A MULTICENTER, OPEN-LABEL, OUTPATIENT STUDY TO EVALUATE THE SAFE AND EFFECTIVE USE OF A ZILUCOPLAN AUTO-INJECTOR COMBINATION PRODUCT FOR SUBCUTANEOUS SELF-ADMINISTRATION BY STUDY PARTICIPANTS WITH GENERALIZED MYASTHENIA GRAVIS

PROTOCOL DV0013

PHASE 3B

SHORT TITLE:

An open-label, outpatient study to evaluate the safe and effective use of a zilucoplan auto-injector for self-administration by study participants with generalized myasthenia gravis

Sponsor:
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Confidential Material

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History		
Document	**Date**	**Type of amendment**
Original Protocol	15 Dec 2023	Not applicable

SERIOUS ADVERSE EVENT AND MEDICATION ERRORS REPORTING

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

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

Reporting of adverse device effects (serious and nonserious) and device deficiencies for UCB devices used in the study (24h)	
eCRF	The mechanism for reporting an adverse device effects and device deficiencies to UCB (or its representative) will be the electronic data collection tool.
Email	**Global:** qactscomplaints@ucb.com Note: In case of a device related event or a device deficiency for UCB devices or device constituents these should be captured in the electronic data collection tool and an investigational medicinal product (IMP) complaint form should be filled.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol title:

A multicenter, open-label, outpatient study to evaluate the safe and effective use of a zilucoplan auto-injector combination product for subcutaneous self-administration by study participants with generalized myasthenia gravis

Short title:

An open-label, outpatient study to evaluate the safe and effective use of a zilucoplan auto-injector for self-administration by study participants with generalized myasthenia gravis

Rationale:

Myasthenia gravis (MG) is a serious, sometimes life-threatening, debilitating condition associated with numerous symptoms including muscular weakness and fatigue. Some patients can manage their symptoms with oral medications such as oral acetylcholinesterase inhibitors, corticosteroids, or nonsteroidal immunosuppressants. In addition, intravenous immunoglobulin G and plasma exchange treatment could be utilized. For those whose symptoms are not well managed by these medications, a potential alternative is long-term treatment with approved intravenous (IV) C5 inhibitors (eg, eculizumab or ravulizumab) which have proven effective at treating MG symptoms.

Zilucoplan (RA101495; ZLP) was recently approved in the US and EU and is currently available as a prefilled syringe (PFS) for subcutaneous injection (sc). The PFS reduces drug administration burden and can be used by patients with difficult venous access or who are in underserved or rural populations where economic access to IV infusions is prohibitive. However, it is expected that there will be a need to have different treatment administration options available for the administration of ZLP and that individuals may prefer to have the option to administer their ZLP medication using an auto-injector (AI). The AI device may improve the handling of the drug administration and improve compliance. DV0013 will, therefore evaluate the safe and effective self-administration with the zilucoplan-auto-injector (ZLP-AI) as an administration option.

Objectives and estimands/endpoints

Objectives	Estimands/endpoints
Primary	
• To evaluate the effectiveness of ZLP-AI self-administration	Primary estimand • Treatment: Zilucoplan • Target Population: Participants aged ≥18 years with gMG, already treated with zilucoplan (currently participating in MG0011 or treated with commercial zilucoplan) • Endpoint: Effective self-administrations of zilucoplan using the ZLP-AI from Visit 1 to Visit 8. Effective self-administration is defined as: – Complete dose delivery: completeness of the delivery as confirmed by the Investigator. The entire dose of IMP should be completely delivered (ie, the yellow plunger that can be seen through the device window should be completely depressed) • Intercurrent event: – No intercurrent event is defined • Population level summary: – Proportion of effective self-administrations overall (total number of self-administrations from Visit 1 to Visit 8), along with the 95% CI
Secondary	
• To evaluate the effectiveness of ZLP-AI self-administration using additional effectiveness endpoints	Secondary estimands • Treatment: Zilucoplan • Target Population: Participants aged ≥18 years with gMG, already treated with zilucoplan (currently participating in MG0011 or treated with commercial zilucoplan) • Endpoints: – Effective self-administration of zilucoplan using ZLP-AI at Visit 8. Effective self-administration is defined as complete dose delivery. – Effective self-administration of zilucoplan using ZLP-AI at Visit 1. Effective self-administration is defined as complete dose delivery o Complete dose delivery: completeness of the delivery as confirmed by the Investigator. The entire dose of IMP should be completely delivered (ie, the yellow plunger that can be seen through the device window should be completely depressed)

Objectives	Estimands/endpoints
	• Intercurrent event handling: – No intercurrent event is defined • Population level summary: – Proportion of participants, along with the 95% CI
• Evaluate the safety and tolerability of the ZLP-AI self-administrations	Secondary endpoint: • Occurrence of SAEs, TEAEs, ADEs (serious and nonserious) from Visit 1 up to the SFU Visit
Other objectives	
• Evaluate the PK of the ZLP-AI for self-administration	Other PK endpoint: • Measurement of plasma concentrations for zilucoplan and main metabolites CCI [redacted]
• Evaluate the safety and tolerability of the ZLP-AI self-administrations	Other safety endpoints: • Occurrence of ISRs • Occurrence of medication errors associated with adverse reaction
• Evaluate the safety of the ZLP-AI	Other safety endpoint: • Occurrence of SADEs related to the use of the ZLP-AI that would preclude continued use of the ZLP-AI for self-administration (ie, SADEs and/or SADEs leading to withdrawal from the DV0013 study)
• Evaluate the structural and mechanical integrity of the ZLP-AI after completion of self-administration	Other endpoint: • Occurrence of used ZLP-AI combination products identified as having structural or mechanical integrity issues after completion of self-administration. • Investigator observed and reported device deficiencies. Note: An independent assessment of the structural and mechanical integrity of all used ZLP-AI devices will additionally be performed by UCB. The outcome will be reported separately from the study results.
• Evaluate the study participant's experience of self-administration with ZLP-AI as assessed by the SIAQ©	Other endpoint: • Preinjection SIAQ (SIAQ PRE module) domain scores at Visit 1 • Postinjection SIAQ (SIAQ POST module) domain scores following self-administration using the ZLP-AI at Visit 1 and Visit 8

Objectives	Estimands/endpoints
• Explore the study participant's preference for zilucoplan PFS (as used in MG0011 or commercial supply) vs ZLP-AI following the use of the ZLP-AI	Other endpoint: • Patient Preference Question at Visit 8

ADE=adverse device effects; CI=confidence interval; gMG=generalized myasthenia gravis; IMP=investigational medicinal product; ISR=injection site reaction; PFS=prefilled syringe; PK=pharmacokinetics; SADE=serious adverse device effects; SAE=serious adverse event; SFU=Safety Follow-Up; SIAQ=Self-Injection Assessment Questionnaire; TEAE=treatment-emergent adverse event; ZLP-AI=zilucoplan-auto-injector

Overall design

DV0013 is a Phase 3b, multicenter, open-label study to evaluate the safe and effective use of a ZLP-AI combination product for sc self-administration of ZLP solution (the IMP) by study participants with generalized myasthenia gravis (gMG), planned to be conducted in Europe and the US.

The study will aim to reflect real-world use scenarios by including participants who are already self-administering ZLP using the PFS on a once-daily dosing regimen as part of the MG0011 long-term open-label extension (OLE) study or who are on commercial ZLP treatment for at least 1 month prior to Screening.

DV0013 will consist of 9 visits (2 clinic visits and 7 remote telephone visits) and 14 self-administrations using the ZLP-AI:

Treatment Period

- Visit 1 (Screening/Day 1): Each study participant will be provided with training by study personnel in self-administration using the ZLP-AI and will receive the written instructions for use (IFU). Following the training, the study participant will perform self-administration at the clinic using the ZLP-AI.
- Visit 2 to Visit 7: No additional training will be performed; however, the IFU will be available. The study participant will perform self-administration at home using the ZLP-AI. These visits will be remote visits using a telephone call. During the call, the Investigator will ask about the self-administration and document any adverse events and adverse device effects (AEs and ADEs), any changes in concomitant medication use, and/or medication errors occurring in the course of the self-administration. Telephone visits which would be scheduled to occur on a weekend day may be skipped, and the data for the respective days (Saturday and Sunday) will be collected on the next clinic business day (Monday).
- Visit 8: The study participant will perform self-administration at the clinic using the ZLP-AI. The Investigator will collect all used devices from participants and will check completeness of the delivery for the collected devices. All used devices will be returned to UCB for an assessment of structural and mechanical integrity.
- At Visits 1 and 8 , the Investigator is required to witness and evaluate the study participant's use of the ZLP-AI, document any adverse events (AEs and ADEs) and/or

medication errors occurring in the course of the self-administration, and, following the completion of the self-administration, perform a visual inspection of the ZLP-AI to check that the yellow plunger that can be seen through the viewing window is completely depressed.

