A PHASE 3B, MULTICENTER, OPEN-LABEL, SINGLE-ARM STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND EFFICACY OF ZILUCOPLAN IN PARTICIPANTS WITH GENERALIZED MYASTHENIA GRAVIS SWITCHING FROM INTRAVENOUS COMPLEMENT COMPONENT 5 INHIBITORS TO SUBCUTANEOUS ZILUCOPLAN

PROTOCOL MG0017

PHASE 3b

SHORT TITLE:

An open-label study to evaluate the safety, tolerability, and efficacy of subcutaneous zilucoplan in participants with generalized myasthenia gravis who were previously receiving intravenous complement component 5 inhibitors

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

Regulatory agency identifying number:

IND Number:	134340

Confidential Material

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History		
Document	**Date**	**Type of amendment**
Amendment 3	30 Nov 2022	Not applicable
Amendment 2	21 Oct 2022	Not applicable
Amendment 1	15 Jul 2022	Not applicable
Original Protocol	24 May 2022	Not applicable

Amendment 3 (30 Nov 2022)

Overall Rationale for the Amendment:

The protocol amendment introduces an optional Extension Treatment Period that allows access to zilucoplan for participants who wish to continue receiving it after completing the 12-week Main Treatment Period of the study. It allows for study participants to continue receiving zilucoplan treatment until the approval of the marketing application for the indication of generalized myasthenia gravis (gMG) in the US or until further notice from the Sponsor.

The table below does not include correction of minor typographical errors and formatting/stylistic changes.

Section # and Name	Description of Change	Brief Rationale
Section 1.1, Synopsis Section 3, Table 3-1 Objectives and estimands/endpoints Section 4.1, Overall design Section 4.2, Scientific rationale for study design Section 4.4, End of study definition Section 6.1, Treatments administered Section 6.8, Treatment after the end of the study Section 7.1.2, QTc stopping criteria Section 8.1.1.6, Patient Preference assessment Section 8.1.1.8, Time to first receipt of rescue therapy	Endpoints updated to define the duration. Overall design of the study, treatment groups and duration updated to include the Extension Treatment Period.	To include an Extension Treatment Period in the study and allow eligible participants who have completed the 12-week Main Treatment Period to have continued access to zilucoplan.

Section # and Name	Description of Change	Brief Rationale
Section 8.1.1.9, Change in SOC therapy dose regimen		
Section 1.2, Schema	Figure 1-1 updated to include the Extension Treatment Period. Footnotes “d,” “e,” "f," "g," and "h" added. Footnote “b” modified for clarity reasons.	As above.
Section 1.3, Schedule of Activities	Table 1-2 updated to include the Extension Treatment Period and time points for data collection. Footnote “b,” “c,” “k,” and “u” updated. Footnote “w” and “x” added.	As above. Footnotes “k” and “u” modified for clarity reason.
Section 2.3, Benefit/risk assessment	Reference to Advisory Committee on Immunization Practices added.	Clarification.
Section 5.1, Inclusion criteria	Inclusion Criterion 2 (now 2a) modified for clarity reason.	Clarification.
	Inclusion Criteria 7, 8, and 10 (now 7a, 8a, and 10a, respectively) modified.	Modified to account for the Main Treatment Period and clarification added on the entire study.
	Reference to Advisory Committee on Immunization Practices added to exclusion criterion 9 (now 9a).	Clarification.
Section 5.2, Exclusion criteria	Exclusion Criteria 3, 12, 14 (now 3a, 12a, and 14a, respectively) modified.	Modified to account for the Main Treatment Period and/or Extension Treatment Period.
Section 6, Study Treatments	Second paragraph modified.	Modified to account for the Main Treatment Period and the Extension Treatment Period for more clarity.
Section 6.5.1, Permitted concomitant treatments (medications and therapies)	Modified due to addition of Extension Treatment Period to the study.	Modified to account for the Main Treatment Period and Extension Treatment Period.
Section 6.5.2, Prohibited concomitant treatments (medications and therapies)	The last paragraph modified.	Updated due to the addition of the Extension Treatment Period to the study.
Section 6.5.3, Vaccines	Reference to Advisory Committee on Immunization Practices added.	Clarification made that withdrawal of participants due to prohibited

Section # and Name	Description of Change	Brief Rationale
		concomitant medication not necessary (except for IV C5 inhibitors).
Section 6.5.4, Rescue medication	Last paragraph changed.	Clarification.
Section 7.1, Discontinuation of study medication	Paragraph updated.	Clarification.
Section 7.2, Participant discontinuation/withdrawal from the study	Criterion 3 updated with general prohibited concomitant medication being replaced with IV C5 inhibitors.	Clarification.
	Sentence on Early Withdrawal and Withdrawal Visits modified.	Updated due to the addition of the Extension Treatment Period.
Section 8.3.1, Time period and frequency for collecting AE and SAE information	Sentence shortened.	Deleted information on the Withdrawal and Safety Follow-Up Visits as this is already given the cross-referenced Section 4.4.
Section 8.3.5, Pregnancy	Withdrawal Visit included.	Updated in line with modifications made in Table 1-2.
Section 8.4, Safety signal detection	"(eg, AEs, vital signs, laboratory, or ECG results)" deleted.	Updated, since in the Extension Treatment Period only a subset of safety variables mentioned in the deleted parentheses will be collected.
Section 9.7, Planned interim analysis and data monitoring	Interim analysis was added.	Updated due to the addition of the Extension Treatment Period.
Section 10.4, Appendix 4, Contraceptive guidance and collection of pregnancy information	Contraception guidance updated to include the whole study rather than just the Main Treatment Period.	As above.

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
Fax	**US and Canada:** +1 800 880 6949 or +1 866 890 3175
Email	**Global:** DS_ICT@ucb.com (for interventional clinical studies)

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol title: A Phase 3b, multicenter, open-label, single-arm study to evaluate the safety, tolerability, and efficacy of zilucoplan in participants with generalized myasthenia gravis switching from intravenous complement component 5 inhibitors to subcutaneous zilucoplan

Short title: An open-label study to evaluate the safety, tolerability, and efficacy of subcutaneous zilucoplan in participants with generalized myasthenia gravis who were previously receiving intravenous complement component 5 inhibitors

Rationale:

Myasthenia gravis (MG) is a serious, sometimes life-threatening, debilitating condition associated with numerous symptoms including muscular weakness and fatigue. There remains a need for safe and effective treatments to conveniently treat patients with MG, including generalized myasthenia gravis (gMG), where the disease progresses beyond the ocular muscles and affects multiple muscle groups throughout the body. Some patients can manage their symptoms with oral medications such as an oral acetylcholinesterase inhibitors, corticosteroids, or nonsteroidal immunosuppressants. In addition, intravenous immunoglobulin G and plasma exchange treatment could be utilized as well. For those whose symptoms are not well managed by these medications, a potential alternative is long term treatment with approved intravenous (IV) complement component 5 (C5) inhibitors (eg, eculizumab or ravulizumab) which have proven effective at treating MG symptoms. However, there remains a need for new therapeutic options available to patients for whom IV infusions represent a high administration burden, have difficult venous access, or who are in underserved or rural populations where economic access to IV infusions is prohibitive. MG0017 aims to evaluate the disease control and safety and tolerability after switching from an approved IV C5 inhibitor to subcutaneous (SC) zilucoplan (ZLP), as well as the evaluation of patient satisfaction and preference.

Objectives and endpoints

Table 1–1: Objectives and estimands/endpoints

Objectives	Estimands/endpoints
Primary	
To evaluate the safety and tolerability of switching from IV C5 inhibitors to SC ZLP in study participants with gMG	The primary safety endpoints are: • Incidence of TEAEs over the Main Treatment Period • Incidence of TEAEs leading to withdrawal of study medication over the Main Treatment Period

Table 1–1: Objectives and estimands/endpoints

Objectives	Estimands/endpoints
Secondary	
To evaluate the efficacy of SC ZLP after switching from IV C5 inhibitors in study participants with gMG	The secondary efficacy estimand is: • Treatment: ZLP administered by daily SC injections (0.3mg/kg/day) • Target population: Adult study participants with gMG currently receiving an IV C5 inhibitor approved for the treatment of gMG according to the protocol-specified inclusion/exclusion criteria • Endpoint: CFB to Week 12 in MG-ADL score • Intercurrent event handling: The intercurrent events considered in this study are: – Administration of rescue therapy or changes in SOC dose regimens. Data collected at and after the point of the intercurrent event will be used as collected to gain understanding of clinical practice. – Participant discontinuation from the study. It will be assumed that the participant had remained on their treatment (regardless of rescue therapy administration) throughout the study (ie, a "hypothetical strategy" assuming participants did not discontinue the study and remained on treatment). • Population level summary: The mean of the endpoint
To evaluate the efficacy of SC ZLP after switching from IV C5 inhibitors on an additional efficacy endpoint in study participants with gMG	The secondary efficacy endpoint is: • CFB to Week 12 in the QMG score This endpoint will be analyzed following the same estimand structure as defined for the MG-ADL score. The endpoint assessed will change accordingly.
To evaluate safety and tolerability of SC ZLP after switching from IV C5 inhibitors on additional safety measures in study participants with gMG	The secondary safety endpoints are: • Incidence of serious TEAEs over the Main Treatment Period • Incidence of study withdrawal over the Main Treatment Period
Other	
To further explore the efficacy of SC ZLP on additional efficacy endpoints after switching from IV C5 inhibitors in study participants with gMG	The other efficacy endpoints are: • Time to first receipt of rescue therapy over the Main Treatment Period • Change in SOC therapy medication dose regimen for gMG during the Main Treatment Period

Table 1–1: Objectives and estimands/endpoints

Objectives	Estimands/endpoints
	• Achievement of Minimal Manifestation Status per MGFA-PIS at Week 12 without rescue therapy • Achieving MSE, defined as an MG-ADL of 0 or 1 at Week 12 without rescue therapy • CFB to Week 12 in QMG subscores: ocular, bulbar, respiratory, limb • CFB to Week 12 in MG-QOL15r score • MG-ADL score responder rate (responder is defined as achieving ≥3-point improvement from Baseline [decrease] at Week 12 and not having taken rescue therapy) • QMG score responder rate (responder is defined as achieving ≥5-point improvement from Baseline [decrease] at Week 12 and not having taken rescue therapy)
To explore the time needed for administration of SC ZLP	The other endpoint is: • Time needed for administration of SC ZLP
To explore study participants' treatment satisfaction following the use of SC ZLP	The other endpoint is: • CFB to Week 12 in TSQM-9 scores
To explore study participant preference following the use of SC ZLP	The other endpoint is: • Patient Preference assessment at Week 12
To further evaluate the safety and tolerability of SC ZLP after switching from IV C5 inhibitors on other safety measures in study participants with gMG	The other safety endpoints are: • CFB[a] to Week 12 in clinical laboratory tests • CFB[a] to Week 12 in physical examination • ECG[a] • C-SSRS • Incidence of TEAEs
To evaluate the PK of SC ZLP after switching from IV C5 inhibitors	The other PK endpoint is: • Plasma concentrations of ZLP and its major metabolites over the Main Treatment Period [redacted]
To evaluate the PD of SC ZLP after switching from IV C5 inhibitors	The other PD endpoint is: • sRBC lysis assay for evaluation of classical complement pathway activation over the Main Treatment Period

[a] In this study, the clinical laboratory, physical examination, and ECG assessments conducted at Screening will be considered the baseline values for evaluating of the other safety endpoints.

C5=complement component 5; CFB=change from Baseline; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; gMG=generalized myasthenia gravis; IV=intravenous; MG-ADL=Myasthenia Gravis-Activities of Daily Living; MG-QOL15r=Myasthenia Gravis – Quality of Life revised;

Table 1–1: Objectives and estimands/endpoints

Objectives	Estimands/endpoints

MGFA-PIS=Myasthenia Gravis Foundation of America Post-Intervention Status; MSE=Minimal Symptom Expression; PD=pharmacodynamic(s); PK=pharmacokinetic(s); QMG= Quantitative Myasthenia Gravis; SC=subcutaneous; SOC=standard of care; sRBC=sheep red blood cell; TEAE=treatment-emergent adverse event; TSQM-9=9-item Treatment Satisfaction Questionnaire for Medication; ZLP=zilucoplan

Overall design

MG0017 is a Phase 3b, multicenter, open-label, single-arm study to evaluate the safety, tolerability, and efficacy of ZLP in adult study participants (≥18 years of age) with gMG switching from their current IV C5 inhibitor to SC ZLP.

To be eligible to participate in this study, participants must be currently receiving an IV C5 inhibitor approved for the treatment of gMG for at least 3 months (for eculizumab) or 4 months (for ravulizumab) prior to Screening (with the last dose being administered at the Screening Visit ±3 days), considered to have a clinically stable disease as per the Investigator's judgment prior to Screening, and willing to switch from their current IV C5 inhibitor to SC ZLP.

The study includes a 2-week or 8-week Screening Period (for participants receiving eculizumab or ravulizumab, respectively), a 12-week Main Treatment Period, and an optional Extension Treatment Period. A Safety Follow-up (SFU) Visit should be performed 40 days (±7 days) after the last dose of study medication.

The Screening Visit should be scheduled to coincide with the regularly scheduled study participant's IV C5 inhibitor administration (±3 days). Up to and including the time of the Screening Visit, study participants will continue to receive their IV C5 inhibitor at the recommended dose regimen.

On Day 1, study participants will receive ZLP 0.3mg/kg administered SC. Following in-clinic education and training, all study participants will self-inject daily SC doses of study medication for the subsequent 12 weeks. Of note, there will be no washout period during the study where study participants are not receiving treatment for MG.

During the Main Treatment Period, study participants will be contacted via phone call at Week 1, Week 4, and Week 8 to assess safety and tolerability. During these phone call visits, the Myasthenia Gravis-Activities of Daily Living (MG-ADL) assessment will also be performed. Study participants will return to the clinic at Week 2 and Week 12 to evaluate safety, tolerability, and efficacy. Additional assessments will include questionnaires, pharmacokinetics (PK), and pharmacodynamics (PD).

All study participants who complete the 12-week Main Treatment Period without discontinuing study medication will have the option to continue ZLP treatment in the Extension Treatment Period after the Week 12 visit. Participants who withdraw during the Main Treatment Period will complete an Early Withdrawal (EW) Visit followed by a SFU Visit 40 days (±7 days) after the last dose of study medication. Participants who opt not to continue into the Extension Treatment Period will complete a SFU Visit 40 days (±7 days) after the last dose of study medication.

