AN OPEN-LABEL, SINGLE-DOSE STUDY TO ASSESS THE CONCENTRATION OF ROZANOLIXIZUMAB IN THE BREAST MILK OF HEALTHY LACTATING WOMEN

PROTOCOL UP0141

PHASE 1

SHORT TITLE:

A study to assess rozanolixizumab in breast milk of healthy lactating women

Sponsor:
UCB Biopharma SRL
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Regulatory agency identifying number(s):

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History		
Document	**Date**	**Type of amendment**
Original Protocol	11 Sep 2024	Not applicable

SERIOUS ADVERSE EVENT REPORTING

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

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

Reporting of adverse device effects (serious and nonserious) and device deficiencies for non-UCB devices used in the study (24h)	
CRF	Drug delivery devices and breast milk pump: The mechanism for reporting adverse device effects (ADEs) and device deficiencies to UCB (or its representative) will be the electronic data collection tool. Note: In case of an ADE or device deficiency with a non-UCB device, a copy of the Adverse Event and Device Deficiency Form should also be forwarded to the respective device manufacturer by the contract research organization (CRO)
Email	Complete paper Adverse Event and Device Deficiency Form and email to CRO responsible for forwarding to device manufacturer

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol title:

An open-label, single-dose study to assess the concentration of rozanolixizumab in the breast milk of healthy lactating women

Short title:

A study to assess rozanolixizumab in breast milk of healthy lactating women

Rationale:

Women with immunoglobulin G (IgG) autoantibody-mediated conditions who are breastfeeding, and their treating physicians, would benefit from the availability of information about the transfer of rozanolixizumab into mature breast milk to provide estimated daily infant dosage and relative infant dose exposure.

This study is considered to be a postmarketing Phase 1 (Clinical Pharmacology) study.

Objectives and endpoints

Objectives	Endpoints
Primary	
• To assess the concentration of rozanolixizumab in mature breast milk of healthy study participants following administration of a single dose of rozanolixizumab	The primary PK endpoint is concentration of rozanolixizumab in breast milk over a 7-day Sampling Period. The secondary PK endpoints are: • Estimated daily infant dosage • Relative infant dose of rozanolixizumab from breast milk
Secondary	
• To assess the safety of a single dose of rozanolixizumab administered to healthy study participants	The secondary safety endpoint is occurrence of TEAEs from Day 1 through the SFU Visit.
Exploratory/Other	
• To determine PK parameters of rozanolixizumab in mature breast milk and plasma of healthy study participants following administration of a single dose of rozanolixizumab	The exploratory/other PK endpoints are: • C_{max}, t_{max}, $AUC_{(0\text{-}7d)}$ in breast milk and plasma • $Ae_{,7d}$ and Fe in breast milk • Milk:plasma $AUC_{(0\text{-}7d)}$ ratio

$Ae_{,7d}$=cumulative total amount of drug excreted in milk to Day 7; $AUC_{(0\text{-}7d)}$=area under the concentration-time curve from 0 to 7 days; d=day; C_{max}=maximum plasma concentration; Fe=fraction of dose excreted in milk; PK=pharmacokinetic(s); SFU=Safety Follow-Up; TEAE=treatment-emergent adverse event; t_{max}=time to maximum plasma concentration

Overall design

This is a postmarketing, open-label, Phase 1 (Clinical Pharmacology) study to assess the concentration of rozanolixizumab in mature breast milk of healthy lactating women following administration of a single dose of rozanolixizumab.

The study will enroll healthy lactating women who on Day 1 of the study (rozanolixizumab dosing day) will be at least 6 weeks postpartum and who have voluntarily decided, prior to having knowledge of the study, to wean their infant(s). Additionally, to be eligible to participate in the study, participants must agree to collect all expressed breast milk over the 7-day Sampling Period and to not resume breast milk feeding (by any means) or donate expressed breast milk between the end of the breast milk Sampling Period and the Safety Follow-Up (SFU) telephone call 8 weeks after dosing (ie, on Day 57). Participants may decide to resume breast milk feeding 8 weeks after administration of rozanolixizumab, with the agreement that any breast milk collected (to maintain milk supply) during that 8-week period will be discarded. A lactation consultant will be available from the Screening Period up until 30 days after the SFU telephone call to support the cessation and potential resumption of breast milk feeding following the SFU.

Number of participants

Up to 20 healthy study participants are planned to be screened to ensure that a minimum of 12 study participants and a maximum of 15 study participants provide data to assess whether there is transfer of rozanolixizumab into breast milk. No formal sample size estimation was conducted. This number was selected based on feasibility and considered to be sufficient to meet the primary objective.

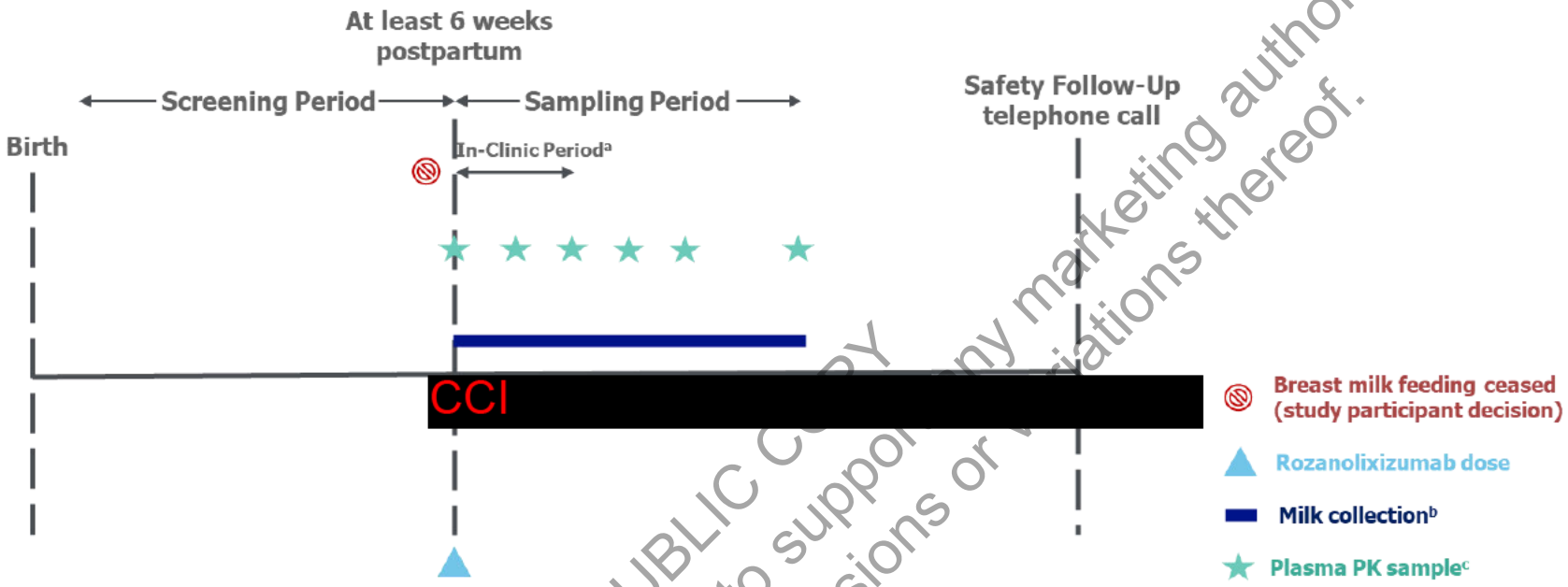
Treatment groups and duration

For each study participant, the total duration of participation in this study is up to 12 weeks, including a Screening Period of up to 4 weeks, a Sampling Period of 7 days including an In-Clinic Period from Day 1 (or Day -1) to Day 3, and a SFU telephone call 8 weeks after dosing (ie, on Day 57). During the Sampling Period, on Day 1, study participants will receive a single dose of rozanolixizumab based on their body weight (Table 4-1).

1.2 Schema

The study schematic is presented in Figure 1-1.

Figure 1-1: Study schematic



D=Day; PK=pharmacokinetic(s)

[a] Study participants can be admitted to the clinic either in the early morning of D1 or the day before (Day -1) in the evening. Discharge can occur from D3 onward after all planned assessments to be conducted at the clinic on D3 are completed.

[b] The breast milk collection and sampling time points will be: within 30 minutes predose and 0 to ≤3, >3 to ≤6, >6 to ≤9, >9 to ≤12, >12 to ≤24, >24 to ≤36, >36 to ≤48, >48 to ≤60, >60 to ≤72, >72 to ≤84, >84 to ≤96, >96 to ≤108, >108 to ≤120, >120 to ≤132, and >132 to ≤144 (Day 7) hours after the start of infusion.

[c] Blood sampling: predose (within 60min before dosing) and 6h (±6min), 9h (±6min), 12h (±12min), 24h (±30min) (Day 2), 48h (±30min) (Day 3), 72h (±30min) (Day 4), 96h (±30min) (Day 5), and 144h (±24h) (Day 7) after the start of infusion.

1.3 Schedule of activities

The schedule of activities is provided in Table 1-1. In addition to those detailed in Table 1-1, additional assessments may be required in case of adverse events of special monitoring (AESM) of severe and/or serious headache, or suspected aseptic meningitis (Section 8.3.7, and Appendix 9 [Section 10.9]).

