PROTOCOL UP0106 AMENDMENT 2

A RANDOMIZED, PARTICIPANT-BLIND, INVESTIGATOR-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF ROZANOLIXIZUMAB ADMINISTERED SUBCUTANEOUSLY VIA MANUAL PUSH VERSUS SYRINGE DRIVER TO HEALTHY PARTICIPANTS

PHASE 1

SHORT TITLE:

A Phase 1 study comparing the safety, tolerability, pharmacokinetics, and pharmacodynamics of subcutaneous rozanolixizumab administered via manual push vs syringe driver to healthy participants

Sponsor:
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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**
Protocol Amendment 2	03 Jun 2021	Substantial
Protocol Amendment 1	16 Mar 2021	Non-substantial
Original protocol	04 Feb 2021	Not applicable

Amendment 2 (03 Jun 2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The primary reason for this protocol amendment is to add 2 time points for the clinical chemistry assessment, at 6 hours and 12 hours after the start of infusion. Additionally, the minimum time period between COVID-19 vaccination and the Screening Visit has been clarified, and one exploratory endpoint has been updated. Other changes include the addition of respiratory rate to the list of vital signs and phosphate to the list of clinical chemistry parameters. Additional updates have been incorporated to provide further clarity on the protocol and/or to correct errors.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 3 Objectives and endpoints	The exploratory endpoint/estimand "Exact volume of IMP administration, determined by syringe and infusion line weights" has been changed to "Volume of IMP administration."	To reflect the change in the method used to assess the volume of IMP administration. The volume of IMP infused will be based on the volume (mL) indicated by the graduations on the syringe.
1.3 Schedule of activities	Table 1-1: Added 2 time points for the clinical chemistry assessment, at 6 and 12 hours after the start of infusion.	To ensure adequate monitoring of clinical chemistry parameters during the first 24 hours after the start of infusion.
1.3 Schedule of activities 8.9 Biomarkers 10.2 Appendix 2: Clinical laboratory tests	Table 1-1, Table 1-2, text in Section 8.9, and footnote d of Protocol-Required Safety Laboratory Assessments table have been updated.	Corrected to clarify that complement and cytokine sampling are taken at 4 and 8 hours **post event**, only if an infusion reaction or AE of special monitoring is observed.
1.3 Schedule of activities	Table 1-1: Footnote i has been updated to clarify that vital signs are also assessed predose.	Updated to be consistent with the study design.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of activities 8.2.2 Vital signs 9.4.1.3 Vital signs and electrocardiograms	Table 1-1: Footnote i and text in Section 8.2.2 and Section 9.4.1.3 have been updated to add respiratory rate to the list of vital signs.	For consistency with the following other safety endpoint "Vital signs measurements (blood pressure, pulse rate, respiratory rate, and body temperature), 12-lead electrocardiogram, and local tolerability assessments at each scheduled assessment during the In-Clinic and SFU Periods."
1.3 Schedule of activities	Table 1-1: Footnote i has been updated to remove "at the start of infusion."	There is no 12-lead ECG assessment at the start of infusion in this study.
1.3 Schedule of activities 8.2.5 Local tolerability	Table 1-1: Footnote m and text in Section 8.2.5 have been updated to clarify that the assessment of local tolerability of SC infusion for the "0" time point will be completed predose. The time point "at the end of infusion" has also been added.	Updated to be consistent with the study design.
1.3 Schedule of activities 8.9 Biomarkers	Table 1-1: Footnote t and text in Section 8.9 have been updated to clarify that backup samples could be stored for later biomarker analyses (up to 20 years).	Updated to provide further clarification.
1.3 Schedule of activities	Table 1-1: A new footnote has been added, Footnote u: Anti-rozanolixizumab antibodies will be assessed predose and on Days 10, 16, 22, and 57.	Added to clarify the anti-rozanolixizumab antibodies sampling time points.
2.3 Benefit/risk assessment	The text has been updated to clarify the mechanism of action of rozanolixizumab with respect to COVID-19 vaccination.	Added to clarify the potential interaction between COVID-19 vaccine and the IMP.
2.3 Benefit/risk assessment 8.2.12 COVID-19 precautions	The text has been updated to clarify that the Screening Visit should not be scheduled before at least 2 weeks after the COVID-19 vaccination.	Added to clarify the minimum time period between COVID-19 vaccination and the Screening Visit.
6.5.2 Prohibited concomitant treatments (medications and therapies)	The text has been updated to clarify that vitamins are permitted during the study.	To clarify that vitamins are permitted during the study.
10.2 Appendix 2: Clinical laboratory tests	Phosphate has been added to the list of clinical chemistry parameters.	For consistency with related studies.

Section # and Name	Description of Change	Brief Rationale
Global	Minor formatting changes have been made.	Minor, therefore have not been summarized.

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
Fax	**Europe and Rest of the World:** +32 238 66561
Email	PSRapidalert@ucb.com
Phone	**UCB Study Physician:** +44 (0) 1753 443 290 **24h Rapid Response Helpline:** +44 808 164 0230

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

A randomized, participant-blind, investigator-blind, placebo-controlled study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of rozanolixizumab administered subcutaneously via manual push versus syringe driver to healthy participants

Short Title:

A Phase 1 study comparing the safety, tolerability, pharmacokinetics, and pharmacodynamics of subcutaneous rozanolixizumab administered via manual push vs syringe driver to healthy participants

Rationale:

For chronic diseases requiring long-term or life-long therapies, alternate modes of subcutaneous (SC) dosing broaden patient options for ease of use and flexibility in how they can conduct their drug by self-administration. The manual push (MP) technique (also referred to as "rapid push") is a well-established mode of self-administration of SC immunoglobulin G (IgG), which offers the advantages of independence from constant use of a syringe driver, reduced infusion times (median [redacted] for abdominal sites), as well as reduced material costs (Bienvenu et al, 2018). Currently, in clinical studies, SC administration of rozanolixizumab occurs via a programmable syringe driver at a targeted [redacted]. To enable an alternative to SC dosing via a syringe driver, there is considerable clinical interest in the possibility of employing the MP method for rozanolixizumab, particularly in light of the relatively low volumes involved in rozanolixizumab therapy for adults as well as the low volumes involved in treating pediatric patients. The current study aims to generate and characterize safety, tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) profiles, including between-participant variability for the MP technique compared with the currently used programmable syringe driver, in the SC dosing of rozanolixizumab.

Objectives and Endpoints

Objectives	Endpoints/Estimands
Primary	
• To evaluate the safety and tolerability of a [redacted] SC dose of rozanolixizumab administered to healthy participants by MP vs syringe driver	• Incidence of TEAEs
Secondary	
• To assess the PK and PD of a [redacted] SC dose of rozanolixizumab administered by MP vs syringe driver	PK endpoints: • C_{max}, t_{max}, $AUC_{(0-t)}$ PD endpoints: • Baseline-corrected area under the Total IgG-time curve • R_{min} • t_{min}
Exploratory	
• To compare the PK and PD of a [redacted] SC dose of rozanolixizumab administered by MP vs syringe driver	• PK comparisons: C_{max}, $AUC_{(0-t)}$ • PD comparison: Baseline-corrected Total IgG AUC
• To evaluate the immunogenicity of rozanolixizumab following SC administration	• Anti-rozanolixizumab antibody screening status (positive or negative screen), confirmatory status (positive or negative immunodepletion), and the titer for "positive immunodepletion" samples at each scheduled assessment during the In-Clinic and SFU Periods
• To evaluate the effects of rozanolixizumab on the concentrations of IgG on tetanus, influenza A virus-specific IgG antibody, and COVID-19 vaccinated/previously infected participants	• Values and change from Baseline in serum IgG concentrations at each scheduled assessment during the In-Clinic and SFU Periods • Values and change from Baseline in tetanus, influenza A virus-specific IgG antibodies, and COVID-19 vaccinated/previously infected participants during the In-Clinic and SFU Periods

Objectives	Endpoints/Estimands
• To assess total volume, total time, and infusion rate for MP and syringe driver	• Volume of IMP administration • Time from start to completion and resultant infusion rate of IMP administration • Time of infusion setup for both modes of administration
• To assess acceptability of SC rozanolixizumab administration by MP vs syringe driver	• Postdose infusion site pain visual analog scale with IMP administration
• To assess the experience with SC infusions	• Pre- and postdose SIAQ for MP administration • Postdose ISRQ for syringe driver administration
Other Safety	
• To evaluate changes from Baseline in vital signs, 12-lead electrocardiogram, and laboratory measurements following [redacted] doses of rozanolixizumab administered by SC MP vs syringe driver in healthy study participants	• Vital signs measurements (blood pressure, pulse rate, respiratory rate, and body temperature), 12-lead electrocardiogram, and local tolerability assessments at each scheduled assessment during the In-Clinic and SFU Periods • Changes from Baseline in clinical laboratory assessments will consist of hematology including coagulation, clinical chemistry, and urinalysis at each scheduled assessment during the In-Clinic and SFU Periods
• To further evaluate the safety and tolerability of a [redacted] SC dose of rozanolixizumab administered to healthy participants by MP vs syringe driver	• Occurrence of serious TEAEs • Occurrence of treatment-related TEAEs • Occurrence of TEAEs leading to withdrawal • Occurrence of AEs of special monitoring • Comparison of TEAEs for MP vs syringe driver • Serum complement (C3, C4), and cytokines and plasma complement (C3a, C5a)

AE=adverse event; AUC=area under the concentration-time curve; $AUC_{(0-t)}$=area under the concentration-time curve from 0 to time t; C_{max}=maximum plasma concentration; COVID-19=coronavirus disease-19; IgG=immunoglobulin G; IMP=investigational medicinal product; ISRQ=injection site reaction questionnaire; MP=manual push; ISRQ=injection site reaction questionnaire; PD=pharmacodynamic(s);

Objectives	Endpoints/Estimands

PK=pharmacokinetic(s); R_{min}=maximum decrease in total plasma IgG; SC=subcutaneous(ly); SFU=Safety Follow-Up; SIAQ=self-injection assessment questionnaire; TEAE=treatment-emergent adverse event; t_{max}=time to maximum plasma concentration; t_{min}=time to minimum IgG level

Overall Design

This Phase 1 study is a randomized, participant-blind, investigator-blind, placebo-controlled safety/tolerability, PK, and PD evaluation of a [redacted] rozanolixizumab SC dose administered to healthy participants by either a programmed syringe driver or by MP via self-administration. As rozanolixizumab has not been administered SC to humans by MP, this study represents a preliminary assessment of the MP method prior to recommendation of this administration technique in the clinical dosing of rozanolixizumab.

Participants will be divided into 2 body weight categories: ≥35 to <50kg and ≥50kg. Within the higher body weight category, 16 participants will be randomly allocated to syringe driver or MP cohorts and, subsequently, to rozanolixizumab or placebo. Due to the paucity of clinical data for [redacted] in the lower body weight range, the primary rozanolixizumab dose for assessment in this study is [redacted] as a dose level for adults weighing ≥35kg to 50kg. A [redacted] dose is also being assessed in low body weight participants to support future rozanolixizumab pediatric development programs. Within the lower body weight category, the first eight subjects will receive either [redacted] rozanolixizumab or placebo via syringe driver, and the following 8 subjects will receive either [redacted] rozanolixizumab or placebo via MP.

The specific treatments administered to each cohort are described below. Two sentinel study participants (1 active + 1 placebo) will be incorporated into Cohort 1 and a Safety Monitoring Committee (SMC) will convene to evaluate all available safety and tolerability data following completion of the 72-hour evaluation period and prior to dosing of the remaining participants in Cohort 1. As a further precautionary step for Cohort 1, dosing of the 6 post-sentinel participants will be staggered such that no more than 2 participants will be dosed in a 72-hour period with a minimum of 48 hours between participants. In addition, the Rapid Alert process is in place throughout the study to ensure that exposure to the study medication is stopped if a reported event meets the stopping criteria (see Appendix 8 [Section 10.8]).

Two sentinel study participants (1 active + 1 placebo) will also be incorporated into Cohorts 2 and 4. Based on review of 48-hour post dose safety and tolerability data by the SMC, dosing will commence in remaining participants. Even if the stopping criteria, as outlined in Section 7, are not met, it is still at the discretion of the SMC not to proceed to the further dosing. More details will be provided in the SMC Charter.

The eligibility of study participants will be determined during a Screening Period of up to 4 weeks (Day -28 to Day -2). Once eligibility is confirmed, the study participant will be admitted to the site (at Day -1 or the evening of Day -2) and will enter an In-Clinic Period through Day 5. Each study participant will receive a [redacted] SC dose of rozanolixizumab on Day 1 and may be discharged beginning at Day 5 at the discretion of the investigator. Each participant will only receive [redacted] investigational medicinal product (IMP) administration.

Beginning at Day 6, study participants will be ambulant and will attend the clinical site for study visits through Day 57 to allow sufficient time for systemic IgG levels to return to Baseline and for the assessment of anti-drug antibodies.

Number of Participants

Approximately 32 participants will be randomly assigned to study medication such that at least 6 evaluable participants per cohort are expected to complete the study.

