# AN OPEN-LABEL, SINGLE CENTER, RANDOMIZED, 2-WAY CROSSOVER, SINGLE-DOSE, BIOEQUIVALENCE STUDY OF ZILUCOPLAN INJECTED SUBCUTANEOUSLY EITHER BY A PREFILLED SYRINGE OR AN AUTO-INJECTOR IN HEALTHY ADULT PARTICIPANTS

## PROTOCOL DV0012

## PHASE 1

## SHORT TITLE:

An open-label, single center, randomized, 2-way crossover, single dose, bioequivalence study of zilucoplan injected subcutaneously in healthy adult participants

Sponsor:
UCB Biopharma SRL
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# PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

| Document History | | |
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| **Document** | **Date** | **Type of amendment** |
| Original Protocol | 11 Dec 2023 | Not applicable |

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## SERIOUS ADVERSE EVENT REPORTING

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

## SAFETY REPORTING OF ADVERSE EVENTS (SERIOUS AND NONSERIOUS) AND DEVICE DEFICIENCIES

| Safety reporting of adverse events (24h) | |
|---|---|
| **Email** | **Global**: DS_ICT@ucb.com |
| **Fax** | +32 2 386 24 21 |

## SAFETY 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<br><br>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 (EDC) tool and an investigational medicinal product (IMP) complaint form should be filled. |

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# 1 PROTOCOL SUMMARY

## 1.1 Synopsis

**Protocol title:**

An open-label, single center, randomized, 2-way crossover, single dose, bioequivalence study of zilucoplan injected subcutaneously either by a prefilled syringe or an auto-injector in healthy adult participants

**Short title:**

An open-label, single center, randomized, 2-way crossover, single dose, bioequivalence study of zilucoplan injected subcutaneously in healthy adult participants

**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 (IV) immunoglobulin G and plasma exchange treatment can be utilized as well. For those whose symptoms are not well managed by these medications, a potential alternative is long term treatment with approved IV complement component 5 (C5) inhibitors (eg, eculizumab or ravulizumab) which have proven effective at treating MG symptoms.

Zilucoplan (RA101495; ZLP) has recently been approved in Japan, the US, and the EU. It reduces the administration burden, 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. Zilucoplan is currently approved as a pre-filled syringe (PFS) for subcutaneous (sc) injection; 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). DV0012 will, therefore, assess the bioequivalence of ZLP pharmacokinetics (PK) between a single sc injection of ZLP from a ZLP-PFS and ZLP-AI, and evaluate the ZLP PK, safety, and tolerability in healthy study participants who receive a single sc injection of ZLP from a ZLP-PFS and ZLP-AI.

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## Objectives and endpoints

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To establish the bioequivalence of ZLP pharmacokinetics (PK) after a single sc injection with ZLP safety syringe (ZLP- PFS) and ZLP-AI | • Area under the plasma concentration-time curve from time 0 to infinity (AUC)<br>• Area under the plasma concentration-time curve from time 0 to time t ($AUC_{0-t}$)<br>• Maximum observed plasma concentration ($C_{max}$) |
| **Secondary** | |
| • To evaluate the safety and tolerability of ZLP after a single sc injection with ZLP-PFS and ZLP-AI | • Occurrence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse device effects (ADEs, serious and nonserious) from Day 1 up to the End of Study (EOS) or Early Termination (ET) Visit |
| **Exploratory** | |
| • To further evaluate the safety and tolerability of ZLP after a single sc injection with ZLP-PFS and ZLP-AI<br>• To further evaluate the PK of ZLP after a single sc injection with ZLP-PFS and ZLP-AI<br>• To evaluate device deficiencies | • Change from Baseline in clinical laboratory tests (hematology, clinical chemistry, and urinalysis)<br>• Terminal half-life ($t_{½}$)<br>• Apparent plasma clearance (CL/F)<br>• Time to maximum observed concentration ($t_{max}$)<br>• Apparent volume of distribution (Vz/F)<br>• Device deficiencies as reported via the electronic case report form (eCRF) |

## Overall design

DV0012 is a Phase 1, open-label, single-center, randomized, 2-way crossover study in 14 healthy study participants designed to establish bioequivalence in ZLP PK between a single sc injection of ZLP from a ZLP-PFS (reference) and a ZLP-AI (test), and to investigate the PK, safety, and tolerability in healthy study participants who receive a single sc injection of ZLP.

The crossover design allows each participant to receive a single ZLP injection with each of the 2 devices (ZLP-PFS and ZLP-AI). Zilucoplan will be administered as a single sc injection in the abdomen to evaluate the potential impact of using 2 different devices (ZLP-PFS and ZLP-AI) on the PK endpoints. The volume of ZLP will differ from participant to participant depending on their body weight on Treatment Period 1 Day -1.

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Study personnel will administer 1 injection of ZLP to the study participant on Day 1 of each Treatment Period following detailed instructions that will have been provided. Injections into the abdomen must avoid the 5 cm/2-inch area around the belly button (navel). No injections should be administered into an area that is tender, red, bruised, hard, or that has scars or stretch marks.

Fourteen healthy study participants will be randomized 1:1 to treatment sequence AB or BA, where treatment A is ZLP-PFS injection device and treatment B is ZLP-AI injection device (see study schematic in Section 1.2). Following completion of the first Treatment Period and a 7-day Washout Period, study participants will then complete the second Treatment Period with the same dose level as in Treatment Period 1 but using the alternate device.

Study participants will have End of Study (EOS) procedures performed on the last sampling day (Day 35) of Treatment Period 2, in addition to the Day 35 procedures.

Study participants who are unable to complete the study will return to the study center for the Early Termination (ET) Visit as soon as possible after the time of withdrawal and will have all Day 35 and EOS procedures performed (ie, Day 35 of the Treatment Period in which they withdrew from the study).

**Number of participants**

A sufficient number of study participants will be screened to ensure that 7 study participants are randomized to each of the 2 treatment sequences (14 study participants in total), with the objective of having at least 12 study participants complete the study. See Section 9.8 for more details. Study participants who withdraw or are withdrawn from the study after dosing will not be replaced. However, if the number of dropouts exceeds initial expectations, study participants who withdraw or are withdrawn might be replaced at the discretion of the Sponsor.

**Treatment groups and duration**

Zilucoplan will be provided as a single-use injection in a needle safety device (ZLP-PFS) or a ZLP-AI device using weight-bracketed dosing (ie, participants will be provided ZLP-PFS or ZLP-AI containing fixed amounts of ZLP based on their weight, and each fixed amount will cover a range of participant weights).

The total maximum study duration per study participant will be up to 15 weeks, as follows:

- Screening Period: Up to 35 days (Days -35 to -2).
- In-Clinic Period (BL): 1 day (Day -1).
- Treatment Period 1 and Treatment Period 2: 5 weeks each (Days 1-35; approximately 5 times the half-life of ZLP). Each Treatment Period includes:
  - a 2-day In-Clinic Period (Days 1 and 2).
  - a 33-day Observation Period.
    - On Days 3, 5, 8, 15, 22, 29, and 35 of the Observation Period, participants will attend the study center to allow study assessments to be completed.
- Washout Period between Treatment Period 1 and Treatment Period 2: 1 week (7 days).
- The EOS Visit procedures will be performed on Day 35 of Treatment Period 2 (ie, on Study Day 77).