The Extension Treatment Period consists of in-clinic visits every 12 weeks (±7 days) and will continue until all participants are withdrawn, until ZLP is approved and available in the US, or

until further notice from the Sponsor. During these visits, ZLP accountability and resupply will be performed, medications updated, and safety will be assessed. Participants who withdraw or discontinue ZLP during the Extension Treatment Period will complete a Withdrawal Visit followed by a SFU Visit 40 days (±7 days) after the last dose of study medication. Participants who transition to commercially available ZLP will complete a Withdrawal Visit but will not require a SFU Visit. If by the time a participant completes the Main Treatment Period ZLP is commercially available, the participant may transition to commercially available ZLP directly following the Week 12 visit at the end of the Main Treatment Period.

Number of participants

Twenty study participants are planned to be enrolled in the study.

Treatment groups and duration

Study participants will be treated with SC ZLP (0.3mg/kg/day).

The duration of the study depends on the participant's decision to continue into the Extension Treatment Period and on the commercial availability of ZLP in the US (or until further notice from the Sponsor).

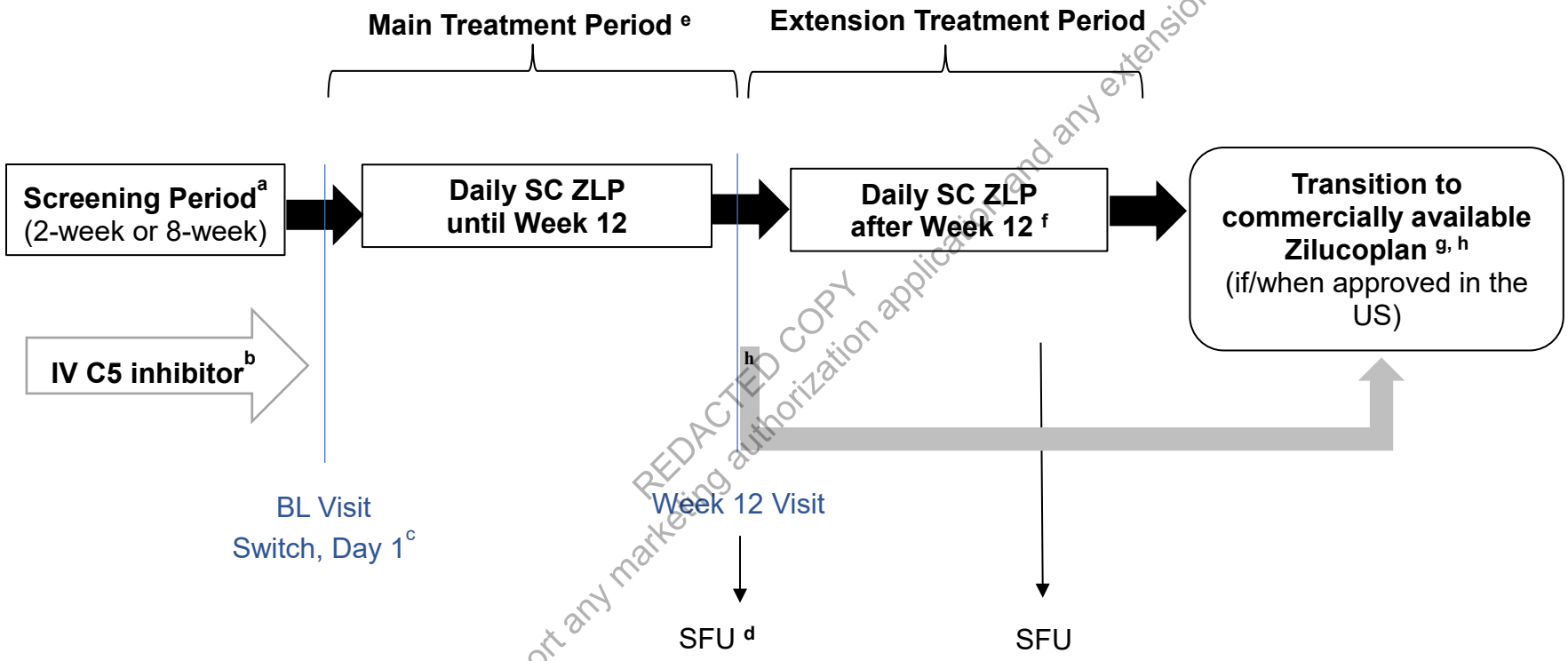
The total duration of the study per participant completing the Main Treatment Period and not continuing into the Extension Treatment Period will be approximately 20 to 26 weeks:

- 2-week Screening Period for study participants receiving eculizumab or an 8-week Screening Period for study participants receiving ravulizumab
- 12-week Main Treatment Period
- An SFU Visit 40 days (±7 days) after the last dose of study medication.

1.2 Schema

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

Figure 1–1: MG0017 study schematic



BL=Baseline; C5=complement component 5; EW=Early Withdrawal; IV=intravenous; MG-ADL=Myasthenia Gravis-Activities of Daily Living; SC=subcutaneous; SFU=Safety Follow-up; ZLP=zilucoplan

[a] The Screening Visit should be scheduled to coincide with the regularly scheduled study participant IV C5 inhibitor administration (±3 days).

[b] Up to and including the time of the Screening Visit, study participants will continue to receive their IV C5 inhibitor at the recommended dose regimen. The last regularly scheduled IV C5 inhibitor administration must occur at the Screening Visit (±3 days) to ensure approximately a 2-week (eculizumab) or 8-week (ravulizumab) interval between the last regularly scheduled IV C5 inhibitor administration and the first SC ZLP administration at the Baseline Visit, respectively.

[c] At Day 1 of the Main Treatment Period (BL) in case of no more than a 2-point change in study participants' MG-ADL score compared to the Screening Visit (±3 days), study participants will switch to SC ZLP (0.3mg/kg/day).

[d] For participants who complete the Main Treatment Period but decide not to continue into the Extension Treatment Period: An SFU Visit will be performed 40 days (±7 days) after the last dose of study medication.
[e] If a study participant permanently withdraws from the study prior to the Week 12 visit, an EW Visit will be performed.
[f] For study participants continuing into the Extension Treatment Period, SC ZLP will be provided after completion of the Main Treatment Period until they discontinue ZLP, or are able to receive commercial ZLP (if/when available in the US), or until further notice from the Sponsor. For participants who discontinue ZLP during the Extension Treatment Period, a Withdrawal Visit and a SFU Visit will be conducted 40 days (±7 days) after the last dose of study medication.
[g] Participants who transition to commercially available ZLP (if/when approved in the US) will complete a Withdrawal Visit but will not require a SFU Visit.
[h] If ZLP is commercially available by the time a participant completes the Main Treatment Period, the participant may transition to commercially available ZLP directly following the Week 12 visit at the end of the Main Treatment Period.

1.3 Schedule of Activities

The schedule of study activities is provided in Table 1–2.

Table 1–2: Schedule of Activities

Study Period	Screening Period[a]	Main Treatment Period						Extension Treatment Period	EW/ Withdrawal Visit[b,w] (In-clinic)	SFU Visit (In-clinic)[c]	Rescue Therapy Visit (If applicable)[d]
Visit name	Screening Visit (In-clinic)	Baseline[e] (In-clinic)	Week 1 (Phone call)	Week 2 (In-clinic)	Week 4 (Phone call)	Week 8 (Phone call)	Week 12 (In-clinic)	Week 24, 36, 48… every 12 weeks (In-clinic)			
Visit #	1	2	3	4	5	6	7	8, 9, 10…	–	–	–
Day	-14 or -56	1	8	15	29	57	84	168, 252, 336…		(Last dose +40 days)	
Visit Window[f]	±3d	±2d	±2d	±2d	±2d	±2d	±2d	±7d		±7d	
Procedure/activity											
Informed consent[g]	X										
Verification of inclusion/exclusion criteria[g]	X	X									
Study participant safety card issued		X									
Demography	X										
Medical/surgical history[h]	X										
Reason for switch from IV C5 inhibitor	X										
Height and weight[i]	X						X	X	X		
Prior and concomitant medications[j]	X	X	X	X	X	X	X	X	X	X	X

Table 1–2: Schedule of Activities

Study Period	Screening Period[a]	Main Treatment Period						Extension Treatment Period	EW/ With-drawal Visit[b,w] (In-clinic)	SFU Visit (In-clinic)[c]	Rescue Therapy Visit (If applicable)[d]
Visit name	Screening Visit (In-clinic)	Baseline[e] (In-clinic)	Week 1 (Phone call)	Week 2 (In-clinic)	Week 4 (Phone call)	Week 8 (Phone call)	Week 12 (In-clinic)	Week 24, 36, 48… every 12 weeks (In-clinic)			
Visit #	1	2	3	4	5	6	7	8, 9, 10…	–	–	–
Day	-14 or -56	1	8	15	29	57	84	168, 252, 336…		(Last dose +40 days)	
Visit Window[f]	±3d	±2d	±2d	±2d	±2d	±2d	±2d	±7d		±7d	
Procedure/activity											
Neisseria meningitidis vaccination[k]	X	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC		
Pregnancy test[l]	X	X		X		X	X	X	X	X	
Clinical laboratory tests (hematology, clinical chemistry, and urinalysis)[m, n]	X			X			X		X		X
Complete physical examination[n]	X						X		X	X	X
Vital signs	X	X					X		X	X	X
12-lead ECG[n]	X			X			X		X	X	
Adverse events[o]	X	X	X	X	X	X	X	X	X	X	X
C-SSRS[p]	X	X					X	X	X	X	
MG-ADL[r]	X	X	X	X	X	X	X		X		X
QMG scale[q, r]		X		X			X		X		X

Table 1–2: Schedule of Activities

Study Period	Screening Period[a]	Main Treatment Period						Extension Treatment Period	EW/ With-drawal Visit[b,w] (In-clinic)	SFU Visit (In-clinic)[c]	Rescue Therapy Visit (If applicable)[d]
Visit name	Screening Visit (In-clinic)	Baseline[e] (In-clinic)	Week 1 (Phone call)	Week 2 (In-clinic)	Week 4 (Phone call)	Week 8 (Phone call)	Week 12 (In-clinic)	Week 24, 36, 48… every 12 weeks (In-clinic)			
Visit #	1	2	3	4	5	6	7	8, 9, 10…	–	–	–
Day	-14 or -56	1	8	15	29	57	84	168, 252, 336…		(Last dose +40 days)	
Visit Window[f]	±3d	±2d	±2d	±2d	±2d	±2d	±2d	±7d		±7d	
Procedure/activity											
MG-QOL15r[r]		X		X			X		X		X
MGFA Post-Intervention Status							X		X		X
TSQM-9[r]		X					X		X		
Patient Preference assessment[r]							X		X		
Blood sampling for PK[s,t]				X			X		X		X
Blood sampling for PD[s,t] (sRBC lysis assay)		X		X			X		X		X
Last regularly scheduled IV C5 inhibitor administration[u]	X										
SC ZLP dispensed[x]		X		X			X	X			
SC ZLP administration[v]		X	X	X	X	X	X	X			X
Time needed for administration of SC ZLP				X			X				

Table 1–2: Schedule of Activities

Study Period	Screening Period[a]	Main Treatment Period						Extension Treatment Period	EW/ Withdrawal Visit[b,w] (In-clinic)	SFU Visit (In-clinic)[c]	Rescue Therapy Visit (If applicable)[d]
Visit name	Screening Visit (In-clinic)	Baseline[e] (In-clinic)	Week 1 (Phone call)	Week 2 (In-clinic)	Week 4 (Phone call)	Week 8 (Phone call)	Week 12 (In-clinic)	Week 24, 36, 48… every 12 weeks (In-clinic)			
Visit #	1	2	3	4	5	6	7	8, 9, 10…	–	–	–
Day	-14 or -56	1	8	15	29	57	84	168, 252, 336…		(Last dose +40 days)	
Visit Window[f]	±3d	±2d	±2d	±2d	±2d	±2d	±2d	±7d		±7d	
Procedure/activity											
Date of first receipt of rescue therapy											X

AChR=acetylcholine receptor; AE=adverse event; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; C5=complement component 5; COVID-19=coronavirus disease 2019; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; EW=Early Withdrawal; FDA=Food and Drug Administration; gMG=generalized myasthenia gravis; IV=intravenous; MG=myasthenia gravis; MG-ADL=Myasthenia Gravis-Activities of Daily Living; MGFA=Myasthenia Gravis Foundation of America; MG-QOL15r=Myasthenia Gravis-Quality of Life Revised; PD=pharmacodynamic(s); PLEX=plasma exchange; PK=pharmacokinetic(s); QMG=Quantitative Myasthenia Gravis; SAE=serious adverse event; SC=subcutaneous(ly); SFU=Safety Follow-up; SOC=standard of care; sRBC=sheep red blood cell; TSQM-9=9-item Treatment Satisfaction Questionnaire for Medication; ZLP=zilucoplan

[a] The Screening Visit should be scheduled to coincide with the regularly scheduled study participant IV C5 inhibitor administration (±3 days) (Figure 1–1).

[b] If a study participant permanently withdraws from the study prior to the Week 12 visit, the study participant should return to the clinic for an EW Visit as soon as possible but no later than the next scheduled visit.

[c] Study participants who discontinue ZLP at any point in the study will be required to return to the clinic for a SFU Visit performed at 40±7 days after their last dose to gather additional safety information, including information about on ongoing AEs and the reporting any new SAEs since the last study visit.

[d] For study participants who require rescue therapy (see Section 6.5.4), a Rescue Therapy Visit should be conducted prior to the initiation of rescue therapy. If the Rescue Therapy Visit coincides with a regularly scheduled study visit, then overlapping study procedures do not need to be duplicated. The study participant will continue ZLP treatment while undergoing rescue therapy if it is considered by the Investigator to be in his/her best interest.

[e] In circumstances where COVID-19 disruptions lead to a study participant being unable to return for Day 1 after 14 or 56 days of the Screening Period, respectively, additional days may be included in the Screening Period. Contact with the Medical Monitor is requested in such situations.

