the instructions for storing study medication has been updated to add "and in the IMP Handling Manual."	Updated to provide clarity.

Section # and name	Description of change	Brief rationale
6.2.1 Drug/Device accountability	The text in reference to the recording of study medication dispensing has been updated to replace “case report form" with “Drug/Device Accountability form.”	Updated to provide clarity.
6.3 Measures to minimize bias: randomization and blinding	Cross-references to Table 1-1 and details pertaining to the IRT at Visit 2 have been added.	Updated to provide further clarity.
6.4 Treatment compliance	The text in reference to the photographic documentation has been updated.	To clarify that a mobile phone will be used for the photographic documentation and that further details are provided in the IMP Handling Manual.
6.6 Dose modification	The following text has been added “ie, study participants must maintain either the [redacted] dose or the [redacted] dose (based on body weight as recorded at Screening) throughout.”	To provide clarity.
7.1.2 Temporary IMP discontinuation	The temporary IMP discontinuation criteria in relation to COVID-19 infection have been updated.	To adapt the withdrawal criteria to the evolution of the medical practices and local guidelines with regards to COVID-19 management.
7.1.2 Temporary IMP discontinuation 7.1.3 Study medication permanent discontinuation criteria	Added a new criterion (#3) on the temporary discontinuation of IMP (*must be*) in the event of a first diagnosis of suspected aseptic meningitis. Added a new criterion (#9) on the permanent discontinuation of study medication in the event of recurrence of aseptic meningitis. Deleted criterion #7 on the permanent discontinuation of study medication in the event of serious or recurrent (ie, >2 occurrences) severe AE of headache which is considered related to the study medication. Subsequent criteria have been renumbered.	The accumulated safety data on rozanolixizumab led to an update of the discontinuation criteria which is in line with the revisions to adverse events requiring special monitoring.
7.1.2 Temporary IMP discontinuation	Added a new criterion (#3) on the temporary discontinuation of	Updated to be consistent with the rozanolixizumab clinical

Section # and name	Description of change	Brief rationale
	IMP (*may be*) at the discretion of the investigator in cases deemed strictly necessary for the participant's medical care.	program and to allow for investigator discretion.
7.1.2 Temporary IMP discontinuation	A cross-reference to Section 8 has been added to the text. The text in reference to IMP treatment resumption has been updated.	Updated to provide clarity.
7.1.3 Study medication permanent discontinuation criteria	The text in reference to rozanolixizumab discontinuation at the discretion of the investigator has been updated to add "or becomes unable to comply."	Updated to provide clarity.
7.1.3 Study medication permanent discontinuation criteria	The text has been updated to add that the handling of replacement participants is described in Section 7.2.	Updated to provide clarity.
7.2 Participant discontinuation/withdrawal from the study 8.2.9 Suicidal risk monitoring	Criterion #4 on the withdrawal from the study in the event of active suicidal ideation has been moved to Section 7.1.3 (study medication permanent discontinuation criteria, criterion #10). The cross-reference to Section 7.2 has been replaced with a cross-reference to Section 7.1.3.	Updated in order to increase the consistency and clarity of the IMP discontinuation criteria throughout the protocol.
7.2 Participant discontinuation/withdrawal from the study	The wording in reference to the replacement of study participants has been updated to replace "before the end of the second Treatment Period" with "before the end of the Self-administration Period 2."	Updated to be consistent with the study design.
8 Study assessments and procedures	Added wording on contingency measures in case of exceptional circumstances.	Updated to be consistent with the rozanolixizumab clinical program.
8.2.5 Physical examination	The details of the brief physical examination have been added.	Added to provide clear guidance to investigators on the brief physical examination.
8.2.5 Physical examination	The details of the full neurological assessment in the event of severe and/or serious	Added to provide clear guidance to investigators on the management of AESM of severe

Section # and name	Description of change	Brief rationale
	headache or suspected aseptic meningitis have been added.	and/or serious headache or suspected aseptic meningitis.
8.2.6 Vital signs	Blood pressure measurements have been updated to 1 reading.	Updated to be consistent with the rozanolixizumab clinical program.
8.2.10.1 Tuberculosis assessment	Added cross-reference to new Appendix 19.	To provide clarity and remain consistent with remainder of protocol.
8.2.11 COVID-19 precautions	Added cross-reference to Section 7.1.2.	To provide clarity and remain consistent with remainder of protocol.
8.3.7 Medication errors associated with self-administration 8.3.8 Adverse events of special monitoring 10.12 Appendix 12: Medication errors associated with self-administration	Added new section on medication errors associated with self-administration. Subsequent subsections have been renumbered. The AESM related to medication error has been updated to "medication error associated with adverse reaction(s)." Added new appendix on the definition of medication errors. Subsequent appendices have been renumbered.	To clarify medication errors, their classification and reporting procedures, and medication errors identified as AESM.
8.5 Treatment of overdose	In the numbered point #3, 3 days has been replaced with 72 hours.	Updated to be consistent with remainder of protocol.
8.6 Pharmacokinetics	Text updated to add that PK blood sample in the event of PDILI could be collected as described in Appendix 6.	Updated to provide further clarification.
9.1 Definition of analysis sets	The Safety Set has been renamed Randomized Safety Set, the Training Safety Set has been renamed Safety Set, and their definition has been updated. A Full Analysis Set has been added.	To update the analysis sets and their definition.
9.2 General statistical considerations	The text in reference to summary statistics by sequence and overall has been updated to delete "AEs."	Details will be provided in the SAP.

Section # and name	Description of change	Brief rationale
9.3.1 Analysis of the primary safety endpoint 9.3.2 Analysis of the secondary safety endpoint 9.3.3 Other safety analyses 9.7 Handling of dropouts or missing data	The text has been updated to add or update the analysis set(s) on which the analyses will be based.	To align with the updates in the analysis sets.
9.3.2 Analysis of the secondary safety endpoint	The text in reference to medication errors has been updated to add "associated with adverse reactions." The analysis of medication errors during the Training Period has been deleted.	To align with the updates in the secondary safety endpoint.
9.3.2 Analysis of the secondary safety endpoint 9.3.3 Other safety analyses	The analysis of TEAEs by rozanolixizumab-naïve or non-naïve participants has been deleted.	To update the analysis of TEAEs.
10.1.3 Informed consent process	Information on caregiver's informed consent (if applicable) has been added.	To provide clarity on the informed consent process in case of a caregiver.
10.1.5 Committees structure	Further details pertaining to the review process of safety data have been added.	To provide clarity on the review process of safety data.
10.1.7.2 Apps	The text has been updated to add Japan to the listed countries.	To add Japan to the listed countries where the app falls outside medical device regulations.
10.1.7.2 Apps	The following has been deleted "Finally, the screenshots of the app should be made available during ethics committee review of the clinical trial protocol."	To simplify the protocol text.
10.3 Appendix 3: Adverse events – Definitions and procedures for recording, evaluating, follow-up, and reporting	The cross-reference to the contacts for SAE reporting has been updated.	To align with the updates in the safety reporting contact page of the protocol.
10.9 Appendix 9: Country-specific requirements, Japan	Clarified that country-specific requirements for Japan aligned with Japan-GCP will be provided separately in Protocol Exhibit.	Clarification.