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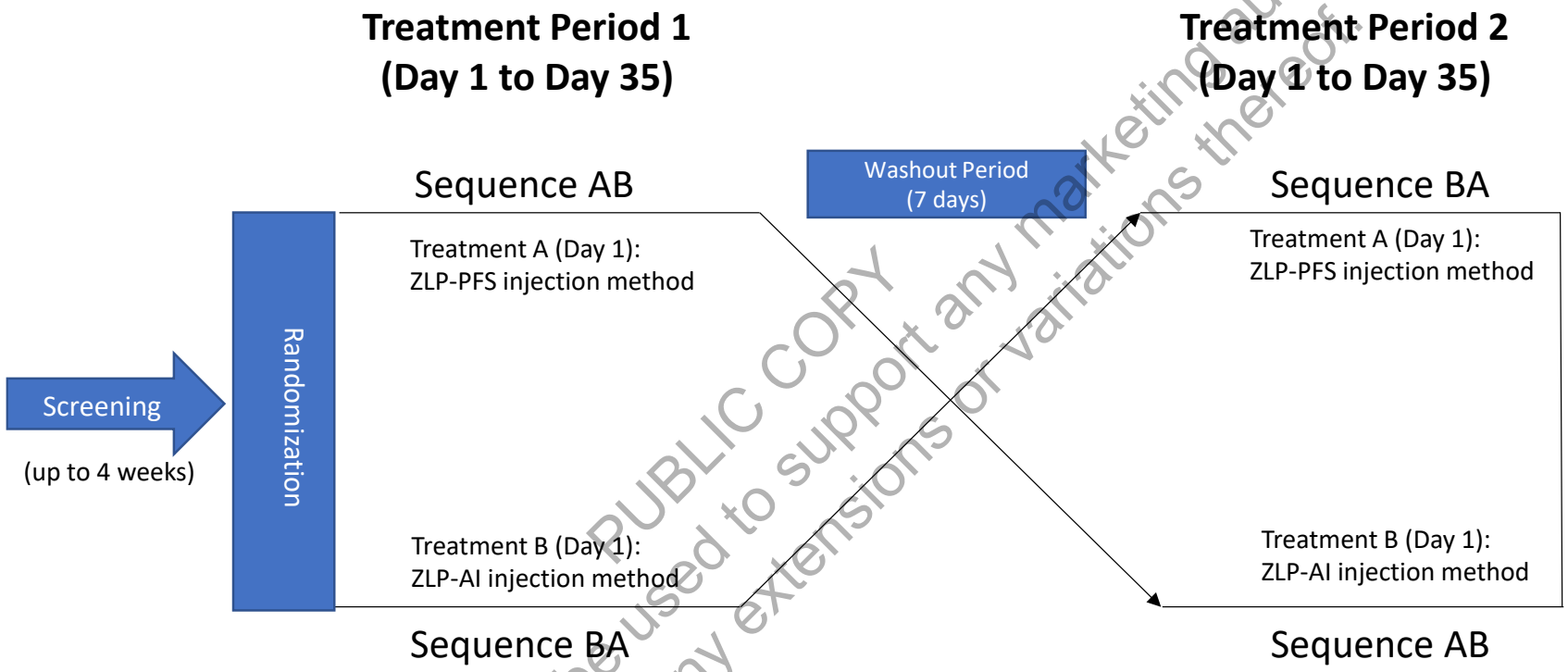
## 1.2 Schema

**Figure 1-1: Study schematic**




ZLP-AI=zilucoplan-autoinjector; ZLP-PFS=ZLP prefilled syringe

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## 1.3 Schedule of Activities

### Table 1-1: Schedule of study assessments

| Procedure | Screening Period | In-Clinic Period (BL)[c] | Treatment Periods 1 and 2[d] | | | | | | | | | EOS/ET[e] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | In-Clinic Period[c] | | Observation Period[c] | | | | | | | |
| Day[a] | -35 to -2 | -1 | 1 | 2 | 3 | 5 | 8 | 15 | 22 | 29 | 35 | |
| Written informed consent | X | | | | | | | | | | | |
| Inclusion/exclusion criteria | X | X | | | | | | | | | | |
| Demography | X | | | | | | | | | | | |
| Medical/surgical history | X | | | | | | | | | | | |
| Physical examination[f] | X | X | | | | | | | | | X | |
| Pregnancy test[g] | X | X | | | | | | | | | | |
| Height and weight[h] | X | X | | | | | | | | | | |
| Serum FSH level[i] | X | | | | | | | | | | | |
| Viral serology (HBsAg, HCV, HIV, and syphilis) | X | | | | | | | | | | | |
| Urine drug test | X | X | | | | | | | | | | |
| Alcohol breath test | X | X | | | | | | | | | | |
| COVID-19 precautions[j] | X | X | | | | | | | | | | |
| Vital signs[k] | | X[b] | | | | | | | | | | |
| Clinical laboratory tests (hematology, clinical chemistry, and urinalysis) | X | X[b] | | | | | | X | | | | X |

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## Table 1-1: Schedule of study assessments

| Procedure | Screening Period | In-Clinic Period (BL)[c] | Treatment Periods 1 and 2[d] | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | In-Clinic Period[c] | | Observation Period[c] | | | | | | | |
| Day[a] | -35 to -2 | -1 | 1 | 2 | 3 | 5 | 8 | 15 | 22 | 29 | 35 | EOS/ET[e] |
| Throat swab for *N. meningitidis* | X | | | | | | | | | | | |
| 12-lead ECG | X | | | | | | | | | | | |
| Recording of prior and concomitant medication and procedures | X | X[b] | X | X | X | X | X | X | X | X | X | |
| Recording of AEs | X | X[b] | X[l] | X[l] | X | X | X | X | X | X | X | X |
| *N. meningitidis* vaccination[m] | X | SoC | SoC | SoC | SoC | SoC | SoC | SoC | SoC | SoC | SoC | SoC |
| Randomization | | X[n] | | | | | | | | | | |
| IMP administration[o] | | | X | | | | | | | | | |
| Blood sampling for PK[p] | | | X | X | X | X | X | X | X | X | X | |
| Recording of device deficiencies and product quality complaints[q] | | | X | | | | | | | | | |

AE=adverse event; BL=Baseline; COVID-19=coronavirus disease 2019; ECG=electrocardiogram; eCRF=electronic case report form; EOS=end of study; ET=early termination; FSH=follicle-stimulating hormone; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IMP=investigational medicinal product; *N. meningitidis*=*Neisseria meningitidis*; PK=pharmacokinetic, SoC=standard of care

[a] Day -35 to -2 is relative to Day 1 in Treatment Period 1; all other days are relative to Day 1 within each Treatment Period.