Treatment Groups and Duration

The treatment groups are planned to be as follows:

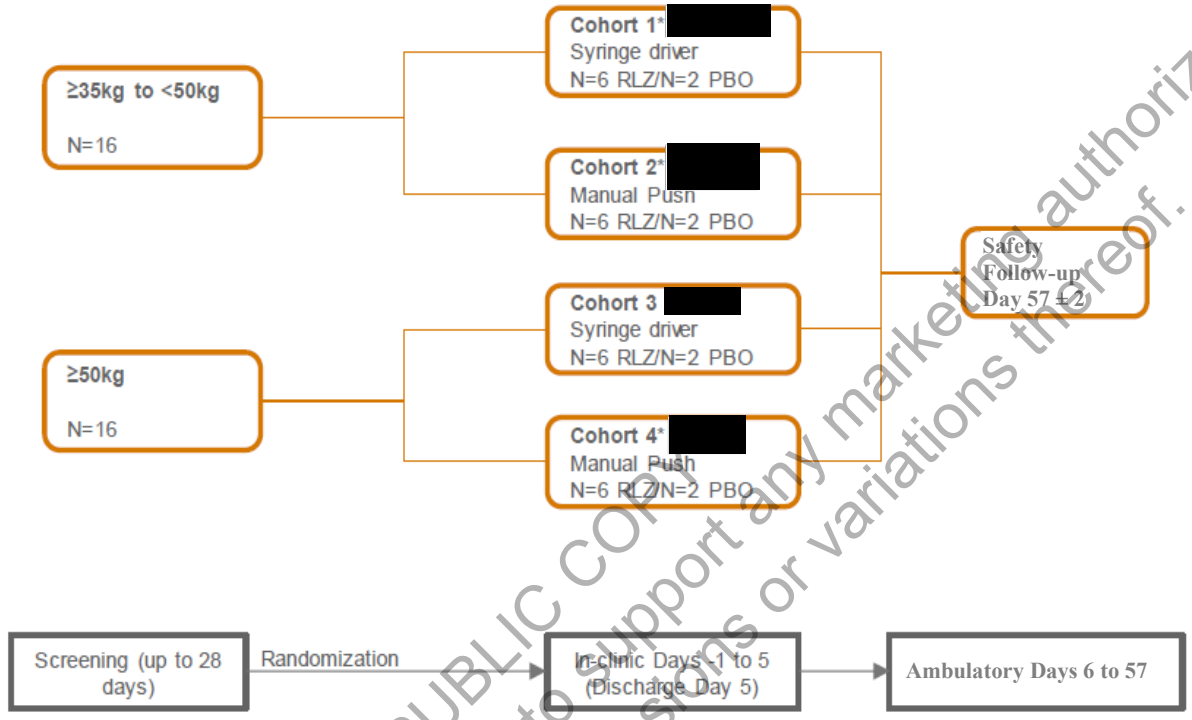
- Cohort 1 (participants with a body weight of ≥35kg to <50kg) is planned to have 6 participants receive rozanolixizumab [redacted] and 2 participants receive placebo via syringe driver at a [redacted].
- Cohort 2 (participants with a body weight of ≥35kg to <50kg) is planned to have 6 participants receive rozanolixizumab [redacted] and 2 participants receive placebo via MP through self-administration at a [redacted].
- Cohort 3 (participants with a body weight of ≥50kg) is planned to have 6 participants receive rozanolixizumab [redacted] and 2 participants receive placebo via syringe driver at a [redacted].
- Cohort 4 (participants with a body weight of ≥50kg) is planned to have 6 participants receive rozanolixizumab [redacted] and 2 participants receive placebo via MP through self-administration at a [redacted].

The total maximum study duration per study participant is up to 12 weeks. This includes a 4-week Screening Period, a 5-day In-Clinic Period, and an ambulatory Safety Follow-Up Period from Day 6 through Day 57.

1.2 Schema

A schematic diagram of the study is provided in Figure 1-1.

Figure 1-1: Study schematic



PBO=placebo; RLZ=rozanolixizumab
Note: * Includes 2 sentinel participants (1 RLZ + 1 PBO).

1.3 Schedule of activities

The Schedule of Activities is presented in Table 1-1.

Table 1-1: Schedule of activities

Assessments	Screening Period	In-Clinic Period										Ambulatory Period								
		Admission	Dosing																	SFU/WD
Weeks	**-4 to -1**	**0**	**1**									**1**	**2**	**2**	**3**	**3**	**4**	**5**	**7**	**8**
Days	**-28 to -2**	**-1**[a]	**1**					**2**	**3**	**4**	**5**[b]	**7**	**10**	**13**	**16**	**19**	**22**	**29**	**43**	**57**
Hours			**0**	**4**	**6**	**8**	**12**	**24**	**48**	**72**	**96**									
Informed consent	X																			
Inclusion/exclusion criteria	X	X																		
Randomization[c]			X																	
IMP administration[d]			■																	
Demography	X																			
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SARS-CoV-2 testing (PCR)	X	X									X									X
Influenza, tetanus, and SARS-CoV-2 antibody assessment	X	X									X									X
Study participant card[e]			X																	
Medical/procedure history	X																			
Physical examination[f]	X	X									X									X
Pregnancy test[g]	X	X																X		X
Serum FSH level[h]	X																			
Tuberculosis test and questionnaire	X																			
Alcohol urine test and urine drug screen	X	X																		

Table 1-1: Schedule of activities

Assessments	Screening Period	In-Clinic Period										Ambulatory Period								
		Admission	Dosing																	SFU/WD
Weeks	**-4 to -1**	**0**	**1**									**1**	**2**	**2**	**3**	**3**	**4**	**5**	**7**	**8**
Days	**-28 to -2**	**-1**[a]	**1**					**2**	**3**	**4**	**5**[b]	**7**	**10**	**13**	**16**	**19**	**22**	**29**	**43**	**57**
Hours			**0**	**4**	**6**	**8**	**12**	**24**	**48**	**72**	**96**									
Vital signs[i]	X	X	X[i]	X[i]	X	X	X	X	X	X	X	X	X	X	X					X
Body weight and height (height once at Screening)	X	X																		
12-lead ECG	X	X	X	X			X	X	X	X	X			X						X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serology[j]	X																			
Hematology (including coagulation)	X	X						X			X		X							X
Clinical chemistry	X	X			X		X	X			X		X							X
PK sampling[k]			X	X	X	X	X	X	X	X	X	X	X	X	X					
Total IgG	X	X						X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis (dipstick)[l]	X	X						X			X		X							X
Local tolerability of SC infusion[m]			■	■	■	■	■	■	■	■	■									
Infusion Questionnaire (SIAQ)			X[n]																	
Injection Site Reaction Questionnaire (ISRQ)			X[o]																	
Injection site pain VAS			X[p]																	
Infusion site photograph			X[q]																	

Table 1-1: Schedule of activities

Assessments	Screening Period	In-Clinic Period									Ambulatory Period								
		Admission	Dosing																SFU/WD
Weeks	**-4 to -1**	**0**	**1**								**1**	**2**	**2**	**3**	**3**	**4**	**5**	**7**	**8**
Days	**-28 to -2**	**-1[a]**	**1**					**2**	**3**	**4**	**5[b]**	**7**	**10**	**13**	**16**	**19**	**22**	**29**	**43**	**57**
Hours			**0**	**4**	**6**	**8**	**12**	**24**	**48**	**72**	**96**									
Anti-rozanolixizumab antibodies[u]			X										X		X		X			X
Headache questionnaire[r]			X	X	X	X	X	X	X	X	X									
Neurological assessment[s]			X	X	X	X	X	X	X	X	X									
Serum complement (C3, C4), and cytokines and plasma complement (C3a, C5a)[t]			X																	

AE=adverse event; CSF=cerebrospinal fluid; CT=computed tomography; ECG=electrocardiogram; FSH=follicle-stimulating hormone; IgG=immunoglobulin G; IMP=investigational medicinal product; ISRQ=injection site reaction questionnaire; MP=manual push; PCR=polymerase chain reaction; PK=pharmacokinetic(s); SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SC=subcutaneous(ly); SFU=Safety Follow-Up; SIAQ=self-injection assessment questionnaire; VAS=visual analog scale; WD=withdrawal

[a] Participants may be admitted into the clinic in the evening of Day -2 for the In-Clinic Period.

[b] Participants discharged during Day 5 at the discretion of principal investigator.

[c] Randomization should be performed on Day 1 before dosing and after all predose assessments and procedures have been completed.

[d] Rozanolixizumab will be administered as an SC infusion by syringe driver at a [redacted] or by MP through self-administration at a [redacted]

[e] This card is an emergency contact card and will be given to the participant when he/she is randomized in the clinical study (Day 1).

[f] A full physical examination will be performed at the Screening Visit, Day -1, and SFU. A brief symptom-led physical examination should be performed on Day 5.

[g] Serum pregnancy tests will be performed at the Screening Visit and on Day -1 and 29 and at the SFU Visit for all women with childbearing potential.

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

[i] Vital signs will be measured predose and at 1, 2, 3, and 4 hours after the start of infusion and then prior to each PK sampling. Measurements will include blood pressure, pulse rate, respiratory rate, and tympanic body temperature. Vital signs and ECGs should be measured/taken before PK sampling, where applicable.

Single 12-lead ECGs will be taken at Screening, Admission, predose, at 4, 12, and 24 hours after the start of infusion, and once a day on Days 3, 4, and 5 until discharge. All ECG recordings should be taken with the study participant resting in the supine position for at least 5 minutes before the recording.

[j] Serology panel: Hepatitis B surface antigen, hepatitis B core antibody (both IgG and immunoglobulin M), hepatitis C virus antibody, and human immunodeficiency virus 1 and 2 antibody.

[k] The PK sampling time points will be: predose, immediately at the end of infusion, 4, 6, 8, 12, 24, 36, 48, 72, and 96 hours after start of infusion, and on Days 7, 10, 13, and 16.

[l] Dipstick urinalysis includes: pH, protein, glucose, ketone, urobilinogen, bilirubin, blood, nitrite, leukocytes; urine spot collections for albumin:creatinine ratio, total protein, albumin, creatinine, alpha-1 microglobulin, and beta-2 microglobulin; specific gravity; and microscopic examination (if blood or protein is abnormal).

[m] Assessment of local tolerability of SC infusion (by the investigator or designee) will be completed predose, at the end of infusion, and 4, 6, 8, 12, 24, 36, 48, 72, and 96 hours after the start of infusion.

[n] The SIAQ will be completed predose and 30 minutes to 1 hour postdose by study participants (MP cohorts only).

[o] The ISRQ will be completed 30 minutes to 1 hour postdose by participants (syringe driver cohorts only).

[p] Injection site pain VAS will be completed by all cohorts 30 minutes to 1 hour postdose.

[q] Photographs of IMP injection site to be taken predose and 30 minutes after the end of the IMP administration, and additionally upon occurrence of any injection site reaction. An additional photograph will be taken if an injection site reaction occurs.

[r] Applicable only to participants experiencing severe and/or serious headache(s). The Headache Questionnaire will be performed daily until resolution (ie, if headache becomes moderate or mild, normal collection of AEs should apply). Headache Questionnaire should be assessed after Day 5 (at the investigator's discretion) if participants are kept longer in the unit for severe headache.

[s] A neurological assessment is to be performed by the investigator or designee for those participants who experience severe and/or serious headaches with a frequency as clinically indicated. This assessment will include:

1) General appearance, including posture, motor activity, vital signs, and meningeal signs, if indicated;
2) Cranial nerves;
3) Motor system, including muscle tone and power and sensory system – light touch;
4) Reflexes, including deep tendon reflexes;
5) Coordination, gait (if possible);
6) Fundoscopy.

The neurological assessment may be performed after Day 5 (to the investigator's discretion) if headache continues. The neurological assessment may be repeated if headache continues and it is clinically indicated and at the discretion of the investigator. In study participants who report severe headache, other diagnostic procedures including a CT scan (if indicated, and at the discretion of the investigator) and lumbar puncture for CSF collection (if clinically indicated, and at the discretion of the investigator) should be performed (see Section 8.3.7.1.3 and Section 8.3.7.1.4, respectively).

[t] Complement and cytokine sampling taken predose for all participants and at 4 and 8 hours post event only if an infusion reaction or AE of special monitoring is observed. Backup samples could be stored for later biomarker analyses (up to 20 years).

[u] Anti-rozanolixizumab antibodies will be assessed predose and on Days 10, 16, 22, and 57.

In addition to those detailed in Table 1-1, the assessments in Table 1-2 may be required in case of infusion reactions or adverse events (AEs) of special monitoring (severe headache, severe gastrointestinal disorders [eg, diarrhea, abdominal pain, vomiting]). Note that additional vital sign measurements may be taken based on the timing of the assessments.

Table 1-2: Additional study assessments

Assessment	When applicable
For study participants who experience infusion reactions (excluding local injection site reactions):	
Complement and cytokines	In study participants who experience an infusion reaction within the first 4 hours after dosing, a sample should be taken at 4 and 8 hours post event. Additionally, sampling is taken in case of a suspected hypersensitivity event or any clinical indication of an unexpected immune response.
For study participants who experience an AE of special monitoring, including severe headache, moderate to severe diarrhea, moderate to severe abdominal pain, or moderate to severe vomiting: If the AE is initially reported during a telephone call, the study participant should be reviewed at the study site as soon as is practically possible for further investigation.	
Complement and cytokines/Exploratory biomarkers	In study participants who experience an AE of special monitoring (as defined in Section 8.3.6) within the first 4 hours after dosing, a sample should be taken at 4 and 8 hours post event.
For study participants who experience severe and/or serious headache, the following should be conducted:	
Headache Questionnaire	In study participants who report severe and/or serious headache, this assessment should be performed daily until resolution (ie, if headache becomes moderate or mild, normal collection of AEs should apply) (see Section 8.3.7.1). The Headache Questionnaire may be repeated if clinically indicated and at the discretion of the investigator.
Full neurological examination	In study participants who report severe and/or serious headache, a full neurological examination (including fundoscopy) should be performed (see Section 8.3.7.1.2). This assessment should include general appearance (including posture, motor activity, vital signs, and meningeal signs, if indicated), cranial nerves, motor system (including muscle tone/power and sensory system), reflexes (including deep tendon reflexes), coordination (gait, if possible), and fundoscopy. The neurological assessment may be repeated if headache continues and it is clinically indicated and at the discretion of the investigator.
CT scan and lumbar puncture for CSF collection	In study participants who report severe and/or serious headache, other diagnostic procedures including a CT scan (if indicated, and at the discretion of the investigator) and lumbar puncture for CSF collection (if clinically indicated, and at the discretion of the investigator) should be performed (see Section 8.3.7.1.3 and Section 8.3.7.1.4, respectively).