Table 1-1: Schedule of activities

Visit frequency									
Period	**Scr Period**	**Sampling Period**							
		In-Clinic Period			**Home or In-Clinic Assessments [c]**				
Name	**Scr Visit**	**V2 [b]**	**V3**	**V4 [c]**	**V5**	**V6**	**V7**	**V8/EW [d]**	**SFU [a]**
Visit #	[redacted]								
Week									
Day									
Visit window		**±0day**	**±0day**	**±0day**	**±0day**	**±0day**	**±0day**	**±0day**	**±5day**
Procedure/activities									
Written informed consent	X								
Verification of inclusion/exclusion criteria	X [e]	X [f]							
Demographic and Baseline characteristics	X								
General medical history	X	X [g]							
Prior and concomitant medications and medical procedures	X	X	X	X	X	X	X	X	X
Alcohol urine test and urine drug screen	X	X							
Height and weight [h]	X	X							
Complete physical examination	X	X [i]		X					
Vital signs [j]	X	X	X	X	X	X	X	X	

Table 1-1: Schedule of activities

Visit frequency									
Period	**Scr Period**	**Sampling Period**							
		In-Clinic Period			**Home or In-Clinic Assessments [c]**				
Name	**Scr Visit**	**V2 [b]**	**V3**	**V4 [c]**	**V5**	**V6**	**V7**	**V8/EW [d]**	**SFU [a]**
Visit #	CCI								
Week									
Day									
Visit window		**±0day**	**±0day**	**±0day**	**±0day**	**±0day**	**±0day**	**±0day**	**±5day**
Procedure/activities									
12-lead ECG [k]	X								
Pregnancy test [l]	X	X						X	
Clinical laboratory tests (hematology, clinical chemistry, urinalysis) [m]	X	X [n]		X					
Blood sampling (rozanolixizumab concentration) [o]		X	X	X	X	X		X	
Mature breast milk collection and sampling (rozanolixizumab concentration) [p]		X	X	X	X	X	X	X	
Rozanolixizumab administration	CCI								
Adverse event review [q]	X	X	X	X	X	X	X	X	X

AESM=adverse events of special monitoring; ECG=electrocardiogram; EW=early withdrawal; Scr=Screening; SFU=Safety Follow-Up; V=Visit

[a] A SFU telephone call will occur on Day 57 (±5 days).

[b] Study participants can be admitted to the clinic either in the early morning of Day 1 or the day before (Day -1) in the evening.
[c] Study participants may be discharged beginning on Day 3 after completion of all planned assessments to be conducted at the clinic. Study participants, at their own discretion, may remain at the clinic and be discharged on a subsequent Study Day through Day 7 after completion of all planned assessments for that day's visit. After discharge, visits may be completed in the study participant's home setting in the presence of a qualified nurse. To facilitate these visits, the study participant should have access to a telephone. Alternatively, study participants may visit the clinic for assessments and blood sampling, and/or to bring into the clinic the collected breast milk.
[d] Study participants who withdraw from the study during the Sampling Period will be asked to undergo the EW Visit procedures and will be encouraged to have a SFU telephone call on Day 57 (±5 days).
[e] Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened under certain circumstances (see Section 5.4).
[f] Study participant's eligibility will be rechecked. Results of clinical laboratory tests (hematology, clinical chemistry, urinalysis) from the Screening Visit may be used at the investigator's discretion.
[g] Changes in medical history since the Screening Visit will be collected.
[h] Height will be measured at Screening only. Weight will be measured with the study participant wearing no shoes and light clothing at Screening and predose on Day 1.
[i] A complete physical examination will be performed predose on Day 1. A complete physical examination includes, at a minimum, general appearance; ear, nose, and throat; eyes, hair, and skin; and assessments of the cardiovascular, respiratory, gastrointestinal neurological, musculoskeletal, and hepatic systems, breasts, nipples (for signs of mastitis or nipple cracks), and, if relevant, post-Cesarean scar (for signs of infection or abscess).
[j] Vital signs comprise systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature, and should be measured in a semi-supine position after 5 minutes rest. On Day 1, vital signs will be measured predose and at approximately 15 minutes and 3 hours after the end of the infusion. On Days 2, 3, 4, 5, 6, and 7, vital signs will be measured once per day. Vital signs should be measured/taken before blood sampling, where applicable. Study participants will be monitored for clinical signs and symptoms of hypersensitivity reactions during rozanolixizumab administration.
[k] All ECG recordings should be taken with the study participant resting in the supine position for at least 5 minutes.
[l] Serum pregnancy test at Screening and urine pregnancy test on Day 1 and on Day 7.
[m] See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed. Laboratory tests with values considered clinically significantly abnormal should be repeated as described in Section 8.2.5.
[n] Clinical laboratory tests (hematology, clinical chemistry, and urinalysis) will be performed predose on Day 1.
[o] The blood sampling time points will be: predose (within 60min before dosing) and 6h (±6min), 9h (±6min), 12h (±12min), 24h (±30min) (Day 2), 48h (±30min) (Day 3), 72h (±30min) (Day 4), 96h (±30min) (Day 5), and 144h (±24h) (Day 7) after the start of infusion.
[p] The breast milk collection and sampling time points will be: within 30 minutes predose and 0 to ≤3, >3 to ≤6, >6 to ≤9, >9 to ≤12, >12 to ≤24, >24 to ≤36, >36 to ≤48, >48 to ≤60, >60 to ≤72, >72 to ≤84, >84 to ≤96, >96 to ≤108, >108 to ≤120, >120 to ≤132, and >132 to ≤144 (Day 7) hours after the start of infusion.
[q] In addition to those detailed in this table, additional assessments may be required in case of AESM of severe and/or serious headache, or suspected aseptic meningitis (Section 8.3.7 and Appendix 9 [Section 10.9]).

2 INTRODUCTION

Rozanolixizumab is a humanized IgG 4 monoclonal antibody that is being developed as an inhibitor of the activity of the neonatal Fc receptor (FcRn) for IgG.

By blocking the activity of FcRn, rozanolixizumab accelerates the catabolism of IgG antibodies, including IgG autoantibodies. The aim is to reduce the concentration of pathogenic IgG in patients with autoimmune diseases mediated by the action of IgG autoantibodies.

Rozanolixizumab binds with high affinity to FcRn at both neutral and acidic pH. Immunoglobulin G that is constitutively taken up by pinocytosis into cells fails to bind to FcRn, even at the acidic pH found in the endosome. It is, therefore, not recycled and is trafficked to the lysosomes for degradation.

Production of pathogenic IgG autoantibodies is the major pathophysiology leading to a number of autoimmune diseases, including myasthenia gravis (MG).

As individual disease entities, IgG autoantibody-mediated conditions are relatively rare. Treatment of these disorders remains a difficult clinical problem, requiring, in many of these conditions, the long-term use of corticosteroids alone or combined with cytotoxic agents. These therapeutic approaches are not effective in all patients and conditions and have broad immunosuppressive effects, causing considerable toxicity and treatment-related morbidity.

Treatments aimed at reducing the quantity of circulating IgG autoantibodies, including plasmapheresis, immunoadsorption, or high-dose intravenous immunoglobulin, are being used for primary and secondary therapy of autoimmune disease, particularly where corticosteroid-based immune suppression is not or no longer effective (eg, immune thrombocytopenia, MG, Guillain-Barré syndrome, pemphigus vulgaris). The therapeutic approach of these treatments is thought in part to be based on lowering levels of pathogenic autoantibodies, which represents rational and effective treatment modalities of autoimmune diseases.

Therefore, removal of the IgG autoantibodies by FcRn blockade may provide an effective therapeutic option for IgG autoantibody-mediated autoimmune disorders.

More detailed information regarding the nonclinical and clinical development programs for rozanolixizumab, including all completed and ongoing studies, can be found in the latest version of the Investigator's Brochure (IB).

2.1 Study rationale

Women with IgG autoantibody-mediated conditions who are breastfeeding, and their treating physicians, would benefit from the availability of information about the transfer of rozanolixizumab into mature breast milk to provide estimated daily infant dosage and relative infant dose exposure.

This study is considered to be a postmarketing Phase 1 (Clinical Pharmacology) study.

2.2 Background

Autoimmune diseases can affect women of childbearing age. Depending on the severity and condition, active disease may necessitate therapy even during lactation. There is a clear need for adequate treatment during lactation that does not adversely impact the infant. However, due to

the fact that clinical studies in general exclude lactating women, there are limited data available on the effects of drugs on the infant and on the transfer of drugs to the infant during breastfeeding (through lactation). This lack of data leaves lactating women, and treating physicians, in a difficult situation when considering whether to initiate or continue therapy and creates an imperative to gather more information.

There are no adequate and well-controlled studies of rozanolixizumab in lactating women. For rozanolixizumab, there is insufficient information on the excretion of rozanolixizumab in human or animal breast milk.

During the first 6 months of life, breast milk is the optimal source of nutrition for infants. Research has shown that as a result of the content of breast milk, breastfed infants have better gastric motility, mucosal mass, intestinal host defenses, brain, and retinal growth. The Centers for Disease Control and Prevention Breastfeeding report card 2020 indicates that, in 2017, 84.1% of mothers in the US initiated breastfeeding, 58.3% were breastfeeding at 6 months, and 35.3% were breastfeeding at 12 months (CDC, 2020). Many factors may contribute to this reduction in percentage of mothers breastfeeding across the first year of their infant's life, including the mother's need to take medication and concern over the fact that the breastfed infant could be exposed to drugs via breast milk.

UP0141 is a postmarketing, open-label, Phase 1 (Clinical Pharmacology) study to assess the concentration of rozanolixizumab in mature breast milk of healthy lactating women following administration of a single dose of rozanolixizumab.