[b] Baseline Day -1 procedures are repeated on Day -1 prior to Treatment Period 2, unless otherwise stated. Procedures to be repeated on the second Baseline Day -1 include vital signs, laboratory assessments, and recording of concomitant medications and AEs.

[c] Days -1, 1, and 2 are part of the In-Clinic Period; on Days 3, 5, 8, 15, 22, 29, and 35 of the Observation Period, participants will attend the study center to allow study assessments to be completed.

[d] Each participant will attend 2 Treatment Periods. There will 7 days of washout after completion of the first Treatment Period before returning to the study center for the second Treatment Period.

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[e] Study participants will have EOS procedures performed on the last sampling day (Day 35) of Treatment Period 2, in addition to the Day 35 procedures. Participants who prematurely withdraw from the study will return to the study center for the ET Visit as soon as possible after the time of withdrawal and will have all Day 35 (ie, Day 35 of the Treatment Period in which they withdrew from the study) and EOS procedures performed.

[f] A full physical examination will be performed on all participants at Screening. On all other clinic visit days, the physical examination will be symptom directed.

[g] For all women of childbearing potential, pregnancy testing will consist of a urine pregnancy test at the Screening and Baseline visits. 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] Height will be measured only at the Screening Visit.

[i] Only for postmenopausal women (for at least 1-year post-menopause before the Screening Visit) not using hormonal contraception or hormone replacement therapy.

[j] COVID-19 precautions: latest procedure; site should follow local procedures/local policy for the management of COVID-19.

[k] Systolic and diastolic blood pressure, pulse rate, and oral body temperature. Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant.

[l] If an injection site reaction is observed or reported by the participant, it should be recorded as an AE in the Case Report Form.

[m] To reduce the risk of meningococcal infection (*N. meningitidis*), all study participants must be vaccinated against meningococcal infections (with a quadrivalent vaccine and serogroup B vaccine) within 3 years prior to, or at least 2 weeks prior to the start of initiating the IMP.

[n] Treatment Period 1 only.

[o] Study personnel will administer 1 injection to the study participant into the abdomen on Day 1 of each Treatment Period. The same dose of IMP will be administered for both Treatment Periods.

[p] The PK sampling timepoints for each treatment period will be on Day 1 at predose and at 0.5h, 1h, 2h, 3h, 4h, 6h, 8h, and 12h and at 24h (Day2), 48h (Day 3), 96h (Day 5), 168h (Day 8), 336h (Day 15), 504h (Day 22), 672h (Day 29), and 816h (Day 35) postdose.

[q] 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.

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# 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, IV immunoglobulin G and plasma exchange treatment can be utilized as well. For those whose symptoms are not well managed by these medications, a potential alternative is long term treatment with approved IV C5 inhibitors (eg, eculizumab or ravulizumab) which have proven effective at treating MG symptoms.

Zilucoplan (RA101495; ZLP) has recently been approved in Japan, the US, and the EU. It reduces the administration burden, 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. Zilucoplan is currently approved as a PFS for sc injection; 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. DV0012 will, therefore, assess the bioequivalence of ZLP PK between a single sc injection of ZLP from a ZLP-PFS and ZLP-AI, and evaluate the ZLP PK, safety, and tolerability in healthy study participants who receive a single sc injection of ZLP from a ZLP-PFS and a ZLP-AI.

## 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 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 generalized MG (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).

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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) (Howard et al, 2021), 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 IB.

## 2.3 Benefit/risk assessment

This study will not provide a benefit to the study population, ie, healthy study participants.

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 2 weeks 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 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.

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

More detailed information about the known and expected benefits and risks and reasonably expected AEs of ZLP may be found in the ZLP IB and Zilbrysq summary of product characteristics (SmPC).

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# 3 OBJECTIVES AND ENDPOINTS

**Table 3-1: Objectives and endpoints**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To establish the bioequivalence of ZLP PK after a single sc injection with ZLP safety syringe (ZLP- PFS) and ZLP-AI | • AUC<br>• $AUC_{0-t}$<br>• $C_{max}$ |
| **Secondary** | |
| • To evaluate the safety and tolerability of ZLP after a single sc injection with ZLP-PFS and ZLP-AI | • Occurrence of TEAEs, SAEs, and ADEs (serious and nonserious) from Day 1 up to the EOS or ET visit |
| **Exploratory** | |
| • To further evaluate the safety and tolerability of ZLP after a single sc injection with ZLP-PFS and ZLP-AI<br>• To further evaluate the PK of ZLP after a single sc injection with ZLP-PFS and ZLP-AI<br>• To evaluate device deficiencies | • Change from Baseline in clinical laboratory tests (hematology, clinical chemistry, and urinalysis)<br>• $t_{½}$<br>• CL/F<br>• $t_{max}$<br>• Vz/F<br>• Device deficiencies as reported via the eCRF |

ADE=adverse device effect; AUC=area under the plasma concentration-time curve from time 0 to infinity; $AUC_{0-t}$=area under the plasma concentration-time curve from time 0 to time t; $C_{max}$= maximum observed plasma concentration; eCRF=electronic case report form; EOS= End of Study; ET= early termination; PK=pharmacokinetics; PFS=prefilled syringe; SADE=serious adverse device effects; SAE=serious adverse event; sc=subcutaneous; $t_{½}$=terminal half-life; TEAE=treatment-emergent adverse event; $t_{max}$=time to maximum observed concentration; Vz/F= apparent volume of distribution; ZLP-AI=zilucoplan-autoinjector; ZLP-PFS=zilucoplan-prefilled syringe

# 4 STUDY DESIGN

## 4.1 Overall design

DV0012 is a Phase 1, open-label, single-center, randomized, 2-way crossover study in 14 healthy study participants designed to establish bioequivalence in ZLP pharmacokinetics (PK) between a single sc injection of ZLP from a prefilled syringe (ZLP-PFS; reference) and an auto-injector device (ZLP-AI; test), and to investigate the safety, tolerability, and PK in study participants who receive a single sc injection of ZLP.

The crossover design allows each participant to receive a single ZLP injection with each of the 2 devices (ZLP-PFS and ZLP-AI). Zilucoplan will be administered as a single sc injection in the abdomen to evaluate the potential impact of using 2 different devices (ZLP-PFS and ZLP-AI) on

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the PK endpoints. The volume of ZLP will differ from participant to participant depending on their body weight on Treatment Period 1 Day -1.

Study personnel will administer 1 injection of ZLP to the study participant on Day 1 of each Treatment Period following detailed instructions that will have been provided. Injections into the abdomen must avoid the 5 cm/2-inch area around the belly button (navel). No injections should be administered into an area that is tender, red, bruised, hard, or that has scars or stretch marks.

A sufficient number of study participants will be screened to ensure that 7 study participants are randomized to each of the 2 treatment sequences (14 study participants in total), with the objective of having at least 12 study participants complete the study. See Section 9.8 for more details.