Table 1-2: Additional study assessments

Assessment	When applicable
For study participants who experience moderate or severe diarrhea, stool should be collected:	
Stool sample assessment	In study participants who report moderate or severe diarrhea, stool collection and analysis should be performed (1 sample per episode of diarrhea). The frequency of stool sampling should be as clinically indicated in the opinion of the investigator. Analysis of stool samples will be performed locally (see Section 8.3.7.2.1).

AE=adverse event; CSF=cerebrospinal fluid; CT=computed tomography

2 INTRODUCTION

Rozanolixizumab is a humanized IgG4 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.

The FcRn recycles IgG and albumin and transports it bidirectionally across epithelial barriers. Multiple studies have shown that FcRn rescues both IgG and albumin from intracellular lysosomal degradation by recycling it from the sorting endosome to the cell surface (Roopenian and Akilesh, 2007). The FcRn may also mediate transcytosis of IgG to facilitate its distribution within tissues. Rozanolixizumab has been specifically designed to block IgG binding to FcRn without blocking the binding and recycling of albumin.

Rozanolixizumab binds with high affinity to FcRn at both neutral and acidic pH. Immunoglobulin G that is constitutively taken up by pinocytosis into cells fails to bind to FcRn, even at the acidic pH found in the endosome. Therefore, it is 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, which include myasthenia gravis (MG), pemphigus vulgaris, immune thrombocytopenia (ITP), Goodpasture's syndrome, neuromyelitis optica, Guillain-Barré Syndrome, and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

As individual disease entities, IgG autoantibody-mediated conditions are relatively rare. Treatment of these disorders remains a difficult clinical problem, with many of these conditions requiring 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, which cause 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, ITP, 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, specific 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).

For chronic diseases requiring long-term or life-long therapies, alternate modes of subcutaneous (SC) dosing broaden patient options for ease of use and flexibility in how they conduct their drug self-administration. The manual push (MP) technique is a well-established mode of self-administration of SC IgG, which offers the advantages of independence from a syringe driver, reduced infusion times, and reduced material costs. The current study aims to generate and characterize the safety, tolerability, PK, and PD profile for the MP technique compared with the currently used programmable syringe driver, for the SC dosing of rozanolixizumab in healthy participants.

The MP method for SC injection of rozanolixizumab appears to be feasible because the injection volumes of SC rozanolixizumab administered in the clinical program are typically smaller than for SC IgG products ([redacted] [HIZENTRA, GAMMANORM]), and the formulation viscosities are comparable (12.0mPa.s vs 14.7mPa.s for Hizentra [Maeder, 2011] and 8.7mPa.s for Gammanorm [Gardulf, 2016]).

The MP technique involves the manual syringing of an investigational medicinal product (IMP) SC with a butterfly needle (eg, 23-25G) (Jolles, 2013). A retrospective analysis of 104 patients self-administering SC IgG found that for push administration using a syringe, volumes of [redacted] (Shapiro, 2010). More than 80% of patients using the MP technique used only 1 infusion site per session, with [redacted] as the most common (67.3% of patients) total volume infused. In particular in the pediatric population, MP was preferred in the patient groups of <2 years of age and >10 years of age and has been shown to be a safe and convenient alternative to the pump infusion in children with primary immune deficiency (Shapiro, 2013). Recently, another comparative study switching patients from intravenous IgG infusions to SC IgG infusions demonstrated that the manual push method was similar in tolerability and safety profile (Milota et al, 2019).

2.1 Study rationale

For chronic diseases requiring long-term or life-long therapies, alternate modes of SC dosing broaden patient options for ease of use and flexibility in how they conduct their drug self-administration. The MP technique (also referred to as "rapid push") is a well-established mode of self-administration of SC IgG, which offers the advantages of independence from constant use of a syringe driver, reduced infusion times (median [redacted] for abdominal sites), and reduced material costs (Bienvenu et al, 2018). Currently, SC administration of rozanolixizumab occurs via programmable syringe drivers at a targeted [redacted]. To enable an alternative to SC dosing via a syringe driver, there is considerable clinical interest in the possibility of employing the MP method for rozanolixizumab, particularly in light of the relatively low volumes involved in rozanolixizumab therapy. The current study aims to generate and characterize the safety, tolerability, PK, and PD profile, including between-participant

variability, for the MP technique compared with the currently used programmable syringe driver, for the SC dosing of rozanolixizumab in healthy participants.

2.2 Background

Clinical experience with rozanolixizumab is as follows: a completed first-in-human study in healthy participants (UP0018), a completed Phase 2 study in MG (MG0002), a completed Phase 2 study (TP0001) and ongoing Phase 3 studies (TP0003, TP0006, and TP0004) in primary ITP, a completed Phase 1 study in healthy Japanese, Chinese, and Caucasian participants (UP0060), ongoing Phase 3 studies in MG (MG0003, MG0004, and MG0007), and ongoing Phase 2 studies in CIDP (CIDP01/CIDP04). All clinical dosing of rozanolixizumab has been via the SC route using a syringe driver, except for the evaluation of several escalating intravenous doses in UP0018.

In UP0018, a Phase 1 study in Caucasian healthy study participants, rozanolixizumab was tolerated with an acceptable safety profile after [redacted] administration of up to [redacted] intravenous and [redacted] SC doses. The most frequently reported treatment-emergent adverse events (TEAEs) considered related to IMP per investigator in the rozanolixizumab total SC group were headache (27.8%) and diarrhea (16.7%). Consistent with rozanolixizumab's mechanism of action, plasma IgG concentrations in UP0018 were found to decrease in a dose-dependent fashion, with a maximum percentage change from Baseline of [redacted] for [redacted] SC, respectively. Following SC dosing in UP0018, no plasma samples had detectable rozanolixizumab concentrations at a dose of [redacted] and only 2 study participants had detectable concentrations at [redacted]. The only calculable maximum and total rozanolixizumab exposures by the SC route were for the [redacted] dose (maximum plasma concentration [C_{max}]: 12.41µg/mL and area under the concentration-time curve from 0 to time t [$AUC_{(0-t)}$]: 643.3h*µg/mL). As no [redacted] dose is planned in UP0106 participants, information regarding redosing at the same infusion site is not necessary.

In UP0060, [redacted]-dose SC administration of rozanolixizumab to healthy Japanese, Chinese, and Caucasian study participants was generally well tolerated with an acceptable safety profile after [redacted] SC administration of [redacted] doses. Overall, patterns in the incidence of TEAEs observed in Japanese and Chinese study participants were generally comparable to those observed in Caucasian participants. In all study participants, a numerically higher incidence of TEAEs was reported for study participants receiving rozanolixizumab (38 participants [77.6%] reported 115 TEAEs) compared with placebo (10 participants [62.5%] reported 23 TEAEs). Among participants receiving rozanolixizumab, there was a trend towards increased incidence of TEAEs with higher doses (55.6%, 75.0%, and 90.0% of participants in the rozanolixizumab [redacted] dose groups, respectively). Three participants (6.1%) reported 4 TEAEs of special monitoring (diarrhea [2 events], abdominal pain [1 event], and vomiting [1 event]) in the [redacted] cohort, all of moderate intensity. The [redacted] dose was concluded by the investigator to be not well tolerated by 1 Caucasian volunteer who reported moderate headache. Dose-dependent reductions in IgG and IgG subclasses, similar to that observed in UP0018, were seen following administration of rozanolixizumab in all 3 ethnicities. Tetanus- and influenza A virus-specific IgG concentrations over time were similar to total IgG following the administration of rozanolixizumab, generally reaching the lowest levels around Day 10 and returning close to Baseline by Day 57; the geometric mean concentrations for tetanus- and influenza A virus-specific antibodies generally remained at acceptable levels for

protection time in all ethnic and dose groups. Overall, the mean value of albumin remained within the normal range over time, and no clinically relevant changes from Baseline were observed. All injection site reactions observed for rozanolixizumab were self-limiting, short-term, and of mild intensity.

2.3 Benefit/risk assessment

The healthy study participants included in this study will receive no medical benefit from participation. The risks from taking part in the study will be minimized through the selection of appropriate dose levels, selection of appropriate study participants defined by the inclusion/exclusion criteria, and safety monitoring. In UP0106, safety and tolerability of rozanolixizumab will be monitored through the use of sentinel pair dosing (Section 4.1 and Section 4.2), and predefined stopping rules will apply to all cohorts (see Section 6.7). Safety will be reviewed by a Safety Monitoring Committee (SMC) (Section 9.7). In addition, the Rapid Alert process will be in place throughout the study to ensure that exposure to the study medication is stopped if a reported event meets the stopping criteria (see Appendix 8 [Section 10.8]).

To date, human clinical data available for rozanolixizumab are derived from completed Phase 1 studies (UP0018 and UP0060) in healthy study participants and completed Phase 2 studies in study participants with primary ITP (TP0001) and generalized MG (MG0002). Based on other observations from the current nonclinical and clinical studies with rozanolixizumab and clinical studies with other IgG antibodies in humans, the potential adverse effects that may be anticipated include gastrointestinal disturbances, headaches, infusion and hypersensitivity reactions, local tolerability and injection site reactions, and effects on vaccination response.

Clinical development for rozanolixizumab is proceeding with dosing via the SC route of administration only. The Reference Safety Information provided in the current IB is therefore based on the safety experience with SC dosing and is the Reference Safety Information for all ongoing and planned clinical studies with rozanolixizumab. It will be used to perform the event expectedness assessments for expedited reporting and annual safety reporting.

Vaccinations, including coronavirus disease-19 (COVID-19) vaccination, are not allowed during the study (Section 6.5.2). Restrictions on use of live vaccines have been identified in the exclusion criterion #29. If vaccination with non-live vaccines (including current available COVID-19 vaccines) is considered necessary, the degree of protection afforded by vaccination under treatment may be compromised during and after treatment with rozanolixizumab.

Based on its mechanism of action, rozanolixizumab will reduce total IgG levels including vaccine-specific IgG. However, it is unlikely that the immune response to the vaccine will be compromised by FcRn inhibition, particularly after administration of a [redacted] dose of rozanolixizumab.

In order to keep potential confounding of safety variables to a minimum and to allow differentiation of safety profiles of the IMP and COVID-19 vaccine, the Screening Visit should not be scheduled before at least 2 weeks after the COVID-19 vaccination (Section 8.2.12).

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of rozanolixizumab may be found in the IB. The current IB

reflects the safety profile of SC rozanolixizumab as it is known and may change with the accumulation of additional data.

3 OBJECTIVES AND ENDPOINTS

The objectives and corresponding endpoints for this study are presented in Table 3-1.

Table 3-1: Study objectives and endpoints

Objectives	Endpoints/Estimands
Primary	
• To evaluate the safety and tolerability of a [redacted] SC dose of rozanolixizumab administered to healthy participants by MP vs syringe driver	• Incidence of TEAEs
Secondary	
• To assess the PK and PD of a [redacted] SC dose of rozanolixizumab administered by MP vs syringe driver	PK endpoints: • C_{max}, t_{max}, $AUC_{(0-t)}$ PD endpoints: • Baseline-corrected area under the Total IgG-time curve • R_{min} • t_{min}
Exploratory	
• To compare the PK and PD of a [redacted] SC dose of rozanolixizumab administered by MP vs syringe driver	• PK comparisons: C_{max}, $AUC_{(0-t)}$ • PD comparison: Baseline-corrected Total IgG AUC
• To evaluate the immunogenicity of rozanolixizumab following SC administration	• Anti-rozanolixizumab antibody screening status (positive or negative screen), confirmatory status (positive or negative immunodepletion), and the titer for "positive immunodepletion" samples at each scheduled assessment during the In-Clinic and SFU Periods

Table 3-1: Study objectives and endpoints

Objectives	Endpoints/Estimands
• To evaluate the effects of rozanolixizumab on the concentrations of IgG on tetanus, influenza A virus-specific IgG antibody, and COVID-19 vaccinated/previously infected participants	• Values and change from Baseline in serum IgG concentrations at each scheduled assessment during the In-Clinic and SFU Periods • Values and change from Baseline in tetanus, influenza A virus-specific IgG antibodies, and COVID-19 vaccinated/previously infected participants during the In-Clinic and SFU Periods
• To assess total volume, total time, and infusion rate for MP and syringe driver	• Volume of IMP administration • Time from start to completion and resultant infusion rate of IMP administration • Time of infusion setup for both modes of administration
• To assess acceptability of SC rozanolixizumab administration by MP vs syringe driver	• Postdose infusion site pain visual analog scale with IMP administration
• To assess the experience with SC infusions	• Pre- and postdose SIAQ for MP administration • Postdose ISRQ for syringe driver administration
Other Safety	
• To evaluate changes from Baseline in vital signs, 12-lead electrocardiogram, and laboratory measurements following [redacted] doses of rozanolixizumab administered by SC MP vs syringe driver in healthy study participants	• Vital signs measurements (blood pressure, pulse rate, respiratory rate, and body temperature), 12-lead electrocardiogram, and local tolerability assessments at each scheduled assessment during the In-Clinic and SFU Periods • Changes from Baseline in clinical laboratory assessments will consist of hematology including coagulation, clinical chemistry, and urinalysis at each scheduled assessment during the In-Clinic and SFU Periods

Table 3-1: Study objectives and endpoints

Objectives	Endpoints/Estimands
• To further evaluate the safety and tolerability of a [redacted] SC dose of rozanolixizumab administered to healthy participants by MP vs syringe driver	• Occurrence of serious TEAEs • Occurrence of treatment-related TEAEs • Occurrence of TEAEs leading to withdrawal • Occurrence of AEs of special monitoring • Comparison of TEAEs for MP vs syringe driver • Serum complement (C3, C4), and cytokines and plasma complement (C3a, C5a)

AE=adverse event; AUC=area under the concentration-time curve; $AUC_{(0-t)}$=area under the concentration-time curve from 0 to time t; C_{max}=maximum plasma concentration; COVID-19=coronavirus disease-19; IgG=immunoglobulin G; IMP=investigational medicinal product; MP=manual push; ISRQ=injection site reaction questionnaire; PD=pharmacodynamic(s); PK=pharmacokinetic(s); R_{min}=maximum decrease in total plasma IgG; SC=subcutaneous(ly); SFU=Safety Follow-Up; SIAQ=self-injection assessment questionnaire; TEAE=treatment-emergent adverse event; t_{max}=time to maximum plasma concentration; t_{min}=time to minimum IgG level

4 STUDY DESIGN

4.1 Overall design

This Phase 1 study is a randomized, participant-blind, investigator-blind, placebo-controlled safety/tolerability, PK, and PD evaluation of a [redacted] rozanolixizumab SC dose administered to healthy participants by either a programmed syringe driver or by MP via self-administration. As rozanolixizumab has not been administered SC to humans by MP, this study represents a preliminary assessment of the MP method prior to recommendation of this administration technique in the clinical dosing of rozanolixizumab.