Table 1–2: Schedule of Activities

Study Period	Screening Period[a]	Main Treatment Period						Extension Treatment Period	EW/ With-drawal Visit[b,w] (In-clinic)	SFU Visit (In-clinic)[c]	Rescue Therapy Visit (If applicable)[d]
Visit name	Screening Visit (In-clinic)	Baseline[e] (In-clinic)	Week 1 (Phone call)	Week 2 (In-clinic)	Week 4 (Phone call)	Week 8 (Phone call)	Week 12 (In-clinic)	Week 24, 36, 48… every 12 weeks (In-clinic)			
Visit #	1	2	3	4	5	6	7	8, 9, 10…	–	–	–
Day	-14 or -56	1	8	15	29	57	84	168, 252, 336…		(Last dose +40 days)	
Visit Window[f]	±3d	±2d	±2d	±2d	±2d	±2d	±2d	±7d		±7d	
Procedure/activity											

[f] The visit windows provided are with respect to the Baseline Visit with the exception of the SFU Visit, in which the visit window applies to 40 days after the last dose of study medication.

[g] Procedures performed as SOC during the Screening Period may be used to determine eligibility. Informed consent must be obtained prior to performing any study-specific procedures that are not SOC.

[h] Screening includes disease history with documented diagnosis of gMG by the MGFA criteria (Class II-IVa) and documented serology for AChR autoantibodies.

[i] Height will be measured only at Screening.

[j] All prescriptions and over-the-counter medications taken during the 30 days prior to Screening through the last study visit will be documented. Note: A complete history of medications taken for the treatment of gMG will be collected.

[k] To reduce the risk of meningococcal infection (*Neisseria meningitidis*), all study participants must be vaccinated against meningococcal infections, with at least 1 dose of quadrivalent meningococcal vaccine and meningococcal serotype B vaccine at least 14 days prior to the first dose of ZLP if not vaccinated within 3 years prior to the start of study medication. The second dose of the primary vaccination cycle can be administered during the study. Participants who initiate study medication less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics (eg, penicillin V 500mg twice daily, third generation cephalosporin) until at least 2 weeks after the initial dose of vaccine(s). The use of fluoroquinolone or macrolide antibiotics is not recommended due to the potential for exacerbation of MG. Booster vaccinations should be administered in accordance with the most current relevant guideline (ie, Advisory Committee on Immunization Practices, United States).

[l] For all female study participants of childbearing potential, a negative serum pregnancy test must be documented at Screening. All other pregnancy tests will be performed via urine. At the Week 2 Visit, study participants will receive a home pregnancy testing kit with instruction to complete the test on the day of the Week 8 Visit prior to the conduct of the phone call visit, such that the result will be available to report to the site staff during the call.

Table 1–2: Schedule of Activities

Study Period	Screening Period[a]	Main Treatment Period						Extension Treatment Period	EW/ Withdrawal Visit[b,w] (In-clinic)	SFU Visit (In-clinic)[c]	Rescue Therapy Visit (If applicable)[d]
Visit name	Screening Visit (In-clinic)	Baseline[e] (In-clinic)	Week 1 (Phone call)	Week 2 (In-clinic)	Week 4 (Phone call)	Week 8 (Phone call)	Week 12 (In-clinic)	Week 24, 36, 48… every 12 weeks (In-clinic)			
Visit #	1	2	3	4	5	6	7	8, 9, 10…	–	–	–
Day	-14 or -56	1	8	15	29	57	84	168, 252, 336…		(Last dose +40 days)	
Visit Window[f]	±3d	±2d	±2d	±2d	±2d	±2d	±2d	±7d		±7d	
Procedure/activity											

[m] Samples for hematology, clinical chemistry, and urinalysis should be obtained prior to administration of study medication at applicable visits. Clinical chemistry tests include AST/serum glutamic-oxaloacetic transaminase, ALT/serum glutamic-pyruvic transaminase, ALP, total and direct bilirubin, amylase, and lipase.

[n] Clinical laboratory, physical examination, and ECG assessments conducted at Screening will be considered the baseline values for evaluating of the other safety endpoints.

[o] All AEs and SAEs should be monitored until resolution or stabilization. Serious AEs that occur within 40 days after the last dose of study medication should be reported using the procedures outlined in Appendix 3 (Section 10.3).

[p] In accordance with the draft FDA Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials Guidance (Food and Drug Administration, Guidance for Industry, 2012) study participants will be asked to complete the C-SSRS at study visits as specified.

[q] The QMG should be performed at approximately the same time of day prior to dosing (preferably in the morning) and administered by the same well-trained evaluator (eg, neurologist, physical therapist, or other study staff) at each visit throughout the study.

[r] Myasthenia Gravis-Quality of Life Revised, TSQM-9, Patient Preference assessment, QMG, and MG-ADL should be performed prior to dosing and prior to any other study procedures.

[s] For local Rescue Therapy Visits only, blood samples for PK and PD analyses will be collected within 1 hour prior to administration of each round of rescue therapy. If a study participant receives PLEX treatment as rescue therapy, PK will be measured in the exchanged plasma. If rescue therapy is administered at a location separate from the clinical site, then there is no need to collect blood samples for PK/PD analyses.

[t] Blood samples for PK and PD analyses will be obtained at planned visits prior to dosing (within 1 hour of dosing). Back-up specimens may be retained for future exploratory biomarker analyses.

Table 1–2: Schedule of Activities

Study Period	Screening Period[a]	Main Treatment Period						Extension Treatment Period	EW/ With-drawal Visit[b,w] (In-clinic)	SFU Visit (In-clinic)[c]	Rescue Therapy Visit (If applicable)[d]
Visit name	Screening Visit (In-clinic)	Baseline[e] (In-clinic)	Week 1 (Phone call)	Week 2 (In-clinic)	Week 4 (Phone call)	Week 8 (Phone call)	Week 12 (In-clinic)	Week 24, 36, 48… every 12 weeks (In-clinic)			
Visit #	1	2	3	4	5	6	7	8, 9, 10…	–	–	–
Day	-14 or -56	1	8	15	29	57	84	168, 252, 336…		(Last dose +40 days)	
Visit Window[f]	±3d	±2d	±2d	±2d	±2d	±2d	±2d	±7d		±7d	
Procedure/activity											

[u] Up to and including the time of the Screening Visit, study participants will continue to receive their IV C5 inhibitor at the recommended dose regimen. The last regularly scheduled IV C5 inhibitor administration cannot occur beyond the Screening Visit (±3 days) to ensure approximately a 2-week (for eculizumab) or 8-week (for ravulizumab) interval between the last regularly scheduled IV C5 inhibitor administration and the first SC ZLP administration at the Baseline Visit, respectively).

[v] Following the first in-clinic administration of ZLP at Baseline and in-clinic education and training, all study participants will self-inject daily SC doses of study medication. During the Main Treatment Period, dosing on in-clinic study visit days should be withheld until all assessments have been completed. On days when rescue therapy is concurrently administered, dosing should be withheld until after administration of rescue therapy and PK/PD sampling.

[w] Participants who withdraw during the Extension Treatment Period will complete a Withdrawal Visit as soon as possible but no later than the next scheduled visit. At the Withdrawal Visit, only the following study assessments need to be completed: prior and concomitant medications, weight, pregnancy testing (for women of childbearing potential), C-SSRS, and collection of AEs.

[x] At the Week 12 Visit, ZLP dispensation only occurs for study participants continuing into the Extension Treatment Period.

2 INTRODUCTION

2.1 Study rationale

Myasthenia gravis is a serious, sometimes life-threatening, debilitating condition associated with numerous symptoms including muscular weakness and fatigue. There remains a need for safe and effective treatments to conveniently treat patients with MG, including gMG, where the disease progresses beyond the ocular muscles and affects multiple muscle groups throughout the body. Some patients can manage their symptoms with oral medications such as an oral acetylcholinesterase inhibitors, corticosteroids, or nonsteroidal immunosuppressants. In addition, intravenous immunoglobulin G (IVIG) and plasma exchange (PLEX) treatment could be utilized as well. For those whose symptoms are not well managed by these medications, a potential alternative is long term treatment with approved IV C5 inhibitors (eg, eculizumab or ravulizumab) which have proven effective at treating MG symptoms. However, there remains a need for new therapeutic options available to patients for whom IV infusions represent a high administration burden, have difficult venous access, or who are in underserved or rural populations where economic access to IV infusions is prohibitive. MG0017 aims to evaluate the disease control and safety and tolerability after switching from an approved IV C5 inhibitor to SC ZLP, as well as the evaluation of patient satisfaction and preference.

2.2 Background

Myasthenia gravis is a rare complement-mediated autoimmune disease characterized by the production of autoantibodies targeting proteins that are critical for the normal transmission of neurotransmitter signals from nerves to muscles. The prevalence of MG in the US and EU is estimated at approximately 60,000 and 191,000 cases, respectively. In 15% of patients with MG, symptoms remain confined to the ocular muscles. In approximately 85% of patients, MG progresses beyond the ocular muscles to affect multiple muscle groups throughout the body, a condition that is typically referred to as gMG (Gilhus, 2016).

Patients with gMG present with muscle weakness that characteristically becomes more severe with repeated use and recovers with rest. Symptoms are typically at their mildest in the morning, when overnight inactivity enables replenishment of acetylcholine levels in presynaptic motor nerve terminals, and worsen during the course of the day. Muscle weakness can be localized to specific muscles, but often progresses to more diffuse muscle weakness (Gilhus, 2016; Gilhus and Verschuuren, 2015; Chamanza et al, 2010). Generalized MG symptoms can become life-threatening when muscle weakness involves the diaphragm and intercostal muscles in the chest wall that are responsible for breathing. The most dangerous complication of gMG, known as myasthenic crisis, requires hospitalization, intubation, and mechanical ventilation. Approximately 15% to 20% of patients with gMG will experience a myasthenic crisis within 2 years of diagnosis (Ramizuddin, 2014).

Zilucoplan (RA101495) is a 15-amino acid macrocyclic peptide complement inhibitor designed for the treatment of conditions in which inappropriate activation of C5 has been demonstrated to play a role. Zilucoplan binds to C5 with high affinity and prevents its cleavage by C5 convertases into the cleavage products C5a and C5b. Inhibition of C5 cleavage prevents the downstream assembly and cytolytic activity of the membrane attack complex. Pharmacologically, ZLP has demonstrated dose-dependent inhibition of C5a and C5b formation

following activation of classical or alternative complement pathways, as well as inhibition of red blood cell lysis in the serum/plasma from various species.

Zilucoplan is being investigated in patients with amyotrophic lateral sclerosis and gMG, and also other complement-mediated diseases are being considered.

Inhibition of C5 for the treatment of gMG has already been shown to be effective in clinical studies with the C5-blocking antibodies, eculizumab (Howard, 2018; Howard et al, 2013) and ravulizumab (Vu et al, 2022), which established that inhibition of the terminal complement cascade by blocking cleavage of C5 is a clinically validated approach for treating gMG. However, unlike eculizumab and ravulizumab, ZLP provides patients with the advantages of SC self-administration at home.

The clinical efficacy of ZLP in gMG has been shown in a Phase 2 study, MG0009 (previously RA101495-02.201), and in a Phase 3 study, MG0010 (previously RA101495-02.301). In addition, ZLP has shown a favorable safety and tolerability profile across all completed studies. Further details are provided in the ZLP Investigator's Brochure (IB).

2.3 Benefit/risk assessment

Zilucoplan is being developed to treat patients with gMG.

In the Phase 2 study, MG0009, ZLP 0.3mg/kg/day showed a statistically significant and clinically meaningful benefit as measured by improvement on the primary endpoint, the Quantitative Myasthenia Gravis (QMG) score, compared to placebo over 12 weeks, as well as on the MG-ADL (key secondary endpoint), the Myasthenia Gravis-Quality of Life Revised (MG-QOL15r), and the Myasthenia Gravis Composite (MGC) score (Howard et al, 2020).

In the pivotal Phase 3 study, MG0010, a clinically meaningful and statistically significant improvement from Baseline in MG-ADL total score at Week 12 (primary endpoint) was observed for the ZLP treatment group (ZLP 0.3mg/kg/day) vs placebo. Significant improvements from Baseline in QMG, MGC, and MG-QoL15r scores were also observed at Week 12 for the ZLP treatment group vs placebo. Zilucoplan was well tolerated, and no major unexpected safety findings were identified compared to earlier ZLP studies.

Moreover, in both of these studies, the placebo-corrected clinical efficacy of ZLP 0.3mg/kg/day administered SC as measured by the QMG and MG-ADL at Week 12 was numerically superior to the efficacy observed in the Phase 3 study with the approved IV C5 inhibitors eculizumab and ravulizumab at Week 26 after treatment initiation with a similar safety and tolerability profile (Howard et al, 2017; Vu et al, 2022).

Given the known increased risk of meningococcal infection (*Neisseria meningitidis*) associated with inhibition or inherited deficiency of C5, participants who participate in this study with ZLP will be required to have documentation of at least 1 dose of *N. meningitidis* vaccination at least 2 weeks prior to study medication administration. In addition, while on treatment with ZLP, study participants will be monitored closely for signs and symptoms of *N. meningitidis* infection. A study participant safety card detailing the signs and symptoms of infection, with instructions to seek immediate medical attention if any such symptoms occur, will be provided to each study participant. Study participants must be vaccinated with at least 1 dose each of quadrivalent meningococcal vaccine and meningococcal serotype B vaccine against *N. meningitidis* at least 14 days before the first administration of SC ZLP if not vaccinated within 3 years prior to the

start of study medication. The second dose of the primary vaccination cycle can be administered during the study. Booster vaccinations should be administered according to the most current relevant guideline (ie, Advisory Committee on Immunization Practices, United States). (Section 1.3).

Given the safety and tolerability profile of ZLP, the efficacy data from the Phase 2 study, MG0009, the Phase 3 study, MG0010, and the efficacy and safety profile of IV C5 inhibitors approved for the treatment of gMG, the overall risk to the participants in this study is deemed to be low and the benefit-risk balance for study participants is anticipated to be favorable.