Fourteen healthy study participants will be randomized 1:1 to treatment sequence AB or BA, where treatment A is ZLP-PFS injection device and treatment B is ZLP-AI injection device (see study schematic in Section 1.2). Following completion of the first Treatment Period and a 7-day Washout Period, study participants will then complete the second Treatment Period with the same dose as in Treatment Period 1.

Study participants will have End of Study (EOS) procedures performed on the last sampling day (Day 35) of Treatment Period 2, in addition to the Day 35 procedures.

Study participants who are unable to complete the study will return to the study center for the Early Termination (ET) Visit as soon as possible after the time of withdrawal and will have all Day 35 and EOS procedures performed (ie, Day 35 of the Treatment Period in which they withdrew from the study).

## 4.2 Scientific rationale for study design

The current study is considered a 'single dose' study with a single dose given twice to each study participant, once by each injection device. The participants will receive the same dose during both Treatment Periods based on the weight reported at Day -1 of Treatment Period 1. The order of injection devices will be defined by the sequence each study participant is randomly allocated to in the 2-period crossover design, either ZLP-PFS followed by ZLP-AI (sequence AB) or ZLP-AI followed by ZLP-PFS (sequence BA). Comparisons will be based upon within study participant variability. Administration of a single dose with each injection device is an efficient and relevant means to evaluate differences in the PK of ZLP delivered by 2 different injection devices.

### 4.2.1 Patient input into design

Not applicable.

## 4.3 Justification for dose

[redacted]

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**Table 4-1: Zilucoplan weight-bracketed dosing**

| Actual dose (mg) | Weight range (kg) |
|---|---|
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |

Note: the weight to be used to determine the actual dose in both periods will be the weight taken at Day -1 of Treatment Period 1.

## 4.4 End of study definition

A participant is considered to have completed the study if they have completed all periods of the study, including Treatment Period 1 and Treatment Period 2, and the EOS Visit.

The global end of the study is defined as the date of the last EOS Visit for the last participant in the study.

# 5 STUDY POPULATION

Fourteen healthy adult male and female participants who meet the required inclusion and exclusion criteria will be randomized in this study.

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

## 5.1 Inclusion criteria

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

### Age

1. Participant must be 18 to 55 years of age inclusive, at the time of signing the informed consent.

### Type of participant and disease characteristics

2. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.
3. Participants must be vaccinated with a quadrivalent vaccine and serogroup B vaccine against meningococcal infections (*N. meningitidis*) at least 2 weeks before the first administration of IMP if not previously vaccinated within 3 years prior to the start of IMP administration. Study participants who are not previously vaccinated may receive Menactra® (quadrivalent vaccine) and Bexsero® (serogroup B vaccine) during the Screening Period, 2 weeks prior to initiating IMP.

### Weight

4. Body mass index (BMI) ≥18.5 to ≤30.0kg/m$^2$ at the Screening Visit.

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### Sex

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

### Informed consent

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

## 5.2 Exclusion criteria

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

**Medical conditions**

1. Participant has a history of or current significant medical disorder, psychiatric disorder, or laboratory abnormality that in the opinion of the Investigator makes the study participant unsuitable for participation in the study, including any previous or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrinological, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking IMP; or interfering with the interpretation of data.
2. Current or recent systemic infection within 2 weeks before the first administration of IMP or infection requiring intravenous antibiotics within 4 weeks before the first administration of IMP.
3. Current history of alcohol or drug use disorder, as defined in Diagnostic and Statistical Manual of Mental Disorders V, within the previous 6 months.
4. Participant has a known hypersensitivity to any components of the IMP or comparative drugs (and/or an investigational device) as stated in the protocol.

**Prior/Concomitant therapy**

5. Intended use of over-the-counter or prescription medication, vitamins, herbal/traditional medicines (including St John's Wort) or dietary supplements (excluding medicines for

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external use), with the exception of those specified in Section 6.5.1, within 2 weeks before the first administration of IMP.

6. Participant has used hepatic enzyme-inducing drugs (eg, glucocorticoids, phenobarbital, isoniazid, phenytoin, rifampicin) within 2 months before the first administration of IMP.

**Prior/Concurrent clinical study experience**

7. 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.
8. Participant has participated in another study of an IMP (and/or an investigational device) within the previous 30 days or 5 half-lives (whichever is longer), or is currently participating in another study of an IMP (and/or an investigational device).

**Diagnostic assessments**

9. Participants with clinically relevant abnormalities in a standard 12-lead electrocardiogram (ECG) at the Screening Visit as judged by the Investigator.
10. Presence of hepatitis B surface antigen at the Screening Visit or within 3 months prior to dosing.
11. Positive hepatitis C antibody test result at the Screening Visit or within 3 months prior to starting IMP. NOTE: Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled if a confirmatory negative hepatitis C ribonucleic acid (RNA) test is obtained.
12. Positive hepatitis C RNA test result at the Screening Visit or within 3 months prior to first dose of IMP. NOTE: Test is optional and participants with negative hepatitis C antibody test are not required to also undergo hepatitis C RNA testing.
13. Positive human immunodeficiency virus antibody test at the Screening Visit.
14. Positive syphilis test at the Screening Visit.
15. Positive throat swab for *N. meningitidis* at the Screening Visit or a prior history of meningitis.

**Other exclusions**

16. Study participant has donated blood or plasma or has experienced blood loss >400mL within 90 days, >200mL within 30 days, or has donated any blood or plasma within 2 weeks before the first administration of IMP.
17. Study participant is a current smoker or used nicotine-containing products (eg, tobacco, patches, gum) within 30 days before the first administration of IMP.
18. Participant must abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) on Day 1 of each Treatment Period.
19. Participant tests positive for alcohol breath test at the Screening Visit or on Day -1. Participants must abstain from alcohol consumption for at least 24 hours prior to admission at the study center in each Treatment Period.

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20. Study participant has a positive drug test (urine test) at the Screening Visit or on Day -1. Participants must abstain from using any recreational drug, medical marijuana, and cannabidiol throughout the duration of the study.
21. Participant must abstain from strenuous exercise throughout the duration of the study. Study participants may participate in light recreational activities (eg, watching television, reading).
22. Participant has any condition that makes a local assessment or injection difficult or not possible (eg, skin condition, tattoos, skin burns, nevus, or a missing limb).

### 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 (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

## 6 STUDY TREATMENTS/INVESTIGATIONAL DEVICE

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 Treatments administered

The treatment administered in DV0012 is presented in Table 6-1.