Participants will be divided into 2 body weight categories: ≥35 to <50kg and ≥50kg. Within the higher body weight category, 16 participants will be randomly allocated to syringe driver or MP cohorts and, subsequently, to rozanolixizumab (6 participants total) or placebo (2 participants total) (Figure 1-1). Participants of lighter body weights between ≥35 to <50kg are being investigated to a) support the newly recommended rozanolixizumab dosing with a fixed dose of [redacted] in adults of ≥35kg to 50kg (via syringe driver administration) and (b) to assess the MP method for a [redacted] IMP volume.

Within the lower body weight category, the allocation to either syringe driver or MP will be determined by order of recruitment rather than randomization. The first 8 participants will be allocated to the syringe driver cohort and randomly allocated to receive either rozanolixizumab [redacted] (6 participants total) or placebo (2 participants total). The subsequent 8 participants will be allocated to the MP cohort and randomly allocated to receive either rozanolixizumab [redacted] (6 participants total) or placebo (2 participants total).

The treatment groups are planned to be as follows:

- Cohort 1 (participants with a body weight of ≥35kg to <50kg) is planned to have 6 participants receive rozanolixizumab [redacted] and 2 participants receive placebo via syringe driver at a [redacted].
- Cohort 2 (participants with a body weight of ≥35kg to <50kg) is planned to have 6 participants receive rozanolixizumab [redacted] and 2 participants receive placebo via MP through self-administration at a [redacted].
- Cohort 3 (participants with a body weight of ≥50kg) is planned to have 6 participants receive rozanolixizumab [redacted] and 2 participants receive placebo via syringe driver at a [redacted].
- Cohort 4 (participants with a body weight of ≥50kg) is planned to have 6 participants receive rozanolixizumab [redacted] and 2 participants receive placebo via MP through self-administration at a [redacted].

Since a [redacted] rozanolixizumab fixed dose has not been investigated thus far in lower weight (35 to 50kg) healthy participants, 2 sentinel study participants (1 active + 1 placebo) will be incorporated into Cohort 1 in order to collect safety and tolerability data over a 72-hour period. The SMC will convene to evaluate all available safety and tolerability data following completion of a 72-hour evaluation period and prior to staggered dosing of remaining participants in Cohort 1. As a further precautionary step for Cohort 1, dosing of the 6 post-sentinel participants will be staggered such that no more than 2 participants will be dosed in a 72-hour period with a

minimum of 48 hours between participants. In addition, the Rapid Alert process is in place throughout the study to ensure that exposure to the study medication is stopped if a reported event meets the stopping criteria (see Appendix 8 [Section 10.8]). Cohorts are not obliged to run in numerical sequence (ie, cohorts could run in parallel).

Since MP IMP administrations in this study will likely be at higher infusion rates than the [redacted] SC rate undertaken in all rozanolixizumab clinical studies to date, 2 sentinel study participants (1 active + 1 placebo) will be incorporated into Cohorts 2 and 4. Review of 48-hour postdose safety data by the SMC will enable dosing of the remaining participants (see Section 9.7 and Appendix 8 [Section 10.8]).

The eligibility of study participants will be determined during a Screening Period of up to 4 weeks (Day -28 to Day -2). Once eligibility is confirmed, the study participant will be admitted to the site (at Day -1 or the evening of Day -2) and will enter an In-Clinic Period through Day 5. Each study participant will receive a [redacted] SC dose of rozanolixizumab on Day 1 and may be discharged beginning at Day 5 at the discretion of the investigator. Each participant will only receive [redacted] IMP administration.

Beginning at Day 6, study participants will enter the Ambulatory Period and will attend the clinical site for study visits through Day 57 to allow sufficient time for systemic IgG levels to return to Baseline and for the assessment of anti-drug antibodies (ADAs).

The total maximum study duration per study participant is up to 12 weeks. This includes a 4-week Screening Period, 5-day In-Clinic Period, and the Ambulatory Period from Day 7 through Day 57.

Photographs of the infusion site will be taken, without participant personal or facial identification, for all participants prior to start and 30 minutes after the end of the IMP administration, and additionally upon occurrence of any injection site reaction.

4.2 Scientific rationale for study design

Rozanolixizumab dosing in this study is supported by the results of UP0018 and UP0060, where rozanolixizumab was found to be well tolerated with an acceptable safety profile (see Section 2.2 for further information). Dosing in some of the recently initiated rozanolixizumab clinical development program has been changed from a body weight-tiered mg/kg to a fixed (mg) basis (see Section 4.3), with the intention of simplifying rozanolixizumab dosing to be more convenient to patients and prescribers.

As described in Section 4.1, since a [redacted] rozanolixizumab dose has not been investigated in lower weight (35 to 50kg) healthy participants, the study will initially dose 2 sentinel study participants (1 active + 1 placebo) in Cohort 1 to confirm safety and tolerability over a 72-hour period before proceeding further. Additionally, the remaining 6 participants after the sentinels have been dosed in Cohort 1 will be staggered such that no more than 2 participants are dosed in a 72-hour period, within a minimum 48 hours between participants.

Rozanolixizumab dose equivalents of [redacted] and [redacted] have previously been investigated in healthy participants in UP0018 and UP0060, with highest unit SC rozanolixizumab doses being [redacted] (81kg participant) in UP0018 and [redacted] (88.5kg participant) in UP0060. Since UP0018 and UP0060 investigated body weight-adjusted (mg/kg), rather than fixed (mg) dosing, the lowest body weight participants in these previous 2 studies received SC rozanolixizumab doses

of [redacted] (60.0kg and 60.3kg participants, respectively) in UP0018 and [redacted] (46.2kg participant) in UP0060. Accordingly, a [redacted] rozanolixizumab dose has not been administered to healthy participants weighing <50kg to date. The specific rozanolixizumab formulation being used is similar to that of the formulation used in UP0060.

4.3 Justification for dose

The planned dose of rozanolixizumab for this study is [redacted], consistent with the primary recommended rozanolixizumab dose of [redacted] SC in future clinical dosing of rozanolixizumab in MG and ITP. Simulations from a population PK/PD analysis of clinical rozanolixizumab data demonstrated comparable systemic rozanolixizumab exposure and IgG response for a [redacted] fixed dose and [redacted] and [redacted] doses (both these latter doses being clinically effective in Phase 2 studies) for adults weighing ≥35kg. The dose of [redacted] is identical to a weight-tiered dose of [redacted] for participants weighing ≥70kg, a weight-tiered dose of [redacted] for participants weighing 50kg to <70kg, and a weight-tiered dose of [redacted] for participants weighing 35kg to <50kg. A [redacted] dose is also being assessed in low body weight participants to support future rozanolixizumab pediatric development programs.

4.4 End of study definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the Safety Follow-Up Visit (Day 57).

The end of the study is defined as the date of the last visit (the Safety Follow-Up Visit, Day 57) of the last study participant in the clinical study.

5 STUDY POPULATION

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

5.1 Inclusion criteria

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

Age

1. Study participant must be 18 to 65 years of age, inclusive, at the time of signing the informed consent.

Type of participant

2. Study participants who are overtly healthy in the opinion of the investigator as determined by medical evaluation including medical history, a general clinical examination, including physical examination and laboratory tests, and cardiac monitoring.
3. Study participant must be considered reliable and capable of adhering to the protocol, according to the judgment of the investigator, and are able to communicate satisfactorily with the investigator and comply with all clinical study requirements.
4. Study participant has blood pressure (BP) and pulse within normal range in a supine position after 5 minutes of rest (systolic BP: 90 to 140mmHg, diastolic BP: 50 to 90mmHg, pulse:

40 to 90bpm). If the study participant has results outside the stated range, repeat measurement may be allowed once at the discretion of the investigator.

5. Study participant has clinical laboratory test results within the reference ranges of the testing laboratory or not clinically significant if outside the specified ranges, in the opinion of the investigator. If the study participant has results outside the stated range, repeat measurement may be allowed once at the discretion of the investigator.
6. Study participant has a body temperature between 35.0°C and 37.5°C, inclusive.
7. Study participant's electrocardiogram (ECG) is considered "normal" or "abnormal but clinically nonsignificant" (as interpreted by the investigator). If the study participant has test results outside the specific range that are deemed potentially clinically significant, repeat of the investigation may be allowed once at the discretion of the investigator.

Sex

8. Study participants may be male or female:
   (a) A male participant must agree to use contraception as detailed in Appendix 4 (Section 10.4) for at least 90 days after the end of the study and refrain from donating sperm up to 3 months after the end of the study.
   (b) A female participant is eligible to participate if she is not pregnant (see Appendix 4 Section 10.4), not breastfeeding, and at least 1 of the following conditions applies:

   Not a woman of childbearing potential (WOCBP) as defined in Appendix 4 (Section 10.4) OR a WOCBP who agrees to follow the contraceptive guidance in Appendix 4 (Section 10.4) for at least 90 days after the final IMP dose.

Weight

9. Participant has a body mass index of 18 to 32kg/m2, with a minimum body weight of 35kg.

Informed consent

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

5.2 Exclusion criteria

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

Medical conditions

1. History or presence of/significant history of or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrinological, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study intervention; or interfering with the interpretation of data. Study participant has active neoplastic disease or history of neoplastic disease within the previous 5 years of entry in the clinical study (except for basal or squamous cell carcinoma of the skin or carcinoma in situ that has been definitively treated with standard of care approaches).

Study participant has a history of a major organ transplant or hematopoietic stem cell/marrow transplant.

2. Any medical (acute or chronic illness) or psychiatric condition that, in the opinion of the investigator, could harm the study participant or would compromise the study participant's ability to participate in this study.
3. Abnormal BP, as determined by the investigator.
4. Symptomatic herpes zoster within 3 months prior to Screening.
5. Allergies to humanized monoclonal antibodies.
6. Female who is pregnant or lactating.
7. Clinically significant multiple or severe drug allergies, intolerance to topical corticosteroids, or severe posttreatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, and exfoliative dermatitis).
8. Participant has a known hypersensitivity to any components of the study medication or to any components of the licensed device.
9. Evidence of active or latent tuberculosis (TB) as documented by medical history and examination, TB testing via a positive (not indeterminate) QuantiFERON TB Gold test, and responses to the TB Signs and Symptoms Questionnaire.
10. Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).

    For randomized participants with a Baseline result greater than the upper limit of normal (ULN) for total bilirubin, a Baseline diagnosis and/or the cause of any clinically meaningful elevation must be understood and recorded in the electronic Case Report form (eCRF).
11. Bilirubin >1.0×ULN (isolated bilirubin <1.5×ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%). Tests that result above the exclusion limit may be repeated once for confirmation.
12. Alanine transaminase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) >1.0×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 not be considered to have met the exclusion criteria.
13. 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.
14. Breast cancer within the past 10 years.
15. Absolute neutrophil count $<1.5\times10^9$/L and/or lymphocyte count $<1.0\times10^9$/L.
16. Corrected serum calcium of >11.5mg/dL (>2.9mmol/L) or <8.0mg/dL (<2.0mmol/L).
17. Predicted inability to comply with being free of caffeine and ethanol from 72 hours prior to clinic admission and during the In-Clinic Period of the study.