2.3 Benefit/risk assessment

The healthy female study participants included in this study will receive no medical benefit from participation. It is not known whether rozanolixizumab is excreted in human milk or absorbed systemically after ingestion. To remove the risk of exposing infants to rozanolixizumab, only lactating women who have voluntarily decided to cease or suspend breast milk feeding and who have established alternative sources of nutrition for their infant(s) will be eligible to participate in the study. Considering the uncertainty of how long rozanolixizumab could be present in the mammary glands (via binding to mammary tissue FcRn), breast milk feeding or resumption of breast milk feeding will not be allowed between the end of the breast milk Sampling Period and the SFU telephone call 8 weeks after dosing (ie, on Day 57). Participants may decide to resume breast milk feeding 8 weeks after administration of rozanolixizumab, with the agreement that any breast milk collected (to maintain milk supply) during that 8-week period will be discarded. A lactation consultant will be available from the Screening Period up until 30 days after the SFU telephone call to support the cessation and potential resumption of breast milk feeding following the SFU.

Based on rozanolixizumab mechanism of action and observations from the current nonclinical and clinical studies with rozanolixizumab and potential risks generally associated with biologic immunomodulators, treatment with rozanolixizumab may be associated with increased risk of serious infections, aseptic meningitis (drug-induced aseptic meningitis [DIAM]), hypersensitivity reactions including injection site reactions, and may temporarily impair vaccination efficacy.

Headache is the most common side effect of rozanolixizumab. Headaches are mostly mild to moderate and managed with over-the-counter medications. Other side effects include diarrhoea,

pyrexia, nausea, upper respiratory tract infections, arthralgia, rash, injection site reactions, vomiting, myalgia, herpes simplex infections, and aseptic meningitis.

The risks from taking part in the study will be minimized through the selection of appropriate study participants defined by the inclusion/exclusion criteria, a single dose administration (body weight-based), safety monitoring throughout participation in the study, and protocol withdrawal criteria. Investigators will be provided with full guidance on the management of specified side effects including the management and expedited reporting requirements of AESM (severe and/or serious headache and suspected aseptic meningitis) to UCB. Study participants will also be informed via the informed consent form (ICF).

More detailed information about the known and expected benefits and risks and adverse drug reactions of rozanolixizumab can be found in the IB, which summarizes the safety profile of subcutaneous rozanolixizumab.

3 OBJECTIVES AND ENDPOINTS

Table 3-1: Objectives and endpoints

Objectives	Endpoints
Primary	
• To assess the concentration of rozanolixizumab in mature breast milk of healthy study participants following administration of a single dose of rozanolixizumab	The primary PK endpoint is concentration of rozanolixizumab in breast milk over a 7-day Sampling Period. The secondary PK endpoints are: • Estimated daily infant dosage • Relative infant dose of rozanolixizumab from breast milk
Secondary	
• To assess the safety of a single dose of rozanolixizumab administered to healthy study participants	The secondary safety endpoint is occurrence of TEAEs from Day 1 through the SFU Visit.
Exploratory/Other	
• To determine PK parameters of rozanolixizumab in mature breast milk and plasma of healthy study participants following administration of a single dose of rozanolixizumab	The exploratory/other PK endpoints are: • C_{max}, t_{max}, $AUC_{(0\text{-}7d)}$ in breast milk and plasma • $Ae_{,7d}$ and Fe in breast milk • Milk:plasma $AUC_{(0\text{-}7d)}$ ratio

$Ae_{,7d}$=cumulative total amount of drug excreted in milk to Day 7; $AUC_{(0\text{-}7d)}$=area under the concentration-time curve from 0 to 7 days; d=day; C_{max}=maximum plasma concentration; Fe=fraction of dose excreted in milk; PK=pharmacokinetic(s); SFU=Safety Follow-Up; TEAE=treatment-emergent adverse event; t_{max}=time to maximum plasma concentration

4 STUDY DESIGN

4.1 Overall design

This is a postmarketing, open-label, Phase 1 (Clinical Pharmacology) study to assess the concentration of rozanolixizumab in mature breast milk of healthy lactating women following administration of a single dose of rozanolixizumab.

The study will enroll healthy lactating women (herein referred to as study participants) who on Day 1 of the study (rozanolixizumab dosing day) will be at least 6 weeks postpartum and who have voluntarily decided, prior to having knowledge of the study, to wean their infant(s). Additionally, to be eligible to participate in the study, participants must agree to collect all expressed breast milk over the 7-day Sampling Period and to not resume breast milk feeding (by any means) or donate expressed breast milk between the end of the breast milk Sampling Period and the SFU telephone call 8 weeks after dosing (ie, on Day 57). Participants may decide to resume breast milk feeding 8 weeks after administration of rozanolixizumab, with the agreement that any breast milk collected (to maintain milk supply) during that 8-week period will be discarded. A lactation consultant will be available from the Screening Period up until 30 days after the SFU telephone call to support the cessation and potential resumption of breast milk feeding following the SFU.

Up to 20 healthy study participants are planned to be screened to ensure that a minimum of 12 study participants and a maximum of 15 study participants provide data to assess whether there is transfer of rozanolixizumab into breast milk. The study is planned to be conducted in the US.

For each study participant, the total duration of participation in this study is up to 12 weeks, including a Screening Period of up to 4 weeks, a Sampling Period of 7 days, including an In-Clinic Period from Day 1 (or Day -1) to Day 3, and a SFU telephone call 8 weeks after dosing (ie, on Day 57) (Section 1.3).

4.1.1 Screening Period

At Screening, all elements of eligibility will be confirmed. A detailed description of study assessments to be performed at Screening is provided in the schedule of activities (Section 1.3).

4.1.2 Sampling Period

After the Screening Period, eligible study participants will enter a 7-day Sampling Period. Study participants can be admitted to the clinic either in the early morning of Day 1 or in the evening of the day before (Day -1) and may be discharged beginning on Day 3 after all planned assessments to be conducted at the clinic on Day 3 are completed (Section 1.3). Study participants, at their own discretion, may remain at the clinic and be discharged on a subsequent Study Day through Day 7 after completion of all planned assessments for that day's visit.

After discharge, visits may be completed in the study participant's home setting in the presence of a qualified nurse. To facilitate these visits, the study participant should have access to a telephone. Alternatively, study participants may visit the clinic for assessments and blood sampling, and/or to bring into the clinic the collected breast milk. Study participants who withdraw from the study during the Sampling Period will be asked to undergo the Early Withdrawal (EW) Visit procedures and will be encouraged to have a SFU telephone call on Day 57 (±5 days).

On Day 1, study participants will receive a single dose of rozanolixizumab based on their body weight (Table 4-1). Milk samples and blood samples will be collected to measure rozanolixizumab concentration throughout the Sampling Period and in accordance with the schedule of activities (Section 1.3). For each milk sampling interval, both breasts will be emptied by pumping, and any breast milk expressed will be stored and combined to provide the total volume of breast milk collected for that interval. A predose breast milk collection is taken on Day 1 (within 30 minutes predose) to ensure that both breasts are emptied prior to dosing. The time and date of the milk expression/sample collection must be recorded. Safety assessments will also be performed.

4.1.3 SFU

A SFU assessment (via telephone with study staff) will be performed 8 weeks (±5 days) after dosing. Study participants who withdraw prematurely from the study will be encouraged to have a SFU telephone call 8 weeks (±5 days) after dosing.

4.2 Scientific rationale for study design

The study is designed in accordance with the 2019 draft guidance from the US Food and Drug Administration (FDA): Clinical Lactation Studies: Considerations for Study Design (FDA, Guidance for Industry, 2019). Since this study is being undertaken in healthy study participants, only a single dose of rozanolixizumab is being investigated. Based on previous rozanolixizumab single-dose healthy volunteer studies, the majority of a single-dose plasma rozanolixizumab AUC is quantified by 7 days postdose. The breast milk Sampling Period encompasses 1 week (7 days) following the single rozanolixizumab dose to quantify total rozanolixizumab AUC in breast milk.

During this study, milk collection will occur at a minimum of 6 weeks postpartum to ensure mature milk is being produced, breast milk production is well established, and that this study is not an incentive for ceasing breastfeeding earlier than 6 weeks. An in-clinic stay of at least 48 hours will be used because the frequency of required plasma pharmacokinetic (PK) and breast milk sampling from predose to 48 hours postdose would be difficult to accomplish outside of the clinic and to enable the study participant to experience the breast milk sampling procedures prior to when the visits may be completed at the study participant's home.

Considering the uncertainty of how long rozanolixizumab could be present in the mammary glands (via binding to mammary tissue FcRn), breast milk feeding or resumption of breast milk feeding will not be allowed until 8 weeks after administration of rozanolixizumab, with the agreement that any breast milk collected (to maintain milk supply) during that 8-week period will be discarded. To remove the risk of exposing infants to rozanolixizumab, only lactating women who have voluntarily decided to cease or suspend breast milk feeding and who have established alternative sources of nutrition for their infant(s) will be eligible to participate in the study.

4.3 Justification for dose

Healthy study participants enrolled in UP0141 will receive a single weight-tiered dose of rozanolixizumab, as summarized in Table 4-1, administered using a commercially available syringe driver. The proposed weight-tiered doses of rozanolixizumab are consistent with the recommended doses in the FDA-approved US Prescribing Information (RYSTIGGO, 2023).

Table 4-1: Rozanolixizumab weight tiers

Body weight of study participant	Dose	Volume to be infused
<50kg	420mg	3mL
≥50kg to <100kg	560mg	4mL
≥100kg	840mg	6mL

4.4 End of study definition

A study participant is considered to have completed the study if she has completed all periods of the study including the SFU or the last scheduled procedure shown in the schedule of activities (Section 1.3).

End of study is defined as the date of the last scheduled procedure shown in the schedule of activities for the last study participant in the study.