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

3 OBJECTIVES AND ENDPOINTS

Table 3–1: Objectives and estimands/endpoints

Objectives	Estimands/endpoints
Primary	
To evaluate the safety and tolerability of switching from IV C5 inhibitors to SC ZLP in study participants with gMG	The primary safety endpoints are: • Incidence of TEAEs over the Main Treatment Period • Incidence of TEAEs leading to withdrawal of study medication over the Main Treatment Period
Secondary	
To evaluate the efficacy of SC ZLP after switching from IV C5 inhibitors in study participants with gMG	The secondary efficacy estimand is: • Treatment: ZLP administered by daily SC injections (0.3mg/kg/day) • Target population: Adult study participants with gMG currently receiving an IV C5 inhibitor approved for the treatment of gMG according to the protocol-specified inclusion/exclusion criteria • Endpoint: CFB to Week 12 in MG-ADL score • Intercurrent event handling: The intercurrent events considered in this study are: – Administration of rescue therapy or changes in SOC dose regimens. Data collected at and after the point of the intercurrent event will be used as collected to gain understanding of clinical practice. – Participant discontinuation from the study. It will be assumed that the participant had remained on their treatment (regardless of rescue therapy administration) throughout the study (ie, a "hypothetical strategy" assuming participants did not discontinue the study and remained on treatment).

Table 3–1: Objectives and estimands/endpoints

Objectives	Estimands/endpoints
	• Population level summary: The mean of the endpoint
To evaluate the efficacy of SC ZLP after switching from IV C5 inhibitors on an additional efficacy endpoint in study participants with gMG	The secondary efficacy endpoint is: • CFB to Week 12 in the QMG score This endpoint will be analyzed following the same estimand structure as defined for the MG-ADL score. The endpoint assessed will change accordingly.
To evaluate safety and tolerability of SC ZLP after switching from IV C5 inhibitors on additional safety measures in study participants with gMG	The secondary safety endpoints are: • Incidence of serious TEAEs over the Main Treatment Period • Incidence of study withdrawal over the Main Treatment Period
Other	
To further explore the efficacy of SC ZLP on additional efficacy endpoints after switching from IV C5 inhibitors in study participants with gMG	The other efficacy endpoints are: • Time to first receipt of rescue therapy over the Main Treatment Period • Change in SOC therapy medication dose regimen for gMG during the Main Treatment Period • Achievement of Minimal Manifestation Status per MGFA-PIS at Week 12 without rescue therapy • Achieving MSE, defined as an MG-ADL of 0 or 1 at Week 12 without rescue therapy • CFB to Week 12 in QMG subscores: ocular, bulbar, respiratory, limb • CFB to Week 12 in MG-QOL15r score • MG-ADL score responder rate (responder is defined as achieving ≥ 3-point improvement from Baseline [decrease] at Week 12 and not having taken rescue therapy) • QMG score responder rate (responder is defined as achieving ≥5-point improvement from Baseline [decrease] at Week 12 and not having taken rescue therapy)
To explore the time needed for administration of SC ZLP	The other endpoint is: • Time needed for administration of SC ZLP
To explore study participants' treatment satisfaction following the use of SC ZLP	The other endpoint is: • CFB to Week 12 in TSQM-9 scores
To explore study participant preference following the use of SC ZLP	The other endpoint is: • Patient Preference assessment at Week 12

Table 3–1: Objectives and estimands/endpoints

Objectives	Estimands/endpoints
To further evaluate the safety and tolerability of SC ZLP after switching from IV C5 inhibitors on other safety measures in study participants with gMG	The other safety endpoints are: • CFB[a] to Week 12 in clinical laboratory tests • CFB[a] to Week 12 in physical examination • ECG[a] • C-SSRS • Incidence of TEAEs
To evaluate the PK of SC ZLP after switching from IV C5 inhibitors	The other PK endpoint is: • Plasma concentrations of ZLP and its major metabolites over the Main Treatment Period [redacted]
To evaluate the PD of SC ZLP after switching from IV C5 inhibitors	The other PD endpoint is: • sRBC lysis assay for evaluation of classical complement pathway activation over the Main Treatment Period

[a] In this study, the clinical laboratory, physical examination, and ECG assessments conducted at Screening will be considered the baseline values for evaluating of the other safety endpoints.

C5=complement component 5; CFB=change from Baseline; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; gMG=generalized myasthenia gravis; IV=intravenous; MG-ADL=Myasthenia Gravis-Activities of Daily Living; MG-QOL15r=Myasthenia Gravis – Quality of Life revised; MGFA-PIS=Myasthenia Gravis Foundation of America Post-Intervention Status; MSE=Minimal Symptom Expression; PD=pharmacodynamic(s); PK=pharmacokinetic(s); QMG= Quantitative Myasthenia Gravis; SC=subcutaneous; SOC=standard of care; sRBC=sheep red blood cell; TEAE=treatment-emergent adverse event; TSQM-9=9-item Treatment Satisfaction Questionnaire for Medication; ZLP=zilucoplan

3.1 Estimand/intercurrent event handling rationale and impact on the study

The estimand corresponding to the efficacy objective to evaluate the efficacy of SC ZLP after switching from IV C5 inhibitors in study participants with gMG, is described below:

- Treatment: ZLP administered by daily SC injections (0.3mg/kg/day).
- Target population: Adult study participants with gMG currently receiving an IV C5 inhibitor approved for the treatment of gMG according to the protocol-specified inclusion/exclusion criteria.
- Endpoint: Change from Baseline (CFB) to Week 12 in MG-ADL score.
- Intercurrent event handling: The intercurrent events considered in this study are:
  - Administration of a rescue therapy (Section 6.5.4) or changes in standard of care (SOC) dose regimens. Data collected at and after the point of the intercurrent event will be used as collected to gain understanding of clinical practice.
  - Participant discontinuation from the study. It is assumed that the participant had remained on their treatment (regardless of rescue therapy administration) throughout the study (ie,

a "hypothetical strategy" assuming participants did not discontinue the study and remained on treatment).

- Population-level summary: The mean of the endpoint.

One of the efficacy objectives of this Phase 3b study is to evaluate the efficacy of SC ZLP after switching from IV C5 inhibitors in study participants with gMG who are willing to switch to SC ZLP in a situation which can be common in clinical practice (with the arrival of new therapeutic agents). Thus, the intercurrent event handling strategy to consider data after the use of rescue therapy in the analysis and to assume that the study participant had remained on their treatment or on rescue therapy after study discontinuation is aligned with the study objective.

The same estimand structure defined for the MG-ADL score will be used to analyze the endpoint of CFB to Week 12 in QMG score.

4 STUDY DESIGN

4.1 Overall design

MG0017 is a Phase 3b, multicenter, open-label, single-arm study to evaluate the safety, tolerability, and efficacy of ZLP in study participants with gMG switching from their current IV C5 inhibitor to SC ZLP.

To be eligible to participate in this study, participants must be adults (≥18 years of age) with a documented diagnosis of gMG (Myasthenia Gravis Foundation of America [MGFA] Class II-IVa), currently receiving an IV C5 inhibitor approved for the treatment of gMG for at least 3 months (for eculizumab) or 4 months (for ravulizumab) prior to Screening (with the last dose being administered at the Screening Visit ±3 days), considered to have a clinically stable disease as per the Investigator's judgment prior to Screening, and willing to switch from their current IV C5 inhibitor to SC ZLP.

The planned enrollment is 20 study participants in the US.

The study includes a 2-week or 8-week Screening Period (for participants receiving eculizumab or ravulizumab, respectively), a 12-week Main Treatment Period, and an optional Extension Treatment Period. A SFU Visit should be performed 40 days (±7 days) after the last dose of study medication (Section 6.8, Section 1.2).

The Screening Visit should be scheduled to coincide with the regularly scheduled study participant's IV C5 inhibitor administration (±3 days). Up to and including the time of the Screening Visit, study participants will continue to receive their IV C5 inhibitor at the recommended dose regimen. The last regularly scheduled IV C5 inhibitor administration cannot occur beyond Day -14 (±3 days) of the Screening Period for study participants receiving eculizumab or beyond Day -56 (±3 days) of the Screening Period for study participants receiving ravulizumab to ensure approximately a 2-week or 8-week interval between the last regularly scheduled IV C5 inhibitor administration (administered at the Screening Visit ±3 days) and the first SC ZLP administration at the Baseline Visit, respectively.

At the end of the Screening Period and in case of no more than a 2-point change in study participants' MG-ADL score compared to the Screening Visit, study participants will enter the Main Treatment Period and will switch to SC ZLP (IV C5 inhibitor should not be administered after the Screening Visit). On Day 1, study participants will receive ZLP 0.3mg/kg administered

SC. Following in-clinic education and training, all study participants will self-inject daily SC doses of study medication for the subsequent 12 weeks. Single-use pre-filled syringes in injection devices will be provided for use during the study. Of note, there will be no washout period during the study where study participants are not receiving treatment for MG.

During the Main Treatment Period, study participants will be contacted via phone call at Week 1, Week 4, and Week 8 to assess safety and tolerability. During these phone call visits, the MG-ADL assessment will also be performed. Study participants will return to the clinic at Week 2 and Week 12 to evaluate safety, tolerability, and efficacy. Additional assessments will include questionnaires, PK, and PD. Safety assessments will include AE monitoring, physical examination, clinical laboratory tests, and Columbia-Suicide Severity Rating Scale (C-SSRS) in accordance with the Schedule of Activities (Section 1.3).

The time needed for preparation and administration of SC ZLP will also be measured during the Screening Period and Main Treatment Period in accordance with the Schedule of Activities (Section 1.3).

Study participants are expected to remain on a stable dose regimen of all medications unless medically indicated changes become necessary. All SOC therapy medications for gMG should be kept at the same dose regimen throughout the Main Treatment Period, including corticosteroids and immunosuppressant therapy (IST) drugs. If rescue therapy becomes necessary due to major deterioration of a study participant's clinical status, or risk of MG crisis as per the Investigator's judgment, the study participant may receive IVIG or PLEX treatment as rescue therapy (Section 6.5.4).

Additionally, if deemed needed as per the Investigator's judgment, study participant may be readministered their previous IV C5 inhibitor or administered a different IV C5 inhibitor after discontinuation of the study medication.

All study participants who complete the 12-week Main Treatment Period without discontinuing study medication will have the option to continue ZLP treatment in the Extension Treatment Period after the Week 12 visit. Participants who withdraw during the Main Treatment Period will complete an EW Visit followed by a SFU Visit 40 days (±7 days) after the last dose of study medication. Participants who opt not to continue into the Extension Treatment Period will complete a SFU Visit 40 days (±7 days) after the last dose of study medication.

The Extension Treatment Period consists of in-clinic visits every 12 weeks (±7 days) and will continue until all participants are withdrawn, until ZLP is approved and available in the US, or until further notice from the Sponsor. During these visits, ZLP accountability and resupply will be performed, medications updated, and safety will be assessed. Participants who withdraw or discontinue ZLP during the Extension Treatment Period will complete a Withdrawal Visit followed by a SFU Visit 40 days (±7 days) after the last dose of study medication. Participants who transition to commercially available ZLP will complete a Withdrawal Visit but will not require a SFU Visit. If by the time a participant completes the Main Treatment Period ZLP is commercially available, the participant may transition to commercially available ZLP directly following the Week 12 visit at the end of the Main Treatment Period.

4.2 Scientific rationale for study design

The clinical efficacy, safety, and tolerability of ZLP 0.3mg/kg/day administered SC has been evaluated over 12 weeks in both MG0009 and MG0010. These studies demonstrated a statistically significant and clinically meaningful benefit of ZLP treatment on efficacy measures and a favorable safety and tolerability profile over placebo (Section 2.3). MG0017 is an open-label, single-arm study to evaluate the safety, tolerability, and efficacy of ZLP in study participants with gMG switching from their current IV C5 inhibitor to SC ZLP. The open-label, single-arm design without the inclusion of a placebo control is acceptable for this study since SC ZLP has already been shown to be numerically superior to the efficacy observed with the approved IV C5 inhibitors eculizumab and ravulizumab (Section 2.3), and it also allows all study participants to continue to receive an effective treatment (as opposed to an inert control). The 12-week treatment duration of the Main Treatment Period in this study was chosen as it is consistent with the pivotal Phase 3 study (MG0010). In the MG0010 study, a rapid separation of efficacy between ZLP and placebo was observed after 1 week which was maximized within 4 weeks and was then maintained through the course of the 12-week study. The rationale for dose selection in this study is provided in Section 4.3. The Extension Treatment Period was added to provide access to ZLP for participants with gMG who have completed the Main Treatment Period and who wish to continue receiving ZLP.

The study population will include adults with gMG who have been receiving an IV C5 inhibitor approved for the treatment of gMG for at least 3 months (for eculizumab) or 4 months (for ravulizumab) prior to Screening with a clinically stable disease as per the Investigator's judgment. Only study participants who are willing to switch from their current IV C5 inhibitor to SC ZLP will be included in the study. There is no minimum number of study participants switching from either eculizumab or ravulizumab in this study in order to keep with real world clinical practice for the treatment of patients with gMG.

4.3 Justification for dose

[redacted]

[redacted]

4.4 End of study definition

Completion of main treatment period for the participant

A participant is considered to have completed the **Main Treatment Period** if he/she completed the Week 12 visit and:

- Decided to enter the Extension Treatment Period.

OR

- Transitioned to commercially available ZLP directly after the Week 12 visit (no Withdrawal or SFU visit required).

OR

- Decided not to enter the Extension Treatment Period and completed a SFU visit.

Completion of study for the participant

A participant is considered to have **completed the study** if he/she completed the Main Treatment Period and:

- Did not enter the Extension Treatment Period.

OR

- Entered the Extension Treatment Period and:
  - withdrew from the Extension Treatment Period, discontinued ZLP, and completed the Withdrawal and SFU Visits.

  OR

  - transitioned to commercially available ZLP and completed the Withdrawal Visit. No SFU Visit is required.

End of study

The 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 between 18 years and 85 years of age, inclusive, at the time of signing the Informed Consent form (ICF).

Type of participant and disease characteristics

2a. Participant has been treated with an IV C5 inhibitor approved for the treatment of gMG at the recommended dose regimen for at least 3 months (for eculizumab) or 4 months (for ravulizumab) prior to Screening with a clinically stable disease as per the Investigator's judgment.
NOTE: The last dose of the IV C5 inhibitor must be taken at the Screening Visit (±3 days) (Section 4.1). Participant is willing to switch from his/her current IV C5 inhibitor to SC ZLP.

4. Participant has a documented diagnosis of gMG (MGFA Class II-IVa) at Screening based on participant history and supported by previous evaluations.