Section # and name	Description of change	Brief rationale
10.10 Appendix 10: Abbreviations and trademarks	Several additions and one deletion have been made to the list of abbreviations.	General update.
10.11 Appendix 11: Protocol amendment history	Details of the previous amendment (protocol amendment 1) have been added.	General update.
10.12 Appendix 12: Management of headaches, infusion reactions or hypersensitivity reactions, and infections and hypogammaglobulinemia	Has become Section 10.13 and the title has been updated to "Appendix 13: Management of infusion reactions or hypersensitivity reactions and infections and hypogammaglobulinemia."	To align with the updates in the adverse events requiring special monitoring and their management.
10.12.1 Management of headache	The protocol guidance for the management of headache has been updated and moved to Section 10.14 (Appendix 14). Subsequent subsections have been renumbered.	
10.14 Appendix 14: Management of adverse event of special monitoring	New appendix: Added to provide guidance on the management of AESM. Subsequent appendices have been renumbered.	
10.19 Appendix 19: Tuberculosis Questionnaire	New appendix has been added.	To provide the tuberculosis questionnaire.
11 References	One reference has been added to the list of references.	General update.

Amendment 1 (31 Aug 2022)

Overall rationale for the amendment

The primary reason for this protocol amendment is to clarify that there is no formal rollover from study MG0007 to MG0020.

One exclusion criterion was also updated to align with the current approach agreed for the rozanolixizumab clinical program.

Section # and name	Description of change	Brief rationale
1.1 Synopsis (overall design) 4.1 Overall design	Overall design wording updated to remove "Study participants from study MG0007 and rozanolixizumab-naïve	Updated to provide clarity to the sites that there is no formal rollover from study MG0007 to MG0020.

	participants will be included in the study."	
5.2 Exclusion criteria	Criterion #7 (now 7a) has been updated to include "or a BCG vaccine within 1 year before starting treatment;"	Updated to align with the current approach agreed for the rozanolixizumab clinical program.

10.12 Appendix 12: Medication errors associated with self-administration

The definitions and procedures detailed in this appendix are in accordance with the pharmacovigilance obligations detailed in Title IX of Directive 2001/83/EC and Regulation (EC) 726/2004, Chapter 3, Article 28 with regard to the recording, reporting, and assessment of suspected adverse reactions (serious and nonserious) associated with an error in prescribing, storing, dispensing, preparing for administration, or administering a medicinal product for human use authorized in the EU, which have been adapted as per MG0020 protocol specifications. All medication errors will be recorded and reported to the sponsor or designee as indicated in Section 8.3.7.

Medication Error Definition

Medication error: A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient. A failure in the drug treatment process does not refer to lack of efficacy of the drug, rather to human- or process-mediated failures.

The medication error can be further classified based on the factual information on the case, into the following categories:

- **Medication errors associated with adverse reaction(s)**: result from an error (which has already occurred or accomplished) in the medication use associated with harm to the study participant-this is an adverse event of special monitoring (AESM)-please see Section 10.14.
- **Medication errors without harm**: result from an error (which has already occurred or accomplished) in the medication use associated with no harm to the study participant.
- **Intercepted medication errors (or near miss)**: in which an intervention (eg, the timely check of the incorrect preparation and administration of the study medication) has prevented an actual harm being caused to the study participant.
- **Potential medication errors**: are the recognition of circumstances that could lead to a medication error, which may or may not involve a study participant.

  The term potential medication error refers to all possible mistakes in the storing, preparation for administration, or administration of the investigational medicinal product (IMP) by the study participant and may lead to:

  – A medication error with harm, but without knowing the actual cause
  – A medication error without harm and without knowing the actual cause
  – A medication error without harm, but with the awareness of the actual cause

10.13 Appendix 13: Management of infusion reactions or hypersensitivity reactions and infections and hypogammaglobulinemia

10.13.1 Management of infusion reactions or hypersensitivity reactions

Study participants must be closely monitored for reactions during and after rozanolixizumab administration. Standard precautions must be taken for the study participants with regard to potential infusion-related reactions. Suggested management guidelines for infusion-related reactions and anaphylaxis at the study site are provided in Table 10-4. Definitions of the severity of the relevant events will be consistent with NCI-CTCAE version 5.0 (Appendix 3 [Section 10.3]). It is recommended that for study participants who self-administer at home, consideration is given to readily-available emergency medical services in case of an infusion reaction or hypersensitivity reaction. During study drug administration, the participant's home or alternative location must not be so remote that a reasonable arrival time of an ambulance could not be predicted.

Table 10-4: Suggested management guidelines at the study site for infusion reactions

Type of reaction	Suggested action
Acute – Mild Grade 1	Monitor vital signs every 10 minutes. If the reaction worsens to Grade 2, follow the instructions 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 or IM. Consider administering paracetamol or nonsteroidal anti-inflammatory drugs. Monitor vital signs initially every 5 minutes. If the reaction improves and upon further assessment it is clear that the event is not an anaphylaxis, restart the infusion cautiously. Continue to monitor vital signs every 5 minutes. If reaction recurs or worsens to Grade 3, discontinue infusion.

Table 10-4: Suggested management guidelines at the study site for infusion reactions

Acute – Severe Grade 3 or anaphylaxis	Discontinue rozanolixizumab 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 minutes. – Hospitalize, if condition not improving or worsens. – Monitor study participant until symptoms resolve.

CTCAE=Common Terminology Criteria for Adverse Events; IM=intramuscular; IV=intravenous
Note: Management criteria were adapted from the CTCAE v5.0 (National Cancer Institute, 2017).

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

10.13.2 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.

If a study participant has a significant infective episode including but not limited to bacteremia or sepsis, infectious meningitis, septic arthritis, osteomyelitis, complicated pneumonia, or visceral abscess which may or may not result in hospitalization, they MUST discontinue IMP, perform the Early Withdrawal Visit and may enter the Safety Follow-up Period. This list is not intended to be all inclusive and the investigator is expected to apply his/her judgment on continuing IMP based on the clinical situation at hand.