18. Known hypersensitivity to oral paracetamol (acetaminophen).
19. History of known inflammatory bowel disease, active diverticular disease, or a history of confirmed duodenal, gastric, or esophageal ulceration in the previous 6 months.
20. History of hyperprolinemia, since L-proline is a constituent of rozanolixizumab.
21. Twelve-lead ECG with abnormalities considered to be clinically significant upon medical review: male study participants with QT interval corrected for heart rate using Fridericia's formula (QTcF) >450msec and female study participants with QTcF >470msec, left bundle branch block, or evidence of myocardial ischemia.
22. Renal impairment, defined as a creatinine concentration in serum of ≥1.4mg/dL (≥123µmol/L) for female participants and ≥1.5mg/dL (≥132µmol/L) for male participants.
23. Known viral hepatitis (B and C) (positive serology test for hepatitis B surface antigen, hepatitis B core antibodies [both IgG and immunoglobulin M], hepatitis C virus antibodies) or human immunodeficiency virus 1/2 antibodies or has a past medical history or family history of primary immunodeficiency or antibodies to human immunodeficiency virus type 1 and/or type 2 at Screening.
24. Participant has a positive test result for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in reverse transcriptase-polymerase chain reaction on admission to the unit.
25. Participant has clinical signs and symptoms consistent with SARS-CoV-2 (eg, fever, dry cough, dyspnea, sore throat, fatigue) or confirmed infection by appropriate laboratory test within the previous 14 days prior to Screening or on admission.
26. Participant has active infection or is symptomatic with SARS-CoV-2 or is currently in quarantine (has been in contact with a SARS-CoV-2 positive individual in the last 14 days).
27. Participant has had a severe course of SARS-CoV-2 (eg, requiring extracorporeal membrane oxygenation, mechanical ventilation, or hospitalization).

Prior/concurrent therapy

28. Past or intended use of over-the-counter or prescription medication (including herbal medications) within 14 days prior to dosing until Day 57 (specific medications listed in Section 6.5.1 are allowed).
29. Live vaccine(s) within 8 weeks prior to Screening or plans to receive such vaccines during the study or is within a dosing cycle to receive a second dose of a coronavirus disease-19 (COVID-19) vaccine.
30. 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

31. Exposure to more than 3 new chemical entities within 12 months prior to dosing.
32. Has previously been assigned to treatment in a clinical study of rozanolixizumab.

33. Participated in another study of an IMP (or a medical 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 (or a medical device).

Diagnostic assessments

34. Presence of hepatitis B surface antigen (HBsAg) at Screening or within 3 months prior to dosing.
35. Positive hepatitis C antibody test result at Screening or within 3 months prior to starting study intervention. NOTE: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled if a confirmatory negative hepatitis C ribonucleic acid test is obtained.
36. Positive hepatitis C RNA test result at Screening or within 3 months prior to first dose of study medication. NOTE: Test is optional and participants with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing.
37. Presence of the hepatitis B core antibody (HBcAb) even if HBsAg is negative.
38. Immunoglobulin G <7g/L or >16g/L at the Screening Visit.
39. Positive pre-study drug/alcohol screen.

Other exclusions

40. Participant is splenectomized or has had an active clinically significant infection within the last 6 weeks.
41. Donated or lost >500mL of blood or blood products in the 3 months preceding the start of dosing or plans to donate blood during the clinical study.
42. Employee or direct relative of an employee of the contract research organization (CRO) or UCB.
43. 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 21 units for males and 14 units for females 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).
44. Smoked on average >5 cigarettes/day (or equivalent) during the last 3 months and is not able to stop smoking during the In-Clinic Period.
45. Excessive consumption of beverages or food containing xanthine bases (including caffeinated drinks, coffee, chocolate, etc.), equating to >400mg caffeine per day.

5.3 Lifestyle restrictions

5.3.1 Meals and dietary restrictions

None.

5.3.2 Caffeine, alcohol, and tobacco

Participants will abstain from alcohol from the start of dosing until after collection of the final PK and/or PD sample. Study participants who drink alcohol will be instructed that alcohol will not be permitted while they are in the clinic. Study participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are in the clinic. Caffeine and alcohol use are prohibited for 72 hours prior to clinic admission (Day -1).

5.3.3 Activity

Study participants will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests. Study participants may participate in light recreational activities during the study.

5.4 Screen failures

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

Study participants may be rescreened once under conditions such as the following:

- Study participant falls outside the Screening Period
- If a study participant does not meet the inclusion criteria at Screening or on Day -1 due to an out-of-range laboratory result or a minor illness, he/she can be rescreened once at the discretion of the investigator. Provided all inclusion criteria are met at the second Screening, the study participant can be included. The repeat visit should be planned within the time frame of 28 days between the initial screening day and Day 1. In case study participants missed the 28 days window, the full screening assessments should be repeated.

Study participants may be included if the repeat values for the laboratory screening criteria are within normal ranges and/or if repeat values show normalization of the out-of-range safety laboratory values, and/or after the study participant makes a complete recovery from the mild or moderate illness and if all other screening criteria are met.

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), or placebo or medical devices intended to be administered to a study participant according to the study protocol.

6.1 Treatments administered

[redacted]

[redacted]

Study treatment details are presented in Table 6-1.

Table 6-1: Study treatments

Study Treatment Name:	Rozanolixizumab		Placebo	
	Syringe Driver	Manual Push	Syringe Driver	Manual Push
Dosage formulation:	Solution for injection		Solution for injection	
Unit dose strength:	[redacted]		Not applicable	
Dose level	[redacted] (MP or Syringe Driver)		Not applicable	
Volume	[redacted]		[redacted]	
Route of Administration	Subcutaneous infusion		Subcutaneous infusion	
Use	Investigational		Placebo	
Infusion site:	Abdomen		Abdomen	
Infusion rate:	[redacted]	Unspecified (individually variable)	[redacted]	Unspecified (individually variable)
Expected Duration of infusion:	[redacted]	Unspecified (individually variable)	[redacted]	Unspecified (individually variable)

MP=manual push

6.1.1 Administration methods

For details, please refer to the IMP handling manual.

6.2 Preparation, handling, storage, and accountability requirements

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

Only participants enrolled in the study may receive study medication and only authorized site staff may supply or administer study medication. All study medication must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance

with the labeled storage conditions with access limited to the investigator and authorized site staff.

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

In case an out-of-range temperature is noted for longer than 15 minutes, 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 medication are provided in the IMP Handling Manual.

6.2.1 Drug accountability

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

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

6.3 Measures to minimize bias: randomization and blinding

A CRO (ie, ICON) randomization biostatistician will create the program to generate the randomization list and code break envelopes. The randomization biostatistician will be independent of the study. A dummy randomization list will be prepared by the randomization biostatistician following the documented and approved design in the randomization plan. The dummy randomization list will be reviewed and approved by the Clinical Study Biostatistician to ensure that the code meets the study requirements.

After finalization of the dummy code, the randomization program will be run with a different seed number to create the final randomization list. The generation of the randomization list will occur in a secure environment. The final randomization list will be released to the appropriate unblinded contacts stated in the randomization plan. Electronic files will be password protected, and instructions will be supplied on how to obtain the password.

The final randomization list will be retained by ICON in a secure location until the end of the study (ie, until after database lock).

All study participants and investigational site staff involved in the study will be blinded to the IMP assignment throughout the study, with the exception of unblinded site pharmacy staff members involved in IMP preparation, dispensing, and dosing staff.

Copies of the randomization lists will be sent before the start of the study in a secure fashion directly from the contracted CRO to the following:

- Sponsor Patient Safety staff for SAE reporting
- Bioanalytical staff (to identify samples to be measured)
- Unblinded member of pharmacy involved in IMP preparation and dispensing
- Independent Biostatistician/Statistical Programmer

[redacted]

No stratification factors will be used in the randomization process.

At the Screening Visit, each study participant will be assigned a unique 5-digit participant number (randomization number) from a range of numbers supplied by Global Biometry Standards.

Once the investigator determines that the study participant is eligible for the study, and before IMP administration, a central person in charge of issuing the randomization numbers will manually allocate the next randomization number on the list to the study participant. Each specific randomization number will be linked to the treatment regimen on the randomization schedule, which will be dispensed by the [redacted]. The randomization numbers will also be recorded in the eCRF.

6.3.1 Procedures for maintaining and breaking the treatment blind

6.3.1.1 Maintenance of study treatment blind

All study participant treatment details (cohort and treatment) will be allocated and maintained with randomization lists and emergency envelopes (or equivalent).

6.3.1.2 Breaking the treatment blind in an emergency situation

In the event of an emergency, it will be possible to determine to which treatment arm and dose the study participant has been allocated using emergency envelopes (or equivalent) which should be stored in a secure area and can be accessed immediately by investigators. The responsibility to break the treatment code resides solely with the study investigators.

An emergency envelope (or equivalent) containing the treatment allocation will be printed for each study participant and must not be broken, except for emergency situations. In case of a medical emergency with a study participant that is managed at an external medical facility, unblinding of the study treatment may also be requested, if considered medically appropriate. Study participant unblinding from an external medical facility can be requested using the contact details provided on the Subject Identification Card (ie, via a phone call to the Principal investigator, Study Physician or the Study Unit operating 24/7).

The Clinical Project Manager must be informed immediately when a code is broken. Any unblinding of the IMP performed by the investigator must be recorded in the source documents and on the Study Termination eCRF page.

6.4 Treatment compliance

Designated site personnel will ensure treatment compliance by overseeing SC infusion of the IMP by the participant. Drug accountability must be recorded on the Drug Accountability form. Any incomplete administration of IMP will require documentation of how much was infused (including start and stop times).

6.5 Concomitant medication(s)/treatment(s)

6.5.1 Permitted concomitant treatments (medications and therapies)

The following concomitant medications are permitted during the study:

- With approval from the investigator, paracetamol is permitted for the treatment of mild symptoms (eg, headache or pain), given at most [redacted], not exceeding 2g/day, and with a total of no more than 10g per [redacted].
- Hormonal contraceptives, implants, patches, intrauterine hormone-releasing system, or intrauterine devices delivering progesterone or postmenopausal hormonal replacement therapy (HRT) are allowed in female participants.

6.5.2 Prohibited concomitant treatments (medications and therapies)

With the exception of vitamins and the permitted concomitant treatments noted in Section 6.5.1, all prescription medication (including herbal medications) or over-the-counter medicines are prohibited from 14 days prior to dosing until follow-up (Day 57), unless required to treat an AE, including pretreatment. Vaccinations are not allowed during the study.

6.5.3 Rescue medication

In the case of prolonged hypogammaglobulinemia, the study participant will be considered for treatment with prophylactic antimicrobial therapy and, where appropriate, a commercially available intravenous immunoglobulin. Study participants will be followed up until immunoglobulin levels return to within the normal range. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

6.6 Dose modification

No dose modifications are allowed during the study for an individual study participant.

6.7 Criteria for study hold or dosing stoppage

A rapid response procedure (Rapid Alert) for communicating serious and/or severe AEs or any other safety findings as described below will be operational during the study. A description of Rapid Alert procedures and how they may be used to facilitate prompt decision making regarding stopping exposure to study medication/procedures is provided in Appendix 8 (Section 10.8). The Rapid Alert Process should occur for any SAE or any severe AEs, regardless of relatedness to IMP that occurs during the study period. Detailed procedures for reporting SAEs and other safety events that may meet study hold criteria are provided in Appendix 3 (Section 10.3) and Appendix 8 (Section 10.8).

6.7.1 Stopping rules for all cohorts

If any of the following stopping criteria are met in any of the study cohorts, further dosing will be placed on hold:

- One study participant in the cohort has an SAE considered related to the IMP as judged by the investigator.
- One study participant in the cohort has anaphylaxis considered related to the IMP as judged by the investigator (Appendix 12 [Section 10.12]).
- More than one study participant within the same cohort has a severe nonserious AE considered related to the IMP as judged by the investigator.

If any of the stopping criteria has been met, further dosing will be suspended in all cohorts until further information is collected to assess the relationship with IMP. If additional information shows there is no relationship with IMP (eg, study participant was on placebo after unblinding), dosing can continue as planned. If it is deemed appropriate to restart dosing, a request to restart dosing with pertinent data will then be submitted as a request for a substantial amendment.

All safety and tolerability data (including serious and nonserious AEs) will be reviewed on a rolling basis by the investigator and sponsor's Study and Safety Physician (or designee). Safety evaluation of all available information across all cohorts will be completed by the SMC, including all serious AEs considered related to the IMP. In case of a safety signal, the SMC can recommend at any time to hold further dosing in a cohort. Restart of dosing within a cohort can be decided by the SMC if, after proper investigation, the safety signal is deemed to be not clinically relevant and when the below stopping criteria are not met.

Following case review to confirm causality and seriousness and/or severity of reported events, UCB will halt further dosing if during the study there is an SAE or 2 severe or clinically significant AEs considered to be at least possibly related to the IMP. A severe AE is defined as a Common Terminology Criteria for Adverse Events grade ≥3. If following an internal safety review, it is appropriate to restart the study, a substantial amendment will be submitted to the regulatory authority and independent ethics committee (IEC). The study will not restart until the amendment has been approved by the regulatory authority and IEC.

If no further dosing is planned due to the stopping criteria described above, previously randomized and dosed study participants will continue the study as planned. Safety assessments will be performed per the protocol. Pharmacokinetic and PD assessments will be performed if deemed to be relevant and agreed by the investigator and sponsor without compromising the safety of a study participant.

Other reasons for stopping and terminating the study will be:

- A pattern of AEs occurs that, in the opinion of the investigator and/or SMC, contraindicates further dosing of enrolled/additional study participants.
- If the sponsor or its designee judges it necessary for medical, safety, regulatory, or any other reasons consistent with applicable laws, regulations, and Good Clinical Practice (GCP).
- The sponsor decides to terminate the study, and no further dosing will be scheduled.

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

Events that may lead to discontinuation of study medication are described in Section 7.1.1 through Section 7.1.3.