Safety Follow-Up Visit

- Visit 9: For all participants, a Safety Follow-up (SFU) via telephone call, 7 days (±3 days) after their final study dose using the ZLP-AI, will be required. Any AEs, serious adverse events (SAEs), ADEs, or serious adverse device effects (SADEs) will be recorded. Participants who were enrolled into DV0013 from MG0011 will roll back into MG0011 on the next day following Visit 8 and will continue to be followed up as part of the MG0011 protocol. Participants who were enrolled following treatment with commercial ZLP treatment will continue with their prescribed treatment; for AEs occurring after the SFU telephone call and up to 40 days after the last administration, participants will be instructed to contact the site or follow the safety reporting according to the label.

Number of participants

Participants from MG0011 or those who are currently being treated with commercial ZLP and are on a stable dosing regimen for at least 1 month will be screened at approximately 20 sites in the US and Europe in order to enroll at least 25 participants who use the ZLP-AI at Visit 1 and to obtain approximately 350 self-administrations. See Section 9.8 for the determination of sample size.

Treatment groups and duration

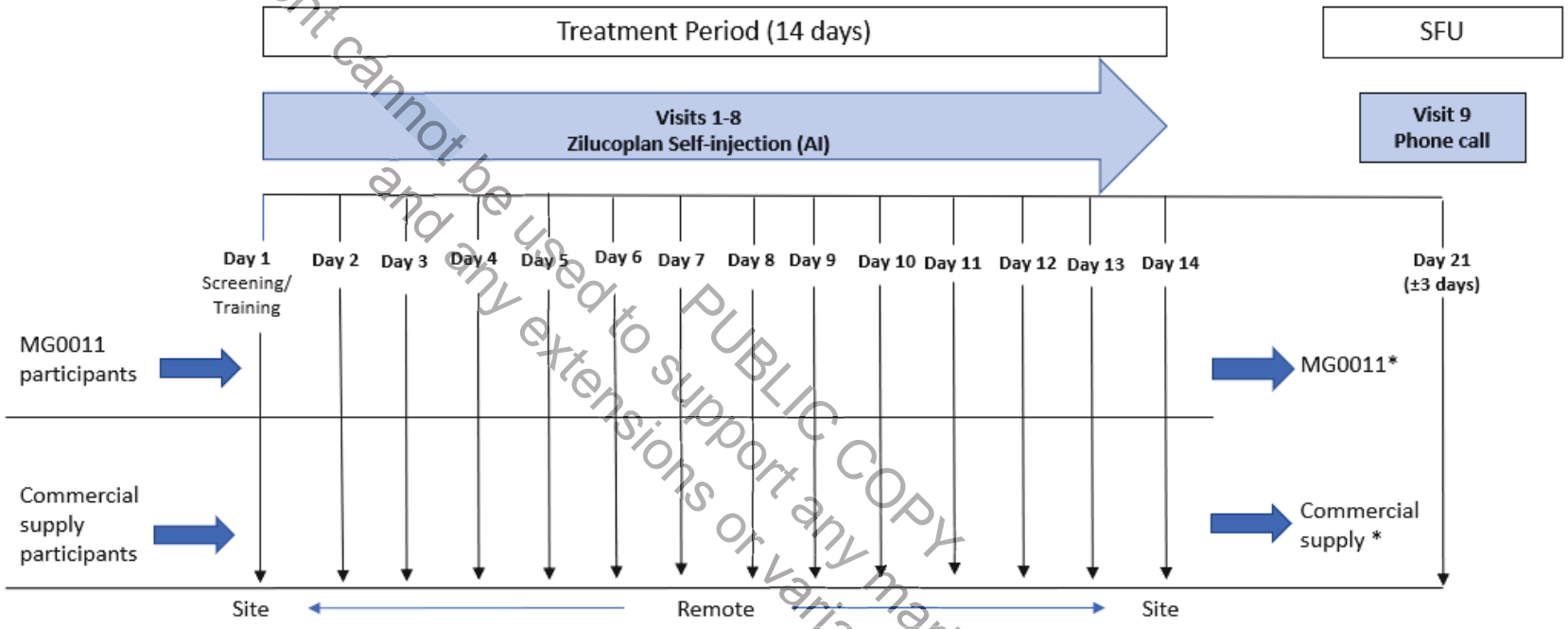
Zilucoplan will be provided in ZLP-AI devices for self-injection using weight-bracketed dosing (ie, participants will be provided ZLP-AI devices containing fixed amounts of ZLP based on their weight, and each fixed amount will cover a range of participant weights). Participants will receive the same weight bracketed dosing as currently received in MG0011 or by prescription.

The study duration for each participant will be approximately 21 days. The end of the study is defined as the date of the last SFU phone call for the last participant in the study.

No Data Monitoring Committee will be established for this study.

1.2 Schema

Figure 1-1: Study schematic



AI=auto-injector; SFU=Safety Follow-Up
Note: *=Participants roll back into MG0011 or go back to self-administration with commercial supply on the next day after Visit 8.

1.3 Schedule of Activities

Table 1-1: Schedule of study assessments

Period	Screening Period	Treatment Period								EW[b] (In-clinic)	SFU Visit[c] (Phone call)
Name	Screening (In-clinic)	Day 1 (In-clinic)	Day 2 (Phone call)[a]	Day 4 (Phone call)[a]	Day 6 (Phone call)[a]	Day 8 (Phone call)[a]	Day 10 (Phone call)[a]	Day 12 (Phone call)[a]	Day 14 (In-clinic)		
Visit #	1		2	3	4	5	6	7	8		9
Day	1		2	4	6	8	10	12	14		(Final dose +7±3 days)
Written informed consent	X										
Demographic data	X										
Verification of inclusion/exclusion criteria[d]	X										
Vaccination history	X										
Review withdrawal criteria										X	
General medical/procedures history	X										
Physical examination[e]		X							X	X	
Vital signs[f]	X										
Urine pregnancy test (βHCG)[g]	X								X		
MGFA classification	X										
Contact IXRS	X								X		
Recording of concomitant medication	X		X	X	X	X	X	X	X	X	X

Table 1-1: Schedule of study assessments

Period	Screening Period	Treatment Period								EW[b] (In-clinic)	SFU Visit[c] (Phone call)
Name	Screening (In-clinic)	Day 1 (In-clinic)	Day 2 (Phone call)[a]	Day 4 (Phone call)[a]	Day 6 (Phone call)[a]	Day 8 (Phone call)[a]	Day 10 (Phone call)[a]	Day 12 (Phone call)[a]	Day 14 (In-clinic)		
Visit #	1		2	3	4	5	6	7	8		9
Day	1		2	4	6	8	10	12	14		(Final dose +7±3 days)
Recording of final ZLP dose and dose date taken in MG0011/commercially available ZLP prior to dosing in DV0013[h]	X										
Participant completes preference question[i]									X		
Participant completes preinjection SIAQ (SIAQ PRE module)[j]		X									
C-SSRS[k]	X								X	X	
Dispense ZLP-AI device		X									
Participant training on self-administration with ZLP-AI device		X									
Participant self-administers ZLP with ZLP-AI device		X	X	X	X	X	X	X	X		
Study personnel evaluation of self-injection and of used ZLP-AI device[l]		X							X		

