AN OPEN-LABEL, RANDOMIZED, PARALLEL-GROUP, SINGLE-DOSE BIOEQUIVALENCE STUDY OF BIMEKIZUMAB GIVEN AS 1X2ML OR 2X1ML SUBCUTANEOUS INJECTION USING AN AUTOINJECTOR IN HEALTHY STUDY PARTICIPANTS

PROTOCOL UP0119 AMENDMENT 1

PHASE 1

SHORT TITLE:

A bioequivalence study of bimekizumab administered as 1x2mL or 2x1mL subcutaneously in healthy study participants.

Sponsor:
UCB Biopharma SRL
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1070 Brussels
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Regulatory agency identifying number(s):

Eudra CT Number:	2021-005334-41
IND Number	128707

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History		
Document	**Date**	**Type of amendment**
Amendment1	21 Mar 2022	Substantial
Original Protocol	23 Nov 2021	Not applicable

Amendment 1 (21 Mar 2022)

Overall Rationale for the Amendment

This amendment addresses recommendations from the Standing Committee on Vaccination for the provision of COVID-19 documentation at Screening for study participants in Germany. Corrected section headings and implemented terminology to align with changes in adverse device effect language that have been implement in the protocol template. Additional changes include clarification of body weights for pairing of study participants, clarification of exclusion criteria, clarification of footnotes in the Schedule of activities, and clarification of names of central laboratories.

Section # and name	Description of change	Brief rationale
1.1 Synopsis, 4.1 Overall design, and 6.3 Measures to minimize bias: randomization and blinding	Clarified that body weights in each pair should differ by ≤10kg and that ideally the participant's body weight at admission (Day -1) should be used for pairing	Clarification
1.3 Schedule of activities	Corrected footnote j to clarify the HBc-Ab sample included both IgG and IgM	Correction
2.3.1 Risk assessment for coronavirus disease 2019 And 5.3.4 Other restrictions	Added requirement for documentation of COVID-19 vaccination at Screening for study participants in Germany	Addition
5.2 Exclusion criteria	Renumbered criterion 23 as 23a, clarified alcohol equivalent volume, removed examples	Clarification
8.3.7 Medical device – adverse device effects and device presentation deficiencies and 11 References	Corrected publication year of ISO 14155 to reflected updated version	Correction
8.3.7 Medical device – adverse device effects and device presentation deficiencies and subsections	Corrected section headings and terminology to align with changes in adverse device effect language in template	Correction

8.4 Safety signal detection	Added terminology to align with changes in adverse device effect language in template	Addition
Section 10.2 Appendix 2: Clinical laboratory tests	Clarified names of central laboratories performing laboratory tests	Clarification
Section 10.7 Appendix 7: Medical device presentation ADEs and Device Deficiencies: – definition and procedures for recording, evaluating, follow up, and reporting and subsections	Corrected section headings and terminology and deleted subsections to align with changes in adverse device effect language in template	Correction

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
Fax	**Europe and Rest of the World:** +32 2 386 24 21
Email	**Global:** DS_ICT@ucb.com

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

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

Reporting of device deficiencies (24h)	
Email	**Global:** qactscomplaints@ucb.com

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol title:

An open-label, randomized, parallel-group, single-dose bioequivalence study of bimekizumab given as 1x2mL or 2x1mL subcutaneous injection using an autoinjector in healthy study participants.

Short Title:

A bioequivalence study of bimekizumab administered as 1x2mL or 2x1mL subcutaneously in healthy study participants.

Rationale:

The bimekizumab 320mg dose was assessed in Phase 3 psoriasis [PSO] studies and was approved in the European Union (EU) on 20 Aug 2021 for the treatment of moderate to severe PSO. Currently, the dose is administered as 2x1mL subcutaneous (sc) injections of 160mg. To provide additional options to healthcare professionals and patients, it is considered of benefit by UCB to develop bimekizumab 320mg device presentations (ie, functional secondary packaging) where the dose can be delivered as a single 2mL sc injection. The primary objective of this study is, therefore, to compare the pharmacokinetics (PK) of bimekizumab 320mg when administered sc using a 2mL auto-injector (AI; bimekizumab-AI-2mL, test) versus 2x1mL auto-injector (bimekizumab-AI-1mL, reference) to support the development of the 2mL AI device presentation.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare the PK of a single sc dose of BKZ when administered using the bimekizumab-AI-2mL presentation (test) versus the bimekizumab-AI-2x1mL presentation (reference) in healthy study participants	• AUC, $AUC_{(0-t)}$, C_{max}
Secondary	
• To assess the safety and tolerability of a single sc dose of BKZ when administered using the bimekizumab-AI-2x1mL or bimekizumab-AI-2mL presentation in healthy study participants	• TEAEs and treatment-emergent SAEs
• To assess additional PK parameters of a single sc dose of BKZ when administered using the bimekizumab-AI-2x1mL or bimekizumab-AI-2mL presentation in healthy study participants	• $t_{½}$, t_{max}
Other/exploratory	
• To assess additional PK parameters of a single sc dose of BKZ when administered using the bimekizumab-AI-2x1mL or bimekizumab-AI-2mL presentation in healthy study participants	• $\%AUC_{ex}$, CL/F, V_z/F
• To assess immunogenicity of a single sc dose of BKZ when administered using the bimekizumab-AI-2x1mL or bimekizumab-AI-2mL presentation in healthy study participants	• Incidence of BKZ antidrug antibodies
• To assess additional safety and tolerability of a single sc dose of BKZ when administered using the bimekizumab-AI-2x1mL or bimekizumab-AI-2mL presentation in healthy study participants	• Vital signs (pulse rate, BP, and tympanic body temperature) • Safety laboratory data (hematology [including coagulation/hemostasis tests], clinical chemistry, and urinalysis) • 12-lead ECG assessments

AI=autoinjector; AUC=area under the plasma concentration-time curve from time zero to infinity; $\%AUC_{ex}$=percentage of the AUC extrapolated from C_{last}; $AUC_{(0-t)}$=area under the plasma concentration-time curve from time zero to the last quantifiable concentration; BKZ=bimekizumab; BP=blood pressure; CL/F=apparent total body clearance; C_{last}=last observed quantifiable plasma drug concentration; C_{max}=maximum observed plasma drug concentration; ECG=electrocardiogram; PK=pharmacokinetic; SAE=serious adverse event; sc=subcutaneous; TEAE=treatment-emergent adverse event; $t_{½}$=apparent terminal half-life; t_{max}=time of occurrence of C_{max}

Overall Design

This is a Phase 1, open label, randomized, parallel-group, single dose, 2-arm bioequivalence (BE) study to compare the PK of bimekizumab 320mg when administered as either a 1x2mL or 2x1mL sc injection in healthy male and female study participants using an AI presentation. The 2 arms will be:

1. Bimekizumab-AI-2mL (test)
2. 2xBimekizumab-AI-1mL (reference)

Number of Participants

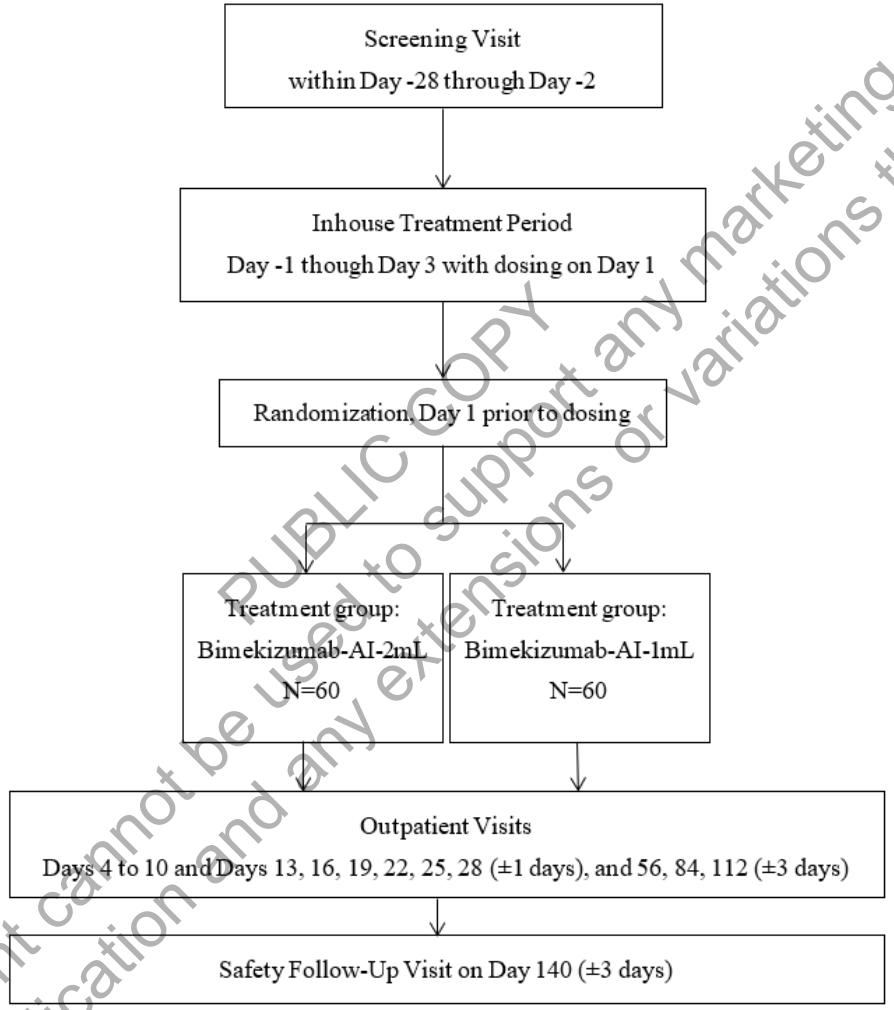
Assuming a dropout rate and nonevaluable study participants of approximately 10%, 60 study participants per group for a total of approximately 120 study participants are to be enrolled in the study. Study participants who withdraw from the study may be replaced at the discretion of the Investigator and Sponsor. Any replacement must match the gender and weight (≤10kg difference between the 2 participants) of the remaining participant being replaced and receive the same treatment as the participant being withdrawn from treatment.

Treatment Groups and Duration

Each study participant will receive a single-dose administration of bimekizumab 320mg administered sc either using a single 2mL AI (bimekizumab-AI-2mL, test) or two 1mL AIs (bimekizumab-AI-1mL, reference). The duration of the study will be approximately 168 days, including 27 days of Screening, admission on Day -1, an inhouse Treatment Period from Day 1 to Day 3, Outpatient Visits until Day 112, and a Safety Follow-Up (SFU) Visit on Day 140. Randomization will occur on Day 1 prior to dosing.