5 STUDY POPULATION

The study will enroll adult (≥18 years of age) healthy lactating women who on Day 1 of the study (rozanolixizumab dosing day) will be at least 6 weeks postpartum and who have voluntarily decided, prior to having knowledge of the study, to wean their infant(s). Additionally, to be eligible to participate in the study, participants must agree to collect all expressed breast milk over the 7-day Sampling Period and to not resume breast milk feeding (by any means) or donate expressed breast milk between the end of the breast milk Sampling Period and the SFU telephone call 8 weeks after dosing (ie, on Day 57). Participants may decide to resume breast milk feeding 8 weeks after administration of rozanolixizumab, with the agreement that any breast milk collected (to maintain milk supply) during that 8-week period will be discarded (Section 4.2).

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 the following criteria apply:

Age

1. Study participant must be minimum 18 years at the time of signing the ICF.

Type of participant and disease characteristics

2. Study participant is overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.
3. Study participant has a body temperature between 35.0°C and 37.5°C, inclusive on Day 1.
4. Study participant is lactating and will be at least 6 weeks postpartum on Day 1 of the study.

5. Study participant has voluntarily decided, prior to having knowledge of this study, to cease breast milk feeding (by any means) in relation to her current period of lactation.

   Study participant agrees to cease or suspend breast milk feeding by Day 1 of the study and to not resume breast milk feeding (by any means) or donate expressed breast milk for 8 weeks following administration of rozanolixizumab. Participants may decide to resume breast milk feeding 8 weeks after administration of rozanolixizumab, with the agreement that any breast milk collected (to maintain milk supply) during that 8-week period will be discarded.

6. Study participant agrees to maintain an adequate milk supply through regular breastfeeding or pumping (eg, pumping 3 to 4 times per day) for at least 4 weeks prior to Day 1 of the study and to collect all expressed breast milk over the 7-day Sampling Period.

7. Alternative nutritional sources to breast milk have already been established for the study participant's infant(s).

8. As assessed by the investigator, study participant has sufficient breast milk production to meet the breast milk requirements of the study.

Weight

9. Study participant has body weight ≥35kg at Screening and body mass index ≥18.5kg/m^2.

Sex

10. Study participant is female.

    – A female participant is eligible to participate if she is not pregnant (see Appendix 4 [Section 10.4]) and at least 1 of the following conditions applies:

      ◦ A woman of childbearing potential (WOCBP) who agrees to follow the contraceptive guidance in Appendix 4 (Section 10.4) during the Sampling Period and for at least 1 week after the last dose of study treatment.

      OR

      ◦ Not a WOCBP (ie, premenopausal female with documented hysterectomy, documented bilateral salpingectomy, or documented bilateral oophorectomy).

Informed Consent

11. Study participant is capable of giving signed informed consent as described in Appendix 1 (Section 10.1.3) which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2 Exclusion criteria

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

Medical conditions

1. Study participant has history or presence of/significant history of or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrinological, hematological, neurological disorders, or chronic infectious diseases capable of significantly altering the absorption,

metabolism, or elimination of drugs; constituting a risk when taking the study intervention; or interfering with the interpretation of data.

2. Study participant has any medical, obstetrical, or psychiatric condition, or plans a surgical intervention that, in the opinion of the investigator, could jeopardize or would compromise the study participant's ability to participate in this study.
3. Study participant has history of breast implants, breast augmentation, or breast reduction surgery.
4. Study participant has clinically significant multiple or severe drug allergies.
5. Study participant has a known hypersensitivity to any components of the study medication or other anti-FcRn medications, or has a known history of hyperprolinemia, since L-proline is a constituent of the rozanolixizumab formulation.
6. Study participant has alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) >1.0× upper limit of normal (ULN). Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit may be repeated once for confirmation. This includes rescreening. If the repeat values are below the ULN, the study participant will be considered to not meet the exclusion criteria.
7. Study participant has bilirubin >1.0×ULN (isolated bilirubin <1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%). For study participants with a Baseline result >ULN for total bilirubin, a Baseline diagnosis and/or the cause of any clinically meaningful elevation must be understood and recorded in the case report form (CRF).
8. Study participant has current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
9. Study participant has 12-lead electrocardiogram (ECG) with abnormalities considered to be clinically significant upon medical review.
10. Study participant has had lymphoma, leukemia, or any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years.
11. Study participant has absolute neutrophil count $<1.5 \times 10^9$/L and/or lymphocyte count $<1.0 \times 10^9$/L.
12. Study participant has history of known inflammatory bowel disease, active diverticular disease, or a history of confirmed duodenal, gastric, or esophageal ulceration in the previous 6 months.

Prior/Concomitant therapy

13. Study participant has past or intended use of over-the-counter or prescription medication (including herbal medications) within 14 days prior to dosing until the end of the Sampling Period (specific medications listed in Section 6.5.1 are allowed).
14. Study participant has received live vaccine(s) within 4 weeks prior to Screening or plans to receive such vaccines during the study.
15. Study participant has received treatment with biologic agents (such as monoclonal antibodies including marketed drugs) within 3 months or 5 half-lives (whichever is longer) prior to dosing.

Prior/Concurrent clinical study experience

16. Study participant donated or lost >500mL of blood or blood products in the 4 weeks preceding the start of dosing or plans to donate blood during the study.
17. Study participant has had exposure to more than 3 new chemical entities within 12 months prior to dosing.
18. Study 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.
19. Study participant has participated in another study of an investigational medicinal product (IMP) (and/or an investigational device) within the previous 90 days or 5 half-lives prior to Day -1 (whichever is longer) or is currently participating in another study of an IMP (and/or an investigational device).

Diagnostic assessments

20. Study participant has IgG <5.5g/L at Screening.
21. Study participant has positive prestudy drug/alcohol screen.

Other exclusions

22. Study participant has had an active clinically significant infection within the last 6 weeks. Note: Study participants with mastitis at Screening that do not meet the criteria for clinically significant infection may be rescreened after the infection is completely resolved.
23. Study participant smoked on average >5 cigarettes/day (or equivalent) during the last 3 months and is not able to stop smoking during the Sampling Period.
24. Study participant has history of alcohol and/or drug abuse up to 12 months before Screening. Alcohol abuse is defined as follows: study participant has an alcohol consumption of more than 14 units per week (1 unit of alcohol is equivalent to 10mL ethanol; for example, 330mL of 5% alcohol by volume beer=1.7 units; 125mL of 12% wine=1.5 units; 50mL of spirits=2 units).
25. Study participant has regular use of known drugs of abuse.

5.3 Lifestyle restrictions

No lifestyle restrictions are required.

5.4 Screen failures

Screen failures are defined as study participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure study participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened under certain circumstances (eg, resolution of mastitis infection). Rescreening must be discussed with the Medical Monitor, with a decision to rescreen made on a case-by-case basis.

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

6 STUDY TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Treatments administered

Study treatment details are presented in Table 6-1.

Table 6-1: Study treatments

Arm name	**Rozanolixizumab**
Intervention name	Rozanolixizumab
Type	Biologic
Dose formulation	Solution for injection
Unit dose strength	A 6mL glass vial, containing no less than 2.0mL extractable volume of rozanolixizumab at a concentration of 140mg/mL
Dosage levels	Single dose of 420mg for study participants <50kg, 560mg for participants ≥50kg to <100kg, or 840mg for participants ≥100kg
Route of administration	Subcutaneous infusion
Use	Experimental
IMP and NIMP/AxMP	IMP
Sourcing	Provided centrally by the sponsor
Packaging and labeling	Packaging will be described in the IMP Handling Manual. Packaging will be labeled as required per country requirement.
Excipients	Rozanolixizumab at a concentration of 140mg/mL, formulated with 30mM L-histidine, 250mM L-proline, 0.03% (w/v) polysorbate 80, at pH 5.6
Former name	UCB7665

AxMP=auxiliary medicinal product; IMP=investigational medicinal product; NIMP=noninvestigational medicinal product

6.1.1 Medical devices

The approved medical devices (not manufactured by or for UCB) provided for use in this study are:

- Drug delivery devices
- Breast milk pump

All medical device deficiency (including malfunction use error, and inadequate labeling) shall be documented and reported by the investigator throughout the study (see Section 8.3.8) and appropriately managed by the sponsor.

6.2 Preparation, handling, storage, and accountability requirements

The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all study treatment received, and any discrepancies are reported and resolved before use of the study treatment.

Only study 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.

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

6.2.1 Drug accountability

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

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

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

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

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

6.3 Measures to minimize bias: randomization and blinding

All study participants will receive a single dose of rozanolixizumab under close and continued attention of the investigator or designee; thus, there is no opportunity for bias. Based on this study design, (ie, open-label), randomization and blinding are not possible and are therefore not applicable to this study.

6.4 Treatment compliance

Study participant compliance will be ensured by the administration of study medication by designated site personnel.

6.5 Concomitant medication(s)/treatment(s)

6.5.1 Permitted concomitant treatments (medications and therapies)

Any treatment, including over-the-counter products and supplements, must be recorded in the study participant's notes (source documentation), and provided on the CRF. This record should include the name of the drug, the dose, the route, and date(s) of administration, and the indication for use.

Information on past/prior/concomitant medications will be captured from the first day after delivery, but not exceeding 30 days prior to Screening.

For the purposes of this study:

- Past medications are those that stopped prior to entering the Screening Period (but not exceeding 30 days).
- Prior medications are those that were ongoing or started prior to entering the Screening Period (but not exceeding 30 days).
- Concomitant medications are medications with at least 1 day in common with the Screening or Sampling Period.

Prior medications may include both past medications and concomitant medications.

Permitted concomitant treatments are presented in Table 6-2.