Table 1-1: Schedule of study assessments

Period	Screening Period	Treatment Period									
Name	Screening (In-clinic)	Day 1 (In-clinic)	Day 2 (Phone call)[a]	Day 4 (Phone call)[a]	Day 6 (Phone call)[a]	Day 8 (Phone call)[a]	Day 10 (Phone call)[a]	Day 12 (Phone call)[a]	Day 14 (In-clinic)	EW[b] (In-clinic)	SFU Visit[c] (Phone call)
Visit #	1		2	3	4	5	6	7	8		9
Day	1		2	4	6	8	10	12	14		(Final dose +7±3 days)
Participant completes postinjection SIAQ (SIAQ POST module)[j]		X							X		
Study personnel collect ZLP-AI devices from each participant to send to UCB for structural/mechanical integrity assessment[m]		X							X		
Drug and device accountability									X		
Record TEAEs, SAEs, ADEs, SADEs, medication errors, ISR, and device deficiencies[n]		X	X	X	X	X	X	X	X	X	X
Blood sampling for ZLP plasma concentrations[o]	CCI [redacted]										

ADE=adverse device effect; AE=adverse event; AI=auto-injector; βHCG=beta human chorionic gonadotropin; C-SSRS=Columbia-Suicide Severity Rating Scale; EW=early withdrawal; IMP=investigational medicinal product; ISR=injection site reaction; IXRS=interactive response technology; MGFA=Myasthenia Gravis Foundation of America; PK=pharmacokinetic; SADE=serious adverse device event; SAE=serious adverse event; SFU=Safety Follow-Up; SIAQ=Self-Injection Assessment Questionnaire; ZLP=zilucoplan

[a] Telephone visits which would be scheduled to occur on a weekend day may be skipped, and the data for the respective days (Saturday and Sunday) will be collected on the next clinic business day (Monday).

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

[c] Study participant will be required to perform a SFU telephone call 7 days (±3 days) after their final study dose of ZLP using the ZLP-AI.

Table 1-1: Schedule of study assessments

Period	Screening Period	Treatment Period									
Name	Screening (In-clinic)	Day 1 (In-clinic)	Day 2 (Phone call)[a]	Day 4 (Phone call)[a]	Day 6 (Phone call)[a]	Day 8 (Phone call)[a]	Day 10 (Phone call)[a]	Day 12 (Phone call)[a]	Day 14 (In-clinic)	EW[b] (In-clinic)	SFU Visit[c] (Phone call)
Visit #	1		2	3	4	5	6	7	8		9
Day	-1	1	2	4	6	8	10	12	14		(Final dose +7±3 days)

[d] Participants may rescreen twice (total of 3 screenings).
[e] The full physical exam will include examination of the following systems: eyes, hair, and skin; respiratory; cardiovascular; and gastrointestinal systems. The Investigator should examine the injection site at each scheduled visit for injection site reactions (eg, bruising, pain, swelling, pruritis, and hematoma). Any abnormalities should be reported as AEs. Height and weight will also be measured and recorded at Visit 1. A full physical exam will be performed at Visit 1 and Visit 8. Any findings will be reported as AEs as appropriate. Any clinically significant changes since the physical examination at Visit 1 will be recorded as AEs.
[f] Vital signs (sitting systolic and diastolic blood pressure, pulse rate, and temperature) are to be measured prior to blood sampling and prior to dosing, where applicable.
[g] For women of childbearing potential, pregnancy testing will consist of urine pregnancy tests at Visits 1 and 8 only. Pregnancy test results must be negative prior to administering IMP. Positive urinary test will be exclusionary. Participant may rescreen at a later time if pregnancy not confirmed subsequently with a serum test.
[h] When recording the final dose taken prior to enrolling in DV0013, the time of self-administration should also be recorded. Participants should continue on the same weight-based dose that they were self-administering in MG0011 or commercial ZLP dose they were on prior to enrolling in DV0013.
[i] A single question will be asked at Visit 8 postdose, assessing the study participant's preference for administration method.
[j] The preinjection SIAQ (SIAQ PRE module version 2.1) will be completed preinjection at Visit 1; the postinjection SIAQ (SIAQ POST module version 2.1) will be completed directly following self-injection and no later than 30 minutes postinjection at Visit 1 and Visit 8 during the study Treatment Period.
[k] In accordance with the draft Food and Drug Administration 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.
[l] At Visits 1 and 8, the Investigator will observe the participant self-administrating with the ZLP-AI device. The used ZLP-AI devices will be visually inspected by the Investigator to determine if the entire dose was completely delivered (ie, the yellow plunger that can be seen through the device window is completely depressed).
[m] All used AI devices will be sent to UCB for assessment of structural and mechanical integrity and damage (ie, clear evidence of damage/compromised structural integrity—not superficial, cosmetic imperfections).
[n] Note that ADEs, SADEs, ISRs, and medication errors can only be recorded on the 14 days that the participant is using the ZLP-AI, and device deficiencies will also be collected during those 14 days. Device deficiencies will be reported via the eCRF. In addition, sites will fill out a product quality complaint form; all product quality complaints will be investigated by UCB.
[o] A single PK sample will be collected CCI [redacted].

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. Some patients can manage their symptoms with oral medications such as oral acetylcholinesterase inhibitors, corticosteroids, or nonsteroidal immunosuppressants. In addition, intravenous immunoglobulin G and plasma exchange treatment could be utilized. 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.

Zilucoplan (RA101495; ZLP) was recently approved in the US and EU and is currently available as a PFS for sc injection. The PFS reduces drug administration burden and can be used by patients with difficult venous access or who are in underserved or rural populations where economic access to IV infusions is prohibitive. However, it is expected that there will be a need to have different treatment administration options available for the administration of ZLP and that individuals may prefer to have the option to administer their ZLP medication using an AI. The AI device may improve the handling of the drug administration and improve compliance. DV0013 will, therefore evaluate the safe and effective self-administration with the ZLP-AI as an administration option.

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 globally is estimated to be 12.4 (range 10.6 to 14.5) per 100,000 persons (Salari et al, 2021), hence, MG affects up to approximately 760,000 people worldwide. Myasthenia gravis most commonly affects young adult women (under 40) and older men (over 60), but it can occur at any age. Epidemiological studies reveal an increasing prevalence over the past 50 years, due in part to an increase in the frequency of diagnosis in the elderly (Sanders et al, 2016). As the population has aged, the average age at onset has increased correspondingly. 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 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.

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) (Howard et al, 2023). 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

The primary risk associated with C5 inhibitors as a class is increased susceptibility to infections with encapsulated bacteria, such as *Neisseria* spp. Specifically, this risk is related to suppression of the innate immune response and subsequent infections, particularly meningococcal infections. It is well established that inhibition of C5 and the terminal complement pathway increases the susceptibility to *Neisseria* spp. infections. Given the known increased risk of meningococcal infection (*Neisseria. meningitidis*) associated with inhibition or inherited deficiency of C5, participants in this study will be required to have documentation of *N. meningitidis* vaccination at least 14 days prior to IMP administration, if not vaccinated within 3 years prior to the start of treatment. Participants must be vaccinated with a quadrivalent vaccine (where available and in accordance with local standard of care) and serogroup B vaccine against meningococcal infections (*N. meningitidis*), and booster vaccinations should be administered in accordance with local standard of care. In addition, while on ZLP, study participants must be monitored closely for signs and symptoms of *N. meningitidis* infection, including self-monitoring and caregiver monitoring based on detailed instructions about signs and symptoms of possible meningococcal infections. To date, no meningococcal infections have been identified with ZLP treatment in clinical studies, as the risk of *Neisseria* infection is well-managed by appropriate prophylactic vaccination.

Together, the nonclinical and clinical data generated by investigations with ZLP support the use of ZLP in patients with gMG. While both benefits and risks may be associated with the administration of any investigational medicine, to date, ZLP has shown good tolerability and a favorable safety profile across studies in healthy adult study participants and adult study participants with CCI [redacted], immune-mediated necrotizing myopathy, gMG, paroxysmal nocturnal hemoglobinuria, coronavirus Disease 2019 (COVID-19)-associated respiratory syndrome, and amyotrophic lateral sclerosis. The bioequivalence of the AI device is under investigation in DV0012; however the AI device may improve the handling of the drug administration and improve compliance.