In the event of a nonserious 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 nonserious persisting or recurrent infection with a serum total IgG level between ≥1g/L and <2g/L. Upon resolution of infection and the IgG returning to the level of ≥2g/L, the study participant may be allowed to resume treatment with the IMP. Ad hoc assessments of IgG levels may be performed to monitor their recovery. The blood samples collected for the ad hoc IgG assessments should be sent to both the local and the central laboratories. Decisions on whether the study participant can resume treatment may be taken based on the local laboratory results (IgG ≥2g/L as per local laboratory). In such cases, the local laboratory results must be entered in the eCRF.

Treatment may 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. Ad hoc assessment may be performed to monitor the recovery of IgG levels. The blood samples collected for the ad hoc IgG assessments should be sent to both the local and the central

laboratories. Decisions on whether the study participant can resume treatment may be taken based on the local laboratory results (IgG ≥2g/L as per local laboratory). In such cases, the local laboratory results must be entered in the eCRF.

10.14 Appendix 14: Management of adverse event of special monitoring

Adverse events of special monitoring are defined as product-specific AEs, adverse reactions, or safety topics requiring special monitoring by one or more regulatory authorities or by UCB.

For rozanolixizumab, AESM (defined by UCB) are:

- Severe and/or serious headache
- Suspected aseptic meningitis
- Medication error associated with adverse reaction(s)

Occurrence of AESM require immediate reporting (within 24 hours regardless of seriousness) to UCB. Upon reception of AESM by UCB, a medical follow-up questionnaire will be sent to the site to gather extensive medical information about the AESM. See Table 1-4 for additional assessments that may be required in case of AESM of severe and/or serious headache or suspected aseptic meningitis.

Aseptic meningitis (suspected)

Drug-induced aseptic meningitis is a diagnosis of exclusion after ruling out infectious causes (Jolles et al, 2000). A few cases of aseptic meningitis (drug-induced) have been reported in the rozanolixizumab program. Consequently, aseptic meningitis (suspected) is being managed as an AESM (Section 8.3.8).

Participants should be monitored for signs and symptoms suggestive of central nervous system (CNS) involvement and evaluated immediately if meningitis is suspected. A full neurological workup should be strongly considered including, but not limited to imaging eg, computed tomography (CT) scan, or preferably gadolinium-enhanced magnetic resonance imaging (MRI), a lumbar puncture with cerebrospinal fluid (CSF) analysis inclusive of glucose, protein, differential complete blood count (CBC), cultures, gram stain, and/or viral polymerase chain reactions (PCRs) as appropriate. Whenever possible, CSF should be stored for assessment of rozanolixizumab pharmacokinetic, pharmacodynamic, specific antibody titers, or other biomarkers. A concurrent blood sample should be collected as per local practice. The ultimate investigative procedures are at the discretion of the investigator or the treating physician. For studies where a neurologist is not the investigator, a neurological consultation is also recommended to aid in decision making and patient management. In addition, blood samples for exploratory safety biomarkers (see Section 8.8) should be collected for participants with a diagnosis of DIAM preferably within 72 hours after onset of symptoms. These investigations will be performed to further understand the potential mechanisms of DIAM in the participants.

All procedures related to the diagnosis, treatment, and investigation of meningitis should be recorded in the eCRF, and preliminary data should be included on the SAE form used for reporting the event as an AESM within 24 hours (ie, preliminary data reported on the first reporting may not have CSF results yet, but the reporting should occur as soon as there is a

suspected diagnosis. Full results should be communicated in subsequent exchanges with the sponsor).

Treatment must be temporarily held if a participant has a diagnosis of suspected meningitis of any cause until the diagnostic workup is complete. Based on CSF findings, negative cultures, absence of other disease causes, and relationship with IMP, a diagnosis of DIAM can be made. If deemed appropriate by the investigator and agreed upon by the participant and the sponsor, the study treatment can resume upon the complete resolution of symptoms. The benefit and risk of the treatment should be carefully considered prior to reinitiating the IMP. If a participant experiences a second episode of similar symptoms suggestive of DIAM, then the participant must permanently discontinue the IMP.

Participants experiencing an event of DIAM should be strongly encouraged to remain in the study regardless of IMP discontinuation. This will allow for monitoring and follow-up of the participant including a complete neurological exam on subsequent physical examinations. Longer term follow-up on any AEs related to DIAM that are ongoing may be warranted until resolution.

Associated symptoms with aseptic meningitis should be managed at the investigator's discretion.

Severe and/or serious headache

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

Determination of the severity of headache will be consistent with NCI-CTCAE version 5.0. Severe headache is defined as severe pain limiting self-care activities of daily living (ADL). Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, and taking medications.

In the event of a headache, the investigators should take the medical history of previous headaches, concomitant medication, and comorbidities (eg, asthma) into consideration.

If the severe and/or serious headache is initially reported at a home visit or during a telephone call, the study participant should be evaluated by HCP as soon as possible for further investigations. Study participants should be monitored for signs and symptoms suggestive of CNS involvement and evaluated immediately if other causes (eg, meningitis, intracranial bleeding) are suspected (please see Section 1.3.1 [Table 1-4]). 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.

Should the investigator elect to hold IMP for severe and/or serious headache, if deemed appropriate by the investigator and agreed upon by the study participant and the sponsor, the IMP can resume upon the resolution of symptoms. The benefit and risk of the treatment should be carefully considered before reinitiating the IMP.

Headaches will be treated as clinically indicated according to national guidelines. It is recommended that the study participant has an analgesic available in case of headache with the instruction for frequency and dosage provided by an HCP. The analgesic can be started at the

early onset of headache. 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 headache after discussion with the medical monitor. The benefit and risk of continuing treatment with IMP and chronic prophylaxis with analgesics must be carefully evaluated by the investigator.

Medication error associated with adverse reaction(s)

A medication error associated with a suspected (serious and nonserious) adverse reaction(s) is an unintended failure in the self-administration of IMP that leads to harm to the study participant, and should be assessed, recorded, and reported within 24 hours of awareness following the SAE recording and reporting procedures as indicated in Appendix 3 (Section 10.3) and using the Medication Error form as indicated in Section 8.3.7.