1.2 Schema

Figure 1-1: Study schematic



AI=autoinjector

1.3 Schedule of activities

Table 1-1: Schedule of study assessments overview

Assessments	Screening	Inhouse Treatment Period				Outpatient Visits			Early Withdrawal[a]/ SafetyFollow-Up/ Visits
		Day -1	Day 1						
	Day -28 to Day -2	Admission	Pre-dose	0 h	Day 1 postdose to Day 3 postdose	Days 4 to 10	Days 13, 16, 19, 22, 25, and 28 (±1 days)	Days 56, 84, 112 (±3 days)	Day 140 (±3 day)
Ambulatory (A)/inhouse (I) visit	A	I				A	A	A	A
Written informed consent	X								
Verification of inclusion/exclusion and withdrawal criteria	X	X	X						
Demographic data and lifestyle	X								
Medical/procedures history	X								
Urine drug and alcohol screen	X	X							
TB test (QuantiFERON®-TB GOLD PLUS)[b]	X								
TB questionnaire[a]	X								
Smoking habits/Fagerström test	X								
Randomization[c]			X						
Pre-visit COVID-19 questioning[d]		X					X	X	X
IMP administration[e]				X					
Physical examination[f]	X	X			X[f]	X[f]	X[f]	X[f]	X
Vital signs[g, h]	X	X	X		X	X[g]	X[g]	X	X
Body weight	X	X							X

Table 1-1: Schedule of study assessments overview

Assessments	Screening	Inhouse Treatment Period				Outpatient Visits			Early Withdrawal[a]/ SafetyFollow-Up/ Visits
	Day -28 to Day -2	Day -1	Day 1		Day 1 postdose to Day 3 postdose	Days 4 to 10	Days 13, 16, 19, 22, 25, and 28 (±1 days)	Days 56, 84, 112 (±3 days)	Day 140 (±3 day)
		Admission	Pre-dose	0 h					
Height	X								
12-lead ECG[h]	X	X	X		X	X	X	X	X
Prior and concomitant medication	X	X	X		X	X	X	X	X
Concomitant medical procedures	X	X	X		X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X
Device presentation deficiencies				X[i]					
Serology [j]	X								
SARS-CoV-2 RT-PCR[k]		X							
Hematology[l]	X	X			X	X	X	X	X
Clinical chemistry[l]	X	X			X	X	X	X	X
Coagulation/hemostasis[l]	X	X			X	X	X	X	X
Urinalysis (dipstick) [m]	X	X			X	X	X	X	X
Blood samples for BKZ plasma concentrations[n]			X		X	X	X	X	X
Blood samples for ADAbs[o]			X				X	X	X
Pregnancy test[p]	X	X					X	X	X
Follicle-stimulating hormone test[p]	X								

Table 1-1: Schedule of study assessments overview

Assessments	Screening	Inhouse Treatment Period				Outpatient Visits			Early Withdrawal[a]/ SafetyFollow-Up/ Visits
		Day -1	Day 1						
	Day -28 to Day -2	Admission	Pre-dose	0 h	Day 1 postdose to Day 3 postdose	Days 4 to 10	Days 13, 16, 19, 22, 25, and 28 (±1 days)	Days 56, 84, 112 (±3 days)	Day 140 (±3 day)

A=ambulatory; Ab=antibody; ADAb=antidrug-antibody; AE=adverse event; BKZ=bimekizumab; BP=blood pressure; COVID-19=coronavirus disease 2019; ECG=electrocardiogram; FSH=follicle stimulating hormone; h=hour; HBc-Ab=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HCV-Ab=hepatitis C virus antibody; HIV=human immunodeficiency virus; HIV1/2-Ab=HIV1/2 antibody; HIV1-Ag=HIV1 antigen; I=inhouse; IgG=immunoglobulin G; IgM=immunoglobulin M; IMP=investigational medicinal product; PK=pharmacokinetic(s); RT-PCR=real-time reverse transcriptase polymerase chain reaction; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; sc=subcutaneous; SFU=Safety Follow-Up; SOP=Standard Operating Procedure; TB=tuberculosis

Note: At the Investigator's discretion, an Unscheduled Visit may be completed at any time during the study but prior to the SFU Visit, if deemed necessary for the study participant's safety and well-being. The same assessments as performed on the SFU Visit, or alternatively as advised by the Investigator, should be performed if a study participant is attending an Unscheduled Visit during the study.

[a] If a study participant withdraws prior to completion of the study, an Early Withdrawal Visit will be conducted at the time of withdrawal and the same assessments planned for the SFU Visit will be performed.

[b] Refer to UCB g-q-100573 Tuberculosis Detection Procedure Guideline for details regarding TB infection status, detection procedures, and the related exclusion criteria.

[c] Randomization will occur prior to dosing on Day 1, provided all information for eligibility is known. The study identification card will be given to the study participant following IMP administration.

[d] Within 24 hours of the indicated visit study participants will be asked to record signs and symptoms of COVID-19 or any contact with persons having confirmed SARS-CoV-2 infection. In case of signs/symptoms or contact, the visit will be cancelled and reason for cancellation will be appropriately documented documented in the eCRF.

[e] Bimekizumab will be administered as a sc injection as detailed in Section 6.1

[f] A full physical examination will be performed at the Screening Visit, Day -1, and the Early Withdrawal/SFU Visit. On all other days (Days 2, 3, 9, 25, 56, 84, and 112) a physical examination is planned, it will be performed symptom-driven, ie, in case of an AE.

[g] Vital signs include BP, pulse rate, and tympanic body temperature. At outpatient visits without regular vital signs measurements, only tympanic body temperature will be collected. The number of readings to be collected will be determined by local SOPs at the sites.

[h] During the inhouse treatment period, vital signs and ECGs should be measured/taken prior to blood sampling, where applicable, with the study participant resting in the supine position for at least 3 minutes. Vital signs and ECGs will be measured on Day 1 at predose, at 1.5h, 5h, and 11h postdose, on Day 2 at 24h postdose, and on Day 3 at 48 hours postdose, then on Days 9, 25, 56, 84, 112, and 140.

[i] As this is a single-dose study, device presentation deficiencies are only to be captured on Day 1 (ie, the day when IMP is administered during the inhouse treatment period).

[j] Serology variables include HbsAg, HBc-Ab (both IgG and IgM), HCV-Ab, HIV1-Ab, HIV1-Ag, and HIV-2 Ab.

[k] The frequency of SARS-CoV-2 RT-PCR will be assessed in compliance site-specific procedures and local regulations.

[l] Blood sampling for hematology (including coagulation and hemostasis) and clinical chemistry will be performed at the Screening Visit, and Days -1, 2, 9, 25, 56, 84, 112, and the SFU Visit.

[m] Urinalysis via dipstick will be performed at Screening, Day-1, Days 2, 9, 25, 56, 84, 112, and 140.

[n] The PK sampling time points will be as follows: predose (within a maximum of 60 minutes prior to dosing), 1.5h, 5h, 24h, 48h postdose, and from Day 4 onwards at every visit (ie, Days 4 to 10, 13, 16, 19, 22, 25, 28, 56, 84, 112, and 140).

Table 1-1: Schedule of study assessments overview

Assessments	Screening	Inhouse Treatment Period				Outpatient Visits			Early Withdrawal[a]/ SafetyFollow-Up/ Visits
		Day -1	Day 1						
	Day -28 to Day -2	Admission	Pre-dose	0 h	Day 1 postdose to Day 3 postdose	Days 4 to 10	Days 13, 16, 19, 22, 25, and 28 (±1 days)	Days 56, 84, 112 (±3 days)	Day 140 (±3 day)

[o] ADAb samples will be taken predose and on Days 13, 28, 56, 84, 112, and 140; blood samples will be processed as specified in the laboratory manual. If feasible, an additional blood sample for PK and ADAb analysis should be collected from participants who develop a hypersensitivity reaction. The sample should be obtained close to the time of the event using an unscheduled visit if needed.

[p] Pregnancy tests will be performed at the Screening Visit, Day-1, Days 28, 56, 84, 112, and Day 140. Prior to dosing (at Screening and Day -1), the test should be performed in serum; post dosing the test may be performed in urine. The FSH test will be performed in postmenopausal women at the Screening Visit. Additional details are provided in Appendix 4 (Section 10.4).

Table 1-2: Study assessments from dosing Day 1 to Day 3, 48h after IMP administration

	Day 1						Day 2	Day 3
Assessments	**Predose**	**Dosing 0h**	**1.5h**	**3h**	**5h**	**11h**	**24h**	**48h**
Physical examination							X	X
Vital signs[a]	X		X		X	X	X	X
12-lead ECG	X		X		X	X	X	X
Hematology							X	
Clinical chemistry							X	
Coagulation/hemostasis							X	
Urinalysis (dipstick)							X	
IMP administration		X						
Blood samples for BKZ plasma concentrations	X [b]		X		X		X	X
Blood samples for ADAbs	X							
Concomitant medication	X		X	X	X	X	X	X
Concomitant medical procedures	X		X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X
Device presentation deficiencies		X[c]						

ADAb=antidrug antibody; BKZ=bimekizumab; ECG=electrocardiogram; h=hour; IMP=investigational medicinal product; SOP=standard operating procedure

[a] The number of readings to be collected will be determined by local SOPs at the sites.

[b] Within a maximum of 60 minutes prior to dosing.

[c] As this is a single-dose study, device presentation deficiencies are only to be captured on Day 1 (ie, the day when IMP is administered during the inhouse treatment period).

Table 1-3: Study assessments from Day 4 to 10 after IMP administration

Assessment	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
Physical examination						X	
Vital signs[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X	X[a]
12-lead ECG						X	
Hematology						X	
Clinical chemistry						X	
Coagulation/hemostasis						X	
Urinalysis (dipstick)						X	
Blood samples for BKZ plasma concentrations	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X
Concomitant medical procedures	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X

BKZ=bimekizumab; ECG=electrocardiogram; IMP=investigational medicinal product; SOP=standard operating procedure

[a] At outpatient visits without regular vital signs measurements, only tympanic body temperature will be collected. The number of readings to be collected will be determined by local SOPs at the sites.

Table 1-4: Study assessments from Day 13 to 140 after IMP administration

Assessment	Day 13	Day 16	Day 19	Day 22	Day 25	Day 28	Day 56	Day 84	Day 112	Day 140
Pre-visit COVID-19 questioning[a]	X	X	X	X	X	X	X	X	X	X
Physical examination					X		X	X	X	X
Vital signs[b]	X[b]	X[b]	X[b]	X[b]	X	X[b]	X	X	X	X
Body weight										X
12-lead ECG					X		X	X	X	X
Hematology					X		X	X	X	X
Clinical chemistry					X		X	X	X	X
Coagulation/hemostasis					X		X	X	X	X
Urinalysis (dipstick)					X		X	X	X	X
Urine pregnancy test						X	X	X	X	X
Blood samples for BKZ plasma concentrations	X	X	X	X	X	X	X	X	X	X
Blood samples for ADAbs	X					X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X
Concomitant medical procedures	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X

ADAb=antidrug antibody; BKZ=bimekizumab; COVID-19=coronavirus disease 2019; ECG=electrocardiogram; eCRF=electronic Case Report form; IMP=investigational medicinal product; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SOP=standard operating procedure

[a] Within 24 hours of the indicated visit study participants will be asked to record signs and symptoms of COVID-19 or any contact with persons having confirmed SARS-CoV-2 infection. In case of signs/symptoms or contact, the visit will be cancelled and reason for cancellation will be appropriately documented in the eCRF.