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

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

3 OBJECTIVES AND ENDPOINTS

Table 3-1: Objectives and estimands/endpoints

Objectives	Estimands/endpoints
Primary	
• To evaluate the effectiveness of ZLP-AI self-administration	Primary estimand • Treatment: Zilucoplan • Target Population: Participants aged ≥18 years with gMG, already treated with zilucoplan (currently participating in MG0011 or treated with commercial zilucoplan) • Endpoint: Effective self-administrations of zilucoplan using the ZLP-AI from Visit 1 to Visit 8. Effective self-administration is defined as: – Complete dose delivery: completeness of the delivery as confirmed by the Investigator. The entire dose of IMP should be completely delivered (ie, the yellow plunger that can be seen through the device window should be completely depressed) • Intercurrent event: – No intercurrent event is defined • Population level summary: – Proportion of effective self-administrations overall (total number of self-administrations from Visit 1 to Visit 8), along with the 95% CI
Secondary	
• To evaluate the effectiveness of ZLP-AI self-administration using additional effectiveness endpoints	Secondary estimands • Treatment: Zilucoplan • Target Population: Participants aged ≥18 years with gMG, already treated with zilucoplan (currently participating in MG0011 or treated with commercial zilucoplan) • Endpoints: – Effective self-administration of zilucoplan using ZLP-AI at Visit 8. Effective self-administration is defined as complete dose delivery. – Effective self-administration of zilucoplan using ZLP-AI at Visit 1. Effective self-administration is defined as complete dose delivery

Table 3-1: Objectives and estimands/endpoints

Objectives	Estimands/endpoints
	– Complete dose delivery: completeness of the delivery as confirmed by the Investigator. The entire dose of IMP should be completely delivered (ie, the yellow plunger that can be seen through the device window should be completely depressed) • Intercurrent event handling: – No intercurrent event is defined • Population level summary: – Proportion of participants, along with the 95% CI
• Evaluate the safety and tolerability of the ZLP-AI self-administrations	Secondary endpoint: • Occurrence of SAEs, TEAEs, ADEs (serious and nonserious) from Visit 1 up to the SFU Visit
Other objectives	
• Evaluate the PK of the ZLP-AI for self-administration	Other PK endpoint: • Measurement of plasma concentrations for zilucoplan and main metabolites [redacted]
• Evaluate the safety and tolerability of the ZLP-AI self-administrations	Other safety endpoints: • Occurrence of ISRs • Occurrence of medication errors associated with adverse reaction
• Evaluate the safety of the ZLP-AI	Other safety endpoint: • Occurrence of SADEs related to the use of the ZLP-AI that would preclude continued use of the ZLP-AI for self-administration (ie, SADEs and/or SADEs leading to withdrawal from the DV0013 study)
• Evaluate the structural and mechanical integrity of the ZLP-AI after completion of self-administration	Other endpoint: • Occurrence of used ZLP-AI combination products identified as having structural or mechanical integrity issues after completion of self-administration. • Investigator observed and reported device deficiencies. Note: An independent assessment of the structural and mechanical integrity of all used ZLP-AI devices will additionally be performed by UCB. The outcome will be reported separately from the study results.

Table 3-1: Objectives and estimands/endpoints

Objectives	Estimands/endpoints
• Evaluate the study participant's experience of self-administration with ZLP-AI as assessed by the SIAQ©	Other endpoint: • Preinjection SIAQ (SIAQ PRE module) domain scores at Visit 1 • Postinjection SIAQ (SIAQ POST module) domain scores following self-administration using the ZLP-AI at Visit 1 and Visit 8
• Explore the study participant's preference for zilucoplan PFS (as used in MG0011 or commercial supply) vs ZLP-AI following the use of the ZLP-AI	Other endpoint: • Patient Preference Question at Visit 8

ADE=adverse device effect; CI=confidence interval; gMG=generalized myasthenia gravis; IMP=investigational medicinal product; ISR=injection site reaction; PFS=prefilled syringe; PK=pharmacokinetics; SADE=serious adverse device effect; SAE=serious adverse event; SFU=Safety Follow-Up; SIAQ=Self-Injection Assessment Questionnaire; TEAE=treatment-emergent adverse event; ZLP-AI=zilucoplan-auto-injector

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

Only observed data will be analyzed. There will be no special procedures for handling missing data. All imputation of missing or partial dates for safety assessments will be detailed in the Statistical Analysis Plan.

4 STUDY DESIGN

4.1 Overall design

DV0013 is a Phase 3b, multicenter, open-label study to evaluate the safe and effective use of a ZLP-AI combination product for sc self-administration of ZLP solution (the IMP) by study participants with gMG, planned to be conducted in Europe and the US.

The study will aim to reflect real-world use scenarios by including participants who are already self-administering ZLP using the PFS on a once-daily dosing regimen as part of the MG0011 long-term OLE study or who are on commercial ZLP treatment for at least 1 month prior to Screening.

DV0013 will consist of 9 visits (2 clinic visits and 7 remote telephone visits) and 14 self-administrations using the ZLP-AI:

Treatment Period

- Visit 1 (Screening/Day 1 visit): Each study participant will be provided with training by study personnel in self-administration using the ZLP-AI and will receive the written IFU. Following the training, the study participant will perform self-administration at the clinic using the ZLP-AI.

- Visit 2 to Visit 7: No additional training will be performed; however, the IFU will be available. The study participant will perform self-administration at home using the ZLP-AI. These visits will be remote visits using a telephone call. During the call, the Investigator will ask about the self-administration and document any adverse events (AEs and ADEs), any changes in concomitant medication use, and/or medication errors occurring in the course of the self-administration. Telephone visits which would be scheduled to occur on a weekend day may be skipped, and the data for the respective days (Saturday and Sunday) will be collected on the next clinic business day (Monday).
- Visit 8: The study participant will perform self-administration at the clinic using the ZLP-AI. The Investigator will collect all used devices from participants and will check completeness of the delivery for the collected devices. All used devices will be returned to UCB for an assessment of structural and mechanical integrity.
- At Visits 1 and 8, the Investigator is required to witness and evaluate the study participant's use of the ZLP-AI, document any adverse events (AEs and ADEs) and/or medication errors occurring in the course of the self-administration, and, following the completion of the self-administration, perform a visual inspection of the ZLP-AI to check that the yellow plunger that can be seen through the viewing window is completely depressed.

Safety Follow-Up Visit

- Visit 9: For all participants, an SFU via telephone call, 7 days (±3 days) after their final study dose using the ZLP-AI, will be required. Any AEs, SAEs, ADEs, or SADEs will be recorded. Participants who were enrolled into DV0013 from MG0011 will roll back into MG0011 on the next day following Visit 8 and will continue to be followed up as part of the MG0011 protocol. Participants who were enrolled following treatment with commercial ZLP treatment will continue with their prescribed treatment; for AEs occurring after the SFU telephone call and up to 40 days after the last administration, participants will be instructed to contact the site or follow the safety reporting according to the label.

The study duration for each participant will be approximately 21 days.

4.2 Scientific rationale for study design

It is expected that there will be a need to have different treatment administration options available for the administration of licensed ZLP and that individuals may prefer to have the option to administer their ZLP medication using an AI. DV0013 will therefore evaluate the safe and effective self-administration with the ZLP-AI as an administration option.

The study will aim to reflect real-world use scenarios by including participants who are already self-administering ZLP using the PFS on a once-daily dosing regimen as part of the MG0011 long-term OLE or who are on commercial ZLP treatment for at least 1 month prior to Screening.

4.3 Justification for dose

CCI

[redacted]

CCI [redacted]

Table 4-1: Zilucoplan weight-bracketed dosing

CCI [redacted]	

4.4 End of study definition

A participant is considered to have completed the study if he/she has completed all periods of the study including the Treatment Period and SFU phone call.

The global end of the study is defined as the date of the last SFU phone call for 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. Study participant is male or female and must be at least 18 years of age at the time of signing the informed consent form (ICF).

Type of participant and disease characteristics

2. Study participant must have a documented diagnosis of gMG, based on study participant's history and supported by previous evaluations.
3. Study participant is currently participating in ZLP study MG0011 or is administering commercial ZLP on a stable dosing regimen for at least 1month prior to Screening.
4. Study participants on commercial ZLP need to receive ZLP per the approved local labeling.
5. Study participant is considered reliable and capable of adhering to the study protocol (eg, able to understand and complete questionnaires and able to adhere to the visit schedule) according to the judgement of the Investigator.
6. Study participant is willing and capable of self-administering ZLP using the ZLP-AI according to the IFU, ie, does not have any visual, physical, or other disability or impairment that interferes with his/her capacity to self-administer; if the participant has a caregiver, he/she may assist the participant with the injection.
7. Vaccination with a quadrivalent meningococcal vaccine and, where available, meningococcal serotype B vaccine at least 14 days prior to IMP administration, if not vaccinated within

3 years prior to the start of treatment. Booster vaccination(s) should also be administered as clinically indicated, according to the local standard of care, for participants who have been previously vaccinated against *Neisseria meningitidis*.