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**Table 6-1: Treatment administered**

| **ARM Name** | ZLP-PFS | ZLP-AI |
|---|---|---|
| **Intervention name** | ZLP | |
| **Type** | Drug product (15-amino acid macrocyclic synthetic peptide) associated with a functional secondary packaging | |
| **Dose formulation** | Syringe (containing the solution for injection) within a needle safety device | Prefilled pen containing the solution for injection |
| **Unit dose strength(s)** | Drug solution [redacted] | |
| **Dosage level(s)** | 3 body weight ranges:<br>[redacted] ZLP<br>[redacted] ZLP<br>[redacted] ZLP<br>Frequency: once | |
| **Route of administration** | Subcutaneous injection into the abdomen | |
| **Use** | Experimental | |
| **IMP and NIMP** | IMP | |
| **Sourcing** | Provided centrally by the Sponsor | |
| **Packaging and labeling** | Study intervention will be provided in a box that protects from light or damage. Each box will be labeled as required per country requirement. | |
| **Excipients** | Isotonic buffered solution of RA101495 sodium (drug substance), containing standard excipients | |
| **Current/Former name(s) or alias(es)** | RA101495 | |

AI=auto-injector; IMP=investigational medicinal product; PFS-prefilled syringe; NIMP=non-investigational medicinal product ZLP=zilucoplan; ZLP-AI=zilucoplan auto-injector

The ZLP formulation has been designed for convenient sc injection by daily self-administration at home. Zilucoplan injection is currently provided in multiple strengths: [redacted], [redacted], and [redacted]. Dose strength variation is accomplished by varying the syringe fill volume; each is a [redacted] solution of ZLP.

Treatment of the injection site with an anesthetic or other topical products (eg, steroids) prior to dosing is not permitted. Additional instructions for device use, including the injection angle, are provided in the instructions for use.

Participants will receive the doses of IMP listed in Table 6-1 based on their weight at Day -1 of Treatment Period 1.

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### 6.1.1 Devices

The ZLP drug product will be supplied as:

- ZLP-PFS: A sterile, preservative-free aqueous solution prefilled into a syringe within a needle safety device. The ZLP-PFS is a single-integral, non-reusable drug-device combination product.
- ZLP-AI: A sterile, preservative-free aqueous solution prefilled into a syringe inside an autoinjector. The ZLP-AI-1mL is a single-integral, non-reusable drug-device combination product.

All Adverse Device Effects (serious and nonserious) and device deficiencies (including malfunction use error and inadequate labeling) for all devices, shall be documented and reported by the Investigator throughout the study (see Section 8.2.8) 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 or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the Investigator and authorized site staff.

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

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

The Investigator (or designee) will instruct the participant to store the IMP 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 eCRF will be used to record IMP dispensing and return information on a by-participant basis and will serve as source documentation during the course of the study. Details of any IMP 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 IMP until returned or destroyed.

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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 IMP is used only in accordance with the protocol.

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

## 6.3 Measures to minimize bias: randomization and blinding

Randomization will be involved only in the assignment of study participants to the treatment sequences as per the crossover design.

The contract research organization (CRO) or designated vendor will generate the randomization lists (a main list and a replacement list) for the treatment sequence allocation. Dummy randomization lists will be reviewed by the Clinical Trial Statistician at UCB to ensure that the list meets the study requirements. A master randomization list will be produced using a different seed by the CRO or vendor.

In addition to the main randomization list, a replacement randomization list will be provided in order to replace withdrawn study participants; the replacement participant will receive the same treatment sequence as the corresponding withdrawn participant.

This is an open-label study; therefore, there is no treatment blind for study participants and Investigators at the site. However, in an effort to minimize selection bias, assignment of treatment sequence for each study participant will not be revealed to the study participant or Investigator prior to the time of dosing on Day 1 of each Treatment Period. Only the site pharmacist (and any other designated operational site staff, if deemed necessary) will receive the master randomization schedule, and such personnel will be listed in the randomization specification. Study participants will be allocated a randomization number in the order that they successfully complete Screening assessments, and this number will be used for allocating treatment sequences using the randomization schedule.

## 6.4 Treatment compliance

Drug accountability must be recorded on the Drug Accountability form.

## 6.5 Concomitant medication(s)/treatment(s)

### 6.5.1 Permitted concomitant treatments (medications and therapies)

The following concomitant medications are permitted during the study:

- Paracetamol/acetaminophen for the treatment of mild symptoms (eg, headache or other pain), given at most every 6 to 8 hours, not exceeding 2g per day, and with a total of no more than 5g over 7 days.
- Ibuprofen, not exceeding 1.2g per day.
- Intranasal corticosteroids for seasonal rhinitis and topical corticosteroids for controlled dermatological conditions.

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- Reliable contraceptives: Oral contraceptives not exceeding 30µg ethinyl estradiol or postmenopausal hormone replacement therapy or implants, patches, or intrauterine devices/intrauterine systems delivering progesterone (for female study participants).

The use of concomitant medications to treat AEs should be discussed between the Investigator and the Medical Monitor. All concomitant medications necessary for the health and well-being of a participant will be permitted.

### 6.5.2 Prohibited concomitant treatments (medications and therapies)

The following concomitant medications are prohibited during the study:

- Over-the-counter medications or prescription medications, vitamins, herbal/traditional medicines (including St John's Wort) or dietary supplements (excluding medicines for external use), with the exception of those specified in Section 6.5.1, within 2 weeks before the first administration of ZLP.
- Hepatic enzyme-inducing drugs (eg, glucocorticoids [except where permitted in Section 6.5.1], phenobarbital, isoniazid, phenytoin, rifampicin) should not be used within 2 months before the first administration of ZLP. In case of uncertainty, the Medical Monitor should be consulted.

### 6.5.3 Rescue medication

Not applicable.

## 6.6 Dose modification

No dose modifications are allowed during the study. Study personnel will administer 1 injection to the study participant into the abdomen on Day 1 of each Treatment Period. The same dose of IMP will be administered for both Treatment Periods.

## 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 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.

Dosing stoppage for individual participants is not applicable for this study given this is a single dose study and the safety experience of ZLP from clinical studies. Refer to the IB for details.

## 6.8 Treatment after the end of the study

There is no treatment following the end of the study.

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# 7 DISCONTINUATION OF IMP AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1 Discontinuation of IMP

Not applicable.

## 7.2 Participant discontinuation/withdrawal from the study

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

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

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

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

See the Schedule of Activities for data to be collected at the time of study withdrawal.

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

1. The study participant develops a clinically relevant medical condition (physical [eg, meningococcal disease] or psychiatric) that, in the opinion of the Investigator, jeopardizes or compromises the study participant's ability to participate in the study or makes it unsafe to continue.
2. Participant is noncompliant with the study procedures or medications in the opinion of the Investigator.
3. The study participant takes prohibited concomitant medications as defined in this protocol.
4. The study participant withdraws their consent.
5. The Sponsor or a regulatory agency requests withdrawal of the study participant.
6. The study participant has a confirmed positive serum pregnancy test.
7. The study participant has an anaphylactic reaction after their first injection.

Investigators should attempt to obtain information on study participants in the case of withdrawal.

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

## 7.3 Lost to follow-up

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

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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 their 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, they will be considered to have withdrawn from the study with a primary reason of lost to follow-up documented in the eCRF.

# 8 STUDY ASSESSMENTS AND PROCEDURES

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

Protocol waivers or exemptions are not allowed.