7.1.1 Hypersensitivity stopping criteria

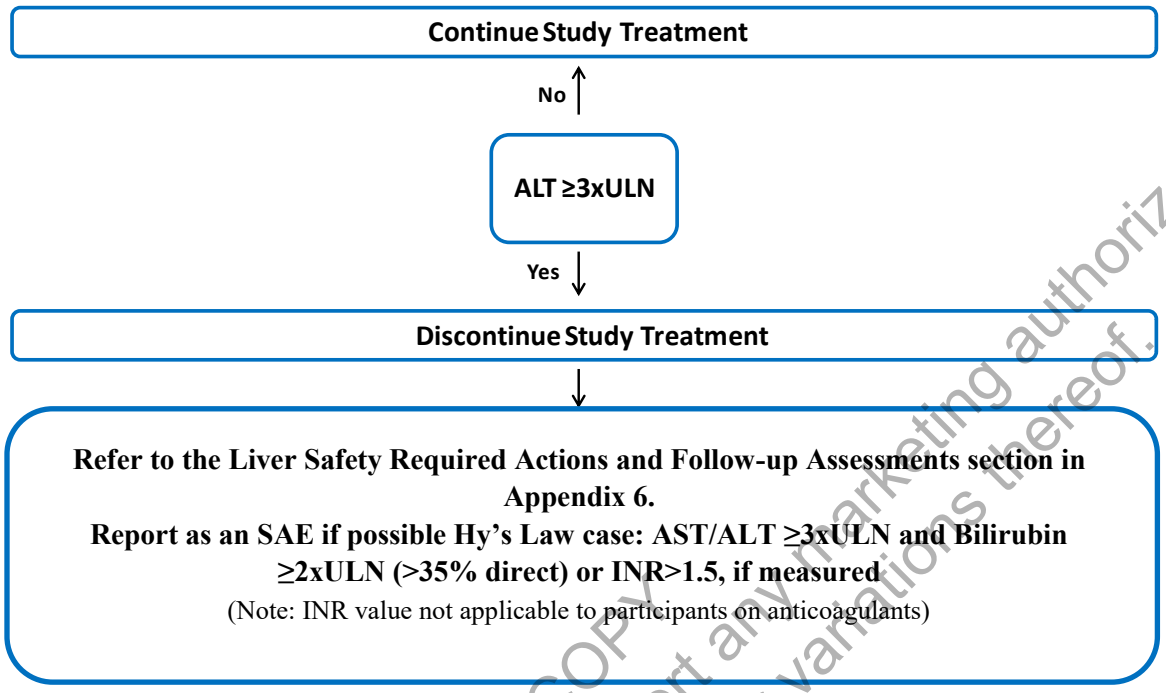
During the study, study participants will receive a [redacted] dose of investigational medicinal product (IMP) administered SC via a programmed syringe driver or by MP.

This will be performed under close and continued attention of the investigator or designee. 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. Rapid Alert procedure (Appendix 8 [Section 10.8]) should be followed, if indicated. See Appendix 12 (Section 10.12) and Appendix 13 (Section 10.13) for procedures to follow in the instance of infusion reactions and anaphylaxis, respectively.

7.1.2 Liver chemistry stopping criteria

The following liver chemistry stopping criteria for discontinuation of study medication do not apply (Figure 7-1). See Appendix 6 (Section 10.6) for procedures to follow in the instance of elevated liver function tests.

Figure 7-1: Liver chemistry stopping algorithm



ALT=alanine aminotransferase; AST=aspartate aminotransferase; INR=international normalized ratio; SAE=serious adverse event; ULN=upper limit of normal
Note: Suggested assessments and follow-up actions for potential drug-induced liver injury are provided in Appendix 6 (Section 10.6).

7.1.3 QTc stopping criteria

A participant who meets either bulleted criterion based on the ECG reading will be withdrawn from the study:

- QTcF >500msec
- Change from Baseline: QTcF >60msec

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

See Table 1-1 for data to be collected at the time of treatment discontinuation and follow up and for any further evaluations that need to be completed.

7.2 Participant discontinuation/withdrawal from the study

Participants are free to withdraw from the study at any time, without prejudice to their continued care. The study is designed to collect data on 24 participants that receive rozanolixizumab (6 per cohort). If study participants discontinue before the end of the safety evaluation period, replacement participants may be considered at the discretion of the sponsor, depending on how the discontinuation affects the study's ability to collect sufficient data to support the study

objectives. For each case of participant discontinuation, the decision on whether to recruit a replacement and the reason behind the decision will be documented.

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

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records. Participants who withdraw from the study will be encouraged to return to the clinic to complete the Withdrawal Visit (see Table 1-1).

See Table 1-1 for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

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

1. Participant develops an illness that would interfere with his/her continued participation.
2. Participant is noncompliant with the study procedures or medications in the opinion of the investigator.
3. Participant takes prohibited concomitant medications as defined in this protocol that might interfere with the outcome of the study or might be an increased risk to the study participant.
4. Participant withdraws his/her consent.
5. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.
6. The sponsor or a regulatory agency requests withdrawal of the participant.

7.3 Lost to follow-up

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

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

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in Table 1-1.

Protocol waivers or exemptions are not allowed.

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

Adherence to the study design requirements, including those specified in Table 1-1, is essential and required for study conduct.

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

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for Screening or Baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in Table 1-1.

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

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. A protocol amendment will be considered as appropriate. The IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

8.1 Efficacy assessments

As this is a Phase 1 study in healthy study participants; efficacy will not be assessed.

8.2 Safety assessments

Planned time points for all safety assessments are provided in Table 1-1. The acceptable deviation times for study procedures will be included in a separate manual.

8.2.1 Physical examination

A complete physical examination will include: general appearance; head, ears, eyes, nose and throat; thyroid; lymph nodes; back and neck; heart; chest; lungs; abdomen; skin; and extremities; and musculoskeletal and neurological systems will be assessed.

A brief symptom-led physical examination will be carried out on Day 5. Investigators should pay special attention to clinical signs related to previous serious illnesses.

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

8.2.2 Vital signs

Vital signs will be measured in a supine position after 5 minutes rest and will include tympanic body temperature, respiratory rate, systolic and diastolic BP, and pulse rate.

All vital signs should be taken before any blood sampling (except at the end of infusion) and with the study participant resting in the supine position for at least 5 minutes before the recording.

Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

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

8.2.3 Electrocardiograms

Twelve-lead ECGs will be obtained as outlined in Table 1-1 using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7.1.3 for QTcF withdrawal criteria and any additional QTcF readings that may be necessary.

All ECG recordings should be taken before any blood sampling (except at the end of infusion) and with the study participant resting in the supine position for at least 5 minutes before the recording.

8.2.4 Clinical safety laboratory assessments

See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and Table 1-1 for the timing and frequency.

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

All laboratory tests with values considered clinically significantly abnormal during participation in the study until the final follow-up visit should be repeated until the values return to normal or Baseline or are no longer considered clinically significant by the investigator or Study Physician.

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 Table 1-1.

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

8.2.5 Local tolerability

Assessment of local tolerability of SC infusion via syringe driver and MP (by the investigator or designee) will be completed predose, at the end of infusion, and 4, 6, 8, 12, 24, 36, 48, 72, and 96 hours after the start of infusion. Injection site reaction, ie, any pain, burning, erythema, itching, and/or swelling at the injection site, will be assessed.

8.2.6 Self-injection assessment questionnaire

The self-injection assessment questionnaire (SIAQ) measures the overall experience with SC self-injection and will be assessed predose and 30 minutes to 1 hour postdose by participants in the MP cohorts only.

8.2.7 Injection site reaction questionnaire

The ISRQ will be assessed 30 minutes to 1 hour postdose by participants in the syringe driver cohorts only. For participants with an injection site reaction, the questionnaire will be performed at any time that they have an injection site reaction.

8.2.8 Injection site pain visual analog scale

The injection site pain visual analog scale will be assessed 30 minutes to 1 hour postdose by participants in both the syringe driver and MP cohorts.

8.2.9 QuantiFERON Test

A QuantiFERON-TB GOLD test will be performed at the Screening Visit to identify those participants who have had TB or may have active or latent TB. Results of this test will be reported as positive, negative, or indeterminate. Participants with a positive test result will not be included in the study. If the result is reported as indeterminate, then the test can be repeated once. If the repeat test result is reported as indeterminate, then the participant will not be included in the study.

8.2.10 Tuberculosis signs and symptoms questionnaire

The questionnaire "Evaluation of signs and symptoms of tuberculosis" should be used as a source document. The questionnaire will assist with the identification of study participants who may require therapy for TB. A study participant who answers "Yes" to the question "Has the participant been in close contact with an individual with active TB, or an individual who has recently been treated for TB?" at Screening is excluded. A "Yes" response to any of the other questions within the questionnaire at Screening should trigger further careful assessment to determine if study participant has latent or active TB (see Section 5.2; exclusion criterion #9).

8.2.11 Infusion site photographs

Photographs of the IMP injection site are be taken prior to start and 30 minutes after the end of the IMP administration, and additionally upon occurrence of any injection site reaction. The photographs are for all participants and no facial identification will appear in the photos.

8.2.12 COVID-19 precautions

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

Study participants who are invited to receive their COVID-19 vaccination must not schedule the Screening Visit for UP0106 before at least 2 weeks after having received their vaccination to not confound the Screening Baseline results for safety parameters with potential transient changes

due to the COVID-19 vaccine. This time period will also result into an approximately 4-week time period between the COVID-19 vaccination and IMP dosing allowing clear differentiation of the safety profile of the IMP and the vaccine.

Study participants will be closely monitored for any signs and symptoms of COVID-19 (ie, fever, dysgeusia [taste loss/change], dysosmia [loss or distortion/change of smell], or persistent cough) throughout the study. If symptoms and/or clinical signs of infection are identified, the investigator will decide whether these findings will be handled as suspected or confirmed COVID-19. The use of testing for SARS-CoV-2 will be determined by reference to the regulatory and healthcare guidance in place locally at the time. In the case that COVID-19 is suspected or confirmed, the investigator will determine in discussion with the UCB Study Physician how soon the participant may be discharged from the clinical study center and whether this will be to their home or another healthcare facility.

8.3 AEs and SAEs

The definitions of device-related safety events, adverse device effects (ADEs), and serious adverse device effects can be found in Appendix 7 (Section 10.7).

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

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the participant to discontinue the study (see 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 until the Safety Follow-up/Withdrawal Visit at the time points specified in Table 1-1. Medical occurrences that begin before the start of study medication but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF and not the AE section.

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

All SAEs will be recorded and reported to the sponsor or designee within 24 hours as indicated in Appendix 3 (Section 10.3) and the procedure for rapid alert will be followed as indicated in Appendix 8 (Section 10.8). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

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

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

8.3.2 Method of detecting AEs and SAEs

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

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and nonserious AEs of special interest (Section 8.3.6) will be followed until resolution, stabilization, the investigator determines that it is no longer clinically significant, the event is otherwise explained, or the 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 by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study medication under clinical investigation are met.

The sponsor has a legal responsibility to notify regulatory authorities about the safety of a study medication under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IEC, and investigators.

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

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 IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study medication and until 1 month after the end of the study for female participants and 3 months after the end of the study for female partners of male participants.

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

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

- The participant should return for an early discontinuation visit.

- A Safety Follow-Up Visit should be scheduled ≤7 days after the participant has informed the sponsor of the pregnancy.

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

8.3.6 Adverse events of special interest

An AE of special interest is any AE that a regulatory authority has mandated be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a UCB product/compound. For rozanolixizumab, the following events require immediate reporting (within 24 hours regardless of seriousness) to UCB:

- 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 AE of special interest (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should then be reported if an alternative etiology is identified during investigation and monitoring of the participant.

8.3.7 Adverse events of special monitoring

For rozanolixizumab, AEs of special monitoring that require immediate reporting to UCB are:

- Severe headache
- Severe gastrointestinal disturbances (ie, abdominal pain, diarrhea, or vomiting)
- Opportunistic infection

These events require immediate reporting to UCB (within 24 hours), regardless of seriousness, using the fax and email details for SAE reporting.

8.3.7.1 Severe headache

Severe headache is defined as severe pain limiting self-care activities of daily living (ADL) or new/prolonged hospitalization for management of headache or life-threatening consequences requiring urgent medical intervention. Self-care ADLs refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications. Treatment of headache will be provided as clinically indicated according to the local guidelines.

The following safety assessments are applicable only to study participants experiencing severe and/or serious headache(s): the Headache Questionnaire, a neurological assessment (including fundoscopy), a computed tomography (CT) scan (if indicated, and at the discretion of the investigator), and a lumbar puncture for cerebrospinal fluid (CSF) collection (if clinically indicated and at the discretion of the investigator) will be performed.

8.3.7.1.1 Headache questionnaire

The Headache Questionnaire is applicable only to study participants experiencing severe and/or serious headaches and will be performed daily until resolution (ie, if headache becomes moderate or mild, normal collection of AEs should apply); this assessment will be followed by a neurological assessment (including fundoscopy), a CT scan (if indicated, and at the discretion of

the investigator), and a lumbar puncture for CSF collection (if indicated, and at the discretion of the investigator).

8.3.7.1.2 Neurological assessments

Neurological assessments will be performed only for those study participants who experience headaches with a frequency as clinically indicated (and at the discretion of the investigator). This assessment may include general appearance (including posture, motor activity, vital signs, and meningeal signs, if indicated), cranial nerves, motor system (including muscle tone/power and sensory system), reflexes (including deep tendon reflexes), coordination (gait, if possible), and fundoscopy.

8.3.7.1.3 CT scan

For study participants experiencing severe headache(s), a CT scan may be performed if indicated, and at the discretion of the investigator.

8.3.7.1.4 CSF sampling

For study participants experiencing severe headache(s), a lumbar puncture for CSF collection may be performed if clinically indicated, and at the discretion of the investigator.

8.3.7.2 Moderate or severe diarrhea

Moderate or severe diarrhea is defined as an increase of ≥4 stools per day over Baseline or incontinence due to urgency of diarrhea or new/prolonged hospitalization for management of diarrhea or limiting self-care ADL or life-threatening consequences requiring urgent medical intervention.