10.15 Appendix 15: Evaluation by HCP at site of safe and successful self-administration (to collect data for primary endpoints)

10.15(a): HCP evaluation checklist following self-administration at site at Visit 13 ([redacted]) and Visit 19 ([redacted])

	Study participant/caregiver is able to perform following steps	Visit 13 Yes/No	Comments	Visit 19 Yes/No	Comments
1	Identify and prepare all supplies required				
2	Confirm that the vial is safe to use				
3	Prepare and plan sufficient time for the infusion as well as make sure the medication reaches room temperature gradually before the infusion starts (without the use of heating devices)				
4	Prepare and clean all work surfaces thoroughly				
5	Ensure hands are washed thoroughly before the infusion				
6	Position themselves comfortably next to the work surface				
7	Ensure rozanolixizumab supplies are ready for assembly and infusion				
8	Fill the syringe/ infusion system with prescribed dose of rozanolixizumab and check for/remove any air bubbles				
9a	**Syringe driver** set up as per manufacturer's instructions/IMP manual				
9b	**Manual Push**: Set up as per IMP manual				
10	Prepare the infusion site on the abdomen				
11	Insert the needle into the subcutaneous tissue				
12	Secure the needle to the skin				
13	Start the infusion and record start time				
14	End the infusion and record end time				
15	Apply a dressing				
16	Safely and correctly dispose of the syringe, transfer device, needle, vials including those containing any unused liquid and the infusion line				

10.15(b): HCP conclusions following evaluation of self-administration at site at Visit 13 ([redacted] and Visit 19 ([redacted])

	Visit 13 Yes/No	Comments	Visit 19 Yes/No	Comments
Did the study participant administer rozanolixizumab at the correct infusion site?				
Did the study participant successfully administer rozanolixizumab subcutaneously?				
Did the study participant administer the intended dose of rozanolixizumab (based on the study participant's body weight at Screening)?				

10.15 HCP evaluation checklist (a) and HCP conclusions (b) are also applicable following self-administration at home at Visits 10 to 12 ([redacted]) and Visits 16 to 18 ([redacted]).

10.16 Appendix 16: Participant's preferred method of rozanolixizumab administration questions

You have tried two methods of subcutaneous infusions (i.e., infusions under the skin) to administer the study drug:

- Manual push: the drug is delivered by pressing the syringe plunger by hand.
- Pump: the drug is delivered through a pump that is connected to the syringe which presses on the syringe plunger.

You have also received the subcutaneous infusions both at the hospital and at your home.

We would now like to ask you some questions about your preferences regarding the subcutaneous infusions.

1. Which method of administering the subcutaneous infusions did you prefer? (Please select one answer)

   Manual push ☐

   Pump ☐

   No preference ☐

2. In general, who did you prefer administering the infusions? (Please select one answer)

   Myself ☐

   A nurse or other healthcare professional ☐

   No preference ☐

3. Where did you prefer to receive the subcutaneous infusions? (Please select one answer)

   At my home ☐

   At the hospital ☐

   No preference ☐

4. During the Training Period when you were receiving the subcutaneous infusions **at the hospital**, who did you prefer administering the infusions? (Please select one answer)

   Myself ☐

   A nurse or other healthcare professional ☐

   No preference ☐

Please record any other feedback you have about how the infusions were administered:

I have answered the questions alone ☐

I have answered the questions together with a family member (or other persons who have accompanied me during the subcutaneous infusions of the study drug) ☐

10.17 Appendix 17: Myasthenia Gravis Activities of Daily Living

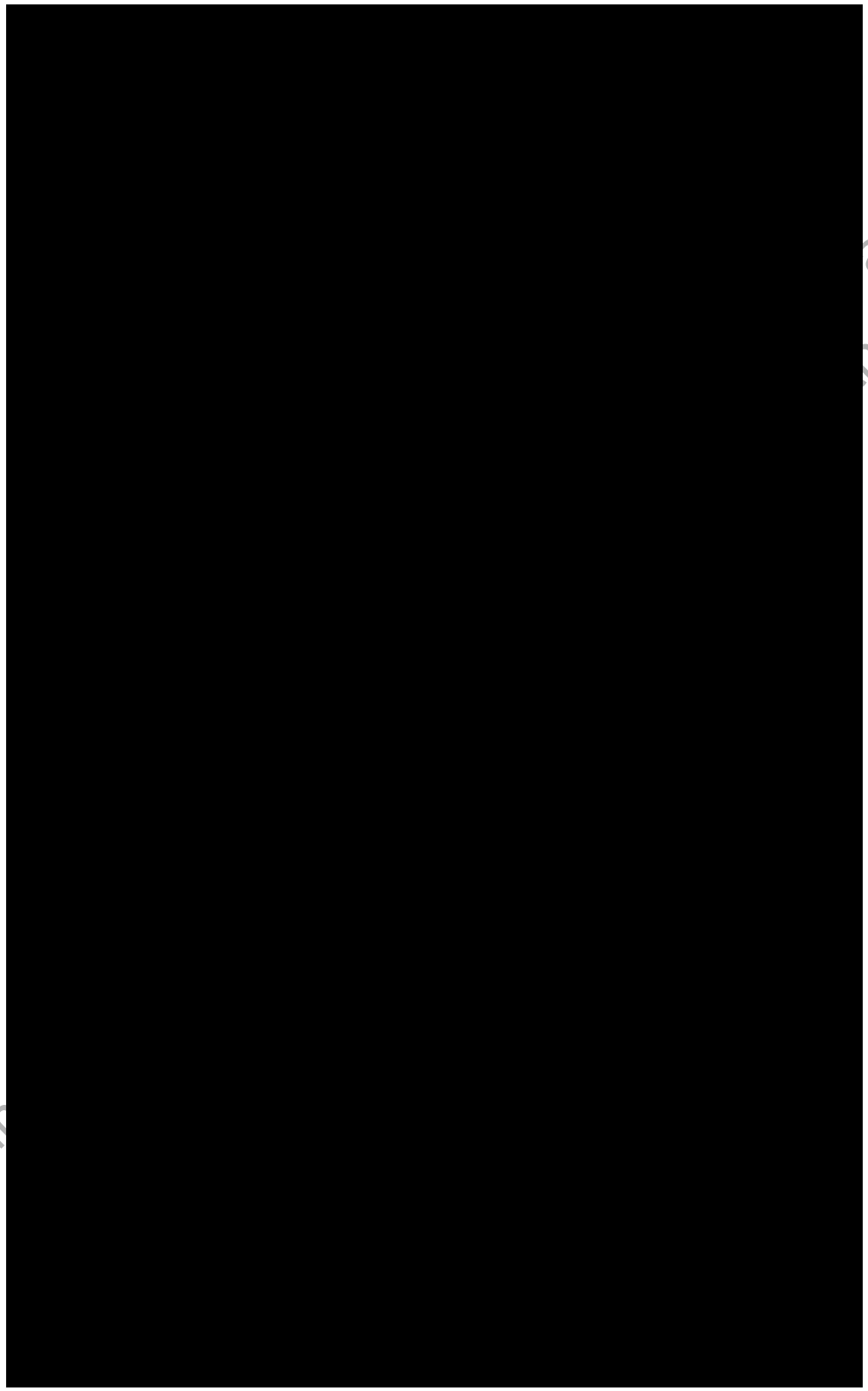
MG Activities of Daily Living (MG-ADL) profile