Table 6-2: Permitted concomitant treatments

Permitted medications	Dose threshold	Comment
Paracetamol	Every 6 to 8 hours, not exceeding 2g/day, and with a total of no more than 10g per 14 days	With approval from the investigator, paracetamol is permitted for the treatment of mild symptoms (eg, headache or pain)
Ibuprofen	Every 6 to 8 hours, not exceeding 2400mg/day	With approval from the investigator, ibuprofen is permitted for the treatment of mild symptoms (eg, headache or pain)
Hormonal contraceptives, implants, patches, intrauterine hormone-releasing system, or intrauterine devices delivering progesterone	NA	None

NA=not applicable

6.5.2 Prohibited concomitant treatments (medications and therapies)

Prohibited concomitant treatments are presented in Table 6-3.

Table 6-3: Prohibited concomitant treatments

Prohibited medications	Dose threshold	Comment
Prescription medication (including herbal medications) or over-the-counter medicines	All doses are prohibited from 14 days prior to dosing until the end of the Sampling Period	With the exception of vitamins and the permitted concomitant treatments noted in Section 6.5.1, and unless required to treat an adverse event, including pretreatment
Vaccines	All doses	Vaccinations are not allowed during the study

6.6 Dose modification

No dose modifications are allowed during the study.

6.7 Criteria for study hold or dosing stoppage

Not applicable.

6.8 Treatment after the end of the study

Not applicable. This is a Phase 1 study in healthy participants; therefore, no treatment will be provided after the end of the study.

7 DISCONTINUATION OF STUDY MEDICATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of study medication

During the study, study participants will receive a single dose of rozanolixizumab administered subcutaneously. This will be performed under close and continued attention of the investigator or designee.

7.1.1 Hypersensitivity stopping criteria

In case of any signs of an infusion reaction or anaphylaxis, the infusion will be stopped immediately, and appropriate treatment will be initiated, as necessary, at the discretion of the investigator. This includes the use of antihistamines for urticaria and appropriate management in case of potentially life-threatening events such as anaphylaxis. Infusion may be restarted in mild reactions only if clinically appropriate. The study participant should be followed until resolution of the event. See Appendix 7 and Appendix 8 (Section 10.7 and Section 10.8, respectively) for procedures to follow in the instance of infusion reactions or anaphylaxis. Study participants will be monitored during treatment with rozanolixizumab and for 15 minutes after the administration is complete for clinical signs and symptoms of hypersensitivity reactions.

7.1.2 Liver chemistry stopping criteria

In UP0141, a single dose of rozanolixizumab will be administered to healthy study participants; therefore, no individual liver chemistry stopping criteria apply.

Specific assessments and follow-up actions for potential drug-induced liver injury are provided in Appendix 5 (Section 10.5).

7.1.3 QTc stopping criteria

No QTc stopping criteria apply.

7.2 Study 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 her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

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

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

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

Study participants who withdraw from the study during the Sampling Period will be asked to undergo the EW Visit procedures and will be encouraged to have a SFU telephone call on Day 57 (±5 days).

Study participants withdrawn from the study will not be allowed to re-enter the study.
A study participant withdrawing from the study before Day 7 may be replaced.

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

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

1. Study participant develops an illness that would interfere with her continued participation.
2. Study participant is noncompliant with the study procedures or medications in the opinion of the investigator.
3. Study participant takes prohibited concomitant medications as defined in this protocol (Section 6.5.2).
4. Study participant withdraws her consent.
5. The sponsor or a regulatory agency requests withdrawal of the study participant.
6. Study participant needs a surgical intervention during the Sampling Period.

7.3 Lost to follow up

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

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

- The site must attempt to contact the study participant and reschedule the missed visit as soon as possible 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 study participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (at least 1 phone call and 1 written message to the participant) and document his/her effort (date and summary of the phone call and copy of the written message in the source documents), to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the study participant, must be recorded in the source documents. The CRF must document the primary reason for withdrawal.

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

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the schedule of activities (Section 1.3).

Protocol waivers or exemptions are not allowed.

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

Adherence to the study design requirements, including those specified in the schedule of activities, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential study 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 study participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the schedule of activities (Section 1.3).

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

8.1 Breast milk sample collection

For each time breast milk is obtained, milk will be pumped from both breasts using an electronic breast pump and both breasts should be emptied. The milk from both breasts will be combined. If multiple expressions take place within a milk sampling interval, all breast milk collected will

be combined before a sample is taken. Total volume of breast milk expressed within a sampling interval will be recorded before a sample is taken.

Samples will be transferred by the study staff into transport tubes and stored at -20°C for shipment to the central laboratory. Participants with mastitis infection should not have samples collected until the infection is completely resolved.

8.2 Safety assessments

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

8.2.1 Physical examination, including vital signs

A complete physical examination will include, at a minimum, general appearance; ear, nose, and throat; eyes, hair, and skin; and assessments of the cardiovascular, respiratory, gastrointestinal neurological, musculoskeletal, and hepatic systems, breasts, nipples (for signs of mastitis or nipple cracks), and, if relevant, post-Cesarean scar (for signs of infection or abscess). Only abnormalities from the physical examination need to be recorded. Height and weight will also be measured and recorded.

Vital signs will be measured in a semi-supine position after 5 minutes rest and will include body temperature, systolic and diastolic blood pressure (BP), pulse rate, and respiratory rate. Vital signs should be measured/taken before blood sampling, where applicable.

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

Clinically relevant findings or worsening of previous findings will be recorded as adverse events (AEs).

8.2.2 Neurological evaluation

A full neurological examination will include: (1) general appearance, including posture, motor activity, and meningeal signs and, if indicated, the following assessments will be performed; (2) cranial nerves examination; (3) motor system examination, including muscle tone and power and sensory system examination – light touch; (4) reflexes, including deep tendon reflexes; (5) coordination, gait (if possible); and (6) fundoscopy.

A full neurological examination should be performed for any participant who experiences severe and/or serious headache (see Appendix 9, Section 10.9) and for study participants who experience aseptic meningitis.

8.2.3 Height and weight

Weight will be measured with the study participant wearing no shoes and light clothing (weight should be recorded to 1 decimal place) according to the schedule of activities (Section 1.3). Height will only be measured at Screening.

8.2.4 ECGs

Electrocardiogram is for screening purposes only. A single 12-lead ECG will be obtained as outlined in the schedule of activities (Section 1.3) 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.

8.2.5 Clinical safety laboratory assessments

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

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

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

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

All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the schedule of activities (Section 1.3).

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

8.3 AEs and SAEs

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

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

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs and SAEs will be collected from the signing of the ICF and at the time points specified in the schedule of activities (Section 1.3).

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

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

The investigator is specifically requested to collect and report to UCB (or its representative) any SAEs (even if the investigator is certain that they are in no way associated with the study medication), up to 30 days from the end of the study for each study participant and to also inform participants of the need to inform the investigator of any SAE within this period. Serious AEs that the investigator thinks may be associated with the study medication must be reported to UCB regardless of the time between the event and the end of the study.

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

8.3.2 Method of detecting AEs and SAEs

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

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each study participant at subsequent visits/contacts. All SAEs and non-serious AEs of special interest and special monitoring (as defined in Section 8.3.6 and Section 8.3.7, respectively) will be followed until resolution, stabilization, the investigator determines that it is no longer clinically significant, the event is otherwise explained, or the study participant is lost to follow up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

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

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB), and investigators.

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

An investigator who receives an investigator safety report describing 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 IB and will notify the IRB, if appropriate according to local requirements.

8.3.5 Pregnancy

Details of all pregnancies in participants will be collected after the start of study medication and until the end of the study.

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).

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

8.3.6 Adverse events of special interest

An AE of special interest (AESI) is any AE that a regulatory authority has mandated to be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a UCB product/compound. An AESI should be reported within 24 hours. Potential Hy's Law, defined as ≥3 × ULN ALT or AST with coexisting ≥2 × ULN total bilirubin in the absence of ≥2 × ULN ALP, with no alternative explanation for the biochemical abnormality must always be reported to UCB as an AESI (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should be reported if an alternative etiology is identified during investigation and monitoring of the study participant.

All AESIs will follow the SAE recording and reporting procedures as indicated in Appendix 3 (Section 10.3).

8.3.7 AESM

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

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

- Severe and/or serious headache
- Suspected aseptic meningitis

Procedures for the management of AESM are provided in Appendix 9 (Section 10.9). All AESM will follow the SAE recording and reporting procedures as indicated in Appendix 3 (Section 10.3).

8.3.8 Device – AEs, ADE, SAEs, serious adverse device effects, unanticipated serious adverse device effect, and device deficiencies

Devices may include standalone medical devices or device constituents of combination products. Devices are being provided for use in this study for the purposes of administering study medication and collecting breast milk. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of ADEs, serious adverse device effects (SADEs), and device deficiencies that occur during the study with such devices.

Adverse events will be reported according to ISO 14155:2020, while recognizing and following requirements including reporting timelines specified in other specific laws, regulations,

directives, standards and/or guidelines as appropriate and as required by the countries in which the clinical investigation is conducted.

The definition of an ADE, SADE, unanticipated serious adverse device effect (USADE), and device deficiency can be found in Appendix 6 (Section 10.6).

NOTE: Events fulfilling the definition of an AE/SAE will also follow the processes outlined in Appendix 6 (Section 10.6) of the protocol.

8.3.8.1 Time period for detecting ADEs and device deficiencies

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

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

The method of documenting ADEs and device deficiencies is provided in Appendix 6 (Section 10.6).

8.3.8.2 Follow-up of ADEs and device deficiencies

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

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

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

8.3.8.3 Prompt reporting of ADEs and device deficiencies to the sponsor

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

The sponsor will be the contact for the receipt of ADE and device deficiency reports.

For non-UCB devices, ADE and device deficiency reports will be forwarded to the corresponding device manufacturer using the Adverse event and device deficiency report form by email. The device manufacturer is responsible for the subsequent vigilance evaluation and reporting, as applicable.