For study participants with moderate or severe diarrhea, stool samples will be collected.

8.3.7.2.1 Stool sampling

Stool collection will be performed for study participants with a severe AE of gastrointestinal disturbance that is considered related to the IMP (1 sample per episode of diarrhea).

8.4 Safety signal detection

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

The Study Physician or medically qualified designee/equivalent will conduct an ongoing review of SAEs and perform ongoing SAE reconciliations in collaboration with the Patient Safety representative. In addition, an SMC will be implemented to review ongoing study data as appropriate (see Section 10.1.5).

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

8.5 Treatment of overdose

Excessive dosing (beyond that prescribed in the protocol and including overdose) should be recorded in the Drug Accountability module of the eCRF. 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. Inform sponsor's Study Physician immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until study medication can no longer be detected systemically (at least 56 days from the last dose), as appropriate.
3. Obtain a plasma sample for PK analysis within 10 days from the date of the last dose of study medication if requested by the Study Physician (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

8.6 Pharmacokinetics

Planned time points for all PK assessments are provided in Table 1-1.

Samples will be collected for measurement of plasma concentrations of rozanolixizumab as specified in Table 1-1. Blood samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. Instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the laboratory manual. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples collected for analyses of rozanolixizumab plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

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

8.7 Genetics

Not applicable; genetics are not evaluated in this study.

8.8 Pharmacodynamics

Venous blood samples will be collected at timepoints specified Table 1-1 for the measurement of Total IgG. Instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the laboratory manual.

8.9 Biomarkers

Details on processes for collection and shipment and destruction of these samples can be found in the Laboratory Manual.

Serum complement (C3, C4), cytokines, and plasma complement (C3a, C5a) are to be taken predose for all participants and at 4 and 8 hours post event, only if an infusion reaction or AE of special monitoring is observed.

Remaining backup samples could be stored at -80°C for up to 20 years for later exploratory analyses.

Detailed information on sample analyses will be provided in a bioanalytical report.

8.9.1 Immunogenicity assessments

Immunogenicity testing will occur via a tiered analysis approach consisting of a Screening, confirmatory, and titration assay. Anti-drug antibodies to rozanolixizumab will be evaluated in plasma samples collected from all study participants according to Table 1-1.

Additionally, for study participants withdrawing from the study an unscheduled sample should be taken for ADA analysis upon his/her last withdrawal visit. These samples will be tested by the sponsor or sponsor's designee.

Plasma samples with a "positive screen" result will enter a confirmatory ADA analysis whereupon addition of excess rozanolixizumab to the sample is performed in an attempt to immunodeplete the ADA signal. For samples with a "positive immunodepletion," an ADA titer will be determined.

The detection and characterization of antibodies to rozanolixizumab, vaccinations, and previous SARS-CoV-2 infections will be performed using a validated assay method under the supervision of the sponsor. Samples for ADA analysis may be stored for a maximum of 20 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the sponsor to enable further analysis of immune responses to rozanolixizumab.

8.10 Medical resource utilization and health economics

Medical resource utilization and health economic 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). Deviations in analyses from the final SAP will be documented in the Clinical Study Report.

9.1 Definition of analysis sets

The following are the defined analysis sets:

- Enrolled Set: All study participants who have signed the ICF.
- Randomized Set: All enrolled study participants who were randomized.
- Safety Analysis Set: All randomized study participants who received IMP. Analysis of this set will be according to the treatment the study participants actually received and will be used for the demographic and safety analyses.
- PK Per Protocol Set: All study participants that received active study medication and had at least 1 observable PK measurement. If a study participant in the PK Per Protocol Set is missing individual time points or are otherwise unobservable, they will be included in the PK Per Protocol Set but those time points will be omitted from the PK summaries, as appropriate.
- PD Per Protocol Set: Is a subset of the Safety Analysis Set, consisting of those study participants who had no important protocol deviations affecting the PD variables, as confirmed during a pre-analysis review of the data prior to database lock.

9.2 General statistical considerations

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

Statistical evaluation will be performed by UCB or designee and supervised by the Statistics Department of UCB. Analysis of PK data will be performed using Phoenix® WinNonlin® software.

Data will be summarized by dose level, body weight category, treatment, and method, where applicable. For continuous variables, summary statistics will include number of study participants, treatment mean, median, standard deviation, minimum, and maximum. Categorical endpoints will be summarized using number of study participants, frequency, and percentages. In addition, all data will be listed.

Baseline will be the last nonmissing data collected prior to the IMP administration, and measurement-specific Baseline values will be defined in the SAP.

9.3 Planned efficacy/outcome analyses

Not applicable; efficacy is not evaluated in this study.

9.4 Planned safety and other analyses

9.4.1 Safety analyses

All safety variables will be analyzed by descriptive methods and presented by treatment (rozanolixizumab or placebo), method (MP or syringe driver), body weight, and dose level. All IMP administration details (including date, time of infusion start and stop, and volume given) will be listed. Additionally, safety parameters may be summarized by weight group. Frequency and intensity of TEAEs will be assessed as the primary safety variable in this clinical study. Additional analyses are described in the SAP.

9.4.1.1 Adverse events

All AEs will be coded using the Medical Dictionary for Regulatory Activities and characterized as pretreatment and treatment-emergent according to the intake of the IMP. 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.

Only TEAEs will be included in the summary tables and listings.

The frequency of all TEAEs during the study period will be presented separately by system organ class, high level term, and preferred term. The data will be displayed as number of participants experiencing the TEAEs, percentage of participants, and number of TEAEs, by treatment, method, body weight, and dose level.

Additional tables will summarize TEAEs leading to study medication interruption, TEAEs by maximum intensity, TEAEs by intensity, TEAEs by relationship to study medication, TEAEs of special interest, and TEAEs of special monitoring. Additional analyses are described in the SAP.

9.4.1.2 Clinical laboratory tests

Laboratory variables and changes from Baseline will be summarized by descriptive statistics at each time point by treatment, method, body weight, and dose level. Shift tables from Baseline to each post-Baseline time point will be presented by treatment, method, body weight, and dose level. Values outside the reference range will be flagged in the listings.

9.4.1.3 Vital signs and electrocardiograms

Vital sign variables (BP, pulse rate, respiratory rate, and body temperature) and changes from Baseline will be summarized by descriptive statistics at each time point by treatment, method, body weight, and dose level.

The individual mean at each time point will be calculated as raw parameters for descriptive analysis. The raw parameters and change from Baseline will be summarized by descriptive statistics at each time point by treatment, method, body weight, and dose level.

9.4.1.4 Physical examinations

Physical examination abnormalities will be listed.

All other safety assessments (including but not limited to: local tolerability of SC infusion, neurological assessment, Headache Questionnaire, and CSF data) will be listed.

9.4.2 PK analyses

Pharmacokinetics will be determined by non-compartmental analysis in Phoenix (Certara, USA) using the PK Per Protocol Set.

For calculation of the plasma PK parameters of rozanolixizumab, the actual sampling time points will be used in order to evaluate the PK parameters.

The plasma concentration-time profiles and PK parameters of rozanolixizumab will be summarized by method, body weight, and dose level using descriptive statistics (number of available observations, arithmetic mean, standard deviation, the geometric mean, the coefficient of variation of the geometric mean, median, minimum, and maximum). Values below the lower limit of quantification (LLOQ) will be reported with a clear sign indicating that they were below the LLOQ. Descriptive statistics of concentrations will be calculated if at least two-thirds of the individual data points are quantifiable (≥LLOQ).

Individual concentration time profiles will be displayed graphically on a linear-linear scale and semi-logarithmic scale. Geometric mean plasma concentrations-time curves including 95% confidence intervals will be displayed by method, body weight, and dose level.

The comparability of dose-adjusted PK parameters (C_{max}/D and $AUC_{(0-t)}$/D) between the methods (MP and the syringe driver) will be assessed within an analysis of variance model with Method (MP vs syringe driver) as a main effect.

9.4.3 PD analyses

Total IgG (observed values, change from Baseline, and percentage change from Baseline) will be listed and summarized for the PD Per Protocol Set. The geometric mean Total IgG concentration with 95% confidence interval will be displayed graphically.

Derived parameters for the Total IgG response curve (AUC, maximum decrease in total plasma IgG, and time to minimum plasma concentration) will be listed and summarized for the PD Per Protocol Set.

The comparability of the total IgG Baseline-corrected AUC(IgG)/D between MP and the syringe driver will be assessed within an analysis of covariance model analogous to the analysis of variance model used to evaluate the PK parameters described above. The Baseline IgG value will be fitted as a covariate.

9.4.4 Other analyses

Plasma concentrations of anti-rozanolixizumab antibodies will be summarized by descriptive statistics at each time point by treatment, method, body weight, and dose level. In addition, anti-rozanolixizumab antibody positive study participants will be summarized in terms of numbers of positive study participants by ethnic group and treatment group at each time point and at any time postdose.

Immunogenicity variables will be listed, plotted, and summarized. Further details will be provided 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 PK and PD and key safety for an individual study participant. The criteria for identifying important protocol deviations will be defined within the appropriate protocol-specific document. Important protocol deviations will be reviewed as part of the ongoing data cleaning process and all important deviations will be identified and documented before unblinding to confirm exclusion from analysis sets.

9.6 Handling of dropouts or missing data

In general, there will be no imputation of missing data. Handling of missing or partial dates and/or times for safety assessments will be described in the SAP.

9.7 Planned interim analysis and data monitoring

No formal interim analyses are planned for this study.

9.8 Determination of sample size

No formal statistical sample size calculation has been performed as this study constitutes a preliminary assessment of SC rozanolixizumab delivery by MP. The primary objective of the study is to evaluate the safety and tolerability of a [redacted] SC dose of rozanolixizumab administered to healthy participants by MP vs syringe driver. A total sample size of approximately 32 participants randomly assigned to study medication resulting in at least 6 evaluable participants per cohort is considered 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 IEC, as defined in local regulations, International Council for Harmonisation (ICH)-GCP, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

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

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

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

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

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

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

10.1.2 Financial disclosure

Insurance coverage will be handled according to local requirements.

Finance and insurance are addressed in the investigator and/or CRO agreements, as applicable.

10.1.3 Informed consent process

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

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

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

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

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

10.1.4 Data protection

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

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

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

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

10.1.5 Committees structure

An SMC will be implemented to review ongoing available study safety data according to the study design outlined in Section 4.1. The composition and operational conduct of the SMC will be detailed in the study SMC Charter. The principal investigator will participate in the decision

of continuing dosing of the remaining participants on each of these cohorts based on the safety data obtained from the sentinel participants dosing. The SMC will review all available safety/tolerability data in this study (including at a minimum; safety laboratory, vital signs, ECG, AE, any infusion-related reactions, and hypersensitivity reactions) and PK data as necessitated by the SMC to make recommendations as appropriate.

10.1.6 Data quality assurance

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

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

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

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

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

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

10.1.6.1 Electronic case report form completion

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

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

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

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

Detailed instructions will be provided in the eCRF Completion Guidelines.

10.1.7 Source documents

All source documents must be accurate, clear, unambiguous, permanent, and capable of being audited. They should be made using some permanent form of recording (ink, typing, printing,

optical disc). They should not be obscured by correction fluid or have temporary attachments (such as removable self-stick notes).

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

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

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

10.1.8 Study and site closure

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

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

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

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

10.1.9 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 participants are detailed in Section 5.1 and Section 5.2 of the protocol, respectively.

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 Indices: MCV MCH %Reticulocytes	Coagulation: INR prothrombin time activated partial thromboplastin time fibrinogen	WBC Count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	RBC Count			
	Hemoglobin			
	Hematocrit			
Clinical Chemistry[a]	Blood Urea Nitrogen	Potassium	AST/Serum Glutamic-Oxaloacetic Transaminase	Total Protein
	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	
		Phosphate	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			
Stool sampling volume[b]	• Occult blood, microscopy, culture, and lactoferin			
CSF[c]	• Cell count, Gram staining, culture, protein, glucose, exploratory biomarkers			
Immunology[d]	• Complements and cytokines			

Laboratory Assessments	Parameters
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) • Serology (Hepatitis B surface antigen, hepatitis B core antibody [both immunoglobulins G and M], hepatitis C virus antibody, and human immunodeficiency virus 1 and 2 antibody) • Tuberculosis test • Screening for influenza, tetanus, and SARS-CoV-2 vaccinations/antibodies to previous SARS-CoV-2-infection • 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; INR=International Normalized Ratio; LDL=low-density lipoprotein; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; RBC=red blood cell; 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 1.1 and Appendix 6 (Section 10.6). All events of ALT ≥3×ULN and bilirubin ≥2×ULN (>35% direct bilirubin) or ALT ≥3×ULN and INR >1.5, if INR measured, may indicate severe liver injury (possible Hy's Law) and must be reported as a serious adverse event (excluding studies of hepatic impairment or cirrhosis).

[b] Only for study participants with moderate or severe diarrhea (1 sample per episode of diarrhea).

[c] 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).

[d] In study participants who experience an infusion reaction within the first 4 hours after dosing, a sample should be taken at 4 and 8 hours post event. Additionally, sampling is taken in case of a suspected hypersensitivity event or any clinical indication of an unexpected immune response.

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

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

10.3.1 Definition of AE

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

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

10.3.2 Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Important medical events: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include, but are not limited to, potential Hy's law, invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Recording and follow-up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to UCB in lieu of completion of the UCB/AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by UCB. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to UCB.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

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

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

Assessment of Causality

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

Follow-up of AEs and SAEs

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

10.3.4 Reporting of SAEs

SAE Reporting to UCB via an Electronic Data Collection Tool

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

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

10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

10.4.1 Definitions

10.4.1.1 Woman of childbearing potential

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

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

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

   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, a single follicle-stimulating hormone 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.