8. Female participants of childbearing potential must have a negative urine pregnancy test prior to the first dose of study drug.

Sex

9. Male and/or female study participants
   - A male participant must agree to use contraception as detailed in Appendix 4 (Section 10.4) during the Treatment Period and for 40 days 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 1 of the following conditions applies:
     - Not a woman of childbearing potential (WOCBP) as defined in Appendix 4 (Section 10.4)
       OR
       A WOCBP who agrees to follow the contraceptive guidance in Appendix 4 (Section 10.4) during the Treatment Period and for 40 days after the last dose of study medication.

Informed consent

10. 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. Study participant has any medical or psychiatric condition that, in the opinion of the Investigator, could jeopardize or would compromise the study participant's ability to participate in this study.
2. Female participants who are breastfeeding, pregnant, or plan to become pregnant during the study.
3. Study participant has a known hypersensitivity to any components of the study medication (and/or an investigational device) as stated in this protocol.
4. Study participant has a clinically relevant active infection or a history of serious infection (resulting in hospitalization or requiring intravenous antibiotic treatment) within 6 weeks before Visit 1.
5. Study participant has a history of meningococcal disease.

Prior/concurrent clinical study experience

6. 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 (except studies MG0009, MG0010, or MG0011, which are not excluded, unless the participant was required to withdraw from said studies for a safety reason which could reasonably recur).
7. Participant has participated in another study of an IMP (and/or an investigational device) different from ZLP within the previous 3 months or 5 half-lives, whichever is longer, or is currently participating in another study of an IMP (and/or an investigational device).

Diagnostic assessments

8. Current unstable liver or biliary disease at Screening (Visit 1), per Investigator assessment, defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice, or cirrhosis. NOTE: with exception of stable hepatobiliary conditions (including Gilbert's syndrome, asymptomatic gallstones).

5.3 Lifestyle restrictions

There are no lifestyle restrictions during the study.

5.4 Screen failures

Screen failures are defined as 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 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 TREATMENT

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.

6.1 Treatment administered

The treatment administered in DV0013 is presented in Table 6-1.

Table 6-1: Treatment administered

ARM name	ZLP-AI
Intervention name	Zilucoplan
Type	Drug product (15-amino acid macrocyclic synthetic peptide) associated with a functional secondary packaging
Dose formulation	Prefilled pen containing the solution for injection (also known as the AI)
Unit dose strength(s)	Drug solution 40mg/mL
Dosage level(s)	Three dose levels based on participant body weight: • <56kg: 16.6mg ZLP • ≥56 to <77kg: 23.0mg ZLP • ≥77kg: 32.4mg ZLP Frequency: once daily
Route of administration	Subcutaneous injection
Use	Experimental
IMP and NIMP/AxMP	IMP
Sourcing	Provided centrally by the Sponsor
Packaging and labeling	The IMP will be provided in a box that protects from light or damage. The IMP is manufactured, packaged, and labeled according to GMP guidelines and in accordance with all applicable laws or regulations. Each IMP carton will be labeled according to individual country requirements. Details of the packaging and labeling will be provided in the IMP Handling Manual.
Excipients	Isotonic buffered solution of RA101495 sodium (drug substance), containing standard excipients

AI=auto-injector; AxMP=auxiliary medicinal product; GMP=Good Manufacturing Practices; IMP=investigational medicinal product; NIMP=noninvestigational medicinal product; ZLP=zilucoplan; ZLP-AI=zilucoplan-auto-injector

In DV0013, the term IMP refers to the ZLP-AI, which consists of the naked PFS (primary packaging containing ZLP drug product used for all Phase 3 studies and in the ZLP safety syringe 1mL) inside an auto-injector.

Each participant will be provided with self-injection training and IFU for the ZLP-AI, as specified in the Schedule of Activities (SoA) (Section 1.3).

Study participants will be instructed to self-inject sc doses daily at approximately the same time each day. Participants may inject study drug into the abdomen (preferred site), front part of the thigh, or back part of the upper arm. Participants will be requested to choose a different site each time they give themselves an injection; if they wish to use the same injection site, they should ensure that it is at least 1 inch (approximately 2.5cm) from the spot previously used.Treatment of

the injection site with an anesthetic or other topical products (eg, steroids) prior to dosing is not permitted.

Participants will receive the doses of IMP listed in Table 6-1 based on their weight and their established dosing regimen in MG0011/commercial supply.

Regardless of the assigned dose regimen, participants will perform a single self-administration with the ZLP-AI, as specified in the SoA (Section 1.3) on Days 1 to 14.

6.1.1 Devices

The ZLP-AI-1mL consists of the naked PFS (primary packaging containing ZLP drug product used for all Phase 3 studies and in the ZLP safety syringe 1mL) inside an auto-injector. The PFS volume will be administered from the same primary container, a 1mL long glass syringe, and a 29-gauge thin wall half inch stacked needle. The ZLP-AI-1mL is a single dose, disposable, nonsterile combination product.

Additional instructions for device use, including the injection angle, are provided in the IFU. Participants will be instructed to retain and return all ZLP-AI devices administered at home when they return to the clinic, as specified in the SoA (Section 1.3). Devices will be individually numbered for tracking purposes.

All device deficiencies (including malfunction use error and inadequate labeling) shall be documented and reported by the Investigator throughout the study (see Section 8.3.8) and appropriately managed by the Sponsor.

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 treatment received and any discrepancies are reported and resolved before use of the study treatment.

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

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for IMP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

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

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

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

6.2.1 Drug accountability/device accountability

The electronic case report form (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.

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.

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 at the site according to local laws, regulations, and UCB standard operating procedures (SOPs) and returned to UCB for assessment. Investigational medicinal product intended for the study cannot be used for any other purpose than that described in this protocol. Assessment of post-use structural and mechanical integrity of ZLP-AI will be done at UCB, and data will be reported on file (Section 8.1.2).

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.

To enroll a study participant (Visit 1), the Investigator or designee will contact the interactive response technology (IXRS) and provide brief details about the participant to be enrolled. Each participant will receive a 5-digit number assigned at Screening that serves as the participant identifier throughout the study. Participants enrolling from MG0011 will receive a unique 5-digit number for DV0013 and the participant ID from MG0011 will be recorded in the eCRF. The participant number will be required in all communication between the Investigator or designee and the IXRS regarding a particular participant. Participant numbers and kit numbers will be tracked via the IXRS.

The IXRS will allocate kit numbers to the participant based on the participant number during the course of the study.

6.4 Treatment compliance

Participants must return all unused study medication and empty study medication containers as specified in the SoA (Section 1.3). Drug accountability must be done in the participant's presence in order to obtain explanations regarding discrepancies in compliance with the dosing regimen. Drug accountability must be recorded on the Drug Accountability form.

If a 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.

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 while in this study. All concomitant medications ongoing from MG0011 will be documented in the eCRF.

6.5.1 Permitted and prohibited concomitant treatments (medications and therapies)

In addition to the permitted and prohibited concomitant treatments described in the local labeling for zilucoplan:

- Treatment of the injection site with an anesthetic or other topical medications (eg, steroids) prior to dosing is not permitted.

6.5.2 Vaccinations

Study participants should be up to date with their vaccination schedule, and their vaccination history will be reviewed as specified in the SoA (Section 1.3). If vaccination is due, the study participant should receive it. 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 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 SARS-CoV-2 vaccinations in ZLP clinical studies.

If administration of a vaccine is planned, all relevant information (ie, name of vaccine, dose, date of administration) should be captured in the eCRF Concomitant Medication Page.

There is a known increased risk of meningococcal infection (*N.meningitidis*), which is associated with the inhibition, or inherited deficiency, of C5. Therefore, to reduce the risk of meningococcal infection (*N.meningitidis*), all study participants must have documentation of vaccination with a quadrivalent meningococcal vaccine and, where available, meningococcal serotype B vaccine. A study participant must agree to receive a booster vaccination during the study, if clinically indicated according to the local standard of care, for participants who have been previously vaccinated against *N.meningitidis*. In addition, while on-treatment with ZLP, participants will be monitored closely for signs and symptoms of *N.meningitidis* infection.