5. Participant has a well-documented record of positive serology for acetylcholine receptor binding autoantibodies prior to Screening.

6. Participant has no more than a 2-point change in MG-ADL score at Baseline compared with the Screening Visit.

7a. Participant has had no change in corticosteroid dose during the Screening Period and no change in corticosteroid dose is anticipated to occur during the 12-week Main Treatment Period.

8a. Participant has had no change in immunosuppressive therapy, including dose, during the Screening Period and no change in immunosuppressive therapy is anticipated to occur during the 12-week Main Treatment Period.

9a. Participant has a record of vaccination with at least 1 dose of a quadrivalent meningococcal vaccine and meningococcal serotype B vaccine at least 14 days prior to the first dose of ZLP if not vaccinated within 3 years prior to the start of study medication.

Participants who initiate study medication less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics (eg, penicillin V 500mg twice daily, third generation cephalosporin) until at least 2 weeks after the initial dose of vaccine(s). The use of fluoroquinolone or macrolide antibiotics is not recommended due to the potential for exacerbation of MG.

A booster vaccination should also be administered, as clinically indicated, to participants who have been previously vaccinated against *N. meningitidis* in order to be eligible for inclusion in this study. Participants also must agree to receive a booster vaccination during the study according to the most current relevant guideline (ie, Advisory Committee on Immunization Practices, United States).

Sex

10a. Male and/or female

- A male participant is recommended to agree to use contraception as detailed in Appendix 4 (Section 10.4) of this protocol during the study and for at least 40 days (5 half-lives) after the last dose of study medication, and refrain from donating sperm during this period.
- A female participant is eligible to participate if she is not pregnant (see Appendix 4 [Section 10.4]), not breastfeeding, and at least one of the following conditions applies:
  - Not a woman of childbearing potential (WOCBP) as defined in Appendix 4 (Section 10.4)
    OR
    A WOCBP who agrees to follow the contraceptive guidance in Appendix 4 (Section 10.4) during the study and for at least 40 days (5 half-lives) after the last dose of study medication.

Informed consent

11. Participant is capable of giving signed informed consent as described in Appendix 1 (Section 10.1), which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2 Exclusion criteria

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

Medical conditions

1. Participant has any medical or psychiatric condition that, in the opinion of the Investigator, could jeopardize or would compromise the participant's ability to participate in this study.
2. Participant has a known hypersensitivity to any components of the study medication as stated in this protocol.

3a. Participant has had a thymectomy within 6 months prior to Baseline or has one scheduled to occur during the 12-week Main Treatment Period.

4. Participant has a history of meningococcal disease.
5. Participant has or has had a current or recent systemic infection within 2 weeks prior to Baseline or an infection requiring IV antibiotics within 4 weeks prior to Baseline.
6. Participant has active malignancy (except curatively resected squamous or basal cell carcinoma of the skin) requiring surgery, chemotherapy, or radiation within the prior 12 months (participants with a history of malignancy who have undergone curative resection

or otherwise not requiring treatment for at least 12 months prior to Screening with no detectable recurrence are allowed).

7. Participant has a lifetime history of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt), or has had suicidal ideation with at least some intent to act in the past 6 months as indicated by a positive response ("Yes") to either question 4 or question 5 of the "Screening/Baseline" version of the C-SSRS at Screening.
8. Participant has alanine transaminase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) >2.5x upper limit of normal (ULN).
9. Participant has bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
10. Participant has current unstable liver or biliary disease per Investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice, or cirrhosis.

    NOTE: Stable chronic liver disease (including Gilbert's syndrome, asymptomatic gallstones, and chronic stable hepatitis B or C) is acceptable if the participant otherwise meets entry criteria.

    For study 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 understood and recorded in the electronic case report form (eCRF).

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

    Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit may be repeated once for confirmation.
11. QTc interval >450msec for male participants, QTc >470msec for female participants, or QTc >480 msec in participants with bundle branch block.
    NOTE: The QTc is the QT interval corrected for heart rate according to Fridericia's formula (QTcF). It is either machine read or manually overread.

Prior/Concomitant therapy

12a. Participant has had recent surgery requiring general anesthesia within 2 weeks prior to Screening or is expected to have surgery requiring general anesthesia during the 12-week Main Treatment Period.
13. Participant has received a treatment with an experimental drug within 30 days or 5 half-lives of the experimental drug (whichever is longer) prior to Baseline.
14a. Participant has received treatment with rituximab within 6 months prior to Baseline or treatment is planned to occur during the study.
15. Participant has received treatment with IVIG, SC immunoglobulin, or PLEX 4 weeks prior to Baseline or participant is on chronic IVIG, SC immunoglobulin, or PLEX.

Prior/Concurrent clinical study experience

16. Participant has previously participated in this study or participant has previously been assigned to treatment in a study of the medication under investigation in this study.
17. Participant has participated in another study of an investigational study medication (and/or an investigational device) within the previous 30 days or is currently participating in another study of an investigational study medication (and/or an investigational device).

Diagnostic assessments

18. Participant has known positive serology for muscle-specific kinase.

5.3 Lifestyle restrictions

There are no lifestyle restrictions during the study.

5.4 Screen failures

Screen failures are defined as study participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials 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).

In case of screen failure, the study participant can be rescreened twice following discussion with the UCB Medical Monitor and/or Study Physician.

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.

Up to and including the time of the Screening Visit, study participants will continue to receive their IV C5 inhibitor at the recommended dose regimen. Study treatment (ZLP) will be administered during the Main Treatment and Extension Treatment Periods.

6.1 Treatments administered

The treatment administered in MG0017 is presented in Table 6–1.

Table 6–1: Treatment administered

Arm name	Zilucoplan
Intervention name	Zilucoplan
Type	Drug
Dose formulation	Pre-filled syringe
Unit dose strength(s)	16.6mg in 0.416mL 23.0mg in 0.574mL 32.4mg in 0.810mL
Dosage level	0.3mg/kg/day
Route of administration	Subcutaneous injection
Use	Experimental
IMP	IMP
Sourcing	Provided centrally by the Sponsor
Packaging and labeling	Study medication will be provided in kits containing 7 prefilled syringes. Each syringe and kit will be labeled as required per country requirement.
Excipients	[redacted]
Former names	RA101495

IMP=investigational medicinal product; NIMP=noninvestigational medicinal product

Zilucoplan 0.3mg/kg/day administered SC is the selected dose for this study. As in other ZLP studies, the dose presentation will be selected using the following weight brackets (Table 6–2).

Table 6–2: ZLP dose presentations by weight brackets

Minimum (nominal) target dose (mg/kg/day)	Actual dose (mg)	Weight range (kg)	Dose range (mg/kg/day)
0.3	16.6	≥43 to <56	0.30 to 0.39
0.3	23.0	≥56 to <77	0.30 to 0.41
0.3	32.4	≥77 to 150	0.22 to 0.42

Study participants who present with a higher body weight (≥150kg) or a lower body weight (<43kg) will be accommodated on a case-by-case basis, in consultation with the Medical Monitor.

Study participants will be instructed to self-inject SC doses daily for the duration of the study. The study participant may inject study drug into the abdomen (preferred site), thigh, or upper arm.

6.2 Preparation, handling, storage, and accountability requirements

The Investigator or designee 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 and only authorized site staff may supply or administer study medication. All study medications must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the Investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study 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 Investigational Medicinal Product (IMP) Handling Manual.

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

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

6.2.1 Drug accountability

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

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

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

The Investigator must ensure that the study medication is used only in accordance with the protocol.

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

For further details about drug accountability, refer to the IMP Handling Manual.

6.3 Measures to minimize bias: randomization and blinding

This is an open-label, single-arm study. Therefore, no blinding or randomization is required.

6.4 Treatment compliance

At each visit after study medication is dispensed, participants must return sharps containers containing used syringes or any expired or defective product. Drug accountability must be done in the study 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.

If a study participant is found to be persistently noncompliant, the Sponsor, in conjunction with the Investigator, will make a decision as to whether the participant should be withdrawn from the study.

Study personnel will assess study medication compliance at every visit to record whether any doses were missed.

If a study participant misses 1 dose (ie, 1 day) of study medication, he/she should take the next planned dose as scheduled and the Investigator should be contacted as soon as possible.

If a study participant misses 2 or more doses, he/she must notify the Investigator immediately and the Medical Monitor should be consulted. Ten or more consecutive missed doses will be considered a major protocol deviation.

6.5 Concomitant medication(s)/treatment(s)

Concomitant medications include any prescription or over-the-counter medication that is ongoing on Day 1 or that is initiated following the first dose of study medication on Day 1.

6.5.1 Permitted concomitant treatments (medications and therapies)

Medications, including over the counter therapeutics, natural products, and vitamins, should not be changed during the study, unless medically necessary.

Participants are expected to remain on stable dose regimens of SOC therapy for gMG throughout the Main Treatment Period, including corticosteroids and IST drugs. If during the Extension Treatment Period the Investigator determines that dose reduction of SOC therapy for gMG may be a reasonable course of action, dose reduction may be initiated, after contacting the Medical Monitor. Study participants receiving pyridostigmine treatment may reduce the dose if the Investigator identifies intolerable side effects clearly related to pyridostigmine. Prior to altering the dose of pyridostigmine, the Investigator should contact the Medical Monitor. Any cholinesterase inhibitor, regardless of the dosing regimen, is to be withheld for a minimum of 10 hours prior to the QMG clinical evaluation (not a requirement for the MG-ADL assessment).

6.5.2 Prohibited concomitant treatments (medications and therapies)

The following concomitant medications are prohibited during the study:

Absolute contraindications:

- Aminoglycosides, colomycin, polymyxin, telithromycin, injectable cyclin, macrolides, fluoroquinolones
- Quinines, quinidine, hydroxychloroquine, procainamide
- Beta-blockers (even in eye drops)

- Diphenylhydantoin, trimethadione
- Dantrolene
- D-penicillamine
- Magnesium

Relative contraindications:

- Curariform agents: use of nondepolarizing molecules of rapid degradation, such as atracurium, is possible but requires precise monitoring
- Benzodiazepines
- Neuroleptics (phenothiazine)
- Carbamazepine
- Lithium

IV C5 inhibitor must not be administered while the participant is receiving ZLP. If deemed needed as per the Investigator's judgment, study participant may be readministered their previous IV C5 inhibitor or administered a different IV C5 inhibitor after discontinuation of the study medication and completion of an EW/Withdrawal Visit. The participant should return for a SFU Visit 40 days (±7 days) after the last dose of ZLP.

6.5.3 Vaccines

Administration of live and nonlive vaccines is allowed during the study at the discretion of the Investigator and should be documented. This includes administration of nonlive coronavirus disease 2019 (COVID-19) vaccines authorized at the time of issuance of this protocol. Current medical and scientific evidence does not suggest that there is any medical or scientific reason for restricting severe acute respiratory syndrome coronavirus 2 vaccinations in ZLP clinical studies.

Additionally, given the increased risk for *N. meningitidis* infection with C5 inhibition or deficit, study participants who receive ZLP are required to have documentation of at least 1 dose of quadrivalent meningococcal vaccine and meningococcal serotype B vaccine at least 14 days prior to the first dose of ZLP if not vaccinated within 3 years prior to the start of study medication (Section 5.1). The second dose of the primary vaccination cycle can be administered during the study. A booster vaccination should also be administered according to the most current relevant guideline (ie, Advisory Committee on Immunization Practices, United States) to study participants who have been previously vaccinated against *N. meningitidis.*

6.5.4 Rescue medication

If rescue therapy becomes necessary due to major deterioration of a study participant's clinical status or risk of MG crisis, as per the Investigator's judgment, the study participant may receive the following rescue medications:

- IVIG
- PLEX

If such rescue therapy becomes necessary, the choice of IVIG vs PLEX, as well as the frequency and duration of such therapy, will be determined by the Investigator. Escalation of doses of corticosteroids or IST drugs for rescue is not permitted.

The Sponsor should be notified immediately upon determination that rescue therapy is necessary in any given study participant. A Rescue Therapy Visit should be performed prior to initiation of rescue therapy (see Section 1.3 for a list of applicable study procedures).

If the Investigator, in consultation with the Medical Monitor, considers to be in the best interest of the study participant, the study participant will continue ZLP treatment and complete all study-specified assessments while undergoing rescue therapy and through the end of the study. The date and time of rescue medication administration, the name and dosage regimen of the rescue medication, and the reason for initiation of rescue medication must be recorded.

6.6 Dose modification

No dose modifications are allowed during the study.

6.7 Criteria for study hold or dosing stoppage

Not applicable for this study given the safety experience of ZLP from clinical studies. Refer to the IB for details.

6.8 Treatment after the end of the study

At the conclusion of the Main Treatment Period, study participants will have the option to continue ZLP treatment in the Extension Treatment Period, during which SC ZLP will continue to be provided until the approval of the marketing application for the indication of gMG in the US or until further notice from the Sponsor.

If at the end of the Main Treatment Period a study participant chooses not to participate in the Extension Treatment Period, the participant will complete an SFU Visit 40 days (±7 days) after the last dose of study medication and receive SOC treatment off-study, as recommended by the treating physician.

If during the Extension Treatment Period a study participant discontinues ZLP, he/she will transition to SOC treatment off-study as recommended by the treating physician. These participants will complete a Withdrawal Visit and a SFU Visit 40 days (±7 days) after the last dose of study medication.

If a participant is in the Extension Treatment Period at the time ZLP becomes commercially available, he/she will transition to ZLP treatment outside of the study. He/she will complete a Withdrawal Visit and will not need to complete a SFU Visit. If by the time a participant completes the Main Treatment Period ZLP is commercially available, the participant may transition to commercially available ZLP directly following the Week 12 visit at the end of the Main Treatment Period.