8.3.8.4 Regulatory reporting requirements for ADEs and device deficiencies

The investigator will report all ADEs and device deficiencies immediately and under no circumstance should this exceed 24 hours for any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies. For non-UCB medical devices the sponsor will then notify the device manufacturer in order for the manufacturer to fulfill vigilance responsibilities.

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

8.4 Safety signal detection

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

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

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

8.5 Treatment of overdose

Excessive dosing (beyond that prescribed in the protocol and including overdose) should be recorded in the Drug Accountability module of the CRF. Any SAE or nonserious AE associated with excessive dosing must be followed as any other SAE or nonserious AE. These events are only considered AEs or SAEs if there are associated with clinical signs and symptoms or if the act of taking the excess medicine itself is an AE or SAE (eg, suicide attempt).

For this study, any dose of rozanolixizumab greater than that prescribed in the protocol will be considered an overdose. Overdose events are only considered AEs or SAEs if there are associated clinical signs and symptoms or if the act of taking the excess study medication itself is an AE or SAE (eg, suicide attempt).

UCB does not recommend specific treatment for an overdose. In the event of an overdose, the investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the study participant for any AE/SAE and laboratory abnormalities (at least 56 days).
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

8.6 Pharmacokinetics

Maternal breast milk samples and blood samples will be collected for measurement of rozanolixizumab 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. The actual date and time (24-hour clock time) of each sample will be recorded. The overall blood volume to be drawn from each study participant participating in the study will not exceed 450mL, ie, the amount of a blood donation.

Time deviations for specified PK sampling time points are given in Table 8-1.

Table 8-1: Irrelevant time deviations for PK blood sampling

PK blood sampling times	Deviation from scheduled time considered irrelevant
0h (predose)	Within 60min before dosing
6 to 9h	±6min
12h	±12min
≥24 to 96h	±30min
144h (Day 7)	±24h

PK=pharmacokinetic

Samples will be used to evaluate the concentrations of rozanolixizumab in maternal plasma and mature breast milk of healthy study participants and to estimate the daily infant rozanolixizumab dose. Samples may be used for assay development or establishing assay parameters (eg, PK selectivity assessment).

The concentration of rozanolixizumab in breast milk and plasma will be assessed utilizing validated bioanalytical assays, consistent with FDA Bioanalytical Method Validation Guidance for Industry (May 2018).

The following PK parameters will be computed for rozanolixizumab in breast milk for each study participant, if possible:

- C_{max}, t_{max}, $AUC_{(0\text{-}7d)}$
- $Ae_{,7d}$ (mg)=cumulative total amount excreted in milk to Day 7
- Fe=$Ae_{,7d}$/administered dose (mg) × 100%
- Milk:plasma $AUC_{(0\text{-}7d)}$ ratio
- Relative Infant Dose=[(Estimated) Daily Infant Dosage (mg/kg/day)/Maternal Dosage (mg/kg/day)] × 100% (see Section 9.3.1.1 for details on the calculation of the estimated daily infant dosage)

The following parameters will be derived for rozanolixizumab in plasma:

- C_{max}, t_{max}, $AUC_{(0\text{-}7d)}$

All PK data analyses will be performed under the supervision of the Quantitative Clinical Pharmacology Department, UCB using validated software (Phoenix 64, Pharsight, a Certara Company, USA).

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment.

Pharmacokinetic samples for concentration measurement of rozanolixizumab may be stored for a maximum of 5 years (or according to local regulations) following submission of the study to Health Authorities at a facility selected by the sponsor. Surplus unused predose milk samples may be stored and used for potential future biomarker research (including PK assay

development/optimization). Samples may be stored at a facility selected by the sponsor for a maximum of 20 years (or according to local regulations) following the last study participant's last visit for the 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 (SAP).

9.1 Definition of analysis sets

The following are the defined analysis sets:

- All Study Participants Set: All study participants who sign the ICF.
- Safety Set (SS): All study participants who receive a full or partial dose of the IMP.
- PK Set (PKS) (for breast milk and plasma): All study participants in the SS who receive a full dose of the IMP and provide at least 1 valid measurement of rozanolixizumab concentration in plasma or breast milk.

9.2 General statistical considerations

All analyses will be performed using SAS® version 9.4 or later (SAS Institute, Cary, NC, US).

All summaries of PK variables will be based on the observed or calculated values. No imputation of missing data will be used.

The analyses in this study will not be performed using any formal estimand framework and no inferential statistical analyses are planned.

9.3 Planned efficacy/outcome analyses

9.3.1 Analysis of the primary endpoint

The primary objective of this study is to assess the concentration of rozanolixizumab in mature breast milk of healthy study participants. The concentration of rozanolixizumab in breast milk will be summarized descriptively for all time points based on the PKS.

9.3.1.1 Calculation of estimated daily infant dosage and relative infant dose from breast milk

The estimated daily infant dosage will be used to determine the relative infant dose of rozanolixizumab from breastmilk, both of which are secondary endpoints that fall under the primary objective of the study.

Estimated daily infant dosage from breast milk

The estimated daily infant dosage of rozanolixizumab from breast milk will be calculated based on the concentration of rozanolixizumab in mature human breast milk for the PKS.

The amount of rozanolixizumab that the infant may consume following single rozanolixizumab dosing to the mother will be calculated as follows:

1. Estimated daily infant dosage (mg/kg/day)=M/P ratio × $C_{av,plasma}$ × 150mL/kg/day

Where M/P ratio is the milk:plasma ratio based on $AUC_{(0-7d)}$ and $C_{av,plasma}$ is the average maternal plasma concentration calculated as $AUC_{(0-7d),plasma}$/7 days.

This is based on the standardized mean milk consumption for a fully breastfed 2-month old infant of 150mL/kg/day.

2. Daily infant dosage (mg/day)=total drug concentration in each 24-hour breast milk collection period (over 7 days post-dose) × the expressed milk volume.

Relative infant dose from breast milk

The relative infant dose of rozanolixizumab from breast milk will be calculated as follows:

Estimated daily infant dosage (mg/kg/day)/maternal rozanolixizumab dosage (mg/kg/day) × 100

9.3.2 Other efficacy/other outcome analyses

The following parameters will be derived for rozanolixizumab in breast milk:

- C_{max}, t_{max}, $AUC_{(0-7d)}$
- $Ae_{,7d}$ (mg)=cumulative total amount excreted in milk to Day 7
- Fe=$Ae_{,7d}$/administered dose (mg) × 100%
- Milk:plasma $AUC_{(0-7d)}$ ratio

The following parameters will be derived for rozanolixizumab in plasma:

- C_{max}, t_{max}, $AUC_{(0-7d)}$

9.4 Planned safety and other analyses

9.4.1 Safety analyses

Where applicable, Baseline is defined as the latest available assessments prior to a study participant receiving rozanolixizumab.

AEs

Adverse events will be captured from the time of consent until the SFU Visit. All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

The occurrence and incidence of treatment-emergent adverse events (TEAEs) will be summarized by MedDRA system organ class and preferred term for the SS. A TEAE is defined as any AE with a start date/time on or after the dosing of study medication until 8 weeks after dosing of study medication. The occurrence and incidence of TEAEs will also be summarized by intensity and by relationship to rozanolixizumab. Adverse events leading to discontinuation and SAEs will also be summarized.

Further details on all safety analyses will be given in the SAP.

9.5 Handling of protocol deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on study conduct or on the key safety or PK outcomes (if applicable) for an individual study participant. The criteria for identifying important protocol deviations will be defined within the important protocol deviations document. Important protocol deviations will be reviewed as part of the ongoing data cleaning process and data evaluation. All important deviations will be identified and documented prior to database lock.

9.6 Handling of dropouts or missing data

There will be no special procedures for handling missing data. All imputation of missing or partial dates for safety assessments, as well as handling values below the lower limit of quantitation in the PK data, will be detailed in the SAP.

9.7 Planned interim analysis and data monitoring

No formal interim analysis is planned for this study.

All safety and tolerability data (including SAEs and nonserious AEs) will be reviewed on a rolling basis by the investigator and sponsor's Study and Safety Physician (or designee).

9.8 Determination of sample size

No formal sample size calculations have been performed as there are no statistical hypotheses being tested. It is expected that up to 20 healthy study participants will need to be screened to ensure that a minimum of 12 participants and a maximum of 15 participants provide data to assess whether there is transfer of rozanolixizumab into breast milk after a single dose and to calculate the estimated daily infant dosage and relative infant dose from breast milk. This number was selected based on feasibility and considered to be sufficient to meet the primary objective.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Regulatory and ethical considerations

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

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

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

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

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

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

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

10.1.2 Financial disclosure

Insurance coverage will be handled according to local requirements.

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

10.1.3 Informed consent process

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

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

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

If the ICF is amended during the study, the investigator (or the sponsor, if applicable) must follow all applicable regulatory requirements pertaining to the approval of the amended ICF by the IRB and use of the amended form.

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

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

10.1.4 Data protection

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

The investigator agrees that representatives of UCB, its designee, representatives of the relevant IRB, or representatives of regulatory authorities will be allowed to review that portion of the study 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 her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the study participant.

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

10.1.5 Data quality assurance

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

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

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

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

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

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

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

10.1.5.1 CRF completion

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

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

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

The investigator should maintain a list of personnel authorized to enter data into the electronic CRF.

Detailed instructions will be provided in the CRF Completion Guidelines.

10.1.6 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 study participant's source documents. The investigator will facilitate the process for enabling the monitor to compare the content of the printout and the data stored in the computer to ensure all data are consistent.

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

10.1.7 Dissemination of clinical study data

This study will be registered and results posted on public registries as required and in line with UCB policies. A plain language summary of results may also be written. Investigators may request access to anonymized individual participant-level data and redacted study documents after product approval in the US and Europe. However, once the study completes, if the risk of re-identifying study participants is determined to be too high, then individual participant-level data will not be made available.