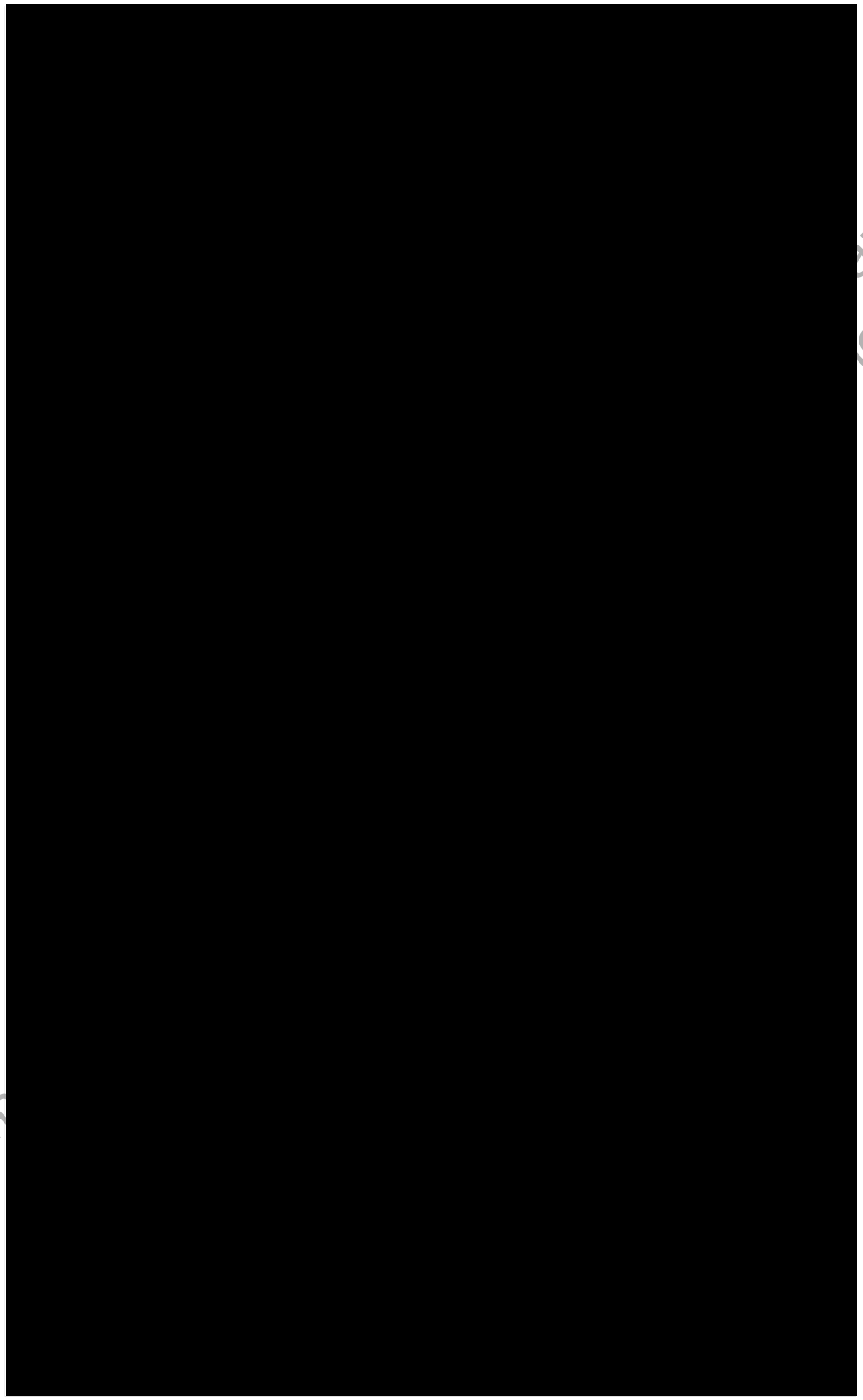
Grade	0	1	2	3	Score (0,1,2 or 3)
1. Talking	Normal	Intermittent slurring or nasal speech	Constant slurring or nasal, but can be understood	Difficult to understand speech	
2. Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube	
3. Swallowing	Normal	Rare episode of choking	Frequent choking necessitating changes in diet	Gastric tube	
4. Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence	
5. Impairment of ability to brush teeth or comb hair	None	Extra effort, but no rest periods needed	Rest periods needed	Cannot do one of these functions	
6. Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance	
7. Double vision	None	Occurs, but not daily	Daily, but not constant	Constant	
8. Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant	
				MG-ADL score total (items 1-8) =	

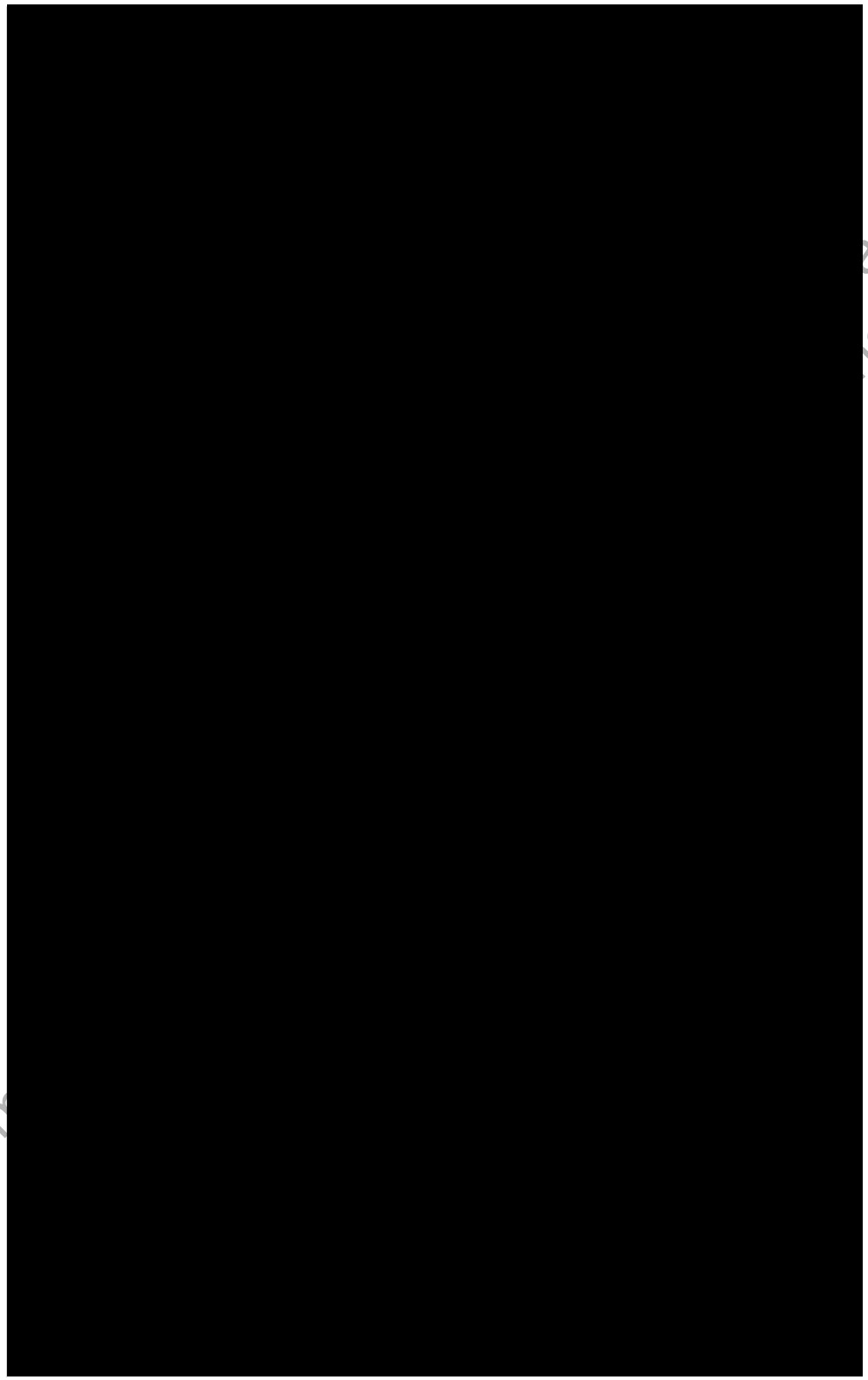
MG-ADL - United States/English
MG-ADL_AU1.1_eng-USori.docx