[b] At outpatient visits without regular vital signs measurements, only tympanic body temperature will be collected. The number of readings to be collected will be determined by local SOPs at the sites.

2 INTRODUCTION

Bimekizumab is a humanized, full-length monoclonal antibody (mAb) of immunoglobulin G1 (IgG1) subclass with 2 identical antigen binding regions that selectively binds with high affinity to interleukin (IL)-17A, IL-17F, and IL-17AF cytokines. This property makes bimekizumab distinctly different from the other IL-17-targeting agents, like secukinumab and ixekizumab (selective anti-IL-17A cytokine targeting mAb) or brodalumab (anti-IL-17 receptor targeting mAb). Bimekizumab-SS-1ml and bimekizumab-AI-1ml device presentations were approved in the EU on 20 Aug 2021 and the United Kingdom on 25 Aug 2021 for the treatment of moderate to severe PSO.

Antibodies targeting IL-17A cytokines have demonstrated efficacy in study participants with psoriatic arthritis (PsA), axial spondyloarthritis (axSpA), and hidradenitis suppurativa (HS) and parallel development programs in these inflammatory diseases are ongoing.

As of the current Investigator's Brochure (IB) clinical cutoff date of 23 Oct 2021, the following studies with bimekizumab have been completed:

- First-in-human study UP0008
- Bioavailability studies RA0124 and UP0031
- Phase 1 studies PA0007, UP0042, UP0033, UP0034, and UP0074
- Phase 2 studies PS0018 (open-label extension [OLE] of PS0016), and HS0001
- Phase 2a studies RA0123, UC0011 (discontinued study), PS0016, and AS0013
- Phase 2b studies PS0010, PS0011 (OLE of PS0010), PA0008, PA0009, and AS0008
- Phase 3 studies PS0008, PS0009, PS0013, DV0002, and DV0006

The ongoing and planned studies with bimekizumab, as well as additional information on the clinical and nonclinical data for bimekizumab are available in the current version of the IB.

2.1 Study rationale

The bimekizumab 320mg dose was assessed in Phase 3 psoriasis [PSO] studies and was approved in the EU on 20 Aug 2021 for the treatment of moderate to severe PSO. Currently, the dose is administered as 2x1mL sc injections of 160mg. To provide additional options to healthcare professionals and patients, it is considered of benefit by UCB to develop bimekizumab 320mg device presentations (ie, functional secondary packaging) where the dose can be delivered as a single 2mL sc injection. The primary objective of this study is, therefore, to compare the PK of bimekizumab 320mg when administered sc using a 2mL AI (bimekizumab-AI-2mL, test) versus 2x1mL AI (bimekizumab-AI-1mL, reference) to support the development of the 2mL AI device presentations.

2.2 Background

UCB is currently developing 4 self-injection, single-use, device presentations, including two 1mL presentations (bimekizumab-SS-1mL and bimekizumab-AI-1mL) and two 2mL presentations (bimekizumab-SS-2mL and bimekizumab-AI-2mL), to provide study participants with multiple needle-safe self-injection options. The bimekizumab-SS-1mL and the bimekizumab-SS-2mL device presentations provide study participants with control over the self-injection process (eg, needle visibility, skin penetration by needle, control speed of self-injection) while the bimekizumab-AI-1mL and the bimekizumab-AI-2mL device presentations provide study participants with a more automated self-injection.

Clinical use substudies demonstrated that study participants with moderate to severe chronic PSO (DV0002 and DV0006) could self-inject bimekizumab across all 4 device presentations (bimekizumab-SS-1mL, bimekizumab-AI-1mL, bimekizumab-SS-2mL, and bimekizumab-AI-2mL) in a safe and effective manner. The bimekizumab-SS-1mL and bimekizumab-AI-1mL presentations were approved in the EU on 20 Aug 2021 for the treatment of moderate to severe PSO.

UP0033 (EudraCT number: 2017-004403-48) was a single-dose healthy participant study that investigated the PK of bimekizumab-SS-1mL (test 1; P5 drug substance) or bimekizumab-AI-1mL (test 2; P5 drug substance) in comparison to the PK of bimekizumab 320mg when administered sc with the bimekizumab-True North (TN; reference; P4 drug substance). Bioequivalence was demonstrated across device presentations and an acceptable safety profile was demonstrated.

UP0068 (UP0068-EudraCT number: 2019-002378-30) was a single-dose healthy participant BE study that investigated the PK of bimekizumab 320mg when administered sc using the bimekizumab-SS-2mL presentation (test 1) versus the bimekizumab-SS-1mL presentation (reference 1) or the bimekizumab-AI-2mL presentation (test 2) versus the bimekizumab-AI-1mL presentation (reference 2). This study was closed prematurely, prior to enrollment of all study participants, due to coronavirus disease 2019 (COVID-19) and several lock-downs that delayed recruitment. BE was demonstrated for the 2mL SS but the sponsor was not able to conclude that BE was demonstrated for the 2mL AI device.

UP0119 is an open-label, randomized, parallel-group, single-dose BE study of bimekizumab given as 1x2ml or 2x1ml sc injection in healthy study participants using the bimekizumab-AI-2mL presentation (test) versus the bimekizumab-AI-2x1mL presentation (reference).

2.3 Benefit/risk assessment

Participation in this study does not have any therapeutic benefit for the healthy study participants. Healthy study participants will benefit from complete health check-ups and regular routine blood tests throughout the course of the study. Nonetheless, the participation of healthy study participants in the study is of importance to the patients and the development of the bimekizumab-AI-2mL for administration of bimekizumab. Currently, bimekizumab 320mg is administered as 2x1mL sc injections; therefore, UCB considers it a beneficial option for healthcare professionals and patients to administer bimekizumab 320mg as a single 1x2mL sc injection.

Healthy study participants who participate in this study may be exposed to the:

- Risks of the study procedures
- Known and unknown risks related to the exposure to the IMP

Procedure-related risks

The use of an indwelling cannula for blood sampling may be accompanied by mild bruising and in rare cases, by transient inflammation of the wall of the vein. After initial irritation, the presence of an indwelling cannula is usually painless and hardly noticeable. The same applies to vein puncturing for further blood sampling. In very rare cases, a nerve might be injured while inserting the cannula. This could be followed by paresthesia, reduced sensitivity, and/or pain.

The total volume of blood drawn during the entire study per study participant is estimated at approximately 450mL. No health-related risk to healthy study participants is expected from this blood withdrawal.

Drug-related risks and safety measures

Bimekizumab has a generally favorable clinical safety profile, and the drug is not associated with serious adverse events (SAEs) that would suggest a high risk to study participants in this study.

The main safety concerns associated with bimekizumab include an increase in the risk for infection, in particular nonserious upper respiratory tract infections. Other types of nonserious infections (gastrointestinal, ear infection, conjunctivitis, bronchitis, mucocutaneous fungal infections) have also been commonly reported. The risk to study participants in this study will be minimized by the enrollment of healthy adult study participants who will be exposed to bimekizumab 320mg, dosed only once, by the implementation of conservative eligibility criteria, and that all study participants will be screened for chronic infections, including tuberculosis (TB).

More detailed information about the known and expected benefits and risks and reasonably expected AEs of bimekizumab may be found in the current IB.

2.3.1 Risk assessment for coronavirus disease 2019

Bimekizumab is a humanized, full-length IgG monoclonal antibody, with high affinity for both human IL-17A and IL-17F. While the risk related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or COVID-19 is not yet fully researched, a safety concern cannot be excluded based on bimekizumab being an immunomodulatory antibody and dual inhibitor of 2 cytokines. Interleukin-17 is a family of pleiotropic pro-inflammatory cytokines released by

activated T cells in the epithelial mucosal barrier upon stimulation with IL-23, which is mainly secreted by activated dendritic cells, macrophages, or monocytes. Interleukin-17 is often associated with allergic responses and autoimmune diseases, such as psoriasis. Interleukin-17A and IL-17F are the best characterized members of the IL-17 family, and IL-17A and IL-17F seem to be differently expressed in different tissues. Interleukin-17 is pivotal in innate and adaptive immune reaction to bacterial and viral infection, but has controversial effects. Studies suggest that the infectious dose may act as a determining factor regarding the protective or pathologic role of IL-17 during viral infection and was associated with the exacerbated pathology following viral infections, such as Epstein Barr Virus in mice (Ohta et al, 2013). There is growing evidence that inhibition of IL-17 might be beneficial in patients with COVID-19 to reduce the cytokine storm that causes the acute respiratory distress syndrome and vascular destruction, and studies are currently being conducted with other IL-17 inhibitors to investigate a potential beneficial effect.

Based on these assumptions, the study is feasible in the appropriate population of healthy study participants. The risk of the study participants to be exposed to SARS-CoV-2 or to suffer from COVID-19 will be acceptable in comparison to the general population. However, the risk of exposure to infected people cannot be completely excluded as the participants may need to share public spaces and communal areas with other members of the public (eg, commute to the site) and have additional human contact (eg, with site staff and other participants of the clinical study).

Measures to mitigate the additional risks caused by COVID-19 are:

- This study will start enrolling only when the Sponsor and contract research organization (CRO) in collaboration deem it is safe to start the study.
- Current national laws and local recommendations for prevention of pandemic will be strictly adhered to.
- In Germany, at the time of Screening, study participants must provide documentation of COVID-19 vaccination corresponding to the recommendation of the Standing Committee on Vaccination.
- Study participants will be closely monitored for any signs and symptoms of COVID-19, including fever, dry cough, dyspnea, sore throat, and fatigue throughout the study. Once clinical signs of infection are reported by participants, the Investigator needs to determine whether samples can be collected and safety data can be recorded on site. If not, AEs and concomitant medications will be obtained via phone calls. Tympanic body temperature measurements during inhouse stay and outpatient visits will be implemented.
- The Investigator will not dose participants upon identification of any signs of COVID-19 infection within the previous 14 days.
- Confirmation of COVID-19 by laboratory assessment will be conducted with approved tests: a SARS-CoV-2 real-time reverse transcriptase polymerase chain reaction (RT-PCR) will be conducted on admission and participants with a negative test will be randomized.
- The probability of virus transmission will be controlled as much as possible by:

- Advice for study participants to adhere to local requirements for social distancing and to minimize potential exposure to and/or transmission of the virus that causes COVID-19.
- All participants within 24 hours of the indicated visit will be questioned (as per the schedule of activities) for assessing COVID-19 symptoms and signs and will be asked not to attend the site in case of suspected infection. In addition, participants will be asked for any contact with a person who has tested positive for SARS-CoV-2. If applicable, participants will be referred to the local health care system for further follow up and treatment.
- Physical distancing and person-to-person contact restrictions will be applied during site admission and inhouse confinement.
- Personal protective equipment will be used by study participants (eg, surgical face mask, gloves) and staff (for example but not limited to masks, gloves, protectors, medical suits) as guided by local requirements.