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

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

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

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

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 100mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

## 8.1 Pharmacokinetics

Blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of IMP as specified in the Schedule of Activities (Section 1.3) Instructions for the collection and handling of biological samples will be provided by the Sponsor or designee. The actual date and time (24-hour clock time) of each sample will be recorded.

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The maximum deviations from scheduled sampling times considered irrelevant for PK are defined in Table 8-1.

**Table 8-1: Time Windows for PK sampling**

| PK blood sampling times | Maximum deviation from scheduled time |
|---|---|
| 0 hours (predose) | Within 60 minutes before dosing |
| ≤4 hours | ±3 minutes |
| 6 to 8 hours | ±6 minutes |
| 12 hours | ±12 minutes |
| ≥24 to 144 hours | ±30 minutes |
| >144 hours | ±60 minutes |

PK=pharmacokinetic

Each plasma sample will be divided into 2 aliquots (1 each for PK and a backup). Samples collected for 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.

## 8.2 Safety assessments

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

### 8.2.1 Adverse events and serious adverse events

The definitions of device-related safety events, adverse device effects (ADEs) and serious adverse device effects (SADEs) can be found in Appendix 7 (Section 10.7). Device deficiencies are also 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 withdraw from the study (see Section 7).

### 8.2.2 Time period and frequency for collecting AE and SAE information

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

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 IMP 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.

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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 IMP), up to 40 days from the end of the study for each participant, and to also inform participants of the need to inform the Investigator of any SAE within this period. Serious AEs that the Investigator thinks may be associated with the IMP must be reported to UCB regardless of the time between the event and the end of the study.

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

### 8.2.3 Method of detecting AEs and SAEs

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

### 8.2.4 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, and non-serious AEs of special interest (as defined in Section 8.2.1), 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).

### 8.2.5 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, IEC, and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary. SUSAR reporting will be in adherence to requirements of EU pharmacovigilance legislation, 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 IEC, if appropriate according to local requirements.

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### 8.2.6 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 EOS Visit.
- The participant should immediately stop the intake of the IMP or be down-titrated as instructed at the EOS Visit.

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

### 8.2.7 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.

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

Devices are being provided for use in this study 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 ISO 14155:2020, while recognizing and following requirements including reporting timelines specified in other specific laws, regulations, directives, standards and/or guidelines as appropriate and as required by the countries in which the clinical investigation is conducted.

The definition of a ADE, SADE, USADE, an 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 8.2.4 and Appendix 3 of the protocol.

#### 8.2.8.1 Time period for detecting ADEs and device deficiencies

Adverse device effects and device deficiencies or malfunctions of the device that result in a reportable event 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.

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

#### 8.2.8.2 Follow-up of ADEs and device deficiencies

Follow-up applies to all study participants, including those who discontinue IMP 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.

#### 8.2.8.3 Prompt reporting of ADEs and device deficiencies to Sponsor

Adverse device effects and device deficiencies will be reported to the Sponsor within 24 hours after the Investigator determines that the event meets the protocol definition of an ADE or device deficiency.

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

The Adverse Event and Device Deficiency Report Form will be sent to the Sponsor using the paper form. Adverse device effects and device deficiency reports will be forwarded to the corresponding device manufacturer. The device manufacturer is responsible for the subsequent vigilance evaluation and reporting, as applicable.

#### 8.2.8.4 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 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 IEC.

### 8.2.9 Clinical safety laboratory assessments

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

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or after the last dose of IMP should be repeated until the values return to normal or

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baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

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

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

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

### 8.2.10 Vital signs

Vital signs (systolic and diastolic blood pressure, pulse rate, and oral body temperature) 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) 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.

### 8.2.11 Electrocardiograms

12-lead ECG will be obtained at Screening only using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

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

Three individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

### 8.2.12 Physical examination

A full physical examination will include, at a minimum, general appearance; and a review of systems (dermatologic, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal, neurologic and psychiatric systems).

A symptom-directed abbreviated physical examination will include, at a minimum, an assessment of the general appearance, skin, cardiovascular system, respiratory system, and/or abdomen based on the presenting symptoms.

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

Physical examination findings will be listed, including clinical significance. Clinically significant physical examination abnormalities will be reported as AEs.

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## 8.3 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 IMP so that Investigators, clinical study participants, regulatory authorities, and 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 IMP, medically qualified personnel at UCB may identify additional safety measures (eg, AEs, vital signs, laboratory or ECG results) for which data will be periodically reviewed during the course of the study.

## 8.4 Treatment of overdose

For this study, any dose of ZLP greater than the intended 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 IMP 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.

## 8.5 Biomarkers

Biomarkers are not evaluated in this study.

## 8.6 Immunogenicity assessments

Immunogenicity is not evaluated in this study.

## 8.7 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

The All Study Participants Set will consist of all study participants who signed informed consent.

The Randomized Set will consist of all study participants who are randomized. Note: This set will only be produced if it differs from the Safety Set.

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The Safety Set will consist of all study participants who are randomized and receive at least 1 dose of ZLP. Study participants will be classified according to the sequence to which they were randomly assigned.

The Pharmacokinetic Set will consist of all study participants who are randomized, receive at least 1 dose of ZLP, and have at least 1 observable PK concentration measurement.

If a study participant in the PK set is missing individual time points or these are otherwise unobservable, the study participant will be included in the PK set but those time points will be omitted from the PK summaries, as appropriate.

Note that some study participants in the PK set may not have a complete set of PK parameters as some parameters may not be able to be calculated based on the PK concentrations collected.

## 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.

Baseline is defined as the last nonmissing measurement collected at the first In-Clinic Period (Day -1) for both Treatment Periods.

## 9.3 Planned PK analyses

### 9.3.1 Analysis of the primary endpoint

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

Pharmacokinetics will be determined by non-compartmental analysis in Phoenix WinNonlin using the PK set.

The PK parameters of ZLP will be computed using the actual blood sampling time points.

The plasma concentration time profiles and PK parameters of ZLP will be summarized by injection device using descriptive statistics. The descriptive statistics will include: n, mean, standard deviation, geometric mean and associated 95% confidence interval (CI), geometric standard deviation (GeoSD), geometric coefficient of variation (GeoCV), minimum, median, and maximum.

Individual plasma ZLP concentration time profiles will be displayed graphically on a linear-linear scale and semi-logarithmic scale (including spaghetti plots). Geometric mean plasma concentrations-time curves including their 95% CIs will be displayed by injection device.