During the study, participants will be counseled and reminded of the early signs and symptoms of *N.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.

6.6 Dose modification

No dose modifications are allowed during the study. Participants should continue on the same weight-based dose that they were self-administering in MG0011 or commercial ZLP dose they were on prior to enrolling in DV0013.

6.7 Criteria for study hold or dosing stoppage

UCB reserves the right to temporarily suspend or prematurely discontinue this study either at a single site, multiple sites, or at all sites at any time for reasons including, but not limited to,

safety or ethical issues, inaccurate or incomplete data recording, noncompliance, or unsatisfactory enrollment with respect to quality or quantity.

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

6.8 Treatment after the end of the study

Participants who were enrolled into DV0013 from MG0011 will roll back into MG0011 and will continue to be followed up as part of the MG0011 protocol.

Participants who enrolled in DV0013 from commercial ZLP treatment will roll back to self-administration with commercial supply.

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 (eg, suspected pancreatitis)

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 must discuss with the study participant the options for continuation of the assessments in the SoA (Section 1.3), including different options of follow up (eg, in person, by phone/mail, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints and AEs. Study participants who discontinue study medication should not be automatically removed from the study. Whenever safe and feasible, it is imperative that study participants remain on the study to ensure safety surveillance and/or collection of outcome data. The Investigator must document the level of follow up that is agreed to by the study participant, any changes to the scheduled visits and assessments, and the plan for follow up that is agreed to by the participant. In regard to changes to scheduled visits, for the level of follow up, it is recommended that the Early Withdrawal Visit and the SFU Visit be prioritized. 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.

7.2 Participant discontinuation/withdrawal from the study

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

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

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

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

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

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 withdraws his/her consent.
4. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test. If the study participant was enrolled from MG0011, the study participant should roll back into MG0011, and MG0011 protocol procedures should be followed. Participants recruited from commercial supply should go back to using commercial supply and follow the guidance in the regional-approved product label.
5. The Sponsor or a regulatory agency requests withdrawal of the participant.
6. The Investigator is of the opinion that the participant's continued participation in the study is not in the best interest of the participant.
7. Participant experiences a severe or serious injection site reaction (eg, bleeding, bruising, or pain) or a SAE that would, in the opinion of the Investigator, preclude the participant's further participation in the study.

Study participants who withdraw from DV0013, ie, study participants who have a medical condition or personal preference that precludes further self-administration, must perform a SFU telephone call or equivalent 7 days (±3 days) after their final DV0013 dosing visit.

Study participants who withdraw from DV0013 and do not have a safety event that would require termination of ZLP treatment may return to MG0011 or to prescribed treatment.

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

7.3 Lost to follow up

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

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

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3).

Protocol waivers or exemptions are not allowed.

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

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

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

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening (Visit 1) purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (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 approximately 4mL. 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 SoA (Section 1.3).

8.1.1 Effective self-administration of ZLP-AI

Effective self-administration is defined as:

- Complete dose delivery: completeness of the delivery as confirmed by the Investigator. The entire dose of IMP should be completely delivered (ie, the yellow plunger that can be seen through the device window should be completely depressed).

8.1.2 Evaluation of post-use structural and mechanical integrity of ZLP-AI

The visual inspection of the used devices will check for structural/mechanical integrity and damage (ie, clear evidence of damage/compromised structural integrity and not any superficial, cosmetic imperfections). All evaluations will be performed by appropriately trained site staff.

All devices will be retrieved post-use and will be assessed for structural and mechanical integrity internally by the technical team at UCB. Results from the assessments will be reported as data on file.

The tests to be performed to assess structural and mechanical integrity of ZLP-AI are summarized in Table 8-1.

Table 8-1: Summary table of structural and mechanical integrity tests

Control	Methodology	Acceptance criteria
Integrity of the syringe barrel	Visual inspection	Attribute (pass/fail)
Syringe should be completely empty	Visual inspection	Attribute (pass/fail)
Locking mechanism that protects the needle is deployed and locked	Qualitative inspection	Attribute (pass/fail)

8.1.3 SIAQ

The Self-Injection Assessment Questionnaire (SIAQ) version 2.1 is a self-administered Patient-Reported Outcome, which will be used to assess the participants' self-injection experience, including the perceived advantages and the potential limitations of self-injection of a sc medication (Keininger and Coteur, 2011).

The preinjection SIAQ (SIAQ PRE module) is composed of 7 items grouped into 3 domains (feelings about injection, self-confidence, and satisfaction with the current mode of administration). The postinjection SIAQ (SIAQ POST module) is composed of 21 items grouped into 6 domains (feelings about injection, self-image, self-confidence, injection site reactions, ease of use, and satisfaction with self-injection). Each domain score of both pre- and post-modules range from 0 to 10, where higher scores indicate a more positive self-injection experience.

The preinjection SIAQ will be completed before self-administration at Visit 1, and the postinjection SIAQ will be completed within 30 minutes after each self-injection (ie, at Visit 1 and Visit 8).

8.1.4 Patient Preference Question

The Patient Preference Question is a self-administered, single question that will be asked at Visit 8 postdose, assessing the study participant's preference for administration method:

"Think about your experience with the auto-injector you used during this clinical trial compared with the prefilled syringe used prior to this clinical trial. All things considered, which injector did you prefer? (please select one answer):

- Auto-injector (used in this clinical study)
- Prefilled syringe (prior to the clinical study)
- No preference"

Given the limitations of the study design, this question 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.

8.2 Safety assessments

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

8.2.1 Physical examination

A full physical examination will include eyes, hair, and skin; and assessments of the respiratory, cardiovascular, and gastrointestinal systems. The Investigator should examine the injection site at each scheduled visit for injection site reactions (eg, bruising, pain, swelling, pruritis, and hematoma). Any abnormalities should be reported as AEs.

Height and weight will also be measured and recorded.

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

Clinically relevant findings or worsening of previous findings since the physical examination at Visit 1 will be recorded as AEs.

8.2.2 Vital signs

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

Vital signs (to be taken before blood collection for laboratory tests and prior to dosing) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the eCRF.

8.2.3 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 Investigator.

Suicidality will be assessed by trained study personnel using the Columbia-Suicide Severity Rating Scale (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 for participants coming from commercial ZLP treatment, and the "Since Last Visit" version will be completed at all other time points. The "Since Last Visit" version will be completed at all time points for participants coming from MG0011 as detailed in the SoA (Section 1.3).

8.3 Adverse events and serious adverse events

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

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

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

For results disclosure on public registries (eg, ClinicalTrials.gov), treatment-emergent AEs (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 SFU Visit, at the time points specified in the SoA (Section 1.3).

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

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 participants who were enrolled following treatment with commercial ZLP treatment or last contact in DV0013 for participants who were enrolled from MG0011, and also to 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 participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the Investigator determines that it is no longer clinically significant, the event is otherwise explained, or the participant is lost to follow up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

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

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.

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

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

8.3.5 Pregnancy

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

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

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

- The participant should return for an early discontinuation visit.
- The participant should immediately stop the intake of the study medication or be down-titrated as instructed at the early discontinuation visit.

- An SFU Visit should be scheduled 7±3 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 Medication errors associated with self-administration

The definitions of medication errors can be found in Appendix 12 (Section 10.12). The medication errors reported by the study participant (or, when appropriate, by a caregiver, or observed by the Investigator) shall be recorded in the paper Medication Error form by the Investigator and emailed to the contact found in SERIOUS ADVERSE EVENT AND MEDICATION ERRORS REPORTING. All medication errors will be recorded and reported to the sponsor or designee within 7 days of awareness. Medication errors that are associated with an adverse reaction will be recorded and reported within 24 hours following the SAE recording and reporting procedures as indicated in Appendix 3 (Section 10.3) and using the Medication Error form.

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of a medication error and remain responsible for following up medication errors that are associated with adverse reaction.

8.3.7 Adverse events of special monitoring

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.

8.3.8 Device – adverse events (ADEs, UADEs, SAEs, SADEs, and USADEs) and device deficiencies

Devices are being provided for use in this study for the purposes of sc ZLP dosing (see Section 6.1.1). In order to fulfill regulatory reporting obligations worldwide, the Investigator is responsible for the detection and documentation of events meeting the definitions of ADEs, SADEs, and device deficiency that occur during the study with such devices.