7 DISCONTINUATION OF STUDY MEDICATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of study medication

Dosing of a study participant must be immediately and permanently discontinued if:

- Study participant is diagnosed with meningococcal disease
- In the opinion of the Investigator and/or Sponsor, it is unsafe for the study participant to continue dosing with study medication
- There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test

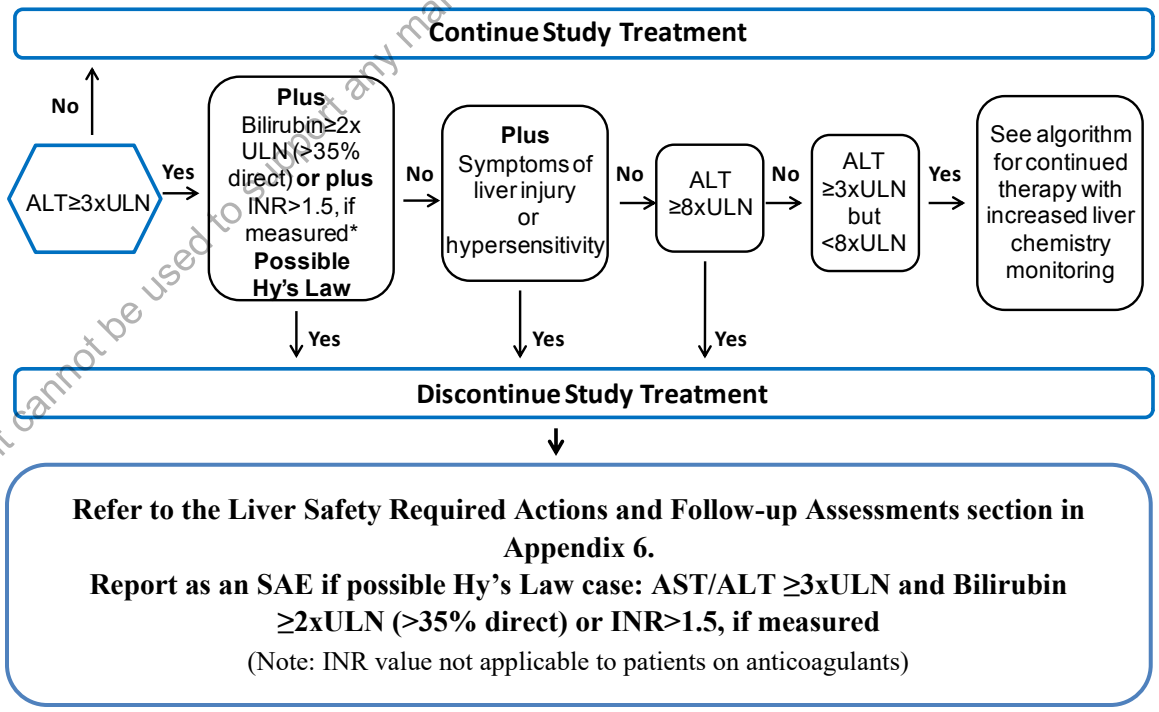
In circumstances where permanent discontinuation from study medication may occur, the Investigator is to discuss with the study participant the appropriate processes for discontinuation from study medication and further assessments as part of an EW or Withdrawal Visit, followed by the SFU Visit. If the study participant does not want to continue the study medication and withdraws consent (Section 7.2), the Investigator should contact the Medical Monitor, whenever possible, to discuss the withdrawal of a participant in advance.

7.1.1 Liver chemistry stopping criteria

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

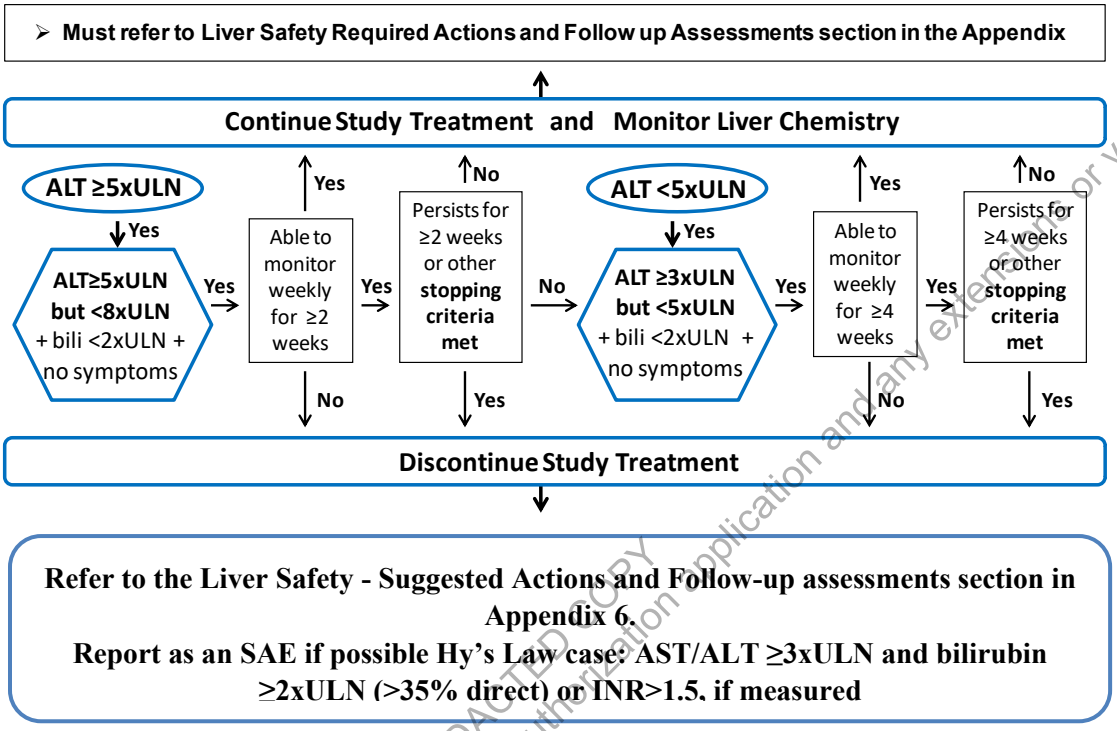
Study medication will be discontinued immediately and permanently for a participant if liver chemistry stopping criteria are met.

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

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 QTc stopping criteria

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

If any of the criteria as listed below based on the ECG reading are met, the ECG will be repeated to confirm the finding. In the event that a study participant meets the confirmed criteria, the Medical Monitor will be contacted to decide whether the participant will discontinue the study. In case the decision is to proceed to discontinuation, an EW/Withdrawal Visit will be performed, and the study participant will be required to return to the clinic for a SFU Visit 40±7 days after their last dose. The study participant should be referred to a specialist (ie, cardiologist) and managed as per local guidance.

- QTc >500msec OR uncorrected QT >600msec

- Change from Baseline of QTc >60msec

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

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

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

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

7.2 Participant discontinuation/withdrawal from the study

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

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

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

See the Schedule of Activities (Section 1.3) for data to be collected at the time of study discontinuation.

Participants should be withdrawn from the study if any of the following events occur:

1. Participant develops an illness that would interfere with his/her continued participation.
2. Participant is noncompliant with the study procedures or medications in the opinion of the Investigator.
3. Participant restarts administration of previous IV C5 inhibitor or is administered a different IV C5 inhibitor (Section 6.5.2).
4. Participant withdraws his/her consent.
5. The Sponsor or a regulatory agency requests withdrawal of the participant.
6. Participant has active suicidal ideation with some intent to act without specific plan, as indicated by a positive response (“Yes”) to question 4 of the “Since Last Visit” version of the C-SSRS. The participant should be referred immediately to a mental healthcare professional and may be withdrawn from the study based upon the Investigator’s judgment of benefit/risk of continuing the participant in the study/on study medication.

7. Participant has active suicidal ideation with a specific plan as indicated by a positive response ("Yes") to question 5 of the "Since Last Visit" version of the C-SSRS. The participant should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.

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

If a study participant withdraws from the study, the participant will not be replaced.

If a study participant withdraws from the study, the participant should immediately stop the intake of the study medication and will be required to return to the clinic for an EW/Withdrawal Visit (depending on whether the participant withdrew during the Main Treatment Period or during the Extension Treatment Period) as soon as possible but no later than the next scheduled visit and for a SFU Visit 40±7 days after their last dose of study medication to gather information on ongoing AEs and report any new SAEs since the last study visit (Section 1.3).

7.3 Lost to follow up

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

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

- The site must attempt to contact the study participant and reschedule the missed visit as soon as possible, 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 study 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 study participant, must be recorded in the source documents. The eCRF must document the primary reason for withdrawal.

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

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 medication.

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

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

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

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

8.1 Efficacy assessments

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

8.1.1 Clinical efficacy assessments

Clinical evaluators must be adequately trained prior to conducting any efficacy assessments.

All self-administered patient-reported outcomes (PROs) (MG-QOL15r, 9-item Treatment Satisfaction Questionnaire for Medication [TSQM-9], and Patient Preference assessment) will be filled out by the study participant prior to meeting with the physician and prior to dosing or any other study procedures. Patient-reported outcomes should be administered in the following order: MG-QOL15r, TSQM-9, Patient Preference assessment, and MG-ADL. All remaining clinical efficacy assessments should be performed at approximately the same time of day prior to dosing (preferably in the morning) and be administered by the same well-trained evaluator (eg, neurologist, physical therapist, or other study staff experienced in clinical assessments), where applicable, in the same order at each visit throughout the study.

8.1.1.1 MG-ADL

The MG-ADL is a brief 8-item interviewer-administered PRO designed to evaluate MG symptom severity. The MG-ADL targets symptoms and disability across ocular, bulbar, respiratory, and axial symptoms. Each item is assessed on a 4-point scale, where a score of 0 represents normal function and a score of 3 represents severely decreased ability to perform that function. The total MG-ADL score ranges from 0 to 24, with a higher score indicating more disability. A 2-point change in MG-ADL score is considered clinically meaningful (Muppidi et al, 2011; Wolfe et al, 1999).

The MG-ADL assessment will be performed at Screening to assess study participant's eligibility and at each study visit (either at the site or over the phone) according to the Schedule of Activities (Section 1.3). Detailed instructions regarding the administration of the MG-ADL will be provided to sites.

Minimal Symptom Expression, which is designed to assess how many study participants become free or virtually free of MG symptoms as measured by achieving an MG-ADL total score of 0 or 1 on therapy (Vissing et al, 2020), will be assessed at Week 12.

8.1.1.2 QMG scale

The QMG is a standardized and validated quantitative strength scoring system that was developed specifically for MG. If a study participant is receiving a cholinesterase inhibitor, the dose must be withheld for at least 10 hours prior to the assessment. The scale tests 13 items, including ocular and facial involvement, swallowing, speech, limb strength, and forced vital capacity. Higher scores are representative of more severe impairment. Scoring for each item ranges from no weakness (0) to severe weakness (3), with an overall score range from 0 to 39. A change in the QMG score of 3 points or more may be considered clinically meaningful in a typical clinical study population of patients with MG (Katzberg et al, 2014; Barohn et al, 1998).

8.1.1.3 MG-QOL15r

The MG-QOL15r is a 15-item self-administered PRO that was designed to assess quality of life in patients with MG. Each item is scored on a 0 to 2-point scale (0=Not much at all, 1=Somewhat, 2=Very much). The total score is the sum of the 15 individual item scores, ranging from 0 to 30. Higher scores indicate more severe impact of the disease on aspects of the patient's life (Burns et al, 2016; Burns et al, 2010).

8.1.1.4 Myasthenia Gravis Foundation of America Post-Intervention Status

The Myasthenia Gravis Foundation of America Post-Intervention Status is a physician-determined assessment of clinical symptoms of MG after initiation of MG-specific therapy. Minimal Manifestation is defined as follows:

"The patient has no symptoms of functional limitations from MG but has some weakness on examination of some muscles. This class recognizes that some patients who otherwise meet the definition of Complete Stable Remission or Pharmacologic Remission do have weakness that is only detectable by careful examination."

For the purpose of the current study, Minimal Manifestation will be determined at Week 12, the EW Visit, or a Rescue Therapy Visit (rather than after 1 year). Change in status (improved, unchanged, worse, exacerbation, or died) of MG will also be determined.

8.1.1.5 TSQM-9

The TSQM-9 is a self-administered PRO with Likert-type response options that assesses satisfaction with medication use over 3 domains: Effectiveness (items 1 through 3), Convenience (items 4 through 6), and Global Satisfaction (items 7 through 9). Each domain score ranges from 0 to 100, with higher scores indicating increased satisfaction. See TSQM user manual version 1.1 for instructions on calculation of scores. The instrument is not disease specific. The TSQM-9 and previous versions have undergone qualitative and psychometric testing and were found to be valid and reliable (Regnault et al, 2012; Bharmal et al, 2009; Atkinson et al, 2005; Atkinson et al, 2004).

8.1.1.6 Patient Preference assessment

The Patient Preference assessment is a self-administered PRO. A single question will be asked at the end of the Main Treatment Period and the EW/Withdrawal Visits, assessing the study participant's preference for treatment:

"Think about your experience of the subcutaneous treatment you received during the clinical trial compared with your previous intravenous treatment.

All things considered, which treatment did you prefer? (please select one answer)

- Intravenous infusion
- Subcutaneous injection
- No preference"

Given the limitations of the study design, this question/assessment will not produce robust and generalizable patient preference data, but it will generate exploratory data into patient preferences based on this sample's experience with the 2 treatments. To generate robust patient preference evidence within a clinical study, a cross-over study design is typically used.

8.1.1.7 Time needed for administration of SC ZLP

The time it takes for study participants to administer SC ZLP will be recorded (ie, the time it takes for the dose to be delivered into the skin/body). The time needed for administration of SC ZLP will be assessed by site staff using a stopwatch to record the time needed for study participants to complete the administration. Timing using the stopwatch will start at removal of the pre-filled syringe needle cap and will stop when the syringe is completely removed from the skin.

8.1.1.8 Time to first receipt of rescue therapy

The date of the first receipt of rescue therapy during the 12-week Main Treatment Period will be recorded.

8.1.1.9 Change in SOC therapy dose regimen

Any changes to SOC therapy that occur during the study will be recorded.

8.1.2 Pharmacodynamics

Blood sampling for PD analysis of complement activation will be performed as specified in the Schedule of Activities (Section 1.3). Blood samples for PD analyses will be obtained prior to dosing (within 1 hour of dosing). Instructions for the collection and handling of biological samples will be provided by UCB. The actual date and time (24-hour clock time) of each sample will be recorded.

The sheep red blood cell lysis assay will be used to evaluate classical complement pathway activation.

All back-up samples already planned for collection will be stored for all participants in this study to support potential future exploratory biomarker research, which could include, but is not limited to the evaluation of biomarkers relative to disease biology and progression, study medication treatment and response, and/or mechanism of action of the study medication treatment.