Log-transformed PK parameters of area under the plasma concentration-time curve from time 0 to infinity (AUC), area under the plasma concentration-time curve from time 0 to time t($AUC_{0-t}$), and maximum (or peak) observed plasma concentration ($C_{max}$) will be analyzed using a mixed-effects model with period, treatment and sequence as fixed effects and study participant as a random effect. The ZLP-PFS device will be considered the reference for the comparisons. The primary analysis to determine if bioequivalence is established will use data from study participants who have evaluable primary PK endpoints for both Treatment Periods. If one or more study participants do not have evaluable primary PK endpoints for both Treatment Periods, an additional analysis, using the same model except with the inclusion of Satterthwaite's correction for degrees of freedom, will be carried out using all data available. The least squares

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(LS) means and their associated 95% CIs for each treatment, and the difference in LS means and its 90% CI between the 2 injection devices (ZLP-AI versus ZLP-PFS) will be estimated from both models. All estimates will be back-transformed to provide geometric means and 95% CI for each injection device, and the ratio of geometric means (ZLP-AI/ZLP-PFS) and its 90% CI will also be provided. Inter- and intra-participant variability of PK parameters will be derived from the results of this analysis.

#### 9.3.2 Exploratory endpoint analyses

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

The PK parameters $t_{½}$, apparent plasma clearance (CL/F), and apparent volume of distribution (Vz/F) will be summarized by the injection device using descriptive statistics as for the PK parameters described in Section 9.3.1. For the PK parameter $t_{max}$, only median, minimum, and maximum will be reported.

## 9.4 Planned safety and other analyses

### 9.4.1 Safety analyses

#### 9.4.1.1 Secondary endpoint analyses

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

The secondary endpoints in this study are the occurrence of serious adverse events (SAEs), treatment-emergent adverse events (TEAEs), and adverse device effects (ADEs, serious and nonserious) from Day 1 up to the EOS or ET visit.

All AEs (including effects associated with the use of the device that fulfil the definition of an AE, ie, ADEs) will be coded using the most recent Medical Dictionary for Regulatory Activities (MedDRA®) and characterized as pretreatment (prior to the first dose) and treatment-emergent according to the administration of ZLP. Treatment-emergent AEs that occur in the week between the 2 Treatment Periods (ie, Washout Period) will be assigned as treatment-emergent with regards to the treatment in Treatment Period 1.

The occurrence and incidence of TEAEs and ADEs will be summarized by MedDRA system organ class and preferred term, overall and by injection device. The occurrence and incidence of TEAEs and ADEs will also be summarized by intensity and TEAEs by relationship to ZLP. Any TEAEs leading to discontinuation and SAEs will also be listed.

Changes from baseline in clinical laboratory tests (hematology, clinical chemistry, and urinalysis) are exploratory safety parameters. Further details regarding analyses of these endpoints are provided in Section 9.4.1.

#### 9.4.1.2 Exploratory endpoint analyses

Clinical laboratory tests (hematology, clinical chemistry, and urinalysis) and changes from Baseline (Day -1 of each Treatment Period) will be summarized by descriptive statistics at each time point by injection device. Values outside the reference range will be flagged in the listings.

Electrocardiograms will be recorded. The raw data will be listed by injection device. Abnormal findings for the ECG will be listed.

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Physical examination findings will be listed, including clinical significance. Clinically significant physical examination abnormalities will be reported as AEs.

### 9.4.2 Other analyses

#### 9.4.2.1 Exploratory endpoint analyses

Device presentations are being provided for use in this study. In order to fulfill regulatory reporting obligations worldwide, the Investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such device presentations.

- 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.
- 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.

Device deficiencies will be listed. Summaries will be provided if there are sufficient data.

## 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 PK, safety, 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.

## 9.7 Planned interim analysis and data monitoring

No interim analysis or data monitoring are planned.

## 9.8 Determination of sample size

The minimum required sample size for PK bioequivalence studies as recommended by the Food and Drug Administration (FDA; Statistical Approaches to Establishing Bioequivalence, 2022) is 12 study participants.

This study is designed to establish the bioequivalence of ZLP-PFS (reference) and ZLP-AI (test). Bioequivalence is established if the 90% CI for the geometric mean ratio is contained entirely within the acceptance range of 0.80 to 1.25 for all 3 PK parameters (AUC, $AUC_{0-t}$, and $C_{max}$).

The sample size estimation is based on the intra-participant variability observed in UP0115. This was a recent study in healthy study participants which included the ZLP-PFS device to estimate

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the relative bioavailability when the ZLP-PFS device was used at different injection sites (1 group compared the abdomen and thigh, and a second group compared the abdomen and upper arm). Since each participant in UP0115 only had 1 injection in the abdomen, the intra-participant coefficient of variation (CV)% was estimated by pooling across injection sites. The highest intra-participant CV% reported for $AUC_{0-t}$ or $C_{max}$ was 7.74% and this was used in the sample size calculation.

Assuming a geometric mean ratio between 0.90 and 1.11, and intra-participant CV% of 7.74%, 12 study participants (6 study participants per treatment sequence) are required to have evaluable primary PK endpoints (AUC, $AUC_{0-t}$, and $C_{max}$) from the 2 Treatment Periods to have at least 95% power to establish bioequivalence.

Therefore, 12 study participants would fulfill FDA requirements and give more than adequate power to establish bioequivalence.

It is not planned to replace study participants who withdraw from the study; rather the number to be randomized has been increased to 14, if a dropout rate of 10% is assumed. If more than 1 study participant withdraws from each treatment sequence, then study participants who withdraw may be replaced at the Sponsor's discretion, and if replaced, the new study participant will be allocated to the same treatment sequence as the withdrawn study participant. The new study participant would be expected to complete both Treatment Periods.

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

The Investigator/UCB will ensure that an appropriately constituted 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 IEC for its review and approval.

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

The Investigator will also promptly report to the 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 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 IEC as allowed.

As part of the IEC requirements for continuing review of approved studies, the Investigator will be responsible for submitting periodic progress reports to the IEC (based on 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 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 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 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 (CRO) agreements, as applicable.

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### 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 their legal representative, and by the person who conducted the informed consent discussion (Investigator or designee). The participant or their 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 their medical records for study-related monitoring, auditing, 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 IEC and use of the amended form.

The participant may withdraw their consent to participate in the study at any time. A participant is considered as enrolled in the study when they have 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 their 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 IEC, or representatives of regulatory authorities will be allowed to review that portion of the participant's primary medical records that directly concerns this study (including, but not limited to, laboratory test result reports, ECG reports, admission/discharge summaries for hospital admissions occurring during a participant's study participation, and autopsy reports for deaths occurring during the study).

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

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

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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 1-4 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 1-4 clinical studies will be developed and shared on UCB's website.

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

Due to the small sample size in this study, individual patient-level data cannot be adequately anonymized as there is a reasonable likelihood that individual participants could be re-identified. For this reason, data from this study cannot be shared.

### 10.1.7 Data quality assurance

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

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

#### 10.1.7.1 Case report form completion

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

Detailed instructions will be provided in the eCRF Completion Guidelines.

#### 10.1.7.2 Apps

Not applicable.

### 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).

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

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

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

### 10.1.9 Study and site start and closure

**The start of recruitment**

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

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**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 IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further IMP 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.