Logistical improvements of the site and structural measures of the study site building were implemented to further improve physical distancing.

3 OBJECTIVES AND ENDPOINTS

Table 3-1: Objectives and estimands/endpoints

Objectives	Endpoints
Primary	
• To compare the PK of a single sc dose of BKZ when administered using the bimekizumab-AI-2mL presentation (test) versus the bimekizumab-AI-2x1mL presentation (reference) in healthy study participants	• AUC, $AUC_{(0-t)}$, C_{max}
Secondary	
• To assess the safety and tolerability of a single sc dose of BKZ when administered using the bimekizumab-AI-2x1mL or bimekizumab-AI-2mL presentation in healthy study participants	• TEAEs and treatment-emergent SAEs
• To assess additional PK parameters of a single sc dose of BKZ when administered using the bimekizumab-AI-2x1mL or bimekizumab-AI-2mL presentation in healthy study participants	• $t_{½}$, t_{max}
Other/exploratory	
• To assess additional PK parameters of a single sc dose of BKZ when administered using the bimekizumab-AI-2x1mL or bimekizumab-AI-2mL presentation in healthy study participants	• $\%AUC_{ex}$, CL/F, V_z/F
• To assess immunogenicity of a single sc dose of BKZ when administered using the bimekizumab-AI-2x1mL or bimekizumab-AI-2mL presentation in healthy study participants	• Incidence of BKZ antidrug antibodies
• To assess additional safety and tolerability of a single sc dose of BKZ when administered using the bimekizumab-AI-2x1mL or bimekizumab-AI-2mL presentation in healthy study participants	• Vital signs (pulse rate, BP, and tympanic body temperature) • Safety laboratory data (hematology [including coagulation/hemostasis tests], clinical chemistry, and urinalysis) • 12-lead ECG assessments

AI=autoinjector; AUC=area under the plasma concentration-time curve from time zero to infinity; $\%AUC_{ex}$=percentage of the AUC extrapolated from C_{last}; $AUC_{(0-t)}$=area under the plasma concentration-time curve from time zero to the last quantifiable concentration; BKZ=bimekizumab; BP=blood pressure; CL/F=apparent total body clearance; C_{last}=last observed quantifiable plasma drug concentration; C_{max}=maximum observed plasma drug concentration; ECG=electrocardiogram; PK=pharmacokinetic; SAE=serious adverse event ;sc=subcutaneous; TEAE=treatment-emergent adverse event; $t_{½}$=apparent terminal half-life; t_{max}=time of occurrence of C_{max}

4 STUDY DESIGN

4.1 Overall design

This is a Phase 1, open label, randomized, parallel-group, single dose, 2-arm BE study to compare the PK of bimekizumab 320mg when administered as either a 1x2mL or 2x1mL sc injection in healthy male and female study participants using an AI presentation. The 2 arms will be:

1. Bimekizumab-AI-2mL (test)
2. 2xBimekizumab-AI-1mL (reference)

The aim of this study is to demonstrate the BE of bimekizumab administered as either 1x2mL or 2x1mL sc injections using the bimekizumab-AI presentation in healthy study participants.

Approximately 120 healthy male and female study participants will participate at a maximum of 2 centers in the study (approximately 60 study participants in each of 2 arms). Enrollment between the 2 sites will be balanced, with an approximate 1:1 ratio. Each study participant will receive a single dose administration of bimekizumab 320mg, as either 1x2mL or 2x1mL sc injections.

Each eligible study participants will be matched with another participant for gender and body weight prior to randomization. The intention is that the body weights in each pair should differ by ≤10kg. Ideally, the participant's body weight at admission (Day -1) should be used for pairing. One participant within each pair will be randomly allocated to receive 1 of the 2 treatments; the other participant will be allocated to the other treatment.

The duration of the study will be approximately 168 days, including 27 days of Screening, admission on Day -1, an inhouse Treatment Period from Day 1 to Day 3, Outpatients Visits until Day 112, and a SFU Visit on Day 140. Randomization will occur on Day 1 prior to dosing.

4.2 Scientific rationale for study design

The study design for UP0119 is based on the recommendation of the guideline on the investigation of BE and the feedback received from the European Medicine Agency (EMA) in the Scientific Advice procedure EMEA/H/SA/3306/1/FU/1/2017/III (Sep 2017) on the 1mL device presentations and from FDA on the 1mL and 2mL device presentations (Aug 2017, Mar 2018, and Nov 2019). The parallel design was chosen with regard to the long half-life of bimekizumab of approximately 28 days.

UCB is currently developing 4 self-injection, single-use, device presentations, including two 1mL presentations (bimekizumab-SS-1mL and bimekizumab-AI-1mL) and two 2mL presentations (bimekizumab-SS-2mL and bimekizumab-AI-2mL), to provide study participants with multiple needle-safe self-injection options. The bimekizumab-SS-1mL and the bimekizumab-SS-2mL device presentations provide study participants with control over the self-injection process (eg, needle visibility, skin penetration by needle, control speed of self-injection) while the bimekizumab-AI-1mL and the bimekizumab-AI-2mL device presentations provide study participants with a more automated self-injection. The aim of this study is to demonstrate the BE of bimekizumab administered as either 1x2mL or 2x1mL sc injections using the bimekizumab AI in healthy study participants.

4.3 Justification for dose

The dose selected in this study was the dose used in the pivotal Phase 3 studies in PSO and is the approved dose in EU for the treatment of moderate to severe PSO.

4.4 End of study definition

A study participant is considered to have completed the study if he/she has completed all phases of the study including the Day 140 SFU Visit or the last scheduled procedure shown in the schedule of activities (Section 1.3).

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

5 STUDY POPULATION

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 years and ≤65 years of age inclusive, at the time of signing the informed consent.

Type of study participant

2. Study participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, vital signs, 12-lead electrocardiogram (ECG), and laboratory tests, during the Screening Period and on admission.
3. Study participant has a body temperature between 35.0°C and 37.5°C, inclusive, at Screening and on admission.

Weight

4. Body weight minimum of 50kg for male and 45kg for female study participants and a maximum of 100kg for all study participants, and body mass index (BMI) within the range 18 to 32kg/m^2 (inclusive) at the Screening Visit.

Sex

5. Male or female. Contraception guidelines (as per the standard UCB contraceptive guideline) will be applicable.
   - A male study participant must agree to use contraception as detailed in Appendix 4 (Section 10.4) of this protocol during the inhouse treatment period and for at least 20 weeks after the administration of study treatment, and refrain from donating sperm during this period.

- A female study participant is eligible to participate if she is not pregnant (see Appendix 4; Section 10.4), not breastfeeding, and at least one of the following conditions applies:
  - Not a woman of childbearing potential (WOCBP) as defined in Appendix 4 OR
  - A WOCBP who agrees to follow the contraceptive guidance in Appendix 4 during the inhouse treatment period and for a period of 20 weeks after the administration of IMP.

Informed consent

6. An Independent Ethics Committee (IEC)-approved written Informed Consent Form (ICF) is signed and dated by the study participant prior to the initiation of any study-specific assessment at the Screening Visit, as described in Appendix 1 (Section 10.1.3).

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 cardiovascular, respiratory, hepatic, renal, gastrointestinal (including inflammatory bowel disease), endocrinological, hematological, or neurological disorders constituting a risk when taking the study intervention; or interfering with the interpretation of data.
2. Study participant has any medical or psychiatric condition that, in the opinion of the Investigator, could jeopardize or would compromise the study participant's ability to participate in this study.
3. Study participant has a current history of alcohol or drug use disorder, as defined in Diagnostic and Statistical Manual of Mental Disorders (DSM) V, within the previous 1 year prior to the Screening Visit.
4. Study participant has a known hypersensitivity to any components of the bimekizumab (and/or an investigational device) as stated in this protocol.
5. Study participant has cardiovascular or cerebrovascular disease, including hypertension, angina, ischemic heart disease, transient ischemic attacks, stroke, peripheral arterial disease sufficient to cause symptoms, and/or requires therapy to maintain stable status.
6. Study participant has an active infection or history of infections as follows:
   - Any active infection (except common cold) within 14 days prior to Screening Visit
   - A serious infection, defined as requiring hospitalization or iv anti-infectives within 2 months prior to the Screening Visit
   - A history of opportunistic, recurrent, or chronic infections that, in the opinion of the Investigator, might cause this study to be detrimental to the study participant. Opportunistic infections are infections caused by uncommon pathogens (eg,

pneumocystis jirovicii, cryptococcosis) or unusually severe infections caused by common pathogens (eg, cytomegalovirus, herpes zoster).

7. Study participant has a history of a positive TB test or evidence of possible TB or latent TB infection at Screening Visit. Refer to g-q-100573 Tuberculosis Detection Procedure Guideline for details regarding TB infection status, detection procedures, and the related exclusion criteria.

Prior/Concomitant therapy

8. Study participants receiving any live (includes attenuated) vaccination within the 8 weeks prior to the Screening Visit (eg, inactivated influenza and pneumococcal vaccines are allowed, but nasal influenza vaccination is not permitted). Live vaccines are not allowed during the study or for 20 weeks after the last dose of the investigational medicinal product (IMP).
9. Past or intended use of prescription medication within 14 days or 5 half-lives prior to dosing. Specific medications listed in Section 6.5.1 may be allowed.
10. 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

11. Study participant has previously participated in this study or a study participant has previously been assigned to bimekuzimab treatment in any other study.
12. Exposure to 3 or more new chemical entities within 12 months prior to dosing.
13. Current enrollment or past participation within the last 30 days before signing the ICF in any other clinical study involving an investigational study intervention or any other type of medical research.

Diagnostic assessments

14. Study participant has concurrent acute or chronic viral hepatitis B or C or human immunodeficiency virus (HIV) infection. Study participants who have evidence of, or tested positive for hepatitis B or hepatitis C are excluded. A positive test for the hepatitis B virus (HBV) is defined as:
    - Positive for hepatitis B surface antigen (HBsAg+); or
    - Positive for anti-hepatitis B core antibody (HBc-Ab+) (IgM)

    A positive test for the hepatitis C virus (HCV) is defined as:
    - Positive for hepatitis C antibody (anti-HCV-Ab), and
    - Positive via a confirmatory test for HCV (for example, HCV polymerase chain reaction)
15. Study participant has any of the following hematology values at Screening Visit and Day -1:
    - For women, hemoglobin <10.5g/dL; for men, <13.0g/dL
    - Absolute neutrophil count $<1.5x10^9$/L

16. Study participant has alanine transaminase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) >1.0x upper limit of normal (ULN).
17. Study participant has total bilirubin >1.0xULN (isolated bilirubin <1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
18. Study participant has current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
19. Study participant has 12-lead ECG with changes considered to be clinically significant (eg, QT interval corrected using Fridericia's formula >450ms, bundle branch block, or evidence of myocardial ischemia) at Screening Visit or on Day -1.
20. Study participant has abnormal blood pressure (BP) at the Screening Visit and on Day -1 as follows: mean systolic BP ≥140mmHg; mean diastolic BP ≥90mmHg. Study participants with a BP within this range but who, in the opinion of the Investigator, have a high risk for cardiovascular accident based on, eg, family anamneses, smoking, BMI, or lipid spectrum can be excluded.