8.2 Safety assessments

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

8.2.1 Physical examination

A complete physical examination will include, at a minimum, abdomen; cardiac; general appearance; eyes, ear, nose, and throat; head and neck; musculoskeletal; neurological; respiratory; and skin/mucosal. Height and weight will also be measured and recorded. Height will only be measured at Screening.

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.

8.2.2 Vital signs

Temperature, pulse rate, respiratory rate, and blood pressure will be assessed.

Blood pressure and pulse measurements will be assessed in the sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available. Blood pressure measurements should preferably be made using the nondominant arm, and the same measurement technique should be used throughout the study for the same participants.

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

8.2.3 Electrocardiogram

A 12-lead ECG will be obtained as outlined in the Schedule of Activities (see Section 1.3) using an ECG machine that automatically measures the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7 for QTc withdrawal criteria and any additional QTc readings that may be necessary.

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

8.2.4 Clinical safety laboratory assessments

See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and the Schedule of Activities (Section 1.3) for the timing and frequency.

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

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

If such values do not return to normal/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 (Section 1.3).

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

8.2.5 Suicidal risk monitoring

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

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

Suicidality will be assessed by trained study personnel using the C-SSRS (Posner et al, 2011; Mundt et al, 2010). The "Screening/Baseline" version of the C-SSRS will be completed during the Screening Visit and the "Since Last Visit" version will be completed at all other time points detailed in the Schedule of Activities (Section 1.3). Criteria for participant withdrawal based on response to the C-SSRS and Investigator's judgment are defined in Section 7.2.

8.3 AEs and SAEs

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

Adverse events will be reported by the study 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 medication or study procedures, or that caused the participant to discontinue the study medication or the study (see Section 7).

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

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 study participant completes the study (Section 4.4). Collection of AEs and SAEs will be done at the time points specified in the Schedule of Activities (Section 1.3).

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 eCRF even if no study medication was taken but specific study procedures were conducted. This includes all AEs not present prior to the Screening Visit and all AEs that recurred or worsened after the Screening 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 40 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 AEs and SAEs 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 study 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 study participant at subsequent visits/contacts. All SAEs and nonserious AEs of special interest (as defined in Section 8.3.6), will be followed until resolution, stabilization, the Investigator determines that it is no longer clinically significant, the event is otherwise explained, or the study 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 study participants and the safety of a study medication 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 medication under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB), and Investigators.

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

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

8.3.5 Pregnancy

Details of all pregnancies in female study participants and female partners of male study participants who become pregnant will be collected after the start of study medication and until 40 days after the last dose of study medication.

If a pregnancy is reported, the Investigator must immediately inform the Sponsor within 1 working day of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).

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

- The participant should return for an EW/Withdrawal Visit.
- An SFU Visit should be scheduled 40±7 days 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 to be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a UCB product/compound.

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

- Hy's Law
  - Potential Hy's Law, defined as ≥3x ULN 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 study participant.

8.3.7 Monitoring of infection

To mitigate the risk of infection, study participants will be counseled and reminded of the early signs and symptoms of *Neisseria meningitidis* infection. A patient safety card detailing the signs and symptoms of infection, with instructions to seek immediate medical attention if any such symptoms occur, will be provided to each study participant.

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 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 for which data will be periodically reviewed during the study.

8.5 Treatment of overdose

For this study, any dose of ZLP greater than the intended daily dose will be considered an overdose. Overdose events are only considered AEs or SAEs if there are associated clinical signs

and symptoms, or if the act of taking the excess study medication itself is an AE or SAE (eg, suicide attempt).

It is not anticipated that overdose of ZLP will lead to acute or specific systemic TEAEs. In case of overdose, clinically appropriate supportive measures should be instituted as determined by the clinical scenario and in consultation with the Medical Monitor.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the study participant for any AE/SAE and laboratory abnormalities.
3. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

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

8.6 Pharmacokinetics

Blood samples of approximately 2mL will be collected for measurement of plasma concentrations of ZLP and its major metabolites [redacted] as specified in the Schedule of Activities (Section 1.3). Blood samples for PK analyses will be obtained prior to dosing (within 1 hour of dosing). Instructions for the collection and handling of biological samples will be provided by UCB. The actual date and time (24-hour clock time) of each sample will be recorded.

For local Rescue Therapy Visits only, blood samples for PK analysis will be collected within 1 hour prior to administration of each round of rescue therapy. If a study participant receives PLEX treatment as rescue therapy, PK will be measured in the exchanged plasma. If rescue therapy is administered at a location separate from the clinical site, then there is no need to collect blood samples for PK.

Samples will be used to evaluate the PK of ZLP and its metabolites. Samples collected for PK analyses of ZLP and metabolite plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

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

All back-up samples already planned for collection will be stored for all participants in this study to support potential future exploratory biomarker research, which could include, but is not limited to the evaluation of biomarkers relative to disease biology and progression, study medication treatment and response, and/or mechanism of action of the study medication treatment.

8.7 Immunogenicity assessments

Immunogenicity is not evaluated in this study.

8.8 Health economics

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 (SAP).

9.1 Definition of analysis sets

The following are the defined analysis sets:

- Enrolled Set (ES): The ES will include all study participants who signed the ICF.
- Intention-to-Treat (ITT) Population: The ITT Population will include all eligible study participants. Efficacy analyses will be performed on the ITT in case there is a difference of at least 5 participants as compared to the modified Intention-to-Treat (mITT) Population.
- Modified ITT Population: The mITT Population will include all eligible study participants who received at least 1 post-Baseline dose of study medication and had at least 1 post-Baseline assessment. The mITT Population will be used for all efficacy analyses.
- Safety Set (SS): The SS will include all study participants who received at least 1 dose of study medication and will be used for the demography and safety analyses.
- Pharmacokinetic Per-Protocol Set (PK-PPS): The PK-PPS will include all study participants in the safety population who received at least 1 dose of study medication and had at least 1 quantifiable PK measurement postdose of study medication without important protocol deviations that would affect the PK. The PK-PPS will be used for all PK analyses.
- Pharmacodynamic Per-Protocol Set (PD-PPS): The PD-PPS will include all study participants in the safety population who received at least 1 dose of study medication and had at least 1 quantifiable PD measurement postdose of study medication without important protocol deviations that would affect the PD. The PD-PPS will be used for all PD analyses.

Additional detail about analysis sets will be provided in the SAP.

9.2 General statistical considerations

Statistical analysis and generation of tables, figures, and study participant data listings will be performed using statistical analysis system (SAS®, SAS Institute, Cary, NC, US) Version 9.4 or higher using validated program code according to relevant SOP.

For continuous parameters, descriptive statistics will include the number of study participants, arithmetic mean, standard deviation (SD), median, minimum, and maximum (with 25th and 75th percentiles as optional). For categorical parameters, the number and percentage of study participants in each category will be presented.

For ZLP plasma concentration, the geometric mean and corresponding coefficient of variation (CV) will be presented.

Baseline is defined as the last nonmissing measurement collected before the first injection.

9.3 Planned efficacy/outcome analyses

9.3.1 Secondary efficacy estimand/secondary endpoint analyses

For the efficacy endpoint, CFB to Week 12 in MG-ADL score, a one-sample t-test will be used to compare the mean CFB to Week 12 in MG-ADL score to a noninferiority (NI) margin. The NI margin being investigated is a clinically relevant 2-point increase (worsening) at Week 12. The Week 12 CFB will be compared to 2 at a 1-sided α=0.025 level for the mITT Population.

Additional supplementary analyses and sensitivity analyses for the secondary efficacy estimand will be provided in the SAP.

The additional secondary efficacy endpoint (CFB to Week 12 in QMG score) will be analyzed following the estimand structure defined for the MG-ADL score (Section 3.1). These analyses will be descriptive.

9.3.2 Other efficacy endpoint analyses

The other efficacy endpoints analyses will be descriptive. Additional information about these analyses will be provided in the SAP.

9.4 Planned safety and other analyses

9.4.1 Safety analyses

Safety analyses will be performed on the Safety Set.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities. A TEAE is defined as any event that was not present prior to the first administration of study medication or any unresolved event already present before the first administration of study medication that worsens in intensity following exposure to treatment. Incidence rates for TEAEs will be summarized overall, by maximum severity, and by relationship to study medication. Serious AEs will also be summarized.

Laboratory evaluations, physical examinations, and ECG will be presented in listings and summarized over time. In this study, the clinical laboratory, physical examination, and ECG assessments conducted at Screening will be considered the baseline values for evaluating of the other safety endpoints.

A by-participant listing of the C-SSRS questionnaire data will be provided.

9.4.2 Other analyses

Individual PK results will be presented in listings and summarized using descriptive statistics.

Pharmacodynamic endpoints will be presented in listings and summarized at each scheduled assessment time point.

9.5 Handling of protocol deviations

Important protocol deviations are deviations from the protocol which could potentially have a meaningful impact on study conduct or on the key safety, efficacy, or other outcomes for an individual study participant. The criteria for identifying important protocol deviations and the classification of important protocol deviations will be defined within the Important Protocol Deviations Template. To the extent feasible, rules for identifying protocol deviations will be

defined without review of the data and without consideration of the frequency of occurrence of such deviations. Whenever possible, criteria for identifying important protocol deviations will be implemented algorithmically to ensure consistency in the classification of important protocol deviations across all study participants.

All important protocol deviations will be listed by study participant.

A listing of all important protocol deviations related to the COVID-19 pandemic will be provided. Additionally, this listing will be repeated by during and post- the COVID-19 pandemic (in case the pandemic ends before the study is complete) based on the deviation start dates relative to the pandemic cutoff dates.

9.6 Handling of dropouts or missing data

For secondary efficacy analyses, missing data will be handled according to the secondary efficacy estimand definition:

- For missing data of participants who discontinue from the study, a missing at random assumption will be used for imputation. This is in relation to the assumption that the participant had remained on their treatment throughout the study.
- For other missing data, the same missing at random assumption as the one used for imputing missing data of participants who discontinue from the study will be applied.

Missing or partial dates for safety evaluations will be imputed and full details of these algorithms will be presented in the SAP. Baseline is defined as the last nonmissing pretreatment measurement (Section 9.2). Therefore, data from the Screening Visit (if available) will be used as Baseline values if data are missing at Day 1.

No further imputations of any other missing data are planned.

9.7 Planned interim analysis and data monitoring

If ZLP is not commercially available in the US at the time of the last visit of the last participant in the Main Treatment Period, an interim analysis will be conducted. This interim analysis will include all data collected during the Main Treatment Period.

9.8 Determination of sample size

The secondary efficacy estimand will investigate if the Week 12 MG-ADL score is noninferior to the Baseline MG-ADL score with an NI margin of 2. It is assumed that the Week 12 CFB has an SD of 3 and that the true CFB is 0. Given a sample size of 20 study participants, the study has approximately 80% power to detect this, based on a 1-sided alpha of 0.025.

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, as defined in local regulations, International Council for Harmonisation (ICH)-Good Clinical Practice (GCP), and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

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

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

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

The Investigator will not make any changes in the study or study conduct without IRB approval, except where necessary to eliminate apparent immediate hazards to the study 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 as allowed.

As part of the IRB requirements for continuing review of approved studies, the Investigator will be responsible for submitting periodic progress reports to the IRB (based on IRB requirements), at intervals appropriate to the degree of study participant risk involved, but no less than once per year. The Investigator should provide a final report to the IRB 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 will also be informed by the Investigator or the Sponsor, as specified by the applicable regulatory requirements. Where applicable, Investigators are to provide the Sponsor (or its representative) with evidence of such IRB 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

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

Prior to obtaining informed consent, information should be given in a language and at a level of complexity understandable to the study 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 study participant, or his/her legal representative, and by the person who conducted the informed consent discussion (Investigator or designee). The study participant or his/her legal representative must receive a copy of the signed and dated ICF. As part of the consent process, each study participant must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB 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 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 may withdraw his/her consent to participate in the study at any time. A participant is considered as enrolled in the study when he/she has signed the ICF. An eCRF must not be started, nor may any study specific procedure be performed for a given participant, without having obtained his/her written consent to participate in the study.

10.1.4 Data protection

UCB staff (or designee) will affirm and uphold the study 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, or representatives of regulatory authorities will be allowed to review that portion of the participant's primary medical records that directly concerns this study (including, but not limited to, laboratory test result reports, ECG reports, admission/discharge summaries for hospital admissions occurring during a participant's study participation, and autopsy reports for deaths occurring during the study).

The study 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 study participant.

The study 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 members, and by inspectors from regulatory authorities.

10.1.5 Committees structure

Not applicable.

10.1.6 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 eCRF.

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

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

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, legible, contemporaneous, original, and attributable from source documents; that the safety and rights of study 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.

10.1.6.1 Case report form completion

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

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

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

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

Detailed instructions will be provided in the eCRF Completion Guidelines.

10.1.6.2 Apps

Not applicable.

10.1.7 Source documents

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

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

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

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

10.1.8 Study and site closure

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

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

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

- Failure of the Investigator to comply with the protocol, the requirements of the IRB or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of study participants by the Investigator
- Discontinuation of further study medication development

10.1.9 Publication policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

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

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

10.2 Appendix 2: Clinical laboratory tests

The tests detailed in the table below will be performed by the central laboratory.

- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study 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 medication decision or response evaluation, the results must be entered into the eCRF.
- The use of local laboratory results may be considered, if necessary, after consultation with the appropriate Sponsor representative (eg, Clinical Project Manager or Study Physician).
- Protocol-specific requirements for inclusion or exclusion of study 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	RBC indices: MCV MCH %Reticulocytes	WBC count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
	RBC count			
	Hemoglobin			
	Hematocrit			
Clinical chemistry [a]	BUN	Potassium	AST/SGOT	Total and direct bilirubin
	Creatinine	Sodium	ALT/SGPT	Total protein
	Glucose	Calcium	Alkaline phosphatase	Amylase
	Lipase			
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, 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) • Serum hCG pregnancy test (as needed for women of childbearing potential) [b] The results of each test must be entered into the eCRF.			