10.4.2 Contraception guidance

10.4.2.1 Male participants

Male participants with female partners of childbearing potential (including partners who are pregnant or breastfeeding) must use contraception if any of the following criteria are met:

- Genotoxic study medication
- Study medication where reproductive toxicology studies have not yet been conducted
- Study medication with demonstrated or suspected human teratogenicity/fetotoxicity at subtherapeutic exposure levels if relevant systemic concentrations may be achieved in WOCBP from exposure to seminal fluid

Male participants with female partners of childbearing potential are eligible to participate if they agree to 1 of the following (during the protocol-defined time frame in Section 5.1):

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.
- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in the table below when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

In addition, male participants must refrain from donating sperm for the duration of the study and for 3 months after the end of the study.

Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame.

10.4.2.1.1 Female participants

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

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
• Implantable progestogen only hormonal contraception associated with inhibition of ovulation[c] • Intrauterine device • Intrauterine hormone-releasing system • 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 women of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study medication. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

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

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

[c] Hormonal contraception may be susceptible to interaction with the study medication, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the treatment period and for at least 30 days after the end of the study.

10.4.2.2 Pregnancy testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test. Additionally, WOCBP with an implant or an intrauterine device (who may not have menstrual periods) can be included if the method of contraception is documented, used for more than 28 days (if no confirmed menstrual period), and they have a negative serum pregnancy test.

- Additional serum pregnancy testing should be performed on Day 29 and Day 57 and as required locally.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- Serum pregnancy testing, with a sensitivity of 25 mIU/mL will be performed.

10.4.2.3 Collection of pregnancy information

10.4.2.3.1 Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study medication. If the study participant is later found to be on placebo, then pregnancy data collection can stop.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be at least 12 months after the delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

10.4.2.3.2 Female participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, the follow-up will be at least 12 months after the delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study medication by the investigator will be reported to the sponsor as described in Section 8.3.5. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.

10.5 Appendix 5: Genetics

Not applicable

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

Participants with potential drug-induced liver injury must be assessed. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued.

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

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

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

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

Decisions concerning which assessments should be performed are to be made by the Principal Investigator (or delegate). A hepatologist may be consulted if deemed necessary by the investigator.

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

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

Required Actions and Follow-up Assessments	
Actions	**Follow-Up Assessments**
• **Immediately** discontinue study intervention • Report the event to UCB **within 24 hours** • Complete the liver event eCRF, and complete an SAE data collection tool if the event also met the criteria for an SAE[b] • Perform liver function follow-up assessments • Monitor the participant until liver function test abnormalities resolve, stabilize, or return to baseline (see **MONITORING**) • Consider the need for a toxicology screening. **MONITORING:** **If ALT ≥3xULN AND bilirubin ≥2xULN or INR >1.5** • Repeat liver function tests (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver function follow-up assessments within **24 hours.** • Monitor participant twice weekly until liver function test abnormalities resolve, stabilize, or return to baseline. • A specialist or hepatology consultation is recommended. **If ALT ≥3xULN AND bilirubin <2xULN and INR ≤1.5:** • Repeat liver function tests (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver function follow-up assessments within **24 to 72 hours** • Monitor participants weekly until liver function abnormalities resolve, stabilize, or return to baseline	• Viral hepatitis serology[c] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Obtain blood sample for pharmacokinetic (PK) analysis within 2 days after the most recent dose[d] • Serum creatine phosphokinase and lactate dehydrogenase • Fractionate bilirubin, if total bilirubin ≥ 2xULN • Complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury (eg, fatigue, nausea, vomiting, right upper quadrant pain), or hypersensitivity, on the AE eCRF • Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications eCRF • Record alcohol use on the liver event alcohol intake eCRF **If ALT ≥3xULN AND bilirubin ≥2xULN 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 high performance liquid chromatography assay (quantifies potential acetaminophen contribution to liver injury in participants with

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

Liver Chemistry Stopping Criteria – Liver Stopping Event	
ALT-absolute	ALT ≥3×ULN If ALT ≥3×ULN AND bilirubin ≥2×ULN (>35% direct bilirubin) OR INR >1.5, report as an SAE[a,b] See additional actions and follow-up assessments listed below
Required Actions and Follow-up Assessments	
Actions	**Follow-Up Assessments**
	definite or likely acetaminophen use in the preceding week [James et al, 2009]) **NOTE: Not required in China**. • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete liver imaging and/or liver biopsy eCRFs

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; eCRF=electronic case report form; HBsAg=hepatitis B surface antigen; HBcAb=hepatitis B core antibody; IgG=immunoglobulin G; IgM=immunoglobulin M; INR=International Normalized Ratio; 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. If serum bilirubin fractionation is not immediately available, discontinue study intervention if ALT ≥3xULN. Additionally, if serum bilirubin fractionation testing is unavailable, record the absence/presence of detectable urinary bilirubin on dipstick which is indicative of direct bilirubin elevations suggesting liver injury.

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

[c] 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.

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

10.7 Appendix 7: Medical device AEs, ADEs, SAEs, and device deficiencies: definition and procedures for recording, evaluating, follow-up, and reporting

Not applicable

10.8 Appendix 8: Rapid alert procedures

The aim of the Rapid Alert process is to stop the exposure to the study medication or concerned study procedure as soon as possible, following a confirmed or suspected safety issue, preventing its reoccurrence in other study participants. Upon occurrence of an SAE and/or another safety event including stopping rules for all cohorts which may constitute a study hold criteria, irrespective of its relationship with the study medication or the study conduct, the **investigator must notify the study sponsor as soon as possible** (ideally within 2 hours of becoming aware of the event) by the following process:

1. A phone call to the Study Physician to alert them a safety event has been identified.
2. If the investigator is not able to reach the Study Physician, they should call the 24h rapid response helpline number. Upon receipt of a call from an investigator, the 24/7 helpline will contact a physician from UCB who will return the call to the investigator.
3. Additionally, send a completed "Investigator (S)AE Report Form for Development Drug (For Rapid Alert Studies)" to the fax/email for Rapid Alert provided at the front of the protocol. The form should include assessed seriousness, severity, and causality and should be filed in the Study Investigator's File.

   Both the phone call and the completed form from the investigator are crucial in assessing the safety of the study medication and in determining whether the event requires immediate action to place the study on hold and/or expedite reporting to the regulatory authorities. The (S)AE form should be completed in English and provided even if the data are incomplete, or if it is obvious that more data will be needed in order to draw any conclusions about the diagnosis or causality. Additional information (eg, laboratory reports) received by the investigator must be provided within 24 hours. All documents in the local language must be accompanied by a translation in English, or the relevant information included in the same document must be summarized in English in the (S)AE form.

During the call between the investigator and the UCB physician the safety issue will be discussed to determine if there is sufficient evidence to declare a protocol hold criteria has been met. If the investigator and UCB physician agree a stopping a criterion has not been met, dosing of the study may continue as per the study protocol and the discussion between the investigator and the UCB physician should be documented. UCB will not downgrade the investigator decision to halt the study if the investigator considered that a stopping criterion has been fulfilled.

In all other circumstances, the investigator will be instructed to suspend dosing and the UCB physician will arrange an urgent, internal UCB Rapid Alert Team meeting. The Rapid Alert Team will review the information provided at the call along with the (S)AE form to determine whether or not a protocol hold criterion has been met. If it is determined the criterion has not been met, UCB will contact the investigator and inform them to recommence dosing. If it is determined a hold criterion has been met, UCB will contact all investigators and notify them of the formal hold.

If the investigator believes a protocol stopping criterion has been met, and they are unable to contact UCB prior to the next dose being due, they should postpone any further dosing until they

have obtained feedback from UCB. In these circumstances dosing may be restarted if UCB and the investigator subsequently agree that no stopping criteria have been met.

10.9 Appendix 9: Country specific requirements

Not applicable

10.10 Appendix 10: Abbreviations and trademarks

ADA	anti-drug antibody
ADE	adverse device effect
ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
$AUC_{(0-t)}$	area under the concentration-time curve from 0 to time t;
AUC(IgG)	area under the Total IgG-time curve
BP	blood pressure
CSF	cerebrospinal fluid
C_{max}	maximum plasma concentration
COVID-19	coronavirus disease-19
CRO	contract research organization
CT	computed tomography
ECG	electrocardiogram
eCRF	electronic Case Report form
FcRn	neonatal Fc receptor
GCP	Good Clinical Practice
HDL	high-density lipoprotein
HRT	hormonal replacement therapy
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
ICF	informed consent form
IgG	immunoglobulin G
IMP	investigational medicinal product
ISRQ	injection site reaction questionnaire
ITP	immune thrombocytopenia
LDL	low-density lipoprotein
LLOQ	lower limit of quantification

MG	myasthenia gravis
MP	manual push
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
QTc	corrected QT
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous(ly)
SMC	Safety Monitoring Committee
SIAQ	self-injection assessment questionnaire
TB	tuberculosis
TEAE	treatment-emergent adverse event
t_{min}	time to minimum IgG level
ULN	upper limit of normal
WOCBP	woman of childbearing potential

10.11 Appendix 11: Protocol amendment history

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

Amendment 1 (16 Mar 2021)

Overall Rationale for the Amendment

The primary reason for this protocol amendment is to incorporate the changes requested by the Medicines & Healthcare products Regulatory Agency to the original protocol.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, Overall design 4.1 Overall design	The text "with application of the Cohort 1 stopping rule (see Section 6.7)" has been deleted.	Dosing must be halted if any of the stopping criteria are observed in any of the study cohorts and not only if observed in Cohort 1.
1.3 Schedule of activities	Table 1.1: Schedule of activities: The row for "Medical history" has been deleted.	The medical history assessment is captured in the "Medical/procedure history" assessment, and therefore this was a duplicated assessment.
2.3 Benefit/risk assessment	The text has been updated to reflect that the stopping rules are applicable to all cohorts.	Dosing must be halted if any of the stopping criteria are observed in any of the study cohorts and not only if observed in Cohort 1.
5.1 Inclusion criteria	Inclusion criterion #8: This criterion has been updated to clarify that woman of childbearing potential must follow contraceptive guidance for at least 90 days after the final dose of investigational medicinal product (IMP).	To ensure the duration of contraception after the last dose of IMP in case of early termination.
5.4 Screen failures	Updated to clarify that repeat laboratory screening tests are not restricted to those that were out-of-range. In addition, a time frame for the repeat assessments has been added.	To clarify that the repeat (visit) should be planned within the time frame of 28 days between the initial screening day and Day 1 prior to dosing.
6.3.1.2 Breaking the treatment blind in an emergency situation	Clarified that the unblinding procedure in case of an emergency is performed by the investigator.	The responsibility to break the treatment code in emergency situations resides solely with the investigator.

Section # and Name	Description of Change	Brief Rationale
6.7.1 Stopping rules for all cohorts	The title and text have been updated to reflect that the stopping rules are applicable to all cohorts. In addition, it has been clarified that further dosing is suspended if any of the stopping criteria are met.	Dosing must be halted if any of the stopping criteria are observed in any of the study cohorts and not only if observed in Cohort 1.
10.1.5 Committees structure	Updated to include the following sentence: "The principal investigator will participate in the decision of continuing dosing of the remaining participants on each of these cohorts based on the safety data obtained from the sentinel participants dosing."	The UCB Safety Monitoring Committee (SMC) core members includes not only UCB members but also the principal investigator
10.8 Appendix 8: Rapid alert procedures	Updated to clarify the sponsor will not downgrade the investigator decision to halt the study if the investigator considered that a stopping criterion has been fulfilled. In addition, it has been clarified that the stopping rules are applicable to all cohorts.	The investigator is responsible for all study-related medical decisions. Dosing must be halted if any of the stopping criteria are observed in any of the study cohorts and not only if observed in Cohort 1.

10.12 Appendix 12: Suggested management guidelines for infusion reactions

Type of reaction	Sponsor recommendations for management
Acute – Mild eg, flushing, dizziness, headache, sweating, palpitations, nausea	• Stop infusion. • Infuse 0.9% sodium chloride 500-1000mL/h IV. • Administer antihistamine IV/IM. • Administer paracetamol 1g orally. • Monitor vital signs every 10 minutes until back to Baseline. In case all infusion reaction signs and symptoms have resolved and investigator considers infusion restart clinically appropriate, the infusion can be restarted; the [redacted].
Acute – Moderate eg, flushing, chest tightness, dyspnea, hypo/hypertension (change >20mmHg in systolic blood pressure), raised temperature, palpitations, urticaria	• Stop infusion. • Infuse 0.9% sodium chloride 500-1000mL/h IV. • Administer antihistamine IV/IM. • Administer paracetamol 1g orally. • Monitor vital signs every 5 minutes until back to Baseline.
Acute – Severe eg, hypo/hypertension (change >40mmHg in systolic blood pressure), raised temperature with rigors, chest tightness, dyspnea with wheezing, stridor	• Stop infusion. • Alert crash team. • Maintain airway, ensure oxygen is available. • If wheezing, give epinephrine 0.5mg IM (0.5mL 1:1000 epinephrine). • Administer antihistamine IV/IM. • Administer corticosteroids IV. • Monitor vital signs every 2 minutes until back to Baseline.

IM=intramuscularly; IV=intravenous; MP=manual push

10.13 Appendix 13: Management of anaphylaxis

Anaphylaxis is highly likely when any of the following 3 criteria is 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 less than 90mmHg or greater than 30% decrease from that person's Baseline.

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SPONSOR DECLARATION

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

Approval Signatures

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Version: 1.0

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