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## 10.2 Appendix 2: Clinical laboratory tests

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

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**Protocol-Required Safety Laboratory Assessments**

<table>
<tr><th>Laboratory Assessments</th><th colspan="5">Parameters</th></tr>
<tr><td>Hematology</td><td>Platelet Count<br>RBC Count<br>Hemoglobin<br>Hematocrit</td><td colspan="2">RBC Indices:<br>MCV<br>MCH<br>%Reticulocytes</td><td colspan="2">WBC Count with Differential:<br>Neutrophils<br>Lymphocytes<br>Monocytes<br>Eosinophils<br>Basophils</td></tr>
<tr><td>Clinical Chemistry</td><td>Blood Urea Nitrogen (BUN)</td><td>Potassium</td><td>Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)</td><td colspan="2">Total and direct bilirubin</td></tr>
<tr><td></td><td>Creatinine</td><td>Sodium</td><td>Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)</td><td colspan="2">Total Protein</td></tr>
<tr><td></td><td>Glucose (nonfasting)</td><td>Calcium</td><td>Alkaline phosphatase</td><td colspan="2"></td></tr>
<tr><td>Routine Urinalysis</td><td colspan="5">• Specific gravity<br>• pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick<br>• Microscopic examination (if blood or protein is abnormal)</td></tr>
<tr><td>Other Screening Tests</td><td colspan="5">• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only)<br>• Urine alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)<br>• Urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[1]<br>• Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody or specify other tests)<br>The results of each test must be entered into the eCRF.</td></tr>
<tr><td colspan="6">NOTES:<br>1. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IEC.</td></tr>
</table>

Investigators must document their review of each laboratory safety report.

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## 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 IMP, whether or not considered related to the IMP.<br>• 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 IMP. |

| **Events meeting the AE definition** |
|---|
| • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease).<br>• Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition.<br>• New conditions detected or diagnosed after IMP administration even though it may have been present before the start of the study.<br>• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.<br>• Signs, symptoms, or the clinical sequelae of a suspected overdose of either IMP 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.<br>• The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE. |

| **Events NOT meeting the AE definition** |
|---|
| • Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.<br>• 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.<br>• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.<br>• Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).<br>• 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. |

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**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**<br>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**<br>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.<br>Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE. |
| **d. Results in persistent disability/incapacity**<br>• The term disability means a substantial disruption of a person's ability to conduct normal life functions.<br>• 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:**<br>• Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.<br>• 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. |

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## 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.

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**Assessment of causality**

- The Investigator is obligated to assess the relationship between IMP 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 IMP 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 one of the criteria used when determining regulatory reporting requirements.

**Follow-up of AEs and SAEs**

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

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## 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 SERIOUS ADVERSE EVENT 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 SERIOUS ADVERSE EVENT REPORTING section at the front of the protocol.

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## 10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

### Definitions

**Woman of childbearing potential (WOCBP)**

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

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

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

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

**Contraception guidance**

**Male participants**

Male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following during the Treatment Period and for at least 40 days after the last dose of IMP:

- 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 WOCBP 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 IMP.

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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 IMP.

**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.

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**Highly effective contraceptive methods[a]**

| |
|---|
| **Highly effective contraceptive methods that are user dependent[b]**<br>Failure rate of <1% per year when used consistently and correctly. |
| Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[c]<br>• Oral<br>• Intravaginal<br>• Transdermal |
| Progestogen only hormonal contraception associated with inhibition of ovulation<br>• Oral<br>• Injectable |
| **Highly effective methods that are user independent[c]** |
| Implantable progestogen only hormonal contraception associated with inhibition of ovulation<br>• Intrauterine device (IUD)<br>• Intrauterine hormone-releasing system (IUS)<br>• Bilateral tubal occlusion |
| **Vasectomized partner**<br>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**<br>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 IMP. 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:<br>a) In case of newly started contraception pills/IUDs, PI should consider the correct timing of starting/applying such methods in relation to the menstrual cycle and the manufacturing instruction as to when these newly started methods would become effective.<br>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.<br>c) Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraceptive method. In this case, two highly effective methods of contraception should be utilized during the Treatment Period and for at least 40 days after the last dose of IMP. |

**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 Schedule of Activities (Section 1.3).

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- 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 IMP. If the study participant is later found to be on placebo, then pregnancy data collection can stop.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 1 working day of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be at least 12 months after the delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

**Female participants who become pregnant**

- Any female participant who becomes pregnant while participating in the study will be withdrawn from 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 1 working day of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, the follow-up will be at least 12 months after the delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be a SAE and will be reported as such. Any post-study pregnancy-related SAE considered reasonably related to the IMP by the Investigator will be reported to the Sponsor as described in Section 8.2.6. 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.

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## 10.5 Appendix 5: Genetics

Not applicable.

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

Not applicable.

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

The definitions and procedures detailed in this appendix are in accordance with ISO 14155 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 devices provided for use in the study. See Section 6.1.1 for the list of Sponsor devices.

### 10.7.1 Definitions of AE and ADE

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

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### 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:<br>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.<br>2. A permanent impairment of a body structure or a body function.<br>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.<br>4. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function. |
| c. Led to fetal distress, fetal death, or a congenital abnormality or birth defect. |
| **SADE definition** |
| • A serious adverse device effect (SADE) is defined as an adverse device effect that has resulted in any of the consequences characteristic of a SAE. |
| **USADE definition** |
| • An unanticipated serious adverse device effect (USADE) is a serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report (see Section 8.2.8). |

### 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. |

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### 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.

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**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.

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### 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 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 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 medical 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 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.

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## 10.8 Appendix 8: Rapid alert procedures

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## 10.9 Appendix 9: Country-specific requirements

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## 10.10 Appendix 10: Abbreviations and trademarks

| | |
|---|---|
| ADE | adverse device effect |
| AE | adverse event |
| C5 | complement component 5 |
| CI | confidence interval |
| CRO | contract research organization |
| CV | coefficient of variation |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| ET | early termination |
| EOS | end of study |
| GCP | Good Clinical Practice |
| gMG | generalized myasthenia gravis |
| FDA | Food and Drug Administration |
| IB | Investigator's Brochure |
| ICH | International Council for Harmonisation |
| IEC | Independent Ethics Committee |
| IMP | investigational medicinal product |
| IUD | intrauterine device |
| LS | least squares |
| MedDRA | Medical Dictionary for Regulatory Activities |
| PK | pharmacokinetic(s) |
| RNA | ribonucleic acid |
| SADE | serious adverse device effect |
| SAE | serious adverse event |
| sc | subcutaneous(ly) |
| TEAE | treatment-emergent adverse event |
| UADE | unanticipated adverse device effect |
| USADE | unanticipated serious adverse device effect |
| WOCBP | female/woman of childbearing potential |
| ZLP | zilucoplan |
| ZLP-AI | zilucoplan-autoinjector |

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| | |
|---|---|
| ZLP-PFS | zilucoplan-prefilled syringe |

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## 10.11 Appendix 11: Protocol amendment history

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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.

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# Approval Signatures

**Name:** dv0012-protocol-ddmmyyyy

**Version:** 1.0

**Document Number:** CLIN-000241366

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