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; eCRF=electronic Case Report form; HBsAg=hepatitis B surface antigen; hCG=human chorionic gonadotropin; INR=international normalized ratio; IRB=Institutional Review Board; MCH=mean corpuscular hemoglobin;

Table 10–1: Protocol-required safety laboratory assessments

Laboratory assessments	Parameters

MCV=mean corpuscular volume; RBC=red blood cell; SAE=serious adverse event; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; ULN=upper limit of normal; WBC=white blood cell

[a] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1.1 and Appendix 6 (Section 10.6). All events of ALT ≥3×ULN and bilirubin ≥2×ULN (>35% direct bilirubin) or ALT ≥3×ULN and INR >1.5, if INR measured, may indicate severe liver injury (possible Hy's Law) and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

[b] Local urine pregnancy testing will be performed at visits subsequent to the Screening Visit.

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 <u>meeting</u> 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 an AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT meeting the AE definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the study 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 study 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 study 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 study 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 eCRF.
- It is **not** acceptable for the Investigator to send photocopies of the study participant's medical records to UCB in lieu of completion of the UCB AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by UCB. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to UCB.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

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

- Mild: An event that is easily tolerated by the study participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of 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 should be used as a supportive standardization instrument to evaluate AEs and SAEs but the final intensity grading by the Investigator must be mild, moderate, or severe.

Assessment of causality

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

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by UCB to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- An AE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the study 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 eCRF.
- The Investigator will submit any updated SAE data to UCB 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 an SAE to UCB will be the electronic data collection tool.
- If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section).
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline 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 offline, then the site can report this information on a paper SAE form (see next section) or to the UCB Study Physician/Medical Monitor by telephone.
- 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 the UCB Study Physician/Medical Monitor.
- 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 study 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

Male participants

For male participants with female partners of childbearing potential it is recommended that they agree to ONE of the following during the study and for at least 40 days after the last dose of study medication:

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

In addition, male participants are recommended to refrain from donating sperm for the duration of the study and for 40 days after the last dose of study medication.

Male participants with a pregnant or breastfeeding partner are recommended to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the study and for at least 40 days after the last dose of study medication.

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 10–2, during the study and for at least 40 days after the last dose of study medication.

Table 10–2: 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[b]
• Implantable progestogen only hormonal contraception associated with inhibition of ovulation • IUD • 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.

IMP=investigational medicinal product; IUD=intrauterine device; IUS=intrauterine hormone-releasing system; WOCBP=woman of child-bearing potential

[a] In case of newly started contraception pills/IUDs, the Investigator 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 will be performed as described in the Schedule of Activities (Section 1.3).
- 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.

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study medication.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 1 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 study medication.
- 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 1 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 poststudy pregnancy-related SAE considered reasonably related to the study medication by the Investigator will be reported to the Sponsor as described in Section 8.3.5. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

10.5 Appendix 5: Genetics

Not applicable.

10.6 Appendix 6: Liver safety – suggested actions and follow-up assessments

Study participants with PDILI must be assessed to determine if study medication must be discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued.

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

Study participants with PDILI should not be withdrawn from the study until investigation and monitoring are complete. All results of these evaluations and observations, as well as the reason(s) for study medication discontinuation and/or participant withdrawal (if applicable), must be recorded in the source documents. The eCRF must document the primary reason for discontinuation of study medication.

A specific monitoring plan must be agreed between the UCB Study Physician and the Investigator for study participants who have ALT >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 study participant safety and to evaluate liver event etiology.

Liver chemistry stopping criteria and follow-up assessments are presented in Table 10–3.

Table 10–3: 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
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 eCRF, and complete an SAE data collection tool if the event also met the criteria for an SAE[b]	• Viral hepatitis serology[d] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Only in those with underlying chronic hepatitis B at study entry (identified by

Table 10–3: Liver chemistry stopping criteria and follow-up assessments

Liver chemistry stopping criteria	
• 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	positive HBsAg): quantitative hepatitis B DNA and hepatitis delta antibody[e] • Obtain blood sample for PK analysis at the earliest time point following confirmation of a liver event[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 eCRF • Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications eCRF. • Record alcohol use on the liver event alcohol intake eCRF • Exclude pregnancy **<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 eCRFs

AE=adverse event; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CPK=creatine phosphokinase; eCRF=electronic 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

Table 10–3: Liver chemistry stopping criteria and follow-up assessments

Liver chemistry stopping criteria

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

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

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

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

[e] If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis delta RNA virus (where needed) (Le Gal et al, 2005).

[f] Record the date/time of the PK blood sample draw and the date/time of the dose of study medication prior to the PK blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the Laboratory Manual.

Liver chemistry increased monitoring criteria with continued study medication are presented in Table 10–4.

Table 10–4: 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 the 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

Table 10–4: Liver chemistry increased monitoring criteria with continued study medication

Liver chemistry increased monitoring criteria	
	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 AEs, adverse device effects, SAEs, and device deficiencies: Definition and procedures for recording, evaluating, follow-up, and reporting

Not applicable.

10.8 Appendix 8: Rapid alert procedures

Not applicable.

10.9 Appendix 9: Country-specific requirements

Not applicable.

10.10 Appendix 10: Abbreviations and trademarks

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
C5	complement component 5
CFB	change from Baseline
COVID-19	coronavirus disease 2019
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	coefficient of variation
ECG	electrocardiogram
eCRF	electronic case report form
ES	Enrolled Set
EW	Early Withdrawal
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
gMG	generalized myasthenia gravis
HRT	hormonal replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent form
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IST	immunosuppressant therapy
ITT	Intention-to-Treat
IV	intravenous
IVIG	intravenous immunoglobulin G
MG	myasthenia gravis
MG-ADL	Myasthenia Gravis-Activities of Daily Living
MGC	Myasthenia Gravis Composite
MGFA	Myasthenia Gravis Foundation of America

MG-QOL15r	Myasthenia Gravis-Quality of Life Revised
mITT	Modified Intention-to-Treat
NI	noninferiority
PD	pharmacodynamic(s)
PDILI	potential drug-induced liver injury
PD-PPS	Pharmacodynamic Per-Protocol Set
PK	pharmacokinetic(s)
PK-PPS	Pharmacokinetic Per-Protocol Set
PLEX	plasma exchange
PRO	patient-reported outcome
QMG	Quantitative Myasthenia Gravis
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)
SD	standard deviation
SFU	Safety Follow-up
SOC	standard of care
SOP	standard operating procedure
SS	Safety Set
TEAE	treatment-emergent adverse event
TSQM-9	9-item Treatment Satisfaction Questionnaire for Medication
ULN	upper limit of normal
WOCBP	woman of childbearing potential
ZLP	zilucoplan

10.11 Appendix 11: Protocol amendment history

Amendment 1 (15 Jul 2022)

Overall Rationale for the Amendment:

The protocol amendment was considered necessary to remove the requirement for the collection of blood samples for exploratory biomarkers, and to add that back-up samples may be retained for future exploratory biomarker analysis. Additional changes include the following: clarified that screening clinical laboratory and physical examination assessments will be considered the baseline values for evaluating the other safety endpoints; removed the requirement for brief physical examinations, and electronic version of the C-SSRS scale; and amended the contraception guidance. The table below does not include correction of minor typographical errors and formatting/stylistic changes.

Section # and Name	Description of Change	Brief Rationale
Section 1.1, Synopsis, Table 1-1	-Added ECG to other safety endpoints -Added footnote "a" to clarify that the clinical laboratory, physical examination, and ECG assessments conducted at screening will be considered the baseline values for evaluating the other safety endpoints.	-Added for the evaluation of updated corrected QT interval (QTc) stopping criteria -As clinical laboratory, physical examination, and ECG assessments are not performed at the Baseline Visit in this study, footnote "a" was added to clarify and confirm that the respective screening assessments will be considered as baseline when evaluating the other safety endpoints.
Section 1.3, Schedule of Activities, Table 1-2	-Removed brief physical examination and footnote "n", regarding brief physical examination at the Baseline Visit.	-Removed in order to have a consistent approach to all study participants, and to reduce study complexity and patient burden.

Section # and Name	Description of Change	Brief Rationale
Section 1.3, Schedule of Activities, Table 1-2	-Removed requirement for blood sampling for exploratory biomarker analyses. -Added to footnote "u" that back-up specimens may be retained for future exploratory biomarker analyses. -Added ECG assessment to Screening Visit, at Week 2, Week 12, Early Withdrawal, and Safety Follow-up visits. -Remove footnote "n" saying that vital signs will be assessed at all complete and brief physical examination. -Added footnote "n" to specify that clinical laboratory, physical examination, and ECG assessments conducted at Screening will be considered the baseline values for evaluating of the other safety endpoints.	-Collection of additional specimens is no longer necessary because the exploratory biomarker specimen analyses could be performed with the existing back-up specimens, which are collected as part of the pharmacokinetic/ pharmacodynamic analyses. -ECG added to evaluate QTc criteria to determine eligibility (see exclusion criteria #11) and added to safety assessments to evaluate QTc stopping criteria. -Timepoints for vital signs evaluations are shown in Table 1-2 and there is need to add a footnote to specify these timepoints. -As clinical laboratory, physical examination, and ECG assessments are not performed at the Baseline Visit in this study, footnote "n" was added to clarify and confirm that the respective screening assessments will be considered as baseline when evaluating the other safety endpoints.
Section 3, Table 3-1	-Added ECG to other safety endpoints. -Added footnote "a" to clarify that the clinical laboratory, physical examination, and ECG assessments conducted at screening will be considered the baseline values for evaluating the other safety endpoints.	-Added for the evaluation of updated QTc stopping criteria. -As clinical laboratory, physical examination, and ECG assessments are not performed at the Baseline Visit in this study, footnote "a" was added to clarify and confirm that the respective screening assessments will be considered as baseline when evaluating the other safety endpoints.

Section # and Name	Description of Change	Brief Rationale
Section 5.2 Exclusion criteria	The following exclusion criteria #11 was added: QTc interval >450msec for male participants, QTc >470msec for female participants, or QTc >480 msec in participants with bundle branch block. NOTE: The QTc is the QT interval corrected for heart rate according to Fridericia's formula (QTcF). It is either machine read or manually overread.	QTc should serve as a criteria to determine eligibility for an individual participant prior to initiation of the study.
Section 6.1 Treatments administered	Changed treatment type from "Biologic" to "Drug" in Table 6-1 Treatment administered.	Correction of classification error.
Section 7.1.2 QTc stopping criteria	Updated QTc stopping criteria.	QTc stopping criteria updated to provide more specific stopping criteria.
Section 8.1.2, Pharmacodynamics Section 8.6, Pharmacokinetics	Added that back-up samples already planned for collection will be stored for all participants in this study to support potential future exploratory biomarker research.	The addition of the text is to clarify that the collected samples for PK and PD can be used for future exploratory analysis as the stand-alone exploratory biomarker samples have been removed from the schedule of assessments.
Section 8.2.3, Electrocardiogram	ECG added to safety assessments.	ECGs added to safety assessments to measure PR, QRS, QT, and QTc intervals.
Section 8.2.5, Suicidal risk monitoring	-Removed statement that an electronic version of the C-SSRS scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study. -Corrected that the "Screening/Baseline" version of the C-SSRS should only be used at the Screening Visit and not anymore at the Baseline Visit, and that the "Since Last Visit" version should be used at all other timepoints, including at the Baseline Visit.	-An electronic version of the C-SSRS scale will not be used in this study. -The Screening/Baseline version of the C-SSRS should only be used at the Screening Visit and not anymore at the Baseline Visit.

Section # and Name	Description of Change	Brief Rationale
Section 8.7, Biomarkers	Removed requirement for blood sampling for exploratory biomarker analyses.	Collection of additional specimens is no longer necessary because the exploratory biomarker specimen analyses could be performed with the existing back-up specimens, which are collected as part of the pharmacokinetic/ pharmacodynamic analyses.
Section 9.4.1, Safety analyses	Added to clarify that ECG will also be presented in listings and summarized over time. Added to clarify that the clinical laboratory, physical examination, and ECG assessments conducted at screening will be considered as baseline values for the assessment of the other safety endpoints.	As clinical laboratory, physical examination, and ECG assessments are not performed at the Baseline Visit in this study, text was added to clarify and confirm that the respective screening assessments will be considered as baseline when assessing the other safety endpoints.
Section 10.4, Appendix 4: Contraceptive guidance and collection of pregnancy information, Table 10-2	Removed footnote "c" regarding hormonal contraception.	No drug-drug interactions are expected; therefore, footnote "c" was removed in order to streamline the contraceptive guidance and to avoid any confusion.

Amendment 2 (21 Oct 2022)

Overall Rationale for the Amendment:

The protocol amendment was considered necessary to remove the SAE reporting requirement from the C-SSRS assessment for a positive response to Question 4. The question asks whether the participant has had suicidal thoughts or ideations since the last visit. Adverse event or SAE reporting following C-SSRS assessment should follow the standard processes as described in Section 8.3 and Section 10.3.

Additional changes include defining the number of missed doses that constitutes a major protocol deviation and clarifying that the withholding of cholinesterase inhibitors for 10 hours is required only prior to the QMG assessment and not prior to the MG-ADL administration. The table below does not include correction of minor typographical errors and formatting/stylistic changes.

Section # and Name	Description of Change	Brief Rationale
Section 6.4, Treatment Compliance	Added statement that if a participant misses 10 or more consecutive doses, he/she must notify the investigator immediately, the medical monitor should be consulted, and this will be considered a major protocol deviation.	To define the threshold of missed doses that will require review by the medical monitor and recording of a major protocol deviation.
Section 6.5.1, Permitted concomitant treatments (medications and therapies)	Clarified that withholding of cholinesterase inhibitors 10 hours prior applies to QMG (not required for MG-ADL assessment).	Withholding of cholinesterase inhibitors is a requirement for QMG, not for MG-ADL.
Section 8.1.1.1, MG-ADL	Removed requirement for withholding cholinesterase inhibitors 10 hours prior to MG-ADL assessment.	Considering the 7 days recall period for answering the questions, withholding of cholinesterase inhibitors is not a requirement for MG-ADL.
Section 8.2.5, Suicidal risk monitoring	Added statement that families and caregivers should be instructed to monitor participants for/ report emergence of unusual changes in behavior or emergence of suicidal ideation and behavior. Removed statement that a positive response to question 4 on the "since last visit" C-SSRS must be reported to UCB via the SAE process.	Removal of ambiguous wording specific to C-SSRS Question 4 and clarification of the role of caregivers in family in reporting changes in behavior. Adverse events or SAEs reporting following C-SSRS assessment should follow the standard processes as described in Section 8.3 and Section10.3.

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SPONSOR DECLARATION

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

Approval Signatures

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