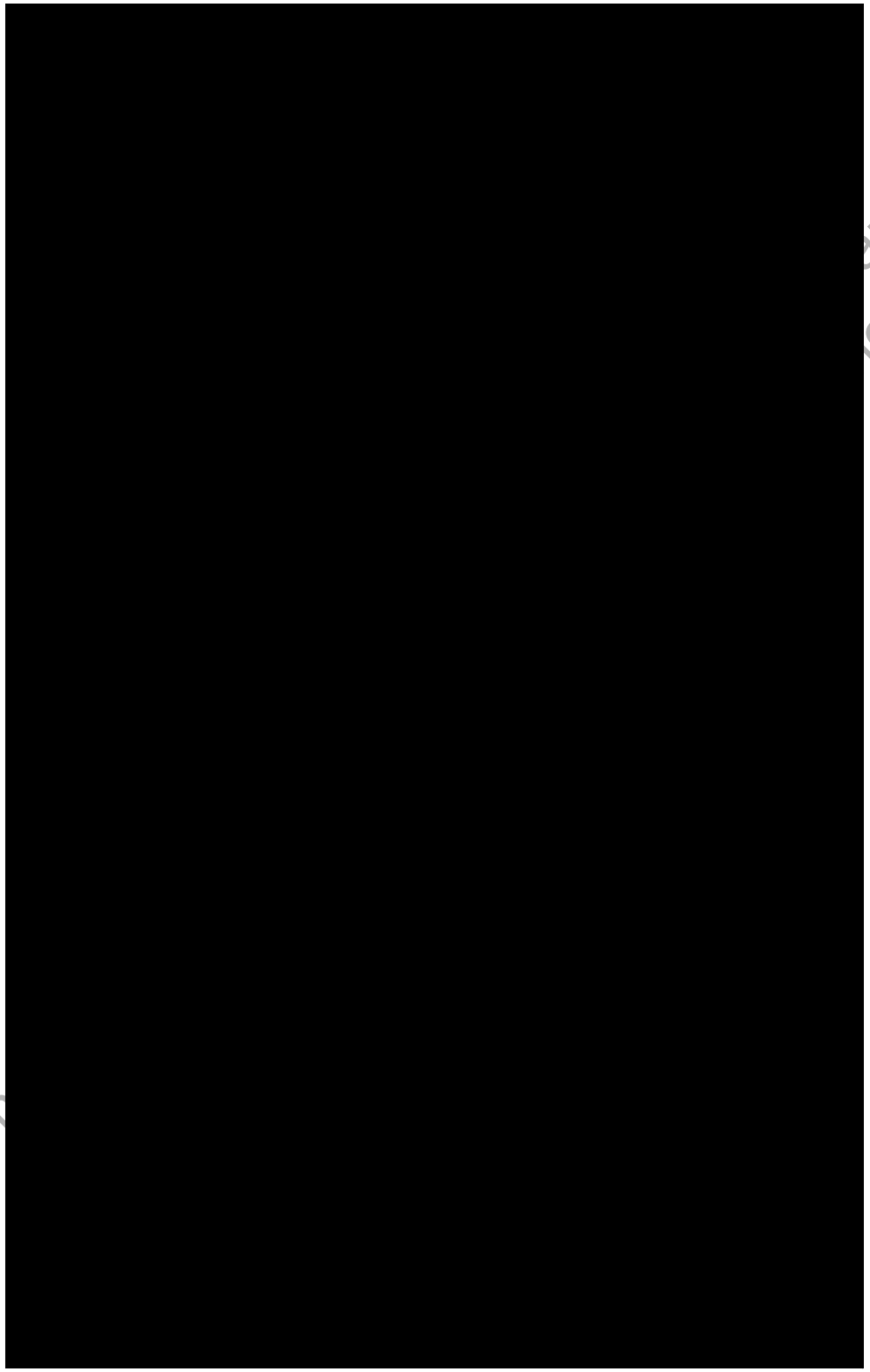
10.18 Appendix 18: Self-Injection Assessment Questionnaire