Other exclusions

21. Study participant has made a blood donation of a blood loss of more than 400mL of blood or blood products within 90 days prior to admission (Day -1) or plans to donate blood during the study.
22. Female study participant who is pregnant, or plans to become pregnant during the study, or lactating, or sexually active with childbearing potential who is not using a medically accepted birth control method (see Appendix 4).

23a. Study participant has an alcohol consumption of more than 21 units (males) or 14 units (females) of alcohol per week (1 unit of alcohol is equivalent to 12.5mL ethanol at room temperature).

24. Study participant tests positive for alcohol or drugs (urine test) at Screening or Day -1.
25. Study participant smokes >10 cigarettes per day or has a score of >4 on the Fagerström Test for Nicotine Dependence.
26. Study participant has a high consumption of xanthine-containing products (≥ 300mg of xanthine-equivalent per day) [1 cup of coffee ≈ 100mg of caffeine; 1 cup of tea ≈ 30mg of caffeine; 1 glass of cola ≈ 20mg of caffeine].
27. Study participant is not willing to avoid heavy physical exertion 48 hours before each assessment visit.
28. Vulnerable study participants (eg, participants kept in detention, protected adults under guardianship or trusteeship, and soldiers or participants committed to an institution by governmental or juridical order), employees of the Sponsor or the contract research organization (CRO) with direct involvement in the proposed study or other studies under the direction of the Investigator or the CRO, as well as family members of the employees or the Investigator.

29. Study participant has a positive test result for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in real-time reverse transcriptase polymerase chain reaction (RT-PCR) on the admission sample.
30. Study participant has clinical signs and symptoms consistent with COVID-19, 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.
31. Study participant who had severe course of COVID-19 (ie, hospitalization, extracorporal membrane oxygenation, mechanically ventilated).
32. Study participant has active neoplastic disease or history of neoplastic disease within 5 years of Screening Visit (except for basal or squamous cell carcinoma of the skin or carcinoma in situ that has been definitively treated with standard of care).

5.3 Lifestyle restrictions

5.3.1 Meals and dietary restrictions

No specific dietary restrictions are required.

5.3.2 Caffeine, alcohol, and tobacco

Study participants should refrain from consuming alcohol, caffeine, and tobacco during the inhouse treatment period.

5.3.3 Activity

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

5.3.4 Other restrictions

During a pandemic or other exceptional circumstance (eg, hurricanes) regulatory authorities accompanied by local or global regulations may implement safety measures and guidelines. In such situation site personnel and study participants may need to adhere and implement these safety measures.

Due to the exceptional circumstance of the evolving COVID-19 pandemic, study participants are advised to adhere to local requirements while ambulatory, to minimize potential exposure to and/or transmission of the virus that causes COVID-19.

In Germany, at the time of Screening, study participants must provide documentation of COVID-19 vaccination corresponding to the recommendation of the Standing Committee on Vaccination.

5.4 Screen failures

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

Individuals who do not meet the criteria for participation in this study (screen failures) may be rescreened (Section 5.5).

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

5.5 Rescreening

Per investigator discretion, 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.

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.

Rescreened study participants are assigned a new study participant number from the number assigned at the initial screening.

6 STUDY TREATMENTS/INVESTIGATIONAL DEVICE

In this study, the term IMP refers to the bimekizumab drug product. The term device presentation refers to 2 different injection device presentations (bimekizumab-AI-1mL and bimekizumab-AI-2mL) that are comprised of drug product (IMP) associated with a functional secondary packaging.

Bimekizumab will be supplied by UCB Clinical Trial Supply Operations or designee as a clear to opalescent, colorless to slightly yellow-brown, sterile, preservative-free solution, suitable for injection by sc administration, in either a 1mL prefilled syringe (PFS) or a 2mL PFS at a nominal concentration of 160mg/mL (55mM sodium acetate, 220mM glycine, 0.04% polysorbate 80 at pH 5.0) for sc administration.

6.1 Treatments administered

The treatments to be administered are presented in Table 6-1.

Table 6-1: UP0119 treatments administered

Study Treatment Name	Bimekizumab-AI-2mL	Bimekizumab-AI-1mL
Drug product:	2mL PFS	1mL PFS
	All treatments: a nominal formulation of 160mg/mL in 55mM sodium acetate, 220mM glycine and 0.04% (w/v) polysorbate 80 at pH5.0	
Total dose:	320mg	320mg
Duration of treatment:	Single dose	Single dose
Number of injections:	1x320mg	2x160mg
Route of administration:	sc	sc
Site of injection:	Thigh (left or right)	Thigh (1 in left and 1 in right)
Device:	2mL AI	1mL AI

AI=auto-injector; PFS=prefilled syringe; sc=subcutaneous

The IMP will be given in the thigh without massage. For bimekizumab-AI-1mL, the injection should continue until a second click is heard (to give an injection time of up to 15 seconds). For the administration of the 2x1mL, each sc injection should be given in a separate thigh (but at the same relative site of the thigh) with a maximum time of 60 seconds between injections. The exact timing of the injection(s) should be recorded in the electronic Case Report Form (eCRF). For bimekizumab-AI-2mL, the injection will take approximately up to 20 seconds until the second click is heard. After the second click, continue to hold down the AI for an additional 5 seconds to ensure the full dose is delivered.

Further details on how to proceed in the event of malfunction of any of the devices will be provided in the IMP handling manual.

6.1.1 Medical devices

All medical device presentation deficiencies, including malfunction use error, and inadequate labelling, shall be documented and reported by the Investigator throughout the study (see Section 8.3.7) and appropriately managed by the Sponsor.

6.1.1.1 Bimekizumab-AI-1mL

The bimekizumab-AI-1mL is a single-use AI with a passive needle-safety mechanism. The bimekizumab-AI-1mL consists of a 1mL glass PFS containing bimekizumab drug product within a customized Ypsomed Ypsomate device. This device presentation was approved in the EU on 20 Aug 2021.

Figure 6-1: Bimekizumab-AI-1mL

AI=auto-injector

6.1.1.2 Bimekizumab-AI-2mL

The bimekizumab-AI-2mL is a single-use AI with a passive needle-safety mechanism. The bimekizumab-AI-2mL consists of a 2.25mL glass PFS containing bimekizumab drug product within an Ypsomed Ypsomate device.

Figure 6-2: Bimekizumab-AI-2mL

AI=auto-injector

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

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

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

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

Appropriate accountability forms that reflect the receipt and use of the IMP and the investigational device presentations including IMP will be supplied to the investigational site. Details of any loss of the IMP and/or injection investigational device presentations due to breakage or wastage, non-use, destruction at the study site, or return to the Sponsor or designee must also be recorded on these 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 IMP and investigational device presentations until returned or destroyed. The Investigator may assign some of the Investigator's duties for drug accountability at the study site to an appropriate pharmacist/designee.

The device presentations should be stored with a proper study participant identification number until the study has been completed. UCB will then instruct the Investigator to destroy them. Used device presentations can be stored at room temperature, preferably placed in the original packaging. Further details are provided in the IMP Handling Manual.

The IMP and investigational device presentations intended for the study cannot be used for any other purpose than that described in this protocol.

6.2.1 Retention samples

As UP0119 is a BE study, retention samples are required to be kept at sites per FDA requirement. All information related to storage and quantity needed on site will be provided in the IMP Handling Manual.

6.3 Measures to minimize bias: randomization and blinding

This is an open-label study.

A PAREXEL Biostatistician (or designee) will write the randomization plan, program and will provide a dummy output of the randomization lists for review and approval in order to ensure compliance to study requirements.

Study participant treatment assignment will be random throughout the study. Study participants will be randomized in a 1:1 ratio to each treatment group as described in Section 4.1.

Copies of each site's randomization list will be sent to the respective site before the start of the study to the following recipients:

- ClinBase ™ setup designer
- Sponsor Drug Safety staff for SAE reporting
- Bioanalytical staff
- Site pharmacist and Pharmaceutical Services staff (for dispensing IMP)

Pharmacokinetic concentration data will not be available to the study team until after the last scheduled procedure for the last study participant in the study, so the decision to replace participants who dropped out or are missing PK visits can be made in an unbiased manner.

At the Screening Visit, each study participant will be assigned a unique 5-digit number from a range of numbers supplied by UCB. Once the Investigator determines that the study participant is eligible for the study, the study participant will be paired to another eligible study participant, matching by gender and bodyweight (≤10kg difference between the 2 participants) and manually assigned to the next 2 available randomization numbers by the Investigator or designee prior to dosing on Day 1. Ideally, the participant's body weight at admission (Day -1) should be used for pairing. Allocating in pairs will improve the precision of the comparison between treatments. Each specific randomization number will identify the pair a study participant belongs to and is tied to the treatment allocation on the randomization schedule, which can then be dispensed by the site pharmacist. This randomization number will also be recorded in the eCRF (ie, ClinBase; see Section 10.1.6).

Participants who withdraw from the study may be replaced at the discretion of the Investigator and Sponsor. Any replacement must match the gender and weight (≤10kg difference between the 2 participants) of the remaining participant being replaced and receive the same treatment as the participant being withdrawn from treatment.

6.4 Treatment compliance

All IMP will be administered by the Investigator or his/her appropriately trained designee.

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:

- Acetaminophen/paracetamol (maximum 2g/day)
- Oral contraceptives
- Hormonal postmenopausal treatment
- Herbal remedy or food supplements (eg, vitamins) within the recommended daily dose limits
- Short-term intake of over-the-counter/non-prescription drugs is allowed if judged by the Investigator to have no potential for drug-drug interactions with the IMP

Non-live vaccines (eg, inactivated influenza and pneumococcal vaccines or non-live COVID vaccines) are allowed up to 2 weeks prior to randomization and 2 weeks after dosing, at

minimum. Investigators can contact the UCB Study Physician or medically qualified designee/equivalent for further guidance.

6.5.2 Prohibited concomitant treatments (medications and therapies)

With the exception of those medications listed in Section 6.5.1 and medications necessary for the treatment of treatment-emergent adverse events (TEAEs) per Investigator discretion, no prescription or nonprescription medicines are allowed within 14 days (3 months for biologic agents) or 5 half-lives of the respective medication (whichever is longer), prior to randomization and until the SFU Visit (Day 140).