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

The definitions of an ADE, SADE, unanticipated serious adverse device effect (USADE), and device deficiency can be found in Appendix 7 (Section 10.7).

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

8.3.8.1 Time period for detecting ADEs and device deficiencies

Adverse device effects and device deficiencies will be detected, documented, and reported during all periods of the study in which the device is used.

If the Investigator learns of any ADEs or device deficiencies at any time after a participant has been discharged from the study, and such event(s) is considered reasonably related to a device provided for the study, the Investigator will promptly notify the Sponsor.

The method of documenting ADEs and device deficiencies is provided in Appendix 7 (Section 10.7).

8.3.8.2 Follow up of ADEs and device deficiencies

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

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

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

8.3.8.3 Prompt reporting of ADEs and device deficiencies to Sponsor

Adverse device effects and device deficiencies will be reported to the Sponsor immediately and under no circumstances should this exceed 24 hours after the Investigator determines that the event meets the protocol definition of an ADE or device deficiency.

The Sponsor will be the contact for the receipt of device deficiency reports.

8.3.8.4 Regulatory reporting requirements for ADEs and device deficiencies

The Investigator will promptly report all ADEs and device deficiencies immediately, and under no circumstance should this exceed 24 hours for any medical device provided for use in the study in order for the Sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

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

8.4 Safety signal detection

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

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

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

8.5 Treatment of overdose

Unintentional overdose events are considered Medication Errors and should be reported as described in Section 8.3.6 and Section 8.3.7.

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 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 participant.

8.6 Pharmacokinetics

Blood samples of approximately 2mL will be collected for measurement of plasma concentrations of IMP and its main metabolites (CCI [redacted]) as specified in the SoA (Section 1.3) Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples collected for pharmacokinetic (PK) analyses may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study. In addition, surplus PK samples may be stored and used for potential future biomarker research (including assay development/optimization), but not for future genetic biomarker research.

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

8.7 Biomarkers

Biomarkers are not evaluated in this study.

8.8 Immunogenicity assessments

Immunogenicity is not evaluated in this study.

8.9 Medical resource utilization and health economics

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

9 STATISTICAL CONSIDERATIONS

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

9.1 Definition of analysis sets

An Enrolled Set will include all participants who have signed an informed consent form.

A Safety Set (SS) will be generated for the administration of ZLP using the ZLP-AI. The SS will consist of all study participants in the study who receive at least 1 dose of ZLP with the ZLP-AI combination product.

The Pharmacokinetic per-Protocol Set will consist of all study participants in the SS who have at least 1 quantifiable PK measurement during the study without important protocol deviations that would affect the PK.

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.

9.3 Planned efficacy/outcome analyses

The study will estimate the true population proportion of self-administration-related endpoints for ZLP-AI. No formal statistical hypothesis testing will be done.

Summary statistics for continuous variables will include:

- Number of available observations
- Mean, standard deviation, minimum, median, and maximum

For categorical variables, the number and proportion of participants, along with the 95% confidence interval (CI) based on the Exact Binomial method (when appropriate), will be presented.

No imputation of missing data will be done on the primary estimand. As a sensitivity analysis, missing data will be imputed as administration failure.

All data recorded in the eCRFs and questionnaires will be listed where appropriate.

All statistical analyses will be descriptive in nature. No inferential statistical analyses are planned.

9.3.1 Primary estimand/primary endpoint analyses

The primary outcome variable is defined in Table 3-1.

The proportion of effective self-administrations will be tabulated for the ZLP-AI combination product using the SS population. The 95% CIs based on the Exact Binomial method will be reported. As a sensitivity analysis, the primary endpoint will also be evaluated, where any missing self-administration will be considered as an administration failure. In addition, the proportion of effective self-administrations may be described by geographical region as well.

9.3.2 Secondary estimand/secondary endpoint analyses

The secondary outcome variables are defined in Table 3-1.

The secondary outcome variables will be analyzed using the SS in the same manner as the primary outcome variable (Section 9.3.1).

9.3.3 Other estimand/other endpoint analyses

The other outcome variables are defined in Table 3-1.

These variables will be summarized using descriptive statistics, and they will be tabulated for the ZLP-AI by geographical region where appropriate using the SS population.

9.4 Planned safety and other analyses

9.4.1 Other analyses

The PK endpoint is trough PK (zilucoplan) levels associated with self-injection using the ZLP-AI.

Zilucoplan and main metabolite CCI [redacted] will be described descriptively (geomean, 95% CI, coefficient of variation, median, minimum, and maximum).

9.4.2 Safety analyses

Safety endpoints are defined in Table 3-1.

- SAEs, TEAEs, SADEs, and ADEs
  - An ADE is an AE related to the use of the AI device. An ADE includes: (1) Adverse event resulting from insufficiencies or inadequacies in the IFU, the deployment, the installation, the operation, or any malfunction of the device. (2) Adverse event that is a result of a use error or intentional misuse of the investigational device.
  - A SADE is an ADE that has resulted in any of the consequences characteristic of an SAE.
- Medication errors associated with adverse reaction
  - The definitions of medication errors can be found in Appendix 12 (Section 10.12). The medication errors reported by the study participant (or, when appropriate, by a caregiver, or observed by the Investigator) will be recorded in the eCRF.
- Injection site reactions
  - Treatment-emergent injection site reactions.

Analyses of the safety data will be done on the SS population.

All AE data will be listed. Only TEAEs, ADEs, SADEs, and medication errors associated with clinical harm will be included in the summary tables. Treatment-emergent AEs are defined as AEs starting after the time of first injection in the study and up to and including 40 days after the final dose (or last contact in the study, depending on which occurs first).

All AEs will be coded and classified by system organ class, high level term, and preferred term according to the Medical Dictionary for Regulatory Activities.

In this study, safety reporting requirements apply to all constituents of the IMP (ZLP-AI combination product which includes: zilucoplan solution contained inside the PFS and the auto-injector housing the PFS) as per 21 CFR 320. Adverse events related to use of the ZLP-AI combination (ADEs) and device deficiencies will be summarized separately. Adverse events will be summarized by the frequency and percent of participants having 1 or more of the events in question. Planned summaries include overall AEs, AEs by intensity, AEs by relationship to study drug, SAEs, AEs leading to withdrawal, AEs leading to death, ADEs, SADEs, and AEs of special interest.

Vital signs and physical examination findings will be recorded in the eCRF only at Screening/Day 1. Clinically relevant changes in subsequent physical examinations will be recorded as AEs.

Physical examination findings at Day 1 will be listed. A by-participant listing of the C-SSRS questionnaire data will be provided.

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.

9.6 Handling of dropouts or missing data

There will be no special procedures for handling missing data.

As a sensitivity analysis on the primary estimand, missing data will be imputed as administration failure.

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

9.7 Planned interim analysis and data monitoring

The final DV0013 study analysis and clinical study report will be prepared once all data have been collected. No Data Monitoring Committee will be established for this study.

9.8 Determination of sample size

This study will not be powered with respect to any endpoint, and sample size is based on practical considerations. The number of participants and their diagnosed conditions are summarized below.

Given the rare diseases framework of the gMG indication and the fact that the device is not life supportive, the sample size is based on previous experience and the operating functions of the ZLP-AI.

Participants from MG0011 or those who are currently being treated with commercial ZLP and are on a stable dosing regimen for at least 1 month will be screened at approximately 20 sites in the US and Europe in order to enroll at least 25 participants who use the ZLP-AI at Visit 1 and to obtain approximately 350 self-administrations.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Regulatory and ethical considerations

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

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

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

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

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

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

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

10.1.2 Financial disclosure

Insurance coverage will be handled according to local requirements.

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

10.1.3 Informed consent process

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

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

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

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

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

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

10.1.4 Data protection

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

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

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

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

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

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

10.1.5 Committees structure

No Data Monitoring Committee will be established for this study.

10.1.6 Dissemination of clinical study data

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

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

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

Data from this study may be requested by qualified researchers 6 months after product approval in the US and/or Europe, or global development is discontinued, and 18 months after study completion. Investigators may request access to anonymized individual patient-level data and redacted study documents which may include analysis-ready datasets, study protocol, annotated case report forms, statistical analysis plan, dataset specifications, and clinical study report. Prior to use of the data, proposals need to be approved by an independent review panel at www.Vivli.org, and a signed data sharing agreement will need to be executed. All documents are available in English only, for a prespecified time, typically 12 months, on a password protected portal. This plan may change if the risk of reidentifying study participants is determined to be too high after the study is completed; in this case and to protect participants, individual patient-level data would not be made available.