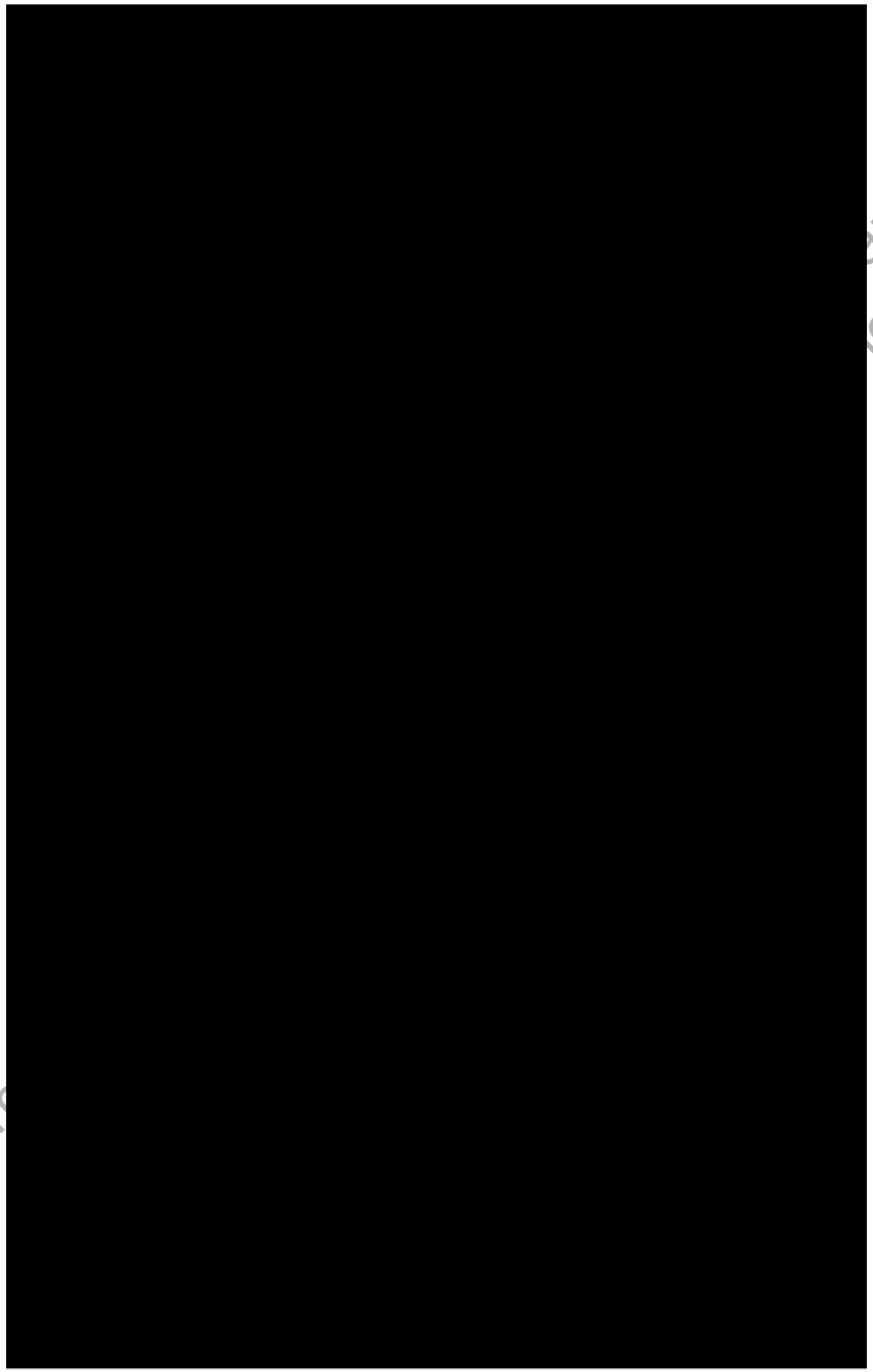
[redacted]