6.6 Dose modification

Not applicable.

6.7 Treatment after the end of the study

Not applicable.

7 DISCONTINUATION OF STUDY MEDICATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of IMP

Not applicable; eligible study participants are randomized to receive a single-dose administration of bimekizumab 320mg in UP0119.

7.1.1 Criteria for study hold due to adverse events

During the study, planned dosing and procedures must be discontinued or suspended for all remaining study participants who are yet to be dosed in the study and appropriate follow-up procedures established for (but not limited to) any of the following reasons:

- A pattern of adverse events (AEs), considered as related to the study drug, occurs that in the opinion of the Investigator and/or Sponsor Study Physician contraindicates the further dosing of 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).

Where it is possible to do so without threatening the safety of study participants, such discontinuation/suspension should be discussed with the UCB Study Physician prior to its implementation.

Study and site closure information is provided in Section 10.1.8.

7.2 Study participant withdrawal from the study

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

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

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

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

Upon study discontinuation, an Early WithdrawalVisit will be conducted at the time of withdrawal and the same assessments planned for the SFU Visit per the Schedule of activities (Section 1.3) will be performed.

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

1. Study participant develops an illness that would interfere with his/her continued participation as per the Investigator's judgment.
2. Study participant is noncompliant with the study procedures in the opinion of the Investigator.
3. Study participant takes prohibited concomitant medications as defined in this protocol.
4. Study participant withdraws his/her consent.
5. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test. Study participants should attend the SFU Visit following withdrawal.
6. The Sponsor or a regulatory agency requests withdrawal of the study participant.
7. Participation in any other study during the duration of this study.

Study participants must be withdrawn by the Investigator based on discussion with the Sponsor under the following circumstances:

- Any confirmed COVID-19 case that warrants discontinuation in the judgment of the Investigator or Sponsor to protect the safety of the study participant, other participants, or study site staff.

Investigators should contact the Medical Monitor, whenever possible, to discuss the withdrawal of a study participant in advance. Study participants will be encouraged to return for an SFU Visit following premature discontinuation from the study.

7.3 Lost to follow up

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

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

- The site must attempt to contact the study participant and reschedule the missed visit as soon as possible and counsel the study participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the study participant wishes to and/or should continue in the study.
- Before a study participant is deemed lost to follow up, the Investigator or designee must make a reasonable effort to regain contact with the study participant (at least 1 phone call and 1 written message to the study participant), and document his/her effort (date and summary

of the phone call and copy of the written message in the source documents), to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the study participant, must be recorded in the source documents. The eCRF must document the primary reason for withdrawal or discontinuation.

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

8 STUDY ASSESSMENTS AND PROCEDURES

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

Protocol waivers or exemptions are not allowed.

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

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

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

The maximum amount of blood collected from each study participant over the duration of the study, including any extra assessments that may be required, will not exceed 450mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy assessments

Not applicable.

8.2 Safety assessments

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

8.2.1 Physical examination

Physical examinations will be performed as per Section 1.3. The physical examination will include general appearance; ear, nose, and throat; eyes, hair, and skin; respiratory; cardiovascular; gastrointestinal; musculoskeletal; hepatic; neurological (including limb reflexes); and mental status. Findings considered as clinically significant changes since the physical examination at the Screening Visit will be recorded as AEs.

A full physical examination will be performed at the Screening Visit, Day -1, and the EarlyWithdrawal/SFU Visit. On all other days a physical examination is planned, it will be performed symptom-driven (ie, in case of an AE).

8.2.2 Body weight and height

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

8.2.3 Vital signs

Vital signs (BP [systolic and diastolic], pulse rate, and tympanic body temperature) will be recorded before taking PK samples and with the study participant resting in the supine position for at least 3 minutes in a quiet setting without distractions (eg, television, cell phones). At outpatient visits without regular vital signs measurements, only tympanic body temperature will be collected. The number of readings to be collected will be determined by local standard operating procedures (SOPs) at the sites.

8.2.4 Electrocardiograms

Single 12-lead ECG will be obtained as outlined in the schedule of activities (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

All ECG recordings should be taken before taking PK samples and with the study participant resting in the supine position for at least 3 minutes.

8.2.5 Clinical safety laboratory assessments

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

Laboratory data will be electronically captured by ClinBase, a software tool that ensures quality assurance and enables comprehensive capture of all relevant medical information gathered during the study (Section 10.1.6). The Investigator can assess the data in ClinBase and sign off on them electronically.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor. If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.

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

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

8.2.6 Tuberculosis test

Refer to g-q-100573, UCB Tuberculosis Detection Procedure Guideline for details regarding TB infection status, detection procedures, and the related exclusion criteria.

A QuantiFERON®-TB PLUS GOLD test and a TB questionnaire will be performed at the Screening Visit to identify those study participants who have had TB or may have active or latent TB. Results of this test will be reported as positive, negative, or indeterminate. Study 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 study participant will not be included in the study.

8.3 Adverse events and serious adverse events

The definitions of device-related safety events (adverse device effects [ADEs]) can be found in Appendix 7. Device deficiencies are addressed in Appendix 7 (Section 10.7).

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

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

Confirmed and suspected cases of SARS-CoV-2 infection will be recorded as AEs (or SAE, as required).

8.3.1 Time period and frequency for collecting AE and SAE information

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

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

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 4 (Section 10.4). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

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

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

8.3.2 Method of detecting AEs and SAEs

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

8.3.3 Follow-up of AEs and SAEs

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

8.3.4 Regulatory reporting requirements for SAEs

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

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, 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 study participants and, if indicated, female partners of male study participants will be collected after the start of the inhouse treatment period and for at least 20 weeks after the administration of IMP (anticipated 5 half-lives).

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

- The study participant should return for an early discontinuation visit.
- A SFU Visit should be scheduled 20 weeks after the date of administration of the study participant's IMP.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and 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 bimekizumab, the following event requires immediate reporting (within 24 hours, regardless of seriousness) to UCB:

- Hy's Law
  - Potential Hy's Law, defined as ≥3xULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should be reported if an alternative etiology is identified during investigation and monitoring of the study participant.

8.3.6.1 Other safety topics of interest

Prespecified safety topics of interest for the study are: infections (serious, opportunistic, fungal and TB), neutropenia, hypersensitivity, suicidal ideation and behavior, major cardiovascular events, liver function test changes/enzyme elevations, malignancies, and inflammatory bowel diseases (with gastroenterology referral, as appropriate).

This is based on findings from the IMP clinical program to date, potential risks generally associated with biologic immunomodulators, or findings from other medicines with a related mechanism of action. There are no specific AE reporting requirements for these topics; however, special monitoring, additional data collection activities, and/or enhanced signal detection activities (within UCB) are in place.

8.3.7 Medical device– adverse device effects and device presentation deficiencies

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

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

The definition of a device deficiency can be found in Appendix 7 (Section 10.7).

8.3.7.1 Time period for detecting medical device presentation deficiencies

Device deficiencies or malfunctions of the device presentation that result in reportable events will be detected, documented, and reported on the date of IMP administration when the medical device presentation is used.

The method of documenting Medical Device Deficiency is provided in Appendix 7.

8.3.7.2 Follow-up of device deficiencies

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

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

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

8.3.7.3 Prompt reporting of device deficiencies to the Sponsor

Device deficiencies will be reported to the Sponsor within 24 hours after the Investigator determines that the event meets the protocol definition of a medical device deficiency.

The Adverse Event and Device Deficiency Report Form will be sent electronically to the Sponsor. The Sponsor will be the contact for the receipt of medical device deficiency reports.

8.3.7.4 Regulatory reporting requirements for device deficiencies

The Investigator will promptly report all device deficiencies occurring with any medical device presentation used in the study in order for the Sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical device presentations being used in clinical studies.

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

8.4 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 IMP and/or device presentation so that Investigators, clinical study participants, regulatory authorities, and IECs will be informed appropriately and as early as possible.

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

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

8.5 Treatment of overdose

For this study, any dose of bimekizumab greater than a single-dose administration of 320mg will be considered an overdose. Overdose events are only considered AEs or SAEs if there are associated clinical signs and symptoms.

8.6 Pharmacokinetics

Whole blood samples will be collected for measurement of plasma concentrations of bimekizumab as specified in the schedule of activities (Section 1.3). Instructions for the

collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded. The overall blood volume to be drawn from each study participant participating in the study will not exceed 450mL, ie, the amount of a blood donation.

Samples will be used to evaluate the PK of bimekizumab.

Genetic analyses will not be performed on these blood samples. Study participant confidentiality will be maintained. At visits during which blood samples for the determination of multiple aspects of bimekizumab will be taken, one sample of sufficient volume can be used.

All PK samples should be drawn from study participants after the ECG has been recorded and the vital signs, including BP, have been measured. The following PK parameters will be derived from the plasma concentrations of bimekizumab:

- Area under the plasma concentration-time curve from time zero to infinity (AUC)
- Area under the plasma concentration-time curve from time zero to the last quantifiable concentration ($AUC_{[0-t]}$)
- Maximum observed plasma drug concentration (C_{max})
- Time of occurrence of C_{max} (t_{max})
- Apparent terminal half-life ($t_{½}$)
- Apparent total body clearance (CL/F) after sc administration, calculated as dose/AUC
- Apparent volume of distribution (V_z/F), calculated as CL/λz
- Percentage of the AUC extrapolated from the last observed quantifiable plasma drug concentration (C_{last}) ($\%AUC_{ex}$)

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

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

Pharmacokinetic samples for concentration measurement of bimekizumab may be stored for a maximum of 5 years (or according to local regulations) following the last study participant's last visit at a facility selected by the Sponsor.

8.7 Genetics

Genetics are not evaluated in this study.

8.8 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.9 Biomarkers

Biomarkers are not evaluated in this study.

8.10 Immunogenicity assessments

Antibodies to bimekizumab will be evaluated in plasma samples collected from all study participants according to the schedule of activities (Section 1.3). If feasible, additional blood samples for PK and anti-drug antibody (ADAb) analysis should be collected from participants who develop a hypersensitivity reaction. This sample should be obtained close to the time of the event using an unscheduled visit if needed. Additionally, plasma samples should also be collected at the final visit from study participants who were withdrawn from the study. These samples will be tested by the Sponsor or Sponsor's designee.

Plasma samples will be screened for antibodies binding to bimekizumab and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to bimekizumab and/or further characterize the immunogenicity of bimekizumab.

The detection and characterization of antibodies to bimekizumab will be performed using a validated assay method by or under the supervision of the Sponsor. Anti-drug-antibodies will be measured using a three-tiered assay approach: screening assay, confirmatory assay, and titration assay. Samples may be stored for a maximum of 5 years (or according to local regulations) following the last study participant's last visit for the study at a facility selected by the Sponsor to enable further analysis of immune responses to bimekizumab.

8.11 Medical resource utilization and health economics

Not applicable.