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

10.1.8 Study and site start and closure

The start of recruitment

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

Study/site termination

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of study participants by the investigator

- Discontinuation of further study medication development

10.1.9 Publication policy

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

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

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

10.2 Appendix 2: Clinical laboratory tests

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

Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet count RBC count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulo-cytes	Coagulation: INR prothrombin time activated partial thromboplastin time fibrinogen	WBC Count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical chemistry [a]	Blood urea nitrogen	Potassium	AST/Serum glutamic-oxaloacetic transaminase	Total protein Albumin
	Creatinine	Sodium	ALT/Serum glutamic-pyruvic transaminase	Lipids Total cholesterol HDL cholesterol LDL cholesterol HDL/LDL ratio Triglycerides
	Glucose (non-fasting)	Corrected calcium	Alkaline phosphatase Total and direct bilirubin	
Routine urinalysis	• Specific gravity • pH, protein, glucose, ketone, urobilinogen, bilirubin, blood, nitrite, and leukocytes by dipstick • Microscopic examination (if blood or protein is abnormal) • albumin:creatinine ratio, total protein, albumin, creatinine, alpha-1 microglobulin, and beta-2 microglobulin			
CSF [b]	• Cell count, gram staining, culture, protein, glucose			
Other screening tests	• Follicle-stimulating hormone (as needed in women of non-childbearing potential only) • Urine alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Serum human chorionic gonadotropin pregnancy test (as needed for women of childbearing potential) • IgG • The results of each test must be entered into the electronic case report form			

ALT=alanine aminotransferase; AST=aspartate aminotransferase; CSF=cerebrospinal fluid; HDL=high-density lipoprotein; IgG=immunoglobulin G; INR=International Normalized Ratio; LDL=low-density lipoprotein; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; RBC=red blood cell;

Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters

SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; ULN=upper limit of normal; WBC=white blood cell

[a] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1.2 and Appendix 5 (Section 10.5). All events of ALT ≥3×ULN and bilirubin ≥2×ULN (>35% direct bilirubin) or ALT ≥3×ULN and INR >1.5, if INR measured, may indicate severe liver injury (possible Hy's Law) and must be reported as a serious adverse event (excluding studies of hepatic impairment or cirrhosis).

[b] Only for study participants with severe headache, if clinically indicated, at the discretion of the investigator (if headache becomes moderate or mild, normal collection of adverse events should apply).

Investigators must document their review of each laboratory safety report.

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

Definition of AE

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

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

Events NOT meeting the AE definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the study participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the study participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Important medical events: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the study participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include, but are not limited to, potential Hy's law, invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and follow up of AE and/or SAE

AE and SAE recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the CRF. • It is **not** acceptable for the investigator to send photocopies of the study participant's medical records to UCB in lieu of completion of the UCB AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by UCB. In this case, all study participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to UCB. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of intensity
The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories: • Mild: An event that is easily tolerated by the study participant, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. • An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of a SAE, NOT when it is rated as severe (eg, a severe AE may be either serious or not serious, depending on whether these criteria are also met). The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) should be used as a supportive standardization instrument to evaluate AEs and SAEs but the final intensity grading by the investigator must be mild, moderate, or severe.

Assessment of causality

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

Follow-up of AEs and SAEs

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

Reporting of SAEs

SAE reporting to UCB via an electronic data collection tool

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

SAE reporting to UCB via paper CRF

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

10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

Definitions

WOCBP

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

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

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

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

Female study participants

Female study participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 10-1.

Table 10-1: Highly effective contraceptive methods [a]

Highly effective contraceptive methods that are user dependent [b] **Failure rate of <1% per year when used consistently and correctly.**
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation [c] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly effective methods that are user independent [c]
• Implantable progestogen only hormonal contraception associated with inhibition of ovulation • IUD • IUS • Bilateral tubal occlusion
Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study medication. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the study participant.

IUD=intrauterine device; IUS=intrauterine hormone-releasing system; WOCBP=women of childbearing potential

[a] In case of newly started contraception pills/IUDs, the investigator should consider the correct timing of starting/applying such methods in relation to the menstrual cycle and the manufacturing instruction as to when these newly started methods would become effective.

[b] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for study participants participating in clinical studies.

[c] Hormonal contraception may be susceptible to interaction with the study medication, which may reduce the efficacy of the contraceptive method. In this case, two highly effective methods of contraception should be utilized during the treatment period and for at least 1 week after the last dose of study medication.

Pregnancy testing

- Serum pregnancy test will be performed at Screening and urine pregnancy tests will be performed on Day 1 and on Day 7.

Female study participants who become pregnant

- The investigator will collect pregnancy information on any female study participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within one working day of learning of a study participant's pregnancy. The study participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the study participant and the neonate and the information will be forwarded to the sponsor. Generally, the follow up will be at least 12 months after the delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be a SAE and will be reported as such. Any post-study pregnancy-related SAE considered reasonably related to the study medication by the investigator will be reported to the sponsor as described in Section 8.3.5. While the investigator is not obligated to actively seek this information in former study participants, he/she may learn of a SAE through spontaneous reporting.

10.5 Appendix 5: Liver safety – suggested actions and follow-up assessments

Phase 1 liver chemistry stopping criteria are designed to assure study participant safety and to evaluate liver event etiology (Table 10-2).

Table 10-2: Phase 1 liver chemistry stopping criteria and follow-up assessments

Liver Chemistry Stopping Criteria	
ALT-absolute	ALT ≥3×ULN If ALT ≥3×ULN **AND** bilirubin ≥2×ULN (>35% direct bilirubin) or INR >1.5, report as a SAE. [a, b] See additional actions and follow-up assessments below.

Required actions and follow-up assessments	
Actions	**Follow-up assessments**
• Report the event to UCB **within 24 hours** • Complete the liver event CRF, and complete a SAE data collection tool if the event also met the criteria for a SAE [b] • Perform liver function follow-up assessments • Monitor the study participant until liver function test abnormalities resolve, stabilize, or return to baseline (see **MONITORING**) • Consider the need for a toxicology screening. **MONITORING:** **If ALT ≥3×ULN AND bilirubin ≥2×ULN or INR >1.5** • Repeat liver function tests (include ALT, AST, ALP, bilirubin) and perform liver function follow-up assessments within **24 hours.** • Monitor study participant twice weekly until liver function test abnormalities resolve, stabilize, or return to baseline. • A specialist or hepatology consultation is recommended. **If ALT ≥3×ULN AND bilirubin <2×ULN and INR ≤1.5:** • Repeat liver function tests (include ALT, AST, ALP, bilirubin) and perform liver function follow-up assessments within **24 to 72 hours**	• Viral hepatitis serology [c] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Serum CPK and LDH • Fractionate bilirubin, if total bilirubin ≥ 2×ULN • Complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury (eg, fatigue, nausea, vomiting, right upper quadrant pain), or hypersensitivity, on the AE CRF • Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications CRF • Record alcohol use on the liver event alcohol intake CRF **If ALT ≥3×ULN AND bilirubin ≥2×ULN or INR >1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG or gamma globulins • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in study

Table 10-2: Phase 1 liver chemistry stopping criteria and follow-up assessments

Liver Chemistry Stopping Criteria	
ALT-absolute	ALT ≥3×ULN If ALT ≥3×ULN **AND** bilirubin ≥2×ULN (>35% direct bilirubin) or INR >1.5, report as a SAE. [a, b] See additional actions and follow-up assessments below.

Required actions and follow-up assessments	
Actions	**Follow-up assessments**
• Monitor study participants weekly until liver function abnormalities resolve, stabilize, or return to baseline	participants with definite or likely acetaminophen use in the preceding week [James et al, 2009]) • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete liver imaging and/or liver biopsy CRFs

AE=adverse event; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CPK=creatine phosphokinase; CRF=case report form; HBsAg=hepatitis B surface antigen; HBcAb=hepatitis B core antibody; HPLC=high performance liquid chromatography; IgG=immunoglobulin G; IgM=immunoglobulin M; INR=international normalized ratio; LDH=lactate dehydrogenase; PK=pharmacokinetic; RNA=ribonucleic acid; SAE=serious adverse event; ULN=upper limit of normal

[a] Serum bilirubin fractionation should be performed if testing is available. Additionally, if serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.

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

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

10.6 Appendix 6: Device AEs, ADEs, SAEs, and device deficiencies: Definition and procedures for recording, evaluating, follow-up, and reporting

The definitions and procedures detailed in this appendix are in accordance with ISO 14155:2020 and the European Medical Device Regulation (MDR) 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 medical devices provided for use in the study. See Section 6.1.1 for the list of medical devices used in the study.

10.6.1 Definition of medical device AE and ADE

Medical device AE and ADE definition

A medical device AE is any untoward medical occurrence in a clinical study participant, users, or other persons, temporally associated with the use of study intervention, whether or not considered related to the device. 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 an investigational medical device. This definition includes events related to the device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to devices.

An ADE is defined as an AE related to the use of a device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the device as well as any event resulting from use error or from intentional misuse of the device.

10.6.2 Definition of medical device SAE, SADE, and USADE

A medical device SAE is an any serious adverse event that:

a. Led to death

b. Led to serious deterioration in the health of the participant, that either resulted in:

- 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.
- A permanent impairment of a body structure or a body function.
- 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 an SAE.
- Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
- Chronic disease (MDR 2017/745).

c. Led to fetal distress, fetal death, or a congenital abnormality or birth defect

SADE definition

An SADE is defined as an ADE that has resulted in any of the consequences characteristic of an SAE.

Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

USADE definition

An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is defined as a serious adverse device effect that by its nature, incidence, severity, or outcome has not been identified in the current version of the medical device manufacturer risk analysis report.

10.6.3 Definition of device deficiency

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 inadequacy of the information supplied by the manufacturer.

10.6.4 Recording and follow-up of device AE and/or SAE and device deficiencies

Device 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.

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/device deficiency form. 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 device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

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 one of the following categories:

- Mild:

  A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

- Moderate:

  A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

- Severe:

  A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Assessment of causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency. The investigator will use clinical judgment to determine the relationship.

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.

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 Instructions for use or product information, for marketed products as part of the assessment.

The investigator must review and provide an assessment of causality for each AE/SAE/device deficiency and document this in the medical notes.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to UCB. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to UCB.

The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of device AE/SAE and 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 form.

The investigator will submit any updated SAE data to UCB within 24 hours of receipt of the information.

10.6.5 Reporting of medical device SAEs

Medical device SAE reporting to UCB via an electronic data collection tool

The primary mechanism for reporting an SAE to UCB will be the electronic data collection tool. If the electronic system is unavailable, then the site will use the paper SAE data collection tool 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 offline to prevent the entry of new data or changes to existing data.

Contacts for SAE reporting can be found in REPORTING OF ADVERSE DEVICE EFFECTS (SERIOUS AND NONSERIOUS) AND DEVICE DEFICIENCIES.

Medical device SAE reporting to UCB via paper data collection tool

Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the UCB Patient Safety.

In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE paper 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 paper data collection tool within the designated reporting time frames.

Contacts for SAE reporting can be found in REPORTING OF ADVERSE DEVICE EFFECTS (SERIOUS AND NONSERIOUS) AND DEVICE DEFICIENCIES.

10.6.6 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 an SAE must be reported to the sponsor immediately and under no circumstance should this exceed 24 hours after the investigator determines that the event meets the definition of a device deficiency.

The sponsor will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs as required by national regulations.

Contacts for SAE reporting can be found in REPORTING OF ADVERSE DEVICE EFFECTS (SERIOUS AND NONSERIOUS) AND DEVICE DEFICIENCIES.

10.7 Appendix 7: Management of infusion reactions or hypersensitivity reactions

Study participants must be closely monitored for reactions during and after rozanolixizumab administration. Standard precautions must be taken for the study participants with regard to potential infusion-related reactions. Suggested management guidelines for infusion-related reactions and anaphylaxis at the study site are provided in Table 10-3. Definitions of the severity of the relevant events will be consistent with NCI-CTCAE (Appendix 3 [Section 10.3]).

Table 10-3: Suggested management guidelines at the study site for infusion reactions

Type of reaction	Suggested action
Acute – Mild Grade 1	Monitor vital signs every 10 minutes. If the reaction worsens to Grade 2, follow the instructions below.
Acute – Moderate Grade 2	Interrupt/hold infusion temporarily to further assess and initiate treatment if necessary. Consider the use of IV fluid and antihistamine IV or IM. Consider administering paracetamol or nonsteroidal anti-inflammatory drugs. Monitor vital signs initially every 5 minutes. If the reaction improves and upon further assessment it is clear that the event is not an anaphylaxis, restart the infusion cautiously. Continue to monitor vital signs every 5 minutes. If reaction recurs or worsens to Grade 3, discontinue infusion.
Acute – Severe Grade 3 or anaphylaxis	Discontinue rozanolixizumab infusion permanently. Alert crash team. Maintain airway; ensure oxygen is available. Administer: – Antihistamine IV/IM, corticosteroids IV, epinephrine IM, and IV fluids as appropriate. – Monitor vital signs every 2 minutes. – Hospitalize, if condition not improving or worsens. – Monitor study participant until symptoms resolve.

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

In case of suspected anaphylaxis, the Sampson's Criteria (Sampson et al, 2006) should be assessed (Section 10.8), and the Sampson Criteria Questionnaire should be completed. The infusion must be discontinued immediately, and emergency resuscitation measures implemented.

10.8 Appendix 8: Sampson's criteria

Anaphylaxis is highly likely when any of the following 3 criteria are fulfilled (Sampson et al, 2006):

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

AND AT LEAST 1 OF THE FOLLOWING

- Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
- Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that study participant (minutes to several hours):
   - Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   - Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
   - Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   - Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that study participant (minutes to several hours): systolic BP of <90mmHg or >30% decrease from that person's Baseline.

10.9 Appendix 9: Management of AESM

Adverse events of special monitoring are defined as product-specific AEs, adverse reactions, or safety topics requiring special monitoring by 1 or more regulatory authorities or by UCB.

For rozanolixizumab, AESM (defined by UCB) are:

- Severe and/or serious headache
- Suspected aseptic meningitis

Occurrence of AESM require immediate reporting (within 24 hours regardless of seriousness) to UCB. Upon reception of AESM by UCB, a standard medical follow-up query will be sent to the site to gather extensive medical information about the AESM. See Table 10-4 for assessments that may be required in case of AESM.

Table 10-4: Additional study assessments

Assessment	When applicable
For study participants who experience severe and/or serious headache and for study participants with suspected aseptic meningitis:	
Headache or suspected aseptic meningitis follow-up questionnaire	Headache follow-up questionnaire which sites will receive after reporting AESM of severe and/or serious headache should be completed promptly and returned to the sponsor via the SAE reporting process. Suspected aseptic meningitis follow-up questionnaire which sites will receive after reporting AESM of suspected aseptic meningitis should be completed promptly and returned to the sponsor via the SAE reporting process.
Full neurological examination	In study participants who report severe and/or serious headache or with a suspected aseptic meningitis at the clinic visit, a full neurological examination and fundoscopy should be performed (see Section 8.2.2). In study participants who report a severe and/or serious headache while at home or features suggestive of aseptic meningitis, a visit to the site for the full neurological examination should be arranged for as soon as is practically possible.
Other	In study participants who report a severe and/or serious headache, other diagnostic procedures including, but not limited to, CT scan, MRI (gadolinium-enhanced preferred) and/or LP for CSF collection are to be performed if indicated at the discretion of the investigator.
For study participants who experience suspected aseptic meningitis:	
LP	In study participants who report signs and/or symptoms of meningitis which require a LP, results of the CSF analysis should be recorded, and preliminary data should be included on the SAE form used for reporting the event as an AESM within 24 hours (ie, preliminary data reported on the first reporting may not have CSF results yet, but the reporting should occur as soon as there is a suspected diagnosis). Full results should be communicated in subsequent exchanges with UCB.
Additional analysis	Results of all investigations should be recorded, and preliminary data should be included on the SAE form used for reporting the event as an AESM. Details on all investigation results including, but not limited to, blood or CSF cultures and analysis/PCR test (including list of microorganisms tested)/MRI scans ± gadolinium should be included.

AESM=adverse events of special monitoring; CSF=cerebrospinal fluid; CT=computed tomography; LP=lumbar puncture; MRI=magnetic resonance imaging; PCR=polymerase chain reaction; SAE=serious adverse event

10.9.1 Severe and/or serious headache

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

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

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

A severe and/or serious headache should be evaluated by a healthcare professional as soon as possible for further investigations. Study participants should be monitored for signs and symptoms suggestive of central nervous system (CNS) involvement and evaluated immediately if other causes (eg, meningitis, intracranial bleeding) are suspected (see Section 10.9.2).

Headaches will be treated as clinically indicated according to national guidelines. It is recommended that the study participants have an analgesic available in case of headache with the instruction for frequency and dosage provided by a healthcare professional. The analgesic can be started at the early onset of headache. Study participants experiencing any treatment-related headache will be followed until resolution of the event.

10.9.2 Suspected aseptic meningitis

Drug-induced aseptic meningitis is a diagnosis of exclusion after ruling out infectious causes (Jolles et al, 2000). A few cases of DIAM have been reported in the rozanolixizumab program. Consequently, suspected aseptic meningitis is being managed as an AESM (see Section 8.3.7).

Participants should be monitored for signs and symptoms suggestive of CNS involvement and evaluated immediately if meningitis is suspected. A full neurological workup should be performed, including, but not limited to, imaging, eg, computed tomography scan, or preferably gadolinium-enhanced magnetic resonance imaging, a lumbar puncture with cerebral spinal fluid (CSF) analysis inclusive of glucose, protein, differential complete blood count, cultures, gram stain, and/or viral polymerase chain reaction as appropriate. A concurrent blood sample should be collected as per local practice. The ultimate investigative procedures are at the discretion of the investigator or the treating physician. For studies where a neurologist is not the investigator, a neurological consultation is also recommended to aid in decision making and study participant management. These investigations will be performed to further understand the potential mechanisms of DIAM in the participants.

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

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

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

10.10 Appendix 10: Abbreviations and trademarks

ADE	adverse device effect
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
AESM	adverse events of special monitoring
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BP	blood pressure
CNS	central nervous system
CRF	case report form
CRO	contract research organization
CSF	cerebral spinal fluid
DIAM	drug-induced aseptic meningitis
ECG	electrocardiogram
EW	Early Withdrawal
FcRn	neonatal Fc receptor
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
MG	generalized myasthenia gravis
HRT	hormonal replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IgG	immunoglobulin G
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities

NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCT number	ClinicalTrials.gov identifier
PK	pharmacokinetic(s)
PKS	Pharmacokinetic Set
SADE	serious adverse device effect
SAE	serious adverse event
SAP	Statistical Analysis Plan
SFU	Safety Follow-Up
SS	Safety Set
TEAE	treatment emergent adverse event
ULN	upper limit of normal
USADE	unanticipated serious adverse device effect
WOCBP	woman of childbearing potential

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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 GCP.

Approval Signatures

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