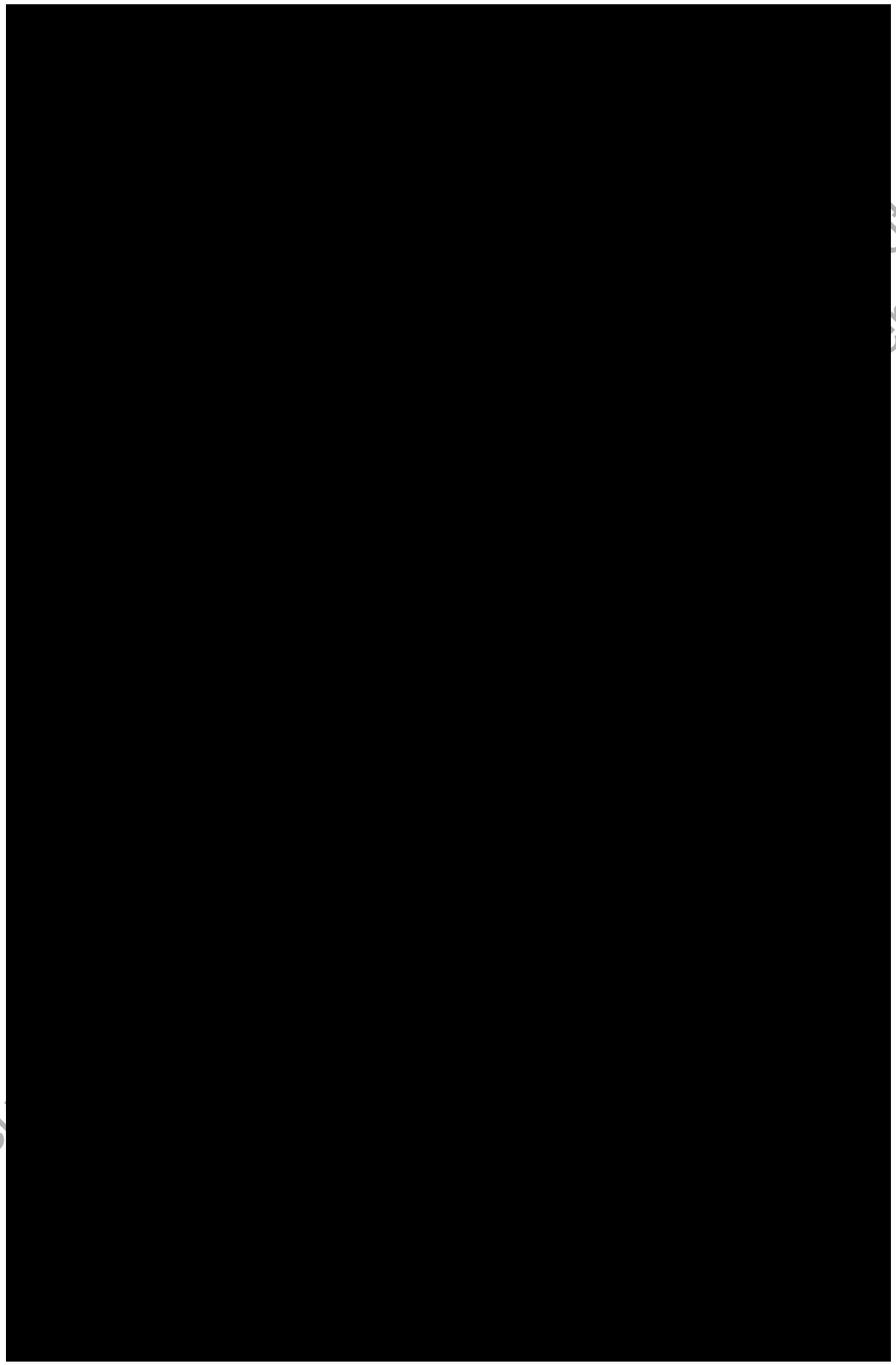




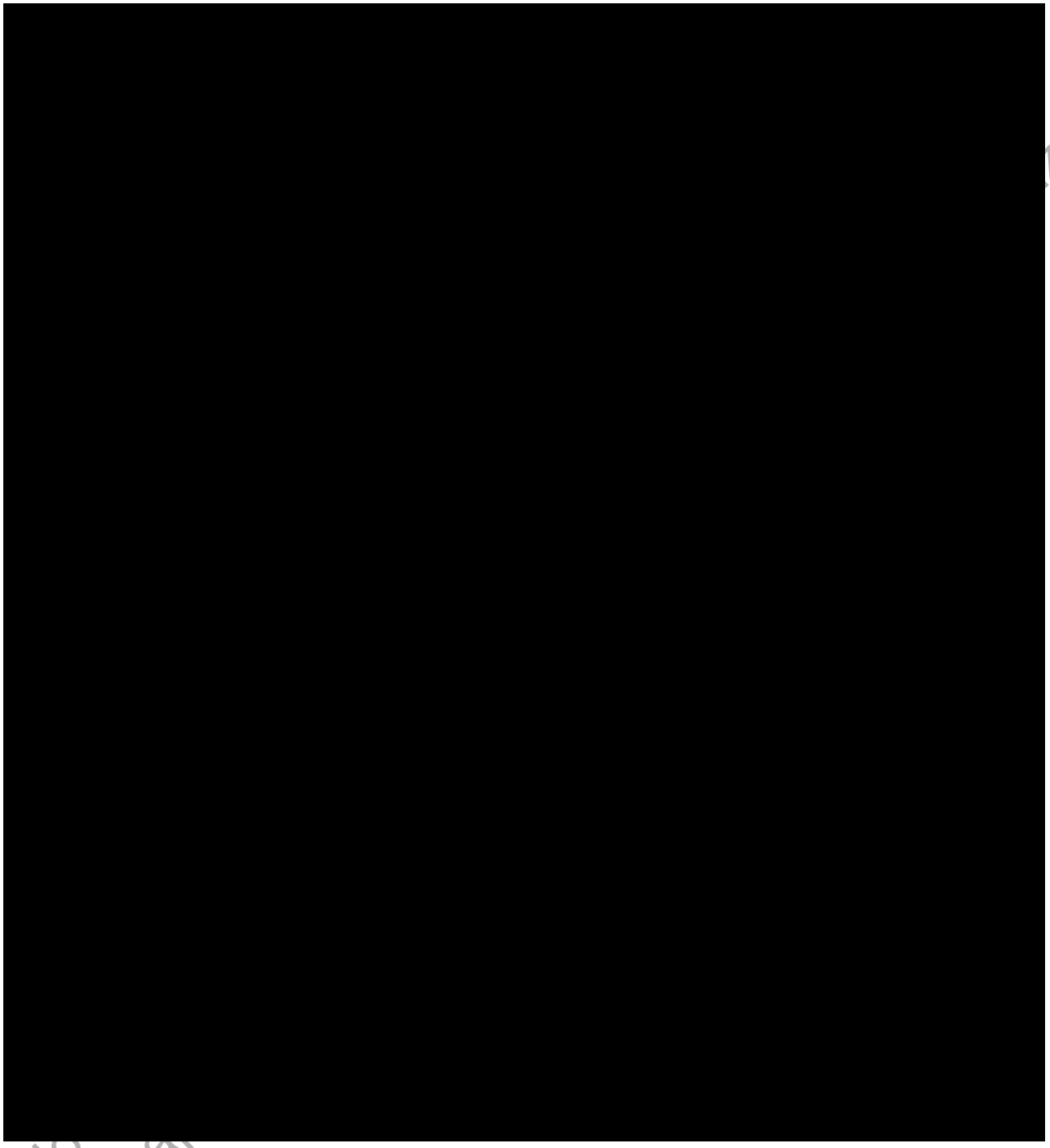








10.19 Appendix 19: Tuberculosis Questionnaire



11 REFERENCES

Clinical Trial Regulation EU 536/2014. April 2014.

Communication from the Commission - Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3'). 2011/C172/01.

ISO 14155:2020 Clinical investigations of medical devices for human subjects – Good Clinical Practice.

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

Alcantara M, Sarpong E, Barnett C, Katzberg H, Bril V. Chronic immunoglobulin maintenance therapy in myasthenia gravis. Eur J Neurol. 2021;28(2):639-646.

Bienvenu B, Cozon G, Mataix Y, et al. Rapid Push vs Pump-Infused Subcutaneous Immunoglobulin Treatment: a Randomized Crossover Study of Quality of Life in Primary Immunodeficiency Patients. J Clin Immunol. 2018;38(4):503-12.

Cowan J, Bonagura VR, Lugar PL, et al. Safety and Tolerability of Manual Push Administration of Subcutaneous IgPro20 at High Infusion Rates in Patients with Primary Immunodeficiency: Findings from the Manual Push Administration Cohort of the HILO Study. J Clin Immunol. 2021;41(1):66-75.

James LP, Letzig L, Simpson PM, et al. Pharmacokinetics of Acetaminophen-Protein Adducts in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos. 2009;37:1779-84.

Jaretzki A 3rd, Barohn RJ, Ernstoff RM, Kaminski HJ, Keesey JC, Penn AS, et al. Myasthenia gravis: Recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. Neurol. 2000;55:16-23.

Jolles S, Sewell WA, Leighton C. Drug-induced aseptic meningitis: diagnosis and management. Drug Saf. 2000;22(3):215-26.

Keininger D, Coteur G. Assessment of self-injection experience in patients with rheumatoid arthritis: psychometric validation of the Self-Injection Assessment Questionnaire (SIAQ). Health Qual Life Outcomes. 2011;13:9:2.

Le Gal F, Gordien E, Affolabi D, et al. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. J Clin Microbiol. 2005;43(5):2363-9.

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

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

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

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

Shapiro RS. Subcutaneous immunoglobulin: rapid push vs. infusion pump in pediatrics. Pediatr Allergy Immunol. 2013;24(1):49-53.

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

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, according to Clinical Trial Regulation EU 536/2014, and according to current Good Clinical Practice.

Approval Signatures

Name: mg0020-protocol-amend-5

Version: 1.0

Document Number: CLIN-000243670

Title: mg0020 Protocol Amendment 5

Approved Date: 01 Dec 2023

Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 01-Dec-2023 04:41:34 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 01-Dec-2023 08:24:38 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Subject Matter Expert Date of Signature: 01-Dec-2023 09:56:56 GMT+0000