9 STATISTICAL CONSIDERATIONS

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

9.1 Definition of analysis sets

All study participants will consist of all study participants who signed the ICF.

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

The Safety Set will consist of all study participants who are randomized and receive full or partial IMP according to the treatment the participants actually received. The Safety Set will be used for summaries of demographics, medical history, prior and concomitant medications, IMP exposure, and general safety outcomes such as AEs, laboratory parameters, vital signs, and ECGs.

The Pharmacokinetic Set (PKS) will be a subset of the Safety Set, consisting of those study participants that received at least 1 total dose of IMP and have at least 1 observable PK measurement. All participants in the PKS will be included in the listings. Study participants with no protocol deviations to impact observed concentrations will be included in summary tables and figures of concentration-time profiles and PK parameters.

9.2 General statistical considerations

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

For continuous variables, summary statistics will include number of study participants, mean, median, standard deviation (SD), minimum, and maximum. Categorical endpoints will be summarized using number of study participants, frequency, and percentages. Missing data will not be imputed.

If not otherwise stated, Baseline will be the last assessment prior to dosing. Measurement of specific Baseline values will be described in the SAP.

9.3 Planned efficacy/outcome analyses

As efficacy is not evaluated in this study, there is no primary efficacy endpoint.

9.4 Planned outcome analyses

9.4.1 Primary endpoint analyses

The PK analyses will be performed on the PKS.

Following $\log_e$-transformation, the primary PK parameters (C_{max}, area under the plasma concentration-time curve from time zero to the last quantifiable concentration [$AUC_{(0-t)}$], and AUC) will each be evaluated according to an analysis of variance (ANOVA) model with a fixed effect term for pair and treatment. The estimate of the ratio of geometric mean for the AI-2mL (test) versus 2xbimekizumab-AI-1mL (reference) treatment along with the associated 90% confidence intervals (CIs) for the ratio will be calculated. Bioequivalence will be concluded if the 90% CIs for the ratio of the comparison is fully included in the acceptance range from 0.8 to 1.25 for AUC, $AUC_{(0-t)}$, and C_{max}.

Two sensitivity analyses will add 1) the main effect of center and 2) both main effect of center and center-by-treatment interaction. Further sensitivity analyses may also be performed on the PK parameters.

9.4.2 Secondary endpoint analyses

Additionally, a similar ANOVA will be also performed on $\log_e$-transformed t½ to compare elimination characteristics between treatment groups. The point estimate and the 90% CI for the median treatment differences for t_{max} will be computed according to the Hodges Lehmann's method.

9.5 Planned safety and other analyses

9.5.1 Safety analyses

All safety parameters will be listed by study participant and treatment group using the Safety Set.

The incidence of TEAEs will be determined by treatment group, where applicable. Absolute and relative frequencies for a given TEAE by preferred term as per the Medical Dictionary for Regulatory Activities (MedDRA®, version 19.0) will be determined within each treatment group and system organ class. Additional tables will summarize TEAEs by maximum event intensity and causal relationship with IMP per treatment group and overall. The actions taken for each

TEAE, the time of onset of the TEAE after dosing, and the duration of each AE will be listed. The TEAEs leading to discontinuation and SAEs will also be summarized.

For continuous laboratory variables, values and changes from Baseline will be summarized at each time point. For categorized values according to the reference range, shift tables from Baseline to each postdose time point will be presented for selected variables. Values outside the reference range will be flagged in the data listings. The reference ranges will be reported.

Normal versus abnormal findings for the various ECG parameters and overall ECG will be analyzed as required, focusing on the identification of outliers and of any trends for changes following administration of IMP with respect to QT/QTc. Descriptive statistics will be presented for ECG value and changes from Baseline over time.

Descriptive statistics will be reported for all vital sign measurements (including systolic and diastolic BP, pulse rate, and tympanic body temperature). Measured values and changes from Baseline will be summarized for all study participants by time point.

Abnormal findings in the physical examination will be presented in listings only.

9.5.2 Immunogenicity analyses

Bimekizumab ADAb levels will be listed per participant and summarized using summary tables and figures. The number (and percentage) of study participants with first occurrence of treatment-induced ADAb positivity will also be summarized at each postdose visit.

9.5.3 Other analyses

9.5.3.1 Study participant disposition and characteristics

The number of study participants who were enrolled and randomized into the study, in each analysis set, and who completed or prematurely discontinued the study, as well as the reason for discontinuation, will be presented by treatment and overall using frequency counts and percentages. In addition, listings will be provided for study discontinuation, study participant disposition, and participant analysis sets.

Study participant characteristics will include a summary and listing of the following:

- Demographics (including sex, age, race, ethnicity, height, weight, BMI, and lifestyle)
- Medical history
- Prior and concomitant medications

Concomitant medical procedures will only be listed.

9.6 Handling of protocol deviations

No protocol deviation is permitted, either in retrospect or prospect.

Important protocol deviations are identified as part of the data cleaning process in the Data Cleaning Plan (DCP). The objective of the data cleaning meeting will be to review and update (if necessary) the important protocol deviations in the DCP and discuss exclusion of study participants from analysis populations.

Furthermore, overall trends in protocol deviations will be discussed at the Data Evaluation Meeting. Through this data cleaning and evaluation process, all decisions regarding important

protocol deviations and exclusions from analysis populations will be made. Protocol deviations (eg, missing assessments or visits) related to COVID-19 may be listed separately.

Accepted deviations from theoretical time points will be described in the appropriate documents and included in the trial master file (TMF).

After resolution of all issues, and documentation of all decisions, the database will be locked.

9.7 Handling of dropouts or missing data

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

9.8 Planned interim analysis and data monitoring

No formal interim analysis is planned for this study.

9.9 Determination of sample size

This is a BE study to compare the PK of bimekizumab-AI-2mL (test) versus bimekizumab-AI-1mL (reference).

The sample size estimation was based upon variability observed in studies UP0033 and UP0068. These were the 2 most recent studies which included the AI device with a single administration of bimekizumab in healthy study participants. The respective inter-participant variabilities (coefficient of variation [CV%]) observed in these studies were up to 32%, 33% (AUC) and 31%, 25% (C_{max}). The geometric mean ratios for all primary PK parameters were between 0.97 and 1.02 (UP0033) and between 1.03 and 1.15 (UP0068). The individual study CV% and geometric mean ratios are presented in Appendix 11 (Section 10.11).

Assuming a geometric mean ratio of 1.08 (or 0.93) and inter-participant variability (CV%) of 32%, 54 study participants per group are required to assess BE with 80% power assuming that BE will be declared if the 90% CI for the geometric mean ratio is contained entirely within the acceptance range (0.8, 1.25).

Sample size estimation was performed using SAS software (version 9.4).

Assuming a dropout rate and non-evaluable study participants of approximately 10%, 60 study participants per group for a total of approximately 120 study participants are to be enrolled in the study.

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 (ICH E6[R2]), and in accordance with the ethical principles that have their origin in the Declaration of Helsinki (1996).

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, ICF, IB, Investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other study participant-related documents to be used for the study to the 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 study participants or others, and any protocol deviations, to eliminate immediate hazards to study participants.

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

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

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

Prior to participation in the study, an IEC-approved, written ICF should be signed and personally dated by the study participant and by the person who conducted the informed consent discussion (Investigator or designee) prior to the initiation of any study-specific assessment at the Screening Visit. The study participant must receive a copy of the signed and dated ICF. As part of the consent process, each study participant must consent to direct access to his/her medical records for study-related monitoring, auditing, IEC review, and regulatory inspection.

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

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

10.1.4 Data protection

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

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 study participant's primary medical records that directly concerns this study (including, but not limited to, laboratory test result reports, ECG reports, admission/discharge summaries for hospital admissions occurring during a participant's study participation, and autopsy reports for deaths occurring during the study).

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

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

10.1.5 Committees structure

Not applicable.

10.1.6 Data quality assurance

The Sponsor will supervise study initiation visits to verify the qualifications of the Investigators, inspect the facilities, and inform the Investigators of responsibilities and procedures for ensuring adequate and correct documentation.

The Investigators must prepare and maintain adequate and accurate records of all observations and other data pertinent to the clinical study for each study participant. Frequent communication between the clinical unit and the Sponsor is essential to ensure that the safety of the study is monitored adequately. The Investigators will make all appropriate safety assessments on an ongoing basis.

All aspects of the study will be carefully monitored with respect to GCP and SOPs for compliance with applicable government regulations. The Study Monitor will be an authorized individual designated by the Sponsor. The Study Monitor will have access to all records necessary to ensure the integrity of the data and will periodically review the progress of the study with the Investigators. Remote monitoring visits may be conducted during the COVID-19 pandemic or under other exceptional circumstances as deemed appropriate to ensure study participants' safety.

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 ClinBase by authorized site personnel are accurate, complete, and verifiable 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 are to be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP/investigational device. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or by an agreement with UCB (CPMP/ICH/135/95, 2002 [Section 4.9.5]). 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 TMF.

10.1.6.1 Case Report form completion

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

Any change or correction to ClinBase 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 ClinBase.

10.1.6.2 Apps

Not applicable.

10.1.7 Data collection and source documents

PAREXEL will use ClinBase to collect medical data during this study.

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

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

Source documents that are computer generated and stored electronically must be printed for review by the monitor (eg, ECG reports). Once printed, these copies should be signed and dated by the Investigator and become a permanent part of the study participant's source documents.

If source documents have been captured by ClinBase, they need to be electronically signed/stamped to indicate review by the Investigator/designee/delegate.

The Investigator/designee 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.

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 study participants by the Investigator
- Discontinuation of further IMP development

- A required adaptation of the maximum insurance sum is not possible (ie, the risk/benefit estimation changes, leading to insufficient insurance coverage while the maximum insurance sum is not adapted)
- The positive evaluation or approval is withdrawn by the IEC or local health authority

The criteria for study holds due to AEs are provided in Section 7.1.1.

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 Table 10-1 below will be performed. The following central laboratories will be used:

- For the site in Germany: at SGS Analytics Germany GmbH (safety laboratory assessments) and Parexel International (urinalysis/urine drug screen and SARS-CoV-2 RT-PCR).
- For the site in the US: at Parexel International (urine drug screen, in-house pregnancy) and GenX Laboratories, Inc. (safety laboratory assessments and everything else required).