10.1.7 Data quality assurance

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

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

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

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

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

All essential documents must be retained by the Investigator for the minimum retention period mandatory under the applicable local laws and regulations. The Investigator will contact UCB for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The Investigator will also notify UCB should he/she relocate or move the study-related files to a location other than that specified in the Sponsor's trial master file.

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

10.1.7.1 Case report form completion

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

10.1.7.2 Apps

The questionnaire data collected on the electronic Patient-Reported Outcome (ePRO) diary (SIAQ) will be uploaded to a central server database and will be 21 CFR Part 11 compliant. Appropriate training will be performed at the study sites. The SIAQ nor ePRO platform are intended to be used to influence treatment decisions of participants during conduct of the study and is also not intended to be used to collect or report safety-related information about the participant. The questionnaire responses will be analyzed at the end of the study.

10.1.8 Source documents

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

Source documents are original records in which raw data are first recorded. These may include hospital/clinic/general practitioner records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records, ECG or other printouts, completed scales, quality of life

questionnaires, or video, for example. Source documents should be kept in a secure, limited access area.

10.1.9 Study and site start and closure

The start of recruitment

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

Study/site termination

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

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

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

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

10.1.10 Publication policy

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

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

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

10.2 Appendix 2: Clinical laboratory tests

Not applicable.

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

Definition of AE

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

Events meeting the AE definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from Visit 1, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study medication administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study medication or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT meeting the AE definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the study participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from Visit 1 is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Important medical events: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 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 participant's medical records to UCB in lieu of completion of the UCB AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by UCB. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to UCB.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

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

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

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

Assessment of causality

- The Investigator is obligated to assess the relationship between study medication and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study medication administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which a SAE has occurred and the Investigator has minimal information to include in the initial report to UCB. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to UCB.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by UCB to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- An AE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the participant is lost to follow up. This follow-up requirement applies to AEs, SAEs, and AEs of special interest.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide UCB with a copy of any postmortem findings, including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

Reporting of SAEs

SAE reporting to UCB via an electronic data collection tool

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

SAE reporting to UCB via paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the 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 the SERIOUS ADVERSE EVENT AND MEDICATION ERRORS REPORTING section at the front of the protocol.

10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

Definitions

Woman of childbearing potential

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

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

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

   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use 1 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

Male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following during the Treatment Period and for at least 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 must 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 must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the Treatment Period 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 the table below.

Highly effective contraceptive methods[a]

Highly effective contraceptive methods that are user dependent[b] Failure rate of <1% per year when used consistently and correctly.
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] • Oral • Intravaginal • Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly effective methods that are user independent[c]
Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study medication. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
NOTES: a) In case of newly started contraception pills/IUDs, 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. c) Hormonal contraception may be susceptible to interaction with the study medication, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the Treatment Period and for at least 40 days after the last dose of study medication.

Pregnancy testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine pregnancy test.
- Additional pregnancy testing will be performed as described in the SoA (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 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow up will be at least 12 months after the delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.
- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, the follow-up will be at least 12 months after the delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be 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 a SAE through spontaneous reporting.

10.5 Appendix 5: Genetics

Not applicable.

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

Not applicable.

10.7 Appendix 7: Device AEs, ADEs, SAEs, and device deficiencies: Definition and procedures for recording, evaluating, follow up, and reporting

The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and the European Medical Device Regulation 2017/745 for clinical device research (if applicable).

Both the Investigator and the Sponsor will comply with all local medical device reporting requirements.

The detection and documentation procedures described in this protocol apply to all Sponsor medical devices provided for use in the study. See Section 6.1.1 for the description of the Sponsor medical device.

10.7.1 Definitions of AE and ADE

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

10.7.2 Definitions of SAE, SADE, and USADE

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

A SAE is an AE that:
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: 1. A life-threatening illness or injury. The term life-threatening in the definition of serious refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe 2. A permanent impairment of a body structure or a body function 3. Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a SAE 4. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
c. Led to fetal distress, fetal death, or a congenital abnormality or birth defect
SADE definition
• A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
USADE definition
• An USADE is a serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report (see Section 8.3.8).

10.7.3 Definition of device deficiency

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

10.7.4 Recording and follow up of AE and/or SAE and device deficiencies

AE, SAE, and device deficiency recording

- When an AE/SAE/device deficiency 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/device deficiency information in the participant's medical records, in accordance with the Investigator's normal clinical practice and on the appropriate form of the eCRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to UCB in lieu of completion of the AE/SAE/device deficiency 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.
- For device deficiencies, it is very important that the Investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence. The Investigator should complete a Product Complaint Form for all reported device deficiencies.

Assessment of intensity

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe.
- An event is defined as serious when it meets at least 1 of the predefined outcomes as described in the definition of a SAE, NOT when it is rated as severe.

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency.
- 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 intervention administration, will be considered and investigated.
- The Investigator will also consult the IB in his/her assessment.
- For each AE/SAE/device deficiency, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/device deficiency and has provided an assessment of causality.
- There may be situations in which a SAE has occurred and the Investigator has minimal information to include in the initial report to UCB. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to UCB.
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow up of AE/SAE/device deficiency

- 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/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- 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 postmortem 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.

10.7.5 Reporting of SAEs

SAE reporting to UCB via an electronic data collection tool

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

SAE reporting to UCB via paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the 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 the SERIOUS ADVERSE EVENT AND MEDICATION ERRORS REPORTING section at the front of the protocol.

10.7.6 Reporting of SADEs

SADE Reporting to UCB

NOTE: There are additional reporting obligations for device deficiencies that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- Any device deficiency that is associated with a SAE must be reported to the Sponsor within 24 hours after the Investigator determines that the event meets the definition of a device deficiency.
- The Sponsor shall review all device deficiencies and determine and document in writing whether they could have led to a SAE. These shall be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
- Contacts for SAE reporting can be found in the SAFETY REPORTING OF ADVERSE EVENTS (SERIOUS AND NONSERIOUS) AND DEVICE DEFICIENCES section at the front of the protocol.

10.8 Appendix 8: Rapid alert procedures

Not applicable.

10.9 Appendix 9: Country-specific requirements

Not applicable.

10.10 Appendix 10: Abbreviations and trademarks

ADE	adverse device effect
AE	adverse event
AI	auto-injector
apps	applications
CI	confidence interval
COVID-19	Coronavirus Disease 2019
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	electrocardiogram
eCRF	electronic case report form
ePRO	electronic Patient-Reported Outcome
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
gMG	generalized myasthenia gravis
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IDE	Investigational Device Exemption
IEC	Independent Ethics Committee
IFU	instructions for use
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
ISO	International Organization for Standardization
IUD	intrauterine device
IV	intravenous
IXRS	interactive response technology
MG	myasthenia gravis
NCT number	ClinicalTrials.gov identifier
OLE	open-label extension

PK	pharmacokinetic(s)
PFS	prefilled syringe
SADE	serious adverse device effect
SAE	serious adverse event
sc	subcutaneous(ly)
SFU	Safety Follow-Up
SIAQ	Self-Injection Assessment Questionnaire
SoA	Schedule of Activities
SOP	standard operating procedure
SS	Safety Set
TEAE	treatment-emergent adverse event
USADE	unanticipated serious adverse device effect
WOCBP	woman of childbearing potential
ZLP	zilucoplan
ZLP-AI	zilucoplan-auto-injector

10.11 Appendix 11: Protocol amendment history

Not applicable.

10.12 Appendix 12: Medication errors associated with self-administration

The definitions and procedures detailed in this appendix are in accordance with the pharmacovigilance obligations detailed in Title IX of Directive 2001/83/EC and Regulation (EC) 726/2004, Chapter 3, Article 28 with regard to the recording, reporting, and assessment of suspected adverse reactions (serious and nonserious) associated with an error in prescribing, storing, dispensing, preparing for administration, or administering a medicinal product for human use authorized in the EU, which have been adapted as per DV0013 protocol specifications. All medication errors will be recorded and reported to the sponsor or designee as indicated in Section 8.3.6.

Medication Error Definition

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

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

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

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

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

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