Protocol-specific requirements for inclusion or exclusion of study participants are detailed in Section 5.1 and Section 5.2 of this protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 10-1: Protocol-required safety laboratory assessments

Laboratory measurements	Variables
Serology	HbsAg, HBc-Ab (both IgG and IgM), HCV-Ab, HIV1-Ab, HIV1-Ag, HIV-2 Ab, SARS-CoV-2 RT-PCR[a]
Hematology	Complete blood count, ie, hemoglobin, hematocrit, RBC, WBC, WBC with differential, platelet count
Coagulation/hemostasis	Prothrombin time, aPTT
Clinical chemistry	Albumin, ALP, ALT, AST, GGT, creatine kinase, LDH, total bilirubin, BUN, creatinine, glucose, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, electrolytes (sodium, potassium, chloride, total calcium), and total protein, FSH
Urine (dipstick) [b]	pH, protein, glucose, ketone, urobilinogen, bilirubin, blood, specific gravity, nitrite, and leukocytes
Urine alcohol test/drug screen	Ethanol will be measured using a urine alcohol test. Urine drug screen includes amphetamines/methamphetamines, barbiturates, benzodiazepines, tetrahydrocannabinol, cocaine, tricyclic antidepressants, phencyclidine, and morphine/opiates
Pregnancy	Prior to dosing, a serum pregnancy test (hCG) will be performed; post dosing the test may be performed in urine. The FSH test will be performed in postmenopausal women at the Screening Visit.

ALP=alkaline phosphatase; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle stimulating hormone; GGT=gamma glutamyltransferase; HBc-Ab=hepatitis B core antibody; HbsAg=hepatitis B surface antigen; hCG=human chorionic gonadotropin; HCV-Ab=hepatitis C virus antibody; HDL=high density lipoprotein; HIV=human immunodeficiency virus; HIV1/2-Ab=HIV1/2 antibody; HIV1-Ag=HIV1 antigen; LDH=lactate dehydrogenase; LDL=low density lipoprotein; RBC=red blood cell; WBC=white blood cell

[a] Sample will be obtained per local requirements.

[b] Upon a positive urine test for leukocytes, blood, nitrite, or protein, the Investigator may require further urine analysis, such as flow cytometry. Results of additional urine analyses will be included in the database. If the flow cytometry examination shows a different result than the urine dipsticks, the urine will be investigated by fully automated digital imaging where leukocytes, erythrocytes, and casts (cellular, granular, hyaline) in urine will be analyzed.

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 IMP, whether or not considered related to the IMP. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of IMP.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • 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 IMP 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 IMP or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

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

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 study participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the study participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is an important medical events:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the study participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include, but are not limited to, potential Hy's law, invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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 study participant's medical records to UCB in lieu of completion of the UCB AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by UCB. In this case, all study participant identifiers, with the exception of the study participant number, will be redacted on the copies of the medical records before submission to UCB.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

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

Assessment of Causality

- The Investigator is obligated to assess the relationship between IMP and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to IMP administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which 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 one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

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

Reporting of SAEs

SAE Reporting to UCB via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to UCB will be the electronic data collection tool. • If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section). • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken 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 bullet) or to the UCB Study Physician by telephone. • Contacts for SAE reporting can be found in SERIOUS ADVERSE EVENT REPORTING.

10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

Definitions

Woman of Childbearing Potential (WOCBP)

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

Contraception Guidance

Male study participants

Male study participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following for a period of 20 weeks after their dose of IMP.

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.
- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Appendix 4 (Section 10.4) when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

In addition, male study participants must refrain from donating sperm for the duration of the study and for at least 20 weeks after IMP administration.

Male study 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.

Female study participants

Female study participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Appendix 4 (Section 10.4).

Table 10-2: Highly effective contraceptive methods [a]

Highly Effective Contraceptive Methods That Are User Dependent[b] Failure rate of <1% per year when used consistently and correctly.
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent[b]
Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the woman of childbearing potential (WOCBP) and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the IMP. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the study participant.

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

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

Pregnancy testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test.
- Additional pregnancy testing should be performed at monthly intervals during the treatment period, and at the SFU Visit at Day 140.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- Pregnancy testing, with a sensitivity of 25mIU/mL will be performed.

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male study participant's female partner who becomes pregnant while the male study participant is in this study and for at least 20 weeks after IMP administration.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 1 working day of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow up will be at least 12 months after the delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

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

10.5 Appendix 5: Genetics

Not applicable.

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

Study participants with 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 participant withdrawal (if applicable), must be recorded in the source documents.

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 study participant safety and to evaluate liver event etiology (Table 10-3).

Table 10-3: Phase I liver chemistry stopping criteria and follow-up assessments

Liver Chemistry Stopping Criteria – Liver Stopping Event	
ALT-absolute	ALT≥3xULN If ALT ≥3xULN AND bilirubin ≥2xULN (>35% direct bilirubin) OR international normalized ratio (INR) >1.5, report as a serious adverse event (SAE).[a,b] See additional actions and follow-up assessments listed below.
Suggested Actions and Follow up Assessments	
Actions	**Follow Up Assessments**
• Report the event to the 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. • Perform liver chemistry follow-up assessments. • Monitor the study participant until liver chemistry test abnormalities resolve, stabilize, or return to Baseline (see MONITORING). MONITORING: If ALT ≥3xULN AND bilirubin ≥2xULN or INR >1.5: • Repeat liver chemistry tests (include ALT, AST, ALP, bilirubin) and perform liver event follow-up assessments within 24 hours. • Monitor study participant twice weekly until liver chemistry test 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 • Serum creatine phosphokinase and LDH • Fractionate bilirubin, if total bilirubin ≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE eCRF • Record use of concomitant medications (including acetaminophen, herbal remedies, and

Table 10-3: Phase I liver chemistry stopping criteria and follow-up assessments

Liver Chemistry Stopping Criteria – Liver Stopping Event	
• A specialist or hepatology consultation is recommended. If ALT ≥3xULN AND bilirubin <2xULN and INR ≤1.5: • Repeat liver chemistry tests (include ALT, AST, ALP, bilirubin) and perform liver chemistry follow-up assessments within 24 to 72 hours. • Monitor study participants weekly until liver chemistry abnormalities resolve, stabilize, or return to Baseline.	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 (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in study participants with definite or likely acetaminophen use in the preceding week [James, 2009]) • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete liver imaging and/or liver biopsy eCRFs

[a] Serum bilirubin fractionation should be performed if testing is available. 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 SAEs (excluding studies of hepatic impairment or cirrhosis). The INR measurement is not required and the stated threshold value will not apply to study participants receiving anticoagulants.

[c] Hepatitis A immunoglobulin M (IgM) antibody; HbsAg and HbcAb; hepatitis C ribonucleic acid; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.

10.7 Appendix 7: Medical device presentation ADEs and Device Deficiencies: – definition and procedures for recording, evaluating, follow up, and reporting

10.7.1 Definitions of a medical device presentation incident

The definitions and procedures detailed in this appendix are in accordance with ISO 14155.

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

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

10.7.2 Definition of ADE

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

10.7.3 Definition of device deficiency

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

10.7.4 Recording and follow up of ADE and device deficiencies

ADE and device deficiency recording

- When an ADE /device deficiency occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant ADE /device deficiency information in the participant's medical records, in accordance with the Investigator's normal clinical practice and on the appropriate form of the CRF.
- 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 ADE/ device deficiency CRF 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 ADE.
- For device deficiencies, it is very important that the Investigator returns the device to the sponsor, and describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence. The Investigator should complete a Product Complaint Form for all reported device deficiencies.

Assessment of intensity

The Investigator will make an assessment of intensity for each ADE /device deficiency reported during the study and assign it to one 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.

Assessment of causality
• The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE to assess if they are ADEs/ /device deficiency. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The Investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. • For each ADE /device deficiency, the Investigator **must** document in the medical notes that he/she has reviewed the ADE/ device deficiency and has provided an assessment of causality. •

Follow-up of ADE /device deficiency
• The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by UCB to elucidate the nature and/or causality of the ADE/ device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • New or updated information will be recorded in the originally completed CRF. • The Investigator will submit any updated ADE data to UCB within 24 hours of receipt of the information.

10.8 Appendix 8: Rapid alert procedures

Not applicable.

10.9 Appendix 9: Country-specific requirements

Not applicable.

10.10 Appendix 10: Abbreviations and trademarks

Ab	antibody
ADAb	anti-drug antibody
ADE	adverse device effect
AE	adverse event
AI	auto-injector
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve from time zero to infinity
$AUC_{(0-t)}$	area under the plasma concentration-time curve from time zero to the last quantifiable concentration
$\%AUC_{ex}$	percentage of the AUC extrapolated from C_{last}
axSpA	axial spondyloarthritis
BE	bioequivalence
BMI	body mass index
BP	blood pressure
CI	confidence interval
CL/F	apparent total body clearance
C_{last}	last observed quantifiable plasma drug concentration
C_{max}	maximum observed plasma drug concentration
COVID-19	coronavirus disease 2019
CRO	contract research organization
CV	coefficient of variation
DCP	Data Cleaning Plan
ECG	electrocardiogram
eCRF	electronic Case Report Form
EU	European Union
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HBc-Ab	anti-hepatitis B core antibody

HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
HS	hidradenitis suppurativa
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFU	Instructions for Use
Ig	immunoglobulin
IL	interleukin
IMP	investigational medicinal product
LDH	lactate dehydrogenase
mAb	monoclonal antibody
MedDRA®	Medical Dictionary for Regulatory Activities
PFS	prefilled syringe
PK	pharmacokinetics
PKS	Pharmacokinetic Set
PsA	psoriatic arthritis
PSO	psoriasis
QTcF	QT interval corrected using Fridericia's formula
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS®	Statistical Analysis System
sc	subcutaneous
SD	standard deviation
SFU	Safety Follow-Up
SOP	standard operating procedure

SS	safety syringe
$t_{½}$	apparent terminal half-life
TB	tuberculosis
TEAE	treatment-emergent adverse event
t_{max}	time of occurrence of C_{max}
TMF	trial master file
TN	True North
ULN	upper limit of normal
Vz/F	apparent volume of distribution
WOCBP	women of childbearing potential

10.11 Appendix 11: Sample size estimation parameters

Study	Formulation	Parameter	CV%	GeoMean ratio	Comments
UP0033 n=63 per arm	SS 1mL	AUC	31.1	97.8	vs TN 1mL, CV% is from individual comparisons data
		C_{max}	28	96.5	vs TN 1mL, CV% is from individual comparisons data
	AI 1mL	AUC	29.9	102	vs TN 1mL, CV% is from individual comparisons data
		C_{max}	22.9	98.25	vs TN 1mL, CV% is from individual comparisons data
	TN 1mL	AUC	32.1		
		C_{max}	30.5		
UP0068 n=~18 per arm	SS 2mL	AUC	32.8	103.4	vs SS 2x1mL, Final Report, CV% is from individual comparison
		C_{max}	25.4	104.0	vs SS 2x1mL, Final Report, CV% is from individual comparison
	AI 2mL	AUC	28.6	115.0	vs AI 2x1mL, Final Report, CV% is from individual comparison
		C_{max}	24.7	114.3	vs AI 2x1mL, Final Report, CV% is from individual comparison

AI=auto-injector; AUC=area under the plasma concentration-time curve from time zero to infinity; C_{max}=maximum observed plasma drug concentration; CV=coefficient of variation; Geomean=geometric mean; SS=safety syringe; TN=True North

10.12 Appendix 12: Protocol amendment history

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

11 REFERENCES

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12 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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